FMD VACCINE AND VACCINATION

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General Considerations on FMD vaccination

- The currently used FMD vaccines are killed virus preparations that are pure, safe, and effective.
- There are seven different types and more than 60 subtypes of FMD virus, and there is no universal vaccine against the disease.
- Vaccines for FMD must match to the type and subtype present in the affected area. When matched to type and subtype, the vaccine will normally protect animals from developing clinical signs of disease, but will not necessarily protect animals against FMD infection.
- Animals that receive the vaccine usually develop some degree of protection against clinical signs of FMD within 7 to 8 days.

FMD control- vaccination challenges

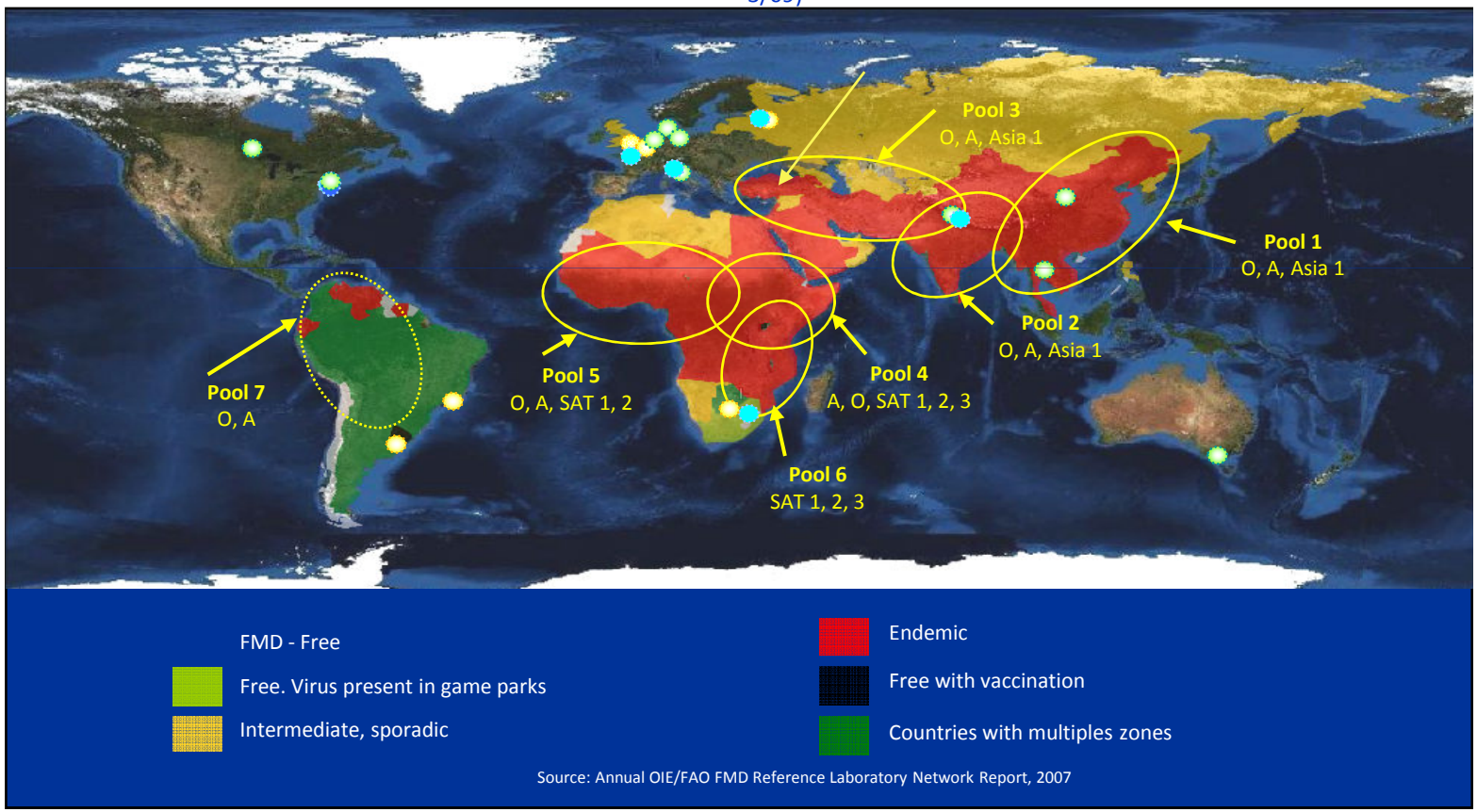
- Highly infectious with rapid transmission
- Multispecies including wildlife
- Multiple serotypes with variation within serotypes
- Some farmers/regions lack motivation to control FMD
- Vaccines:
  - Short lived protection against limited range of strains
  - Expensive & unstable (cold-chain required)
- Subclinical infections
- Livestock population turnover & movements
- Cost/impact of control measures

FMDV distribution

Reference Laboratories and Collaborating Centres

Reference Centres (UK, Belgium, Italy, South Africa, India, Russian Fed – at 3/09)

Regional/National Reference Centres



FMDV serotypes distribution

Table 1 Various serotypes in FMDV distribution areas

Area	Main serotypes in FMDV distribution areas						
	Type O	Type A	Type C	Type Asia I	SAT-1	SAT-2	SAT-3
China	+	+	-	+	-	-	-
Southeast Asia	+	+	-	+	-	-	-
Africa	+	-	-	-	+	+	+
Middle East	+	+	+	+	-	-	-
United Kingdom	+	-	-	-	-	-	-
South America	+	+	+	-	-	-	-

"+" means positive, and "-" means negative.

Zhang et al., Virology Journal, 2011

ANTIGENIC DIVERSITY OF FMD VIRUS

Serotype	Antigenic diversity	Distribution
O	++++ 3 topotypes: ME-SA; SEA; CHY.	Most widespread
A	+++++ New variants emerge frequently.	Second most widespread
C	+	Very restricted distribution
SAT 1-3	++++	Restricted distribution with occasional excursions to new regions e.g. Recent SAT 2
Asia 1	++	Middle East and Asia.

Adapted from A. Donaldson presentation, Bangkok, 2012

Vaccine use considerations

- The choice of vaccination as a key tool to control FMD requires:
  - Vaccine storage and transport infrastructure,
  - Trained personnel in adequate numbers,
  - Necessary equipment (administrative & technical) and small technical materials for vaccine application.
- Insure best use:
  - Well-organized national campaigns with the consensus of all stakeholders
  - At least 90% of the targeted animals are vaccinated, and counted.
  - National individual identification!

Vaccine use considerations (continued)

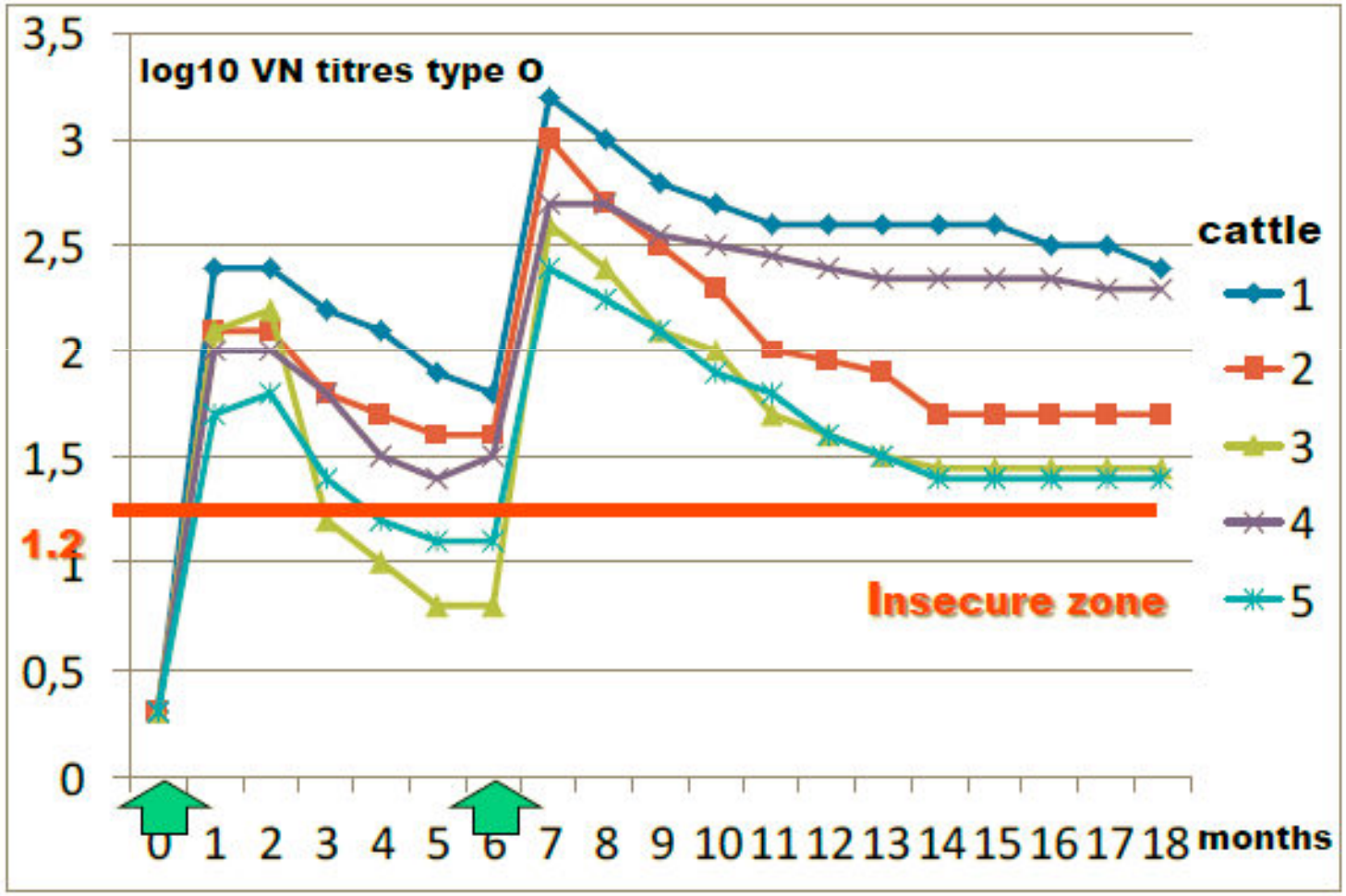
- Vaccination campaign should be short (1-3 months) and massive
- Vaccine supply should be secured as well as the entire logistical environment
- Evaluation of the effects of a vaccination campaign shall be finished before starting revaccination

FMD vaccine presentation

VACCINE	Alhydrogel Saponine	Single Emulsion Oil in Water	Single Emulsion Water in Oil	Double Emulsion Water in Oil in Water
Route	strictly S/cut.	S/cut or I.M.	strictly I.M.	S/cut or I.M. (I.D. in pigs)
SPECIES	Bovidae Sheep Goats	Pigs Sheep Goats	Cattle Sheep (pigs)	All Species but mainly Pigs
REGIONS	Europe Africa Middle-East	S.E. Asia Middle-East	South America	S.E. Asia

Adapted from Lombard presentation, Bangkok, 2012

All available aqueous vaccines performed well and provided satisfactory level of protection after vaccination with $3PD_{50}$

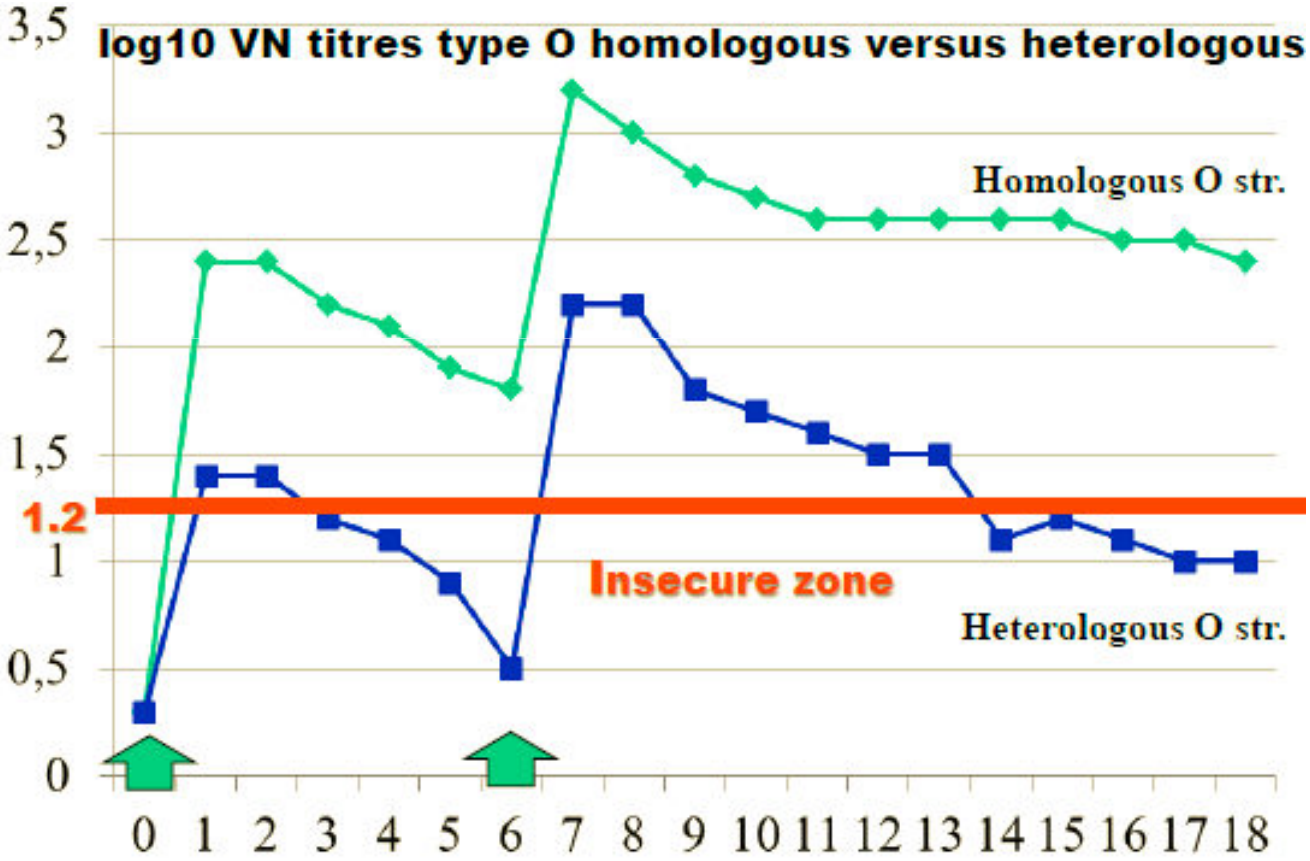


Adapted from Lombard presentation, Bangkok, 2012

Factors influence outcome

- Correspondence field virus / vaccine strain (vaccine matching)
- Antigen pay load drives efficacy
- Influence of the time of revaccinations
- Maternally derived Antibodies

Vaccine matching



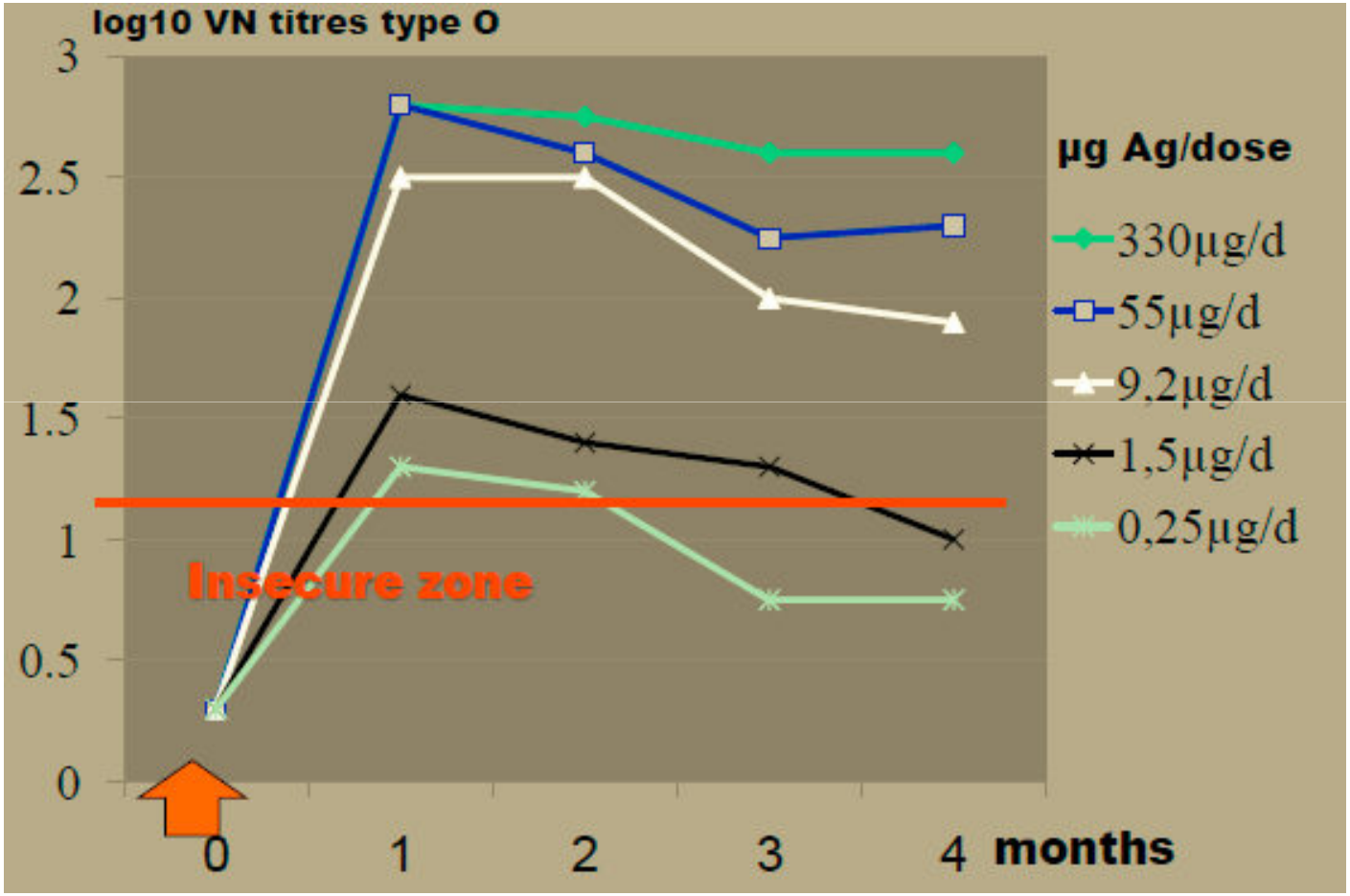
Adapted from Lombard presentation, Bangkok, 2012

Vaccine Matching

$$r_1 = \frac{\text{Titre of bovine serum against field isolate of interest}}{\text{Titre of bovine serum against reference vaccine strain}}$$

- Interpretation from ELISA
  - 0.4 to 1.0 protection expected
  - 0.2 to 0.39 some protection expected
  - <0.19 protection not expected

Antigen pay load drives efficacy

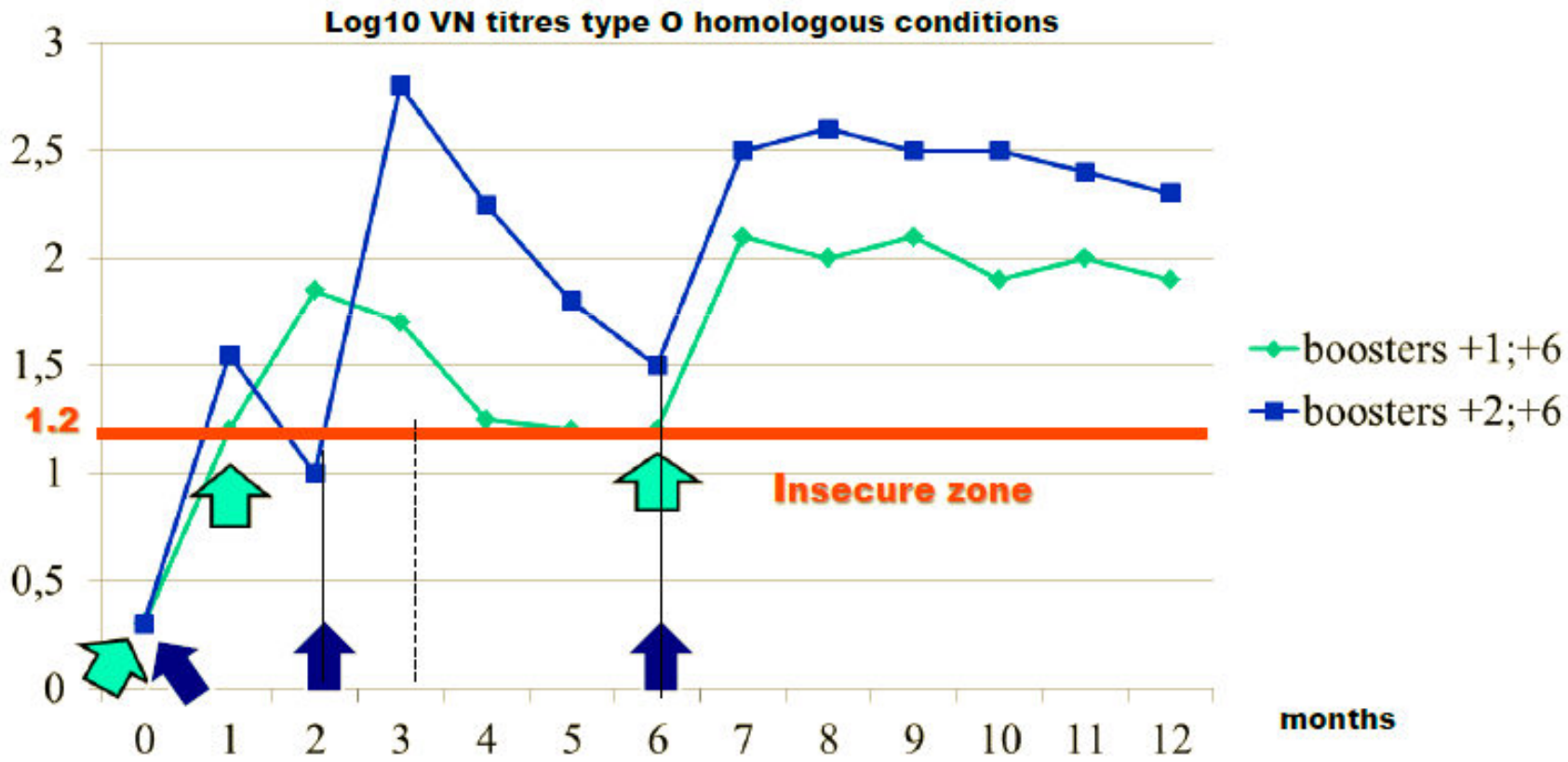


Adapted from Lombard presentation, Bangkok, 2012

Antigen pay load drives efficacy

- Low or altered Ag pay load leads to limited potency
- OIE standards --→ $3PD_{50}$
- Inadequate antigen pay load may lead to creating new FMDV subtypes.

Influence of time of vaccination



Adapted from Lombard presentation, Bangkok, 2012

Maternally derived Antibodies

- “Using oil vaccines calves can be vaccinated at about 2 month of age, when MDA level in many animals falls below protective values.
- Then, they can be revaccinated between 2 and 6 months in order to enter into the 6 month vaccination cycle which is recommended for cattle under 2 years of age.
- In this way the number of unprotected animals in cattle population can be reduced considerably.”

FMD vaccination strategies

- Vaccination is one of the tools of the Global FAO/OIE Strategy for the Control of FMD.
- Strategy follows two main phases:
  - Primarily, a conceptual phase involving stakeholders to create the larger possible consensus in the country to control FMD following the FAO-Progressive Control Pathway set of control stages.
  - Secondarily, an executive phase in the field with actors following instructions and procedures.

Vaccination strategy at PCP-2

- In Stage 2 of FMD-PCP, a good start in vaccination strategy on the national level is required.
  - A targeted vaccination is aimed at protecting the dairy sector.
  - Or in the high producing herds (cattle feed lots – intensive pig production premises…).
  - Development of Public Private Partnership (PPP) for vaccine delivery and use.

Vaccination in PCP-2

- Responsibilities:
  - Private vaccination programs in high producing herds with veterinarians
  - Public vaccination programs (uncertain) in small farm sector

Vaccination in PCP-3

- FMD vaccination in PCP-3 is more aggressive
  - In PCP-3: it is essential to unify the efforts
  - Sole responsibility of the government
  - Well organized program
  - Refined according to results surveillance
  - Endorsed by OIE
  - PPP leads to optimal results
  - Mandatory vaccination

Failure in vaccination strategies

- Vaccine quality:
- Delivery systems
- Combination of poor quality, poor timing and poor coverage
  - results in gaps that allows infection to circulate. Confidence is therefore eroded, among veterinarians as well as stakeholders.
- Vaccine supply

FMD Vaccination program evaluation

- **Estimated FMD doses used per year:**

Region	Million doses/Year	Comments
China	1.6 billion doses	5 government producers
South America	500	Brazil: 350 million doses
Asia (excluding China)	200	India: 150 million doses
Middle East	20	
European region	15	Mainly Turkey
Africa	15	

Estimated global FMD vaccine use (Hamond, 2011)

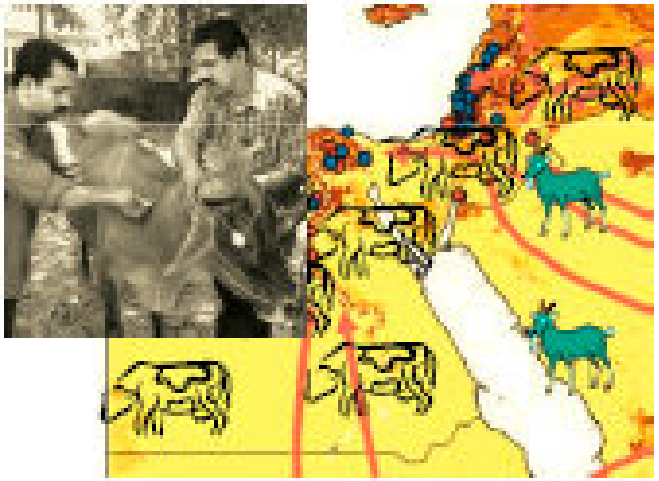
FMD Vaccination program evaluation

Essential components

- Problems at any stage will reduce programme impact

1) High efficacy vaccine
-varies with field strain
-vaccine schedule

2) Correct storage and delivery
-cold chain
-shelf-life



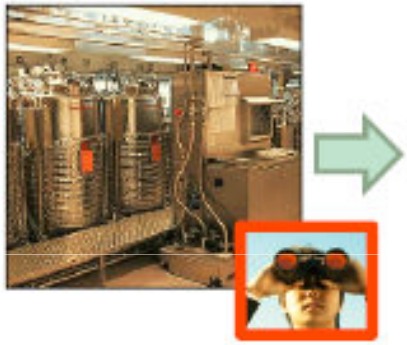
3) Vaccinate target population
-coverage
-biosecurity
-schedule/ongoing
-timing

FMD Vaccination program evaluation

- If problems not identified and solved…
- Still have the cost of vaccination but the population is still susceptible

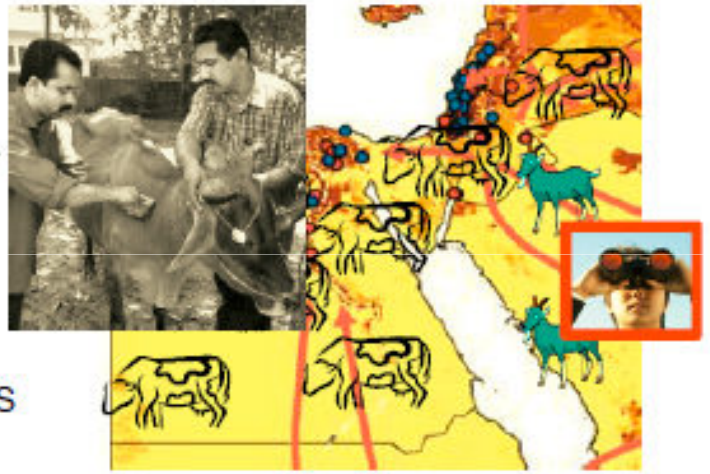
Vaccination CCPs

- Problems at any stage will reduce programme impact



1) Vaccine potency
2) Vaccine matching
3) Batch testing
4) Quality assurance [independent]

1) Auditing adherence to SOPS
2) Cold chain monitoring



1) Coverage
2) Population immunity (SP serology)
3) Post-vaccinal response (SP serology)
4) Disease surveillance
   -Passive and active surveillance
   -Clinical and serological
5) Monitor field virus
6) Outbreak investigation
   -Vaccine effectiveness

1) Appropriate objectives and strategy
2) Stakeholder support

Is my program controlling FMD?

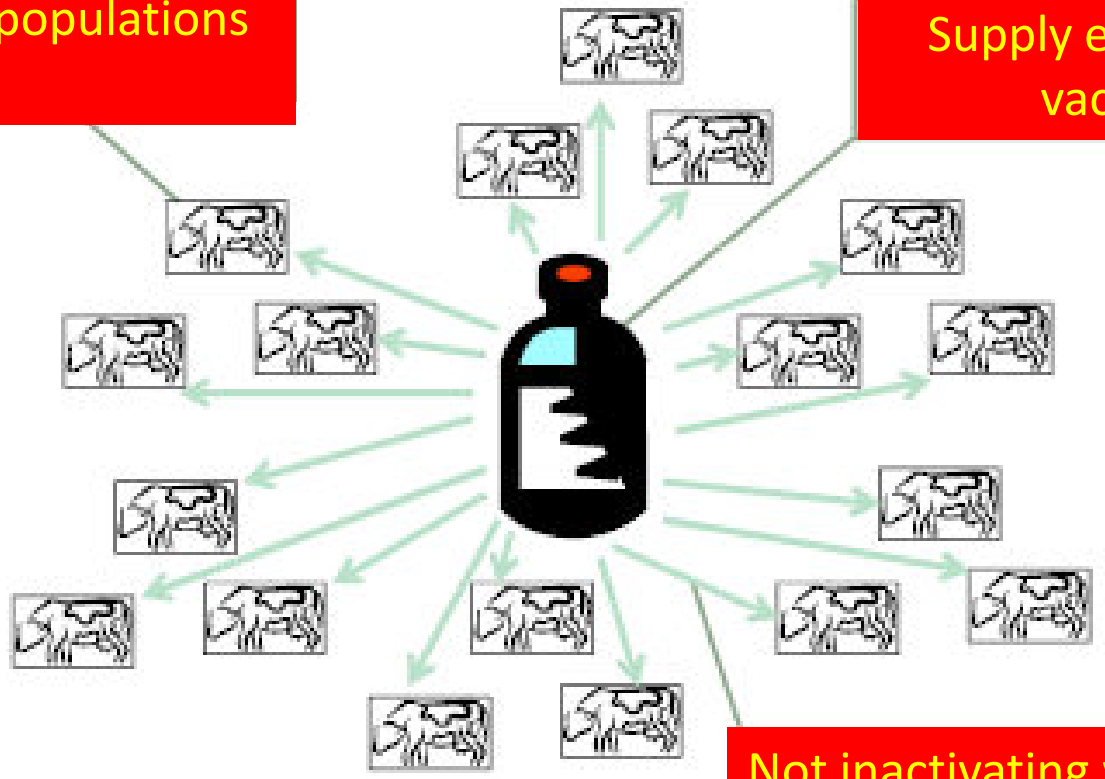
- Are the animals being vaccinated?
  - Vaccine coverage
- Are vaccinated animals protected?
  - Vaccine effectiveness

Vaccine efficacy -> under controlled trial
Vaccine effectiveness - > observational study (field study)

Is my program controlling FMD?

Deliver vaccine to target populations

Supply efficacious vaccine



Not inactivating vaccine during delivery

Are animals in the field protected?

- Serology
  - Post-vaccinal SP serology
  - Population immunity SP serology
- Outbreak investigation
  - Vaccine effectiveness study
- Surveillance –assess FMD incidence
  - NSP survey
  - Active surveillance

SP serology

- Structural protein (SP) serology
  - Induced by vaccination or infection
  - Serology titer >1/100 (varies) implies protection against vaccine strain
    - **Actual protection depends on match with field virus**
- Post vaccinal serology
  - Are vaccinated animals responding to the vaccine
- If problem stay or increased, investigate vaccine & delivery - revaccinate

The FMD Vaccine

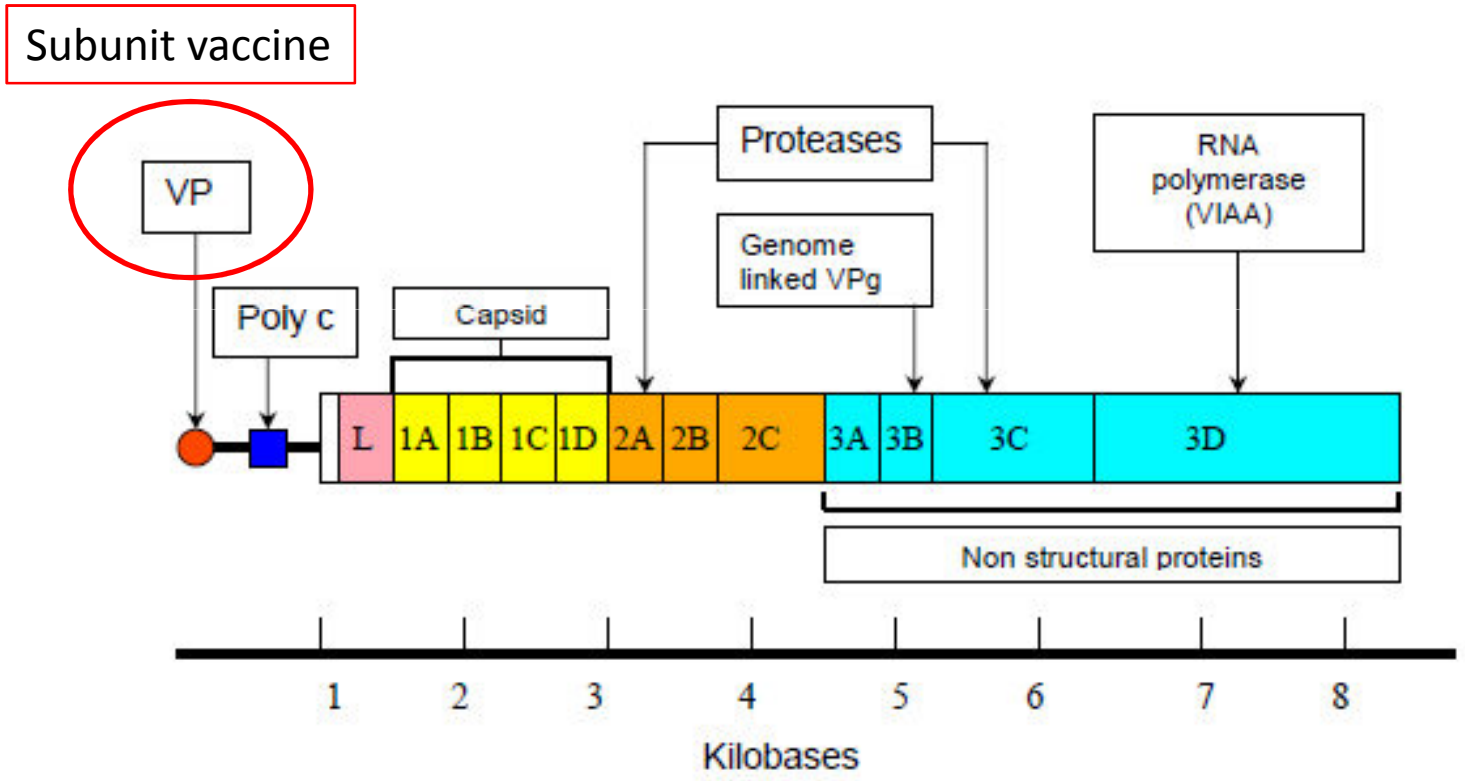
Ideal FMD Vaccine

Criteria	Current vaccine	Ideal vaccine
Duration of immunity	Short (4-6months)	Long (1 to 2 years)
Onset of immunity	4-21 d post vaccination	2-3 days post vac
Cost of production	High	Low or moderate
Potency experiments	Cumbersome	Simple without animal experimentation
Thermal stability	Poor, required cold-chain	High even at room Temp
DIVA enabled	Depends on Manufacturer	Enables DIVA
Route of administration	Deep IM or S/C	Aerosal or mucosal
Adjuvant Efficacy	Adjutants required	Adjuvant use optional
Spectrum of activity	Serotype specific	Immunity for multiple serotypes
Carrier status. Sterile Immunity	Hardly achieved	Easily achievable

New generation FMD vaccines

- Subunit vaccines:
  - Expression of VP1 in different host systems and testing their immunogenicity.
  - Expression of P1-2A3C to generate empty virus particles in bacteria or yeast cells
- DNA vaccination:
  - P1-2A
  - P1-3A3C (better immunity in mice)
- Synthetic peptides:
  - 140-160 a.a. of the VP1 protein
  - Overlapping peptides of the VP1 (Pepscan method)

FMDV genome


Subunit vaccine
VP
Poly c
Capsid
Proteases
Genome linked VPg
RNA polymerase (VIAA)
L
1A
1B
1C
1D
2A
2B
2C
3A
3B
3C
3D
Non structural proteins
1
2
3
4
5
6
7
8
Kilobases

Subunit vaccines

Example: Expression of P12A3C in silkworm pupae

Table 1. Analysis of cattle after challenge with FMDV.

Animal number	Vaccine[a]	LPB-ELISA antibody[b] 0dpv	14dpv	21dpv	28dpv	Days of onset of pyrexia [c]	Duration of Pyrexia (days)	Lesion scores[d]	Protection[e]
7	rBm(P12A3C)	<8	90	128	128	–	–	–	+
15	rBm(P12A3C)	<8	128	256	180	–	–	–	+
25	rBm(P12A3C)	<8	45	90	90	–	–	–	+
200	rBm(P12A3C)	<8	128	128	180	–	–	–	+
195	rBm(P12A3C)	<8	16	32	22	Day2	3	4+mouth	–
5	BmBacPAK-6	<8	<8	<8	<8	Day2	3	4+mouth	–
32	BmBacPAK-6	<8	<8	<8	<8	Day2	3	4+mouth	–

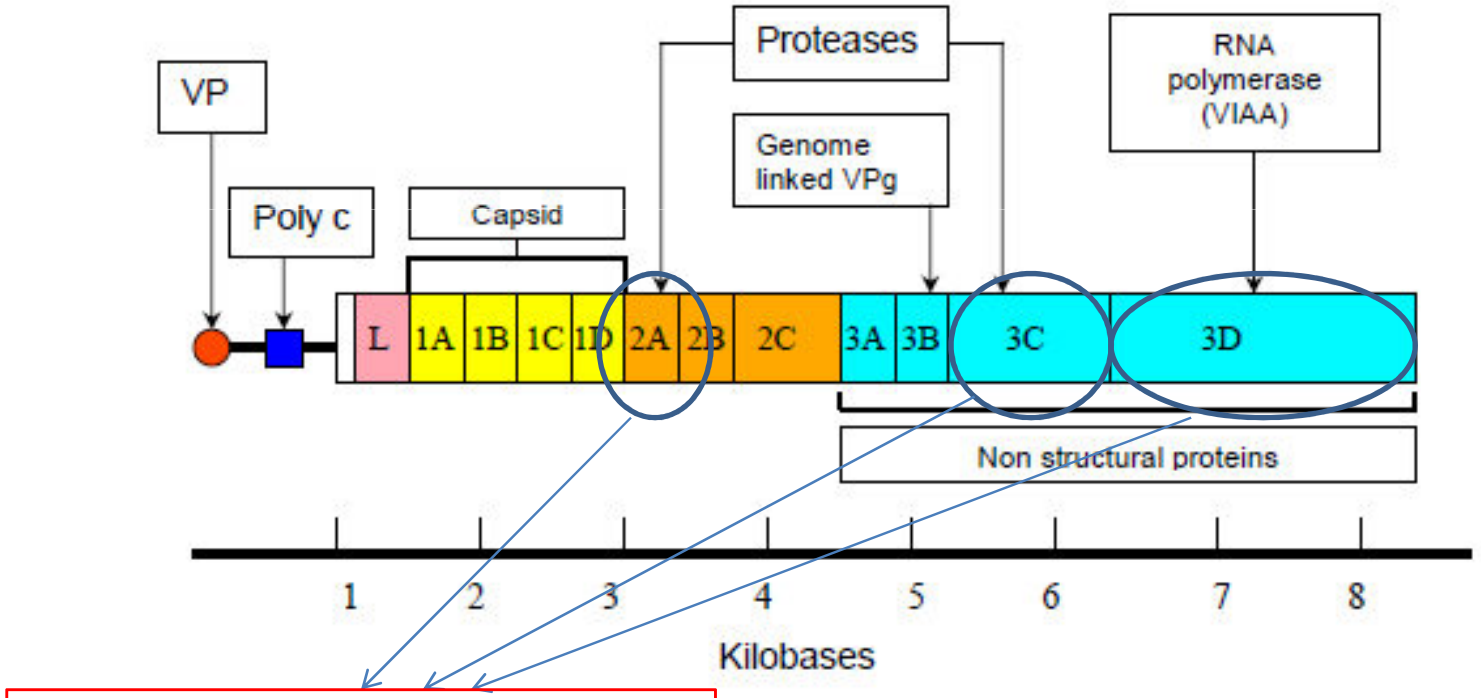
[a]Cattle were vaccinated with extracts from silkworm pupae infected with rBmNPV(P1-2A3C) or the control (BmBacPAK-6) and challenged 28 days later.
[b]FMDV-specific antibody titer determined by LPB-ELISA.
[c]Pyrexia defined as body temperature ≥40°C.
[d]Lesion score is the number of feet on which the cattle exhibited.
[e]Protection was determined by no obvious FMD clinical signs during the observation period (10 days post-challenge).

Zhiyoung et al., 2012

New generation FMD vaccines (continued)

- Hybrid vaccines:
  - Construction of P1 from one serotype into another serotype
- Vectored vaccines:
  - VP1/P1 in vaccinia virus
  - P1 in fowl pox virus
  - Adenovirus vectored
    - P1-2A3CD in Adeno (HAd5) was found very promising in cattle.

FMDV genome



Adenovirus vectored FMD vaccine

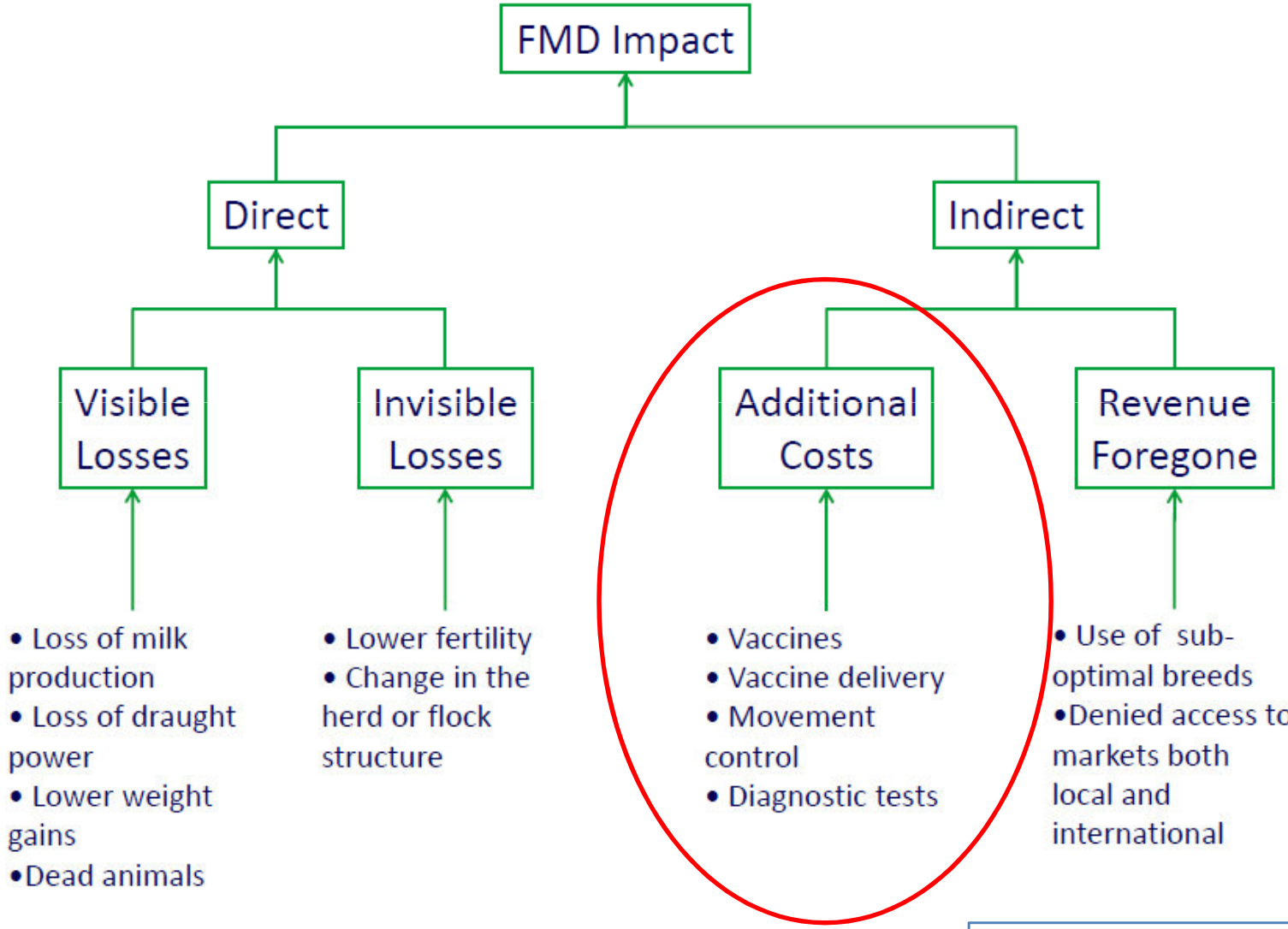
Novel vaccines

Table 3 Advantages and disadvantages of different novel vaccines

Novel vaccines	security of production	security of vaccinated animal	shelf life	duration of immune response	vaccination effectiveness	Differentiation of infected animals from vaccinated ones
Subunit vaccine	Yes	Yes	Normal	Normal	Low	Yes
Live vector vaccine	Yes	Yes	Normal	Long	High	Yes
Nucleic acid vaccine	Yes	Risk to recombinant to other genomes	Long	Long	Low	Yes
Novel attenuated vaccine	Yes	Risk to toxicity reversion but low	Normal	Long	High	Yes
Synthetic peptide vaccine	Yes	Yes	Normal	Short	Low	Yes

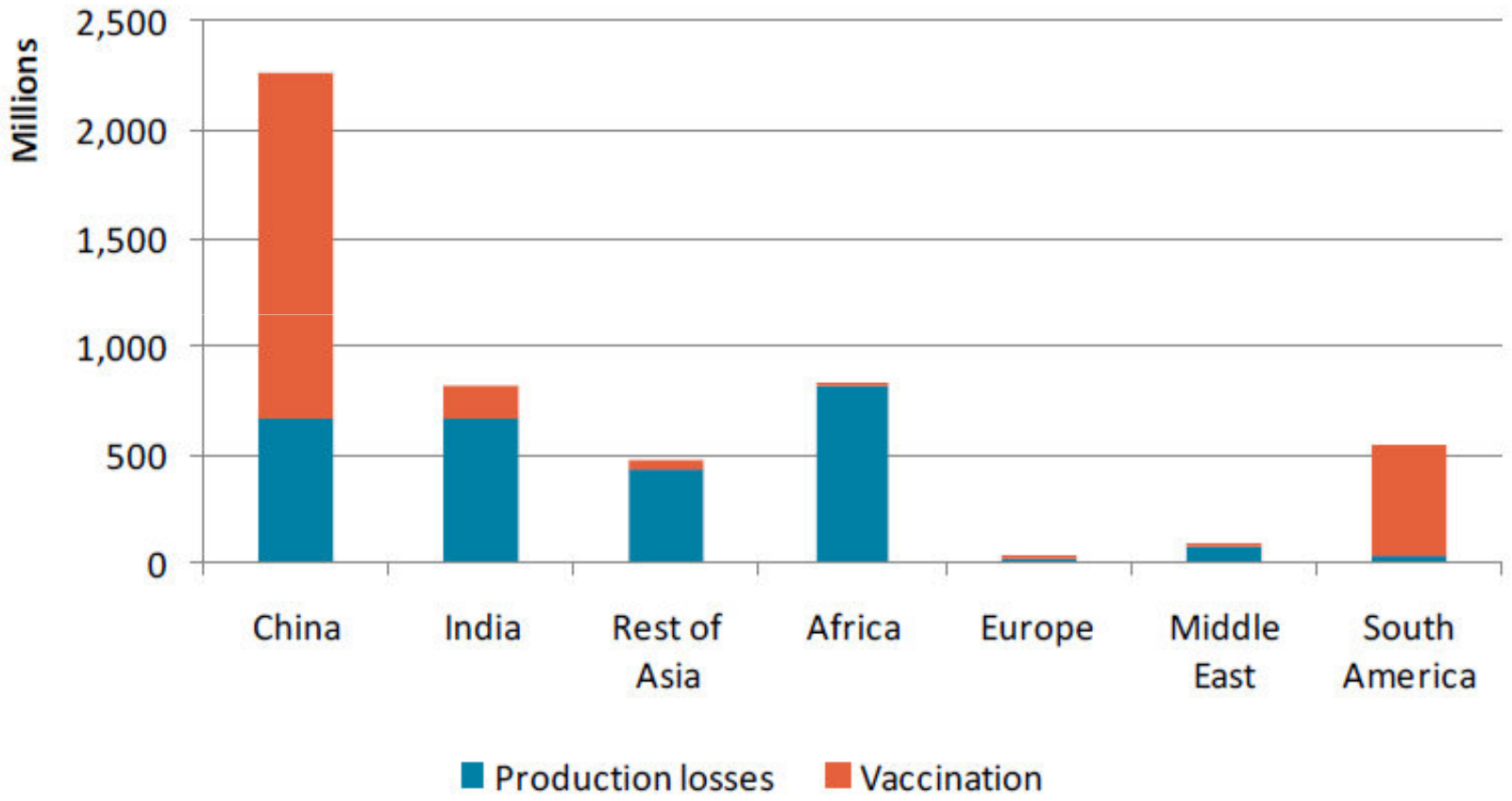
Zhang et al., Virology Journal, 2011

Cost of vaccination



Adapted from J. Rushton

Cost of vaccination



Adapted from J. Rushton

Thanks for your kind attention!