Research and technological developments required for more rapid control and eradication of foot and mouth disease

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Summary: Foot and mouth disease (FMD) is the major disease barrier to international trade in animals and animal products. Countries free of the disease take severe measures to exclude the virus, to avoid the potentially devastating consequences of an outbreak, particularly for the animal export trade. Consequently, FMD-free countries either refuse to trade with sporadically or endemically infected countries, or else apply stringent and often expensive safeguards before agreeing to import animals or animal products.

Technological advances can assist countries which are free of FMD to maintain this status. Such advances also aid countries in which the disease is sporadic or endemic, by accelerating the progress of control and eradication programmes.

The authors review recent advances in tests for the diagnosis of FMD, in addition to advances in surveillance, vaccinology and information technology, i.e. computing and networking. Furthermore, the authors examine the application of these advances to improve programmes for the control and eradication of FMD, and identify the requirements for further research into the disease.


INTRODUCTION

Foot and mouth disease (FMD) is the major disease constraint to international trade in livestock and animal products. Countries free of the disease enjoy access to world markets, but countries endemically or sporadically affected by FMD suffer productivity losses within their territory and have greatly reduced opportunities for export trade. Consequently, FMD-free countries take strong measures to avoid the introduction of the disease, and generally have well-established contingency plans to mount a rapid and effective response, should the virus gain entry and cause an outbreak.

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For FMD-free countries, the application of research findings and technological developments plays a role in ensuring that the FMD virus is more effectively excluded, e.g. through the application of specific and sensitive tests on animals and germplasm (sperm and embryos) before importation. Moreover, if the virus does gain entry, it is crucial that these countries can provide technical support to ensure that the virus is rapidly diagnosed and eliminated.

Those countries which have achieved freedom from FMD are rewarded by the increased productivity of livestock and better trade opportunities. Such countries have encouraged others which are endemic or sporadically infected to follow suit and establish control and eradication programmes. However, the progress of such infected countries in achieving this goal has been constrained, in some cases, by technical problems, for example, poor and short-lasting protection from vaccines.

This paper identifies the research and technological needs of FMD-free countries, to increase their security, as well as the needs of sporadically and endemically infected countries, to accelerate their progress towards eradicating the disease.

**RESEARCH AND TECHNOLOGICAL DEVELOPMENTS FOR FOOT AND MOUTH DISEASE-FREE COUNTRIES OR ZONES**

**Import testing**

The first priority for an FMD-free country is to avoid the introduction of the virus. The greatest risk of importing FMD virus is through trade in animals and it is, therefore, essential that tests on animals originating from countries which could pose a risk are highly sensitive and specific. To ensure that animals involved in trade are free of infection, both direct tests for FMD virus and indirect serological tests for antibody to the virus are carried out before the animals or animal products are allowed into the territory of the importing country. In regard to indirect tests, there is scope for the development of serological tests which give fewer false-positive results – all serological tests give some. It is likely that competitive, monoclonal antibody-based tests will be used increasingly, possibly in conjunction with genetically engineered antigens. Such tests could be readily standardised and, if the monoclonal antibody was directed against a non-structural protein of the virus, would be serotype independent, thereby eliminating the need to test for antibodies against a range of serotypes.

Direct tests on animals involved in trade most commonly involve taking samples of oesophageal-pharyngeal fluid from the throat with a ‘probang’ sampler and checking for the presence of the FMD virus or viral ribonucleic acid (RNA). The most sensitive system for isolating FMD virus is primary bovine thyroid (BTY) cells (14), but these are available to few laboratories. Recently, progress has been made in the development of immortalised BTY cells (N.P. Ferris, unpublished findings) and this may offer an opportunity to provide an alternative system. Another approach would be to test nasal swabs for the presence of viral RNA by the polymerase chain reaction (PCR) method. Preliminary results are encouraging (10). An advantage of this method is that it is simpler and less invasive for animals than probang sampling.
Disease awareness

The potential for the spread of infection is especially high in FMD-free countries which do not vaccinate, so the rapid recognition of a suspected case, followed by laboratory diagnosis and the speedy implementation of control measures, are essential for the rapid eradication of the disease. Farmers and veterinarians are in the front line, so it is essential that they are aware of the key features of the disease. They should be alerted when the risk of entry is high, for example, when there are reports of outbreaks in neighbouring countries. Illustrated booklets and video films on FMD should be made available to veterinarians and farming organisations, to increase awareness. In the near future, personal computer-based, multimedia systems (e.g. AVIS) will offer a convenient method of disseminating information on the disease. In addition, national and regional FMD laboratories should, where possible, offer veterinarians, particularly those in the notifiable diseases sections of national Veterinary Services, the opportunity of seeing clinically affected animals.

Contingency plans

It is crucial that the national Veterinary Service of an FMD-free country prepare a set of emergency contingency plans for the control and eradication of FMD, and that the members of the national Veterinary Service be trained in the implementation of those plans. There should be access to a contingency fund to compensate farmers fully and speedily when a 'stamping-out' policy is applied. Guidelines for formulating contingency plans, jointly compiled by the Food and Agriculture Organisation (FAO), Office International des Epizooties (OIE) and European Union (EU), have been published by the FAO (6).

Advantage should be taken of developments in computing and networking to accelerate the transfer of epidemiological and disease data, both within the country and internationally. Mock training exercises are important to ensure a high level of efficiency in the event of a real emergency.

It is likely that, in the near future, computer-based systems for the management of FMD epidemics will become available for operational use (e.g. EpiMAN) (13). Such systems would have the advantages of an enhanced processing capacity, speed, objective analysis and prediction.

Vaccine banks

Many countries have either joined vaccine banks or have made arrangements with private vaccine producers for the provision of emergency vaccine in the event of an outbreak, so that these countries have the option of deploying vaccination as part of their contingency control measures. Generally, vaccination would be used as an adjunct to the stamping-out programme, and at a time when there are clear indications that that policy alone will not be successful.

Tests of highly potent emergency vaccines have shown that they give an early and high level of immunity against challenge, even after just one dose (4, 5). As with other FMD vaccines, however, they have a disadvantage, in that a proportion of animals which are challenged by live virus are not protected against the establishment of the carrier state. Therefore, countries deciding to employ emergency vaccine in the face of an outbreak are likely to encounter an extended trade embargo.
It would be a considerable advantage if vaccines intended for emergency use could immunise the respiratory tract of ruminants against persistent infection. It is likely that this will require the development of live vector agents which express FMD immunogens within the respiratory tract, or can provoke a response in that region when administered parenterally.

**Diagnostic tests**

There is a continuing need to improve diagnostic tests, thereby offering more effective support to disease control and eradication measures during emergencies. It is unlikely that the speed of direct serotyping by enzyme-linked immunosorbent assay (ELISA) will greatly increase from its present time of approximately three hours. However, if the test incorporated panels of monoclonal antibodies, it should be possible to serotype, characterise the strain and select the most appropriate vaccine strain simultaneously. In the case of the last requirement, this would shorten present test procedures by several days.

There is also a need for more rapid sero-surveillance tests during outbreaks to identify silent infection in animals which commonly do not show overt clinical signs of FMD, i.e. sheep and goats. These tests should also be carried out when outbreaks have ended, to confirm that the virus is no longer circulating. In such circumstances, the national veterinary authority may be willing to authorise the use of pen-side tests. Such tests would greatly accelerate investigations and shorten the duration of requirements for movement stand-still. This approach would be particularly time-saving for those countries that do not have a national FMD laboratory, and which are presently obliged to send serum samples for testing to a regional FMD laboratory, or to the OIE/FAO World Reference Laboratory (WRL) for FMD.

Another approach to surveillance would be to test milk rather than serum. This would be non-invasive and, if sufficiently sensitive, should considerably accelerate investigations. Tests have been developed for screening herds for bovine virus diarrhoea and infectious bovine rhinotracheitis virus, and initial steps to develop ELISA-based systems to detect antibodies to FMD virus have shown promise (1).

A reliable, practical, rapid and sensitive test to differentiate the carrier animal from the vaccinated but non-carrier animal, after the use of emergency vaccine, would be a valuable advance but so far this objective has been elusive. Tests developed to date have either been impractical for large-scale use, e.g. have involved immuno-blotting procedures, or have been invasive, e.g. have required the collection of probang samples to test for immunoglobulin A (IgA). In addition, such tests have been of low sensitivity, e.g. the detection of virus infection associated antigen by immunodiffusion, or have sub-optimal specificity, e.g. ELISA-based tests for antibodies to non-structural proteins. However, considerable efforts are being concentrated in this area and preliminary results indicate that these efforts may well be successful (9).

Similarly, the development of non-invasive tests directly to identify carrier animals after a disease episode would be a considerable advance. Researchers in Germany have explored the possibility of testing nasal swabs for the presence of FMD viral RNA by a PCR method and have obtained encouraging results (10).

The speed of molecular biological investigations is steadily improving. For example, it has been shown that an analysis can be made of the sequence of around 200 nucleotides of the 1D coding region of a contemporary field strain of FMD virus...
within two days by reverse-transcription PCR (RT-PCR) (7, 8). Molecular epidemiology has proved to be a very powerful and valuable tool for identifying the probable origin of outbreaks of FMD and for contributing to the development of improved strategies for control and prevention. It was mainly through the use of this technique that a significant proportion of outbreaks in Europe, and later elsewhere, were shown to be due either to faulty vaccines or to escapes from laboratories (3). This provided strong support in favour of the argument to abolish vaccination in Europe, and to rely on the stamping-out policy and tighter import controls.

RESEARCH AND TECHNOLOGICAL REQUIREMENTS FOR SPORADICALLY OR ENDEMICALLY INFECTED ZONES OR COUNTRIES

Countries which are committed to a programme of FMD control usually have the eradication of the virus from their territory as the final goal. Within the time-frame of the programme, different disease control strategies may be applied. For example, if prophylactic vaccination is successful, it may be economically feasible to initiate the more expensive but more effective stamping-out policy, to achieve eradication. Similarly, it may be more acceptable for a country to eradicate the virus zone by zone, rather than initially attempting a nation-wide strategy. The geographical isolation of a country can determine options. Isolated countries, e.g. islands, can act more independently than countries with land boundaries. The latter will be obliged to co-ordinate their programmes with their neighbours.

As in the case of FMD-free countries, the application of developments in research and technology can influence the speed with which FMD is controlled and eradicated in FMD-sporadic or endemic zones.

Epidemiology and surveillance

An intensive and efficient system of epidemiological investigation, including the collection of high-quality case-history data and field samples for analysis which can be fed through a network to a central data bank, is an essential component of national and regional control programmes.

Epidemiological investigations can help in setting priorities for tracing outbreaks of FMD, deciding on other follow-up actions and establishing the origin of outbreaks. These investigations may demonstrate whether control strategies have succeeded and may highlight any need to alter those strategies. An inability to establish the origin of outbreaks may point to organisational deficiencies or a need for further research in certain areas or both.

Access to an FMD laboratory, whether national, regional or the WRL, is essential for the serotyping and characterisation of virus isolates. The Pan American Foot and Mouth Disease Center (PANAFTOSA) has played a leading role in this regard, and is recognised by the FAO and OIE as the organisation which provides technical support and co-ordination for FMD campaigns in South America. This Center acts as a channel of communication between the countries of that region and the WRL at Pirbright, in the United Kingdom (2).
The need to improve diagnostic tests to achieve more rapid control and eradication of FMD has already been discussed in relation to FMD-free countries and zones. Diagnostic tests of optimal sensitivity, specificity and rapidity are also important for sporadically or endemically infected countries or zones. Such countries or zones which use prophylactic vaccines require tests which can accurately and rapidly characterise virus isolates antigenically, to ensure that the strains incorporated in vaccines are appropriate for controlling the strains circulating in the field. Currently this task is performed by the liquid phase blocking ELISA but in the future greater use is likely to be made of panels of monoclonal antibodies. These need to be more widely produced, characterised and exchanged between laboratories.

The capability to undertake large-scale sero-surveillance is also essential for a variety of reasons, including the following:

- to monitor vaccination responses, to ensure that there is adequate and appropriate immunological coverage in regions where the virus is circulating or which are under threat
- to verify, as the campaign progresses, that those regions in which vaccination has ended are free of infection.

Automated and semi-automated ELISA-based work stations for processing large quantities of sera are now available and are likely to find wider use in the future. Apart from the speed gained in processing samples, such systems also provide better opportunities for standardisation and quality assurance.

Vaccines

The potency and safety of FMD vaccines have improved in recent years, enhancing the efficiency and speed of control and eradication campaigns in several countries and regions of the world where FMD was formerly a serious obstacle to sustained development. The contribution made by the PANAFTOSA towards the improvement of vaccines, and the part that those vaccines have played in the success of the Hemispheric Eradication Scheme in South America, provide a striking example of these advances (2).

Significant improvements have been made in the last decade to the speed with which FMD vaccines can induce an immune response, and the duration of that response. The PANAFTOSA has been in the forefront in work on adjuvants and has demonstrated the advantages of oil-based preparations. Further work is needed, however, because – compared to many other vaccines – FMD vaccines are relatively poor in many respects. For example, FMD vaccines do not effectively protect the respiratory tract. As a result, a proportion of vaccinated animals which encounter the virus are likely to become carriers, and thus pose a potential risk to any susceptible animals with which they may come into contact later. The development of FMD vaccines capable of protecting the respiratory tract would be a significant advance, but a greater understanding of both the immune processes in that region, and the production of immunogens which can be targeted at the tract area would be required beforehand. Vector agents which have an affinity for the alimentary or respiratory tract, and which could be bio-engineered to produce secretory immunogens, would seem good candidates for investigation, e.g. Salmonella and Mycobacterium tuberculosis organisms.
The consequences and practicality of applying FMD vaccine in combination with other vaccines should be investigated further. This has been done on a small scale without apparent detriment (11), and would be particularly attractive to farmers involved in extensive husbandry systems. Another approach, though this is still at the experimental stage, would be to use a bio-engineered vaccine which expresses a range of immunogens. Considerable success has been achieved with a poxvirus vector in protecting against other diseases under controlled conditions (12). It should be feasible to extend this work to incorporate genes in the vector which express FMD immunogens.

The ultimate test for evaluating the quality of an FMD vaccine under controlled conditions is the cattle challenge test. This test has, however, many disadvantages, e.g. high cost, disease security risk, ethical considerations, etc., and so there is a need for an alternative in vitro test which is internationally accepted. A number of national, private and regional FMD laboratories have accumulated considerable quantities of data comparing the correlation between in vivo cattle challenge tests and a variety of in vitro serological tests. An international body is required to take the lead in consolidating this data, to determine if it would be possible to replace the cattle challenge test by an in vitro test and, if so, to promote the acceptance of such a test.

**Vaccine quality control and quality assurance**

It is an anachronism that, although the importance of the quality of vaccine in FMD control programmes is well recognised, there are few laboratories world-wide to which a national authority can turn for an independent evaluation of the quality of an FMD vaccine. In general, quality assurance is left to the vaccine manufacturer. One notable exception is the EU Community Co-ordinating Institute for FMD Vaccines at Lelystad, the Netherlands, which is responsible for testing FMD vaccines produced within the EU or used in third countries (i.e. other countries which trade with the EU). Other regions of the world would benefit from a similar arrangement.

**Information technology**

The rapid collection and distribution of information on all aspects of disease control and eradication are essential, not only for the purposes of epidemiological surveillance, but also to ensure that veterinarians, farmers and other interested parties (both within the affected country and throughout the world) are kept well informed. It is vital to have data which can be used to monitor the success of the control and eradication programmes and to sustain them.

Computer-based data banks, linked to networks, provide a way of achieving a rapid collection and flow of information and are essential components of control programmes. The inclusion of a geographical information system should be considered, particularly for the collection and distribution of information on outbreaks. Multimedia systems are likely to find increased application for education and reference purposes.

**CONCLUSIONS**

The benefits of FMD control and eradication are mainly related to the increased opportunities for trade. These benefits are dependent upon the efficiency of the measures taken, not only to eradicate the disease, but also to prevent its re-
introduction. Central to this are the diagnostic methods applied, active epidemiological surveillance, the control of the movement of animals when necessary, and vaccination programmes. Monitoring of vaccine efficiency, diagnosis and the testing of imported animals require similar panels of tests. However, the most essential element is the efficiency with which animals are clinically inspected and suspicious cases acted upon.

Therefore, the first line of defence against FMD is the control of animal movement, especially imports. The tests employed for this must have a high degree of sensitivity and specificity to ensure that trade is not impeded, but also to ensure that the indigenous animal population is not placed at risk. Failure is likely to result in serious economic consequences. Efficient clinical diagnosis is essential to maintain an early warning system and initially to discriminate between different diseases. Nevertheless, the final result and, therefore, the standard of disease control and prevention, will rely on the quality of the diagnostic tests employed. Efficiency is irreversibly linked to the rapidity of accurate identification of infected animals and in some cases animal products, e.g. semen and ova.

The control, application and monitoring of a vaccination programme also rely on epidemiological surveillance. While the tests used are essentially the same as for primary diagnosis and import screening, technological advances have made a valuable additional contribution. These advances owe much to recent developments in computer technology. Many surveillance programmes employ computer-based data management systems and make surveys feasible which would not have been possible earlier. Such knowledge of the epidemiological situation in regions where the disease is either endemic or epidemic is essential if FMD control programmes are to be successful. The information can then be used to design or modify vaccination programmes and monitor the effect of such programmes on disease control. Studies on the application and assessment of new-generation vaccines are also relevant to the potential success of vaccination programmes in the future.

While FMD-free countries can focus on FMD prevention (and rapid control and eradication in the case of an emergency outbreak), countries in which the disease is endemic must direct their efforts towards eradication. Collaboration through various international agencies (e.g. the OIE, the FAO and the Pan American Health Organisation) and the World and Regional Reference Laboratories for FMD will promote the application of effective tests resulting from research and technological advances. It must be remembered that continued vigilance, awareness among farmers and well-trained veterinarians are all essential components for a successful campaign against FMD, as is continued research into the disease. A better understanding of the virus, its antigenicity and host immune responses is essential and the advances achieved so far must be maintained. Only through high-quality research will it be possible to improve disease control strategies and eradication programmes further.

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Résumé : La fièvre aphteuse est la principale maladie entravant le commerce international des animaux et des produits d'origine animale. Les pays indemnes de la maladie appliquent des mesures strictes pour empêcher l'apparition du virus et éviter ainsi les conséquences potentiellement préjudiciables d'une épidémie sur les exportations. C'est pourquoi ils refusent tout échange avec les pays où la maladie s'étend de façon sporadique ou endémique, ou bien imposent des conditions draconiennes et souvent coûteuses à l'importation d'animaux ou de produits d'origine animale.

Les progrès de la technologie peuvent aider les pays indemnes de fièvre aphteuse à conserver leur statut, tout en permettant à ceux où elle sévit de façon sporadique ou endémique d'accélérer la mise en œuvre de programmes de contrôle et d'éradication.

Les auteurs étudient les récentes améliorations des épreuves diagnostiques pour la recherche de la fièvre aphteuse ainsi que les progrès en matière de surveillance épidémiologique, de vaccinologie et de technologie de l'information, à savoir l'informatique et la gestion de réseaux. Ils considèrent également l'application de ces progrès à l'amélioration des programmes de contrôle et d'éradication de la fièvre aphteuse et identifient les domaines qui requièrent des travaux de recherche supplémentaires.


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Resumen: La fiebre aftosa constituye la principal barrera sanitaria al comercio internacional de animales y productos animales. Los países libres de esta enfermedad adoptan medidas muy rigurosas para evitar la posible penetración del virus, pues un brote de esta enfermedad tendría consecuencias devastadoras especialmente sobre la actividad exportadora del país. Por esta razón, los países libres de fiebre aftosa se niegan a comerciar con países infectados (ya sea de forma esporádica o endémica), o en todo caso aplican medidas preventivas muy severas y a menudo onerosas antes de permitir la importación de animales o productos pecuarios.

Las mejoras tecnológicas pueden ayudar a los países libres de fiebre aftosa a conservar dicha condición. De igual modo, estas mejoras pueden acelerar el avance en los programas de control y erradicación, y ayudar así tanto a los países en los que esta enfermedad se da esporádicamente como a aquellos en los que es endémica.

Los autores pasan revista a los progresos más recientes en materia de pruebas de diagnóstico para la fiebre aftosa, así como de vigilancia, de
vacunación y de tecnologías de la información (uso de computadoras y redes de informática). Por otra parte, los autores examinan la posible aplicación de estos avances a la mejora de los programas de control y erradicación de la fiebre aftosa, e identifican las necesidades en términos de investigación sobre esta enfermedad.


REFERENCES


