



Australian Government

Department of Agriculture, Fisheries and Forestry

**REVIEW OF THE POTENTIAL IMPACTS
OF NEW TECHNOLOGIES ON AUSTRALIA'S
FOOT AND MOUTH DISEASE (FMD)
PLANNING AND POLICIES**

report to

**Australian Government
Department of Agriculture, Fisheries and Forestry**

by

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1. Summary and conclusions

This report provides a review of new and developing technologies for the diagnosis of FMD and discusses the application of these technologies in the management of an FMD outbreak in Australia.

AUSVETPLAN was identified as the key policy document for emergency animal disease preparedness and planning.

The AUSVETPLAN Disease Strategy: Foot and Mouth Disease manual has a date of last update of 2002 (Edition 3, version 1.0). In the period since August 2002 the Strategy manual has been reviewed by the Technical Review Group and minor updates incorporated. The Strategy document is currently undergoing technical review following a level 2 update and it is anticipated that a new edition of the Strategy will be released before the end of 2005.

This report considered information within Edition 3, version 1.0 (August 2002) since this was the current strategy at the time this report was prepared.

Vaccination

The current AUSVETPLAN allows for the use of emergency vaccination under certain conditions provided that all vaccinates are identified, subject to strict movement controls and ultimately slaughtered. This policy is considered appropriate for Australia in the light of current information concerning vaccines, OIE guidelines for restoration of disease-free status following an outbreak and available tests to detect vaccinated carrier animals based on detection of antibodies to NSPs.

The OIE Manual lists two NSP tests for use in serosurveillance to distinguish vaccinated from infected animals. These tests are not validated sufficiently for international recognition of their use in individual animals. The OIE has accepted the principle of herd based NSP serosurveillance for regaining disease free status and guidelines for the application of SP tests are contained within the OIE Manual (OIE 2005). Continued development and validation of NSP tests is an active area of research. Currently vaccination-to-live may be considered in cattle with NSP tests being applied at the herd level with a variety of follow-up strategies used to resolve any positive NSP test results. Options for follow-up testing include virus isolation and real time RT-PCR on probang samples as well as additional serological testing and even slaughter and post-mortem of test-positive animals. Validation of NSP tests for small ruminants and other species is also ongoing and is likely to take longer than for cattle.

Developments in vaccine technology are likely to result in the production of alternative vaccines that may induce rapid-onset immunity with minimal or no risk of vaccinated animals forming a carrier state after subsequent exposure to virus, or allow easier detection of carrier animals through the use of vaccine markers combined with specific serological testing. These developments are considered unlikely to occur in less than 10 years. In addition developments in other diagnostic technologies such as novel biomarkers detecting gene expression associated with viral activity or real-time RT-PCR may offer superior tests for detection of carrier animals

amongst vaccinates that may complement or replace NSP tests. Either of these approaches may allow consideration of vaccinate-to-live policies in the control of an FMD outbreak.

The following recommendations concern vaccination policy:

- That efforts continue to evaluate the use of suppressive vaccination (vaccinate-to-die) in a FMD outbreak in Australia.
- That detailed plans be drafted to advise and guide the process of determining whether to implement emergency vaccination and protocols for implementation including consideration of vaccinate-to-live and –to-die alternatives.
- That consideration be given to investigation of the role of carrier animals in transmission of FMDV and factors that influence or modify this risk including strain, vaccination and other factors. Uncertainties should be identified and further specific research aimed at clarifying these issues.
- That developments in diagnostic tests and vaccine technology be monitored for their potential application in Australia and impact on the AUSVETPLAN policy concerning vaccination.
- That continued investment be directed towards development and validation of diagnostic tests capable of differentiating infected from vaccinated animals.
- That emergency vaccine bank requirements be reviewed in light of developments in policy regarding the use of vaccination and also in response to developments in vaccine technology and monitoring of circulating field strains of FMDV.

Diagnostic test methodologies

A number of diagnostic methodologies were reviewed and considered to represent mature technologies that were already implemented within Australia, fully validated and that appear in the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. These include:

- Virus Isolation (VI)
- Antigen Capture ELISA
- Liquid Phase Blocking ELISA (LPBE)
- Solid Phase Competitive ELISA (SPCE)
- Virus Neutralisation (VN)
- Genotyping using PCR/Sequencing

With the exception of the VN test, all these technologies are currently implemented within Australia. In the event of an FMD outbreak VN tests would be developed using field isolates from the outbreak. These technologies were not associated with any potential impacts on the management of an FMD outbreak in Australia.

Several other methodologies were identified that had potential impacts on management of an FMD outbreak in Australia. Impacts and recommendations are summarised below.

Non Structural Protein (NSP) tests

Availability of reliable, validated NSP tests would allow consideration of a vaccinate-to-live policy as an option for emergency vaccination in the face of an FMD outbreak. Consideration of a vaccinate-to-live policy would require review of much of the content of the AUSVETPLAN for FMD control including exit strategies for dealing with vaccinated livestock and regaining disease-free status.

A variety of unresolved issues were identified relating to validation of NSP tests and their application and interpretation. There is much research directed at validation of NSP tests in cattle in particular as well as small ruminants and pigs. Validation for use in cattle with interpretation at the herd-level appears likely to be achieved within a few years.

The following recommendations concern NSP tests:

- Until such time as NSP tests are fully validated in all susceptible species or an alternative test is identified that can distinguish vaccinated from infected animals, it is recommended that Australia continue to consider emergency vaccination only as a vaccinate-to-die (suppressive vaccination) policy.
- Simulation modelling should continue to be used to investigate economic and other impacts resulting from the use of different control options on FMD outbreaks in Australia including consideration of no vaccination, vaccinate-to-die and vaccinate-to-live approaches.
- Australia should continue to contribute to and learn from experiences and research in other countries that have had FMD outbreaks, including efforts to investigate issues associated with NSP tests.

Development of novel test platforms for identifying vaccinated animals that have been exposed to wild FMDV may obviate the need for NSP tests. An example is the use of microarray technology for detecting gene expressions associated with FMD virus activity.

Real-Time RT-PCR including TaqMan[®] RT-PCR

The technology offers a rapid, robust, high sensitivity, high specificity test that is capable of being enhanced with automation to increase capacity in a centralised laboratory, and that can be performed in regional laboratories with suitable training and provision of reagents.

Development and validation of portable tests incorporating real-time RT-PCR capability, and that are capable of being applied outside a conventional laboratory setting (on-farm, regional control centre etc) is considered likely to involve a longer time-scale, in the order of 3–5 years or more.

Real-time RT-PCR has potential application in all aspects of management of an FMD outbreak.

The following recommendations concern Real-Time-RT-PCR tests:

- That Australia continues to develop real-time RT-PCR techniques and works with other researchers and organisations such as OIE towards achieving sufficient validation of these techniques to allow application in index case diagnosis and ongoing control measures.
- That contingency plans be developed for increasing throughput capacity for real-time RT-PCR tests in the event of an outbreak — both within AAHL, and through deploying the technique in regional laboratories with PCR skills and equipment.

- That there be consideration of the development and application of portable technologies incorporating real-time RT-PCR test capability.
- That real-time RT-PCR be evaluated for a potential application in detecting carrier animals either as an alternative option for NSP tests or as a confirmatory test in conjunction with NSP tests.

Luminex xMAP[®] technology

Luminex xMAP[®] has the potential to provide any form of antigen or antibody detection assay in a rapid, reliable, high sensitivity, high specificity test that is capable of being automated and of high throughput capacity. The technology is considered most suitable for situations where multiple tests are required and high sensitivity is a primary objective. Differential diagnostics and serosurveillance appear to be the most suitable applications.

It is considered likely that Luminex technology may replace ELISA in the mid term future including assays devoted to a single serotype (either measuring one or multiple analytes) as well as multiplexed assays measuring multiple analytes for multiple serotypes.

The following recommendations concern Luminex xMAP[®] tests:

- That consideration be given to investment in research and development of Luminex techniques suitable for FMDV diagnosis including detection of FMDV antigen and antibodies directed against structural and non-structural proteins.

Microarray analysis (gene chip or DNA chip)

Microarray technologies may have considerable potential in the differential diagnosis of unknown diseases due to the ability to simultaneously screen a sample for the presence of any of a large number of different antigens. Alternative methods are available for this purpose. The combination of PCR and microarray technologies offers a rapid, high sensitivity, high specificity system capable of detecting many pathogens simultaneously. Major benefits are throughput capacity and multiplexing capability.

Applications include differential testing for large numbers of pathogens in screening tests including diagnosis of disease and ruling out diseases in animals intended for importation into Australia as well as diagnosis of FMD subtype.

Microarray technologies are also capable of being used to detect novel biomarkers including gene expressions indicative of viral activity. This type of test would be applicable in DIVA strategies.

The following recommendations concern Microarray tests:

- Monitor advances in the field.
- That consideration be given to an international collaborative research and development effort aiming at investigating this technology for future potential applications including but not limited to FMD.

Pen-side diagnostics

Likely to have a major potential impact on the management of an FMD outbreak in Australia because they may allow on-the-spot confirmatory tests for the presence of FMDV and greatly facilitate rapid implementation of biosecurity measures and culling.

Incorporation of pen-side tests into an emergency disease control programme may change the structure and function of various components of a response, largely by moving decision making towards the level of the farm, and bundling together in time and space various activities such as initial inspection, diagnosis and culling.

Production of specific pen-side tests is likely to depend on generation of commercial returns to a manufacturing company.

The potential benefits of such tests warrant further development and validation.

The following recommendations concern pen-side tests:

- That consideration be given to investment in further research and development activities aimed at developing and validating pen-side tests for FMDV antigen detection.
- That a review of the economic feasibility of development and maintenance of pen-side tests be developed to determine whether it is likely to be worthwhile for a commercial company to invest in this technology.
- That consideration be given to the feasibility of an international consortium of countries to contribute to the costs of development, validation and maintenance of a 'bank' of pen-side tests for application in the event of an FMD outbreak.

Solid state diagnostics incorporating different diagnostic methodologies embedded within a chip

Lab-on-a-chip technology offers miniaturisation of almost any laboratory based technology and incorporation of these capabilities into small, rapid, affordable devices that can be highly portable. Lab-on-a-chip devices are expected to be able to offer complex separations, enzyme-linked immunoassays (ELISA), and even PCR. In the short to mid term future this technology is seen as a mechanism by which general laboratory capacity will be improved. In the longer term future (over the horizon) development of portable, miniaturised test platforms offers alternative pen-side tests based on sophisticated underlying technology. This platform is considered to have limited impact on Australia's FMD plans or policies in the foreseeable future other than as a means of improving laboratory capacity and efficiency.

The following recommendations concern solid-state diagnostic tests:

- That developments in this field be monitored for possible application.
- That consideration be given to an international collaborative research and development effort aiming at investigating this technology for future potential applications including but not limited to FMD.

Biosensor technologies

Laboratory based diagnostics that incorporate biosensor technology are already available and will continue to be developed. This platform is considered to have limited impact on Australia’s FMD plans or policies in the foreseeable future other than as a means of improving laboratory capacity and efficiency

Remote biosensors have the potential to be implemented as independent environmental sampling systems capable of autonomous action and reporting. Similarly implantable biosensors may allow early detection of exposure of sentinel animals to FMDV. Such advances could offer enhanced capacity for detecting FMDV. However, this platform is considered to have little potential for impact on Australia’s FMD plans or policies in the foreseeable future because of the perceived very long time frame before remote or implantable biosensors might be developed and validated. This technology is considered an example of over-the-horizon technology because of the early state of research and development at the current time.

The following recommendations concern biosensor tests:

- That developments in this field be monitored for possible application.

Future roles for diagnostic platforms

Table 1.1 shows varying diagnostic platforms listed under different applications and at three time points (current, 5-yrs time and 10-yrs time). The expected changes reflect a move towards nucleic acid and gene expression based technologies in the future.

Application	Current	5-yrs time	10-yrs time
Index case	Ag capture ELISA Ab ELISA Virus isolation Real time RT-PCR Electron microscopy Sequencing	Real time RT-PCR Whole of genome sequencing	Nucleic acid technologies
Detection of infection	Ag capture ELISA Ab ELISA Virus isolation Virus neutralisation Real time RT-PCR	Real time RT-PCR Luminex assays Pen-side tests	Nucleic acid technologies Novel biomarkers
Detection of carriers	NSP ELISA Virus isolation Real time RT-PCR	Luminex NSP tests Real time RT-PCR Virus isolation	Novel biomarkers
Confirmation of freedom	Ab ELISA Virus neutralisation	FMD generic ELISA Luminex assays	Nucleic acid technologies
Vaccination	as per vaccine bank	as per vaccine bank	Virus like particles Immunomodulators Anti-virals

Table 1.1: Description of test platforms expected to be used for different purposes at three different time points: currently, in 5-years and in 10-years time (See section 7 for more detail)

Other issues related to diagnostic performance

Developments in diagnostic test platforms in the future are expected to improve sensitivity, specificity, speed and portability (in some cases). Realisation of benefits of these improvements will require effort to ensure that other components of a response are not rate limiting such as sample collection and submission, interpretation and reporting of results and implementation of resulting actions including quarantine, slaughter and disposal.

It is recommended that consideration be given to assessment and improvement (if necessary) of the following areas relating to clinical diagnosis of FMD and logistics relating to diagnostic sampling and reporting:

- effective training in clinical recognition of disease due to FMDV
- Continued development of a response framework that can generate maximal benefit from the expected availability of high speed, high sensitivity, high specificity tests including those that are portable through:
 - implementation of an effective and integrated information management system
 - rapid two-way communication of voice, text and images between field personnel, laboratories and experts to facilitate decision making
 - logistics of rapid transport of samples from point-of-collection to a laboratory
 - decision making criteria that can be applied locally to allow portable tests and rapid provision of test results to reduce the time period between initial visit, diagnosis and action (quarantine, movement control, stamping out).

Surveillance and epidemiological technologies

A brief review is presented of recent developments and issues in the area of epidemiology and data management relating more generally to surveillance as well as emergency animal disease control.

The lack of an integrated information management system (IMS) capable of utilisation in peacetime (in the absence of any emergency disease response) as well as during the management of an FMD outbreak, is identified as an issue of major importance.

It is critical that an integrated information management system (IMS) be designed, implemented and tested in the period prior to an outbreak occurring. Such a system (BIOSIRT) is currently being specified and tenders will be called for in October 2005. Sufficient funds and resources should be directed towards successful completion of this project in as short a time as possible.

Development of rumour and syndrome surveillance capacity is considered to offer potential benefits in early warning of FMD (and other diseases) both outside Australia as well as within the national border.

There should be consideration of the potential application of mass screening tests capable of detecting FMDV or other agents at pre-border, border or post-border locations. Deployment of remote biosensors capable of continuous monitoring for presence of FMDV in high risk areas for example piggeries and saleyards, may have application in early warning systems, but are considered to be more than 10 years from availability in a robust and validated form. Alternatives

include application of high capacity, rapid screening of samples (individual or pooled) from animals or animal products. This option is considered likely to be feasible within the next several years though cost and other impacts on trade for example will need to be reviewed against any perceived increase in biosecurity offered over current methodologies.

A current research project in the AB-CRC portfolio is developing methodologies for incorporating complex data from multiple sources into a quantitative estimate of confidence in disease freedom. It is recommended that this project be expanded to consider options for using this approach for estimating confidence in freedom from FMDV.

The national livestock identification system (NLIS) is already being implemented though there are species variations in the level of information that may be available through NLIS. There also appears to be some uncertainty about how NLIS data might be made available and integrated into an Information Management System and also accessed in the event of an outbreak. It is recommended that contingency plans for availability, access and application of NLIS data in the event of an outbreak, be reviewed and updated.

Introduction of FMDV into a previously free country as the result of an act of bioterrorism is a scenario that needs to be considered. There is a risk of multi-site, multi-serotype introduction in such a scenario, an event that would presumably be considered rare in conventional preparedness and planning. If this were to occur it would impact all stages of a response due to the need to account for differing serotypes in diagnostic tests, vaccine selection, and exit strategies. It is recommended that consideration be given to the potential impact of multi-site, multi-serotype introductions of FMDV on contingency planning and response policies.

Policy implications of advances described in the report

The principles of FMD control as described in the AUSVETPLAN, are not expected to change significantly in the next 10 years.

Realising maximal benefit from advances in diagnostic test platforms in the future will require sufficient resources and infrastructure to rapidly implement policy decisions as well as clear and pre-agreed decision criteria and triggers to allow rapid identification of decision options / actions in the light of near real-time information on disease status and spread. These developments include criteria governing the use of suppressive vaccination (vaccinate-to-die). These developments do not require any major change in Australian policies but are likely to require continued investment and development in infrastructure, resources, communications, laboratory capacity, training and development of detailed plans and decision making criteria.

One example of the potential impact of selected technical advances is the detection of viral antigen in infected animals before they begin to shed large amounts of virus using tests based on nucleic acid detection (real time RT-PCR) or gene expression indicative of viral activity may allow intervention to eliminate or reduce exposure of in-contact animals. This would require the ability to respond extremely rapidly to new information through implementation of quarantine, movement control, stamping out or administration of emergency vaccination / immunomodulation therapy. The likely constraints that may need addressing are in movement of information, triggers for immediate decision making and mobilisation of sufficient resources to implement pre-agreed actions.

Australian policies and plans for preparedness and response to FMD outbreaks are dependent in part on international inputs into regulations and agreements concerning trade such as the OIE recommendations. While Australia is an important contributor to international developments it is also acknowledged that outbreaks of FMD elsewhere in the world may drive changes to OIE recommendations independent of any inputs from Australia. It is reasonable to expect OIE recommendations to change within the next 10 years to reduce or eliminate the difference in time required to regain disease-free status for countries that choose a vaccinate-to-live policy in a FMD response compared to countries that choose to either not vaccinate or implement a vaccinate-to-die policy. This change will be dependent in part on developments in vaccine and diagnostic test technologies (particularly validation of DIVA strategies based on NSP tests). Part of the continual process of review of Australia's FMD response plans and policies will incorporate consideration of vaccinate-to-live options under Australian conditions.