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Review

Control and eradication of foot-and-mouth disease

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1. Introduction

In Europe, foot-and-mouth disease (FMD) has been known for hundreds of years and its contagious nature had been described centuries ago. The first written description was by an Italian monk Girolamo Fracastoro (Hieronymi Fracastorii Veronensis) in 1546, Verona, (cited in Casas Olascoaga et al., 1999).

FMD is a global disease that through the years has affected most countries in the world. Control in most European countries only became possible after the Second World War when vaccines became available. Up to 1991–1992 FMD was controlled and eradicated by systematic vaccination of the whole cattle population. Then, after Europe had been disease free for a number of years vaccination was discontinued. The British Isles, Ireland, Scandinavia, and North America were able to control the disease by 'stamping out' due to their favorable geographic position. Britain had this policy by law from 1892 onwards.

When the European Union (EU) decided to abolish general vaccination, mainly for reasons of trade, a huge susceptible cattle population was created. With the 'open border' policy of the EU, the general deterioration of the emergency preparedness of veterinary services and lack of public awareness, a very dangerous situation emerged. The potential for the 2001 FMD disaster in Europe was created by changes in livestock management in many parts of the world, increased mobility of people, human population encroaching on wildlife, as well as increased animal and animal product movements, and reduced use of FMD vaccination around the globe. In Europe, in Britain in particular, the ensuing epidemics had very serious consequences for the rural society Movement restrictions created huge animal welfare problems, while other measurements hampered sectors like tourism. Export rules did not allow the use of even limited vaccination around the outbreak and only stamping-out was used to control the disease. The large scale ring culling applied to create 'fire breaks' hit many farming families and depopulated large areas of livestock.

South American countries saw the end of FMD vaccination in Europe as a threat to their meat export position. By means of vaccination they became countries that were 'FMD free where vaccination is practiced' (FMD free with vaccination). After some years of freedom of the disease the countries aspired to achieve 'FMD free where vaccination is not practiced' (FMD free without vaccination) status. During the 90s, the countries of the southern region of the South American Continent succeeded in attaining that favorable position and were able to maintain that status for several years. However, the global FMD situation has became increasingly unstable in the past 4 years and complacency and, as a consequence, lack of alertness took its toll. FMD recently, invaded large livestock populations that by then were no longer immune in Argentina, the South of Brazil, Paraguay and Uruguay. In these countries massive cattle vaccination programs were resumed soon after the outbreaks started in 2000 and 2001.

Introduction of the disease into the UK in 2001 and its onward spread to other countries, were other serious

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facts to consider. We were struck by the fact that the measures used to prevent and control FMD were primarily based on agro-economic considerations and that authorities in charge were justifying their policies with doubtful scientific arguments. We heard veterinary authorities state 'To vaccinate means to live with the disease!' The public in general, including veterinary and agricultural communities, were misinformed by scientists and veterinary authorities and raised such basic questions as: 'Would meat from vaccinated animals be fit for consumption?'; 'Can sheep, goats and pigs be protected by vaccination?'; and, 'Does vaccination perpetuate FMD infection?'. We decided, therefore, that we should present the available scientific information as a guideline for future prevention, control and eradication of FMD.

1.1. Historical background

FMD is enzootic in many parts of the world. Regions that traditionally have been free of the disease are Australia, New Zealand, Japan, Central and North America. FMD was introduced in South America during the middle of the 19th century by the importation of European breeding stock.

In Europe, when the contagious nature of the disease became clear, farmers tried to prevent contacts with infected farms, but this was mostly without success. The disease continued to spread from farm to farm slowly but steadily over the continent. The disease often started in Eastern Europe or entered from the Middle East via the Balkan countries or from North Africa.

Until the 1960s, when national vaccination of cattle became general practice, Europe suffered periodic cycles of extensive epidemics. In some countries during the 1937–1939 outbreaks more than half of all farms were affected. For the whole of Europe about 2 million infected premises were reported, in The Netherlands 265 000, in France 379 000 and in Germany more than 700 000 cases (Fogedby, 1963). It was during the 1951–1952 epidemic that FMD hit Europe for the last time on a comparable scale: France 330 000 cases, Germany (Federal Republic) just over 300 000. At that time, The Netherlands was in a starting-up phase of their general vaccination program, which considerably reduced the number of outbreaks. Thereafter, vaccination was gradually introduced into Europe in the form of ring vaccination, or regional programs, often in combination with slaughter of infected farms in order to limit the dissemination of the disease. These measures reduced the number of outbreaks in Europe, limiting the disease to only a few thousand farms. With the advances made in vaccine technology general vaccination became possible in Europe and most countries were able to achieve freedom from the disease in recent decades.

FMD was first recognized in the Western Hemisphere around 1870 on the north-eastern coast of the United States of America (USA), in the province of Buenos Aires in Argentina (1865–1866, 1870), Uruguay (1870), Chile (1871) (Goic, 1971) and in southern Brazil in the state of Rio Grande do Sul and in Minas Gerais (1895). At the beginning of the 20th century the disease had spread to the rest of Brazil, and to Bolivia (1912), Paraguay and Peru (1910). FMD appeared in Venezuela (1950) and Colombia (1950–1951), and ultimately spread to Ecuador in 1956 (Casas Olascoaga, 1984; Casas Olascoaga et al., 1999).

1.1.1. Variety of strains and serotypes

It was soon discovered that in Europe three different types of FMDV virus caused the disease. After the animals recovered they were protected against the causative virus but not against other strains that might appear later on. Initially type O and A were differentiated (Vallée and Carré, 1922) and a few years later type C was added (Waldmann and Trautwein, 1926). Several African field strains collected since 1931, were re-examined by Brooksby in 1948 who demonstrated a new strain from the South African Territories (SAT1). Two more strains from Southern Africa (SAT2 and SAT3) also were identified (Brooskby, 1982). FMD type Asia 1 was identified from a sample originating from Pakistan in 1957 (Brooksby and Roger, 1957)

1.1.2. Aphthisation

Over the centuries farmers have developed pragmatic methods for reducing the impact of FMD. This included aphthisation, the deliberate infection of livestock. This was done with infectious materials obtained from infected farms in the neighborhood, thus avoiding a period of uncertainty and a long lasting period of disease on the farm. In Germany, in Preuszen this was even regulated by law in 1781 (Röhrer and Olechnowitz, 1980). Until the 50s this policy was common practice and still occurs in some developing countries.

In the beginning of the 20th century it became clear that animals could be protected by application of hyper-immune or convalescent serum (Trautwein, 1927, for review see Fogedby, 1963; Röhrer and Olechnowitz, 1980). In some countries this treatment became obligatory shortly before animals were sent to shows and markets. The measure reduced the spread of the virus through these livestock concentration points.

A combination of passive immunization and aphthisation was first proposed by Loeffler in 1898 and many investigators tried this 'Simultanimpfung' in a variety of combinations. Despite frequent failures it became the main method to limit the damage until vaccines became available.

From the 30s to the end of the 40s the so-called 'hemo-prevention' was also used extensively in some

South American countries e.g. in Uruguay. Calves were inoculated with blood of convalescent cattle diluted with 10% sodium citrate (1 ml/kg bodyweight) in combination with aphthisation. Also, in the face of an outbreak hyperimmune serum was used in high-value breeding stock (Rubino, 1946a,b,c).

1.1.3. 'Stamping-out' and vaccination

In 1892 Britain was the first country with a substantial program for FMD control. The decision was made to eradicate every outbreak by 'stamping-out'. This implied the killing and destruction of all infected animals and their immediate susceptible contacts, followed by thorough cleaning and disinfection of the affected premises. Farmers were compensated for their loss of livestock. Later on, Ireland and Norway adopted this policy as well (Fogedby, 1963). The success was largely due to the isolated position of these countries.

Regular incursions in Britain of FMD (usually yearly) created farmer awareness and helped develop an efficient surveillance/control system. Usually five or less secondary outbreaks arose from each primary outbreak, but occasionally a far higher number of secondary outbreaks occurred. It was only during the long lasting 1922–1924 epidemic in the UK with over 4000 cases that, because of exhausted funds, the traditional slaughter policy was partly abandoned and 105 infected farms were just isolated without slaughter. Some other outbreaks were only brought under control after prolonged and considerable stamping-out efforts; the 1967–1968 epidemic in particular, when over 2000 outbreaks were reported.

The USA also successfully applied 'stamping-out'. The last outbreak occurred in 1929. Canada also controlled the 1951–1952 Saskatchewan outbreaks by this method and was declared FMD free in 1953.

In 1946, FMD type A was introduced in Mexico most likely by the importation of Zebu cattle from Brazil. To eradicate the disease, the Mexican government received assistance from the USA to deal with surveillance, quarantine and massive 'stamping-out'. In the beginning of 1947 the US. Congress authorized cooperation with Mexico. Despite an intensive and expensive program, the disease continued to spread. After killing some 500 000 cattle and more than 380 000 sheep, goats, and pigs, the social tension in the rural community became very severe, and some veterinarians and inspectors were killed by the farmers (Machado, 1969). It became obvious that the policy would not lead to eradication of the disease. Therefore, a vaccination program was established using Waldmann vaccine from three European laboratories and one laboratory in Argentina. Local vaccine production in Mexico was based on the harvest of tongue epithelium from inoculated cattle. By the end of the campaign some experimental 'Frenkel-type' vaccine was also produced. Frenkel from The Netherlands and Rosenbusch from Argentina helped to install this plant, one of the very first in the world.

A total of more than 60 million doses of inactivated FMD vaccine, type A were produced and some 25 million cattle and about 35 million sheep, goat and pigs were vaccinated. The last vaccination took place in 1950. During the period that vaccination was carried out it was still necessary to kill and destroy some 10 000 infected animals and thereafter in 1953, more than 23 000 animals were destroyed because of the re-emergence of the disease. In 1949 there was also a limited outbreak of type O, (in hindsight this may have been a vaccine accident, caused by incomplete inactivation of imported vaccine). that was eradicated by immediate 'stamping-out'. The USA contributed to this Mexican campaign with a group of US veterinarians and scientists and approximately US$ 120 000 000 in financial aid.

In Germany, shortly before the Second World War, a vaccine was developed that effectively protected against FMD. It was based on the earlier discovery that virus obtained from infected cattle, could be inactivated by formaldehyde. This inactivated virus raised some immunity when injected in cattle (Vallée et al., 1925, 1926). Virus adsorbed onto aluminium-hydroxide could be protective, but sometimes caused disease (Schmidt, 1938). Waldmann et al. (1937) combined both findings and adsorbed 'Natur Virus' onto aluminium-hydroxide and inactivated the complex with formaldehyde. The inactivated complex protected effectively against the disease (of the same serotype). To produce the virus (antigen) needed for the vaccine, quite large numbers of cattle were inoculated with virus in the dorsal epithelial surface of the tongue. In post-war years in The Netherlands 180 cattle were infected twice a week in stables at the Rotterdam slaughterhouse. The day after the inoculation the animals were slaughtered and tongue blister material was collected. Each infected animal provided sufficient virus to produce approximately 200 doses of vaccine. Thereafter the heads were destroyed and the remaining carcasses were sold for human consumption. Similar virus production took place on a smaller scale in Amsterdam. Thus, a generation of Rotterdam and Amsterdam citizens has grown up eating FMD infected meat with, as far as we know, no harmful effects.

Although these vaccines helped to reduce the number of outbreaks in Europe, production capacity remained insufficient to allow vaccination of all cattle. It was only when Frenkel developed a vaccine based on in vitro culture of FMD virus that sufficient vaccine could be produced. With this revolutionary technology, the virus was produced in so-called surviving bovine tongue epithelium collected at slaughterhouses. The epithelium was incubated in culture medium, and after infection produced enormous amounts of virus. The virus was

adsorbed to aluminum hydroxide and inactivated with formaldehyde as in the Waldmann procedure.

Vaccine produced according to this technology practically liberated The Netherlands from the disease with the exception of some outbreaks at the borders where disease entered from non-vaccinating neighboring countries. Not surprisingly there were also a few outbreaks around Amsterdam, where the FMD institute was located. In the 60s FMD strains (type C and later type O) became very aggressive for unvaccinated pigs. Strategic vaccination of pigs with a potent Frenkel-type vaccine solved these problems.

Other European countries followed the successful Dutch example and in the 60 and 70s most European countries were practically free of the disease. In France, Belgium, and The Netherlands Frenkel-type vaccine was used until 1991 when vaccination was discontinued in the whole of Europe.

In the 60s vaccine technologies were developed that were based on virus antigen production in the BHK cell line (Capstick et al., 1962; Capstick and Telling, 1966) and on inactivation with aziridines. (see the chapter by T. Doel).

With formaldehyde-inactivated vaccines a few outbreaks occurred which were associated either with poorly inactivated vaccine or with virus escapes from vaccine production plants (Beck and Strohmaier, 1987). This seldom had dramatic consequences because surrounding cattle were protected. However, severe outbreaks in the west of France, mainly in pigs, also seemed to be vaccine related (King et al., 1981). In the Netherlands during the 40 years in which the Frenkel-type vaccine was used (over 200 million doses), no such case occurred. This may have been due to the double concentration of formaldehyde (as compared to the Waldmann formula) that was used (Barteling and Woortmeijer, 1984).

In 1985 the EU decided to implement the non-vaccination policy. However, 2 major outbreaks in Italy (in 1985 and 1987) almost frustrated this policy. The severity of the outbreaks was largely due to a change in the organization of the vaccination campaigns and reduced vaccination coverage. In addition, the responsibility for the campaigns had changed from the Ministry of Agriculture to that of Public Health and Hygiene. The medical officers in charge had little knowledge of FMD, and the situation only improved after the responsibilities for the campaigns was again centralized under veterinary supervision in 1987. Europe remained free and in 1991–1992 vaccination was discontinued.

After 1992 outbreaks occurred in Italy (1993), in Greece (1994 and 1996), and on the borders of the EU, in Bulgaria (1994), Albania (1996), Macedonia (1996) and Yugoslavia (1996). Stamping-out was applied within the EU states, but vaccination and stamping-out in the others, usually with EU support. In 1995 and 1996 outbreaks of FMD type O were seen in Thrace (the European part of Turkey) that were controlled by ring vaccination and quarantine measures.

1.1.4. FMD institutes

At the end of the nineteenth century the awareness of FMD and how it spread increased considerably. Löffler and Frosch, 1898 discovered in that the infectious agent could pass through very fine filters that retained bacteria. This finding stimulated research on FMD. Because these studies could not be carried out in veterinary institutes in which other diseases were also studied as cattle intended for other studies too often went down with FMD, special institutes for FMD were created. These were often established in isolated locations or on islands (e.g. Insel Riems, Germany, the island Lindholm in Denmark, and Plum Island, USA) or in the middle of a town (e.g. Amsterdam, Lyons). In those days the institutes had no real provisions for secure containment and escapes of virus occurred, e.g. the SAT outbreak in 1960 near Pirbright Later new laboratory bio-safety provisions improved the situation although these provided no guarantee against escape of the virus (Beck and Strohmaier, 1987). It became clear that bio-containment facilities with adequate technology, bio-safety rules, and regular checks and controls were essential for the containment of FMD within the institutes.

1.1.5. International organisations

1.1.5.1. Europe. In 1924 the Office International des Epizoöties (OIE) was founded in Paris. The organisation was initiated to control rinderpest that had reoccurred in Europe. The original agreement was signed by 28 states and it was the start of a worldwide network for the reporting of the occurrence of contagious diseases. After the control of rinderpest, FMD became a major issue.

Now rules are established within the framework of OIE for the prevention of the spread of contagious diseases through international trade. To that end, workshops and meetings of veterinary specialists are organized. Every year there is a meeting of veterinary representatives in which the international situation is discussed. FMD is a major topic on the agenda. Thus, with the increasing international contacts and trade, the OIE plays an important role in preventing the introduction and spread of FMD. International standards set by OIE are in use as a benchmark by the World Trade Organization (WTO) when evaluating national regulations in sanitary-based trade disputes (Thiermann, 1997).

Both the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) within the

framework of the United Nations became involved in the worldwide struggle against FMD. FAO played a major role in setting up FMD laboratories and vaccine production units in developing countries. However, after the support by FAO was discontinued, vaccine production often ceased because of the lack of sufficient technical infrastructure.

In 1954 under the wings of FAO, a number of European countries created the European Commission for the Control of FMD. This institution stimulated control programs in European countries and also, via its Research Group of the Standing Technical Committee Meetings, encouraged the study of FMD and methods for its improved control.

FAO is also involved-together with the EU—in the so-called Tripartite Committee that implements measures to prevent the spread of FMD from Turkey into Europe. The vaccination of cattle and sheep in Thrace, Turkey, is one of the actions that are supported by this committee.

1.1.5.2. The Americas. As a direct result of the Mexican FMD epidemic and the introduction of FMD serotypes O and A in Venezuela and Colombia in 1950–1951. (Cadena Santos and Estupinan, 1975) the Pan American Foot and Mouth Disease Center (PANAFTOSA) was established in Rio de Janeiro (Blood and Rodriguez Torres, 1951). The Organization of American States established a technical assistance program with the Pan-American Health Organization (PAHO) as the executive agency for PANAFTOSA. In 1968, PANAFTOSA was incorporated within the regular program of PAHO.

PANAFTOSA played a major role in the coordination and organization of FMD prevention and control programs in the setting of standards for diagnosis, for the quality of FMD vaccines and in training human resources for the countries of the Americas. In 1972 the South American FMD Control Commission (COSALFA) was established. The objectives of COSALFA are regional coordination, promotion, and evaluation of FMD prevention, control and eradication programs; harmonization of sanitary standards; and promotion and evaluation of bilateral and multilateral agreements for the control of FMD. PANAFTOSA acts as ex-officio Secretary. In 1982 COSALFA approved the document 'FMD policy and strategies in South America for the decade 1981–1990', which established general action guidelines to achieve elimination of the disease in major livestock areas in the hemisphere.

1.1.5.3. Other parts of the world. In many other parts of the world a status quo is maintained. Although regular vaccination may be carried out on large dairy farms and industrial pig holdings, the 'backyard farmer' or pastoralist often cannot afford the costs of vaccination and the disease is maintained in the area. Moreover, in many countries the price of the vaccine must be kept low, which may impaire the quality of the vaccines and result in incomplete protection. This may give mutants of the virus chances to develop into new field strains causing new problems.

In the Middle East only the isle of Cyprus (last outbreak in 1964) is currently included in the OIE list of 'FMD free countries where vaccination is not practiced'. The other countries try to limit the damage by vaccination of the dairy herds and, in the face of outbreaks, also of their nomadic sheep flocks. However, the vaccination of these flocks is probably not sufficiently consistent. In Europe in the past and in South American countries the disease was, and is, controlled by the vaccination of cattle only, and the disease was not maintained in sheep. In the Middle East this seems to be different. The nomadic behavior and the nature of the trading markets probably gives the disease sufficient chances to be maintained in sheep and goats.

In the Middle East the regular outbreaks of FMD reflect the poor animal health status. Since 1960, six FMD virus serotypes, namely O, A, C, SAT1, SAT2, and Asia 1 have been recorded. Types O, A and Asia 1 are still endemic. Although in Thrace, the geographical European part of Turkey, and in Western Anatolia cattle and sheep are vaccinated to create buffer zones, occasionally FMD occurs in one of the South-Eastern European areas, such as Italy (1992), Bulgaria (1993), Greece (1995 and 1997), and Macedonia and Albania (1998). Turkey tries to improve and increase its vaccine production but, so far, it has not succeeded in producing sufficient vaccine for a general vaccination program of all cattle. Vaccination of sheep and goats is certainly a priority.

So far an international policy for the Middle East region is lacking, although here is some co-operation between Israel, Jordan, and Egypt, which is stimulated by the EU and the US. Israel is the only country in the area with a successful consistent vaccination policy. Their highly productive, zero-grazing dairy cattle are protected by annual vaccination. These cattle are often maintained in close proximity to nomadic flocks of sheep and goats, and, therefore, intensive disease surveillance is carried out. Although these flocks are vaccinated annually against type O, it does not prevent the occasional occurrence of FMD, even of serotype O, but outbreaks remain limited. In Israel the quality of the imported FMD vaccines is controlled by checking, on selected farms, the antibody titers after primary vaccination of young cattle and sheep.

For decennia, Egypt has suffered from type O only. Although Egypt applies annual vaccination of all susceptible animals with aqueous vaccines and the geographically isolated conditions of their livestock area seems to prevent the introduction of other strains, complete eradication of FMD so far does not seem

possible. This might well be due to poor quality of the locally produced vaccines, which lack independent quality control, and/or lack of sufficient containment of the disease during outbreaks.

Saudi Arabia represents a special problem. In this country many of the current strains of FMD are introduced by the importation of millions of sheep annually. A heptavalent vaccine is used in valuable dairy herds without providing full protection. High animal densities in feedlot situations probably exacerbate the situation. During recent years increased competition by vaccine producers seems to have improved the situation (Dr Kitching, personal communication).

In Africa systematic vaccination against the SAT viruses is only applied in the Southern cone. This is done in border zones with fenced areas of endemic FMD, e.g. the Kruger national park in South Africa where the buffalo are permanently infected with SAT-strain viruses (Reviewed by Thomson, 1996). In general this policy keeps the rest of South Africa and large areas in surrounding countries free of FMD. In the beginning of 2001 after excessive rainfall and accompanying floods, fences around the Kruger Park were flushed away and buffaloes and other game broke out of the restricted zones, causing FMD in surrounding districts. Also, at the end of 2000 South Africa suffered from a limited type O_1 outbreak that started at a pig farm where swill from a harbor was fed. Initial attempts were made to control the outbreak by stamping-out but when the disease entered an area with community farming, which made control by stamping-out practically impossible, the outbreak was successfully controlled by ring/area vaccination of all susceptible animals.

Large parts of China and Taiwan suffer from O-type FMD and in 1994 a strain that was very aggressive for pigs destroyed a great deal of the Taiwanese pig export industry. In that country and in the Philippines disease is controlled by vaccination of the pigs with double oil emulsion vaccines. India and Thailand have large scale vaccine production facilities but aqueous vaccines are mainly used for the valuable dairy cattle and consistent control is not reached yet. In some other Asian countries the minimal vaccine production is often connected to national laboratories. In general in this part of the world the disease can take its devastating course by depriving farms from their animals used for traction.

In most of mainland Africa and Asia, reduced Government expenditure on animal health has constrained control, which also has international ramifications for FMD free countries. Geographical isolation is no longer a barrier—even the Sahara can be crossed with lorries. In 1999 FMD swept across Algeria after entry via the smuggling of infected cattle from West Africa across the desert. Individual farmers can protect their stock with vaccination but to obtain an export trade, countries require surveillance and control and eradication programs that can only be achieved with international cooperation and investment. Punitive trade measures against countries that use FMD vaccination limit potential investment, exacerbating the divide between rich and poor countries. Without a global approach to FMD control and eradication, new introductions of FMD into free regions are bound to happen. It is not a question of *if*; it's a question of *when*.

2. Pathogenesis of FMD

From the studies of Loeffler and Frosch (1897) it was clear that FMD was caused by a very small particle that passed an ultra-filter. However, the way the virus finds its first target cells or tissues, and how it is propagated, remained undiscovered for many years. It was clear however, that the virus could spread from animal to animal or through contact with contaminated persons or objects, and through the air (Fogedby, 1963; Röhrer and Olechnowitz, 1980).

In the 30s it was demonstrated that infected hedgehogs exhaled air that could infect other hedgehogs by inhalation (Gibbs, 1931; Edwards, 1934). Korn (1957) reported on early virus multiplication and described histopathological changes in the upper respiratory tract of FMD infected cattle. He indicated that the primary site of virus multiplication was predominantly in the mucous membrane of the nasal passages. The virus multiplied during the pre-viremic state when the classic oral lesions were not yet detectable either macroscopically or microscopically. This idea contradicted the earlier concept that FMD virus gained entrance through the oral epithelium and caused vesicles that were followed by viremia and secondary lesions.

Korn's hypothesis was altered in the light of later investigations, but his idea of air-borne infection still forms the basis of much of the present concepts of the pathogenesis of the disease (McVicar, 1977). Fogedby (1963) reported on air-borne FMD transmission over long distances e.g. from Germany onto Danish islands. Hyslop (1965) detected FMD virus release in the air surrounding diseased cattle and Sellers and Parker (1969) made similar observations in the air surrounding cattle, pigs and sheep even before clinical signs developed. However, virus can also gain entry through abrasions in the epithelium of, for instance, the oral cavity, feet or teats, it is now generally accepted that the common portal of entry of the virus is by the respiratory tract (Sutmoller et al., 1968; Sellers and Parker, 1969; McVicar and Sutmoller, 1976). Most virus will be trapped in the upper respiratory tract, with subsequent multiplication in the mucosa of the oro-pharynx. However, after experimental pulmonary infection of cattle, FMD virus will multiply in lung tissue (Eskildsen, 1969) and virus that reaches the alveoli can also pass readily

into the blood stream (Sutmoller and McVicar, 1976, 1981). FMD virus is then distributed throughout the body, to reach multiplication sites such as the epithelium of the oro-pharynx, oral cavity, feet and the udder. This type of explosive clinical syndrome will take place after contact exposure to infected animals, just prior to the development of clinical signs (Graves, 1971).

Virus can replicate at many sites in the body, and often lesions can be observed at those sites. Best known are the oral, feet, teat, and heart lesions but virus also replicates in the mammary gland. When virus is instilled in the mammary glands of susceptible cows, virus appears in the milk in high titers. Virus replication is accompanied by signs of mastitis, 2–4 days before other clincal signs developed (Burrows, 1968a). Intra-nasal exposure of susceptible cows resulted in the detection of virus in the milk when the cows had generalized lesions (Leeuw et al., 1978).

Virus probably replicates in the pituitary gland (Scott et al., 1965). Involvement of the pancreas with selective necrosis of the islets of Langerhans was reported by Manocchio (1974). Virus reaches high titers in the skin of infected cattle even in areas where there are no gross lesions (Gailiunas and Cottral, 1966). However, gross lesions are most frequently observed in tissues that are subject to vigorous activity or trauma (Potel, 1958; Seibold 1963; Skinner and Knight, 1964).

In the 60s prior to the vaccination programs in Argentina, Uruguay and the southern States of Brazil serious sequels of FMD were seen including survivors with a cardiac-pulmonary syndrome. Also, the 'panting' or 'heat intolerance syndrome' is seen in cattle. The latter may be indicative for FMD virus affecting the pituitary gland (Domanski and Fitko, 1959; Scott et al., 1965). These animals develop hairy shaggy coats and become very sensitive to warm weather and become very poor producers. Similar animals can still be found, for instance in East Africa. (T. Leyland, personal communication).

During the 2001 type A outbreak in Argentina and Uruguay there were several cases of acute cardiac involvement in young animals (calves and piglets), causing mortality, and even of adult cattle with typical 'tiger' hearts. This may be due to the completely naïve immune status of the population as a result of the non-vaccination policy. Strain differences may also play a role. Abortions and mastitis are other common sequels of FMD that very much affects productivity.

When clinical disease develops, the degree of contagiousness peaks just before and during the beginning of the clinical signs and drops rapidly 4–5 days later even though at that time external lesions might still be very evident (Graves, 1971).

During the viremic phase, and thereafter, dependent on the lesions associated with epithelial involvement, virus is present in secretions and excretions (Cottral, 1969; Sellers, 1971). Virus is excreted from all lesions. It is externalized also as an aerosol in exhaled air. Cottral (1969) and Sellers et al. (1971b) reviewed the level of virus in excretions/secretions; unfortunately little information exists on the relative levels of virus from aerosols and secretions for infections of each species with a specific virus strain. Dekker et al. (1996) indicated how differences in aerosol excretion between virus strains, after infection of pigs, could be a major factor in the area at risk around infected pig farms. Virus output varied by as much as 300-fold, with enormous implications for airborne transmission. However virus strains not adapted to produce high level of aerosol excretion such as the Pan-Asia type O strain (Donaldson et al., 2001a), also appear successful in nature. This raises the importance of the level and duration of virus concentrations in excretions/secretions of various host species. Although pigs are major producers of virus aerosols, cattle produce several magnitudes more virus in the epithelium of the tongue, that often sloughs off and is spat out during clinical disease, as well as in saliva, urine, feces and milk. For example, the 10–30 g of tongue blister material which a cow with FMD can spit out may represent not less than a billion infectious units (IU).

These enormous quantities of virus contaminate the environment (boots, clothes, tyres etc.) and, therefore, cattle are probably the main source of environmental contamination.

- FMDV infection is often airborne through the upper and lower respiratory tract.
- FMDV can also enter the new host through abrasions of the mouth epithelium of the skin of feet and udder.
- The peak of infectivity is just prior to or during the development of lesions. Infectivity is much reduced 3–4 days after the lesions develop. Some virus strains are host adapted.
- The clinical manifestations of FMD usually are severe, and sequalae following initial recovery can seriously impair livestock productivity.
- Although pigs are major producers of virus aerosols, cattle produce several magnitudes morevirus. Cattle are probably the main source of environmental FMD contamination.

3. Epidemiology

3.1. Transmission of FMD virus

FMD is very infectious and the virus can be transmitted in many ways. Diseased animals excrete the virus in enormous quantities. The most common way of dissemination is by infected live animals and contami-

nated animal products. Indirect transmission can be by people, vehicles, equipment, hay or bedding contaminated with feces or urine of diseased animals etc. Massive animal movements of all species, as a result of intensive animal husbandry practices are especially hazardous. Over the years illegal activities, have often been attributed to introductions of FMD into non-infected countries, such as the importation of infected meat and feeding to pigs of non-heat treated swill, and the illegal trans-boundary movement of animals. Recently, the danger of spread of FMD by animal movement was clearly illustrated by a shipment of sheep from the UK that disseminated the virus to other animals in a rest-station in western France.

Many authors have described the role of aerosol transmission (Recently, reviewed by Donaldson et al., 2001b). They referred to airborne transmission as 'uncontrollable' spread, while 'controllable' spread is referred to as direct or indirect contact through fomites and people.

3.1.1. Minimum infective dose of FMD virus

Sellers (1971) reviewed the minimum infective dose of FMD virus required to infect susceptible animals of different species and by different routes of exposure and concluded that exposure to even high levels of virus does not necessarily result in infection. The minimal infective dose of a particular virus strain required to infect a susceptible animal varies for different animal species and the route of infection.

Cattle injected in the tongue epithelium with only 1 IU may become infected, while a higher dose of 10–100 IU is required for aerosol exposure.

Pigs need only a very small amount of FMDV (1–10 IU) when inoculated into the skin of the bulb of the heel to set up infection (Burrows, 1966), however a pig would require 1000 or more IU to become infected by the intra-nasal route.

Sheep require 10 000 IU by the intra-nasal and intra-tracheal routes for successful infection (McVicar and Sutmoller, 1968). The low susceptibility and the much lower excretion by sheep, compared to cattle or pigs, likely explains why under the South American conditions FMD is not maintained in sheep.

The usual interpretation of the minimum infective dose is that susceptible animals will not become infected with FMD when exposed to less than the minimum infective dose as is the case with a minimum harmful dose of a chemical contaminant or of radiation (Molak, 1997). For a replicating organism like FMD virus this does not follow, because one infectious FMD virus particle at the right site at the right time will invade a cell, replicate, and produce numerous offspring. These offspring invade other cells, leading to disease. Higher concentrations of virus obviously have a better chance to come in contact, adhere and invade susceptible cells, but exposure of many cells with a low virus concentration also may lead to infection of at least one of those cells. For instance, if the minimum infective dose for a pig by the oral route is 100 000 virus units, feeding 100 pigs with 1 l of milk containing only 500 virus units/l has a probability of about 30% that at least one pig becomes infected (Sutmoller and Vose, 1997). This would initiate an outbreak, even though none of the pigs received the so-called minimum infective dose.

If the amount of agent externalized by an animal is very small, it becomes increasingly difficult to demonstrate the transmission of a disease. The unresolved debate surrounding the infectivity of the persistently infected animal or 'carrier' is a point in case. Risk assessments can estimate the frequency or the chance that minimal amounts of virus will be transmitted and cause disease, taking account of the number of carriers, the probability that carriers contaminate the environment with (minute quantities of) infectious virus and the probability that this would result in an outbreak.

- When many susceptible animals are exposed to less than a minimal infective dose of FMD virus, possibly one of these may become infected. One infected animal in the herd or flock will start an outbreak.

3.1.2. Excretion of FMD virus

FMDV is externalized by lesion material, saliva, milk, feces, urine, semen, nasal discharge and exhaled air. The contagious period usually starts about 24 h prior to the development of clinical signs. The level of transmission drops precipitously 5–7 days after the development of lesions, coinciding with the drop in virus titers and the first development of antibodies (Graves, 1971). Lesions are usually still quite obvious at that time. In estimating the risk of transmission, the first consideration must be the amount of virus that is being released into the environment by infected livestock. Next the probability of the contaminant virus reaching non-infected stock must be taken into account.

It is often stated that pigs give rise to the highest levels of aerosolized virus, followed by cattle and sheep (Sellers et al., 1971b). However, cattle with FMD are usually the greatest producers of FMD virus of all species. It can be estimated that one infected cow, in addition to exhaled air, contaminates the environment with some 10 billion or more IU during the first week of disease with excretions (faeces, urine, milk), salivation, sloughed-off of blister epithelium and vesicular fluid. The total amount of virus excreted by pigs and by sheep is, in general, much smaller than by cattle.

The amount of infectious material released into the environment is also related to the numbers of infected animals. A small herd of cows with low morbidity will probably be much more contagious than that of a large flock of sheep with a high morbidity rate. Although in a

(vaccinated) population with a high level of immunity some sub-clinical infection might occur, very low amounts of virus will be generated and spread into the environment. Serum antibodies limit or inhibit virus replication and generation of aerosols and prevent vesicle formation and excretion from other sites. This also explains why vaccination has frequently been successful despite low levels of bio-security.

The degree of excretion of FMD virus may differ between various strains of the same type of virus. Up to 300-fold difference in level of excretion by pigs by aerosol of strains of virus type O_1 has been reported (Donaldson et al., 1970; Dekker et al., 1996). Spread of the virus is also influenced by individual differences in susceptibility to FMD infection, and in the level of virus excreted by the infected animal, species and possibly, breeds. Excretion by some hosts (e.g. camelids or vaccinated animals that become infected) may be so low that the probability of transmission will be negligible.

- Excretion of virus by cattle, pigs and sheep often peaks before clinical signs occur.
- Cattle produce the greatest total amount of virus and are the major source for the dissemination of FMD.

3.1.3. Dissemination of FMD virus

FMDV may be disseminated through direct contacts between susceptible animals during transport, markets, shows and fairs etc., and through indirect contacts such as farmers, veterinarians, inseminators, contaminated food, trucks used for the transport of livestock etc. Other mechanisms involve the exposure of livestock to contaminated products such as meat, offal and milk. Calves drinking contaminated milk will become infected by this route (Donaldson, 1979). Milk trucks have also been implicated as an important source of virus spread (Sellers et al., 1971a). Pigs, consuming swill containing contaminated meat, organs and offal are particularly at risk. Secondary spread involving feeding of pigs with contaminated skimmed milk was involved in long distance spread to at least two locations in 1967–68 in the UK (Anon, 1969).

Imported meat and meat wrappings accounted for between 97 and 139 (54–77%) of the 179 primary outbreaks in the UK between 1954 and 1967 (Anon, 1969), and primary outbreaks frequently involved pig units. Recent examples have been:

- the Pan-Asia type O outbreak in South Africa in 2000 on a pig farm where swill originating from ships was fed;
- the involvement of a swill-fed pig unit in the spread of FMD during the Pan-Asia type O outbreak in the UK in 2001, although the original source of virus and mode of entry to the farm has not been determined;
- the recent (2000) outbreak of type O in Artigas Department, Uruguay in the border region of Rio Grande do Sul, the most southern State of Brazil, caused by the feeding of contraband slaughterhouse offal to a small number of pigs living in close contact with cattle.

There are many examples where boots, wheels or other objects must have acted as mechanical carriers of the virus. Fogedby (1963) reported a noteworthy incident. In Norway during the Second World War when the Oslo Fjord was blocked by ice and when the country was still free of FMD a shipment of pigs was sent from Denmark to a southern port in Norway and from there by rail to Oslo. The vans that conveyed the pigs were not leak proof. The pigs had symptoms of FMD at arrival in Oslo. Within 1 week after the transport, 10 outbreaks occurred on farms situated along the railway. All farms were within 100 m from the railway track. Only those farms at which people from the farm had crossed the railway were infected. While other farms within the same distance from the railway were not infected. Thus it is likely that boots played a role in bringing the virus onto the farms.

In 1956 there were 5 primary outbreaks in Switzerland along the railway track from Basel to Chiasso at the Italian border. Diseased pigs in transit were the cause.

Even when more obvious sources are controlled, virus may be introduced into a country by contaminated materials. In Scotland in 1908 contaminated hay/straw for ruminant feed was the suspected means of introduction of FMD into the UK. It prompted introduction of the *Foreign Hay and Straw Order* of 1908, permitting only import of hay and straw from FMD free countries.

Imported straw was also assumed to be the source of FMD in Korea in 2000 and might also have been the source of the FMD outbreak in Japan in the spring of 2000 (Sugiura et al., 2001).

Cattle have been infected by entry into decontaminated premises, up to 4 months after culling, cleaning and disinfection had occurred: 12 occurrences of this were reported in the winter of 1967–1968 in the UK. The mechanisms of such infection are unclear, but apparently the virus was able to survive that length of time either in the environment or in some unknown other host.

3.1.3.1. Persistence of FMD virus in the environment. An important factor in the transmission of FMD virus is its relative stability under the right environmental conditions (Cottral, 1969). Relative humidity levels above 55%, cool temperatures and approximately neutral or slightly alkaline conditions favor prolonged survival of infective aerosols and on fomites (Sellers et al., 1971b; Donaldson, 1986).

3.1.3.2. Dissemination of FMD virus by people. People in contact with infected animals are exposed to enormous amounts of virus. Using large-volume air-samplers, Sellers et al. (1971a) found that in a period of 30 min 10 million IU could be collected from the air of a stable housing infected pigs. Consequently, people who work with infected animals or materials will carry FMD virus on their hair and skin and on clothes Therefore, on infected premises it is necessary to wear special clothing that must be changed and left behind and the visiting person should shower when leaving the infected premises. If contaminating virus is not removed by showering and change of clothes there is a high probability that a susceptible contact animal will receive sufficient virus to become infected by fomites, aerosol or handling. In the 1967–1968 epidemic in UK, veterinarians were incriminated in 6 of 51 outbreaks and in 4 other cases non-veterinary personnel were involved (Anon, 1969).

In this context it must be noted that FMDV can be carried for a short period in the throats of people (Sellers et al., 1970). Sampling of human subjects, who had been in contact with diseased animals, showed that virus could be recovered from the nose, throat, and saliva of these people immediately after leaving the room. Nasal swabs of such persons usually contain 100–1000 IU, but some may contain as many as 10 000 IU. A full body shower and change of clothes reduced the amount of virus from nasal swabs by a 100-fold in the 2-h following exposure. When people who had been examining infected animals talked to colleagues for 4 min., virus was subsequently recovered from the nose of one of the colleagues, but the virus could have come from the clothing of the examiners as well as from the exhaled air. No virus could be detected in the upper respiratory tract 24 h after leaving the contaminated room in 7 of the 8 subjects. However, nasal swabs from 1 person that initially contained 5000 IU in the animal room decreased to 100 IU at 24 and 28 h and no virus could be recovered after 48 h. It can be assumed that the amounts of expelled virus decrease proportionally. The probability that FMD virus reaches a susceptible animal is inversely proportional to the distance between the person externalizing the virus and the animal. The greater the distance the lower the probability of infection.

Sellers et al. (1971a) reported that, under exceptional circumstances, FMD virus carried in the nose and throat could be transmitted from man to animals. Shortly after being in contact with infected animals, these researchers discarded clothing, showered and moved to a different compound and succeeded, in transmitting and infecting one steer by examining the animals and at the same time sneezing, snorting, coughing and breathing at the muzzles of the animals. The exposure of each animal to this treatment lasted 30 s for each person. However, in practice, such intimate contacts between people and susceptible cloven-hoofed animals is unlikely but it shows that, for instance, bleeding teams for serological surveillance must carefully observe bio-safety regulations.

There is not much that can be done to decrease the level of contamination of the upper respiratory tract of people exposed to infected animals. Wearing of surgical mouth cloth or an industrial gauze and cotton wool mask reduced the amount of virus inhaled by nearly tenfold but paper masks had no effect (Sellers et al., 1970).

Thus, although FMD virus trapped in the throat of people does not harm people, it can spread to cloven-hoofed animals during a short period of time. People working with infected animals, carcasses or other infected material are therefore required to avoid contact with susceptible cloven-hoofed animals and with people who work with such animals. Persons that might have been exposed to infected animals must avoid direct contact with ruminants for 3–5 days. They should also refrain from visiting farms, shows and markets or abattoirs where cloven-hoofed animals are held. The contamination level of workers handling infected animals could be reduced considerably by the use of heavy or resistant rubber gloves in addition to protective coveralls. For instance, this would prevent the accumulation of heavily contaminated material under the fingernails. Scrubbing of nails before showering is highly recommended.

In epidemic conditions surveillance teams frequently do not know that they have visited infected livestock. If the animals examined are in the incubation phase and not showing signs of FMD, such teams may be a significant source of FMDV transmission through the close oral examination of susceptible ruminants. Where veterinary expertise for surveillance is limited this creates a high-risk situation for spread by surveillance teams. Surveillance teams should therefore work under the assumption that any visited farm is potentially infected.

- FMD is very contagious and spreads in many ways: by direct or indirect contact and through the air by infectious aerosols and fomites.
- Large scale animal movements create a special hazard regarding the spread of FMD.
- Primary infections in FMD free countries have frequently involved pigs; pigs can excrete large quantities of virus (aerosols) before clinical signs develop.
- People can be efficient mechanical transmitters of FMD, in particular if they go from farm to farm and carry out clinical examinations.
- Any person (veterinarians, farmers, sanitary and digester personnel etc.) who had contact with infected

animals or carcasses must take strict bio-safety measures and refrain from contact with susceptible animals for at least 3–5 days.
- Protective clothes and heavy rubber gloves must be worn when handling contaminated materials, particularly infected animals and cadavers.
- Sanitary disposal of contaminated clothing and gloves is essential.

3.1.3.3. Airborne diffusion of FMD virus. Already in the early 1900s it was proposed that FMD virus was exhaled by infected cattle and transported by the wind in saliva particles (Penberthy, 1901) and that German farms had become infected by airborne virus from the Danish islands (Bang, 1912). Possible spread by birds, insects or wind was considered to explain FMD outbreaks in remote places in Ireland (Mettam, 1915).

Since the 1967–1968 epidemic in the UK several authors have suggested that FMD virus can spread by wind (Henderson, 1969; Hugh-Jones and Wright, 1970; Tinline, 1970; Gloster et al., 1981; Gloster, 1982). An analysis of outbreaks indicated that infection of animals downwind was more likely by inhalation than by ingestion. The epidemiological data were integrated with meteorological information to develop numerical models for forecasting and analyzing the airborne spread of FMD (Donaldson, 1983).

Researchers at the Animal Virus Research Institute, Pirbright, UK (Sellers et al., 1971a), obtained infectious aerosols from stables with FMD infected pigs. Pigs were found to give rise to most aerosolized virus, followed by cattle and sheep. Removal of the infected pigs led to an immediate reduction of 25-fold or more in virus concentration, but the infectious virus persisted in the air of the stables for at least 24 h. Spraying down the boxes with water after removal of the infected pigs reduced the concentration of FMD virus in the air, a heavy spray causing a greater fall in infectivity than a light spray. Spraying brought about the greatest reduction of infectivity associated with larger aerosol particles. In contrast, the infectivity associated with the smaller particles remained almost the same (Sellers and Herniman, 1972). This suggests that any intervention that produces an aerosol in the proximity of an animal accommodation might greatly increase the risk of infection originating from virus in milk, urine, feces or the environment. Therefore, aerosol created by high-pressure washing of contaminated vehicles or premises are definitely a hazard. Egress of aerosols containing virus from milk tanks is a recognized risk.

The level of risk is dependant on the quantities of virus aerosols produced and the distance down wind of susceptible animals. Both the disseminating species and the number of the animals at risk play a role. When pigs are involved, more dissemination by aerosol can be expected than with other species.

To minimize the risk of airborne spread, Sellers and Donaldson (1971) recommended the slaughter of affected pigs first, followed by cattle and then sheep. However, it must be remembered that cattle generate the highest total amount of virus and that virus aerosol production by mechanical means or spread by contaminated persons or materials can easily occur.

The minimum dose of FMDV required to infect small ruminants and cattle by aerosol is similar, but since cattle have several times the inhalation volume of adult sheep, their risk of acquiring airborne infection is supposed to be greater. Sellers and Forman (1973) recorded that during the Hampshire epidemic in 1967 the largest cattle herds downwind were those most frequently infected.

Humid and cold weather seems to favor the air-borne dissemination of FMDV (Donaldson, 1972). In cold quiet winter weather, virus aerosols can be carried over smooth surfaces (e.g. over water) by the wind over long distances. Strong winds and rough surfaces (high trees, mountains etc) will reduce the virus concentration in such aerosol clouds. Heavy rains (rainwater often having a $pH < 6.0$) may also reduce the infectivity of virus aerosols. Also, the (superficial) contamination of the environment may be reduced, because FMDV deteriorates quickly under conditions of a low ionic strength and pH, as in rainwater (Bachrach, 1968). In southern Africa the relatively high temperatures and low humidity, rather than ultraviolet light, limits the potential of airborne spread between farms or groups of animals. Therefore, under South African conditions air-borne spread is considered unimportant (Thomson, 1994, 1995). In other tropical regions, however, periods of high humidity can be expected to favor transmission. Historically, in the southern part of South America, FMD is more frequently seen in autumn when high humidity, mild temperature and smooth wind flow are dominants. However, this increase is also due to the fact that movements of young cattle are most intense during that season.

3.1.3.4. Computer and mathematical models to predict FMD dissemination. The likely airborne spread during the British 1967–1968 epidemic has put much emphasis on the importance of the aerosol route in epidemiological models. In these models the role of infected cattle in the prodromal stage or with developing lesions generating enormous amount of virus, albeit not principally by aerosol, seems to be overlooked.

These models assume that, depending of the direction of the wind, so-called 'virus plumes' are created that can infect herds down wind. Quiet winter weather with low wind speeds favors the long distance spread. Strong winds with turbulent air are expected to disperse the aerosols and reduce the area at risk. Daggupaty and Sellers (1990) did a retrospective study of the possible

airborne spread of FMD in Saskatchewan, Canada, 1951–1952. A short-range Gaussian plume dispersion model was used to estimate the concentration of virus downwind and the dose available for individual animals. The investigation suggested that a large virus source due to infected pigs in a feedlot could have been responsible for airborne infection of farms up to 20 km downwind. However, earlier official surveillance reports make no reference to disease in that feedlot.

Sørensen et al. (2000) used computer models that had been developed to simulate the atmospheric dispersion of particles and gases to study the consequences of nuclear accidents. These models simulated the long distance spread of airborne FMD virus from a holding that produced virus aerosols. They concluded that under favorable climatic conditions transmission of FMD virus could have occurred over distances of hundreds of km. Attempts were then made to validate the model by using historical data from FMD outbreaks in France and the UK in 1981. From the simulations they concluded that the concentrations of airborne FMD virus in the plumes generated in France were beneath the infectivity threshold for cattle in the UK. However, in their calculations they did not incorporate the number of potential recipient cattle, which would have reduced the required level for a primary infection considerably. The authors assumed from the analysis: '... the number of pigs infected in France, and therefore the source concentration of airborne virus was probably much higher than was recorded at the time of the outbreak', without giving evidence for that statement.

A similar conclusion was reached from the simulation of Danish outbreaks that were supposed to have been caused by airborne spread from the former German Democratic Republic (GDR) in 1982. The simulation showed that if FMD had been present in at least 1000 clinically diseased pigs in the GDR, sufficient quantities of FMD virus might have reached the first infected premises in Denmark 7–10 days later. This supposition might be true but, as in France, it was not supported by epidemiological data. Again, if the requirements for a primary infection had been compensated for the number of potential recipient cattle the model might have explained the transmission by aerosol.

One of the problems with computer simulations is lack of transparency for the non-mathematician. Another constraint may be the lack of technical knowledge of modelers of the disease in question. Sørensen et al. (2000) stated 'epidemiological expertise would not be required to estimate the amount of virus produced from infected premises'. Recently, Sørensen et al. (2001) reported on more sophisticated computer models to predict the spread of FMD. These were linked to other models so that the predicted 'plumes' could be modified according to topographical conditions. These models are supposed to simulate spread over short or long distances.

Donaldson et al. (2001a) described the relative risks of airborne FMD spread from different species and different numbers of infected animals to susceptible recipient animals at various distances from the source animals. They used experimentally obtained data for the UK 2001 strain as the computer input: the amount of FMDV recovered by air-samplers over a 24-h period were about 1 million virus units per pig and some 50 000 virus units per sheep. They assumed that the amount of aerosol virus generated by cattle would be similar. These amounts were considerably lower than the input data used by Sørensen (2000). The simulation results predicted that one hundred infected pigs were required to transmit sufficient virus to infect cattle up to 2 km away. The simulation also predicted that 100 clinically diseased cattle or sheep could be the source of an airborne infection of cattle at a distance of 200 m downwind. The authors indicated that it was unlikely that there were farms with such large numbers of animals in the prodromal or clinical stage of the disease during the 2001 UK epidemic. The authors concluded that according to the model it is unlikely that infectious aerosols generated by live animals contributed significantly to wind-borne spread of the virus in the UK 2001 outbreak.

Another model on the spread of FMD that greatly influenced the approach of FMD control in Britain was presented by Ferguson et al. (2001). The authors concluded 'Hastening the slaughter of animals with suspected infection is predicted to slow the epidemic, but more drastic action, such as 'ring' culling or vaccination around infection foci, is necessary for more rapid control. Culling is predicted to be more effective than vaccination'. However, the data that were used were from the current epidemic when the large scale circle culling very likely contributed to spread of disease making these data not valid for conclusions on vaccination.

Donaldson et al. (2001b) commented that modeling the spread of FMD using an 'average species' would be an over-simplification. The wide variation between species in terms of quantities of virus excreted, their respective susceptibility to infection and routes of exposure will lead to inaccurate forecasts (Donaldson and Alexanderssen, 2001).

Thus, the value of mathematical epidemiological models for predicting the dissemination of FMD remains to be clarified. Such models must not only consider the dispersion of aerosols generated by exhaled air of diseased animals, but must also take into account all of the other factors mentioned in this and previous sections of this chapter. Of particular importance is the relatively small amount of virus produced in exhaled

aerosols by cattle compared to the enormous quantity of FMD in excretions/secretions (Sellers et al., 1971a).

- High-pressure sprays used for cleaning infected premises and holding facilities, trucks and equipment to haul cadavers of infected animals may generate large amounts of infectious aerosols.
- Milk trucks collecting milk from infected premises may be an important source mechanical transmission and of infectious aerosols.
- Pigs create more infectious aerosols than cattle or sheep.
- The total amount of infectivity from aerosols and lesions together is at least one magnitude higher for cattle than for pigs and is several magnitudes higher for cattle than for sheep.
- Computer models used to predict the airborne spread of FMD can be a useful tools, but the results of the simulations must be interpreted with caution.

3.1.4. Risk of disseminating FMD virus by wildlife and vermin

In another chapter Thomson et al. discuss the role of wildlife in maintenance and spread of FMD. Here we only want to note the role that deer may play in the epidemiology of FMD in temperate climatic zones.

The recent FMD epidemic in the UK has led to the concern that wildlife species (particularly deer) were perhaps playing a role in the maintenance of the epidemic. Similar concerns regarding deer are being expressed in The Netherlands, which also had a FMD epidemic in 2001 (Sutmoller, 2001).

The susceptibility of free-living deer in the UK was studied experimentally in the 1970s following the 1967/1968 epidemic (Forman and Gibbs, 1974; Forman et al., 1974; Gibbs et al., 1974) and in the USA by McVicar et al. (1974). It was observed that deer were susceptible to FMDV by exposure to infected cattle and were able to transmit FMD to their own species and to cattle and sheep. In view of the limited geographical distribution of wild populations in the UK at that time, it was thought that deer would not be important species in the maintenance of FMD in the event of an epidemic.

In the intervening period between these studies in the 1970s and today, the deer populations in many temperate zones of the world have risen significantly. Consequently, the validity of the earlier conclusions on the role of deer in the epidemiology of FMD has to be re-evaluated.

Deer range in fields between farms and visit premises and yards with animal feed and slurry, etc. If FMDV is present in the environment the chance that free roaming deer become infected is many magnitudes greater than the chance of exposure to infection of livestock in pens or stables. Deer might act as sentinels for FMDV, but this does not seem to have happened in UK or The Netherlands. However, if FMDV were to infect the deer population it would be difficult to control the disease in that species. The spread of FMD in the deer population would depend on population density and social organization. Most likely FMD in deer would run its natural course and peter out after several weeks or months.

If stamping-out of livestock were the method of choice to control an outbreak, re-population of the area with susceptible livestock would be risky, because the virus may still be present in the area for some length of time in the deer population. Alternatively, all livestock in the area could be vaccinated or re-vaccinated, preferably within 3 months to obtain an optimum population immunity. The advantage of such an approach would be that re-population of the area with vaccinated livestock would not need to wait for the disappearance of the infection in the deer population.

The opinion that FMD infected deer constitutes a low risk because sick animals hide and probably die, is not valid. Like cattle or sheep, susceptible deer are very infectious prior to the development of lesions while they still actively move and graze. Also deer with sub-clinical or minor lesions will still roam around.

Hedgehogs were shown to be susceptible to FMDV and developed typical blisters (Gibbs, 1931; Edwards, 1934). Hedgehogs spread the virus to other hedgehogs and could presumably infect livestock. Similarly, in South America the capybara (*Hydrochoerus hydrocheris*), a large rodent that lives in groups in close contact with grazing livestock, has been shown to develop clinical disease (Rosenberg and Gomes, 1977). Capybaras were exposed to FMDV type O_1 by the intramuscular route and virus was isolated from most of the organs collected from four animals slaughtered 24–48 h post-inoculation. The remaining capybaras developed vesicular lesions on their feet between 72 and 96 h post-infection and virus was shed with feces until at least 10 days post-infection. The susceptibility of capybaras to this strain of FMDV by intramuscular inoculation does not necessarily mean that they constitutes an actual virus reservoir and the epidemiological significance of FMD in the species is unknown. Most likely cattle are the primary host and capybaras a dead-end host.

Rats, mice and birds might transmit the disease mechanically. Mechanical transmission requires contamination of the animal or bird, transport of the virus for varying distances and availability of sufficient virus for infection of a susceptible host. FMDV has been found in rat feces and urine and in bird droppings. The maximum titer found in rat feces was 1000 ID_{50} per g (Capel-Edwards, 1970). Sellers et al. (1971b) states that the feces from 160 rats would be required to attain sufficient virus to infect cattle by ingestion. However, as explained earlier, the chance of infection will also depend on the numbers of animals contacting the infectious source, raising the likelihood of a transmis-

sion occurring with sources containing low virus loads. It has also been suggested that contamination of dust by rat feces or urine may lead to infection by inhalation. In this instance only a few IU would be required.

It must be emphasized that the role of vermin such as rats is insignificant under conditions of extensive cattle management as occur in South America.

- During epizootics, spread of FMD by deer or other susceptible wildlife species must receive serious consideration. However, if these animals are left in their territory (without hunting and chasing) the disease is likely to fade out.
- Vermin might spread FMD from infected premises, particularly when cleaning and decontamination have eliminated normally available feed sources.

3.2. Persistent infection, the carrier problem

For more than 100 years, it has been suspected that cattle recovered from FMD could initiate outbreaks of the disease. (Reviewed by Fogedby, 1963 Sutmoller et al., 1967; Salt, 1993). This suspicion was raised because of outbreaks that occurred in countries or areas free of FMD following the introduction of healthy convalescent cattle. One of the first cases described occurred in Sweden in 1897 and 1898, when 2 bulls imported from The Netherlands caused a FMD outbreak several months after their introduction into the herds.

Bürgi (1928) surveyed a number of outbreaks in Switzerland from 1920 to 1927. In his opinion about 3% of recovered cattle remained carriers and excreted FMD virus intermittently for at least 5–6 months and probably up to 1 year. Flückiger (1934) pointed out the possible role of carriers in other species such as goats.

Another incident was reported from the UK after the serious 1922–1924 epizootic with over 4000 outbreaks. The traditional slaughter policy was partly abandoned and 105 infected farms were isolated, without slaughter. Eight months later a convalescent bull and a heifer from these farms, were sold to a district where no disease had been observed. After their introduction into the new herd FMD occurred and was attributed to these animals (Fogedby, 1963).

Imported Brazilian Zebu carrier cattle were probably the source of a Mexican outbreak in the late 40s (Sutmoller et al., 1967; Casas Olascoaga et al., 1999). However, these few but interesting reports must be set against the fact that in many countries after outbreaks and before the introduction of vaccination, *millions* of recovered animals were probably carriers. The introduction of vaccination drastically reduced the incidence and morbidity rates and the amount of virus circulating in the livestock population. In countries in which FMD was controlled by the use of systematic vaccination of the cattle population only, transmission of disease from carrier cattle to non-vaccinated or other susceptible species has not been observed. Also, in situations in which, after a period of 'freedom of FMD', vaccination was discontinued there has been no case of FMD linked to the existence of carriers.

3.2.1. Definition

Animals in which FMD virus persists in the pharyngeal region for more than 4 weeks after the infection (persistently infected animals) are called 'carriers' (Sutmoller et al., 1968; Salt, 1993). Martin et al. (1987) assigned the term 'carrier' only to animals that are able to disseminate an infection, yet remain clinically without symptoms of disease. In that regard the long-term FMD 'carrier' does not fit that definition, because apart from historical evidence during the time that FMD was rampant worldwide, transmission of FMD has never been convincingly demonstrated under controlled conditions.

To add to the confusion in terminology, animals in the incubation stage of FMD or those with sub-clinical disease have sometimes been called 'carriers'. Because this has nothing to do with persistent infection, the term carrier should not be used for these cases.

For these reasons, we will use the first definition: carriers are convalescent or sub-clinically infected animals in which FMDV persists in the pharyngeal region for more than 4 weeks after infection. In this chapter we will use terms 'carriers' and 'persistently infection animal' interchangeably, but with the understanding that this does not imply that such animals are contagious.

3.2.2. Detection of persistent infection

3.2.2.1. Virus isolation. The process of screening for persistently infected cattle by the collection of probang samples from the throat was developed in The Netherlands in 1959 (Bekkum et al., 1959) and has been applied as a routine procedure in almost all other countries with FMD outbreaks. Fluid and cellular debris from the pharynx and upper oesophagus (OP fluid) are collected with a small beaker attached to a bowed wire handle (so-called probang or probang-cup) originally developed by Grac and Tallgren (Bekkum et al., 1959; Sutmoller et al., 1967; Hedger and Stubbins, 1971)

At PANAFTOSA and the Plum Island Animal Disease Center isolation of FMDV from OP fluid has routinely been done by the emulsification of 3–15 ml OP fluid specimen with trifluorotrichloroethane (TTE) to liberate the virus from antibodies or other inhibitors (Sutmoller et al., 1967). Early after infection, TTE treatment did not increase the FMD virus titers of the OP fluid. However, from 14 days post-infection onwards titers of the treated OP fluid increase 10 to 100-fold over the untreated sample. McVicar and Sutmoller (1974)

observed virus neutralization activity by local antibodies in the OP fluid at that time.

Other institutes, such as the Animal Virus Research Institute in Pirbright, UK, attempted to isolate FMD virus from smaller volumes of OP fluid, usually not treated with TTE, using more sensitive calf thyroid cell cultures. The choice of cell system and sample volume influences virus isolation and these cells have shown superior sensitivity for FMD virus (Snowdon, 1966). The use of pig kidney or calf kidney cells grown in large stationary or roller bottles (Sutmoller and Cottral, 1967) makes it possible to test 5–10 ml or more of each OP specimen, which is impossible with thyroid cells grown in tubes.

Unfortunately, there has never been a valid comparison of both methods on bovine OP fluid. There is only one report (Hancock and Prado, 1993) comparing the two methods, but the comparison was done at different laboratories and on OP fluids from sheep. In this particular instance the system using calf thyroid cells gave more positive results. Likely, the combination of the TTE treatment of OP fluid and virus isolation in calf thyroid cell would be the most sensitive system.

The probang method has also been applied for sheep and goats (Burrows, 1966; McVicar and Sutmoller, 1968) and camelids (llamas and alpacas) (Lubroth and Yedloutschnig, 1987), deer, antelopes, capibaras etc. (Rosenberg and Gomes, 1977). Usually, these probangs were simply smaller versions of the cattle probang, sometimes, as in the case of sheep, with adaptations to facilitate the removal of the instrument from the animal's throat.

3.2.2.2. Detection of nucleic acid. Virus isolation from probang samples requires careful handling of OP specimen and a bio-safety laboratory for virus isolation. Nucleic acid detection techniques offer potential advantages. Simple and prolonged preservation in the field of viral RNA of samples is possible, even for 4 weeks at 37 °C (Hofmann et al., 2000), while the risk of false negatives associated with poor sample handling is limited. Because virus, if present in the specimen, would be inactivated by RNA extraction it would be acceptable to use lower level bio-security facilities (regional laboratories). Robotic stations for RNA extraction and application of the 'reverse transcriptase polymarse chain reaction' (RT-PCR) exist and are used in screening for human viruses.

Several studies have compared RT-PCR methods with FMDV isolation; sensitive methods (nested or RT-PCR–ELISA) usually reach sensitivities similar to, or greater than virus isolation techniques (Donn et al., 1994; Murphy et al., 1994; Moss and Haas, 1998); a particularly high sensitivity was reported with a RT-PCR–ELISA (Callens et al., 1998). A one tube RT-PCR method (Tosh et al., 1997) reduces assay complexity and potential operator error. For detection of persistently infected animals in the field, a high throughput, high sensitivity robotic RT-PCR method would be needed, especially if intended as an adjunct, or a replacement for serology.

Callahan et al. (2002) report a rapid detection of FMDV using a portable real-time RT-PCR assay. Results indicated that viral RNA could be consistently detected over a seven-log range, the lowest of which corresponded to as few as 10–100 RNA/volume tested. The assay is reported to be capable of detecting all seven serotypes of FMDV. The test detected viral RNA in pre-clinical samples from steers, sheep and pigs that later developed FMD. The test can be performed in 2 h or less on a portable instrument and samples can be held at ambient temperatures. The development of a rapid and simple test for the detection of FMDV antigen using 'Clearview chromatographic strip test technology' for field application is described (Scott et al., 2001). It remains to be seen how well the method would work for probang samples from carrier animals.

During the tail end of the virus recovery curve of persistently infected animals, virus isolation may become irregular, whether by virus isolation or by the use of PCR, because occasionally virus concentrations in the OP fluid fall below detectable levels. Since risk of carriers causing infection is already very small and this risk is probably inversely related to the amount of externalized infective virus, the epidemiological significance of carriers in this phase will be close to zero. Several authors have commented that such very sensitive methods may distort the importance of the result (e.g. Callens et al., 1998).

The availability of a pen-side device for diagnosis would reduce the necessity for sending routine diagnostic samples to FMD laboratories and thereby reduce the delay in diagnosis, which can in some areas be considerable.

3.2.3. Persistent infection in different species

3.2.3.1. Cattle. In the late 50 and early 60s it was shown that in countries with endemic FMD, virus could be isolated from the mucous and cell debris from oro-pharyngeal mucosa in as much as half of the cattle population (Bekkum et al., 1959; Sutmoller and Gagerro, 1965). In general, this was found to be true for all seven serotypes of FMD (Thomson, 1996). However, dependent on the virus strain, type of cattle and local circumstances figures may vary and individual cattle will show differences in duration and level of virus excretion. However, the long-term persistence of FMDV in the pharyngeal area of cattle is measured in years rather than in months.

3.2.3.2. Sheep and goats. Persistent infection in sheep and goats has been less extensively studied than in cattle. In general, sheep and goats less frequently become a carrier and for shorter periods than cattle (Burrows, 1968b) often lasting for only 1–5 months. However, in some animals the carrier state may last up to 12 months (McVicar and Sutmoller, 1969, Sharma, 1978). Unequivocal evidence of transmission from carrier sheep or goats has neither been demonstrated under experimental conditions nor in the field.

In field studies carried out in the Soviet Union (Sarkisyan et al., 1973) India, (Singh, 1979) in Kenya (Anderson et al., 1976), and Turkey (Gurhan et al., 1993) the frequencies of the occurrence of carriers in sheep varied from zero to approximately 30%. The frequency in goats seems to be lower and of shorter duration than in sheep (Anderson et al., 1976; Singh, 1979)

3.2.3.3. Pigs. Using conventional tests, convalescent or vaccinated pigs have never been shown to be persistently infected. Nor have convalescent pigs been incriminated as a cause of outbreaks. This has been challenged recently, by Mezencio et al. (1999) who reported the identification of viral RNA in the blood of recovered swine and fluctuations of virus neutralization activity in the sera shortly after the re-appearance of virus RNA in the serum. This RNA was presumed to be in the form of complexes with the high levels of antibody. However, the epidemiological significance of these findings seem to be insignificant.

3.2.3.4. Camelids. Llamas do not appear to be long-term carriers of FMDV, since virus could not be detected in infected llamas beyond 14 days post-exposure (Lubroth and Yedloutschnig, 1987). OP fluids and sera from 460 llamas, 30 sheep, and 60 cattle were tested from four farms in Argentina, where FMD had been diagnosed in cattle 1–14 months earlier. Carrier virus and antibodies were detected only in the cattle (David et al., 1993).

These same authors also performed a large experimental study by exposing llamas to FMD infected pigs and cattle. No virus could be isolated from OP fluids of the llamas beyond 14 days post-exposure and no transmission of virus to the contact llamas occurred. On day 60 of the experiment 40 susceptible livestock were added (cattle, sheep, goats and pigs) and again no virus transmission took place. Thus, the llamas were poorly susceptible to FMD and the few infected llamas only had virus in their pharyngeal mucosa for a short time. Moreover, recovered animals did not transmit virus to other susceptible species Clearly, to become infected llama's need exceptional infection pressure. The lack of sero-conversion, when exposed to normal outbreak situations, indicates that llama's do not play a role in FMD epidemics.

3.2.3.5. Wildlife. Forman and Gibbs (1974) studied the carrier state in three species of deer in the UK (Red, Fallow and Roe). FMDV was seldom recovered form the pharynx from red and roe deer beyond 14 days post-exposure. Fallow deer carried the virus for a minimum of 5 weeks. Two months after exposure 6 from the12 deer were still positive.

White tailed deer in the USA carried FMD virus regularly up to 5 weeks after exposure, but one deer had virus in the OP fluid as long as 11 weeks post-exposure (McVicar et al., 1974).

Most free-living populations of African buffalo *(Syncerus caffer)* in southern Africa have high infection rates with SAT-type FMD viruses (Esterhuysen et al., 1995). In the Kruger National Park in South Africa rates of persistent infection of buffalo are as high as 60% (Hedger, 1972; Hedger 1976; Anderson et al., 1979). Individual animals may maintain the infection for periods of at least 5 years (Condy et al., 1985) but in most buffalo the rates peak in the 1–3 year age-group (Hedger, 1976). Individual buffalo may be persistently infected with more than one type of FMDV in the pharyngeal region (Hedger, 1972; Anderson et al., 1979). For more on the African buffalo see the chapter of Thomson et al.

Viral persistence in antelope has only been reported in kudu *(Tragelaphus strepsiceros)* in which virus was detected for almost 5 months after artificial infection (Hedger, 1972). In the same investigation two wildebeest (*Connochaetes taurinus*) had SAT1 virus in their OP secretions for 45 days after infection but in a subsequent study (Anderson et al., 1975) no persistence in this species was demonstrable. Transitory persistence—up to 56 days—was found in sable antelope (*Hippotragus niger*) (Ferris et al., 1989). Experimental studies have failed to provide evidence of viral persistence in impala (*Aepyceros melampus*) (Hedger, 1972; Anderson et al., 1975) which, among antelope in southern Africa, are the most frequently affected species (Thomson, 1996).

The capybara (*Hydrochoerus hydrochoeris*) is a large rodent that also lives in close proximity with cattle in extensive areas of South America. Experimentally these animals were been shown to be susceptible to FMD, but not to become carriers (Rosenberg and Gomes, 1977).

- In epidemiological terms a 'carrier' is a persistently infected animal able to disseminate that infection, yet remain clinically without symptoms of the disease. With the exception of the African buffalo, the FMD 'carrier' does not fit that definition because so far there is no real prove that it is contagious.
- The carrier state often occurs in FMD convalescent animals, particularly in cattle and the Cape buffalo.

The duration of the carrier state depends on the individual animal, animal species, and virus strain. Among the domestic species the largest number of carriers occurs in cattle followed by sheep and goats. Neither pigs nor camelids become carriers.

3.2.4. Serological tests to detect potential carriers after vaccination

When animals are immunized with vaccines prepared from purified antigen, such as the vaccines from the European Vaccine Bank, antibodies are raised against the virus coat proteins only. When an animal becomes infected and virus replication takes place, either clinically or sub-clinically, antibodies will be raised not only against the virus particle but also against the proteins that are required for the replication of the virus, the so-called non-structural proteins (NSP). The latter enable discrimination between antibodies induced by vaccination and antibodies induced by infection. Immunized animals that are infected and subsequently become carriers will also develop antibodies against NSP, allowing carrier animals to be identified in vaccinated stock. However, repeated vaccination with non-purified vaccines will also raise antibodies against NSPs, in which that case, anti-NSP antibodies are not necessarily associated with potential carriers. Therefore, if non-purified vaccines have been used, screening for farms with carriers can be carried out on a herd basis by testing young non-vaccinated or once vaccinated animals only.

The agar-gel immuno-diffusion (AGID) test using virus infection-associated antigen (VIA, in fact a mixture of NSPs), isolated from virus cultures, was the first test to be developed (Cowan and Graves, 1969; McVicar and Sutmoller, 1970). Later a liquid phase ELISA which also detected VIA was developed by Alonso et al. (1990) and showed superior sensitivity to the AGID. The test has been used successfully on a herd basis in epidemiological surveys in South America to detect FMDV activity in livestock populations (Rosenberg, 1976; Casas Olascoaga et al., 1999).

Recently, more sensitive tests have been developed. One of these tests, the enzyme-linked immuno-electrotransfer blot (EITB) assay uses a set of purified recombinant DNA derived NSP antigens as serological probes, instead of the traditional VIA (Bergmann et al., 1993, 1996). These authers compared the VIA antibody tests, the EITB test, and the virus isolation assay (from OP fluid) using sequentially collected samples from experimentally infected cattle (Bergmann et al., 1993, 1996). The EITB test was highly sensitive and specific for known positive and negative anti-sera. A set of anti-sera against a number of other, non-FMD viruses were negative. For the detection of past FMD infection it was clearly superior to the other (VIA) tests. Subsequently, EITB assay has been used extensively by South American countries with excellent results (Bergmann et al., 1998).

Brocchi et al. (1998) used monoclonal antibodies against the 3ABC non-structural FMDV proteins in a blocking ELISA. High specificity and sensitivity was obtained in naïve, vaccinated or cattle infected by tongue inoculation. When vaccinated cattle were challenged, 69 of 78 animals developed antibodies against 3ABC protein. Of the remaining nine cattle, seven were clinically protected and did not show local lesions at the site of infection on the tongue, although viral multiplication in pharyngeal tissue cannot be excluded. Only two animals with lesions did not sero-convert.

MacKay et al. (1998) looked for antibodies against 3D, 3AB and 3ABC, all proteins being prepared by recombinant DNA-technology. They found that the majority of vaccinated protected animals, when inoculated with virus in the tongue, developed an antibody response to NSP, particularly 3ABC. However, the carrier state was demonstrated in some vaccinated and protected animals in which no antibody response to any of the NSPs could be detected.

Bergmann et al. (1998) concluded that there was excellent correlation between results obtained with the EITB and the 3ABC ELISA. In vaccinated cattle slightly more false positives were found with the ELISA. It was suggested that some vaccines contain residual NSP, and that recent vaccination with these vaccines could result in false positive tests. Therefore, emergency vaccines should be prepared from purified FMD antigens only. Absence of antibody responses to NSP should be demonstrable for such vaccines.

The highly purified 3ABC (Bergmann et al., 2000) and the 3ABC monoclonal antibody trapping ELISAs (DeDiego et al., 1997) have found application throughout the world in countries which have used emergency vaccination campaigns.

In the documentation that the governments of Argentina, Uruguay and Brazil presented to OIE to obtain the recognition of the FMD free status, serological surveys using the VIA and EITB test results, were important instruments to show the absence of viral activity in the livestock population.

Serotype A outbreaks in Albania and Macedonia were rapidly controlled by vaccines supplied by the EU. Both Brocchi et al. (1998) and Sørensen (2000) screened for remaining foci of infection and, in general, the results from cattle sera were compatible with post-vaccination antibodies. However, in sheep or goats indication of previous infection i.e. antibodies against 3AB and 3ABC were found in sera collected in five different villages. The a-NSP antibodies clustered in villages where clinical disease had been found but also enabled detection of four other villages close to the infected ones which contained animals with a-NSP antibodies, indicating value in its use.

The emergency vaccination program against FMD in Korea in 2000 limited the number of outbreaks to 15 cases only. The vaccination was followed by screening with NSP tests and probang testing of the few positive herd tests. Korea regained the status of 'freedom from FMD without vaccination' in September 2001 (Lee, 2000a,b).

Recently, a commercial test kit has been introduced that screens for the presence of antibodies against the 3 ABC proteins. The kit has been developed in close cooperation with 2 European FMD laboratories and its development has been sponsored by the EU (Anon, 1998).

It has been suggested that measuring secretory anti-FMD virus IgA might be used as a complementary test to determine the existence of persistently infected animals (Archetti et al., 1995; Haas et al., 2001). However, at present insufficient information is available to allow discrimination between non-persistently infected vaccinated animals and persistently infected vaccinated animals on that basis.

- EITB tests and ELISA measuring a-NSP antibodies are useful serological indicators of current and past infection.
- These tests are not 100% sensitive in individual animals, but perform very well if used for screening on a herd basis; combinations of tests can raise the sensitivity yet further.
- Viral isolation (probang) tests and PCR to detect viral RNA can be used to confirm the presence of persistent infection in individual animals. The significance of the detection of viral RNA by PCR remains to be determined.
- Vaccines prepared from presently available highly purified FMD antigens-like those in vaccine banks—will, in combination with tests for antibodies against NSP, perform like a 'marker' vaccine.
- Serological surveillance for anti-NSP antibodies after vaccination does not require bio-security laboratories.
- International experience and data from around the world show that, after emergency vaccination, efficient screening programs can be designed to determine the prevalence of a-NSP positive animals. The risk that vaccinated carriers would not be detected by such screening programs is very low.

3.2.5. Role of persistent infection in the epidemiology of FMD

Earlier in this chapter we mentioned the few historical cases in which healthy convalescent cattle were likely to have caused outbreaks in clean herds. In most of these cases bulls were involved and the significance of this observation might be worth investigating. However, there are numerous cases in which large numbers of convalescent cattle introduced into non-protected herds did not cause new outbreaks (Fogedby, 1963). In Europe FMD was controlled by vaccination of cattle only. Certainly in the years that this policy was introduced (the 50 and the 60s) there must have been many natural carriers and there were many mixed farms with unvaccinated pigs and sheep that did not become infected. Also, calves that gradually lost the protection of maternal antibodies did not become infected by their carrier mothers. In South American countries FMD disappeared following vaccination of cattle only, even though millions of vaccinated cattle, which probably included large numbers of carriers shared pastures with millions of unvaccinated animals.

There were only a few SAT2 outbreaks in cattle in Zimbabwe between 1983 and 1991 in which a role of vaccinated carriers cannot be excluded (Vosloo et al., 1992; Thomson, 1996). However, the African circumstances with extensive breeding do not exclude virus transmission by other means e.g. visitors and vehicles coming from game parks with endemic FMD, connections of the animal caretakers, contaminated materials, improperly inactivated vaccine etc.

A possible infection mechanism was proposed by Bastos et al. (1999). They suggested that sexual transmission of the disease from carrier buffalo bulls to domestic cows could occur, because SAT3 virus was isolated from both semen and from sheath washes from a naturally infected African buffalo. This was considered a persistent infection since the virus genotype had not been currently circulating in the buffalo herd. The virus in the sheath-wash of the buffalo bull presumably originated from the mucosal epithelial tissues of the prepuce.

In contrast to cattle, buffalo can maintain the SAT virus types in small isolated populations. It is thought that carrier buffalo's infect buffalo calves when they loose the protection of the maternal antibodies and that the infected calves infect other game (kudu, impala etc) in the area and likely reactivate the carrier status of the herd.

Thus, SAT serotype viruses have developed an intimate relationship with the Cape buffalo. It is unknown whether this relationship depends on the SAT virus, on the buffalo, or both. To our knowledge there are no reports from African countries of other 'classical' serotypes (O, A, and C) becoming endemic in the buffalo population through the carrier status. However, it is not known whether SAT viruses possess special characteristics that make them such good 'carrier' viruses in the buffalo.

The belief in the role of carriers as disseminators of FMD was originally supported by the observation that coughing by persistently infected cattle spread FMDV into the environment that proved fully virulent when inoculated into pigs (Sutmoller et al., 1968). At that

time, the pathogenesis of FMD was not yet fully understood and the concepts of a 'minimum infective dose' for inhaled FMD virus had not been fully developed.

Several experiments were carried out in attempts to show that carriers could indeed initiate disease. However, close contact exposure of susceptible animals (cattle and pigs) to carriers failed to transmit disease. No transmission of disease occurred even under circumstances where the carrier cattle and the susceptible contacts were stressed in various ways e.g. traumatizing of the hoofs of the contact pigs in order to provide a suitable entry site for the virus (Sutmoller and McVicar (1972). Several other trials also failed (Bekkum et al., 1966; Kaaden et al., 1972; Bauer et al., 1977). Even cattle persistently infected with FMDV when superinfected with virulent IBR virus failed to transmit FMDV to susceptible cattle in contact (McVicar et al., 1977). In fact, FMD virus rapidly became undetectable in the carrier cattle,. It is a fair assumption that many more attempts of transmission by carriers have been made and not reported because of the negative findings. Clearly, transmission must be a very rare event and it is not known whether it happens by a special set of circumstances (e.g. a carrier bull mating with an insufficiently protected cow) or whether it merely is an infrequent stochastic phenomenon (Thomson, 1996) or both.

There is no evidence that 'stress' induces virus excretion. In contrast to some other viral infections (e.g. herpesviruses), that are activated by cortico-steroids, such treatments of FMD carriers have resulted in decreased virus titre in OP fluids (Sutmoller et al., 1968). Also Ilott et al. (1997) reported that dexamethasone inhibits virus production and the secretory IgA response in OP fluid of cattle persistently infected with FMD virus.

Attempts to provoke transmission via stress of carrier animals under experimental conditions have also failed. Thus, there is no support from experimental data for the statements made by Government officials in the UK in 2001 regarding the risk from stressed animals.

A persistently infected animal may remain a carrier after vaccination or a vaccinated animal exposed to FMDV may become a carrier. However, there is evidence that such carriers have lower virus titers in their OP fluid and that the carrier state often is of shorter duration then that of the convalescent animal (Anderson et al., 1974). Therefore, if transmission by 'natural' (convalescent) carriers is an infrequent stochastic phenomenon representing a low risk, the risk of vaccinated carriers transmitting disease is probably considerable lower and close to zero. Anyhow, it would explain why in Europe and South America carrier cattle did not cause outbreaks in pigs or sheep after the introduction of the vaccination of cattle (see above).

Hedger (1970) found that carriers may develop in incompletely vaccinated herds with little or no disease after exposure to FMDV during field outbreaks. However, these carriers did not disseminate FMDV to other vaccinated contiguous herds. The authors concluded that after an outbreak there is little likelihood of virus spreading in a vaccinated population under natural conditions.

No evidence of problems caused by vaccinated carriers has ever been observed. The outbreaks in South America were always caused by animals with active infection, originating from endemic or sporadically infected areas or from active foci (Casas Olascoaga et al., 1999).

Sheep are of particular importance because of their involvement in the 2001 UK FMD episode. There is an interesting reference to Greece, 1994–1995 (cited by Barnet and Cox, 1999) when the virus might have continued as an asymptomatic infection in sheep.

Further reports on the role of sheep and goats, showing the absence of transmission by carriers are by Anderson et al. (1976), Sharma (1978), Bauer et al. (1977) and Callens et al. (1998). To our knowledge, recovered small ruminants have not acted as a source of infection to initiate new cases of FMD, neither under natural conditions anywhere in the world nor under experimental conditions and carrier goats have never been shown to infect susceptible livestock.

Unfortunately, in spite of all the evidence to the contrary, the idea that FMD carriers represent a considerable risk of transmission of the disease appears to be persistent and remains the basis for current rules and regulations for international trade in animals and animal product. In addition, because of the trade consequences, the fact that vaccinated animals can also become carriers has practically banned the use of vaccines when appropriate in outbreak situations.

- Vaccination by itself does not cause the carrier state. A persistently infected animal after vaccination may remain a carrier. A vaccinated animal must be exposed to FMDV to become a carrier. Vaccination suppresses the amount of FMDV in the environment and thus the number of carriers in the population.
- The risk that carrier animals transmit FMD to susceptible livestock by direct contact is very low. The risk that a carrier animal produces an infectious aerosol is negligible or close to zero.
- There are no indications that vaccinated carrier cattle ever caused new outbreaks. Carriers among vaccinated livestock have not hampered FMD eradication efforts.
- Tests to discriminate between carriers and vaccinated animals have been widely used and the results are, in general, internationally accepted. In addition vaccines prepared from purified antigens will not induce

antibody to NSP that interfere with the interpretation of the serological surveys.
- If an FMD outbreak is controlled by vaccination, testing for antibodies against NSP amongst vaccinated livestock contributes even further to risk reduction. A statistically valid serological survey for anti-virus antibodies of the surveillance zone (SZ) around the vaccination zone may, together with the results of the a-NSP test, verify a FMD free status.
- Risk management based on science-based risk assessments must deal with the hypothetical risk of vaccinated carriers. The present zero risk approach is inappropriate.

4. Vaccine

4.1. Developments and application of vaccines in Europe

The introduction of vaccines gradually changed the FMD scene in Europe. The Vallée–Schmidt–Waldmann concept for the preparation of inactivated FMD vaccines was developed before the Second World War. With this technique, virus was obtained from tongue epithelium of deliberately infected cattle (Waldmann et al., 1937, 1941). This so-called 'Nature Virus' was the only source of viral antigen until the early 1950s, when Frenkel, 1947, Frenkel, 1951 made their discovery that the virus could be produced in vitro in slices of bovine tongue epithelium collected at slaughterhouses. The technique enabled large scale vaccine production and The Netherlands was the first European country in which (in 1952) all cattle were vaccinated, first against type O and A and the next year also against type C. From then on there were only a few outbreaks, mostly at the borders of The Netherlands and around Amsterdam where the FMD institute which produced vaccine was located. Other countries, such as France, followed the Dutch example.

Due to their favorable geographic position the UK, Ireland, and the Scandinavian countries could manage without vaccination and by 'stamping out' in case of an outbreak. Denmark vaccinated only at its German border but in the 70s, when Germany became completely disease free, Denmark also discontinued this limited vaccination to enable export to the US and Japan.

Although the success of cattle vaccination changed the incidence figures drastically, it was the middle 60s before all European countries shared a strategic vaccination policy. The role of vaccination in the control of European FMD in the 1960 and 70s was reviewed by Boldrini, 1978.

Large scale vaccine production based on BHK suspension cultures (Mowat and Chapman, 1962; Capstick et al., 1965; Telling and Elsworth, 1965) or on BHK roller bottles (Ubertini et al., 1968) additionally supplied vaccine in sufficient quantity.

Still, occasionally in the 60s the disease caused severe problems, especially in non-vaccinated pigs e.g. in The Netherlands, Belgium, and France, particularly in areas with intense pig breeding industries. However, concentrated Frenkel vaccines proved effective in protecting pigs (Bekkum et al., 1967), and, together with veterinary control measures, Europe became FMD free and with the exception of a large outbreak in pigs in France in 1980 and of 2 Italian outbreaks in the middle 80s, Europe remained free of the disease. The severe Italian outbreaks were mainly due to changes in the bureaucratic system that hampered the annual vaccination programs. When these outbreaks were brought under control vaccination was discontinued in Europe in 1991.

The last outbreak in France, in 1980, was probably caused by the use of improperly inactivated vaccine (King et al., 1981). Although in most laboratories the Waldmann formula for virus inactivation (by formaldehyde) was followed exactly, vaccine producers did not realize that components in the medium may interfere with the inactivation process (Barteling and Woortmeijer, 1984). Consequently, media that differ significantly from the original formulation can influence the safety of vaccines and sometimes vaccines were improperly inactivated and so caused post-vaccination outbreaks (King et al., 1981; Beck and Strohmaier, 1987). Later on, in the 80s most vaccine production laboratories changed to inactivation by aziridins, binary ethylene immine (BEI) in particular, giving a safer product (Bahnemann, 1975). Recently, a synergistic effect has been reported if formaldehyde and BEI are used simultaneously, resulting in a more than 100-fold increased inactivation rate and, therefore, improved safety (Barteling and Ismael Cassim, 2000). So far, the method has only been applied in practice for a labile (SAT2) vaccine strain with favorable results (Dr B. Dungu, personal communication).

The aqueous aluminum hydroxide vaccines did not protect pigs satisfactory, even though outbreaks were finally controlled with a concentrated product, and alternative adjuvant formulations were tried. Emulsification of the antigen in mineral oil according to Freunds' formula of produced a vaccine that protected pigs very well (Michelsen, 1961; Cunliffe and Graves, 1963; McKercher and Farris, 1967). Others found that di-ethyl aminoethyl dextran also worked well in pigs (Wittmann, 1970 Wittmann, 1972) if added to aluminum hydroxide vaccines (Leeuw et al., 1979). However the oil emulsion vaccines are currently preferred for the vaccination of pigs and in outbreak situations because they can be used for the protection of all species (Graves et al., 1968, for review see McKercher and Graves, 1977; Casas Olascoaga, 1978). Oil-adjuvant vaccines induce,

in general, a longer lasting immune response than aqueous vaccines.

Although oil-adjuvant vaccines have never been used on a large scale in Europe, the last outbreak (in Italy) on a large pig holding was controlled by vaccination of all the pigs with an aqueous, aluminum hydroxide-based vaccine emulsified in oil. Only the pigs in affected pens were killed and the last case occurred 5 days after the vaccination (Amadori, personal communication).

Oil emulsion vaccines have also been used for the control of the outbreaks in Albania and Macedonia and for the control of the outbreak in The Netherlands in 2001.

- FMD was eradicated from Europe by the systematic application of classical aqueous aluminum hydroxide-saponin vaccines.
- Oil-adjuvant vaccines were not used extensively in Europe.

4.2. Developments and application of vaccines in South America

In the early days of vaccine usage Waldmann vaccines and later on Frenkel-type vaccines were produced in several countries of South America (Rosenbusch, 1960). In the 70 and 80s huge vaccine production plants based on BHK suspension cultures were constructed to supply the hundreds millions of doses needed for the vaccination campaigns.

Until the mid-70s, FMD control was based on mass vaccination campaigns using aqueous vaccines. However, the vaccines were of questionable quality and were not always available when needed. Also, there was limited control on the extent and manner of their use. All this resulted in low vaccination coverage so that the policy served to maintain the epidemiological status quo and, at best, limited morbidity of the disease. Many of the present misconceptions surrounding the vaccination issue originate from that time. An exception was Chile which was, in 1981, the first South American country to eradicate the disease, using a mass vaccination strategy. This was a result of the use of good quality, well-controlled aqueous vaccine, the relatively isolated location of the country, and epidemiological conditions that facilitated regional quarantine measures.

In most other South American countries farmers, in general, did not receive many benefits from the FMD vaccination campaigns and the obligation to vaccinate was felt mostly as a need to obtain the documents required for animal movements. In several countries there was a basic lack of community participation due to the paternalistic approach by the governmental services.

In the 80s it became clear that under the South American conditions oil-adjuvant vaccines were preferable to aqueous vaccines (Casas Olascoaga, 1978; Goic Martinic, 1988; Dora et al., 1984; Gomes et al., 1980). In South America Abaracon et al. (1980) research on oil-adjuvant had started in the 70s at PANAFTOSA in Rio de Janeiro in collaboration with the Plum Island Animal Disease (cited in PIADC/PANAFTOSA, 1975a,b). During the next two decades researchers at PANAFTOSA, with the support of Veterinary Services of several countries of South America, further investigated and developed vaccine technology (reviewed by Casas Olascoaga et al., 1999). This included the study of different formulations, industrial production procedures, antigen inactivation, different oil-adjuvant and emulsifier formulations, shelf life, duration of immunity, immunological coverage, most appropriate vaccine application schedules, potency testing and the protection conferred in cattle, sheep and pigs. This laboratory research was complemented by a series of safety and efficacy trials in cattle, sheep and swine and pilot studies in the field. The use of the vaccine strains was coordinated by PANAFTOSA. Only a few well performing broadly protective strains were allowed for vaccine production.

4.2.1. Protection of cattle

Oil-adjuvant FMD vaccines induce at least comparable levels of protection (at 4 weeks post-vaccination) and more prolonged antibody responses than the classical aluminum hydroxide-saponin vaccines (Auge de Mello et al., 1977; Auge de Mello, 1982). Revaccination produces a very long sustained immunity (Auge de Mello and Gomes, 1977; Auge de Mello et al., 1980; Gomes et al., 1980). Also, young cattle with maternal antibodies responded either by developing antibody or by became sensitized so that a second vaccination acted as a booster (Auge de Mello et al., 1975, 1989; Gomes, 1984).

4.2.2. Protection of pigs

Neither the type of emulsion nor different routes of application influenced the immune response in pigs (Auge de Mello and Gomes, 1978; Auge de Mello et al., 1978; Gomes, 1979). However, macroscopic and histological examinations of pigs showed the advantage of the double emulsion formulation (Mebus and Auge de Mello, 1981; McKercher and Gailiunas, 1969). Furthermore, oil-adjuvant vaccines protected pigs very well after contact exposure or after challenge by inoculation. Young piglets also reacted very well, and after one vaccination sufficient antibodies persisted for the duration of the (short) life of fattening pigs. Revaccination of sows produced a prolonged duration of high antibody levels (Gomes, 1980). A solid immune status of the sows and, consequently, a relatively long lasting maternal immunity of the fattening pigs can also prevent FMD on the farm.

Field application of the vaccine in the face of an outbreak stopped the spread of the disease in pigs (Gomes, 1979). In South America systematic vaccination of swine is not generally used but it can be used strategically in high-risk areas (Auge de Mello, 1979).

4.2.3. Protection of sheep

Early studies in sheep showed that they respond with even higher and more prolonged antibody levels than cattle and resist FMD exposure (PIADC/PANAFTOSA, 1975; PIADC/PANAFTOSA, 1975a; PIADC/PANAFTOSA, 1975b). Furthermore, no adverse tissue reaction at the site of inoculation of the vaccine was observed (Dias et al., 1981). However, vaccination of sheep was not included in South America in the successful systematic vaccination programs.

Later, oil-adjuvant vaccine was applied in large scale field studies in different South American countries, like Brazil, Argentina, Uruguay, Peru, Ecuador and Colombia (Casas Olascoaga et al., 1990, 1999). These field studies, including nearly two decades of observation, showed the efficacy of the oil-adjuvant vaccine under a variety of epidemiological and ecological, tropical and temperate climatic conditions.

The introduction of potent, well-controlled oil-adjuvant vaccines changed the attitude of the farmers who became co-operative after experiencing the benefits of vaccination. Uruguay and, somewhat later, Argentina, Paraguay, and some Brazilian states followed Chili in eradicating the disease. The successful eradication of FMD in more than 150 million cattle in South America was accomplished by the use of oil-adjuvant vaccines. The products from these vaccinated animals were safe. Many millions of tons of meat of vaccinated cattle were exported to Europe without causing a single outbreak of FMD.

- FMD control and eradication programs in South American countries have applied the systematic vaccination of cattle only using well-controlled oil-adjuvant vaccines. In several countries this was done with great success resulting in complete eradication of FMD.
- In general, oil-adjuvant vaccines produce a longer lasting immunity than aluminum hydroxide-saponine vaccines. They protect cattle of different breeds under a variety of epidemiological and ecological, tropical and temperate climatic conditions.
- Swine can also be protected successfully, but in South America, in general, the systematic vaccination of swine is not used. However, it can be used strategically in high-risk areas.
- Sheep can be very well protected with FMD oil-adjuvant vaccine and a long lasting immunity has been demonstrated in this species. As in Europe, vaccination of sheep is not included in South America in systematic vaccination programs.

4.3. Production and application of vaccines in other parts of the world

In many parts of the world a status quo is maintained. Although regular vaccination may be carried out on large dairy farms and industrial pig holdings, often the backyard farmer or pastoralist cannot afford the costs of vaccination and the disease is maintained in the area. Moreover, in many countries the price of the locally produced vaccine must be kept low, sometimes resulting in low quality vaccines and, consequently, improper protection. This might give mutants of the virus chances to develop into new field strains causing new problems.

Except for the South American production, most of the vaccines produced are of the aqueous types. There are large vaccine plants in Turkey, Thailand, India, and the former Soviet Union, some of them under the wings of internationally operating companies. Also some smaller plants are located in the Middle East and in some countries in the Southern cone of Africa producing the SAT-type vaccines.

In many Asian countries in particular there is a need for more and better vaccines. However, sufficient infrastructure of veterinary service is required to organize vaccination campaigns. Above all the farmers must support vaccination. To obtain and maintain such support, vaccines must protect and their quality must be indisputable. This can only be obtained if the quality of both home produced and of imported vaccines is checked by an independent authority.

4.4. Vaccine banks

When the disease disappeared from Europe, preparedness for new outbreaks became increasingly important. In that context special attention was paid to the protection of pigs because they were not sufficiently protected by the classical aqueous vaccines. With the intensifying pig breeding industry it was clear that in the event of an outbreak the availability of large quantities of vaccine might be needed for this species. To that end inactivated antigen was purified and concentrated and stored at ultra-low temperatures (Barteling and de Leeuw, 1979; Duchesne et al., 1982). From these antigens (oil-emulsion) vaccines can be rapidly formulated; vaccines that protect both cattle and pigs (Barteling and de Leeuw, 1979; Doel and David, 1984).

For these purposes international vaccine banks were established, first in Pirbright (UK). The UK and a number of other countries participated in this bank,

which contained 500 000 dose per type. This would only be sufficient for a first strike in case of a limited outbreak and certainly would not cover a more widespread outbreak in an area with a high density pig population.

When a non-vaccination policy was adopted, European vaccine banks were installed storing a total of 5 million doses of the main serotypes. The US, Mexico, and Canada also share a vaccine bank.

For the international vaccine banks highly potent vaccines of at least 6 PD_{50} (standard is 3 PD_{50}) are required to cover a broader variation of field strains that might occur. The vaccines contained in the European vaccine banks, for instance, all performed better than 10 PD_{50}. These vaccines induced high antibody levels that not only neutralized the vaccine strain but also a wide variety of field strains (Barteling et al., 1979), suggesting protection against a wide variety of strains. However, so far these data are not supported by challenge experiments.

Several studies with potent vaccines, as contained in the international vaccine banks, showed that soon after vaccination (3–5 days) pigs and cattle are protected against contact challenge (Doel et al., 1994; Swam et al., 1994; Salt et al., 1995, 1997, 1998; Cox et al., 1999). These data are in agreement with experiences in the field, as mentioned above for a large pig holding during the last outbreak in Italy (Amadori, personal communication). Also, in The Netherlands the last case in the vaccinated area was 5 days after the vaccination had been carried out with a double oil emulsion type vaccine.

The antigens stored in the International Vaccine Bank at Pirbright and in the European Vaccine Banks can be formulated into a (double) oil-emulsion vaccine. Such vaccines are suited to immunize all susceptible species. For the advances in vaccine technology over the past decades in relation to antigen production, purification and inactivation, we also refer to Barteling and Vreeswijk (1991) and to the chapter by T. Doel.

- FMD antigen stored in (international) vaccine banks can be formulated into oil-adjuvant vaccines of high-potency that can be used to protect all species susceptible to FMD.
- Early protection afforded by such FMD vaccines permits their use for (emergency) ring vaccinations to rapidly control outbreaks.
- To control outbreaks, large stocks of concentrated purified antigens must be available for the rapid preparation of (potent) emergency vaccines.
- After emergency vaccination remaining foci of active virus must be traced by screening vaccinated herds for antibodies against NSP. Therefore, stored concentrated antigens must be sufficiently purified so as not to induce antibodies against NSP.

5. FMD Control and eradication strategies in recent epidemics

Control and eradication strategies have employed different means to obtain the containment of FMDV produced in the course of an epidemic and to prevent the spread of the virus from infected farms to others. The first step in any control program must be an absolute stand-still of all livestock movement in the infected area followed by stamping-out of the infected animals and their immediate contacts. The biggest challenge is the destruction of the infected animals, without the spread of FMDV by heavy equipment, (untrained) people, hauling and disposal of infected cadavers. Cleaning and disinfection of contaminated premises, trucks etc. create additional hazards.

The use of vaccine as an additional and effective tool to contain the outbreak must be considered at an early stage. The selection, based on technical considerations, of the optimal strategy to minimize disruption of the local and national social–economic structure must be weighted against the expected duration of restriction and loss of export trade and markets.

In this section we describe how the UK, the Netherlands and countries in South America have dealt with FMD epidemics in 2001.

In the UK eradication was accomplished by stamping-out and so-called ‘circle culling’. The disease was finally brought under control but at an extremely high cost in terms of animal and human welfare and high socio-economic losses.

In The Netherlands the disease was introduced from the UK after a circuitous route through France. It most likely arrived in The Netherlands in the form of subclinically infected calves. Vaccination and the slaughter of all vaccinated animals followed stamping-out of the first cases. This effectively stopped the spread of the disease, but led to the mass killing of all healthy vaccinated stock.

South American countries that are traditional meat exporters controlled severe FMD epidemics by re-instating vaccination programs. Emphasis will be on Uruguay, where the decision to use strategic vaccination was taken quickly because of opposition of farmers to stamping-out.

5.1. FMD in the UK, 2001

FMD was confirmed in the UK on 20th February 2001, 1 day after suspected FMD was reported in pigs with clinical signs at an abattoir in Essex. The strain concerned was genotyped as the Pan-Asian topotype of type O FMDV. The date of first infection in the UK is unclear, backtracing of infection suggests that the

primary cases of infection may have occurred around the start of February in swill-fed pigs at a farm with a poor record of health and welfare, 350 km distant from the abatoir.

Although there has been considerable speculation that FMD was present in sheep in the UK before February, evidence for this is weak. Subsequent spread from the pig farm to sheep on nearby mixed livestock farms probably occurred via the airborne route. Some of these sheep, possibly only 16 infected animals, were bought by dealers and moved through several markets including the busiest sheep market in Europe in the middle of February, resulting in dissemination in widespread locations from the south of Scotland to the south-west of England, and via traded animals to northern Ireland, and France, and eventually, The Netherlands.

An export ban on British livestock was placed from the 22nd February, and a national animal movement standstill placed by British authorities on the 24th. However, infection had already been shipped to Northern Ireland and to France via illegally imported sheep. All European countries that had imported British animals began a testing programme or precautionary slaughter. Infection spread from Northern Ireland to the republic of Ireland (22nd March) but the single outbreak was controlled by slaughter. In the UK, back-tracing suggests that up to 74 infected premises existed at the time of the national movement standstill, and that the number of final cases might have been considerably reduced if a national standstill had been placed on the 20th (Anon, 2001).

Several factors contributed to the scale of the subsequent epidemic (Fig. 1)

- a steady rise in the density of sheep in the UK as a result of subsidy payments;
- many farmers had turned into the export of live sheep because BSE caused enormous problems in beef trade;
- several very questionable, if not illegal practices involving sheep movement which made the process of tracing sheep movements exceptionally difficult, such as short term lodging of animals on farms to gain subsidy payments; and
- unrecorded sales of sheep moved through markets.

The climatic conditions of February and March were near ideal for transmission, and it is extremely likely that this exacerbated the human element in spreading infection by farm activities, across boundaries, and by disease control activities. The weather and time of year also contributed to severe animal welfare problems, particularly for in-lamb ewes and newborn animals.

The veterinary response has also been widely criticised, with evidence that delay in implementing controls in the first 1–2 months (movement restrictions, and in reporting to slaughter times) contributed to the scale of the epidemic. As the epidemic progressed, the role of cattle became more evident and some argue that the species was the most important overall (Keeling et al., 2001). The majority of the cases occurred in March and April and peaked in late March with over 50 cases per day.

On the advice of epidemiologists using computer models, the slaughter policy was revised from culling only of infected premises and animals on 'dangerous contacts', to slaughter of animals on neighboring (contiguous) farms to an infected farm. In the worst

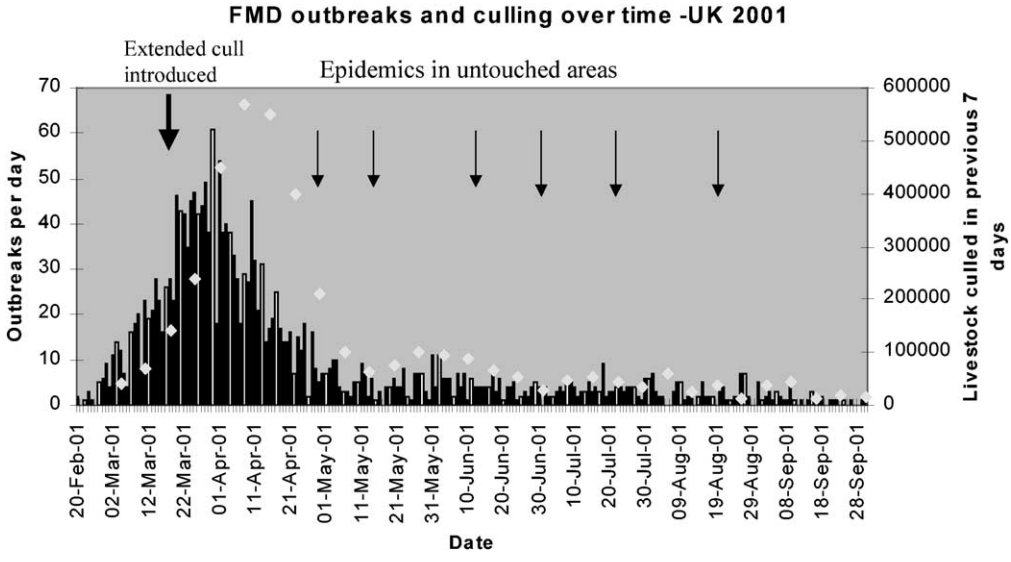

Fig. 1. Time-course of reported FMD cases per day and the number of animals slaughtered per week in control operations. Slaughter data exclude animals culled for welfare reasons. The approximate first date of cases in epidemics occurring in areas which did not have cases before May, is shown as arrows.

affected region, all sheep were culled within 3 km of an infected farm. Additionally some farmers offered their animals for slaughter under voluntary schemes, and a huge number applied for slaughter for welfare reasons, since the movement restrictions had resulted in overcrowding and near starvation conditions.

The revised culling policy (Fig. 1) had enormous logistical implications for the disposal of animals that had not been thought through. Although announced on 15th march it took another 2–3 weeks to implement, with the army providing logistical support. Farmers were outraged at the prospect of slaughter of herds and flocks not showing signs of infection, or where a plausible route of infection had not been demonstrated.

Disposal of the carcasses also presented major problems, since possible BSE infection in older cattle restricted the use of burial, and rendering plant capacity was quickly exceeded. Disposal of cattle by burning on pyres provoked public outrage. Later, to cope with the huge cull of sheep in some regions, enormous burial pits were used with potentially long-term environmental risks.

Farmers were resigned to accept the policy since they had been lead to believe by Government or farmer leaders that vaccination would not provide an alternative control and eradication option. Not until 1 month into the epidemic did the UK request and gain permission from the European Community (EC) to vaccinate cattle in two regions of England, but the price of not culling such animals was to be drastic additional measures on livestock movements and export. Although in mid-April attempts were belatedly made by Government to convince farmers leaders that vaccination of cattle in two major hot-spots would assist disease control, the National Farmer's Union remained implacably opposed.

From late March, local veterinary decision making in disease control was replaced by centralised control, provoking profound misgiving by veterinarians at the 'carnage by computer' that they were expected to administer. The automatic slaughter of cattle (as well as sheep and other species) on neighbouring farms was most controversial, and briefly rescinded in late April.

The confirmed outbreaks per day fell during April as the mass slaughter programme was implemented and fell to single figures of outbreaks per day in May. However the epidemic was far from over; an extended 'tail' lasted until the end of September, with infection 'jumping' to new areas in the north of England. Outbreaks after the start of May had a higher ratio of animals culled on neighborhood farms than those on infected premises. These later 'jumps' of infection have been attributed to poor farmer bio-security or the licensed movement of animals incubating infection.

Initial sero-diagnostic capacity was limited (400 sample per week), limiting the feasibility of identifying infected flocks except by clinical means or the hit-or-miss process of sampling animals for virus/antigens. After April capacity for serology grew as additional bio-secure facilities undertook tests, rising to over 100 000 per week in October, as blood testing became a major tool in lifting of restrictions on protection zone and SZ, on the licensing of movement of animals, and on re-stocking. Enforcement of farm isolation and bio-security was given little serious attention until July–August, and undoubtedly poor bio-security contributed to the size and duration of the epidemic, exacerbated by the fragmentation of farms into disconnected parcels serviced by very few, but very mobile, farm staff. A very significant number of outbreaks (100 between March 5th and July 9th) were attributed to spread by people or vehicles (Gibbens et al., 2001). This amounted to over 70% of all outbreaks for which the route was identified as 'non-local transmission'. In the same period the mechanism of spread was not identified in 91% of outbreaks (1418/1559) which occurred within 3 km of another outbreak, but was called 'local spread', and undoubtedly also involved bio-security breaches. At the time of writing (February, 2002) there have been no outbreaks since 30th September.

In retrospect, the multiple and widespread number of infected premises presented enormous problems for a veterinary service which had not encountered FMD in mainland UK for 33 years. Prior to the first case being reported, infection clustered in 12 locations, with an estimated 74 infected premises across the UK, and over 40 in Cumbria alone (DEFRA, 200126/10/01). However the total number of reported outbreaks (2030) by 26th October, 2001 indicates that control on spread from these infected premises was poor, especially in the first month. However, with a few exceptions the movement restrictions did prevent the extension of infection to virgin areas with high-risk concentrations of livestock, especially dairy and pigs.

Culling of livestock occurred on 9576 farms (= 7% of 140 012 farms placed under restrictions), with estimates of the impact to the UK economy of up to 20 billion pounds, mainly in the non-agricultural sector. The overall ratio of farms slaughtered-out in relation to infected premises was 3.71, but varied from almost 1 at the start to high ratios in April, and after a resurgence, in May. The true number of infected farms is not known since only a proportion of herds culled under the 'contiguous cull' after late March were tested; one study indicated about 25% of non-IP culled farms had evidence of infection, or possibly about 1800 farms, giving a total of approximately 3800 infected premises. In the first month of the epidemic, culling took place on less than 50 farms per day, but this rose to a peak of about 280 farms per day in the week ending 15th April, before dropping to < 50 per day by the week ending 2nd May.

On 94% of infected premises on which outbreaks occurred a single species was involved even though 70% of IPs had both cattle and sheep (Gibbens et al., 2001). The average delay between reporting and slaughter was reduced during the epidemic, from 2.9 days in late February to 1.1 days in early April (Woolhouse et al., 2001). However, the averages mask significant local and regional variation and well reported extreme cases occurred, particularly during the escalation phase in late February and March. Almost 2 million animals were slaughtered between 25th March and 22nd of April. By 26th October 2001, 3 910 000 animals had been slaughtered in disease control, of which 15.3% were cattle (600 000), 81% sheep (3 172 000), 3.55% pigs (139 000). Other animals were goats (3000), deer (1000) and 200 others (mainly camelids). In addition 1.82 million animals were culled under welfare schemes, bringing the total to 5.73 million. The true number is higher—some estimate 8 million in productive animal lives lost—given the number of pregnant ewes culled, and young progeny which were not counted. Almost twice the numbers of pigs were slaughtered on welfare grounds (273 234) than in disease control operations, and applications for slaughter of 1.2 million animals on welfare grounds were rejected. The impact of the cull has been particularly strong on hill sheep, which are adapted to their environment and possess valuable behavioral and disease resistance qualities; 12 of 50 rare breeds of sheep were threatened by reduction of the gene pool through culling.

- The level of surveillance for FMD in each country must be proportionate to the international FMD situation and the legal, and illegal risk of importation.
- Trade in live animals with countries that are 'FMD free without vaccination' is not a zero risk option—FMD was undetected in Britain for 2–3 weeks and spread to 3 other European countries.
- The risk associated with countries must be related to their performance in FMD surveillance and not simply their 'FMD free status'—FMD can occur anywhere.
- In free trade regions (EU etc.), control of animal movements after FMD has been confirmed must be immediate and wide-spread—e.g. EU wide, until the forward and backward tracing has been completed and risk assessed.
- Long distance air-borne spread of the Pan-Asian type O strain was not a significant feature of the epidemic.
- Bio-security measures must be enforced by the authorities from day 1 of an epidemic and be adequate to efficiently control the disease.
- FMD control policies can be extremely damaging to the non-agricultural population and the choice of policy for FMD control must consider the full range of stakeholders in the rural economy.

5.2. FMD in The Netherlands

Compared to the British drama it was a relatively small outbreak. It started shortly after the detection of FMD in Britain. Calves were imported from Ireland on the 22nd of February 2001. The following day the shipment of calves was delivered at 4 locations in The Netherlands. According to European legislation, they had to make a stop-over in the rest-station at Mayenne in the West of France, the place where on March 13th the first outbreak of FMD on mainland Europe was notified. After the confirmation of FMD in Mayenne this shipment of calves was traced by the Dutch authorities.

On the 17th of March at two locations, just south of the major branches of the River Rhine, there was a suspicion of FMD on two neighbouring farms. The cattle on thesefarms, were culled, as were the livestock of the surrounding farms in a 1-km circle and of contact farms, almost 30 in total. Long after the culling, laboratory tests turned out to be negative (April 6th) and the area was declared free of FMD. The Netherlands applied regionalisation and, while in other areas the disease was still going on, the South of the Netherlands could re-start its international trade.

At another farm in the eastern part of the infected area, just West of the Yssel, the Northern branch of the River Rhine, 5 calves had been delivered from the Mayenne transport. The calves had no clinical signs of FMD, but on March 17th goats on the same farm developed FMD, which was confirmed by laboratory tests 5 days later. Three of the five calves had antibodies to FMDV despite having no clinical symptoms. From an epidemiological aspect it is unfortunate that the nature of the antibodies, whether 'early' (IgM) or 'late' (IgG), has not been identified. With hindsight it is also regrettable that the calves were not probang sampled to determine whether they carried FMDV in their throats. We only can assume at this point that the disease probably entered The Netherlands by fattening calves with a sub-clinical form of FMD that spread to adjacent goats, possibly by the farmer, aerosols, feces, or other excretions of the calves and/or fomites.

On the 21st of March there were two more outbreaks in neighboring villages, one at a farm belonging to a brother of the first infected farmer and the other across the river. This was just outside what later became 'the Triangle', an area with sides of approximately 25 km, in a district called De Veluwe in the center of the Netherlands. After that, outbreaks occurred as daily incidences and it was clear that the current policy was not working, even though 1 week after the first outbreak the 1-km 'culling' circle was 'upgraded' to a 2-km circle. Farming

practice and infrastructure, with a high cattle density, many small hobby farmers with sheep and goats, much social and animal trade interactions, made control of the disease by culling additionally difficult.

At that time there were two outbreak locations outside the Triangle. Goats were the source of the outbreak in one location northwest of the Triangle. According to the reports these goats had antibodies. For the other, located southwest of the triangle, the source could not be determined. Clinical signs were very vague, and although some small (5–10 mm) erosive lesions and fevers were reported for over a week, none of the 460 calves on the farm had antibodies. When laboratory tests from one of the samples of one of the animals were reported to be positive, the Veterinary Service applied stamping-out, in a 2-km circle, affecting 200 farms, for the greater part calf fattening farms but also many dairy farms. Over 50 000 animals were culled. Suppressive vaccination was applied for the remaining livestock. Farmers were not convinced there really was FMD on their farms and there was a lot of resistance under the farmers against the cull of their animals. This case caused an extensive political debate and many cases in court.

Because of the high animal population density in The Netherlands it was decided to destroy the FMD carcasses by rendering. However, this required long distance hauling of the cadavers to a rendering plant in the North of the country, with all of the attendant risks of environmental contamination. Later, after vaccination, livestock was also slaughtered in an abattoir within the vaccination area.

At the beginning of April there were also two outbreaks on dairy farms located in the North of The Netherlands, about 100 km from the nearest focus, but relatively close to the rendering plant. The affected farms, as well as the surrounding farms were all large holdings and rather isolated. Here, culling apparently worked well and there were no further cases. There were no indications of FMD found at the other culled farms. It was speculated that the nearby rendering plant, in which all suspected FMD carcasses were destroyed, might have been the source of the outbreak. Indeed, there is a legitimate question whether this rendering plant, and rendering plants in general, maintain sufficient bio-containment to handle FMD carcasses.

Even by the end of March it had become clear that the stamping-out method was not working and, particularly because the rendering capacity proved insufficient, the Ministry decided to vaccinate all livestock in the Triangle. Farmers in the Triangle were first left with the impression that vaccinated animals might not be culled and reacted positively. However, 1 week after the vaccination was carried out, the 'protective' vaccination was turned into a 'suppressive' one on economic grounds, meaning that all the vaccinated animals had to be killed.

As elsewhere in the world, vaccination worked well. The remaining 115 000 animals in the Triangle were vaccinated in 3 days and the last case of clinical FMD occurred 5 days later.). There was one more outbreak east of the river Yssel, outside the vaccination zone close to one of the first outbreaks. This outbreak was eradicated by culling. By the end of May all the vaccinated animals had been slaughtered and on June 16th The Netherlands got its FMD free status back. It was an episode that lasted 1 month with a toll of 26 directly affected farms and 270 000 animals killed on thousands of other farms.

5.2.1. *Spread from The Netherlands?*

FMD remained undetected for 3 weeks in The Netherlands. Therefore, it is amazing that it did not spread into Europe, considering all the export and movement of livestock from The Netherlands into the rest of the EU. In the week preceding the first outbreak (notification) for instance 30 000 pigs had been exported to Germany. On April 4th, there were two farms with 'serious clinical symptoms' in an area where many of the Dutch pigs had been imported. All livestock on the farms together with that of contact farms were culled. Two weeks later the laboratory tests turned out to be negative and, fortunately, Germany could maintain its 'FMD-free' status.

- The decision to complement the stamping-out policy with suppressive vaccination of all livestock resulted in rapid control and eradication of FMD. Insufficient rendering capacity was the main reason for vaccination. Export and trade were the main considerations for the killing of the healthy vaccinated livestock.
- Transport of FMD infected animals and hauling of infected carcasses must be done in sealed containers to prevent escape of virus. Rendering of FMD-infected carcasses must be done under strict bio-safety conditions.

5.3. *FMD in the southern region of South America*

In this section we will summarize the FMD situation in the Southern part of the South American Continent, with emphasis on the way Uruguay dealt with the extensive 2001 outbreak.

In historical background (Section 1.1) we have already described how during the period of 1965–1985, formal national FMD control programs were organized and implemented with the technical cooperation of the PANAFTOSA and with the financial support of the Inter American Development Bank (IDB).

In 1981 Chile was the first country in South America to be declared officially free of FMD. The eradication strategy was based on the gradual elimination of the disease working in a south-to-north direction; applying quarantine measures across different regions of the country and following a vaccination campaign using aqueous vaccines of guaranteed quality, mainly produced in Uruguay. The country suffered two re-introductions of FMD caused by illegal animal movements: one in March 1984 and the second one in March 1987. Both episodes were eradicated by stamping-out and quarantine measures. Chile has been recognized by OIE as free of FMD since 1988.

In 1987, the Fifth Inter-American Meeting at the Ministerial Level requested PAHO through the PANAFTOSA and the South American FMD Commission (COSALFA) to prepare a hemispheric program for eradication of FMD. Also a Hemispheric Committee representing the countries from Southern Cone, Andean Subregion, Mesomerica, the Caribbean and North America was created. In July, 1988 the 'Hemispheric Program for the Eradication of FMD in South America was approved by the countries of the Americas.

At the same time, in 1987, an 'International Technical Cooperation Agreement between the Governments of Argentina, Brazil, Uruguay and the PAHO' was signed and implemented for the control and eradication of FMD in the River Plate Basin. In the period 1988–2000 this project played a key role for the eradication of FMD in the entire region.

In the nineties the EU decision to stop general vaccination of the cattle population provided an important stimulus for the meat exporting countries of South American to proceed with the eradication of FMD from the region. As a result the following countries were recognized by OIE as 'FMD free countries where vaccination is practised': Uruguay (1994), Argentina (1997), Paraguay (1997). In 1998, a zone comprising the southern states of Brazil (Rio Grande do Sul and Santa Catarina) aquired the status of free zone where vaccination is practised'. In 1999, other free zone in Central and Western Regions (Parana, Sao Paulo, Minas Gerais, Goias, Mato Grosso States and the Federal District) followed. In 2000, the states of Mato Grasso do Sul, Tocantins, Minas Gerais of the Central-Western Region and the States of Espirito Santo, Rio de Janeiro, Bahia and Sergipe of the Eastern Region were also included by OIE as 'FMD free zones where vaccination is practised'. This created in the South Cone of South America a FMD free region (with vaccination) with a total of some 193 million cattle.

In order to obtain the status of 'FMD free without vaccination' in 1994 Uruguay discontinued vaccination. This favored status was obtained in1996.

For the same reason Argentina and Paraguay discontinued vaccination in 1999 and Rio Grande do Sul in Brazil followed in 2000. However, this exposed the region to severe FMD risks as a consequence of the following factors:

- Progressive loss of protection against FMD of large cattle populations over a short period of time.
- Continual danger of spread of FMD from regional remaining endemic areas into the susceptible livestock population.
- Movement of large numbers of susceptible young cattle to fattening areas.
- Failing epidemiological surveillance and communication systems between countries and increased vulnerability to spread of disease across country borders.
- Deficiencies in the first barrier of sanitary prevention (movement controls) because of serious limitations in human resources and insufficient logistical support.
- Substantial reduction in communication, education and training of public and private human resources and veterinary services.
- Insufficient assessment of risks and incomplete contingency plans for the transition to a non-vaccination policy.
- Dominance of political and commercial interests over sanitary requirements.
- Serious omissions in the fulfillment of the norms of the International Animal Health Code (OIE, 1999) and international agreements, as well as lack of transparency and veracity of the information on the real sanitary situation.

In short, in a few years time the whole veterinary infrastructure guaranteeing awareness, alertness, and sufficient surveillance was weakened. As a consequence, FMD invaded the southern region of South America and only Chile has maintained (since 1988) its status as a FMD free country.

5.3.1. *Argentina*

In April 2001, the government of Argentina notified the OIE of the epidemic of type A virus of FMD in its territory. The country lost the status as a FMD free country and a new FMD eradication plan was adopted based on massive vaccination of the cattle population that was re-started that month.

5.3.2. *Bolivia*

The country has endemic areas with FMD types O and A. Presently, Bolivia is structuring its surveillance system and vaccination programme.

5.3.3. *Brazil*

In August 2000, the zone comprising the states of Rio Grande do Sul and Santa Catarina had its FMD free

status suspended, due to a FMD outbreaks by type O_1. The outbreaks were eradicated by stamping-out and quarantine measures applied in eight municipalities of the State. A total of 8183 cattle, 2107 pigs, 783 sheep and a few goats were destroyed.

In May 2001 Rio Grande do Sul suffered another introduction of FMD, this time of type A, as a consequence of the expansion of the FMD epidemic of that type in Argentina with spread to Uruguay. Early in May 2001, the State of Rio Grande do Sul re-established systematic vaccination of the whole cattle population.

Thirty outbreaks were notified and the last one occurred in July 2001. Initially, 1164 cattle, 29 sheep and 2 pigs were destroyed but there was strong resistance by the farmers to the stamping-out policy. Later 11 670 contact animals were slaughtered locally in order to comply with OIE regulations.

5.3.4. Paraguay

In October 2000, the Government of Paraguay, in view of the dissemination of FMD in adjacent areas and the vulnerability of its sanitary infrastructure, re-instated general vaccination of its cattle population. At present, Paraguay maintains its status as country free of FMD with vaccination.

5.3.5. Uruguay

Livestock breeding is the principal agricultural activity of Uruguay and the mainstay of the economy. It represents more than 65 percent of the Uruguayan exports in the form of meat, wool, milk, hides and industrialized agriculture by-products. The area of Uruguay is 176 215 km^2 (approximately the size of the UK) of which the greater part is developed for agriculture. The human population is 3.15 million. In 2001 there were 10.6 million cattle, 12.1 million sheep, 480 000 horses, and only 270 000 pigs on 57 100 farms and developed land surface was 16.4 million ha. Cattle and sheep share pastures thanks to the moderate climate and the even distribution of precipitation throughout the year. This mixed grazing and the presence of unvaccinated sheep did not hamper the eradication of FMD by vaccination of the cattle only. The introduction of general cattle vaccination in the late 80s was successful despite the fact that sheep outnumbered cattle by almost threefold.

In October 2000 FMD subtype O_1 was diagnosed on a farm, in Artigas department, very close to the frontier with Rio Grande do Sul, Brazil. The affected herd had 322 cattle, 63 sheep and 47 pigs. The disease first appeared in the pigs with high mortality of suckling pigs.

The outbreak was eradicated by the stamping-out of diseased animals and exposed contact animals within the outbreak area and a nearby suburban area of the Artigas city. The total numbers of animals destroyed were 6924 cattle, 12 371 sheep and 257 pigs. A zone with a radius of 25 km was fully quarantined. All depopulated farms were cleaned and decontaminated. Sentinel young steers and pigs were placed on the premises 30 days after the last depopulation. A serological survey was conducted in a buffer zone with a 5–25 km radius from the infected farm and all the samples were negative for FMD antibodies. The whole affected department was regionalized and quarantined for a considerable period of time. OIE re-established the status of free country in January, 2001.

However, this period of freedom of FMD did not last long. In April 2001, the country again lost this status as a consequence of the introduction and spread of the type A epidemic from Argentina. FMD was reported in Palmitas, Soriano Department, approximately 70 km from the Argentina border, along the Uruguay River which separates Uruguay from Argentina. The infected farm had 430 cattle and 640 sheep, of which 39 of 1–2 years-old steers showed FMD typical signs and lesions. The causative virus was confirmed to be type A (related to A_{24}).

Two days later a second outbreak was detected in the neighboring farm with 773 cattle, 474 sheep and 10 pigs. Interdiction of the affected farms was enforced immediately with a standstill of all animal movements. Simultaneously several FMD outbreaks occurred in the adjacent Colonia Department 25 km from the Uruguay River at a distance of about 40 km from the first discovered cases.

The next day the affected and exposed animals were destroyed and buried (5093 cattle, 1511 sheep and 333 pigs). However, three days later the Government was forced to suspend the stamping-out procedure due to the strong resistance of local farmers and the discovery of spread of the disease to other departments of the country.

Intensive cattle dairy industry as well as cattle fattening and agricultural production systems co-exist in the affected Departments. The factors that contributed to the dissemination of the virus in those Departments were intense movements of people, agricultural equipment and machinery, and trucks for the transport of beef cattle and milk. Moreover, the zone is economically very much integrated with the adjacent region of Argentina where active foci of FMD were ocurring in the neighboring Provinces of Entre Rios, Santa Fe and Corrientes.

Both affected departments were quarantined and on the April 26th ring vaccination was started in an area with a 10-km radius around the infected farms. On the 30th vaccination was extended to form a protective barrier. However a few days prior to the recognition of the outbreak, cattle had been dispersed from an auction to other departments of the country. In that way, the epidemic had already spread to others regions of the

country and from April 27th to the June 7th all movements, transits and trade of animals were prohibited in the whole territory of the country.

On May 5th a massive systematic vaccination was re-established in the total cattle population of the country. In order to protect the Brazilian livestock population against the introduction of the disease, vaccination was immediately instigated to cover all Uruguayan departments adjacent the State of Rio Grande do Sul, Brazil. The first vaccination round ended by June 7th when movement and transit restrictions were relaxed. The re-vaccination round lasted from June 15th to July 22nd. A total of 24 million doses of FMD oil-adjuvant vaccines were distributed during these two rounds of vaccination to cover a population of 10.6 million cattle in each round. The average rate of vaccination was 350 000 cattle per day in each round of vaccination. The veterinary services established a vaccination timetable, scheduling routes, dates and time. Most of the vaccinations were done by the farmers and farmhands. In some cases private veterinarians performed the vaccinations. The official veterinary services had an active role in the control of the vaccination procedures at the farm level. Dairy cattle stock was vaccinated in 1 week with a vaccination rate of 67 000 head per day. By November 2001, an additional 4.5 million young cattle were vaccinated and each animal identified by an ear-tag tracking system.

The total number of outbreaks was 2057 (Fig. 2 shows the distribution of outbreaks in the country) of which 264 were dairy farms. A total of 6937 animals were killed and buried during just the first week of the epidemic. After that infected premises and contact farms were quarantined with total prohibition of livestock movements until 30 days after the last case. The last outbreak occurred on a dairy farm on August 21st. By October 2001 Uruguay was again free of FMD.

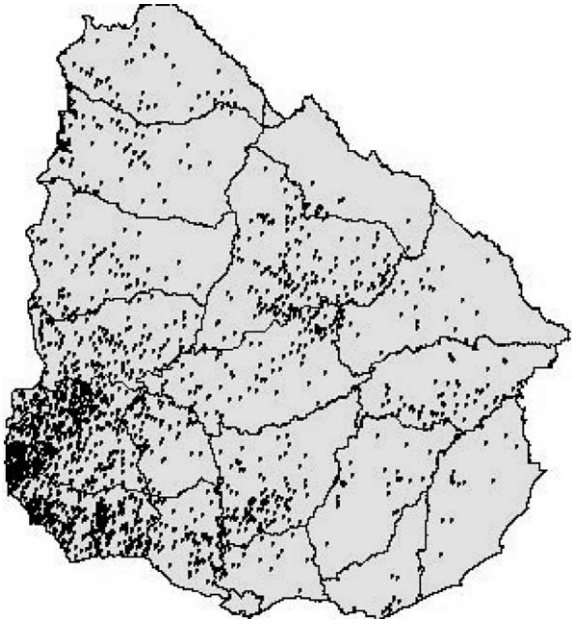

Fig. 2. Uruguay: distribution of infected farms during the 2001 FMD epizootic caused by FMD virus type A (related to A_{24}).

Fig. 3 shows the evolution of the outbreaks caused by type A versus in relation to the vaccination and re-vaccination campaign. It can be seen that at the height of the epidemic there were 40–60 new infected farms per day. Shortly after the end of the first vaccination round, in spite of the relaxing of livestock movement restrictions, the number of new cases decreased dramatically to single numbers. A few day after the completion of the re-vaccination round there only were a few sporadic cases and at the time of writing (February, 2001) 6 months have elapsed without further cases.

Thus, Uruguay was able to control and eradicate this extensive outbreak with the application of livestock movement restrictions and vaccination of the cattle population only, in spite of having a large and fully susceptible sheep population in close contact and proximity to the cattle. The total cost of eradicating the epidemic was 13.6 million US$, of which 7.5 million were spend on the purchase of vaccine, and the remainder on compensation payments to farmers, cleaning and disinfection and operating expenses. These expenses do not include some of the expenses of the Army (for eg. salaries). The Armed Forces collaborated, for instance by controlling border areas for illegal livestock movements.

- Susceptible livestock populations are at risk when the first line of defense against the importation or re-introduction of FMD is not well maintained.
- International collaboration and maintenance of effective surveillance (adequate laboratory support) and reporting systems is essential.
- The transition from a 'FMD free *with* vaccination' status to a 'FMD free *without* vaccination status' requires a different mind set of all stakeholders and the preparation of flexible contingency plans.
- Breaking of the cycle of endemic and active virus niches of the disease can be done by massive and strategic cattle vaccination campaigns.
- Interruption of the cycle of virus transmission from primary endemic areas to secondary ecosystems (epi-endemic, sporadic and free ecosystems) is a must.
- Vaccination of cattle only, in combination with livestock movement standstill can control an extensive outbreak in a very short time, with minimal disruption of the rural society and economy.
- Strong and continuous programs of education and training of the public and private veterinary services as well as farmers and the public in general must be applied.

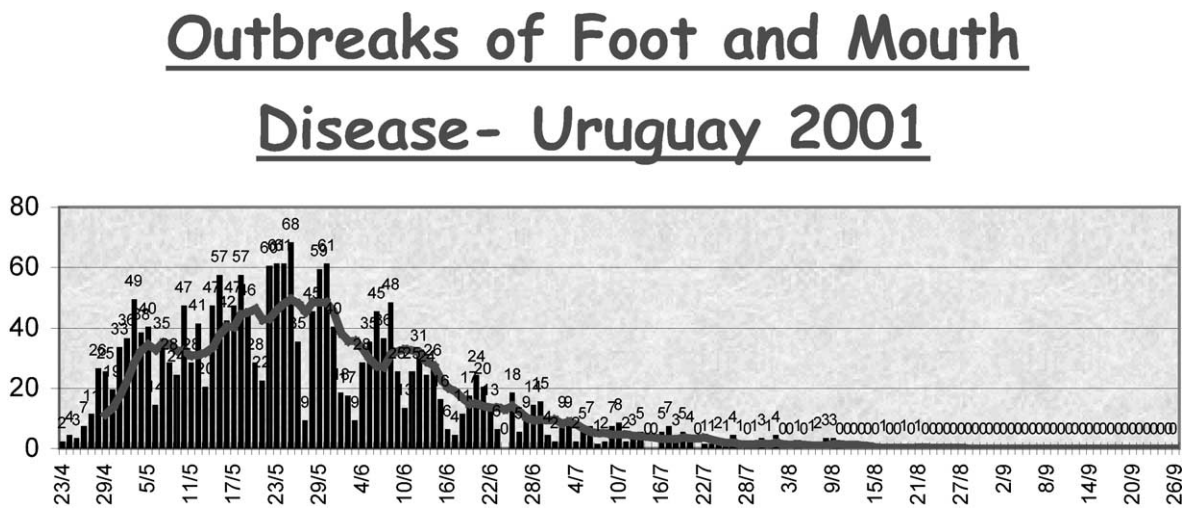

Fig. 3. Evolution of the FMD epidemic in Uruguay 2001. Daily number of outbreaks. Red line: moving 7-day average. *Source:* Direccion General de Servicios Ganaderos, Direccion de Sanidad Animal, Ministerio de Ganaderia, Agricultura y Pesca, R.O. del Uruguay. Red is the average number of infected farms per week.

- FMD banks of purified and potent antigens and vaccines must be available for immediate use and application in sanitary emergency occurrences.

General conclusions of this section

1) The contingency plans for each state or region for FMD control must be regularly updated and emergency practice drills made routine.
2) Emergency use of vaccination, as an adjunct to slaughter, must be a component of all contingency plans, and be able to undertake mass vaccination on a zonal basis within 7 days of any FMD outbreak, and arrangements must be in place for replacement supply from manufacturers.
3) Potential penalties associated with vaccination need to be removed and resolved before outbreaks occur by making arrangements for trade in livestock products from vaccinated herds/districts part of any national contingency plan.
4) There is a strong need for unbiased, independent scientific expertise on FMD that can provide recommendations which are not affected by political pressure, fear of losing position, or the bias of 'lobby' groups within the farming community.

6. What makes sense?

6.1. Basic questions

From all the data discussed in this chapter we asked ourselves: what makes sense for prevention, control and eradication of FMD?

It became clear to us that many of the current approaches are not deduced from science-based risk assessments. For instance, the discussion whether 'to vaccinate or not to vaccinate' was obscured by the consequences for international trade. It was not led by:

- 'How to get rid of the disease soonest?'
- 'How can we minimize impact on animal production and welfare?'
- 'How can we limit the damage to the rural society as a whole?'

The long-term ban on free international trade revolved around the fact that vaccinated animals might, like convalescent or sub-clinical infected animals, become FMD virus carriers. The other argument was that vaccinated animals would have antibodies against FMD and that this might obscure the tracing of the disease.

- Just how large is that risk of creating vaccinated carriers and what would be the risk posed by such animals?
- Does that risk justify the assumed zero risk approach of 'stamping-out' or, when vaccination is used, the killing of the healthy vaccinated livestock?
- Could the risk of infected animals in vaccinated populations be managed effectively by the use of modern diagnostic methodologies?
- Is stamping-out to the bitter end really assuring zero risk?

Present policies of FMD control are apparently either driven by trade considerations and/or by the results of mathematical computer models with disregard of most of the scientific background available and without peer-reviewed appraisal of the levels of risk involved. Was that justified and was the risk of further spreading of disease when applying massive slaughter sufficiently appraised?

Once the disease was brought under control what should be required to restore a FMD free status? What did we learn from the recent experiences? Are the current international rules still adequate? What are the risks of re-introduction of FMD? What are the risks of international trade, tourism, swill feeding, FMD-laboratories and vaccine plants, and terrorist actions? How can these risks be mitigated and managed?

In the following section we will try to evaluate those questions and summarize our conclusions on the basis of scientific knowledge and our own experiences described in the previous sections of this chapter.

6.2. Spread of FMD

Without getting into operational details, we will summarize the various risk factors of spreading the virus that must be taken into account by veterinary authorities, when confronted with FMD epidemics.

6.2.1. Dissemination of FMD virus

Of all species, cattle produce, in general, the greatest total amount of infectious virus particles and, therefore, are the major source for the spread of FMD. Excretion by cattle can easily surpass 10^{14} virus particles per cow per day, representing approximately 10^{10} IU. These quantities of virus behave like a very fine dust that spreads over the infected premises and sticks to all materials, animals, and people.

The total amount of infectious virus from aerosols, saliva, lesion tissue, urine, feces, and milk in general is at least one magnitude higher for cattle than for pigs and is several magnitudes higher for cattle than for sheep. The movement of infected cattle or other livestock during the incubation or sub-clinical phase, is the main source of distant spread of the disease.

In most epidemiological models aerogenic spread in the pre-clinical stage—especially from pigs, is over-emphasised. The main control effort should be on the prevention of all virus escape from infected premises, and of establishing bio-security precautions for all farms at risk to reduce the possibilities of virus entry. Bio-security means not only controls on the 'farm-gate' but also reducing potential 'over-the-fence' transmission for example by separating grazing animals. Animals on infected premises with clinical disease (and/or with high fever) should be killed immediately and the premises disinfected. Final culling and disinfection should be carried out a day or so later obeying rules for biosafety and preventing the creation of virus aerosols.

A particular risk is posed by small ruminants, in which lesions in the acute stage of FMD are often difficult to discern. Consequently, people and materials can become contaminated unknowingly and spread the disease in this way. Also, FMD can easily cross borders by international trade of sheep with sub-clinical disease. However, if not moved, transported, or marketed the role of sheep in the spread of FMD is minor and the same is true for wildlife.

Camelids (llamas and alpacas) are not easily infected, hardly disseminate virus and do not carry the virus to any extent. Therefore, it is unlikely that they play any epidemiological role.

Most zoos contain animals that are susceptible to FMD. In general, their movement is already restricted. In the face of an outbreak susceptible animals should be kept away from direct contact with the public and should be vaccinated, preferably with an oil-adjuvant vaccine. The risk that a vaccinated zoo-animal would ever become a carrier is negligible. The risk that such a carrier would ever transmit disease can be considered near to zero.

6.2.2. Disease surveillance

During outbreak situations, intensive surveillance on farms in the outbreak area must be carried out. However, people carrying out clinical inspections, especially of the mouth, and collecting blood samples present a high-risk of spreading disease. Therefore, rules for bio-security should be applied with the greatest care, even if clinical signs of FMD were not detected.

6.2.3. Animal movement

The main emphasis of control efforts should be on limiting the spread of FMD and the prevention of virus escape from infected premises. Therefore, the prohibition of all livestock movements should be imposed upon the affected region immediately after the diagnosis of a case of suspected vesicular disease. This must be followed by zonal, regional, and, possibly, international standstill of susceptible livestock movements as soon as possible after confirmed diagnosis.

Speed of implementation, enforcement and adequate control is essential in order to prevent additional movements of animals induced by the fear of transport restriction and FMD. These controls should only be relaxed once the whole epidemiological picture becomes clear and the modes of spread are fully evaluated.

6.2.4. Transmission by people

People are very efficient mechanical transmitters of FMD virus. Any person, who has had contact with infected animals or carcasses, such as veterinarians, farmers, sanitary and digester personnel etc., and does not take strict bio-security measures creates a major risk for the transmission of FMD. All personnel and equipment involved in stamping-out operations and ring culling represent a great risk. The contractors that carry out the job are often not trained in bio-security, they will not be aware of the hazard presented by pre-clinical disease, and, therefore, might tend to 'take it easy', with all the associated risks.

Trucks for hauling animals, feed, milk, manure, etc. also are important factors in spreading disease. Farmers may spread the disease indirectly through contacts with other farmers or via contaminated objects ('fomites').

6.3. Control strategies

The operations and activities of different control policies have different levels of risk of disseminating the virus in the process of attempting to control the disease. In particular, we wish to discuss the risks of different policies:

- stamping-out of infected farms and direct potential contagious contacts;
- stamping-out of infected farms plus ring (circle) culling;
- stamping-out of infected farms plus ring or area vaccination followed by slaughter of all vaccinated animals ('suppressive' vaccination);
- stamping-out of infected farms plus ring or area vaccination ('protective' vaccination);
- ring vaccination only without stamping-out of infected farms and slaughter of vaccinated animals
- strategic or general vaccination.

6.3.1. Stamping-out

Stamping-out consists of the killing and disposal of all susceptible livestock on infected farms and their immediate contact farms that are most likely infected followed by a thorough disinfection–cleaning–disinfection procedure of the premises, the first disinfection being to prevent the production of virus aerosols during the cleaning.

In traditionally FMD free countries, stamping-out is the first option to eradicate the disease. As a first line of defense it is often quite successful, at least if the disease has not yet spread too widely and if the density of livestock in the area is relatively low. Also, during the first days of an outbreak a proper vaccine might not be available. The choice of the stamping-out option should also depend on the possibility of tracing dangerous contacts, political will and available resources. If the outbreak farm is located at some distance—from other farms and without intensive contacts, the slaughter of only infected premisesand with surveillance of neighboring farms, might be adequate. In general, however, one must be 'ahead' of the disease and, to that end, also slaughter-out 'dangerous contact farms'. However, the latter are difficult to define and decisions can create feelings of arbitrariness and unfairness.

We have seen that the stamping-out policy had to be abandoned during the Mexican outbreak in the 40s and recently, in Uruguay due to the spread of the disease and the resistance of the farming community. In the UK the fear of 'having to live with the disease' because of carriers and 'the loss of export trade' were the main motives for continuing the circle culling policy to the bitter end (see below).

If stamping-out of the disease succeeds in a relative short period of time it may be the most economical way of dealing with the outbreak. However, there are significant risks involved in the killing of large numbers of (potentially infected) animals, the hauling and destruction of the cadavers and the cleaning and disinfecting of the infected premises:

- Heavy equipment used in these operations is difficult to decontaminate and might be a source of infection or contamination of roads when being driven to another job or back home.
- Disposal of cadavers also presents a risk since virus in lesions, excrements and excretions is not rapidly destroyed after death and might be disseminated by transport of cadavers, by pyres, at burial sites or digester plants.
- To our knowledge, transport systems for carcasses are not bio-secure, neither is the handling of the carcasses at the rendering plants.
- The highest risk comes probably from the involvement of large numbers of contractors not trained in disease containment. These people become heavily contaminated, are from rural areas, often live next door to farmers, and having their social contacts in the farming community.

Intensive, active surveillance is required to detect infection and, as mentioned, such surveillance represents a risk as well.

6.3.1.1. Ring-(circle) culling. So-called 'circle culling' and culling of contiguous farms has been applied in the UK (and in The Netherlands) as an extension of usual stamping-out procedures. The aim of the circle is to eliminate incubating infections that may have spread from the outbreak farm(s) and create a 'fire break' around the outbreak. The diameter of the circle was based on the analysis of spread of FMD during the outbreak using computer models. However, the calculated distance of spread must include spread due largely to the culling process itself as an additional transmission mechanism.

Although ring culling reduces the need for surveillance, it creates potentially much higher numbers of cadavers, some of which might be infected.

The (economic) advantage of the stamping-out policy is that under the current OIE recommendations FMD free status can be obtained shortly after successful completion of the operation.

The main disadvantages are:

- Most culled farms within the circle are not infected and do not represent a risk of further spread of the disease and, therefore, are culled unnecessarily.
- The operation itself has a high-risk of disseminating FMDV over short and long distances.
- A long drawn-out campaign is very disruptive for the rural society as a whole, including sectors like tourism. The rural community may fear the control measures more than the disease, and live under this fear for several months after the last case.
- The consequent application of circle and of contiguous culls pose a threat to zoological collections and valuable (rare) breeding stock.
- Massive killing and destruction of livestock usually is not done with adequate respect for animal welfare and bio-ethical principles.
- The small risk represented by hobby farms and smallholdings is not taken into account.
- An enormous serological surveillance exercise is often required to detect residual infection since new cases could easily re-start the epidemic at its tail end, particularly if movement controls are prematurely lifted.
- Finally, many culls represent a human tragedy and traumatic experience not only for farmers and their families but for many veterinarians as well. The risk-avoidance behavior of farmers leads to social isolation and breakdown of the social–economic and trading patterns of rural communities.

If culling is the method of choice, it should be based on the evaluation of how virus spreads (known risk factors), which are rarely distributed in a circular manner about an infected farm. The principal routes of virus spread to be considered are by:

- animal movements from the farm, during the preclinical phase;
- animal proximity at farm boundaries, e.g. grazing in adjacent fields;
- wind, usually for a limited distance;
- vehicles (e.g. animal transport, machinery) contaminating roads that are used by the farmer's family and associates;
- contaminated vehicles from companies serving the farm:
- people (veterinarians, inseminators, visiting farmers, cleaning and disinfecting crews, etc).

For each potential contact farm epidemiological factors and associated risks should indicate the levels of risk of FMD infection. For instance, a large cattle holdings at some distance from an infected farm may represent a greater risk for air-borne spread of virus, then a small hobby farm nearby.

6.3.2. Vaccination

6.3.2.1. Ring vaccination. It has been demonstrated that early FMD vaccination of herds or flocks round the infected premise creates a cordon of protective animals that can stop effectively the diffusion of the disease. The size of the ring required depends on the rapidity of action of the vaccine and the anticipated rapidity of potential spread of infection from the IP, and location of high-risk farms which might amplify infection for onward spread. For example, to get 'ahead' of the disease with a vaccine would require 4–5 days to stimulate immunity and create an area in which farms/animals are protected before the anticipated first contact with virus. The higher the anticipated aerosol transmission, the larger the area that would be required to ensure an adequately immunised 'ring'. Outbreaks in the vaccinated zone/ring will usually cease within 10 days of effective herd immunity being reached, and frequently cease well before this.

Therefore, ring vaccinations should be performed without delay and should include all susceptible species. Preferably, the vaccination should be carried out from the outside of the 'ring' towards the center of the outbreak. Simultaneously, to protect the most endangered farms as soon as possible, vaccination should proceed from the center towards the outside. In the immediate vicinity of the outbreak farm, the large (cattle) holdings should be vaccinated first because potentially, those are the largest 'aerosol collectors'.

Ring/emergency vaccinations should be included in any contingency plan:

- to avoid all of the above mentioned disadvantages of the massive killing and destruction of infected and healthy animals;
- to stop the disease from spreading;
- to prevent to the maximum extent possible the suffering of animals;
- to ensure that a few weeks after vaccination life in the affected area can resume its normal course, with minimal socio-economic consequences.

The logistics of a vaccination campaign are rather simple. It can be carried out on a large scale by a limited number of (trained) staff under full bio-safety conditions or by farmers and trained farm hands as is common practice in South America. The latter method has the advantage that there will be no risk of cross-contamination between farms because of people movements.

If vaccination offers so many advantages, why is there such an opposition to its use in many parts of the world?

The answer is simple: International trade regulation put a heavy penalty on the use of vaccine against FMD

in the form of import/export restrictions of animals and animal products.

- If FMD occurs in a previously 'FMD free country or zone without vaccination':
  a) If no vaccination is used to control an outbreak and stamping-out and serological surveillance are applied, the FMD free status can be regained and normal trade resumed 3 months after the last case;
  b) If stamping-out and emergency ('suppressive') vaccination are applied the waiting period is 3 months after the last vaccinated animal is slaughtered. A serological surveillance in the zone around the vaccination zone must demonstrate freedom from FMD.
- If FMD occurs in a FMD free country or zone where vaccination is practiced:
  a) If stamping-out is applied to diseased farms and additional (ring-) vaccination is used, it takes 12 month after the last case to obtain the FMD free status;
  b) If vaccination is used, without stamping-outof diseased farms, it takes 24 month after the last case to obtain FMD free status.

These trade regulations are not based on risk assessments, but rather on the notion that vaccination might perpetuate carriers in the population and that those carriers may pose a risk for FMD free countries that do not practice vaccination. Also the assumption is made that there are no methods available for the detection of carriers in vaccinated populations.

6.3.2.2. Ring vaccination followed by slaughter ('suppressive' vaccination). Fear of carriers among vaccinated animals has led to 'suppressive' vaccination. In that approach, vaccination is used to control the outbreak(s), but all vaccinated animals have to be killed before FMD free status can be regained. It was used in The Netherlands in the main outbreak area to control the recent outbreak. In accordance to OIE regulations, the FMD free status was regained 3 months after serological surveillance and the slaughter of the last vaccinated animal. As indicated above the period would be 1 year if the vaccinated animals were not slaughtered.

'Suppressive vaccination'' creates several of the problems mentioned for circle culling, with the exception of the risk of dissemination of the virus. This risk is much reduced, because 4–6 days after vaccination all vaccinated animals will have sufficient protection to prevent dissemination of virus. The vaccinated animals can be killed over a more extended period, depending on incinerator capacity. It is interesting to note that, although vaccinated pigs do not become carriers they still must be slaughtered as well!

Concerns have been raised with regard to human consumption of meat or other products from vaccinated animals. However, neither from the point of view of disease control or public health is there any reason to object to human consumption of the meat of vaccinated animals. In Europe meat from vaccinated animals has been consumed for over 50 years, including the meat originating from South America.

6.3.2.3. Rights of farmers. When the political decision is taken to apply 'suppressive' vaccination of livestock in an infected area, veterinary authorities will want to make sure that a barrier of protected livestock is created to prevent further spread of the disease. Thus the area must be wide enough and preferably have clear natural boundaries such as highways, rivers or railroads.

These borders are probably drawn up by well-intended civil servants. However, the consequences are extreme when, within those borders, all healthy livestock must be destroyed, depriving a whole local society of normal socio-economic activities. It makes sense to ponder the question of whether the farmer's rights and those of the affected communities are not being sacrificed for the benefit of export.

6.3.2.4. Ring vaccination not followed by slaughter ('protective' vaccination). This control option is heavily penalized by present OIE regulations because of the 12–24 months waiting period to regain the status of freedom from FMD, depending on whether or not stamping-out was applied. We believe that these differences are unjustified and that the period should be determined by the ability of the veterinary service to demonstrate, to the satisfaction of the international animal health community, the absence of FMD virus activity in the country.

In the foregoing we have argued that vaccination by itself does not create carriers and that under natural conditions the risks that vaccinated animals become carriers is remote. Moreover, the risk of virus transmission from vaccinated carriers to susceptible animals is close to zero. In addition, methods exist for the detection of potential carriers among vaccinated animals. Risk assessments may even show that the risk of virus dissemination is not more but even less than the risk from 'natural' carriers after a massive culling operation.

6.3.2.5. Screening for anti-NSP antibodies. In non-vaccinated herds foci of hidden infection can be traced by screening for antibodies against the virus. Vaccination will also raise such antibodies and, therefore might frustrate such tracing; another reason for a primary ban on vaccination. However, virus infection raises antibodies not only against the virus particle but also against NSP, the proteins that are needed for virus multi-

plication. These anti-NSP antibodies are also useful indicators of a past infection and, consequently, of potential carriers.

After a single vaccination with non-purified vaccines, a-NSP antibodies will, in general, not be raised. However, after multiple vaccinations such antibodies might be induced as well, In contrast, vaccines prepared from purified FMD antigens, such as those in the international vaccine banks, will raise antibodies to the virus particle only. Even upon repeated vaccination no antibodies against NSP will be raised and past infection can still be traced. Such vaccines, in combination with tests for antibodies against NSP, will perform like a 'marker' vaccine, enabling discrimination between vaccinated animals that are infected (potential carriers) and vaccinated animals that are not infected.

Although in individual animals the tests to detect a-NSP antibodies are not 100% sensitive (which biological test is?), they perform very well if used for screening on a herd basis. If required, testing for the presence of virus e.g. by probang tests or PCR can further reduce the risk of missing an individual animal. Tests to discriminate between potential carriers and vaccinated animals have been widely used by countries to support their claims (at OIE) of freedom of FMDV. Thus, the concern that vaccination blurs the distinction between vaccinated and infected carrier) animals, is no longer founded if purified vaccines are used.

It would make sense if, after any outbreak, the veterinary service were to show- the absence of FMD, to the satisfaction of the international trading community, before normal export could be resumed. This should be required whether stamping-out, stamping-out plus ring vaccination or vaccination only was used to control the outbreak:

- In the case of stamping-out: by a serological survey for the detection of type specific antibodies in a statistical representative sample of the population in the SZ around the outbreak, with emphasis on the herds at closest proximity to known infected farms.
- If vaccination (with or without stamping-out) was used: by a survey of vaccinated livestock for antibodies against NSP. In the SZ around the vaccination zone a statistical valid serological survey for type specific antibodies should be carried out.
- In both surveys positive or doubtful findings must be followed-up by virus detection methods.

Above requirements should not have a set time span. In our views, the sooner the country or region shows the absence of viral activity the earlier normal trade can be resumed. In that case the ministries of agriculture and livestock industry can select the best options for eradication of the disease that cause the least disruption of social and economic life at the least cost to the community. Post-vaccination surveillance should take no longer, and might take less time than the poststamping-out period currently required. The demonstration that serological surveys were carried out rapidly and efficiently would demonstrate to the international community the existence of a well-organized veterinary services that take the eradication of FMD seriously.

6.3.2.6. Outbreaks in FMD free countries that practice vaccination. The requirements to regain the recognition of FMD free status should not have a set time limit of a 12 or 24 month waiting periods. There is no magic cut-off point for the carrier state. The sooner the country or region shows the absence of viral activity the earlier normal trade can be resumed. Post-outbreak surveillance must be based on tests for NSP antibodies or, when available, validated molecular tests for virus RNA.

6.3.2.7. Strategic vaccination. In endemic or epi-endemic regions, strategic or general vaccination is required with vaccine containing the FMD subtypes that are active in the area. This could be carried out with the more classical aqueous vaccine or with oil-adjuvant vaccine.

Cattle—aqueous vaccines must be applied twice yearly. In general, current oil-adjuvant vaccines protect cattle of different breeds more effectively. Cattle up to 2 years should be vaccinated twice yearly. Thereafter, a yearly vaccination will maintain their immune status.

Sheep—classical aqueous vaccines and oil-adjuvant FMD vaccines protect sheep very well. In general, oil vaccines induce a longer lasting immunity. However, vaccination of sheep was not included in European and South American systematic vaccination programs. This did not hamper the final eradication of the disease. Recently, in Uruguay the stand-still of livestock movements and massive vaccination of all 12 million cattle quickly brought a FMD outbreak, which was as extensive as the epidemic in the UK, under control without stamping-out and even without total slaughter of infected premises. As in the past, vaccination of the sheep population was not required to control and eradicate the disease.

Pigs—in general, systematic vaccination of pigs is not recommended, except when the virus strain involved is very aggressive for that species. Oil-adjuvant vaccines can be used with success to protect pigs and can be used strategically in high-risk areas. Industrial pig operations usually maintain high standards of hygiene and biosecurity. The main risk are backyard pigs and pigs on garbage dumps, especially those in the neighborhood of slaughterhouses

To obtain the status of free of FMD with vaccination the country or zone should demonstrate the absence of

viral activity based on tests for non-structural antibodies.

6.4. Risks of introduction of FMD

6.4.1. Risks of trade

There is no trade without the risk of importing infectious diseases. However, these risks can be estimated, reduced and managed.

Although, the status 'Zone free of FMD where vaccination is not practiced' is the most sought after by many regions and countries, recent experience has clearly demonstrated that the paradigm 'free of FMD without vaccination' is not synonymous with 'risk-free'.

The risk that FMD enters a zone or country and remains unnoticed for some time, as happened recently, in Argentina, The Netherlands, the UK and Uruguay, increases with the years of freedom from the disease. FMD becomes a 'faraway' exotic disease. Interest in the disease decreases and funds dry up to train and maintain adequate numbers of professionals in the recognition and prevention of the disease. In addition, the risk of introduction of FMD into FMD free countries may expand significantly, due to changed agricultural practices, increased trade in live animals and animal movements as well as increased trade in animal products and mobility of people. Such changes require revision and adjustments of existing policies to obtain optimal effectiveness of national and international control of FMD. Revised rules should not create unacceptable risks for trade partners but, also, control of FMD outbreaks should be carried out with the least disruption of the farming community and the regional economy as a whole.

6.4.2. Carriers and trade

In a general epidemiological sense the term 'carrier' is assigned only to those animals that are able to disseminate an infection, yet remain clinically without symptoms of the disease. Although the term 'carrier' is used commonly for animals that are persistently infected with FMDV, it does not imply that these animals are contagious.

Animals recovered from FMD, or after sub-clinical infection, may still carry some virus in their throats. Also, a vaccinated and clinically protected animal in a heavily contaminated environment may become a virus carrier. Under normal circumstances carriers do not excrete virus and FMDV cannot be detected in the environment of the carrier.

The evidence for the transmission of FMD by recovered livestock (carriers) is anecdotal and is, over the past 100 years, limited to a few cases only. Dissemination of FMD has never been convincingly demonstrated under experimental conditions. Although we use the terms 'carrier' and 'persistently infected animal' we do so with the implicit understanding that this does not imply that such animals are contagious.

The carrier status often occurs in FMD convalescent domestic animals. The duration of the carrier status depends on the individual animal, animal species, and virus strain. Among domestic species the largest number of carriers occurs in cattle, followed by sheep and goats. For reasons unknown, pigs do not become carriers.

The risk of carrier livestock transmiting FMD to susceptible livestock by direct contact is extremely low. On the basis of comparison with other viral agents it has been sometimes assumed that stress might activate the virus in the throat of a FMD carrier. However, virus titers in the throat did not increase even after severe natural or artificial stress, nor did stressed carriers transmit the disease.

In general, a minimum number of IU is needed (the 'minimum infectious dose') to start an infection. The risk that a carrier produces sufficient virus aerosol to transmit disease is very low. The assumed risk of carriers is based on historical evidence of a few cases over the past 100 years in which convalescent carrier cattle probably played a role in the introduction of FMD into FMD free herds.

The risk of carriers is often confused with the risk of highly contagious animals in the sub-clinical state. For instance a particular risk is posed by the importation of small ruminants, in which lesions in the acute stage of FMD are often difficult to discern. FMD can easily cross borders by international trade of sheep with such sub-clinical disease.

6.4.3. Risks of vaccinated carriers

A misconception is that vaccination causes the carrier status. This is impossible since FMD vaccine is an inactivated, safe vaccine. A vaccinated animal must be exposed to a large quantity of FMDV in order to become a carrier, for instance when vaccinated cattle come in contact with large numbers of diseased pigs. Because vaccination suppresses the amount of FMDV that is released into the environment (low morbidity!) it is very unlikely that vaccinated animals will become carriers.

It is also unlikely that vaccinated animals become carriers through infection by FMDV transmitted by fomites or people and brought from infected farms. It is thus very unlikely that new carriers will be induced in vaccinated herds.

Carriers among vaccinated cattle have not caused FMD outbreaks among susceptible non-vaccinated livestock populations nor have they hampered FMD eradication efforts.

Sometimes the concern is expressed that meat, meat products and milk from vaccinated FMD carriers are a risk for FMD free regions, zones or countries. Apart from the regular risk reduction processes that are

applied to meat and meat products, such as disease surveillance, abattoir inspections and maturation and de-boning of the carcasses, the vaccinated animal offers even less risk. The neutralizing antibodies in the vaccinated animal are the best guarantee that meat, blood, lymph nodes, bone marrow, organs etc. will be free of FMD virus. We also want to point out that millions of tons of meat from vaccinated South American cattle have been imported into the EU without causing FMD.

Another concern is the risk of mechanical contamination of a cattle carcass or organs with 'carrier virus' from the pharyngeal area. However, because of antibodies in blood and other fluids and measures applied during slaughter and processing (e.g. for BSE!) that risk is negligible.

The probability of dissemination of FMD virus by milk from vaccinated carriers also is close to zero because the virus does not persist in the udder and milk from vaccinated herds contains neutralizing antibodies. The importation of milk and milk products from countries that practice vaccination has never caused FMD in FMD susceptible livestock.

6.4.4. Feeding of swill

Primary infections in FMD free countries have frequently involved pigs, often on swill feeding holdings. Swill from ships and aircrafts forms a special risk in this respect. Therefore, swill feeding practices are not compatible with a FMD free status unless the swill is processed in officially validated plants that are well-controlled by the government.

6.4.5. FMD laboratories and vaccine plants

During the past 20 years on at least at two occasions FMDV escaped from technically well-equipped high-containment laboratories causing outbreaks outside the facilities. Therefore, regular international inspection of FMD laboratories and vaccine production plants is needed. Inspection must be carried out on the status of facilities and equipment, on logistics, and on the execution of the internal control on bio-containment and biosafety. This is particularly important for such laboratories in countries with a FMD free status.

6.4.6. Bio-terrorism

Dissemination of FMD in a country with a susceptible livestock population by the action of terrorists no longer seems unrealistic. The virus can rather easily be obtained and be spread in target countries. The availability of large internationally managed vaccine banks, containing a wide variety of antigens, and rapid application of vaccines is the best, if not the only way, for countries to prevent complete disasters. Contingency plans must incorporate such possibilities.

6.5. Systematic surveillance and contingency plans

For a status of freedom of FMD, with or without vaccination, an effective FMD surveillance system must be in place. The system should be rapidly responsive to vesicular disease outbreaks, of FMD in particular. A responsive surveillance system necessitates a level of veterinary information management both, in the field and centrally at the national level. It also requires active participation of a well-informed farming community, private and official veterinarians and extension workers.

Considering the consequences of a non-functioning surveillance system and the associated risk of undetected vesicular diseases (e.g. FMD) trade partners should check on the effectiveness of the surveillance system in countries with the status 'Free of FMD (with or without vaccination)'.

Contingency plans for FMD outbreaks must be available. These plans must be practiced regularly and adapted according to the experiences.

In some countries with a high-risk of (re-) introduction of FMD from neighboring countries or wildlife reserves with endemic FMD, in border zones active surveillance of indicator species should be required for maintaining a FMD free status.

6.6. International cooperation

Europe and several countries in South America became free of FMD by systematic vaccination of their cattle population. This was done within a context of international co-operation. However, when the 'FMD free status' was obtained vaccination was discontinued, which resulted in huge susceptible cattle populations. At the same time, favorable conditions for the re-introduction of FMD were created by a combination of the loss of experience and knowledge concerning the prevention, control and eradication of FMD, an 'open border' policy and increased trade and travel. The consequences have been felt in countries worldwide.

Over the past decade several outbreaks of FMD have occurred in formerly FMD free areas. To reduce the risk of such introductions, emphasis must be on the reduction of FMD outbreaks worldwide. In endemic countries, systematic vaccination of the cattle population is the tool in the struggle against FMD and must be stimulated and supported financially by international co-operation.

A global approach towards FMD control and eradication is more needed then ever.

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