

# Foot and mouth disease: the future of vaccine banks

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## Summary

The authors briefly review the history of vaccine banks for foot and mouth disease, their current location and their constituent serotypes and strains, together with the occasions on which they have been activated. Experimental studies on emergency vaccines are summarised and areas identified for further investigation. The future of such banks is considered, including the principal strengths and weaknesses of existing banks, and suggestions are made for potential improvements.

The fact that the banks have been activated on relatively few occasions over the 25 years of their existence testifies in part to the relatively rare calls which have been made upon them, but also reflects the difficulty in deciding when and how to utilise emergency vaccination. Nevertheless, in an era of increasing global risks of the spread of foot and mouth disease, banks will most certainly continue to have strategic and tactical importance in the control of this most readily communicable of animal diseases.

## Keywords

Emergencies – Foot and mouth disease – Foot and mouth disease vaccine – Vaccination – Vaccine banks .

## Introduction

Since the first foot and mouth disease (FMD) vaccine bank was established in Denmark in 1976, many more banks have been created world-wide to provide vaccines for emergency application in cases of disease outbreaks. Four operate on an international basis while twelve have national footing, eleven in Europe and one in South America. In some instances, individual countries belong to both national and international banks (34). Evidence continues to accumulate for the long-term stability of banked antigens, some of which have been shown to retain immunogenicity when stored for at least 12-13 years at low temperature (8, 19) and which can probably be stored satisfactorily for an indefinite period.

To date, the banks have been activated only rarely, producing vaccines to supply the Balkans in 1996, Turkey, Japan and the Republic of Korea in 2000 and the United Kingdom (UK) in 2001. On several of these occasions, the formulated vaccines were not administered. Nevertheless, the banks continue to provide insurance against the threat of the spread of FMD. This threat has been greatly increased in recent years by political, social and economic developments, including the

following: the expansion of free-trade areas, the increasingly large scale and rapidity of international movement of animals and animal products, the growth of tourism, the migration of refugees and the perceived threat of global bio-terrorism. Some risks have recently become a reality, as exemplified by the devastating outbreaks of FMD in Taipei China in 1997, in Uruguay and Argentina in 2000/2001 and in the UK in 2001. Moreover, in 2000 and 2001, type O, the pan-Asian topotype of FMD virus, spread to areas in which the disease had long been absent (Japan, Republic of Korea, UK) or where the serotype had never previously been recorded (Republic of South Africa).

## A brief history of foot and mouth disease vaccine banks

Foot and mouth disease vaccine banks developed with a concurrence of technical capability and need. The finding that viral antigen could be inactivated, concentrated and stored at a low temperature (typically in the vapour phase over liquid nitrogen) for extended periods with little or no loss of immunogenicity provided the technical basis for the

establishment of vaccine banks (1). Such antigens could be rapidly reconstituted and formulated as potent vaccines. This approach has a number of advantages over conventional, pre-formulated vaccines, including flexibility in the formulation of mono- or polyvalent vaccines, the level of incorporation of antigen and the type of adjuvant used, all of which can be tailored to best meet the epidemiological characteristics of the emergency. In addition, banked antigen can be formulated and used directly in times of need. This contrasts with pre-formulated vaccine which has advantages of immediate availability, but disadvantages of limited shelf-life if unused before the registered expiry date, typically within 12 to 18 months of testing and release.

The Northumberland Committee of Inquiry reported on the costly FMD epidemic of 1967/1968 in the UK and recommended, *inter alia*, the creation of a stockpile of vaccine for use in any future emergency (3). At that time, only reserves of fully formulated vaccine were available. However, by 1974, methods had been developed for the production, purification, concentration and low temperature storage of antigen and the first national FMD antigen bank was established in Denmark in 1976. Subsequently, countries traditionally free of FMD in North America and Australasia, and those in western Europe which were achieving freedom, increasingly recognised the threat of re-introduction and wished to have an emergency vaccine supply. Despite adhering to a stamping-out policy for FMD, they acknowledged the possible development of economic and social circumstances in which emergency vaccination might well be necessary, at least as a short-term control measure. Moreover, during the 1950s and 1960s, many state veterinary institutes, formerly capable of producing FMD vaccine, opted to discontinue this activity. In addition, as routine vaccination decreased in western Europe to total discontinuation by 1991, the prospect arose of possible shortages in the supply of vaccine from commercial sources capable of meeting European Pharmacopoeia criteria of manufacture, safety and potency. The combination of these factors reinforced the need for contingency supplies, and the realisation that vaccine would have to be purposely stored.

Following the precedent in Denmark, several FMD vaccine banks were established. The North American Vaccine Bank (NAVB) was inaugurated in 1982 for the United States of America (USA), Canada and Mexico. In 1985, an International Vaccine Bank (IVB) was established in the UK to serve as a contingency supply for the UK, Australia, New Zealand, Finland, Ireland, Norway and Sweden, with Malta later joining as an associate, non-voting member. The European Union Vaccine Bank (EUVB) was established in 1991 to service the member states. These banks have been described elsewhere (12, 24, 28, 30, 34) and only key characteristics are summarised below. The most recently established bank dates to 1999 in Argentina.

The IVB has a minimum of 500,000 doses of each of the following antigens:

- A<sub>15</sub> Thailand
- A<sub>22</sub> Iraq 24/64
- A<sub>24</sub> Cruzeiro
- Asia 1 India 8/79
- C<sub>1</sub> Oberbayern
- O<sub>1</sub> Lausanne
- O<sub>1</sub> Manisa.

This bank is a non-commercial, inter-governmental facility, located at the Institute for Animal Health, Pirbright, UK, combining antigen storage with the capacity to formulate and test antigens and vaccines. Members pay an annual subscription to cover maintenance costs, including purchase of additional antigens (obtained from commercial manufacturers) and also pay to replace any antigen withdrawal. The bank is administered by the UK State Veterinary Service on behalf of a commission comprising the Chief Veterinary Officers of the participating countries and is managed by the Pirbright Laboratory.

The EUVB was inaugurated in 1993. The original intention was that the bank should hold five million doses, each of ten strains of antigen, as follows:

- O<sub>1</sub> Manisa
- O<sub>1</sub> BFS
- A<sub>24</sub> Cruzeiro
- A<sub>22</sub> Iraq
- C<sub>1</sub> Noville
- Asia 1 Shamir
- A Iran 96
- A Iran 99
- A Malaysia 97
- South African Territories (SAT) 1.

Antigens of serotypes SAT 2 (East Africa), SAT 2 (Southern Africa) and SAT 3 were later added in lesser amounts, in view of the assessment that the SAT viruses posed a much lower threat to Europe than the other serotypes. At present, the bank holds antigen equivalent to between one half and one million doses of the various strains (34).

The EUVB antigens are stored in two national institutes, in Lyons, France, and Brescia, Italy, and at the facilities of a commercial manufacturer in Lyons and Pirbright. Formulation is undertaken by the commercial supplier of the antigen to a potency of at least six 50% cattle protective doses (6 PD<sub>50</sub>) per vaccine dose. Release of antigen for vaccine to be used, either within or outside the European Union (EU), requires the agreement of the Standing Veterinary Committee of the EU.

The NAVB holds substantial stocks of a limited number of key strains. They are kept at the Plum Island Animal Disease Center, USA, with provision for formulation meeting United States registration requirements to be undertaken at a commercial production unit.

As of March 2001, thirteen countries in western Europe held supplementary stocks of FMD antigen (34). Seven of these banks are maintained by commercial producers and the remainder are held in national institutes. The largest national bank is located in Germany, which holds 100,000 doses of formulated vaccines for each of seven strains and 500,000 or 1 million doses of frozen antigen for each of eleven strains. In 2001, Denmark decided to discontinue the national maintenance of what was the first established bank and will in future rely upon the EUVB.

The All Russia Research Institute for Animal Health (ARRIAH) manufactures FMD vaccines for national use and has contracts for emergency supply with a number of countries such as Bulgaria, the Ukraine, Kazakhstan, Belarus, Moldavia and Turkmenistan (40).

A bank was established in Argentina in 1999 under contract with a commercial supplier. The bank holds stocks of O<sub>1</sub> Campos, A<sub>24</sub> Cruzeiro, A<sub>79</sub> Argentina, A<sub>87</sub> Argentina, C<sub>3/85</sub> Argentina and C<sub>3</sub> Indaial – each equivalent to 500,000 doses of vaccine – and of SAT 1, SAT 2 and Asia 1 – each equivalent to 35,000 doses of vaccine (A.A. Schudel, personal communication).

Commercial manufacturers hold stocks of antigen for their own use and there are also examples where they hold stocks under contractual arrangements on behalf of national and international organisations.

## Utilisation of vaccine from foot and mouth disease vaccine banks

Foot and mouth disease vaccine banks have been utilised relatively infrequently, on a rather small scale and predominantly for the emergency vaccination of cattle. Regarding the EUVB, vaccine was first produced in 1996 to supply vaccine to the Balkans when 480,000 doses of type A<sub>22</sub> vaccine were provided to the Former Republic of Yugoslavia and the Former Yugoslav Republic of Albania (FYRA). Counter measures employed included slaughter and movement controls in both places, but the vaccine was only applied in the FYRA. The disease was successfully controlled in both areas (6).

In 1999, type O vaccine was supplied from the EUVB to both Japan (1 million doses) and the Republic of Korea. The vaccine

was applied in Korea, but the disease was controlled in Japan without recourse to vaccination. In 2000, some 1.3 million doses of trivalent (types O, A and Asia 1) vaccine were supplied to and administered in the buffer zone in the Thrace region of Turkey.

Regarding the IVB, the first and only large-scale activation took place in 2001 when 500,000 doses of type O vaccine were formulated for possible use during the epidemic in the UK. The vaccine was not deployed subsequently (7).

There are no reports of large-scale activation of the NAVB. The bank in Argentina was activated in 2001 to supply 500,000 doses of tetravalent vaccine, all of which were applied.

This summary does not take account of the emergency supply of fully formulated vaccines. However, it is noteworthy that the suppressive vaccination administered to cattle against the outbreaks of FMD in the Netherlands in 2001 was a routine, commercial vaccine rather than an emergency vaccine, with a minimum potency of 3 PD<sub>50</sub> per dose.

## A brief summary of experimental studies on emergency vaccines

For vaccine production, FMD virus is grown in continuous cell lines in suspension culture. The harvest is clarified and the virus inactivated, usually with binary ethyleneimine. The viral antigen can be concentrated and partially purified and is then used to formulate adjuvanted vaccine or stored over liquid nitrogen for later formulation. The production and testing of conventional FMD vaccines is described in the Office International des Epizooties (OIE: World organisation for animal health) *Manual of standards for diagnostic tests and vaccines* (32) and in various international pharmacopoeias.

A number of modern biotechnological techniques have been explored towards the development of improved FMD vaccines (17, 39). However, none have yet progressed beyond the experimental stage.

### The onset of immunity

The rapidity of development of protective immunity following emergency vaccination is clearly of extreme importance. Studies have been conducted in cattle (20), sheep (13, 14) and pigs (20, 36, 37), demonstrating that protective immunity to clinical disease can be engendered within 2 to 4 days of vaccination in all these species (13, 14, 20, 36, 37). In one experiment in pigs, full immunity did not develop until 21 days post-vaccination (20) but there are indications that the level of challenge is critical, especially in pigs, and that very severe challenge can overwhelm immunity, as in this experiment.

Note should be taken that clinically immune vaccinates can continue to transmit infection to in-contact, susceptible animals for up to 7 days post-vaccination in the case of pigs (37) and 14 days in the case of cattle (21). Moreover, vaccination does not prevent the acquisition of the asymptomatic FMD carrier state in challenged, clinically immune ruminants. Some limited evidence suggests that high potency vaccine can reduce the acquisition of the carrier state (20). Further research is needed to clarify a number of these issues.

### Adjuvants and vaccine formulation

Pigs show a very poor response to aluminium hydroxide-saponin adjuvanted, aqueous vaccines and double oil emulsion (DOE) formulations are preferred for this species. The oil vaccine is also commonly used for ruminants, especially in South America and is generally accepted as being at least as effective as aluminium hydroxide vaccines in terms of rapidity of development and duration of immunity. Vaccine banks generally have provision for formulation with either type of adjuvant.

Research has been focused on improved adjuvants and especially oils and emulsifiers. Utilisation of Montanide ISA 206 and ISA 25 oils provides significant advantages in terms of facilitation and simplification of vaccine formulation (14). Recent development of an experimental stratified and cryogenically stored (SACS) vaccine in which the oil, aqueous and antigen phases are successively layered and frozen above each other in the final container resulted in potent vaccines. These were complete and ready for application after mixing of the phases in the vial at the time of vaccination (10). Further studies are warranted, including the investigation of possible scale-up, since there is the potential to combine the immediate availability of pre-formulated vaccines with the long-term stability of frozen antigen.

In general terms, the higher the level of antigen incorporation in the vaccine, the greater the potency of the vaccine and the ability of the vaccine to stimulate a rapid response, the broader the spectrum of antigenic cover elicited and the longer the duration of immunity engendered. In contrast, the higher the antigen incorporation level, the more expensive the vaccine and the fewer the number of doses which can be produced from a given amount of antigen. There is, however, evidence for a sigmoidal dose response and a threshold above which further incorporation of antigen elicits little increase in the immune response, at least in respect of the serum-neutralising antibody levels attained (33). Choices have to be made to arrive at the most satisfactory compromise between these characteristics. The current OIE recommendation is that emergency vaccines should contain a minimum of 6 PD<sub>50</sub> per vaccine dose, compared with the minimum recommendation of 3 PD<sub>50</sub> for vaccines produced for routine vaccination. Results for banked antigens have typically exceeded this value by a significant margin, e.g. IVB antigens have produced values ranging from

9 PD<sub>50</sub> to equal or greater than 112 PD<sub>50</sub> per vaccine dose in cattle (8) while those in the EUVB, tested by a different method, have also been shown to have potencies well above the recommended minimum (11).

## Areas for further research

### Antigen preparation

Further research is required on the preparation, and particularly the purification, of antigens for emergency vaccines, firstly to improve the stability of the antigens after formulation and secondly to facilitate differentiation between infected animals and vaccinated animals.

Some vaccines made using concentrated, inactivated FMD antigens have shown reduced stability compared to conventional antigens (7, 19) while this effect has not been observed with other vaccines (11). Possible causes include the presence of proteases from the culture harvest that were co-concentrated with FMD antigen during manufacture and/or the type of formulation employed. This potential problem may not be significant in circumstances where the vaccine is applied within a short time of formulation, but could become an issue if application were to be delayed.

The replication of FMD virus in an animal or in tissue culture cells proceeds through a cascade of intermediate proteins, including the several non-structural proteins (NSPs), to the eventual production of new virus particles. Antibodies are produced to all these proteins during the course of FMD infection in an animal. In contrast, vaccines – depending on their method of manufacture – are composed principally of intact virus particles and so are less likely to produce antibodies to the NSPs, although the production of such antibodies may follow repeated vaccination. This problem can be avoided by producing vaccine of sufficient purity in terms of NSPs (18) and it would be highly desirable to establish NSP purity criteria for all vaccine antigens.

About half of the ruminant animals exposed to FMD virus develop a carrier state, i.e. infective virus can be recovered from the oro-pharyngeal region for more than 28 days after exposure (35). Such virus has been shown to persist for up to three and a half years in cattle, nine months in sheep and four months in goats. The carrier state may also develop in vaccinated animals, even when the animals are immune to the development of clinical disease. The epidemiological significance of the carrier state remains controversial but this state is perceived as a potential threat of infection to susceptible animals and consequently acts as a barrier to national and international trade (35).

Both infection and vaccination result in production of antibodies. This can lead to difficulties in differentiating

between animals which have recovered from disease and those which have been vaccinated, or vaccinated and then subclinically infected. Since vaccination can both mask the presence of infective animals and confound their serological recognition, vaccination programmes carry a penalty for establishment of freedom after an outbreak. This is one of the main reasons for the reluctance of authorities to use vaccine in an emergency situation.

Tests have been developed to assist in this differentiation, the principal test being an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to the three ABC NSPs of FMD virus (15, 29). These tests are currently applicable on a herd rather than an individual animal basis and aspects still require validation. If an emergency vaccine contains immunogenic levels of NSPs, then antibodies may be elicited against them, thereby complicating the testing required to establish freedom from FMD infection.

### The immune response

As indicated above ('The onset of immunity'), further vaccine research would be desirable in target species on the speed of onset of immunity, blocking the transmission of virus from clinically immune vaccinates to in-contact susceptible animals, the duration of immunity and the carrier state and prevention of this state. Much research on the nature of FMD immunity has focused on the humoral response to vaccination and additional studies on the role and possible exploitation of other protective mechanisms, such as innate immunity, cellular immunity, cytokines and mucosal immunity could be profitable.

## Points to consider for the future of foot and mouth vaccine banks

### Deciding on the constitution and ownership of a vaccine bank

Antigen in FMD vaccine banks may be shared in an international bank, or may be exclusively held for the benefit of one country. Members of a multinational bank must agree on access to antigen, the speed of formulation in time of need, the constituent strains and the types and volumes of vaccine that may be required.

Shared ownership reduces costs but could lead to conflict of interest between members. Antigen stored in the IVB is jointly owned by eight countries, each having varying rights of withdrawal proportional to their financial contributions. The countries are widely dispersed throughout the world, thus limiting the risk of concurrent, competing demands. However, that risk remains. For example, Australia and New Zealand have closely aligned quarantine policies with broad acceptance of common disease status resulting in minimal requirements for

import restrictions between the two countries. The occurrence of FMD in one country could lead to appearance of the disease soon after in the other, with immediate implications for antigen accessibility. The same risk applies to Europe, as was demonstrated during 2001 when disease rapidly spread from the UK to Ireland, France and the Netherlands.

Vaccine supplied from banked antigen is likely to meet only the initial emergency demand, whereas the situation may call for vaccination on a much larger scale. No bank holds more than 5 million doses of any one strain of antigen – enough to vaccinate around 2.5 million cattle on two occasions. Should disease rapidly become widespread, this could be inadequate to service the needs of countries with large numbers of susceptible livestock. Australia, for example, has some 27 million cattle, 115 million sheep and 2.5 million pigs. According to current planning, vaccine would only be used there if initial attempts at stamping-out had been unsuccessful, so much larger volumes of vaccine would probably be required than are currently immediately available. Similarly, at the time that vaccination was first considered in the UK in 2001, the availability of vaccine was initially limited to 500,000 doses from the IVB with the possibility of a further 5,000,000 doses from the EUVB. This can be compared with the UK population of some 11 million cattle, 27 million sheep and goats and 6 million pigs. Furthermore, countries have no guarantee that additional emergency supplies would be readily available from commercial sources operating to the required standards of good manufacturing practice (GMP) and in compliance with pharmacopoeial criteria. Manufacturers plan the production of vaccine well in advance against received orders and could already be fully committed when an emergency strikes. These examples underline the difficulties in defining policies on the amount of antigen to be stored, ownership of antigen and the manner in which a bank should be administered.

### Inter-bank co-operation and rationalisation: security of supply

The total amount of antigen available in the European banks alone – excluding stocks held by private companies and the ARRIAH vaccine plant – is equivalent to some 70 million monovalent cattle doses (34) and there is considerable duplication in the types and strains of antigens stored. There are opportunities for further international collaboration and rationalisation of these stocks.

A vaccine bank is a contingency which hopefully will never be used. As such, vaccine banks are most cost-effective if shared by several contributors. If the number of contributors is sufficiently large, then the risk of more than one concurrent demand can be accommodated by storing larger volumes of antigen. Since the anticipated need for antigen would hopefully be a rare event, the most cost-effective type of functioning would be for a client to pay low overhead costs but to be prepared to pay a premium in time of need. For a country

normally free of FMD, that premium would probably be a small fraction of the overall cost of controlling an incursion of disease.

Where antigens are owned by one country, provision can still be made for sharing antigens with others. Members of one bank would have first call on their own, high priority, antigens but may have reciprocal access to other banks, either for antigens they do not store, or for additional stocks of common antigens, where this approach is considered an acceptable risk. Under such circumstances, clear rules would need to be in place to ensure that primary and reciprocating members had defined access to antigens.

### Selection of vaccine serotypes and strains

A range of antigens needs to be available for vaccine formulation in order to meet all likely contingencies. A decision must be made by disease control authorities on how many strains of vaccine would be needed, on what basis strains would be selected, how many doses of each would be needed and what proportion should be held as fully formulated vaccine and/or as antigen.

The immediate usefulness of a bank depends upon the inclusion of serotypes and strains appropriate for an anticipated or actual emergency. A potential weakness lies in the possibility that an outbreak could occur due to a virus which was not adequately matched by those held in the bank. Thus the selection of serotypes and strains must be continuously reviewed to attempt to ensure that all current and emerging threats are covered, while recognising that circumstances may dictate otherwise. Comprehensive and continuous global epidemiological surveillance is an essential component of this process and many improvements are necessary in this respect, since there are large areas of the world for which disease information is scant or absent.

In the past, when a new strain of disease has emerged that was not well matched by existing vaccine strains, the practice has notably been to deploy an existing vaccine of the same serotype, preferably at a high level of antigen incorporation. Revaccination is practised within three to four weeks of primary vaccination and continued in this manner until the new strain becomes available as a vaccine. However, note should be taken that this process takes time, that novel strains are not always easily adapted to tissue culture and that the yield of such antigens or their immunogenicity may be poor.

In the world of today, marked by rapid and extensive movement, both legal and illegal, of people, animals and products, accompanied by the added threat of bio-terrorism, prediction from whence an introduction of FMD might originate is very difficult. The OIE/Food and Agriculture Organization World Reference Laboratory (WRL) makes periodic recommendations on strains to be included in FMD vaccine banks, based on current epidemiological intelligence.

The most recent recommendations were formulated in September 2001 and are listed in Table I in order of priority, although within each group, strains are not in order of importance (5).

**Table I**  
**Recommendations on strains to be included in foot and mouth disease vaccine banks, September 2001 (5)**

Priority	Strain
High	O <sub>1</sub> Manisa (covering the pan-Asian toptotype)
	O <sub>1</sub> BFS or O1 Lausanne
	A <sub>22</sub> Iraq
	A <sub>24</sub> Cruzeiro
	Asia 1 Shamir
	A Iran 96
	SAT 2 Saudi Arabia (or equivalent)
Medium	SAT 2 Zimbabwe
	A <sub>15</sub> Bangkok related strain
	A <sub>87</sub> Argentina related strain
	A Saudi Arabia 23/86 (or equivalent)
	SAT 1 South Africa
	A Malaysia 97 (or equivalent)
	A Eritrea 98
	C <sub>1</sub> Noville
Low	O <sub>1</sub> Taiwan 97 (pig adapted strain or Philippine equivalent)
	A Iran 99
	SAT 2 Kenya
	SAT 1 Kenya
	SAT 3 Zimbabwe
A Kenya	

Antigens held in the IVB are routinely monitored at Pirbright by an *in vitro* virus neutralisation test using bovine sera raised against the strains maintained in the bank, as assayed against selected, current, field virus isolates. These tests enable assessment of the expected level of protection the antigens might afford and also identification of any requirements for the inclusion of additional antigens (9).

### Turnover and replacement of banked antigens

Although antigens stored at low temperature retain immunogenicity for extended periods, some factors may justify the turnover and replacement of stocks. For example, epidemiological situations may change to the point where particular antigens are no longer appropriate. To avoid wastage, antigens should be turned over while still in demand by making antigen available to meet routine orders for vaccine. In such circumstances, the vaccine producer could own the antigen and the vaccine bank would then be based on an agreement for a guaranteed supply of formulated vaccine of specified quality within a certain period of days. The producer could then turn over antigen stocks as appropriate and the main costs to the client would be for antigen storage and the capacity of rapidly providing antigen when required.

Another approach to the periodical turnover of stocks could be to donate a proportion to non-member nations. Many countries that participate in vaccine banks also provide support for animal health activities to developing countries in which FMD is endemic. In the same way that the EU has in the past provided vaccine from the EUVB to neighbouring countries, the practice of providing FMD vaccine from vaccine banks as a form of development assistance could be more widely adopted.

Foot and mouth disease viral antigen harvests for vaccine production may contain residual amounts of bovine materials, such as serum, used as components of culture media. Ethical vaccine producers take great care to source their serum supplies from countries and even specific herds of high health status, the requirements including national freedom from bovine spongiform encephalopathy and herd freedom from bovine pestivirus infection. There is a large international market for serum products and a constant risk of both product substitution and misrepresentation of origin. Thus, vaccine producers must maintain very strict control over the source of their biological ingredients to satisfy themselves and national regulatory authorities of their provenance. Apart from ensuring the absence of adventitious agents, there is a general trend for quality assurance to be more demanding with time. These considerations may constitute additional reasons for the turnover and replacement of antigen stocks.

## Regulatory considerations

Over time, therapeutic and biological products have been subjected to greater regulatory demands. Commonly, Chief Veterinary Officers have the power to over-ride registration requirements in an emergency. However, in an increasingly litigious world, there is a risk in so doing. Additionally, vaccine manufacturers need assurance that in the event of a request to supply vaccine, their product will be acceptable.

Regulatory authorities could advantageously facilitate supply of emergency vaccines by providing provisional registration in advance of need. Registration could encompass most of the normal licensing requirements, including product efficacy and safety, compliance with GMP and periodic audit, as required. Whenever new demands are made for registration, they could be incorporated into provisional registration requirements. Final registration could then be undertaken rapidly by a desktop audit of actual production batches and formulation runs. Such a facility is not presently or commonly available.

Revisions have been proposed to the monograph of the European Pharmacopoeia on FMD vaccines (16). These would improve the standardisation of potency testing and provide for challenge testing in pigs and/or cattle, while encouraging the use of assessment by serological response and other validated, alternative tests. Proposals have been made to introduce new field strains into a range of existing strains without the need for a new registration process. In this context, in-process controls –

in particular the kinetics of inactivation – assume particular importance.

Adoption of these revisions would establish a basis for greater uniformity of standards. The proposition that countries pre-register FMD vaccines on the basis of manufacturers meeting appropriate GMP and quality assurance standards would be more realistic. In addition, the revisions would also enable the rapid registration of formulated vaccine from the vaccine bank of members. Uniform standards would also facilitate the sharing of antigens between banks and member countries.

In many countries, the use of FMD vaccine is controlled under national and international law. For example, vaccination is forbidden in the countries of the EU, except in cases of emergency and with the authorisation of the European Commission. This can lead to bureaucratic delay in the implementation of emergency vaccination. Such delays may be exacerbated when vaccine is to be supplied to non-members of a bank. In Albania in 1996, for example, 26 days elapsed between the first suspicion of disease and the first application of vaccine supplied from the EUVB (6). Since time is of the essence in the control of FMD, contingency planning must include measures to anticipate and minimise such delays.

The recommendations of the OIE contained in the 2001 version of the *International Animal Health Code* (31) are also important, since they specify the conditions for the allocation of disease status for individual countries in the context of international trade in animals and animal products. Regarding FMD, where emergency vaccination is used in an erstwhile disease-free country, that country cannot apply for the re-establishment of the status of 'disease-free without vaccination' until at least three months have elapsed since the last case of disease and at least three months have elapsed since the last vaccinated animal has been slaughtered, all subject to the stamping-out of cases and the satisfactory completion of clinical and serological surveillance. These restrictions weigh heavily in deciding whether or not to apply emergency vaccination, especially in countries where international trade in animals and animal products makes an important contribution to the national economy.

There is a case for re-examining the OIE recommendations, investigating their possible modification to reduce the trading consequences of emergency vaccination, especially if, as discussed above ('Antigen preparation'), standardisation of antigen quality allows discriminatory serology to be undertaken to confirm the absence of concurrent infection. The principles of regionalisation and zoning should also be reviewed in the context of emergency vaccination.

The recent outbreaks of FMD in Europe have focused attention on the need for emergency vaccination of particular groups of animals including rare breeds, zoo animals, certain animals under experimentation and animals of particularly valuable genetic potential. There is a body of opinion that such animals

should be able to be vaccinated in an emergency under special circumstances and conditions, without the country necessarily losing the overall OIE disease status. These topics are also under active consideration.

### Contingency planning

Contingency planning should encompass all the requirements for emergency vaccination, including the provision of supplies of vaccine and vaccination equipment, transport, the cold chain, disinfectants, the recording of immunisation and the training of vaccination teams (2, 22, 25). As discussed above ('Regulatory considerations'), advance provision is important for rapid approval for importation and use of emergency vaccine.

Simulation exercises should also be performed on a regular basis. These can be used to predict projected requirements for emergency vaccine under different scenarios.

### Decision support systems

The concept of emergency vaccination against FMD is simply enunciated and readily accepted. However, for the reasons outlined in this paper, deciding in practice whether or not to apply emergency vaccination, when to vaccinate, which species to vaccinate and where the vaccine should be applied is often extremely difficult. Risk and cost-benefit analyses and computerised scenario modelling can be used in predicting the outcome of different options for the control of outbreaks of FMD, including the use of emergency vaccination, and as an aid to making decisions in this complex field. However, it is essential that such models be sufficiently comprehensive and sophisticated to give reliable predictions and that the basic information underlying the analyses be both accurate and up-to-date.

In 1989, a cost-benefit analysis was undertaken by the European Commission which predicted that significant overall economic benefit would accrue over a ten year period from abandoning the then routine policy of mass prophylactic FMD vaccination and replacing this practice with stamping-out and emergency ring vaccination, even if the anticipated worse-case risk of 13 primary and 150 secondary outbreaks per primary should subsequently ensue (4). The recommendations were adopted and all FMD vaccination ceased in 1991 within the EU. During the following decade, there were incursions of FMD, but they were restricted to countries at the periphery and to relatively few outbreaks, so that the policy appeared to have been justified. However, many circumstances changed between the time of these analyses and the outbreaks in Europe in 2001 when, within a period of eight months, there were 2,030 outbreaks in the UK, 1 in Ireland, 2 in France and 26 in the Netherlands. These events emphasise that contingency planning and cost- and risk-benefit analyses must be undertaken on a regular and comprehensive basis. They must

be modified to take account not only of the emerging epidemiological situation but also of additional factors which may assume differing importance over time. Examples of these include the public acceptability of control options, including the mass destruction and disposal of animals and the overall economic effects, including indirect effects such as loss of income from tourism. These requirements are not easily or cheaply satisfied. Nevertheless, a number of computer-based models are available (23, 26, 27, 38) and further research is needed in this area to refine and validate the models.

## Conclusions

In the aftermath of the widespread outbreaks of FMD during the period 1999-2001, international authorities must closely re-examine existing regulations and control measures, including those appertaining to vaccine banks and emergency vaccination, together with their consequences for trade. The outcome of these deliberations could have far-reaching implications for the control of FMD and other diseases and for commerce in the agricultural sector.

International consensus is required to define standards of antigen quality and to establish agreed methodology for discriminatory serology as requirements to render emergency vaccination a more desirable and practical option. Pressure for vaccination in the face of an outbreak is increasingly apparent from various quarters, arguing for alternatives to mass slaughter with the adverse effects, real or perceived, for animal welfare, the environment and national economies.

The needs for storage of large quantities of multiple strains of antigen (17 strains are recommended as high and medium priority by the WRL) and the recognition that appropriate strains will change over time, raise questions of logistics and funding. Pooling of resources into a large bank would be an efficient mechanism for meeting needs but would probably be resisted by countries seeking a high level of assurance that their requirements would always be accorded priority, despite competing demands from other members. A solution could lie in a reciprocal arrangement by which countries can own the highest priority antigens and have access, as available, to antigens of strains that represent a lower threat. Harmonisation of production and licensing criteria will be an essential element to any antigen-sharing scheme.

Initiatives to be taken at the national and international level include the need for regulatory authorities to develop pre-registration protocols so that emergency vaccines can be rapidly approved for use, without the threat of legal or other challenges.

One lesson from the UK outbreak in 2001 is that contingency planning for FMD should not be restricted to disease control authorities and the livestock industries in isolation.

Contingency planning must also involve all stakeholders and those from sectors in the community that stand to benefit from rapid response and effective control and who can contribute to advanced planning. In addition, contingency plans must be regularly revised to take account of changes in the disease situation, in science and technology and in political, social and economic circumstances. Policy must be defined and agreed in advance so that decisions can be made rapidly in a time of crisis.

A most important means of reducing the threat of FMD for disease-free countries is to improve control of the disease in endemic regions. A more extensive use of vaccine banks could play a part in this objective. In the past, banks have generally been developed as a contingency against outbreaks in developed countries having the resources for their establishment and maintenance. Outbreaks and epidemics of FMD are often poorly controlled in less developed countries through a general lack of resources, but in particular, a lack of foreign exchange to purchase vaccine. Vaccines that are used in these circumstances may be of inappropriate strain composition, include unnecessary additional serotypes, or fail to comply with international pharmacopoeial criteria, but are used because they are all that is available and/or affordable. The participation of vaccine banks could enable donors of development aid to influence the appropriate selection and quality of vaccines and by creating a regular turnover of stocks, ensure that stored antigens satisfy both current quality standards and antigenic relevance.

A broadened objective for vaccine banks, to include the needs of developing countries with endemic or sporadic FMD, could address the humanitarian objectives of development assistance while at the same time reducing the threat of the global spread of FMD by confronting the disease at source.

Decision support systems, such as epidemiological modelling and risk and cost-benefit analyses, can play a useful role in the control of FMD and in the evaluation of options, including emergency vaccination. Existing models should be continuously updated, refined and validated.

Epidemiological intelligence is crucial in underpinning the vaccine bank concept. There is a pressing need to strengthen the comprehensive collection and characterisation of emerging FMD viruses on a global basis, in order to monitor the evolution of the disease, enable the early recognition of new threats and implement preventive action, including the constituents and readiness of vaccine banks.

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## Fièvre aphteuse : l'avenir des banques de vaccins

A.J. Forman & A.J.M. Garland

### Résumé

Les auteurs passent rapidement en revue l'histoire des banques de vaccins contre la fièvre aphteuse, leurs lieux d'implantation actuelle, leurs souches et sérotypes constitutifs, et évoquent les situations qui ont nécessité leur utilisation. L'article dresse un inventaire sommaire des études expérimentales en cours sur les vaccins d'urgence ainsi que les domaines nécessitant des recherches complémentaires. Les auteurs envisagent l'avenir de ces banques en s'attardant sur les forces et faiblesses des banques actuelles ; par ailleurs, ils proposent quelques mesures susceptibles de contribuer à leur amélioration.

Le nombre plutôt limité d'utilisations des banques au cours de leurs vingt-cinq années d'existence s'explique en partie par les sollicitations relativement rares

dont elles ont fait l'objet. Il faut aussi y voir la difficulté de choisir les modalités et le moment adéquats d'utilisation de la vaccination d'urgence. Cependant, dans un contexte de risque accru de dissémination du virus de la fièvre aphteuse dans le monde, les banques continueront à jouer un rôle stratégique et tactique déterminant dans la lutte contre cette épizootie, qui compte parmi les plus contagieuses.

**Mots-clés**

Banques de vaccins – Fièvre aphteuse – Urgences – Vaccin contre la fièvre aphteuse – Vaccination.



## El futuro de los bancos de vacunas contra la fiebre aftosa

A.J. Forman & A.J.M. Garland

**Resumen**

Los autores repasan brevemente la historia de los bancos de vacunas contra la fiebre aftosa, su localización actual y los serotipos y cepas que contienen, y recuerdan las ocasiones en que esos bancos han sido utilizados. Después resumen una serie de estudios experimentales sobre vacunas de emergencia y señalan los ámbitos en que es preciso seguir investigando. También examinan el futuro de estos bancos, deteniéndose a considerar los principales puntos fuertes y débiles de los que ahora existen y formulando propuestas para incorporar posibles mejoras.

El hecho de que esos bancos hayan sido utilizados relativamente pocas veces durante sus 25 años de existencia demuestra, en parte, que se ha recurrido a ellos con relativa infrecuencia, pero también refleja la dificultad de decidir cuándo y cómo conviene utilizar vacunaciones de emergencia. En tiempos como los actuales, sin embargo, con un creciente riesgo mundial de propagación de la fiebre aftosa, parece evidente que los bancos seguirán revistiendo importancia estratégica y táctica en la lucha contra esta infección, la más fácilmente transmisible de las enfermedades animales.

**Palabras clave**

Bancos de vacunas – Emergencias – Fiebre aftosa – Vacunación – Vacuna contra la fiebre aftosa.



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