

# Future research on foot and mouth disease

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## Summary

The recent outbreaks of foot and mouth disease (FMD) in Argentina, Europe, Japan, the Republic of Korea, South Africa and Uruguay have brought to world attention the devastating effects of the disease in a naïve population and the social and economic costs of control and eradication. The fact that much still remains unknown about the natural history of FMD virus came as a surprise to some. This paper attempts to identify where research should be directed in order to be better prepared in the future.

## Keywords

Diagnosis – Foot and mouth disease – Persistent infection – Trade – Vaccines – Wildlife.

## Introduction

The preceding chapters have described the current knowledge on the natural history of foot and mouth disease (FMD), accumulated over the last hundred years. More is known about the structure and molecular biology of the virus and the epidemiology and control of the disease than probably of any other pathogen of purely veterinary importance. Nevertheless, FMD remains the single most important constraint to trade in live animals and animal products and is the disease most feared by those countries with a large and efficient livestock industry. Even virulent rinderpest, the original cattle plague, which has a mortality in affected animals approaching 100%, is second to FMD when considered in terms of control and eradication.

Foot and mouth disease consists of seven separate diseases, clinically indistinguishable, caused by seven antigenically distinct serotypes. Moreover, within each serotype there is a spectrum of strains with their own antigenic and epidemiological characteristics, which makes any generalisation about what to expect in an outbreak impossible (8). The pig-specific strains of serotype O FMD virus (FMDV) found in South-East Asia, behave very differently from those found in South America. The epidemiology of the SAT serotypes differ from each other, although all remain restricted to Africa and when they do escape into the Middle East, they never persist. The ephemeral behaviour of serotype C, which in the last few years has only been seen in East Africa, possibly

maintained by improperly inactivated vaccine, is difficult to explain. Many questions are still being raised, as follows:

- will the virus reappear again in Asia or South America?
- what are the structural constraints on serotype A, which regularly appears as new antigenically distinct strains, requiring new vaccines to bring the disease under control?
- why do so many of the new strains of serotype A disappear just as regularly as they appear (certainly not because of pressure from the new vaccines which frequently only become available when the strain is already in decline)?
- will strains of Asia 1 appear outside the antigenic spectrum of the single vaccine strain that up to present has been used successfully throughout the current distribution of the virus?
- why has Asia 1 never been found in Africa when so many other animal viruses have made the journey from Asia into Africa?

There is still much to learn about this interesting group of viruses, but if research is to be practical, which is necessarily the case due to the limited resources available to study diseases of veterinary importance, in order to attract significant government or international funding, scientists must address the problem of why FMD is such a constraint to trade. This may involve fundamental studies on the behaviour of the virus within the infected cell, or the immunological response of the host, but the objective must be how to control the disease more

effectively and to neutralise the effect the disease has on trade. The International Conference on the Prevention and Control of Foot and Mouth Disease held in Brussels on 12 and 13 December 2001 made it clear that a repeat of the slaughter that took place during the 2001 outbreak in the United Kingdom (UK) would be politically unacceptable and that an alternative approach must be found. The proposed changes in the Office International des Epizooties (OIE: World organisation for animal health) *Code* chapter on FMD (11), reducing the time interval between vaccination and re-establishment of FMD freedom and the introduction of serological tests for antibodies to non-structural proteins (NSPs) may help, but until a true assessment of the risk from carrier animals can be made, these changes are unlikely to convince any country with a large susceptible livestock population to start importing vaccinated animals. The first priority for future research is to understand the carrier state.

## Persistent infection

Much has already been written in this volume on persistent infection and the anecdotal evidence that carrier animals can cause new outbreaks of disease. It has been firmly established that ruminant animals, in particular cattle and African buffalo (*Syncerus caffer*), can become infected with live FMDV for a variable period of time after contact with infection, regardless of whether they were already protected from manifestation of disease at the time of contact (2, 5, 13). Some animals have been identified as being infected with three different serotypes at the same time, namely cattle have been found simultaneously infected with serotypes O, A and Asia 1 (15) and African buffalo with all three South African Territories (SAT) serotypes (14). The central problem is that no currently available test is sufficiently sensitive to identify persistently infected animals with 100% certainty.

The cellular and immunological basis for persistence of FMDV in an animal producing high levels of neutralising immunoglobulin G (IgG) and secretory immunoglobulin A (IgA) is completely unknown. This usually lytic virus must have found a mechanism for preventing cell death and evading the immune system. Wileman *et al.* (unpublished data) have proposed that a mutation of the virus attenuates its lytic nature, allowing survival in pharyngeal cells and that the innate ability of the virus to block cell membrane traffic enables it to evade the cellular immune response by blocking presentation of viral antigens by major histocompatibility complex (MHC) molecules. Such a hypothesis, if shown to be true, could lead to an understanding of what might cause a carrier to excrete sufficient virus to infect a susceptible in-contact animal. The more superficial, purely epidemiological approach of 'stressing' carrier animals to show transmission has not been successful and a more collaborative programme, embracing all the disciplines of disease investigation, is overdue.

An understanding of the viral strategy for establishing persistence may lead to a counter-strategy to cure the persistent

infection. Stimulation of the local pharyngeal immune response, which in the past would have been achieved by applying a 'blister', but today would more likely be by using one of the ever increasing number of identified cytokines, may be successful in eliminating the virus. An alternative may be to investigate some of the viricidal drugs appearing on the market for use in humans.

If persistent infection cannot be prevented or cured, or the perceived risk from a persistently infected animal cannot be reduced to zero, then research must be directed towards a 100% reliable means of identification.

## Improved diagnostic tests

A significant step towards identifying the potentially persistently infected animal was the development of NSP antibody tests (10). These tests can be used to distinguish an animal that is antibody-positive following recovery from infection, from one that is antibody-positive after vaccination. However, as discussed in a previous chapter, these tests may not reliably identify the vaccinated animal which has had contact with live virus and become a carrier without sero-converting to the NSPs (9). The sensitivity of the tests may have to be improved to detect the very low levels of NSP antibodies that must be present if the animal is supporting a live virus infection. Sheep, in particular, are notorious for their often subclinical infections and even unvaccinated sheep that have been infected may fail to appear positive with the NSP antibody tests currently available. The introduction of real time polymerase chain reaction (PCR) machines, which can handle large numbers of samples without the risk of cross contamination, may ultimately allow the rapid screening of large numbers of vaccinated and recovered animals for the presence of viral genome, if not live virus (4).

The recent FMD outbreak in the UK showed that, in addition to better tests to identify the persistently infected animal, there is also a need for more rapid tests which could be used in the field. The 24-hour slaughter policy that was adopted did not allow time for anything other than clinical diagnosis, which in the case of sheep, resulted in a large number of healthy animals being slaughtered because one or more of the flock had a lesion consistent with FMD. The polymerase chain reaction technology may not be possible to implement on farms, but tests using latex bead/monoclonal antibody combinations on cellulose membranes for both antibody and antigen detection may provide an answer (12). Although the free availability of diagnostic tests for FMD outside the control of national veterinary authorities would pose certain problems, such kits could have a significant effect on the success of a control programme if used under the appropriate conditions.

## Improved vaccines

There have been few real improvements in FMD vaccines over the last thirty years. The antigens are purer, the adjuvants have

been improved and inactivation of the FMDV is more reliable, but the basic process of growing large quantities of live virus for vaccine production remains the same. The prospect of using virus peptides expressed in bacterial or viral systems has not yet been successful in providing the same level of protection in vaccinated animals. However, even traditional vaccines provide only short-term immunity and only against strains of FMDV antigenically close to the vaccine strain. In some countries where FMD is endemic, up to eight strains of FMDV need to be incorporated in every vaccine dose. There are the additional problems of maternal antibody interfering with the response to vaccination in the young animal and that vaccination does not prevent infection. Although in terms of value of total sales, FMD vaccine is one of the largest veterinary products on the market, no commercial companies currently support significant research programmes to develop a better vaccine. In part, this is due to the failure of the earlier promise from advances in biotechnology, none of which delivered any improvement on current vaccines (7). Some work is still ongoing on systems which express the structural proteins of FMDV which then self-assemble to form an intact viral capsid without the internal genome (empty capsids) (1). This may prove to be an economically successful solution.

There is the need to develop vaccines that contain a marker or deletion which will allow differentiation between infected and vaccinated animals. The NSP test partially answers this need but as mentioned, the test has shortcomings in sensitivity and specificity.

There is also a need for a heat-stable vaccine. The requirement to maintain a cold chain for the vaccine has restricted use of the vaccine in the developing world.

Live attenuated FMD vaccines have been used in the past, but are no longer considered acceptable because of their tendency to mutate back to virulence. However, whereas in the past, changes in the genome which produced the attenuation of the FMDV were impossible to identify, it is now possible not only to characterise the entire nucleotide sequence of the attenuated strain, but to engineer the changes required. The time may have come to re-examine attenuated FMD vaccines and produce strains which cannot revert to virulence. This will require a better understanding of what sequences are associated with virulence, which may be different in different species, as well as the development of disabled strains unable to transmit. The automatic abhorrence of even the prospect of a live FMD vaccine is no longer defensible. Certainly, immunity following vaccination with a replicating antigen can be expected to be better than that obtained from a dead preparation.

Any new vaccine would still have to address the problem of persistent infection. Whether it is reasonable to expect that a new vaccine would also prevent infection remains to be seen. Some suggest that the use of more potent conventional vaccines reduces the possibility of infection following contact with live virus, but the evidence for this is not conclusive (3).

## The involvement of wildlife

There was considerable controversy during the FMD outbreak that occurred in 2001 in the UK concerning the involvement of wildlife species in the spread and maintenance of the disease. None of the samples collected from susceptible wildlife species during and after the outbreak showed any evidence of infection, but it would have created a significant problem had the deer in the UK become infected. Much has been written about the involvement of the African buffalo in the epidemiology of FMD in sub-Saharan Africa (6, 14). This species has been responsible for causing outbreaks of FMD in cattle and in other wildlife species, but none of these are considered capable of maintaining the virus in the absence of buffalo or cattle. Outside Africa, there have been examples of deer and wild pigs becoming infected with FMDV, but without any evidence that they have transmitted the virus back to domestic stock. However, this may be due to lack of detailed study. The Indian buffalo (*Bubalus bubalis*) are susceptible to FMD, but the involvement of the species in maintaining the virus in either Asia or South America is not known. Nothing is known of the potential for the North American bison (*Bison bison*) or other North American ruminants to act as a reservoir of FMD infection. For a variety of reasons, stocking rates of many of the susceptible species of wildlife has increased in Europe and North America, and it therefore becomes more important to determine whether they should be included in any future FMD control programme, or can be safely ignored.

## Conclusion

Research on FMD and FMDV has been ongoing for many years, reflecting the importance of the disease to trade and intensive livestock production. Considerable progress has been made, but although the virus is by comparison even to other viruses, regarded as a relatively simple organism, the short genome of this virus maintains many mysteries which have still to be solved. Few laboratories around the world are able to work safely with the FMDV. However, these laboratories are encouraged and, to some extent, supported by the international organisations concerned with animal disease control, such as the OIE, the Food and Agriculture Organization, the International Atomic Energy Agency and the European Union. There is an extremely efficient and altruistic exchange of information and collaborative networks have been established. However, money available for research has always been meagre. If more rapid progress is to occur and bearing in mind the cost of controlling an outbreak such as that which recently occurred in Europe, more resources, both financial and human, are required. The infrastructure is already in place.

## Les prochaines recherches sur la fièvre aphteuse

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### Résumé

Les épizooties de fièvre aphteuse qui ont récemment frappé l'Argentine, l'Europe, le Japon, la République de Corée, l'Afrique du Sud et l'Uruguay ont attiré l'attention du monde entier sur les conséquences dévastatrices que cette maladie pouvait entraîner dans une population qui en était auparavant indemne, ainsi que sur le coût social et économique des mesures de prophylaxie et d'éradication. D'aucuns se sont étonnés de l'état encore très lacunaire de nos connaissances sur l'histoire naturelle du virus de la fièvre aphteuse. Dans cet article, l'auteur tente de déterminer les grands axes de recherche à privilégier pour mieux préparer l'avenir.

### Mots-clés

Diagnostic – Échanges internationaux – Faune sauvage – Fièvre aphteuse – Infection persistante – Vaccins.



## Futuras investigaciones sobre la fiebre aftosa

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### Resumen

Los recientes brotes de fiebre aftosa en Argentina, Europa, Japón, la República de Corea, Sudáfrica y Uruguay hicieron que el mundo tomara conciencia de los devastadores efectos que acarrea esa enfermedad en poblaciones animales no expuestas previamente al virus, y de los costos sociales y económicos que entrañan su control y erradicación. Para muchos constituyó una sorpresa que subsistieran aún tantos interrogantes sobre la historia natural del virus de la fiebre aftosa. En este artículo, el autor intenta determinar las direcciones en las que debe apuntar la investigación para lidiar más eficazmente con la enfermedad en el futuro.

### Palabras clave

Comercio – Diagnóstico – Fauna salvaje – Fiebre aftosa – Infección persistente – Vacunas.



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