1. INTRODUCTION

Foot-and-mouth (FMD) vaccination has been applied world-wide to control FMD. Although vaccination alone is not capable of eliminating the disease, along with other control measures it has been shown that FMD can be eradicated. The history of FMD control in the Netherlands (Figure 1) shows that the Netherlands was only successful when our main trading partner, Germany, in 1966 also introduced mass vaccination of their cattle. This history also shows that eradication takes a long time.

![Figure 1: Number of FMD cases in the Netherlands since 1909](image)

The first vaccines were formaldehyde inactivated virus suspensions derived from infected cattle, but when it was possible to culture the virus in vitro and to analyse the virus for its immunogenicity it became clear that the whole virus was more immunogenic than subunits of the virus (T.R. Doel & W.K.T. Chong, 1996). This information is very essential for the development of new vaccines which are discussed in another session (2C).

One of the biggest constraints in vaccination is the antigenic variation. Antigenic variation can be shown using cross-protection studies, serological tests with polyclonal sera, by testing isolates with monoclonal antibodies and by genome analysis. Different tests have different advantages and disadvantages, but this will be discussed in a separate session (2B).

In this paper I will focus on the use of vaccines in the field the problems with duration of immunity, use of different adjuvants and the needs from an epidemiological point of view.

2. DURATION OF IMMUNITY
In many countries FMD vaccines are applied twice a year. Studies in countries that apply vaccination on a regular basis support the need for repeated vaccination (A.K. Sen & S.P. Nair, 1994; M.E.J. Woolhouse et al., 1996). There are however several reports that vaccines in the past induced a longer lasting immune response (T.R. Doel, 2005). Studies in the Netherlands showed that cattle were protected to transmission with homologous FMD virus for three years after three annual vaccinations (C. Terpstra et al., 1990). In fact we have come across one cow still positive for antibodies against type A and O, and negative for type Asia-1, 15 years after a single vaccination with trivalent FMD Frenkel vaccine. Figure 2 shows studies on Oil Emulsion vaccines that also show longer durations of immunity (A. Dekker, Terpstra, C., Barteling, S.J., 1992).

The previous observations were confirmed in later studies (P. Selman et al., 2006). The question remains, why does vaccine not always work that well in field situations. Doel (2005) suggests that the quality of the vaccine might be responsible. A high quality vaccine induces a higher immune response after initial vaccination which will consequently last longer. The quality of vaccines is difficult to measure, although recently a test has been developed that can measure antigen quality in formulated vaccines (see poster session). The quality of the vaccine depends on the amount of antigen in the vaccine, the stability of the antigen in the formulation and most important the quality of the adjuvant. First most vaccines were adjuvanted with aluminium hydroxide, but later saponin was added to aluminium hydroxide vaccine (A. Martins, 1971), or purified quil-A to oil vaccine (C. Xiao et al., 2007). Recent studies in pigs (P.L. Eblé et al., 2007) show that the immune response can be enhanced by using a four-fold dose, which indicates that improvement to adjuvants is still possible and should be studied more extensively. We also studied intradermal vaccination in pigs, which is reported later in this session.

For consumers (mostly governments) of FMD vaccine it is difficult to assess the quality of the vaccine, therefore every batch of vaccine should be tested in at least 5 calves free of maternally derived antibodies in which serum samples are taken before vaccination and preferably at a weekly basis until 6 – 8 weeks after vaccination. Sufficient serum should be stored, that it can be used in comparative serological studies when new batches are procured or batches have to be tested for stability. It should however be acknowledged that some vaccines protect cattle with a lower amount of neutralising antibodies than other vaccines. We have indications that 12S from degraded 146S can induce neutralising antibodies to a good level, without protecting the animals. So serology should be used carefully in the interpretation of cross producer differences, but can be used to study stability of vaccines when results of one vaccine batch are compared after storage.

In this context studies on in vitro assays to measure immunity that relates to protection are essential, but this specific issue is dealt with in session 2D.
3. INTERFERENCE WITH MATERNALLY DERIVED ANTIBODIES

Young animals receive FMD specific antibodies from their dams via the colostrum. These antibodies can interfere with immune response. Earlier studies have shown that the height of the maternally derived antibody titre is crucial for young animals to be able to respond to vaccination (I. Gomes, 1984). Maternally derived antibodies decline very quickly. Recent studies in calves and piglets show a half-life of 16 respectively 15 days. In piglets, however, the antibody titre not only declines due to degradation but mainly due to the growth of the animal. When compensation for the growth of the piglets and the dilution due to increase in blood volume the chemical and physical stability of maternal derived antibodies in piglets is much higher than in calves, in our experiments estimated half-life of 27 – 40 days depending on the growth data and method used for compensating. In old experiments even a longer half-life has been calculated (M.J. Francis & L. Black, 1984a, b).

On farms where prophylactic vaccination is practised it is essential to re-vaccinate in time to have sufficient vaccination coverage on the farm. The right timing will depend on the height of the antibody titre at birth and that is correlated to the antibody titre of the dam. The antibody titre of the dam will depends on the quality of the vaccine, e.g. the type of adjuvant type of antigen (intratype heterologous antigen can more easily induce antibodies), and amount of antigen.

![Graph showing antibody titres over time](image)

**Figure 3:** Antibodies in calves vaccinated with Al(OH)₃ saponine adjuvanted Frenkel vaccine (solid squares) and calves vaccinated with a similar vaccine using double oil emulsion formulation (S.J. Barteling et al., 1990)

In calves born from cows vaccinated with Frenkel vaccine routinely used in the Netherlands calves were selected with different levels of maternally derived antibodies (Figure 3). In calves with titres below 1.0 (10 log) a good antibody response is seen with both Al(OH)₃ saponin adjuvanted vaccine as well as with double oil emulsion (DOE) adjuvanted vaccine. However, in the calves with titres close to 1.0 (10 log) only the DOE adjuvanted vaccine induced an antibody response (S.J. Barteling et al., 1990). Later studies in South-America confirmed this finding (E.J.A. Spath et al., 1995).

In 2006 an outbreak in Turkey occurred with a strain that was better covered with old A₂₂ Iraq antigen. The dams had been vaccinated with A Iran 96 like vaccine and the question rose whether the maternally derived antibodies against A Iran 96 like vaccine would interfere with an A₂₂ Iraq vaccination. A similar situation was studied in our lab and it was shown that homologous A Turkey 14/98 vaccine could not induce antibodies in calves born from A Turkey 14/98 vaccinated dams, but A₂₂ Iraq vaccine could (see poster session). This shows that intratype heterologous vaccination can induce an antibody response and is a possible solution when an outbreak occurs in a area with prophylactic vaccination.

It has been shown that the amount of antigen in a vaccine is well correlated with the probability of protection (T.W.F. Pay & P.J. Hingley, 1987). Increasing the dose of antigen in the vaccine will undoubtedly increase the efficacy, but antigen is often the most expensive part of the vaccine and not always stable. It has been shown that the dose-effect relation studies that the effect of adjuvant is much bigger than the effect of antigen (C. Stellmann et al., 1977). Improving the...
adjuvant is often cheaper. The study in the Netherlands mentioned above also shows that changing the adjuvant can increase the response in cattle with maternally derived antibodies.

It is essential to study the effect of maternally derived antibodies on the antibody response in newborn animals. If newborn animals are vaccinated to soon, the vaccine will not have an effect (E.J.A. Spath et al., 1995). But if the newborn animals are vaccinated to late the gap in immunity might leave the farm susceptible for introduction of FMD virus. In the poster session there will be an example of a study in piglets and during the oral session an example in sheep. Countries relying on prophylactic vaccination should study the immunity in piglets and calves on a regular basis. Vaccination strategies should be adapted if new vaccines induce higher or lower antibody titres.

4. EPIDEMIOLOGICAL NEEDS

Epidemiological models will be discussed in session 5. But when looking at the needs for vaccination the OIE in 1972 defined "At least 70% immediate protection of cattle vaccinated with one dose of vaccine, with a probability of 95%". This definition has been the basis of vaccine potency tests, although the current definitions never followed the OIE definition exactly. Vaccine testing is part of a separate session, but 70% protection in a population would mean that if an infected individual is capable of infecting on average 3.3 susceptible individuals. If the 70% of those individuals are protected, then 30% of 3.3 susceptible animals become infected which is only 1. That means that in all cases transmission will most likely die out. So by setting this standard the OIE has assumed a reproduction ratio $R_0$ of 3.3. In groups of unvaccinated animals the estimates of reproduction ratio’s in cattle ($R_0 = 6$) and pigs ($R_0 = 40$) are higher (P.L. Eblé et al., 2008; K. Orsel et al., 2007). So the potency of vaccines should even be higher. But in case of an outbreak the transmission between farms is important and not the within pen transmission, therefore 3 PD50/dose which always has been used in Europe which is estimated to protect 70 – 80% of the cattle was sufficient if other control measures were in place.

When setting a goal of FMD eradication world-wide means that also transmission within groups of animals should be blocked. The stringent control measures that were applied after outbreaks in Europe are difficult to implement in other countries. We need therefore more potent vaccines, as mentioned earlier studies with a four-fold dose shows that there is still room for improvement also with inactivated vaccines, but knowing the constraints of the stability of these inactivated products, live vector vaccines are probably the only way to achieve world-wide eradication of FMD.

5. LITERATURE


