Foot-and-Mouth Disease Vaccination: A Review

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Milestones in the history of foot-and-mouth disease are: 1514 - the first accurate description of FMD (1), 1897 - FMD was the first animal disease shown to be caused by a filterable agent (2), 1922 - the plurality of viral types was proven (3), 1925 - first successful immunization of calves (4), 1938 - the virst vaccine was produced (5), 1947 - Frenkel developed a commercially feasible method for producing vaccine (6), 1962 - development of suspended cell culture for commercial vaccine production (7), and 1981 - the first cloned viral protein vaccine was produced (8), and 1982 - the first organically synthesized peptide was produced (9).

History of FMD immunization:

Before 1920, FMD losses in Europe were controlled by quarantining the infected area and often deliberately spreading the disease in infected herds. This was done by rubbing the tongues of healthy cattle with a rough towel contaminated with virus from tongues of the first cattle to develop the disease. The reasoning for the deliberate spread was: (a) the exposure would shorten the disease period in the herd; and (b) provided immunity against the next outbreak of FMD. About 1920, the above method was supplemented in some countries by the use of convalescent or hyperimmune serum to protect the more valuable animals. In 1925 the first report on the succesful immunization of calves with a formalized emulsion of vesicular epithelium was published. In 1938, the first FMD vaccine was produced from vesicular fluid and tongue epithelial tissue harvested from cattle inoculated with FMDV. The virus in the preparation was inactivated with formalin and heat and aluminum hydroxide was used as an adjuvant. The disadvantage of this vaccine were: (a) a costly process with limited scope of production; and (b) danger in production because infected animals were used. In 1951, the Frenkel technique for producing FMD vaccine was described. In this procedure, normal bovine tongue epithelium was obtained from slaughtered animals, placed in a nutrient fluid and infected with FMDV. After a period of incubation for viral growth, the preparation was inactivated with formalin and heat and mixed with an adjuvant (aluminum hydroxide). This process produced an effective vaccine and is still in widespread use. One disadvantage of this technique is that it requires a large, constantly available supply of bovine tongues.

In the early 1960's, the production of FMDV *in vitro,* using cells which could be continuously propagated (cell line), made large scale production of FMD vaccine feasible. The virus is currently being produced in both monolayer and suspended cell cultures using a baby hamster kidney cell line. The virus is inactivated and mixed with adjuvant.

There have been many attempts to develop a live virus vaccine for FMD, but these have not met with any large degree of success.

A well-managed, intensive vaccination program using the above inactivated vaccines will control FMD as exemplified by the elimination of FMD from Chile and Denmark (from 1970-1982) and the low incidence of FMD in the Western European countries. Control programs for FMD use approximately 800 million doses of vaccine per year.

FMD vaccination, however, is costly and has problems:

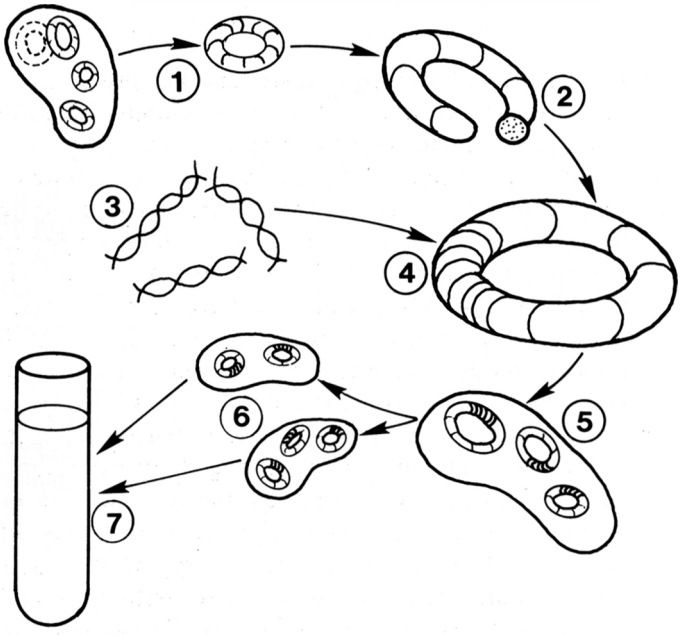
1) Duration of immunity is short. Some countries require cattle to be vaccinated three times a year.
2) Swine respond poorly to most vaccine formulations.
3) The various types and subtypes of FMDV complicate the effectiveness of the vaccine. In Europe and South America, generally, a trivalent vaccine (A, O and C) is used. However, to be effective, the vaccine must contain the same type and subtype that prevails in the field. Most manufacturers attempt to produce vaccine with virus recently isolated from the area unless it is a poor immunizing strain. To complicate matters further, FMDV is frequently being changed by mutations, natural passage through various species of animals or passage through animals with varying levels of antibody. Therefore, this necessitates typing of isolates from primary and widely scattered outbreaks and isolates collected periodically during the course of an epizootic.
4) Outbreaks of FMD have been frequently linked to incompletely inactivated vaccine (formalin).
5) Virus may escape from a production facility.
6) Whole-virus vaccine preparations are unstable and require refrigeration.

Research is helping to solve some of these problems.

1) Fingerprinting of RNA from field isolates and complement fixation and virus neutralization tests using field sera are being used to select the best previously characterized vaccine strain virus for vaccine production. This enables more rapid production of vaccine by eliminating isolation and adaptation of a wild virus for vaccine production.
2) Concentration of virus by ultrafiltration reduces the dose volume for vaccination; also the concentrated FMDV antigen can be stored in the vapor phase of liquid nitrogen for long periods and reconstituted when needed.
3) Inactivation with azuridines rather than formalin is more effective and less detrimental to antigenicity of FMDV.
4) Oil-adjuvants are more effective than aluminum hydroxide - particularly for swine. Methods of microencapsulation of vaccine are now being investigated.

This now brings us to the newest method of producing an FMD vaccine, cloned viral protein vaccine or genetically-engineered vaccine (fig. 1).

RECOMBINANT DNA STRATEGY FOR MAKING FOOT-AND-MOUTH DISEASE VACCINE



LEGEND

Figure 1:

1. Plasmid removed from bacterium. 2. Special enzymes clip plasmid. 3. DNA template from viral RNA. 4. Splice VP3 - specific DNA fragment into plasmids. 5. Plasmids are put back into bacterium. 6. Bacteria produce VP3. 7. VP3 extracted from bacteria.

Research has shown:

1) FMD vaccinated and convalescent animals have antibodies to two components in preparations of purified FMDV.
   (a) intact virion (140S).
   (b) virion protein subunits (12S).
2) The 12S fraction was found to be composed of three polypeptides (VP_1, VP_2, VP_3) which are major capsid proteins.
3) Purified VP_3 can elicit neutralizing antibody.
4) The area of the FMDV RNA genome responsible for production of VP_3 was located and plasmids containing complimentary DNA inserts were prepared.
5) The plasmid, when reinserted into *E. coli*, caused the bacteria to produce VP_3.
6) The bacteria were lysed and the fusion-protein purified.
7) Swine and cattle vaccinated with the fusion-protein, mixed with adjuvant, resisted FMD challenged.

The advantages of the cloned viral protein vaccine are:

1) Safety - since whole virus is never produced, the vaccine can be safely produced anywhere and inactivation is not needed.
2) Storage - the vaccine is stable at room temperature whereas the whole virus vaccine requires refrigeration.
3) Formulation - the vaccine can be lyophilized. It is also a candidate for formulation into slow-release mechanism.
4) Identification of vaccinated animals - a marker can be incorporated into the vaccine so that vaccinated animals can be distinguished from animals vaccinated with whole virus vaccine or from infected animals.
5) Is expected to cost less; however cloned viral protein is type specific; therefore, VP^3 from each FMD type needed will have to be cloned.

Mechanism of protection to FMD induced by conventional and cloned viral protein vaccine: Both vaccines induce circulating neutralizing antibody. Exposed animals may develop FMD infection of the nasal pharyngeal and respiratory tract areas; however, the transport of virus to sites of predilection is blocked, thus no clinical disease. However, these animals may become virus carriers.

The development of cloned viral protein, while a highly significant advancement in the production of FMD vaccine, may be superseded by an organically synthesized vaccine. Once the immunogenic portion of the virion is known and the amino acid sequence determined, the antigen can be produced without using any living organism. The final determinant as to which process, cloned or organically synthesized antigen, will be used will most likely be cost.

In spite of the above difficulties with FMD vaccine, animals properly vaccinated will be protected, thus reducing the number of infected animals which can spread the disease. Experience has shown that highly potent inactivated vaccines can be produced at an acceptable cost and that when properly used in an organized campaign, FMD can be controlled and eventually eradicated.

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