



Foot and mouth disease - present status and future strategy for control

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The Indian dairy farming and agriculture business has grown to Himalayan heights to put to the country as number one milk producer in the world today with above 80 million tons record production. The country has a huge livestock population of cattle, buffaloes, sheep and goats to the tune of 450 million heads. The production of livestock products like milk, meat, wool, hides and other by-products have also increased substantially tremendously in recent years

Improvement in the genetic potential of the livestock by means of cross breeding have made the cross-bred animals, apart from increasing stressful productivity management practices have made animals more susceptible to diseases like foot and mouth disease, infectious bovine rhinotracheitis, haemorrhagic septicaemia, black quarters, brucellosis. Most of these diseases can be controlled by systemic vaccination and monitoring.

The export market of livestock products is ever increasing. The increase is particularly significant to other Asian countries,

countries of the Middle East and Europe. The World Trade Organization (WTO) playing a significant role in determining trade policies, it would be of utmost importance that export products be free of important infectious diseases, especially those listed by the OIE. A stringent monitoring and control policy should be implemented to prevent the spread of these diseases. (FAO/OIE/WTO).

India has followed the OIE proposal for the eradication of Rinderpest disease. Sero-surveillance and disease diagnosis was rigorously followed along with compulsory vaccination of all animals. It should be noted that the OIE would recognize India to be Rinderpest free soon. An immune belt has been created along the borders of the endemic areas.

Many of the Developed Nations are free from most of the diseases listed in OIE particularly FMD and hence their livestock products are better accepted worldwide. **The prevalence of foot and mouth disease in India is a major trade barrier.**

Foot and Mouth Disease is an acute infection caused by a virus. The virus belonging to the picornaviridae family, is the smallest virus known so far. **The disease is characterized by formation of blisters, followed by ulcers on the mucosa of the mouth cavity and on the skin of the feet, hence the name: "Foot and Mouth Disease."**

Animals Susceptible for FMD

All cloven-footed animals including cattle, buffaloes, sheep, goat, pigs, elephants and other ruminants are susceptible to the virus. For obvious reasons, the disease is more important in cattle, buffaloes, bulls and bullocks in India.

Disease Spread

The infected animal is the main source of infection. Infection may spread either through direct contact or by indirect means, the infected feed and fodder, infected utensils, and infected means of transportation or, through carrier cattle attendants. Infection has also been reported to travel through air. However, at most times,





the wide spread of infection results from congregation of animals in cattle fairs, cattle markets or large-scale transportation of agricultural produce in bullock carts.

The **incubation period** for Foot and Mouth disease is as short as 48 to 72 hours and as long as 10 to 14 days. On an average, it varies from 3 to 7 days.

Seven immunologically distinct serotypes of Foot and Mouth disease viruses have been reported worldwide. There is no cross-immunity between serotypes, immunity to one does not confer immunity against any of the other types. Four serotypes, **O, A, Asia-1 and C** are the reported serotypes in India.

Disease Economics

Besides the acute stage of the disease, characterized by the formation of ulcers in the mouth, feet and udder, the virus of foot and mouth exhibits its pathology in some of the vital hormonal glands, which control the metabolic processes of the body. Disordered functioning of heat regulating centres leading to panting is one example. The disturbance in physiological process of lactation leads to a significant reduction in milk yield. In milch animals lesions on teat and udder can lead to mastitis, which may damage the teats and thereby affect the milk yield on permanently.

The **economic losses** to the livestock industry attributed to Foot and Mouth disease are large. The OIE/FAO/APHCA place a massive significance in their attempts to eradicate Foot and Mouth disease worldwide.

Direct losses to livestock sector are due to

1. Abortion in 25% pregnant animals
2. Reduction in meat production by 25% in endemic area.
3. A drop in milk production by 50%.
4. A reduction in wool production by 25% in affected sheep.
5. Mortality rate of upto 5.5% of the affected cases.

Indirect losses to livestock sector are due to

- a) Loss of productive function during the acute phase of disease.
- b) Loss of milk yields on a permanent basis.
- c) Loss of breeding capacity including abortions.
- d) Loss due to reduced draft capacity in working

bullocks.

- e) Interference with food production programme.
- f) Loss in cattle trade both national and international.
- g) Loss resulting from temporary cessation of A. I. programmes.
- h) Loss in flesh in meat-animals.
- i) Mortality in young calves due to heart failure.
- j) Flare up of inter-current infections like theileriosis, babesiosis and anaplasmosis.

'Prevention is better than cure'

This adage is very relevant in the case of Foot and Mouth Disease than other diseases. In countries where Foot and Mouth Disease is wide spread regular programmes of large-scale vaccination using Foot and Mouth Disease vaccines are being followed.

Prevalence

Foot and mouth disease is enzootic in Africa, Asia, South America and parts of Europe. The disease has been reported from various parts of the world except Japan, New Zealand, Australia Canada and the United States of America. Foot and Mouth disease is a reportable disease in most countries and attempts are made by the FAO/OIE to collect data on the prevalence of the disease in various countries. The various reference laboratories are involved in the sero-typing of the viruses. The identification of the various viruses serotypes is based upon complement fixation test, liquid phase blocking ELISA and recently by nucleic acid recognition method (Polymerase Chain Reaction). Overall it has been found that the serotype O and the serotype A occur more frequently than the other serotypes. The disease is endemic in India.

Strategy to Control

Sero-types predominantly occurring in the country are mainly type 'O' (70%) followed by Asia-1 and type A. There has been no report or minor occurrence of type 'C' outbreaks over the past 2 years. Most recent devastating FMD outbreak(s) in Punjab, Uttar Pradesh and Maharashtra in 1998 were predominantly by Type 'O'. The various serotypes of foot and mouth disease virus are antigenically distinct and do not cross react. Depending upon the prevalence of the type of the virus causing disease, the vaccines used in the area are





determined. If a single type of virus is seen prevalent, a monovalent vaccine (with only one type of the virus antigen) is used. If two types are seen, bi-valent vaccines with two types of virus antigens are used. In India, a tetravalent vaccine with antigens from type A, O, C and Asia-1 are used. To prevent antigenic drift, vaccines usually with more than one strain are used in manufacture.

Hoechst Roussel Vet maintains a reference collection of the vaccine strains of FMDV. By comparing outbreak strains with the vaccine strains in the repertoire, an appropriate vaccine strain could be identified. A repertoire of antibodies is also developed to determine shared neutralizing epitopes, thereby giving an indication of the potential value of vaccine strains in helping control the outbreak. Linkages are being established within India, with IVRI, the United Kingdom with Institute for Animal Health, at Pirbright and other institutes globally via the internet.

In 1951-52 over 900,000 outbreaks were reported in Europe, the European countries finally eradicated the disease and from 1992 the member countries of European economic community (EEC) are adopting a non-vaccination and stamping-out policy. This had largely come about by the maintenance of solid vaccination coverage because the European FMD commission in 1957 accepted the systematic vaccination would be necessary for number of years to reduce the incidence of the disease so as to make other measures like slaughter policy an economically feasible.

FMD Vaccines

International standards for FMD vaccines can be found in the British Veterinary Pharmacopoeia, British Veterinary pharmacopoeia Codex, European Pharmacopoeia (Veterinary) (1993) and the OIE Manual of Standards for Diagnostic Tests and Vaccines. National Veterinary Authorities usually exercise control of the use of FMD vaccines. Indian Veterinary Pharmacopoeia is being planned to release shortly. The FAO/OIE is formulating International standards for safety, potency and antigenic mass requirements for the various vaccine strains. The dosage of the vaccine mass depending upon the epidemiological situation of the area is also being worked out.

History of FMD vaccine development

The three critical elements of FMD vaccine production are antigen production, virus inactivation and the addition of suitable adjuvants. Historically, the original source of FMDV for vaccine production was clinically derived material, such as infected cattle tongues in 1926.

In 1951, Frenkel described a new technique for the production of FMDV on an industrial scale in tongue explants. It was FMD vaccine made in this system that was used in the Netherlands in the first of the highly successful mass annual prophylactic vaccination campaigns to be carried out in Europe.

The advantages of this production system were its simplicity, low cost, lack of cellular protein contamination of the virus harvest and the fact that adaptation of the virus to the culture system was not required

A significant development in FMDV antigen production was the transition to tissue culture methods of virus growth. Initially, small-scale production in roller bottles using primary calf kidney cells was instigated in Italy in 1963.

However, following the introduction in 1964 of a continuous cell line derived from baby hamster kidney fibroblasts (BHK 21) that supported the growth of FMDV, this system gained wide acceptance in FMDV vaccine production.

Later a variety of monolayer systems were devised to increase culture vessel surface area, and thus productivity.

However, the greatest scale-up in capacity for FMDV production was the advent of technology, which exploited the ability of BHK-21 cells to grow in deep suspension culture in fermentors (bioreactors) which we are used widely now-a-days.

The Indian Veterinary Research Institute, Mukteshwar in India, carried out pioneering work on the development of foot and mouth disease virus vaccine.

Antigen production

Commercially available FMD vaccines are still based upon inactivated whole virus particles, mostly grown in BHK-21 in a battery of fermentors 100 to 1200 liters capacity located in strict containment area under controlled air conditions.

Virus growth in cell culture systems is followed by a series of treatments to clarify, inactivate, purify and





concentrate the viral harvest.

During FMD antigen production, temperature and pH have to be closely controlled because of thermal instability and the low tolerance of the virus to pH conditions outside the ranges 7.0-8.0. Whole virus particle (146S) content is critical to the potency of the final product and measurement of 146S is used for vaccine formulation calculations.

Inactivation

Inactivation is one of the most critical steps in the production of FMD vaccine. Initially, formaldehyde was used to inactivate alum-adsorbed virus. In process evaluation of this system proved to be difficult and it has mostly been superseded by the use of first order kinetics inactivants of the aziridine group of chemicals, most recently binary-ethylene-imine (BEI). Ideally this procedure is performed twice in separate inactivation vessels.

Good Manufacturing Practice (GMP)

In recent years, there has been a move away from end product testing towards the philosophy of in-process control. This policy has been encouraged at HR Vet. through the promotion of Good Manufacturing Practice (GMP). In process inactivation controls are performed upon the virus harvest by tissue culture titration in sensitive cells, spectrophotometric analysis or serological assays.

Further post inactivation concentration and purification by ultrafiltration or precipitation with polyethylene glycol (PEG) could yield a final virus product with a concentration factor of up to 1000 fold. Post inactivation purification reduces the non-viral protein component of the antigen harvest, which is important in the reduction of potential hypersensitivity reactions in vaccinated animals.

Adjuvants

Inactivated whole virus vaccines against FMD are formulated as mono or polyvalent products with suitable stabilizers, buffers and adjuvants to enhance their potency. In aqueous formulations, the inactivated viral antigen is adsorbed to aluminium hydroxide $[Al(OH)_3]$ and further adjuvanted with saponin

Such vaccines are used successfully worldwide for the immunization of ruminants.

However, commercial aqueous vaccines have not been

successful in immunizing pigs (reactions at the site of injection were observed), and concentrated, inactivated antigens formulated as oil adjuvanted vaccines have been used widely in this species.

Oil adjuvanted FMD vaccines are also used in cattle, particularly in South America. Improved formulations have reduced the local reactions initially seen in this species.

Advantages are claimed for the use of oil-adjuvanted FMD vaccines in cattle in the areas of duration of immunity and the ability to immunize calves. Simple water-in-oil preparations can be made by the emulsification of the antigen in aqueous solution with light mineral oil and an emulsifying agent. Silverson and Ystral on-line pumps are used for the emulsification process and to ensure stability of the emulsion under field conditions.

Alternatively, a more easily injectable formulation can be made by further emulsification in a second aqueous phase to produce a stable water in oil in water emulsion [double oil emulsified (DOE)]. There are several reports of the successful experimental use of these DOE FMD vaccines in cattle and pigs.

Following the completion of the blending process and addition of suitable preservatives, the vaccine is bottled and should be subjected to prescribed in vitro sterility test, and safety/innocuity and potency tests in cattle, as described in the European Pharmacopoeia (Veterinary).

Safety tests are performed *in vivo* using the whole vaccine inoculated into susceptible animals and *in vitro* using eluted antigen inoculated onto sensitive cell culture.

Minimum potency assurance required is assessed by a variety of serological and/or animal challenge procedures.

FMD vaccines have a shelf life of one year if stored at 4°C.

Production Capacity: The production capacities have been increased tremendously to meet the demands of country as well as export. Hoechst Roussel Vet has a current production capacity of 25 million doses and would increase the capacity to 30 million doses by 2000.

Use of FMD Vaccines

In order to establish satisfactory immunity, it is usual





to give a primary course of two inoculations with an interval of 2-4 weeks.

Re-vaccinations may be given at 4-12 month intervals depending upon local epidemiological conditions and the quality of the vaccine. Therefore, the primary vaccination course may be delayed until four months of age in the offspring of regularly vaccinated mothers, although there is some evidence that calves can respond at one month old or younger.

The Role of Vaccination in FMD Control Strategy Prophylactic

The successful control of FMD in countries with endemic or epizootic disease has often been based upon the regular use of inactivated whole virus vaccines as part of a regional FMD control policy.

The short lived nature of protective immunity in cattle following vaccination compared to FMD infection has led to the need to vaccinate annually or bi-annually, and even thrice a year in areas with a high risk of exposure to the virus.

Antigenic variation within a serotype has made it common practice to include more than one strain of a particular serotype in FMD vaccines.

Mass prophylactic vaccination against FMD, usually practiced only in the cattle population, is the first step towards controlling FMD in endemic areas.

The aim of this policy is that, over a period of years the load of FMDV in the environment will be reduced as the number of outbreaks, and therefore animals, with clinical disease will fall. Obviously, good veterinary services are essential to maintain the vaccination campaign and monitor disease status in the country.

If a level of immunity to FMD in the target population in excess of 75% is achieved, the disease should be adequately under control so that extra measures, such as importation control, quarantine and stamping out foci of infection, can be effective.

An example of the successful implementation of these policies was the reduction in outbreaks of FMD in Europe from 30000/year in 1965 to less than 1000/year by 1975.

It is extremely important that an antigenically appropriate vaccine should be used. It is essential that the antigenic relationship between field isolates and the

vaccine strains in use should be ascertained regularly. The next stage of FMD control is to stop mass prophylactic vaccination and, by means of stringent surveillance, rapid diagnosis and importation control, a state of freedom from infection could be achieved. This is the current situation for Uruguay and the European Union countries.

Emergency

General vaccination is recommended for countries where the disease is enzootic, or where the threat of an outbreak is very great. If an outbreak occurs, a booster vaccination with the relevant serotype will increase the resistance of the population.

The process of stamping out of infection is difficult under Indian conditions because of social reasons. Mass vaccination coverage to 80% of the animal population will reduce the incidence of foot and mouth disease in endemic areas. A generation of a vaccine bank that can rush vaccines to an outbreak focus is a top priority. A ring vaccination should be advocated to contain the disease.

Committed people, a proven vaccine, a good delivery system and effective vaccination coverage along with active support from the farmers, Governmental decision makers, government research institutes, non-governmental agencies, and manufacturers of vaccine would effectively control foot and mouth disease in India.

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