Vaccines: types, quality control, matching, supply

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1897: Loeffler and Frosch showed that FMD is caused by a filterable agent (a “virus”).

They demonstrated that animals recovered from FMD were solidly immune and that one inoculation of cattle or sheep with filtered “virus” fluid was protective.
• **1925**: Vallée and Careé produced the first experimental vaccine (vesicular fluid from infected calves inactivated by formaldehyde).

• **1937**: Waldmann et al. produced a vaccine using epithelium and vesicles from tongues of infected cattle, inactivated by formaldehyde in the presence of aluminium hydroxide gel (Vallée-Schmidt-Waldmann vaccine).
• **1947**: Frenkel developed the large-scale production of vaccine by growth of virus in explant cultures of tongue epithelium.

• **1948**: Rosenbusch increased the antigen content.

• **1951**: Espinet showed the advantage of adding saponin as an adjuvant.
1953: Start of large scale vaccination of cattle in the Netherlands.

France, Germany and other countries on continental Europe followed suit.
1950’S – early 1960’s: live attenuated vaccines developed by workers in UK, France, Venezuela, Brazil, Germany and elsewhere.

Skinner at AVRI, Pirbright, did extensive work with mice.

Other workers used chickens, rabbits and tissue culture.

Lengthy process, unpredictable, some attenuated strains reverted to virulence.

Live attenuated vaccines not recommended (OIE/FAO, Paris 2002).
• **1954:** Enders, Weller and Robbins awarded the Nobel Prize (poliovirus grown in various tissues).

• **1960:** Sellers reported the growth of FMD virus in pig and calf kidney cell cultures.
• **1962:** Mowat, Chapman and Capstick showed that FMD virus could be grown in hamster (BHK-21) cell lines.

• **1965:** Telling and Elsworth developed suspension method for BHK-21 cells.
1963-64. Probus (6 x 500 ml) BHK suspension system at AVRI, Pirbright.

ADDITIONAL ADVANCES

• **1959**: Brown and Crick reported the use of aziridine (acetylethyleneimine; AEI) as an inactivant.

• **1975**: Bahnemann – demonstrated inactivation by binary ethylenimine (BEI).

• **1987**: Beck and Strohmaeir recommended that inactivation of FMD vaccine antigens should be by first order inactivants such as AEI or BEI. Formaldehyde inactivation is biphasic and so there is greater risk of residual infectivity.

• Vaccine production regulations for most countries now only permit AEI or BEI.
CONTEMPORARY FMD VACCINE

• Virus grown in BHK-21 cells, inactivated with BEI or AEI, concentrated and purified, formulated with adjuvant, either: (i) Al(OH)$_3$ and saponin; or (ii) oil to form a single or double emulsion

• Alhydrogel-saponin vaccine for cattle; oil adjuvanted vaccine for pigs.

• Oil adjuvanted vaccine less affected by maternal immunity, longer duration of immunity and can be used in all species.

• Oil adjuvanted vaccine has played a key role in the improved control of FMD in South America – reduced frequency of vaccination (x1 or x2/y instead of x3 or x4/y) resulting in better farmer cooperation and greater vaccination coverage.
10,000L CELL SUSPENSION VESSELS
CONTROL OF FMD IN EUROPE

Figure 1. Incidence of FMD outbreaks in Europe from 1970 to 2000 (including Caucasian countries but excluding Turkish FMD outbreaks).
For routine prophylactic purposes FMD vaccine should contain at least 3 x 50% protective cattle dose i.e. 3 PD$_{50}$ per dose.
- A coverage of 100% should be the objective (3PD$_{50}$ vaccines will only protect 75-85% of cattle; Dekker, 2008).

Vaccine with a potency >3 PD$_{50}$ is being applied more often for routine prophylactic use.

For emergency use FMD vaccine should contain at least 6 PD$_{50}$ per dose.
NOVEL (EXPERIMENTAL) FMD VACCINES

- Peptide vaccines
- Sub-unit vaccines
- Empty capsid vaccines
- Vector vaccines - e.g. human adenovirus 5 (replication defective), delivering FMDV capsid proteins has been shown to protect pigs and cattle.
QUALITY CONTROL (QC)

• The history of FMD vaccine with regard to safety is not good:-
  – Beck and Strohmaeir (1987) showed that from 1977-87 around 50% of the “home grown” outbreaks in Europe were due to faulty (formaldehyde) vaccine.
  – The problem continues > Sangula et al. (2011) probable vaccine re-introductions in East Africa.

• Many developing countries lack independent QC organisations and independent vaccine testing laboratories.
Good manufacturing practice (GMP) and quality control (QC). GMP + QC = quality assurance.

GMP

- Licensed facilities (biosecurity etc.).
- Qualified and trained staff.
- Prior testing of raw materials.
- Full documentation of production methods and records.
- Separate production and quality control responsibilities.
- For details see:
QUALITY CONTROLS

• Pre-production checking and testing of:-
  – Seed vaccine strains.
  – Master stocks of cells.
  – Media components.

• In process controls and recording e.g. inactivation.

• Post process controls e.g. safety and potency testing.

• For details see:
  – European Pharmacopoeia (Monograph).
## ANTIGENIC DIVERSITY OF FMD VIRUS

<table>
<thead>
<tr>
<th>SEROTYPE</th>
<th>ANTIGENIC DIVERSITY</th>
<th>GEOGRAPHICAL DISTRIBUTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>++++</td>
<td>Most widespread serotype.</td>
</tr>
<tr>
<td></td>
<td>Three topotypes: ME-SA; SEA; CHY.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>+++++</td>
<td>Second most widespread serotype.</td>
</tr>
<tr>
<td></td>
<td>New variants emerge frequently.</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>Very restricted distribution.</td>
</tr>
<tr>
<td>SAT 1-3</td>
<td>++++</td>
<td>Restricted distribution with occasional excursions to new regions e.g. SAT 2 in 2012.</td>
</tr>
<tr>
<td>ASIA 1</td>
<td>++</td>
<td>Middle East and Asia.</td>
</tr>
</tbody>
</table>
VACCINE MATCHING -1

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

- ELISA and CFT are recommended as screening methods and the VNT for obtaining definitive results. (CFT is rarely used).

- Vaccine matching is not a precise science e.g. lack of field samples, vaccine strains and reagents, lack of information about vaccine strains, tests are not harmonised ... etc
$r_1$ VALUES

- From ELISA
  - 0.4 to 1.0 protection expected
  - 0.2 to 0.39 some protection expected
  - <0.19 protection not expected
VACCINE MATCHING -2

• OIE/FAO Network of Reference Laboratories established to strengthen laboratory cooperation, address deficiencies and provide recommendations on vaccine selection.

• The Global Strategy will focus control on the “virus pool” regions. Vaccine will be the major tool and so the need for recommendations about vaccine selection will increase.

• OIE/FAO Network of Reference Laboratories will face increased demand for recommendations on vaccine selection. The main input to the network comes from the WRL and so it will need more support from existing and new RRLs.
ANTIGENIC CARTOGRAPHY

- Analysis of antigenic variation of viruses is generally done by serological methods and is qualitative.
- By integrating antigenic data with sequencing data it is possible to quantify antigenic variation and determine its correspondence with sequence change (Smith et al., 2004; Horton et al., 2010)
- This approach is called “antigenic cartography” and offers the possibility of understanding how antigenic variation evolves.
- Future method for selecting suitable vaccines and possibly predicting the appearance of new variant strains.
- Application to FMD viruses is under study (Hammond and co-workers).
SUPPLY OF VACCINE - ESTIMATING THE AMOUNT REQUIRED

• Control policies for the Global Strategy will focus on regions and sub-regions and therefore will be different.

• Highly endemic “virus pool” regions will be given high priority.

• Control polices will be based on epidemiological analyses and local information about risk factors.

• Vaccine will be a key component of the control strategies.

• Amount of vaccine required will depend on the strategies formulated for the different regions and sub-regions.
SUPPLY OF VACCINE - SELECTION OF VACCINE

• Selection of a suitable vaccine should take into account:
  – Matching of field isolates and vaccine strains ($r_1$ values and valency of vaccine)
  – Size of the target population and frequency of vaccination (number of doses)
  – Formulation/adjuvant (target species and frequency of vaccination)
  – Potency (risk factors)
  – Cost (potency, quality and valency of vaccine; tendering arrangements)

• Obtaining sufficient quantities of suitable, safe and potent vaccine will be a major challenge for the Global Strategy.
SUPPLY OF VACCINE – MEETING THE DEMAND

• Short term:
  – public-private arrangements to encourage manufacturers to increase vaccine production
  – guarantees for manufacturers with regard to return on their investment and sustainability of the markets

• Mid to longer term:
  – financial support for large-scale testing of existing novel candidate vaccines
  – financial support for research, development and refinement of existing and new novel vaccines

• A novel vaccine that did not have to be produced in biosecure facilities would be much cheaper to produce and could have additional advantages e.g. greater thermo-stability.

• Probable that royalties will be involved and raise the cost of novel vaccine.
CONCLUSIONS -1

• It has been shown in Europe and several countries of South America and elsewhere that the regular mass vaccination of cattle can reduce the incidence of FMD to a level where it becomes economical to stop vaccination and employ “Stamping out” in the event of outbreaks.

• Vaccination alone is not sufficient to control FMD in endemic regions but will be a very important tool for the Global Strategy.

• Obtaining sufficient supplies of vaccine to have an impact in regions of the world where FMD is endemic will be a major challenge for the Global Strategy.
CONCLUSIONS - 2

• Private-public partnerships and guarantees of sustained demand may be incentives for manufacturers to increase vaccine production.

• Development of lower cost novel vaccines could be a solution for increasing supply in the mid to longer term.

• Vaccine employed during the Global Strategy must be both potent and safe.
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