Classical FMD Vaccines

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WHAT CAN THEY ACHIEVE, WHAT CANT THEY ACHIEVE,

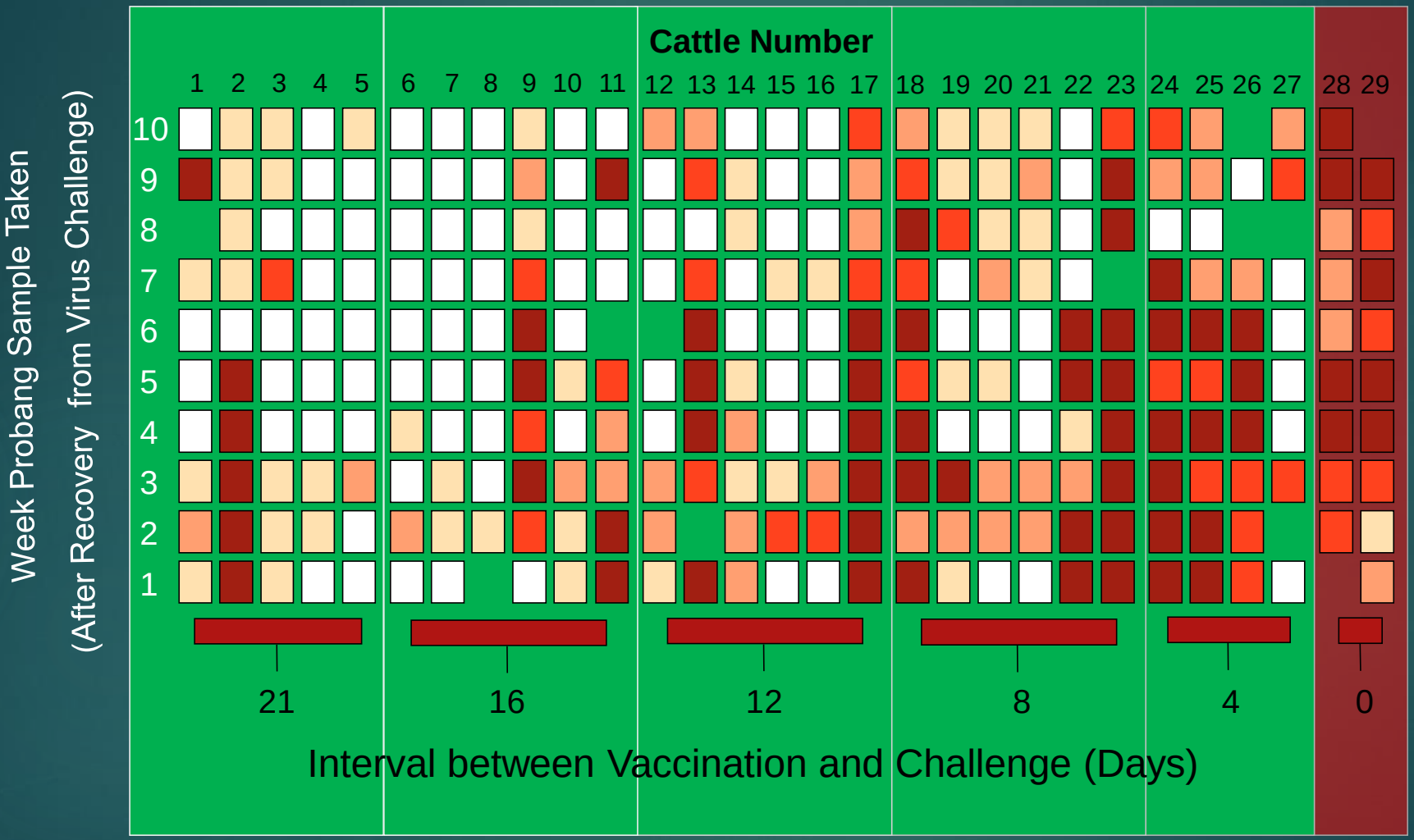
HOW STRAIGHTFORWARD WOULD IT BE TO REPLACE THEM GIVEN AN ALTERNATIVE?

Efficacy

Cattle

1. Vaccination with good quality, but not exceptional/special vaccines, can confer protection in 4 days and, with longer intervals, reduce the probability of persistence after challenge.
2. Similar quality vaccines (Haas, German Bank) have been shown to 'cross-protect' between serologically diverse strains of the A serotype.
3. Large scale trivalent vaccine campaigns (Europe and South America) were very effective and assisted greatly the control and eradication programmes.

Cattle. Protection and Carrier Status Following Vaccination and Challenge.



No Protection (Day 0 Controls)

Full Protection (4,8,12,16,21 DPV)

Adapted from Doel et al, 1994. Phase 1. Vaccination with O Lausanne Vaccine, Challenge O Lausanne..

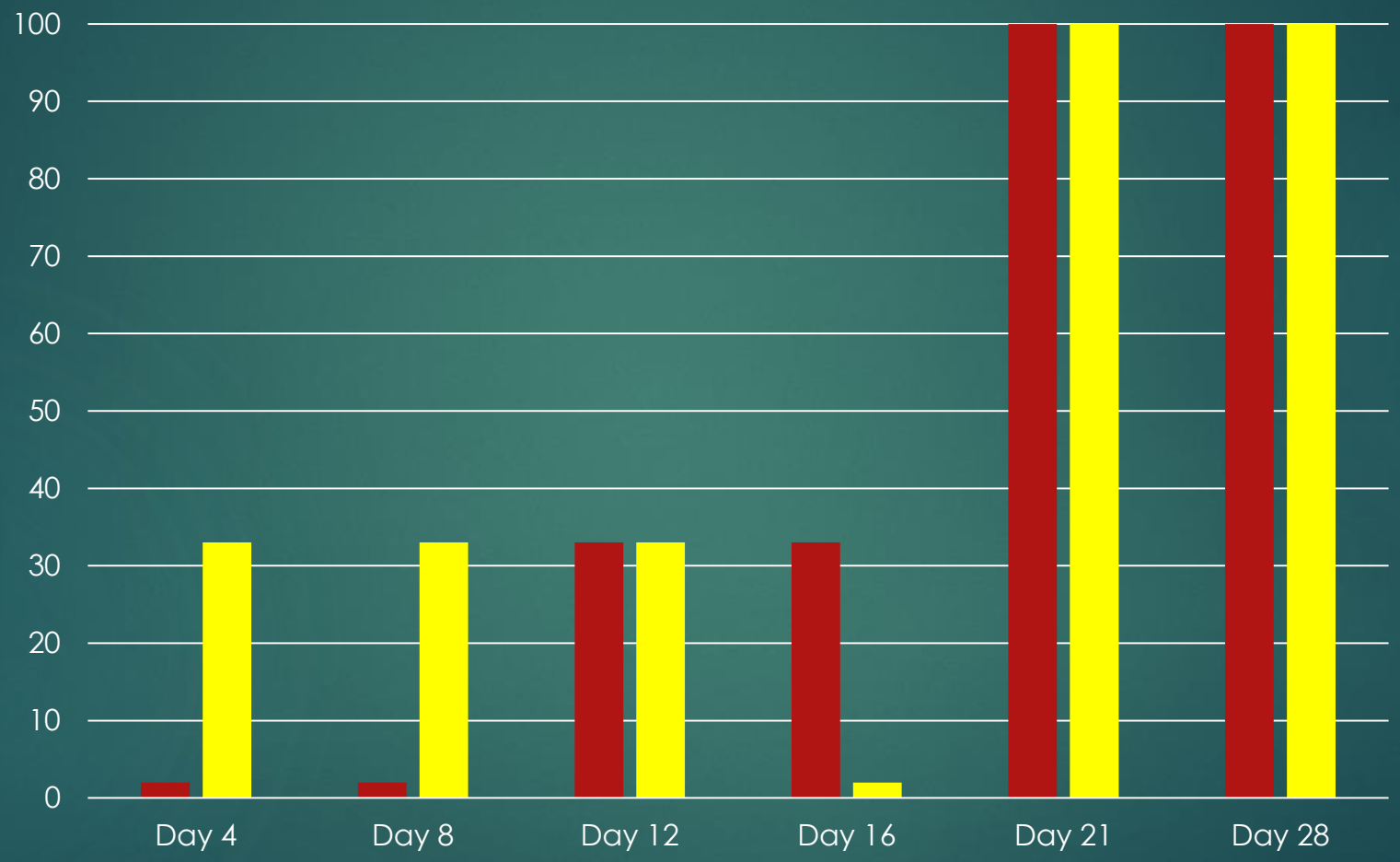
Cattle

Vaccine	PD50 (Ph.Eur Challenge)	Vaccine	PD50 (Ph.Eur Challenge)
A Iran 96	24	A24	14
A Iran 96	12	Asia1 Shamir	18
A Iran 96	32	Asia1 Shamir	6
A Iran 99	32	Asia1 Shamir	18
A Malaysia 97	32	O Manisa	17
A22 Iraq	12	O Manisa	8
A22 Iraq	14	O Manisa	14
A22 Iraq	32	O Manisa	20
A22 Iraq	32	O Manisa	20
A22 Iraq	14	O Manisa	12
A24	12	OBFS	20
A24	24	OBFS	20
A24	14	OBFS	14
A24	32	SAT2 Eritrea	6
A24	14	SAT2 Eritrea	10

Data kindly provided by B.I. Animal Health (ex Merial)

Pigs. Protection Following Vaccination and Challenge.

Percent Protection (3 pigs per group)



Adjuvant

ISA 206
ISA 25

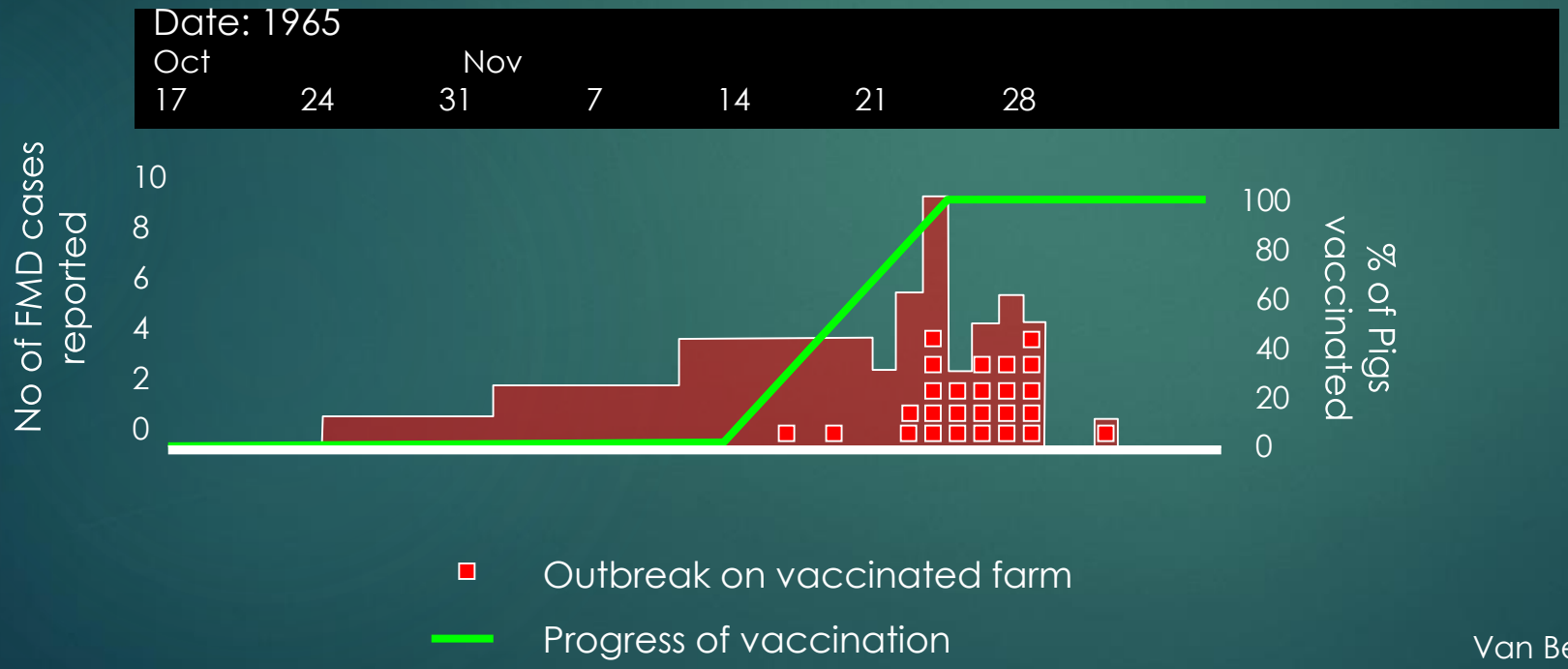
Adapted from Doel et al, 1994. Phase 1. Vaccination with O Lausanne Vaccine, Challenge O Lausanne..

Pigs

1. I have tended to be rather sceptical about some pig protection experiments based on experience where we observed what we considered 'over-challenge'. That is the pigs which became infected within a cohort appeared to act as a super challenge to the other vaccinated pigs.
2. In fact, one approach used by some workers was to remove the infected animals from the cohort as soon as they showed symptoms. Obviously, this would not be remotely representative of an outbreak in a large intensive pig unit where monitoring and 'weeding' out infected animals would not be realistic.
3. This really contrasts completely with our experience of cattle challenge where we routinely used much more challenge virus than the Ph.Eur stipulated and allowed all susceptible animal including controls to remain in contact with each other. Challenge failure was a very rare event and it was common for cattle not to develop lesions on the inoculated tongues.
4. Nevertheless, it is clear that pig vaccines work although not, in my limited experience, as effectively as cattle vaccines.

Pigs

1. Evidence of pig protection in the field goes back to the European FMD era. Van Bekkum reported the benefits of pig vaccination in the face of an outbreak where a single dose of high potency **Frenkel vaccine** (10x cattle dose) was used to assist the control of the disease. The last case was reported 8 days after vaccination.



Deurne Municipality:

Pig Population 41200 on 708 Farms

Van Bekkum et al, 1967

Pigs

1. Various studies have shown that FMD vaccines protect pigs and equally importantly prevent transmission to susceptible pigs.
   - Salt et al, (1998) reported protection of pigs at 4 dpv. Equally importantly, vaccination 7 days prior to challenge prevented contact transmission to healthy control pigs.
   - Eble et al (2006) also reported the reduced excretion of virus from pigs vaccinated 7 days previously.

Sheep

Vaccination of Sheep with Aqueous O Lausanne Vaccine.

Dose	146s (ug)	Protection	Carrier State by O.P. Sample
1/1	3	7/7	0/7
1/10	0.3	7/7	0/7
1/40	0.075	7/7	3/7
Control		0/7	4/7

1. **Vaccine: 0.5 of a bovine dose. Al(OH)3/Sap (Original PD50 of 41, Ph.Eur Challenge Test).**
2. **Indirect pig aerosol challenge at 14 dpv. Pigs removed after 4 hours.**

Barnett et al: Vaccine 22 (2004) 1221–1232

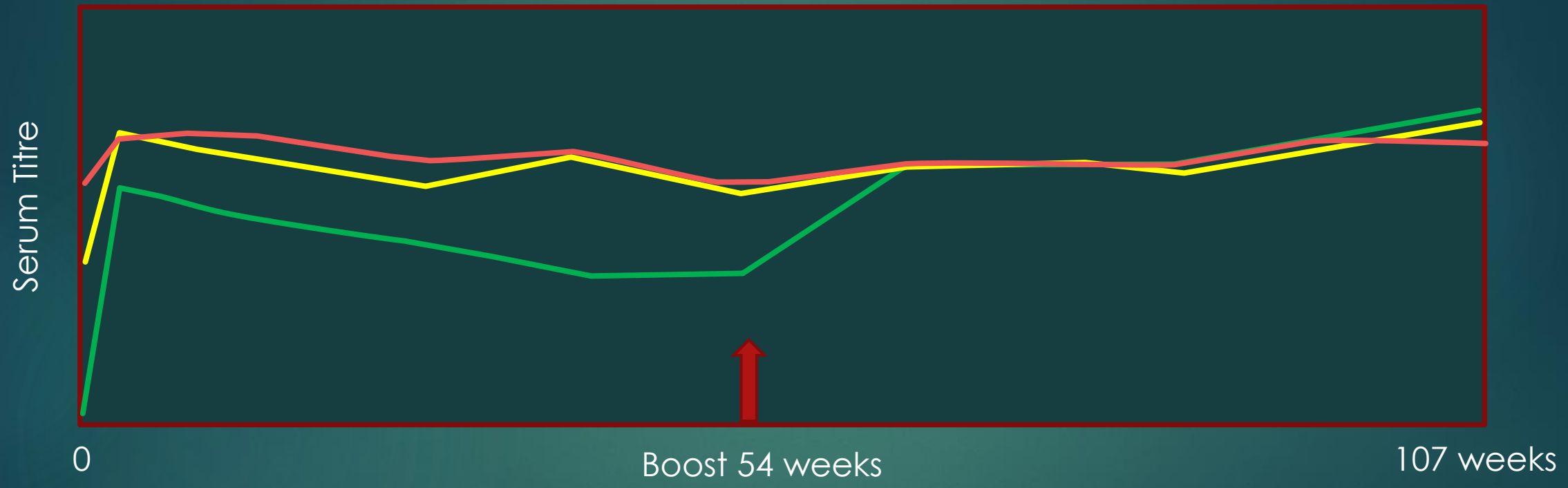
Duration of Immunity

1. It might be supposed that one goal for a vaccine to achieve is to provide a similar level of protection to animals recovered from natural infection.

2. With cattle, long lived immunity has been reported (4.5 years) but it needs to be recognized that the carrier state in cattle almost certainly provide frequent if not continuous immune stimulation throughout the period of the experiment.

3. In contrast, pigs recovered from infection can be re-infected with the homologous virus after about six months.

Cattle. Even with widely spaced annual vaccinations, serum titres are largely maintained in the intervals between vaccinations ~ Van Bekkum et al, 1963



Serotype A

First Vaccination

One Previous Annual Vaccination

Two or more Previous Annual Vaccinations

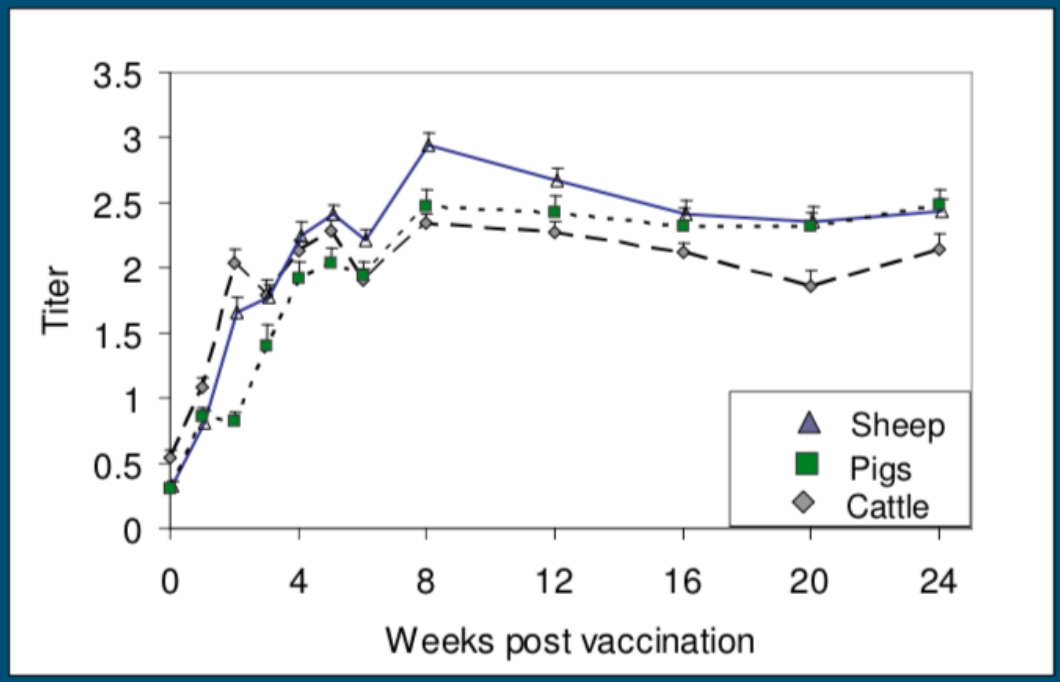
Cattle

1. Following from Van Bekkum's work, it is noteworthy that seropositive cattle were detected in Europe some six or seven years after vaccination was prohibited in the EU.
2. 'Short term duration' of immunity (that is after the initial vaccination) has been shown to protect for up to six months. Cox et al at Pirbright showed complete protection at 6 months after a single vaccination using the A22 Iraq vaccine held by the International Vaccine Bank.

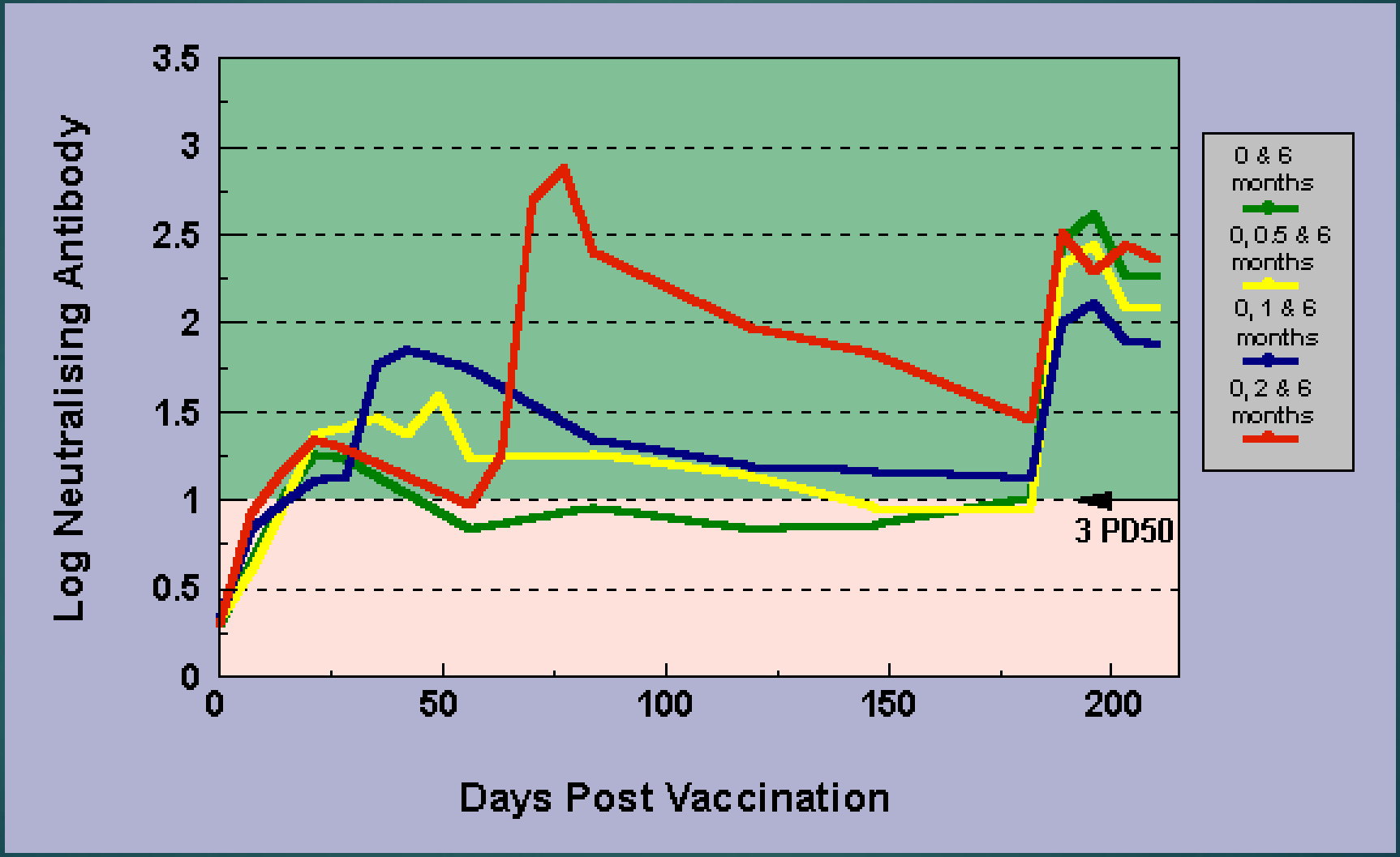
Cattle, Pigs, Sheep

1. Groups of five animals vaccinated **once** with 6 PD50 vaccine (3 vaccine batches, 15 animals per species)
2. Antibody titres still protective at 6 months post vaccination.
3. Source: Selman, Chenard, Dekker, EUFMD 2006

O1 Manisa: VNT results, mean + SEM



Cattle. Improved Sustained Immune Responses with Longer Intervals Between First and Second Doses of Vaccine

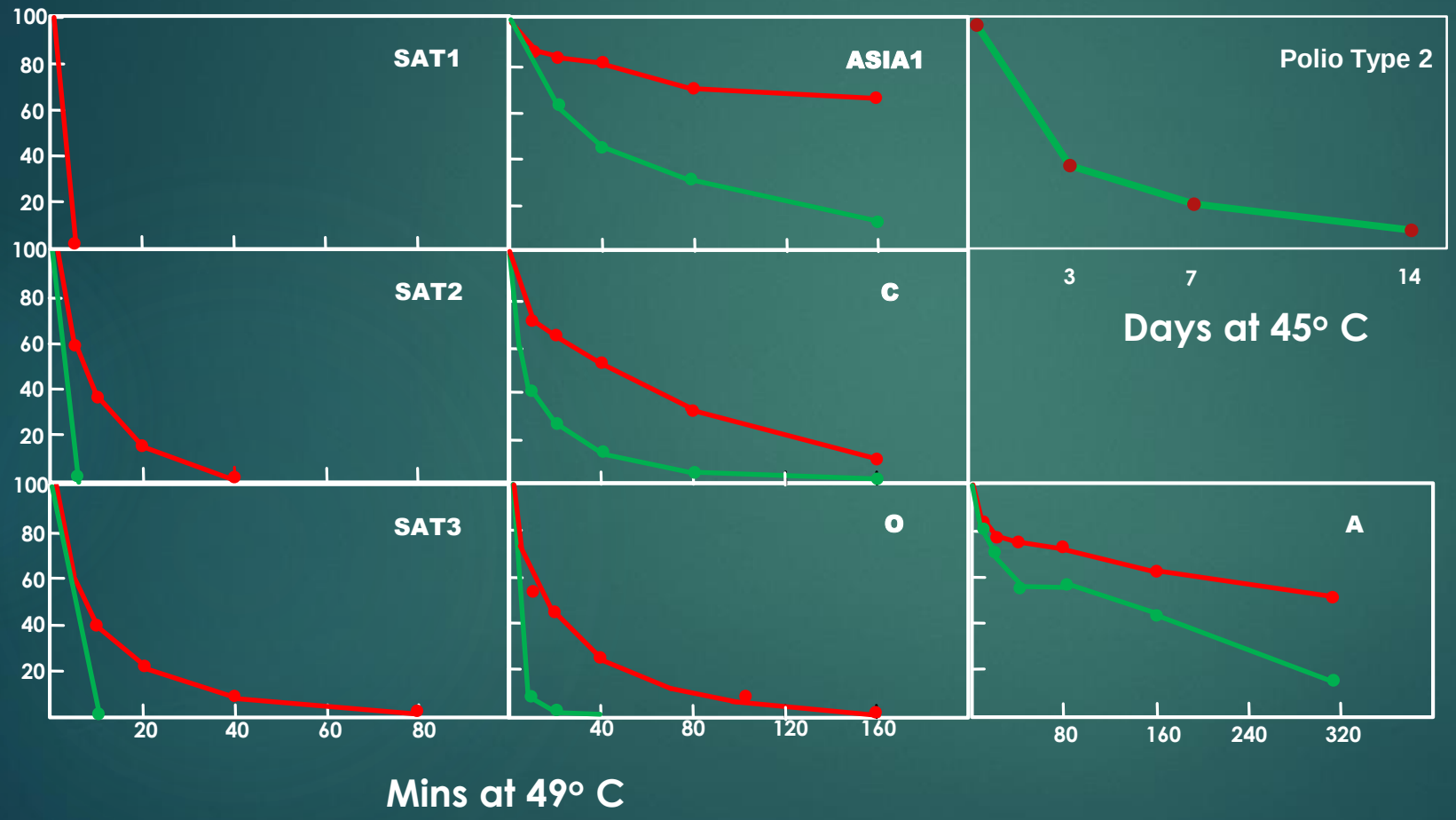


Doel, 1998

Stability

1. FMD 146S particles (and therefore vaccines) are not very stable compared to other picornaviruses such as polio and there are a number of publications covering the pH and temperature stabilities of the different serotypes.
2. This instability represents a well used justification for the development of novel FMD vaccines.
3. However, it is not always appreciated that the recognized instability of the virus (and therefore vaccines) does not represent a problem when good quality GMP products are used and the cold chain is properly implemented and maintained.

Stability



Doel & Baccarini, 1981

Live Inactivated

Doel et al, 1984

Stability

1. It is tempting to suggest that Stability is an absolutely critical factor in the potency of FMD vaccines. After all, it is generally considered that the potency of FMD vaccines based on payload and cattle challenge more or less follow the stability data i.e.

A/ASIA1 > OC > SAT2/SAT1/SAT3

2. Of course, inactivated Polio is even more stable but, unlike FMDV, it doesn't have the challenge of preventing spread of the virus in the population.

Stability

1, To register a new veterinary medicine in Europe, it is necessary to demonstrate shelf life among a host of other requirements. With FMD, this represents three batches of vaccine stored at the recommended temperature for the claimed shelf life + 3months.
2. For example, a vaccine with an initial claim of 3PD50 and a shelf life of 12 months is required to demonstrate 3 PD50 or greater at the time points shown below:

3. For a registered product, a routine stability testing programme is required to demonstrate that the product continues to perform as claimed. This is particularly significant with FMD because of the occasional adoption of new vaccine strains.
4. In addition, some specific properties/constituents of the vaccine are now tested over the same time scale, notably preservatives, viscosity (oil) to demonstrate shelf compliance with the product specifications at T_0.

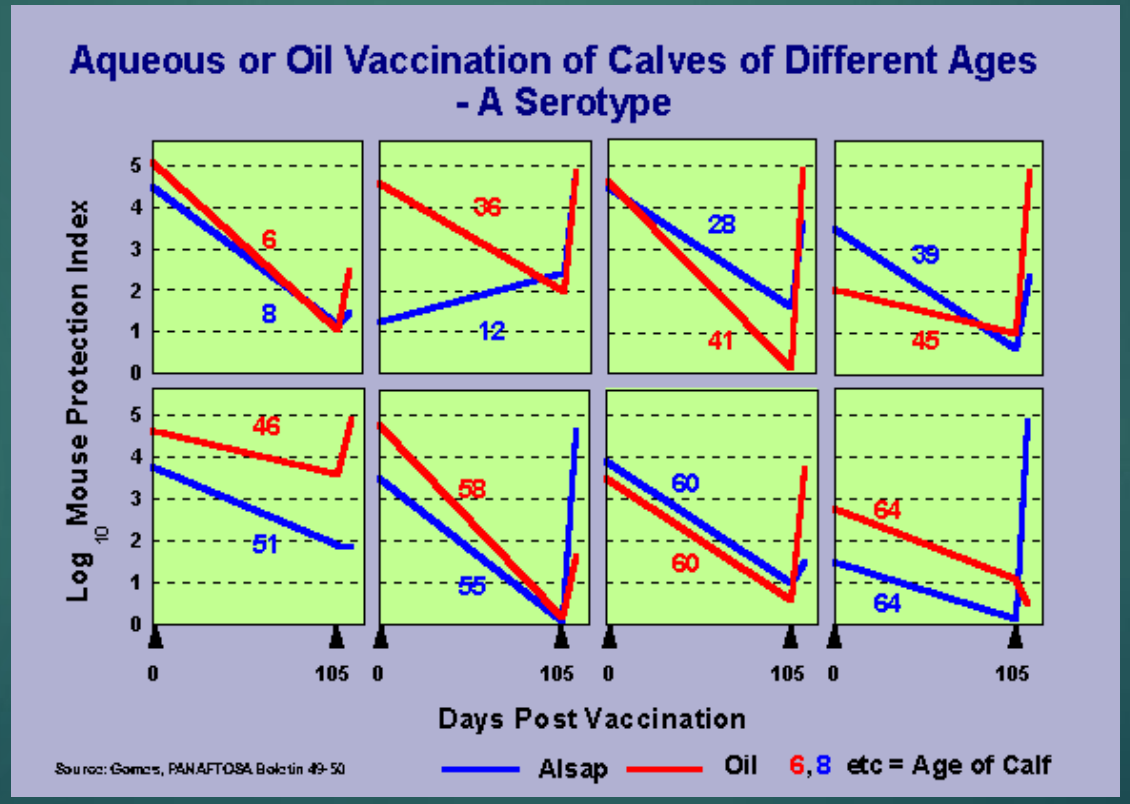
Stability

The 'Bottom Line' is that FMD vaccine stability does not represent an issue when cold chain conditions are properly controlled and maintained and good quality GMP products are used.

BUT – it is recognized that there are many field situations where storage and application of the vaccine will be compromised and stability of the product in general, will have a part to play in the effectiveness of the vaccination campaign.

Practical Problems Facing a Vaccination Programme

Clearly good quality conventional FMD vaccines tick a number of the desirable boxes. The real problems come with their use in some field situations where conditions of storage and use (notably cold chains) may be neglected. There are also the miscellaneous complications such as maternal antibodies:

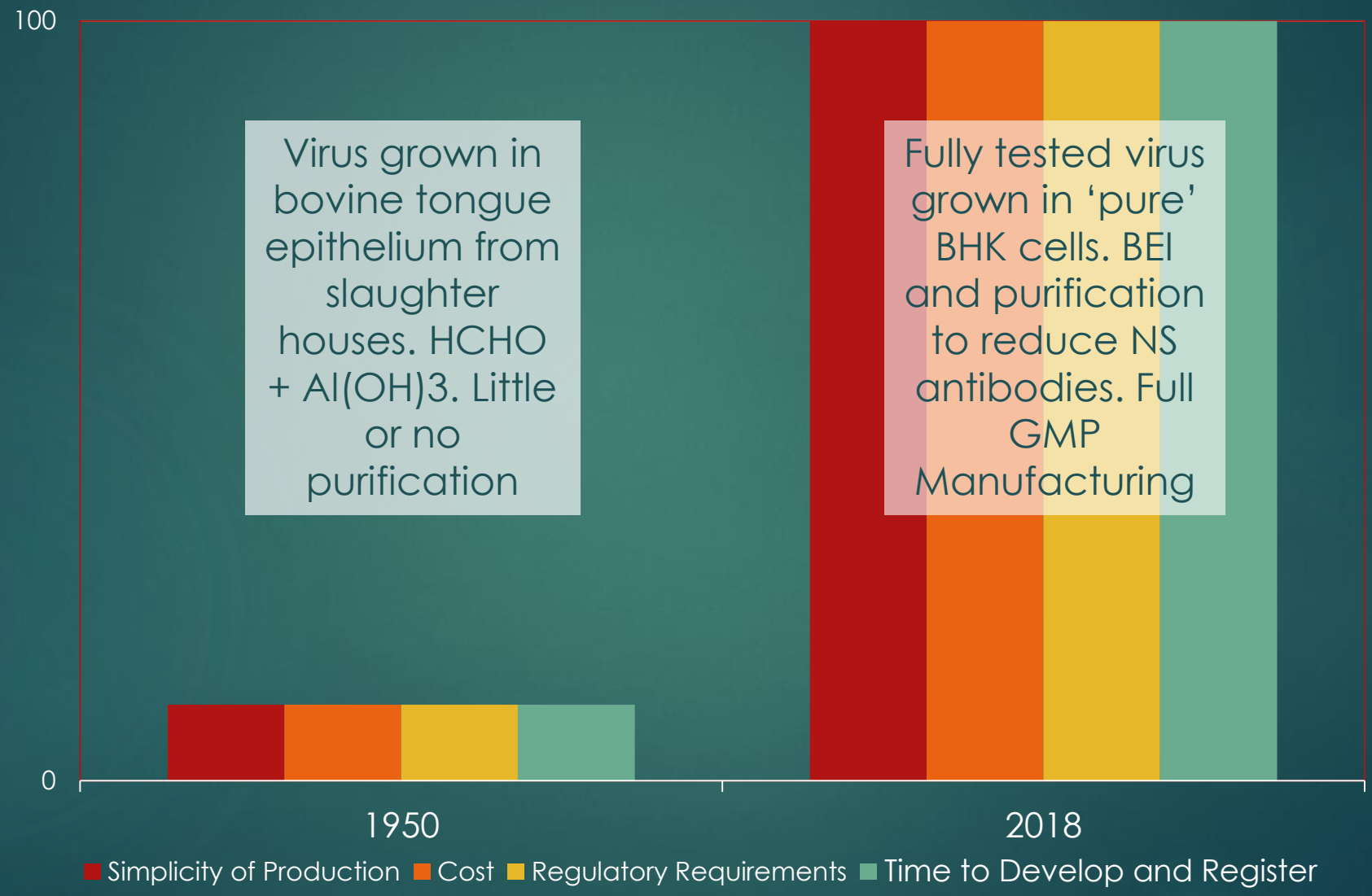


1. It is clear that with all but the most organized vaccination campaigns, young animals with maternal antibodies may be vaccinated too early. Perhaps this is manageable with high value, long lived cattle but high turn-over, large populations of pigs for fattening and slaughter at six months or so of age represent a very challenging situation for conventional or novel FMD vaccines.

2. There is also the complication that many animals may not be available for routine vaccination within a concerted and organized campaign. In this category are nomadic animals and animals kept during the summer months in mountain pasture (Balkans, Leforban 1997).

3. Of course, my preferred primary immunization protocol (0 and 2 months) would be even more difficult to implement.

The Simple Evolution of Costs for Conventional FMD Vaccines



The Challenge to Bring a Novel FMD Vaccine to Market

1. Product Development and Licensing

A huge amount of work (=time and $$$) is required to bring a new medicine to a licensed product with particular respect to safety and efficacy in the target species: That is:

1. The species claimed (cattle, sheep/goats, pigs, buffalo?).
2. Their various physiological conditions (i.e. adult animals, young animals with/without maternally derived antibody including earliest age of vaccination, pregnant animals)

Safety of dose, repeated dose, overdose. Including pathology.

Efficacy by Challenge Unless Fully Acceptable Correlate

Would pigs/sheep/buffalo be permitted to 'piggy' back on cattle efficacy and safety?

2. Manufacturing Cost. While modern pharmaceutical manufacturing equipment is very expensive and requires scheduled maintenance and validation, probably the most important single factor here is the active ingredient productivity achieved with the production facility and will have a significant impact on COGM (Cost of Goods Manufactured).

3. Quality Control of FMD vaccines is also very expensive requiring testing of all batches in the target species as well as occasional safety testing. An important objective for any novel FMD vaccine will be to establish a very robust in vitro method to determine product quality and correlate this closely with a substantial body of animal safety and efficacy data (the ultimate goal being to eradicate the need to test in animals).

4. Quality Assurance in a modern pharmaceutical facility now carries a major cost both in headcount and time spent complying with GMP requirements. I estimated that probably 50% of every employees time is now taken by QA activities.

5. Cost of Buildings. While there would be Biosecurity advantages with the manufacture of a non-infectious active ingredient, I am not convinced the building or operating savings would be very significant. The table illustrates the very demanding conditions required for modern pharmaceutical facilities.

Limits for microbial contamination (EU GMP). Similar limits apply for particles.

Grade	Air cfu/m^3	Settle Plates. Cfu/4 hours	Contact Plates	Cfu/5 fingers of glove	Type of Operation
A	<1	<1	<1	<1	Vaccine Bottling, Sterility Testing
B	10	5	5	5	The Environment for Grade A
C	100	50	25	-	
D	200	100	50	-	

New Product Development, Manufacture and Licensing

Certain, any new veterinary medicine will have a much tougher time obtaining Regulatory approval than previously. In the 16 years I worked for Merial, I saw dramatic changes in the Regulatory Environment with particular respect to increasing GMP alignment with the manufacture of medicines for humans. Just a few additional thoughts:

1. A new product should demonstrate a significant advantage(s) over an existing product to potentially assist the Licensing process. Regulators are naturally conservative by nature and are unlikely to be flexible unless there is an extremely strong advantage over the conventional licensed product. Conventional FMD vaccines have a huge amount of safety and efficacy date to support their continued acceptance by Regulators and Practicioners.
2. The Regulatory Environment is becoming more demanding by the day and international harmonization will only raise rather than lower any required standard (eg FDA & EU GMP).

HOW LONG WILL ALL THIS TAKE?

ABOUT AS LONG AS THIS

Thank You for Your Attention