

# Surveillance strategies for foot and mouth disease to prove absence of disease and absence of viral circulation

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## Summary

Free trade of animals and their products is based on the international or bilateral recognition of the health status of the animal populations being traded. This recognition is based on documentation of their health status by the exporting country, based on the results of continuing surveillance.

According to the *Terrestrial Animal Health Code* of the World Organisation for Animal Health (OIE), this may be based on various methods of surveillance, such as: documenting non-specific surveillance (clinical surveillance, passive notification of suspect cases, etc.); documenting activities that increase the sensitivity of non-specific surveillance (training activities, rewards/sanctions for notification/failure to notify, etc.); documenting all specific surveillance and its results (random surveys, targeted and risk-based surveillance, convenience-testing activities, etc.).

Usually, the infection is the subject of the declaration of freedom.

While clinical and passive surveillance can provide a high level of confidence that foot and mouth disease (FMD) infection is absent, this is not the case in vaccinated populations. In these populations, specific surveillance becomes much more important than non-specific clinical surveillance.

Specific surveillance is severely restricted by the performance of the test(s) employed. The imperfect specificity of any serological test is further complicated when techniques to differentiate infected from vaccinated animals (DIVA) are used, because imperfect purification of the antigen used for vaccination may foster the production of undesired antibodies in the vaccinated animals.

The authors discuss various approaches to overcome this problem; their merits and flaws in documenting the absence of infection or virus circulation for animal diseases in general, and for FMD in particular. Particular attention is paid to finding methods that can be applied in a variety of epidemiological conditions and organisational structures, since these vary greatly among OIE Members.

## Keywords

Documentation – Early detection systems – Foot and mouth disease – Free country – Free zone – OIE – Random survey – Risk-based surveillance – Surveillance – Targeted surveillance – World Organisation for Animal Health.

## Introduction

Freedom from infection implies the absence of the pathogenic agent in a specific population.

In foot and mouth disease (FMD) control, the need to prove absence of disease and viral circulation arises mainly when it is necessary to:

- end an epidemic, whether or not emergency vaccination has been used as a control tool
- assess whether mass vaccination can be phased out in the process of eradication
- document the health status of a population for trade.

The same methods may be used when documenting the absence of virus circulation, although the objectives differ slightly. The main difference is that the third objective must meet internationally accepted standards, which are intended to define a minimum common level of 'confidence' that may be associated with the declaration of freedom.

Available scientific methods cannot provide absolute certainty of the absence of infection. In practice, it is not possible to prove (i.e. be 100% confident) that a population is free from infection (unless every member of the population is examined simultaneously with a perfect test, with both sensitivity and specificity equal to 100%) (18). Documenting freedom from infection or disease is a probabilistic concept and involves providing sufficient evidence to make trading partners reasonably confident that infection, if present in a population, is a very rare event. Moreover, given the intensity of trade in today's globalised society, such documentation cannot guarantee the absence of a recently introduced infection, but can only ensure the absence of endemic infection in the population.

Therefore, to document freedom from infection, Veterinary Services must actively search for infection and its circulation. This search for infection(s) is one of the main routine tasks of Veterinary Services and is carried out using a number of approaches and strategies. The cumulative evidence of an absence of infection and virus circulation provided by various surveillance activities can corroborate a hypothesis of absence of infection, in order to document freedom from infection.

These concepts explain the subtle distinction to be found in the current chapter on FMD in the *Terrestrial Animal Health Code (Terrestrial Code)* of the World Organisation for Animal Health (OIE) (19); namely, the distinction between 'absence of infection' in countries or zones that do not practise vaccination and 'absence of virus circulation' in countries or zones that practise vaccination. This is, in

effect, only a difference in wording. The only difference between countries that practise vaccination and those that do not is that, in the absence of vaccination, the presence of infected animals in any numbers will eventually lead to virus spread (i.e. virus circulation), which makes it virtually impossible not to detect the presence of this infection. However, in mainly vaccinated populations, the presence of a single or a few infected animals might not result in virus circulation and the infection might naturally die out.

The declaration by the OIE that a country is free from infection is a 'third party certification' process, which requires the adoption of transparent, objective, independent and science-based procedures.

## Documenting absence of disease and of viral circulation, according to the *Terrestrial Code* and recent scientific literature

Assessing the disease-free status of a country or zone by using specific surveillance may be achieved through random survey, or non-survey-based surveillance, or through a combination of both.

Three main approaches are considered in the recent international literature:

- random survey and analysis of the results, using classical statistical methods
- random survey and analysis of the results, using hierarchical Bayesian models
- thorough analysis of all the relevant surveillance components in place.

### Random survey and analysis of the results using classical statistics

A survey-based approach has generally been preferred since the 1970s because:

- it is considered able to provide numeric values that, *per se*, are more objective and more defensible (i.e. scientific) than any subjective assessment of the probability of disease being absent from a population
- from the results of a statistically sound random survey, a quantitative estimation of confidence of a disease being absent from a population can easily be calculated

– the survey-based approach requires the least investment of resources and veterinary infrastructure.

Non-random surveillance activities (e.g. passive surveillance, targeted surveillance, checks on traded animals) are only considered able to provide further non-quantifiable elements, subordinate to the results of the random survey.

The random survey approach is sound when a high prevalence of infection/disease is present. It rapidly becomes insufficient when the prevalence declines in the population, particularly if the infection tends to cluster (as, for instance, when mass vaccination is employed) and is not randomly spread throughout the population.

Documentation of freedom from FMD is thus simple when vaccination is not practised or where a high proportion of animals in the population are not vaccinated. In such cases, the presence of FMD infection is easy to detect; the rapid spread of infection quickly leads to a high prevalence of infection (and disease), and the risk of infection is, for all practical purposes, constant across the susceptible population. In such conditions, documentation of FMD freedom may not require the use of any active surveillance activities, if a reliable veterinary infrastructure is in place.

The difficulties arise when vaccination is practised and a high proportion of the susceptible population is vaccinated. In these conditions:

- the number of false-positive results in the survey increases considerably
- the prevalence of infected herds decreases to a very low level, as does the prevalence of infected animals within the infected herds
- the infection tends to cluster between and within herds.

The overall effect is the possible onset of small endemic foci, which are difficult to detect, in a framework of widespread, randomly scattered animals that falsely test positive. The use of active surveillance therefore becomes necessary.

### Detection of endemic foci

The first set of problems arises when the proportion of immunised animals in the population does not reach a minimal value that is able to block the circulation of the virus completely. In these conditions, the level of herd immunity is too high to allow the development of an FMD epidemic, but too low to entirely eliminate virus circulation. This can result in the creation of endemic foci, which are very likely to be clustered in particular production systems or localised to marginal areas. The endemic foci may, from time to time, give rise to an

epidemic of FMD, due to changes in the homeostasis between the virus and the population, e.g. the introduction of susceptible animals into these endemic foci due to fluctuations in trade patterns, or the price of animals, etc. Animals from these endemic foci might also cause epidemics if brought into an environment where vaccination is not carried out or results in a poor level of coverage. The detection of these endemic foci may be a very hard task because:

- the sub-populations involved may be small;
- the factors hampering effective vaccination may also hamper testing of the infected herds;
- most of the adults in the affected herds may be immune, either through vaccination or through having recovered from infection, and the infection may occur mainly in calves with waning passive immunity. Since these young stock may account for only a small proportion of the population, the prevalence of infection at any one time may be very low, and below the ability of any random survey to detect.

The usual method of solving these problems is to perform a stratification of the random survey that includes the sub-population at risk as one of the strata.

Observations from the applications submitted to the OIE for an evaluation of FMD status often indicate that the survey design and type of stratification usually adopted by countries seeking recognition as an 'FMD-free country (or zone) where vaccination is practised' are unlikely to be able to detect small endemic foci. In general, surveys adopt a target prevalence of 1% at the level of the epidemiological unit (a farm or group of farms) and 10% within the epidemiological unit, and the stratification criteria are geographic rather than based on the production system. The number of units within each stratum could vary from thousands to hundreds of thousands, and the animals may number in the millions. This means that, unless the infected units are randomly distributed in the population and their number is in the hundreds, at least, and the infected animals number in the thousands, the odds of detecting the infection are poor indeed.

Another possible option exists; namely, to give up representativeness based on random sampling and perform risk-based sampling of the population at risk. Evaluation of applications to the OIE shows that this option has not generally been exploited by countries seeking recognition of their disease status. This will be discussed in detail below, in 'Analysis of all relevant surveillance components in place'.

### False-positive results

The second set of problems concerns the proper interpretation of positive results and discriminating between true and false positives. Irrespective of the testing

system, the design of the surveillance system should anticipate the occurrence of false-positive reactions. If the characteristics of the testing system are known, the rate at which these false positives are likely to occur can be calculated in advance. There must be an effective procedure for following up such positive reactions to finally determine, with a high degree of confidence, whether they actually indicate infection/circulation or not (19).

Possible ways to deal with this are:

- a) to assess whether the number of observed positive results is statistically more compatible with false-positive results than with true infection, or
- b) to perform a detailed investigation in every herd where positive results are observed and to assess whether virus circulation is taking place or not.

An attempt to solve this problem from a statistical point of view has been made, both at herd level (3) and at country level, by using a frequentist approach and two-stage sampling (4). In other words, this method involves the calculation of sample sizes for herds and for animals within herds, and the maximum admissible numbers of positive herds and positive animals within herds, given the performance (sensitivity and specificity) of the test employed and the expected values for the prevalence of infection. The sample sizes are applied in the survey design and the herds and the country are declared free when the number of positive results is within the acceptable range.

The drawback of this approach is that it only gives meaningful results when the difference between the expected prevalence of infection and the expected number of non-specific positive test results is large. For example, in the case of FMD in an unvaccinated population, where the expected within-herd prevalence of positive results is at least 30%, and the specificity of the tests exceeds 98%, discrimination between false-positive results and infected herds is reliable. With the levels of infection that might be expected in a vaccinated population, however, discriminating between false positives and infected herds is often impossible.

Another way of distinguishing between false-positive results and infected herds is to perform a detailed investigation in all herds that test positive. Whether a country vaccinates or not, and regardless of the serological tests used, a diagnostic follow-up protocol should be in place to resolve any presumptive positive serological test results.

This follow-up procedure should be based on appropriate clinical, epidemiological, serological and, where possible, virological investigations of the reactor animals, of susceptible animals of the same epidemiological unit and

of susceptible animals that have been in contact or otherwise epidemiologically associated with the reactor animals. The aim of the follow-up procedure is to exclude the presence of infection in non-vaccinated populations and the presence of virus circulation in vaccinated populations.

Examples of follow-up procedures, particularly those to be adopted in vaccinated populations, are given in the *Terrestrial Code* (19):

- clinical examination and re-sampling of the animals tested in the initial survey, after an adequate interval of time has elapsed, on the condition that they are individually identified, accessible and have not been vaccinated during this period
- a new serological survey in the holding where positive animals were detected, repeating the primary survey design and ensuring that all animals tested are individually identified and not vaccinated; retesting of the animals after an adequate period of time
- clinical examination and serological testing of representative numbers of cattle that were in physical contact with the primary sampling unit
- in all the cases listed above, the magnitude and prevalence of antibody reactivity observed should not differ in a statistically significant manner from that of the primary sample if virus is not circulating.

Other possible follow-up procedures include the clinical examination and serological testing of epidemiologically linked herds or the use of sentinel animals (e.g. young, unvaccinated cattle or unvaccinated animals of other susceptible species on the same farm).

The testing procedure, for its part, is based on screening followed by a step-by-step confirmation process (structural protein enzyme-linked immunosorbent assay [ELISA] or non-structural protein- [NSP-] ELISA-3ABC, depending on the vaccination status of the population; enzyme-linked immunoelectrotransfer blot, virus neutralisation test, oesophageal-pharyngeal test).

The overall objective of adopting a follow-up procedure is to increase the specificity of the diagnosis, aiming for as close to 100% specificity as possible. However, this increase of specificity has an inherent drawback: a decrease in sensitivity. This decrease of sensitivity must be compensated for by a corresponding increase in the sample size, which may be at the level of epidemiological units, of animals within epidemiological units, or both.

This increase in sample size may rapidly lead to a huge number of samples to be tested, as most of the tests and procedures used are independent from one another and, in the context of independent tests, the overall sensitivity is

the product of the sensitivities of each procedure performed.

### Random survey and analysis of the results using hierarchical Bayesian models

In the last ten years, this approach has been the subject of several publications (1, 9, 15, 16). These papers also present real-life examples of using this method to document disease-free status: i.e. Newcastle disease and porcine reproductive and respiratory syndrome in Switzerland (16), bovine brucellosis in Mexico and paratuberculosis (Johne's disease) in California (1) and classical swine fever in wild boar in Belgium (15). Using this method to analyse survey results has also prompted the development of methods to calculate the required sample size (2, 10).

The Bayesian approach is discussed below, taking into account the two problems already considered when analysing survey results using classical statistics:

- a) detection of endemic foci
- b) false-positive results.

#### Detection of endemic foci

The hierarchical Bayesian analysis of survey results is not designed to compensate for the poor chance that a random survey will detect small endemic foci, which is the likely situation in mass-vaccinated populations. The main purpose of this type of analysis is a proper assessment of the meaning of the results.

#### False-positive results

Hierarchical Bayesian analysis of survey results is performed using Monte Carlo Markov chain methods. This has three advantages compared to classical statistics:

- the data analysis takes into consideration the clustering of true positives within a few infected herds, while false positives are randomly scattered (most of them as single reactors) throughout the entire population (9, 16);
- the analysis may be performed even when the sensitivity and specificity of the tests employed are not known (7, 8, 11);
- the integration of the survey results with existing knowledge can significantly enhance our confidence in the results obtained. Thus, this approach requires a smaller sample size to achieve the same degree of confidence as when using collected data alone (classical statistics) (12, 17).

Existing knowledge that should be used to improve the analysis includes:

- a) the probability distribution of the expected prevalence of infection in infected herds
- b) the probability distribution of the infection at herd level
- c) the probability distributions of sensitivity and specificity of the tests employed.

To be accepted in international trade, this prior knowledge must come from factual data (experimental or gathered in the field), rather than from expert opinion, which always contains an arguable amount of subjectivity. This means that the proper use of the hierarchical Bayesian method requires the preliminary task of data collection during the progress of the eradication programme, before starting surveillance to document freedom from infection. This data-gathering is required to assess the expected prevalence of positive results and its variability in infected herds and herds that return false-positive results.

The drawbacks of this method are that:

- advanced statistical skills are required to use it properly;
- detailed information must be collected on every single animal tested in the survey (i.e. its herd of origin and the test results obtained by each animal in every single test applied);
- since the assessment of the probable true infection status of each herd is heavily conditioned by the probability distribution of the prevalence of infection within an infected herd, accurate prior information on this distribution is required;
- a high level of confidence in freedom from infection may be obtained with this method for diseases in which the expected prevalence in infected herds is high. This is because the lower the expected prevalence of infection, the more difficult it is to document disease-free status. Thus, in the case of FMD, the use of this method is far less effective in vaccinated than in **non-vaccinated populations**.

#### Analysis of all relevant surveillance components in place

A number of different data-gathering activities are used in epidemiological surveillance. Among these activities, the random surveys described above generally play a minor part. Other surveillance data sources include (18):

- disease reporting or notifications
- control programmes/health schemes
- targeted testing/screening
- ante-mortem and post-mortem inspections
- laboratory investigation records
- biological specimen banks

- sentinel units
- field observations
- farm production records
- systematic sampling at slaughter.

The amount of information collected from non-random sources of data is usually much greater than that collected through surveys (18). Nevertheless, this information is usually poorly exploited in the process of documenting freedom from disease.

For a country wishing to have its entire territory or a zone recognised as being free from FMD with vaccination, the pillars of the surveillance system are the following:

- targeted (risk-based) surveillance
- an early detection system
- a disease reporting or notification system
- close monitoring of vaccination.

### Targeted (risk-based) surveillance

According to the *Terrestrial Code*, particular importance should be placed on the **targeted collection of data** (e.g. based on the increased likelihood of infection in particular localities or species), or on regular and frequent clinical inspection and serological testing of high-risk groups of animals (19). In fact, a failure to find infection in a high-risk sub-population (at a given design prevalence) is equivalent to a failure in a random survey with a much lower design prevalence (i.e. at a design prevalence equal to the weighed mean prevalence of the high-risk sub-population and the remainder of the susceptible population). Therefore, risk-based sampling has a better cost-effectiveness ratio than random sampling and provides greater confidence in the absence of disease.

It is amazing that, in everyday life, nobody would ever dream of adopting a random strategy to search for something (from the car keys when leaving home in the morning, to police investigations), whereas, in the search for animal disease, randomness is usually so highly valued. Risk-based surveillance is the most effective way to detect clustered infection and endemic foci.

Detecting clustered infections and endemic foci is generally important in animal health, for reasons that go beyond the recognition of disease-free status. As already stated, when endemic foci exist, there is always the risk of a new epidemic, due to a change in the more-or-less stable equilibrium (homoeostasis) between the virus and the population, particularly when fluctuations are observed in the level of immune coverage of the animal population.

A steady decrease in the level of immunity of the animal population is observed when a vaccination policy changes

into an eradication policy. The progressive increase in the susceptible fraction of the population leads to a progressive increase in the risk of an epidemic developing from possible residual endemic foci. For this reason, before changing the control policy, all activities aimed at detecting the presence of infection must be increased and intensified. This means strengthening the entire veterinary infrastructure, with two main goals:

- a) to identify as many sources of residual infection and risk factors as possible, before the level of population immunity starts to decrease
- b) to develop the necessary preparedness to deal with any outbreak of infection rapidly and effectively.

Particular emphasis will be given to epidemiological capacity and infrastructure and to early detection, through:

- i) strengthening the epidemiological skills of Veterinary Services to enable a more focused search for any residual sources of infection, and greater capacity for efficient investigation
- ii) strengthening the epidemiological infrastructure, by instituting and effectively distributing regional and/or local epidemiological centres
- iii) increasing the sensitivity of the clinical detection system (training field services, including para-veterinarians, training farmers and other lay people involved in animal husbandry)
- iv) decreasing the time needed for laboratory confirmation (territorial spreading of laboratory capacity, improving diagnostic techniques and adopting rapid techniques)
- v) integrating the information systems of Veterinary Services and the laboratory, and developing and strengthening cooperation between diagnostic and field services
- vi) developing increased capacity for a rapid response to the presence of infection by adopting and modifying procedures where necessary.

In all the countries that have succeeded in eradicating FMD, most of the infection clusters and endemic foci were detected under conditions of high levels of population immunity, when mass vaccination was still practised. The only feasible way to detect a clustered infection, especially when the clusters are as small as those expected in a mass-vaccinated population, is to use targeted sampling of the highest risk component of the high-risk sub-populations, i.e. to clinically examine and serologically test young unvaccinated animals in high-risk populations.

Identifying a high-risk sub-population requires accurate investigation and trace-back to the source of the outbreaks during the epidemic. The aim of the investigation is to

identify the specific features of the primary outbreaks that explain the presence and/or persistence of the infection on those particular farms. The potential risk factors are usually specific to the various environments and husbandry systems involved, and should thus be defined after an accurate retrospective analysis of the disease outbreaks that have actually occurred. When this type of approach is used in mass-vaccinated populations, one of the main risk factors that should be considered is the coverage rate and effectiveness of vaccination. This can be assessed in various sub-populations and production systems by monitoring vaccination activities and analysing the results. Other possible risk factors for the presence of infection include herd size, economic conditions and the primary subsistence source of the farmer, type of production system, intensity of trade and the source from which the farm is supplied (5). Finally, other possible risk factors that should be considered will depend on local husbandry practices and characteristics and other local anthropological, social, economic and religious factors.

Identifying risk factors cannot be based solely on 'theoretical'/literature/'expert' sources nor on associations detected in the field with no sound biological grounding. In other words, identifying risk factors when planning 'risk-based surveillance' must be based on the proper application of scientific method:

- i) a theoretical hypothesis of a set of possible risk factors must be founded on the relevant literature;
- ii) each supposed risk factor must be challenged with field data, following a clearly defined and statistically sound procedure. Such a procedure should also be able to assess the possible role of confounding factors;
- iii) only those risk factors that are not contradicted by the field data should be used to plan the risk-based surveillance component.

Precise adherence to scientific methods is necessary to identify risk factors correctly, since any errors in this phase would have catastrophic effects when planning the surveillance.

To challenge theoretical risk factors against field data, a deep analysis of available historical data on past epidemics and outbreaks must be carried out. This analysis should start from a detailed description and evaluation of the available data. The aim of this descriptive analysis is to provide the information needed to design the subsequent inferential process of refutation/acceptance of the risk factors.

Once the risk factors have been identified, all holdings that share these risk factors will become the targeted risk sub-populations.

Applying this approach, and carrying out a quantitative assessment of the results, has shown in one example – documentation of the disease-free status of Denmark for classical swine fever (CSF) – that only 80% of the testing foreseen for a single year's routine, risk-based sampling programme, considered in isolation from the preceding years' negative surveillance findings, and without any additional survey, was sufficient to give 95% confidence that CSF infection was not present in Denmark at an among-herd prevalence of 0.2% or greater (14).

Evidence from other surveillance system components and surveillance from previous years was not considered when arriving at this figure, which is 80% lower than the usual level of design prevalence used in random surveys to document freedom from FMD. A comparison of the levels of safety (in terms of the maximum number of infected holdings) provided by a typical random survey and a risk-based sampling equivalent to that performed in Denmark for CSF is shown in Table I.

**Table I**  
**Results of a typical random survey to determine freedom of infection from foot and mouth disease, in comparison to a targeted sampling equivalent to that performed in Denmark for classical swine fever**

Area of sampling*	Existing holdings	Sampled holdings	Maximum number of infected holdings with 95% probability	
			Results of the random survey	Prevalence 0.2%
Area A	2,967	482	16	6
Area B	42,130	452	268	84
Area C	7,643	501	43	15
Area D	1,280	611	4	3
<b>Total</b>	<b>54,020</b>	<b>2,046</b>	<b>331</b>	<b>108</b>

\* Stratification of sampling

For a proper evaluation of the results, however, we need to consider that, in countries with between ten and 30 million holdings, a prevalence of 0.2% would mean 20,000 to 30,000 infected holdings. Many countries who have acquired OIE recognition of disease-free status with vaccination for specific zones within their borders would come under this category. The maximum level of infection reported in Table I, from the results of risk-based sampling, is less than one-third of the level accepted for international trade. Nevertheless, it would still be too high to consider a change in strategy that involved stopping vaccination (6).

For this reason, only an analysis of the evidence provided by *all* surveillance components can give the assurance and level of confidence required to change the strategy to one of non-vaccination.

### Early detection system

Another indispensable component of the surveillance system – of crucial importance for documenting freedom from an infection (but also for ensuring confidence among trading partners) – is an effective **early detection system**.

The results of any survey are valid only for the period during which the survey was performed. In contrast, a system that operates *continuously*, with clear and sound procedures for early detection – and rapid reaction if an infection/disease does occur – provides much more assurance and dependability for all stakeholders, including trade partners.

According to the *Terrestrial Code* (18), an early detection system should include the following characteristics:

- a) representative coverage of target animal populations by field services
- b) the ability to undertake effective disease investigation and reporting
- c) access to laboratories that are capable of diagnosing and differentiating the relevant diseases
- d) a training programme for veterinarians, veterinary para-professionals and others involved in handling animals, which deals with detecting and reporting unusual animal health incidents
- e) a legal obligation for private veterinarians to communicate/cooperate with the Veterinary Authority
- f) a timely reporting system to notify Veterinary Services of the disease/infection event
- g) a national chain of command.

### Disease reporting

Usually, the main sources of data on the presence of a disease are the **disease reporting or notification systems** (the passive surveillance system). In the case of FMD, the disease reporting systems are the central kernel of surveillance wherever vaccination is not applied. The significance of disease reporting is reduced, however, when vaccination is used. Nonetheless, passive notification should never be neglected because a proportion of susceptible unvaccinated animals are always left within the vaccinated populations, including young replacement calves born after the completion of the last vaccination campaign, pigs, non-bovine ruminants not subject to compulsory vaccination (i.e. sheep, goats, llamas, alpacas, etc.). The importance of these unvaccinated sub-populations varies, as some species are more likely than others to show clinical signs of FMD when infected. Therefore, when mass vaccination of cattle is used, passive and clinical surveillance should be carefully focused by

specifically targeting those strata of the susceptible populations which are most likely to disclose the presence of virus circulation. An intensive educational programme to train potential field observers to spot the clinical signs of the disease is an important component of surveillance in vaccinated populations.

Effective laboratory support is another vital component of any reporting system (19). Reporting systems that rely on laboratory confirmation of suspected clinical cases should use tests that have high specificity and reliable sensitivity. When documenting the results of passive surveillance systems, researchers should never document only the confirmed cases; instead, all instances that prompted a confirmation procedure or an investigation should be reported and documented. This is indispensable to evaluate the predictive values of the system.

Moreover, for a more comprehensive assessment of the system's performance, and to collect the data necessary for an eventual quantitative evaluation of the sensitivity of the surveillance component, it is also important to collect information on the occurrence of conditions that present similar clinical signs to those of FMD, since these must be considered in the differential diagnosis.

### Vaccination monitoring

The fourth main component of the surveillance system is **monitoring vaccination activities** and their effectiveness. Since the objective of vaccination is to decrease the probability, to a negligible level, that animals with circulating neutralising antibody will become infected after contact with the FMD virus, then evaluating the immunity of the population after each vaccination campaign is important for several reasons:

- assessing the success of the vaccination campaign in fulfilling its declared objectives (e.g. population coverage, level of herd immunity, etc.)
- assessing the reliability of farmers' declarations about the vaccinations performed
- detecting and analysing the shortcomings of the vaccination campaign for proper planning of the next campaign
- providing the information needed to perform risk assessments on the consequences of introducing the infection into a population
- providing part of the information needed to properly target 'risk-based surveillance'.

Several sources of data may be exploited to monitor the vaccination campaign. These different sources may provide different types of information; therefore, they should all be used to help evaluate various facets of the campaign and for cross-checking. Possible sources of data include:



- the commercial records of the vaccine producers/retailers
- farmers' declarations
- vaccination reports from governmental teams of vaccinators
- the results of a stratified random survey of the presence of FMD antibodies against all types of virus used in the vaccination campaign.

All the listed components of a routine surveillance system should be able to overcome the two main shortcomings identified for random surveys; namely:

- a) the detection of endemic foci
- b) the proper interpretation of false-positive results.

### False-positive results

When all routine surveillance components are in place, all positive results must be thoroughly followed up, since there can be no uncertainty about the presence of an infection. Any positive result during routine activities should prompt a reaction: either the cause of the positive result must be investigated and the hypothesis of infection eventually refuted, or the infection must be eradicated.

However, the procedure for following up and investigating any positive results must be standardised and consistently followed because **this procedure has the intrinsic consequence of decreasing the sensitivity of the entire system**. Even if a final evaluation of the surveillance system and an assessment of the country's animal health status are usually made on qualitative grounds only, knowing the degree of sensitivity of the diagnostic procedure is an important element of the assessment. This is even more important in the case of quantitative assessment.

The decrease in the sensitivity of diagnosis after the adoption of a confirmatory procedure is an important drawback of random surveys because it requires a compensatory increase in the sample size, which can be as much as double the overall cost of the survey. This drawback does not exist with non-random surveillance systems, due to the very large volume of examination and testing usually involved in routine surveillance activities.

### Documenting the results of surveillance

Documenting freedom from infection implies precise documentation of the design and results of all components of the surveillance system, with the same degree of detail adopted in documenting the design and results of a survey. Moreover, documenting freedom does not necessarily imply carrying out a survey at all.

When precisely documenting the design and results of all components of the surveillance system, we need first to consider, describe and quantify the sub-population(s) targeted by each surveillance stream (i.e. the types of herds and animals, the number of herds and animals submitted to the specific component of the surveillance system). For example, for the component concerning clinical examinations and serological testing of traded animals, a description is needed of the:

- region of origin and production system of the traded animals
- number of herds involved in each sub-population
- number of animals traded, clinically examined and tested, further subdivided by vaccination class (unvaccinated, vaccinated once, vaccinated more than once).

All of this information is necessary because the various sub-populations and production systems of origin may have differing levels of risk. Thus, depending on the proportion of each sub-population tested, as the proportion of traded animals belonging to the high-risk sub-populations increases, so does confidence in the test results. Furthermore, the risk of FMD infection is highest in unvaccinated animals and decreases to virtually nil in animals vaccinated more than once. The testing of great numbers of multiply vaccinated animals will not significantly increase confidence in the freedom of infection status already provided by the clinical examination and testing of unvaccinated or mono-vaccinated animals.

This type of documentation may be provided for each component of the surveillance system. The data generated may be analysed qualitatively or, when precise and reliable quantitative information is available, used to estimate the sensitivity of the surveillance component, i.e. the probability of detecting the presence of infection given the distribution of possible prevalence values in the sub-population under surveillance.

Some methods for a possible quantitative evaluation of a non-random surveillance system have recently been published (12, 13, 14).

## Discussion and conclusions

Animal health surveillance is an essential component for detecting diseases, monitoring disease trends, controlling endemic and exotic diseases, supporting claims for freedom from disease or infection, providing data to support the risk analysis process for both animal health and/or public health, and substantiating the rationale for

sanitary measures. Surveillance data underpin the quality of disease status reports and should satisfy the information requirements for accurate risk analysis, for international trade as well as for national decision-making (18).

The main goal of an FMD surveillance system is to control the disease. Proof of the absence of disease and absence of viral circulation does not require any further surveillance system than that necessary for effective disease/infection control or eradication. The claim for freedom from disease or infection depends upon effective control and/or eradication, and both of these rely upon effective surveillance.

No effective surveillance can exist in the absence of a solid Veterinary Services infrastructure, which is geographically distributed across the country's territory and operates as an integrated system.

This integration must work effectively in various ways:

- in terms of components of the surveillance system: data generated by different components of the system must complement and be integrated with one another. They should not be a series of repeated controls all performed on the same limited pool of epidemiological units;
- in terms of components of the Competent Authority: field and laboratory veterinarians should cooperate and collaborate and have prompt and reciprocal access to data;
- in terms of the production sector becoming actively involved in the surveillance systems. Participatory epidemiology and participatory surveillance of livestock disease, for example, can be used to design better animal health projects and delivery systems, and more successful surveillance and control strategies.

No shortcuts exist to building a solid Veterinary Services infrastructure geographically distributed across the territory. In particular, the use of random surveys as the main means to prove the absence of disease/infection, even if apparently able to provide the required level of confidence with a minimal use of resources, has severe limitations indeed when FMD occurs at a very low level of prevalence, especially in mass-vaccinated populations.

The pillars of a surveillance system able to provide the documentation required for the claim of freedom from disease or infection are the same as those necessary for effective control and eradication of infections:

- targeted (risk-based) surveillance
- an early detection system
- a disease reporting or notification system
- monitoring of vaccination activities.

Continuous targeted risk-based surveillance is the method of choice in cases of low prevalence and clustering, i.e. as in mass-vaccinated populations. The identification of risk factors is a particularly delicate phase, when properly implementing risk-based surveillance systems, if serious drawbacks are to be avoided. These risk factors must be determined from factual data, collected in the populations subject to the risk-based surveillance, and assessed using a proper method.



## Les stratégies de surveillance de la fièvre aphteuse visant à démontrer l'absence de la maladie et l'absence de circulation virale

V. Caporale, A. Giovannini & C. Zepeda

### Résumé

Le commerce sans entraves d'animaux et des produits d'origine animale est basé sur la reconnaissance internationale ou bilatérale du statut sanitaire des populations animales échangées. Cette reconnaissance repose sur les informations enregistrées par le pays exportateur pour étayer son statut sanitaire en consignnant les résultats d'une surveillance exercée sans discontinuer.

Aux termes du *Code sanitaire pour les animaux terrestres* de l'Organisation mondiale de la santé animale (OIE), ces informations sont recueillies au moyen de diverses méthodes de surveillance : informations émanant de la surveillance générale (surveillance clinique, notification passive des cas suspects, etc.) ; informations recueillies grâce aux activités conduites pour améliorer la sensibilité de la surveillance générale (formations, mesures incitatives récompensant les notifications ou au contraire sanctions pénalisant la non-notification, etc.) ; informations émanant des opérations de surveillance spécifique, y compris les résultats de cette surveillance (recherches aléatoires, surveillance ciblée et basée sur le risque, échantillonnages de commodité, etc.). En général, les déclarations de statut indemne se réfèrent à l'absence d'infection.

La surveillance clinique et la surveillance passive permettent de garantir l'absence d'infection par le virus de la fièvre aphteuse avec un niveau de confiance élevé, sauf dans les populations vaccinées. Pour ces populations, la surveillance spécifique s'avère donc plus utile que la surveillance clinique générale.

La surveillance spécifique dépend étroitement des performances de l'épreuve ou des épreuves utilisées. Aux défauts de spécificité d'une épreuve sérologique viennent encore s'ajouter d'autres difficultés lorsque l'on recourt à des techniques visant à différencier les animaux infectés des animaux vaccinés (stratégies dites DIVA) : en effet, la purification imparfaite de l'antigène utilisé pour la vaccination peut favoriser l'apparition d'anticorps non désirés chez les animaux vaccinés.

Les auteurs examinent plusieurs options permettant de résoudre ce problème et analysent leurs faiblesses et leurs avantages respectifs pour démontrer l'absence d'infection, ou l'absence de circulation virale, pour les maladies en général et plus particulièrement pour la fièvre aphteuse. Les auteurs mettent l'accent sur la recherche de méthodes applicables dans divers contextes épidémiologiques et par diverses structures organisationnelles, compte tenu des variations en la matière entre les Pays Membres de l'OIE.

#### **Mots-clés**

Documentation – Fièvre aphteuse – Organisation mondiale de la santé animale (OIE) – Pays indemne – Recherche aléatoire – Surveillance – Surveillance basée sur le risque – Surveillance ciblée – Systèmes de détection précoce.



## **Estrategias de vigilancia de la fiebre aftosa para demostrar la ausencia de enfermedad y de circulación de virus**

V. Caporale, A. Giovannini & C. Zepeda

#### **Resumen**

El libre comercio de animales y productos de origen animal se basa en el reconocimiento internacional o bilateral de la condición sanitaria de las poblaciones animales que son objeto de transacción comercial. Este reconocimiento, a su vez, depende de que el país exportador pueda demostrar fehacientemente dicha condición atendiendo a los resultados de una vigilancia continua.

Según lo dispuesto en el *Código Sanitario para los Animales Terrestres* de la OIE, la documentación al respecto puede dar fe de la aplicación de métodos de vigilancia diversos, por ejemplo: vigilancia inespecífica (vigilancia clínica, notificación pasiva de casos sospechosos, etc.); actividades que confieren mayor sensibilidad a la vigilancia inespecífica (actividades de formación, régimen de recompensas o sanciones por toda notificación u omisión de notificar, etc.); o todas las actividades de vigilancia específica y sus resultados (estudios aleatorios, vigilancia selectiva o basada en el riesgo, muestreo por conveniencia, etc.).

Por lo general, la declaración de ausencia de enfermedad se refiere a la infección.

Mientras que las labores de vigilancia clínica y pasiva pueden garantizar con un elevado nivel de confianza la ausencia de fiebre aftosa, no es este el caso de las poblaciones vacunadas, en las cuales la vigilancia específica cobra una importancia mucho mayor que la vigilancia clínica inespecífica.

La vigilancia específica depende en grado sumo de la eficacia de las pruebas de detección empleadas. A la imperfecta especificidad inherente a toda prueba serológica se agrega una mayor complejidad cuando se emplean técnicas para distinguir entre animales infectados y vacunados (DIVA), porque la imperfecta purificación del antígeno utilizado en las vacunas puede inducir la síntesis de anticuerpos no deseados en el animal vacunado.

Los autores examinan diversos modos de eludir este problema y sus ventajas e inconvenientes para certificar la ausencia de infección o de virus circulantes en las enfermedades animales en general, y en el caso de la fiebre aftosa en particular, tratando especialmente de encontrar métodos que puedan aplicarse en diversas situaciones epidemiológicas y en distintas estructuras organizativas, pues estas pueden ser muy dispares entre los Países Miembros de la OIE.

#### Palabras clave

Documentación – Estudio aleatorio – Fiebre aftosa – OIE – Organización Mundial de Sanidad Animal – País libre de enfermedad – Sistemas de detección rápida – Vigilancia – Vigilancia basada en el riesgo – Vigilancia selectiva – Zona libre de enfermedad.



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