Rev. sci. tech. Off. int. Epiz., 2011, **30** (1), 189-206

Cattle, sheep and pigs vaccinated against foot and mouth disease: does trade in these animals and their products present a risk of transmitting the disease?

A.J.M. Garland [1] & K. de Clercq [2]

(1) Collingwood, Dawney Hill, Pirbright, Surrey, United Kingdom, GU24 0JB
(2) Department of Virology, Section of Vesicular and Exotic Diseases, CODA-CERVA-VAR, Groeselenberg 99, B-1180 Ukkel, Belgium

Summary

The foot and mouth disease (FMD) status of a country or region has a profound bearing on access to export markets for live animals and animal products. In countries without FMD-free status, and in accordance with the international standards of the World Organisation for Animal Health (OIE), restrictions may be applied to trade in both vaccinated and unvaccinated animals and their products.

Available information suggests that, provided there is compliance with essential criteria concerning vaccines, vaccination and other zoosanitary measures (especially quarantine and ante- and post-mortem inspection), the risk of spreading FMD through the importation of vaccinated cattle, sheep and pigs is extremely small. The risk from products derived from vaccinated animals is even smaller, provided that appropriate risk mitigation measures are applied. Knowledge of the zoosanitary status of the exporting country is critical for risk assessment, but can be difficult to verify.

Although empirical evidence and practical experience strongly indicate low risk, it is not possible to assert that the risk is zero for vaccinated animals or their products. In the absence of key factual data, risk analysis is only practicable on a qualitative or semi-quantitative basis. However, a very low level of risk is both unavoidable and acceptable if such trade is to be conducted.

Keywords

Foot and mouth disease – Foot and mouth disease vaccination – Risk analysis – Risk assessment – Risk mitigation – Trade in animal products – Trade in animals.

Introduction

Assessing the risks of transmitting foot and mouth disease (FMD) via vaccinated animals or products derived from them is important, since countries in which FMD vaccination is practised, whether or not they also have circulating virus, are constrained to varying degrees in respect of international trade in both animals and products (106). Importing countries may prohibit such trade or permit it only subject to the application of stringent sanitary measures. These constraints can have severe economic effects, especially for countries in which such export trade contributes, or could potentially contribute, significantly to the national economy. The restrictions are particularly onerous for developing countries in which the immediate effects deny access to lucrative markets while also deterring potential longer-term investment and the development of the livestock sector (60, 62, 73, 74, 89, 90, 91). The assessment of the risk of disease transmission is equally important for the protection of importing countries. Assessing the risks is complex, requiring multiple factors to be considered (102).

Foot and mouth disease is extremely contagious, with seven immunologically distinct virus serotypes, numerous

emergent strains, a wide host range, many modes of dissemination, and significant adverse effects, both direct and indirect (2). For these reasons the World Organisation for Animal Health (OIE) has developed and published measures to minimise the risk of spread. The international standards for ensuring the sanitary safety of livestock and their products are published in the *Terrestrial Animal Health Code* (*Terrestrial Code*) of the OIE (106).

This paper examines the risk of introducing FMD through the importation of live, vaccinated cattle, sheep and pigs and products derived from them through the consideration of direct and indirect lines of evidence. These include:

– published import risk assessments for vaccinated and unvaccinated animals and their products

– data on the titres and survival of FMD virus in these commodities

– lack of direct evidence for the international spread of FMD through these commodities

– critical risk mitigation factors.

Aspects of the *Terrestrial Animal Health Code* related specifically to foot and mouth disease

The *Terrestrial Code* recommends measures designed to ensure safe trading in live cattle, sheep and pigs and products derived from them (a list of these products can be seen in Table I).

This discussion does not deal explicitly with goats and buffalo or their products, although the *Terrestrial Code* considers sheep and goats together as small ruminants and includes recommendations for buffalo together with cattle (106).

Table I
Traded commodities of bovine, ovine and porcine origin considered in the OIE *Terrestrial Animal Health Code*

Species	Commodity
Cattle	Meat (beef: fresh, chilled, frozen, deboned, minced, cured, smoked, and salted)
	Offal (kidneys, liver, pancreas, spleen, thymus, thyroid, brain)
	Intestines
	Milk and dairy products (milk powder, cream, whey, butter, cheese, and yogurt)
	Hides
	Embryos, oocytes
	Semen
	Materials for use in biological and pharmaceutical applications
Sheep	Meat (lamb and mutton: as for beef)
	Offal (as for beef)
	Intestines
	Milk and dairy products (cheese)
	Wool
	Skins
	Embryos, oocytes
	Semen
	Materials for use in biological and pharmaceutical applications
Pigs	Meat (pork: as for beef)
	Offal (as for beef)
	Intestines
	Bristles
	Hides
	Materials for use in biological and pharmaceutical applications

Risk assessment methodology

Import risk analysis is covered in the *Terrestrial Code* and includes hazard identification, risk assessment, risk management and risk communication. Factors typically examined in a risk analysis include: the competence of the Veterinary Services in the exporting country, surveillance capability and results, any zoning or compartmentalisation that may be in place, and zoosanitary measures such as animal identification, movement control, certification, quarantine and vaccination (106). In addition, the OIE has published a *Handbook on Import Risk Analysis for Animals and Animal Products* (102) and guidelines on *Devising Import Health Measures for Animal Commodities* (103). It is notable that these publications make only passing reference to any potential risk mitigation effects of FMD vaccination and that the *Terrestrial Code* states that no single method of risk assessment is likely to be applicable in all circumstances.

Examples of relevant risk assessments

Many publications have analysed the risks of introducing disease through importation of live animals and animal products, and many of these publications focus specifically on FMD. The majority deal with unvaccinated, rather than vaccinated, animals and their products and with cattle rather than sheep or pigs. Nevertheless, they do provide baseline, worst-case scenario information on the levels of infectivity which effective vaccination can reasonably be assumed to reduce.

Several studies address the subject in general (11, 15, 29, 48, 87, 92, 98, 99, 108), while others focus on qualitative or quantitative analyses for specific localities and specific commodities. Callis specifically considered the general, overall risk of the spread of FMD (14), as did Blackwell (8, 9), while Yu *et al.* (107) focused on the FMD risk from the importation of deboned meat. A comprehensive review of the FMD risk from deboned meat, published in 2010 (60), included a detailed critique of many papers which are cited here. Risk analyses for specific geographical localities include the FMD risk from importation of live animals into Spain (45) and into the Malaysia–Thailand–Myanmar peninsula (100). Regional assessments which also address aspects of vaccination include: the risk to the United States from the importation of chilled or frozen beef from Uruguay (94), the importation of deboned beef from Argentina into the United States (16) and importation from Argentina and Uruguay to the Caribbean Community countries (55).

Other examples address overall risks of the introduction of FMD from the transcaucuses by all modes into Russia and the European Union (EU) (49) and from more widespread origins into New Zealand (43, 63). A particularly thorough risk analysis was carried out by the European Food Safety Authority (EFSA) for the countries of the EU in 2006 (25, 26, 27, 28). This included a study of legal and illegal trade in products of animal origin and concluded that commodities imported illegally from endemic areas of Asia through the Middle East and Africa pose a greater risk to Europe than imports from South American countries having an established and regulated meat trade with the continent (25). The report did not consider the effects of vaccination on risk.

Foot and mouth disease virus in unvaccinated animals and their products

There have been many publications on the titre and survival of FMD virus in animals and in materials derived from them (e.g. 8, 9, 14, 15, 17, 23, 37, 38, 42, 43, 50, 52, 60, 69, 71, 74, 75, 78, 85, 93, 101, 107). Although most publications have concerned unvaccinated animals and their products, they are useful in providing baseline data that contribute to a clearer understanding of the risks that effective vaccination protects against. Important publications include the seminal 1948 studies of Henderson and Brooksby in cattle (37) and the later reviews of Cottral (17) and Sellers (77), which covered a wider range of species. The comprehensive review by Ryan and co-workers in 2008 (69) deals with bovine, ovine and porcine tissues during the viraemic phase of FMD, provides infectivity data for products derived from infected animals, and discusses various methods of virus inactivation applicable to the processing of such products (69).

Most published studies deal with the survival of the virus in bovine muscle tissue (meat) and associated tissues such as lymph nodes, residual blood, fat, bone and bone marrow. These studies have been reviewed comprehensively (60) and the elements required for the assessment of the risk from such tissues have been enumerated (35). Astudillo *et al.* (5) specifically considered the FMD risk posed by the importation of South American beef and concluded that any risk was extremely small. The same workers also discussed risk assessment and risk regionalisation based on the surveillance systems in place in the subcontinent (4). Muzio *et al.* (50) addressed the FMD risk from dairy products in the South American context. Milk and dairy products were more widely reviewed for FMD risk by Heng and Wilson in 1993 (38), by Donaldson in 1997 (23) and by Tomasalu and Konstance in 2004 (93).

The risks from other animal products have also been assessed, again usually without explicit consideration of vaccination. Examples include bovine embryos (75, 86, 87) and bovine semen (18, 76, 77, 78).

Foot and mouth disease virus in vaccinated cattle and their products

Few publications have specifically addressed the case of vaccinated animals and their products. One example is a collaborative study between Argentina and the United States (52) that investigated the survival of virus in the tissues of each of three groups of 14 cattle vaccinated repeatedly against South American O, A and C serotypes of FMD, and five unvaccinated control cattle in each group. All were challenged by tongue inoculation with a homologous virus and killed around 32 h later. The experiment was designed to maximise the probability of recovering infectious virus and so animals were slaughtered at the peak of viraemia in unvaccinated control cattle and various tissues, especially draining lymph nodes, were sampled. Whereas virus was detected at the time of slaughter in all lymph nodes sampled from unvaccinated control cattle, it was detected in the nodes of only 1 of 14 vaccinated animals challenged with type O and none of those challenged with type A or C virus. Subsequently the effect of storage was examined by sampling muscle and lymph nodes from the carcasses kept at 3°C to 6°C for 72 h post slaughter. Previous studies on unvaccinated cattle (37) had demonstrated that virus could no longer be

detected in skeletal muscle at that time but could be found in bone marrow, residual blood and lymph nodes. In the collaborative Argentinean–United States study, virus was similarly cleared from muscle while still being detected in the lymph nodes of 14 of 15 unvaccinated control cattle after 3 days of maturation, albeit at much reduced titres compared to those found at the time of slaughter. No virus was detected in pooled lymph nodes from the carcasses of vaccinated animals after the same period of storage. After further storage of muscle and lymph nodes in salt solution for 1 month at 3°C to 6°C, virus was recovered from lymph nodes from 4 of the 15 unvaccinated control cattle but none of the vaccinated animals.

This study (52) demonstrated a markedly reduced likelihood of recovering virus from lymph nodes of repeatedly vaccinated cattle exposed to virus 32 h previously, presumably due, at least in part, to the presence of neutralising antibodies. It can reasonably be assumed that other tissues of such repeatedly vaccinated cattle would be similarly free from virus (apart from possible infectivity in the oropharynx of carriers). However, the authors (52) emphasise a critical limitation of the study, namely the low statistical significance of experiments using relatively small numbers of animals. Subject to certain assumptions, the authors also concluded that the probability of demonstrating virus in fresh lymph nodes from repeatedly vaccinated cattle could be indirectly calculated as 0.024, with an upper 95% confidence limit (CL) of 0.07. The corresponding figures for combined probabilities following the application of vaccination and the maturation and curing treatments varied between 0.087 and 0.032. In other words, in cured meat produced from 100 exposed vaccinated cattle, infective lymph nodes would not be expected to occur on more than three to nine occasions under the conditions of the experiment. As the authors pointed out, if direct estimates were to be obtained then 'such experiments would require many hundreds of animals' and are therefore unlikely to be undertaken for practical, economic and ethical reasons. Another important limitation of these experiments was that the cattle had been vaccinated on six occasions and were then subjected to homologous challenge, leaving open the question of what might be found if animals were challenged after fewer vaccinations or with heterologous virus.

In 2003 Sutmoller and Casas Olascoaga (85) assessed qualitatively the risk of FMD transmission via the importation of vaccinated animals and their products. They drew attention to the possibility that vaccination might mask disease and also to the possibility of a persistent, asymptomatic, FMD virus carrier state in the pharynx of vaccinated or convalescent cattle, sheep and goats (see below). They emphasised that early recognition of clinical disease at source is crucially important and contended that any risks could be reduced to a negligible level provided that disease surveillance, farm biosecurity, animal traceability, control of source cattle and slaughterhouse inspections were all carried out in compliance with the *Terrestrial Code*. They also considered that maturation and deboning of bovine carcasses are important, but possibly over-emphasised, risk reduction measures. It is notable, however, that following the introduction in 1968 of the additional deboning and maturation measures applied to carcasses in the major meat-exporting countries of South America, there have been no instances where such products have been identified as causing outbreaks of FMD (5, 85, 91, 95). Sutmoller and Casas Olascoaga (85) also considered that the possibility of contamination of carcass parts with virus carried in the pharynx is very unlikely during slaughter and processing in a well-managed abattoir. Their risk assessments also concluded that the importation of milk products from countries or zones practising dairy herd vaccination poses a negligible risk, as does the importation of embryos from vaccinated cows and semen from vaccinated bulls, provided that appropriate sanitary measures are applied in accordance with the *Terrestrial Code*. The conclusions of Sutmoller and Casas Olascoaga (85) are similar to those of others who have examined the South American situation with respect to meat and meat products, milk and dairy products, and casings (4, 5, 50).

Foot and mouth disease virus in pigs and porcine tissues

Three papers have assessed the risk of introducing FMD through the importation of pork derived from vaccinated pigs. Lopez *et al.* (42) used a semi-quantitative approach which assumed that the pigs had originated from an area that had regained freedom from disease after an outbreak of FMD. Using data from other publications, they assessed risks using a Monte Carlo model to ascribe probabilities to a cascade of events from farm to matured pork. Their model produced the following results:

– probability of pigs originating from an infected farm: 0.0016%

– probability of pigs infected at slaughter: 0.47%

– probability that infection is not detected at ante-mortem inspection: 79.7%

– probability that infection is not detected at post-mortem inspection: 79.7%

– probability that virus survives post-mortem pH drop in meat: 1.1%.

However, the authors stressed that their assumptions may not be representative of pig management and FMD epidemiology globally and also that specific information is

lacking on the survival of FMD virus in porcine tissues such as skin, lymph nodes, bone marrow and blood, particularly in vaccinated animals.

Greiner and Jensen (35) summarised published data on the survival of FMD virus in tissues from pigs (and cattle) and discussed the effect of the post-mortem drop in the pH of tissues. They also pointed to the scant information available on the survival of FMD infectivity in porcine tissues, the statistical limitations of small sample sizes, and the lack of data on the effects of vaccination.

De Vos and colleagues (22) employed a mathematical model to estimate the probability of exporting infected carcasses from vaccinated pigs following an FMD epidemic. Key variables, including herd prevalence, within-herd prevalence and the probability of detection of the disease at slaughter, were estimated using Bayesian inference, assuming that, despite all serological tests having given negative results, one or more infected pigs were present in the group to be exported. The calculations were applied in two scenarios: first where the slaughter and export take place one month after the final negative screening and, secondly, when they take place six months after that screening. The model calculated the average probability of a processed carcass being derived from an infected pig to be 2×10^{-5} immediately after final screening and 1.7×10^{-5} after a six-month waiting period. Thus, the probability of exporting an infected carcass under these hypothetical conditions was very low and was not substantially reduced by the additional waiting time. They also considered that the results represented worst-case scenarios, since only viraemic pigs pose a threat of disease transmission.

Foot and mouth disease virus in sheep and in ovine tissues

Apart from the 1994 report of Gomes *et al.* (32), there have been few studies on the survival of FMD virus in sheep carcasses; their results are thus considered here in some detail. Twenty-five three-month-old lambs were infected by intradermolingual injection of serotype O, strain O1 Campos FMD virus and then separate groups of three animals were slaughtered at 48 h, 72 h, 96 h and 120 h and at 15 and 30 days post infection (PI). Immediately after slaughter, samples were taken of blood, longissimus dorsi and semimembranosus muscles, prescapular, popliteal, submaxillary and mesenteric lymph nodes, tonsils, oesophagus, heart, liver, spleen and kidney. These samples were placed in glycerol phosphate buffer, pH 7.2 to pH 7.4, and frozen at –20°C. The carcasses were also stored for maturation at 4°C for 24 h, at which time further samples were taken from the same muscle groups and the carcasses transferred to storage at –20°C. After the carcasses had been in storage for four months, a third set of muscle samples was collected. Muscle pH was measured before and after maturation.

Tissue samples were later thawed and suspensions examined in tissue cultures for the presence of FMD virus. Infectivity could be recovered from tissues of sheep which were febrile when slaughtered at 2, 3 and 4 days PI, from both muscle groups, before and after maturation of carcasses and, furthermore, in the absence of foot lesions in animals killed at 2 and 3 days PI. Virus could also be isolated from the same muscles after 4 months of storage at –20°C. Virus was also detected in the lymph nodes and organs of animals killed at 48 h, 72 h, 96 h and 120 h PI, including from kidneys (range $10^{3.0}$ to $10^{3.7}$ median tissue culture infective dose [$TCID_{50}$]) and submaxillary and prescapular nodes and tonsils (range $10^{1.8}$ to $10^{4.9}$ $TCID_{50}$). Virus was not detected in any organ or lymph node of sheep slaughtered at 15 or 30 days PI. The authors discussed the importance of the drop in pH for the inactivation of FMD virus and the effect of various factors on both the rate of fall in pH and the final value attained.

The sheep in this study (32) were not vaccinated. In this context it is important to note that FMD vaccination campaigns have often focused exclusively on cattle, so the majority of sheep presented for slaughter will most probably never have been vaccinated. Although the sheep were infected by an artificial route and bone marrow was not sampled, the study nevertheless illustrates an important feature of FMD in sheep that contrasts with the usual situation in cattle and pigs: infected sheep can harbour significant amounts of virus in the absence of foot lesions.

Foot and mouth disease in sheep is commonly mild or clinically inapparent (2) and so diseased sheep might not be recognised at ante-mortem or post-mortem inspection. For this reason, Gomes *et al.* (32) stressed the importance of epidemiological knowledge of the area of origin of the sheep and also the importance of ante-mortem inspection. An additional safeguard for ante-mortem inspection could be the measurement of body temperature, although, since thousands of sheep can be presented at an abattoir on a single day, this measure may not be routinely practicable. Preliminary results from the use of remote thermal imaging technology hold some promise as a means to screen large numbers of sheep and pigs for fever which could be indicative of FMD (7).

The outbreaks of FMD in the United Kingdom (UK) in 1967 and 1968 were attributed to the importation of infected lamb carcasses from Argentina (41, 65 and see below). Rapoport and Shimshony evaluated the risk of the importation of FMD via the movement of sheep and goat meat in the Middle East (64) and stressed that the disease

mostly travels with live small ruminants rather than in meat. They did not, however, address explicitly the effect of vaccination on this risk. It appears that it has generally been assumed that the data available for cattle, with all their limitations, also apply to sheep. This assumption could be the subject of experimental verification.

No evidence for spread of foot and mouth disease by vaccinated animals or their products

Another approach to examining the possible FMD risk posed by vaccinated animals or their products is to look for evidence that they have been identified as the source of outbreaks. This is problematic in endemic areas because there are many possible sources and it is difficult to pinpoint which is responsible, although the movement of infected animals is by far the most common (2, 60). It could be assumed that the identification of the source might be simpler where an FMD outbreak occurs in an area previously free of the disease. However, even in these situations, investigations to establish the origin are often inconclusive or based on circumstantial evidence only. Exceptions may occur, however, when a serotype or topotype first appears in a new locality. An example was the appearance of topotype O Pan Asia in South Africa in 2000, with the source being attributed to the feeding of pigs with food waste from ships (39).

Modern molecular epidemiology has greatly facilitated the tracing of the sources of new outbreaks (27, 39, 41, 61) but, while this can indicate 'where' the virus came from, it does not necessarily help in determining 'how' the virus was introduced.

The 1951 to 1952 outbreak in Canada began in pigs and was attributed to either importation of infected meat and/or the mechanical carriage of virus on the clothing of an immigrant arriving from Europe (79). The most likely source of the UK outbreaks in Warwickshire in 1967 and in Oswestry (Shropshire) from 1967 to 1968 was frozen lamb carcasses from Argentina (65). It is not known whether the meat supposedly involved in either the Canadian or UK outbreaks came from vaccinated animals. Despite strong circumstantial evidence that infected food waste from shipping or aircraft was the probable cause of the outbreak of FMD type O which began in pigs in Malta in 1975, direct proof was again lacking (80).

In a 2008 review of the incursions of FMD into Europe during the 21-year period from 1985 to 2006, Valarcher *et al.* (95) reported that of the 37 primary outbreaks considered, 22 were either 'origin unknown' or had no origin ascribed, one was definitively ascribed to 'laboratory escape', two to 'possible laboratory escape', and one to 'illegal immigration'. A further eight outbreaks involved the movement of live, infected animals, either legally or illegally (four instances of each), while importation of infected meat was given as the source in three outbreaks (95). An important conclusion was that the vaccination status of the live animals involved was either (a) definitely unvaccinated or (b) unknown, while that of the meat products was unknown (Table II). There is, therefore, no definitive evidence that vaccinated animals or their products were involved in these outbreaks of FMD.

Factors mitigating the foot and mouth disease risk from livestock and their products

The competence of Veterinary Services

When assessing the risk of introducing FMD through the importation of vaccinated animals or their products, it is necessary to examine the epidemiological situation, the reliability of claims made for the absence of the disease, and the resources, competence, efficiency and integrity of the Veterinary Services of the exporting country. In this context, the country's disease-reporting history is informative. Expert missions to evaluate national Veterinary Services and the national disease situation may be organised under the auspices of international organisations such as the OIE or the Food and Agriculture Organization of the United Nations, either alone or together. Additionally, importing countries may carry out their own investigations. However, the OIE is the lead organisation with responsibility for the official designation of country status in respect of FMD and publishes recommendations on how such country evaluations should be carried out (102, 105, 106).

The evaluation of national Veterinary Services, and the use of the OIE Tool for Evaluating the Performance of Veterinary Services, is discussed elsewhere in this publication (73). An important element is the assessment of the country's diagnostic and surveillance capability for FMD. This assessment should cover the techniques used, the quality assurance and good laboratory practices applied, the internal and external quality control systems employed, record keeping and historical review, and the manner in which test results are communicated to the field and to external agencies (20, 21, 27, 30, 33, 34, 57, 58, 61). Diagnostic tests should be in compliance with the OIE

Table II
Primary outbreaks of foot and mouth disease in Europe between 1985 and 2006 involving live animals or animal products as the source of infection

Year / Serotype	Country of outbreak	Origin (confirmed or suspected)	Vaccinal status of animals or products
1993 / O	Italy	Cattle imported with forged certificate	Unknown
1994 / O	Greece	Illegal import of sheep	Unknown
1995 / O	Turkish Thrace	Illegal movement of cattle	Unknown
1995 / O	Moscow, Russia	Import of pork meat	Unknown
1996 / A	Albania	Import of buffalo meat on the bone (falsely labelled as being unboned)	Unknown
1996 / O	Turkish Thrace	Illegal movement of cattle	Unknown
2001 / O	United Kingdom	Legal or illegal import of animal foodstuff and feeding of improperly processed swill to pigs	Unknown
2001 / O	Northern Ireland	Legal movement of sheep	Unvaccinated
2001 / O	Republic of Ireland	Legal movement of sheep	Unvaccinated
2001 / O	France	Legal movement of sheep	Unvaccinated
2001 / O	Netherlands	Legal movement of calves	Unvaccinated

Source: data modified from Leforban Y. & Gerbier G. (41)

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (*Terrestrial Manual*) (104).

It is important to recognise that country evaluations only provide a snapshot of the situation at a particular time and, depending on the geographical extent of a country or region, the scale of livestock farming practised and the surveillance resources available, it may only be possible to undertake a limited, representative inspection. Moreover, both the epidemiological situation and the resourcing and competence of the animal health authorities can and do change over time. Nevertheless, it should also be recognised that countries which already export, or which wish to become exporters, have strong incentives to meet the OIE requirements and to be transparent about their zoosanitary situation and in their international reporting.

Unfortunately, there have been instances where FMD has not been officially reported or is reported only after long delays and sometimes only after intensive investigation of rumoured outbreaks of disease has uncovered the true situation. The reasons for such deficiencies are many but may include fear of the economic consequences of reporting disease, lack of resources or competence to effect comprehensive surveillance, inadequate diagnostic capability, or occult disease discovered only indirectly through laboratory investigation. Deficiencies that have been discovered include the falsification of export documentation (25, 36, 95), errors of animal identification, and samples not corresponding to their declared content (25, 36, 90, 96). Live animals and meat have frequently been smuggled across international borders, or illegally carried by travellers (25, 36, 39, 68, 76, 79, 95, 101).

Since the feeding of infected, waste animal foodstuff to pigs is recognised as a particularly risky activity for the transmission of numerous diseases, including FMD (2, 76), ascertaining the presence or absence of pigs in an importing country and the status of such feeding, whether uncontrolled, controlled or prohibited, is an important aspect of risk assessment.

Despite the possible risk of spread of FMD through the importation of vaccinated animals and their products, many thousands of animals and hundreds of thousands of tonnes of commodities have been exported from countries where vaccination against FMD is practised without reports of their having introduced disease (25, 85). As an example of the scale and geographical spread of this trade, Tables III and IV show the origins, destinations and quantities of beef (fresh/chilled and frozen) imported annually into Western Europe between 2004 and 2008. The quantities originating from vaccinated cattle are not known, but it is likely that a large proportion of the beef originating from South America and Southern Africa will have been from vaccinated animals. There is no evidence to suggest that any of these importations resulted in outbreaks of FMD (60, 82, 84).

Quarantine, ante- and post-mortem inspection

Important measures which provide additional protection against FMD risk include ante- and post-mortem inspection and quarantine (5, 26, 83, 85, 89, 91, 105). Even vaccinated animals may pose a risk of transmitting FMD if, for example, they have been vaccinated improperly or against an inappropriate serotype or strain, are newly vaccinated, or become transiently and externally

Table III
The origins, destinations and amounts of chilled or fresh beef imported annually into Western Europe during the period 2004 to 2008

Year	Number and identity of exporting countries	Number and identity of importing western European countries	Number of consignments	Total net weight (million tonnes)
2004	4 Argentina, Botswana, Brazil, Syria	4 Belgium, France, Sweden, United Kingdom	8	0.17
2005	8 Algeria, Argentina, Botswana, Brazil, Bulgaria, Namibia, Romania, Serbia and Montenegro	18 Austria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom	950	69.6
2006	11 Argentina, Bahrain, Botswana, Brazil, Bulgaria, Greenland, Namibia, Romania, Vietnam, Serbia and Montenegro, St Kitts and Nevis	17 Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom	3,002	54.8
2007	12 Argentina, Botswana, Brazil, Greenland, Namibia, South Africa, Syria, Swaziland, Thailand, Uganda, Vietnam, Serbia and Montenegro	19 Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Sweden, Switzerland, United Kingdom	7,227	100.5
2008	8 Argentina, Botswana, Brazil, Namibia, Paraguay, Swaziland, Thailand, Vietnam	18 Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom	4,234	56.0

Source: Data compiled from the European Commission's Trade Control and Expert System (TRACES) available at: ec.europa.eu/food/animal/diseases/traces (accessed in November 2009)

contaminated through contact with infected animals that show no clinical signs but whose secretions and excretions contain high titres of virus (2, 54). In such circumstances, diseased or contaminated animals may evade detection prior to shipment or at the abattoir. Quarantine may provide protection against these risks (106). However, there are practical and financial constraints on its large-scale application since there are very few facilities worldwide capable of handling the large numbers of live animals traded internationally.

Processing of products to mitigate risk

The *Terrestrial Code* recommends measures which may be applied to reduce or eliminate any FMD infectivity which may be present in products destined for export from countries in which FMD occurs. Thus, for example, the head, feet and viscera of cattle and buffalo, which are predilection sites for FMD virus, should be excluded from fresh meat destined for export.

Inactivation procedures have been reviewed by Sutmoller (83) and EFSA (25) and have recently been considered in depth in respect of deboned beef (60). Carcasses should be deboned and the meat matured to allow for the pH to drop sufficiently to inactivate any virus which might be present (9, 26, 32, 40, 52, 60, 66, 69, 71). Testing which confirms that the pH of muscle has dropped below 6.0 provides useful protection, especially for beef. However, the pH of meat from pigs, or from sheep which are febrile, does not always fall sufficiently low to provide reliable inactivation of FMD virus (35, 60, 66).

Heat treatments may also be used to inactivate FMD virus which might be present in meat or milk (10, 46, 47, 97) although, under certain circumstances, a fraction of the virus in meat (9, 10) and in milk or milk products (10, 23, 38, 50, 93) can exhibit thermal resistance.

Experience over many years indicates that commodities processed as discussed above have not transmitted FMD, although research is still required to provide additional basic information on inactivation (35, 60).

Wherever risk mitigation is dependent on the application of these procedures, it is important that their application be monitored, verified and certified on an ongoing basis.

Vaccines and vaccination

Garland (30) reviewed the elements involved in the successful control of FMD by vaccination and Parida (56) discussed the effectiveness of various strategies of vaccination. Some important aspects are discussed below.

Table IV
The origins, destinations and amounts of frozen beef imported annually into Western Europe during the period 2004 to 2008

Year	Number and identity of exporting countries	Number and identity of importing western European countries	Number of consignments	Total net weight (million tonnes)
2004	2 Argentina, Brazil	3 Cypus, Estonia, United Kingdom	12	37.6
2005	9 Argentina, Botswana, Brazil, Bulgaria, Namibia, Romania, Tunisia, Serbia and Montenegro, St Kitts and Nevis	20 Belgium, Cyprus, Estonia, Finland, France, Germany, Greenland, Ireland, Italy, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland, United Kingdom	657	138.0
2006	9 Argentina, Bahrain, Benin, Botswana, Brazil, Bulgaria, Greenland, Namibia, South Africa	19 Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Sweden, United Kingdom	1,972	115.0
2007	5 Argentina, Botswana, Brazil, Greenland, Namibia	20 Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Switzerland, United Kingdom	4,408	140.2
2008	7 Argentina, Botswana, Brazil, Namibia, Paraguay, South Africa, Uganda	18 Belgium, Bulgaria, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom	1,952	65.7

Source: Data compiled from the European Commission's Trade Control and Expert System (TRACES) available at: ec.europa.eu/food/animal/diseases/traces (accessed in November 2009)

Vaccines

Foot and mouth disease vaccine should contain virus serotype(s) and strain(s) appropriate to the situation in the locality where it is to be used. Determination of appropriate serotypes and strains depends on adequate, up-to-date, epidemiological information. While such information is comprehensively and reliably available in some parts of the world, in others, for various reasons, it may not be (25, 26, 30, 59, 61, 68, 82). Recognition of the disease may sometimes be delayed, as in the case of the 2001 epidemic in the UK where, even in a totally susceptible population, the disease was estimated to have been present for about one month before it was detected (76). Moreover, epidemiological status is dynamic. On rare occasions antigenic shift can produce a strain which is widely different from available vaccine strains (e.g. the emergence of the type A22 virus in the mid-1950s) while antigenic drift is common, especially for type A and SAT strains. In some instances a monovalent vaccine may be appropriate while in others polyvalency is required. The manufacture of vaccines inevitably lags behind the emergence of new strains and there is an interval of, at best, some months between recognising an emerging threat, developing the new vaccine strain and making the matching vaccine available. There are also technical difficulties in the matching of field and vaccine strains (61). Current vaccines can protect against homologous challenge but little is known about the level of protection provided against heterologous challenge. There is some evidence that high potency 'emergency' vaccines made from certain type A vaccine strains can provide useful cross-protection against divergent strains within the same serotype, even when serological tests predict a poor match (13), whereas for certain type O vaccines where serological tests predicted a reasonable level of cross-protection, the cross-challenge protection was shown to be variable, being poor in one report (81) but effective in another (51). These discrepancies may reflect differences in vaccine antigen payload and/or severity of challenge.

Assuming that appropriate serotype(s) and strain(s) of virus have been incorporated in the vaccine, the quality of the vaccine should be assured through compliance with the standards of the OIE *Terrestrial Manual* (104). De Clercq *et al.* (20, 21) emphasised the importance of quality assurance and quality control in the manufacture and testing of FMD vaccines. Important criteria include the following:

a) FMD vaccines for routine, prophylactic use should contain a minimum of three 50% protective doses (PD_{50}) per vaccine dose.

b) FMD vaccines are thermolabile and must be maintained at around 4ºC between manufacture and application.

c) It may be necessary to use vaccine antigens which have been purified with respect to non-structural viral proteins (NSPs) of FMD and have been shown not to elicit antibodies to NSPs after repeated vaccination in order to enable the differentiation of animals which have been infected or vaccinated.

d) The formulation of FMD vaccine that best fits the purpose should be used. Oil-emulsion-adjuvanted vaccines are appropriate for ruminants and pigs, whereas aqueous saponin-alhydrogel-adjuvanted vaccines work well in ruminants but much less well in pigs.

e) Vaccines must be applied within their stated shelf life.

Vaccination

Important aspects of FMD vaccination include the following:

a) Coverage should be at least 80%, with the goal being 100%.

b) Campaigns to vaccinate livestock in a particular area should be completed in the shortest possible time to ensure similar levels of herd immunity are attained as quickly as possible.

c) Vaccination should be programmed to allow for interference in the immune response of young animals from maternal immunity. The programme should incorporate a double course of immunisation for animals being vaccinated for the first time, and regular annual, or more frequent, revaccination thereafter. These criteria may vary according to the epidemiological situation, the vaccine type, the manufacturer's instructions and the objectives of the campaign.

d) Vaccines should be administered in the correct dose by the correct route.

e) The efficacy of vaccination should be monitored by the maintenance and inspection of accurate vaccination records and by conducting statistically designed serological surveys to evaluate both the degree of vaccination coverage and the level of herd immunity over time. Robiolo *et al.* (67) described a serological method for the assessment of herd immunity and expected protection against FMD in cattle which offers significant advantages of speed and economy. Serosurveillance is also recommended to determine whether FMD virus is still circulating in the field (58, 105).

f) The immune response to FMD vaccines takes time to develop (31, 56) and even with high potency emergency vaccines some four to seven days can intervene before protection is sufficient to prevent clinical disease (6, 19, 56). During this lag phase cattle can become infected and transmit infection. In pigs, vaccination results in reduced virus excretion after challenge, and vaccination seven, but not four, days prior to challenge can prevent transmission of FMD (19).

g) Immune animals may still transmit FMD, if they have been in contact with a source of virus, by mechanical transfer. Donaldson and Kitching (24) reported on transmission between cattle which had been vaccinated four to seven days prior to exposure to infection and which were immune to the development of clinical disease.

h) The creation of an adequate level of herd immunity is essential for effective control of FMD. However, a proportion of animals are likely to respond weakly or fail to respond to vaccination altogether. Possible causes include immunological deficiency, immaturity of the immune system in young animals or interference with the response to vaccination due to maternally derived immunity. In extensive, large-scale systems of livestock management it can also be difficult to ensure that every individual receives the correct dose of vaccine.

i) In order to increase the likelihood that animals will have effective levels of immunity, the *Terrestrial Code* recommends that they should be vaccinated at least twice, not less than one month and not more than 12 months before the time of export or slaughter.

This discussion is confined to circumstances where routine, mass, prophylactic FMD vaccination is practised on a continuing basis. Typically this involves the immunisation of cattle at the age of four months by a primary course of immunisation comprising an initial dose followed by a booster dose two to four weeks later (for saponin–alhydrogel vaccines) and subsequently by six-monthly revaccination until the animal is two years old, after which annual vaccination may provide solid protection against the component strains. Oil-adjuvanted vaccines may be given at four months of age with revaccination at 12 months and annually thereafter.

While there are many examples of prophylactic vaccination campaigns playing an important role in the control of FMD (26, 30, 41, 53, 56, 68, 82, 95), vaccination may sometimes fail to control the disease, for a number of reasons (Box 1).

The foot and mouth disease carrier state

An asymptomatic FMD virus carrier state is recognised in cattle, sheep and goats (1, 2, 70). This state does not occur in pigs. Depending on the type and strain of virus involved, the carrier state may occur in about 50% of cattle exposed to infection, irrespective of their immune status

Box 1
Possible causes of ineffective vaccination protection
– Use of defective vaccine (in respect of safety and/or potency)
– Use of time-expired vaccine
– Incorrect vaccine storage (outside the recommended range of temperature)
– Incorrect vaccine application (in respect of dose and/or route)
– Inadequate vaccination coverage
– Insufficient match between the vaccine strain(s) and the outbreak strain(s)
– Maternal antibody interference
– Immunological unresponsiveness
– Antigenic shift in the field challenge virus
– Antigenic drift in the field challenge virus
– Exposure to infection before the development of an adequate level of vaccinal immunity
– Falsification of vaccination records

Associated problems
– Inadequate control of animal movement
– Accidental or illegal movement of infected animals or animal products into a vaccinated population (and/or their presentation for export as live animals or animal products, when it may then be incorrectly assumed that the animals are uninfected and/or vaccinated)

(2). Carriage is localised to the pharyngeal area, with virus detected intermittently and at declining titres for at least 3.5 years in cattle and 9 months in sheep (1, 2).

Experimental data from cattle and sheep have been used in mathematical models to quantify the effect of vaccination on the probability of viral persistence in diseased and subclinically infected animals (72). The results demonstrated that the number of carriers in a group is determined mainly by the number of animals infected initially and that the number of bovine carriers is greater when challenge occurs shortly after vaccination. Detection of carriers is largely dependent upon the quality of inspection. Moreover, as the time interval increases between effective vaccination and exposure to infection the rate of detection of carriers generally decreases. Thus, the timing of vaccination before exposure to infection has a significant effect on the likelihood of detecting persistent infection in cattle and sheep (72).

Other modelling of the effects of vaccination of cattle (3) showed that the prevalence of herds with carriers is likely to be very low, approximately 0.2%, with very few carriers, perhaps only a single animal, in positive herds. For these reasons the testing of all animals in vaccinated herds is recommended to optimise the detection of carriers.

The epidemiological significance of the carrier state remains controversial (1, 2, 83, 84, 85). There is some evidence from the field linking outbreaks to carriers, but all experimental attempts to transmit disease from carrier cattle to susceptible cattle under laboratory conditions have been unsuccessful. However, these studies have involved small numbers of cattle only and few strains of virus. They demonstrate that transmission from carrier cattle is rare but do not preclude the possibility (2). Theoretical calculations have estimated a transmission rate of 0.1128 infections per carrier per month for contact with susceptible cattle (with 95% confidence limits of 0.000 to 0.3078) and a decrease in the proportion of carriers of 0.115 per month (88). These low theoretical values are supported by the observation that many thousands of vaccinated carriers must have been transported within and between countries without there being any authenticated reports of transmission of FMD being attributed to this source (25, 83, 84, 85, 95).

Discussion

The international trade in livestock and animal products is enormous and increasing. For example, Brazil accounts for some 28% of all international commerce in bovine meat and in 2008 the country exported around 2.2 million tonnes with a value of US$5.3 billion. The exports comprised 1.5 million tonnes of fresh meat, 0.5 million tonnes of processed beef, 0.07 million tonnes of offal, 0.08 million tonnes of casings and 0.006 million tonnes of salted materials. Of the fresh meat, 0.65 million tonnes were imported into Western and Eastern Europe and 0.5 million tonnes into Russia (12). The vaccination status of the source cattle is unknown, but Brazilian regions permitted to export to Europe must meet the OIE criteria for an 'FMD-free zone where vaccination is practised'. No introductions of FMD have been associated with these imports.

As evident from this review, there have been relatively few studies published on the quantitative survival of FMD virus in the tissues of vaccinated animals exposed to infection; the investigations which have been carried out have been restricted to a few serotypes only, with information on the SAT and Asia serotypes being particularly sparse (60). The studies have been concerned principally with cattle vaccinated repeatedly and they employed methods of virus detection of lower sensitivity than those currently available. Nevertheless, the limited data suggest that effective vaccination significantly reduces the risk that immunised animals or their products could carry FMD infection (25). However, the lack of information leaves us with a number of unanswered questions, namely:

– what would be the result if cattle were vaccinated less frequently or challenged sooner after vaccination?

– what would be the result of vaccination against each of the seven serotypes and for heterologous virus challenge?

– what would be the result of applying more sensitive methods of virus detection?

– what would be the results of vaccination in sheep and pigs?

These areas could be targeted for further research (35, 60). However, considering (i) the lack of evidence for transboundary transmission, even by unvaccinated animals and their products, when proper safeguards are observed, (ii) the cost of such studies and (iii) the aspect of statistical significance, the question arises of the experiment's expected return on investment, especially when ranked against competing research priorities.

Faced with the paucity of factual data, an alternative approach could be the application of 'scenario tree' methods of combining multiple sources of evidence (44) to determine whether a particular source of live animals and animal products poses a level of FMD risk which meets an importing country's appropriate level of protection (so-called ALOP). This approach has been applied in a number of situations (2, 58, 61, 68, 82, 89) and could be developed further. Vaccination would be one of the factors considered in such a model.

Animals with effective, solid immunity to FMD, having been properly vaccinated with well-controlled vaccines incorporating appropriate strains, pose a very small risk of spreading the disease. The same applies to the products derived from such animals, provided that they comply with the recommendations of the *Terrestrial Code*. However, even though the risk may be small, it cannot be assumed to be zero. Quantitative risk assessment is of limited application because of the lack of key factual data. Nevertheless, and with the provisos discussed, empirical evidence over many years strongly indicates the absence of FMD risk from vaccinated animals or products derived from them.

■

Les échanges internationaux de bovins, d'ovins et de porcins vaccinés contre la fièvre aphteuse et de leurs produits dérivés comportent-ils un risque de transmission de la maladie ?

A.J.M. Garland & K. de Clercq

Résumé

L'accès aux marchés d'exportation pour les animaux vivants et les produits d'origine animale est directement lié au statut sanitaire vis-à-vis de la fièvre aphteuse, du pays ou de la région dont proviennent ces animaux. Conformément aux normes internationales de l'Organisation mondiale de la santé animale (OIE), des restrictions peuvent être imposées aux échanges d'animaux vaccinés et non vaccinés provenant de pays non indemnes de fièvre aphteuse, ainsi qu'à leurs produits.

Les informations disponibles tendent à montrer que le respect des exigences essentielles en matière de vaccins et de vaccination et l'application de mesures zoosanitaires appropriées (telles que la quarantaine et les inspections *ante-mortem* et *post-mortem*) réduisent à des niveaux extrêmement bas le risque de propagation de la fièvre aphteuse consécutive à l'importation de bovins, d'ovins et de porcins vaccinés. Le risque associé aux produits issus d'animaux vaccinés est encore plus infime, à condition que les mesures appropriées d'atténuation du risque aient été appliquées. Il est essentiel de connaître le statut sanitaire

du pays exportateur pour conduire une évaluation du risque, mais ce statut est parfois difficile à vérifier.
Si les données empiriques et l'expérience pratique permettent d'apprécier le risque associé aux animaux vaccinés et à leurs produits dérivés comme étant très faible, il est néanmoins impossible de le considérer nul. En l'absence de données factuelles, l'analyse du risque ne peut être conduite qu'au moyen de méthodes qualitatives ou semi-quantitatives. Toutefois, pour ce type d'échanges commerciaux, un niveau très faible de risque est à la fois inévitable et acceptable.

Mots-clés
Analyse du risque – Atténuation du risque – Échanges internationaux d'animaux – Échanges internationaux de produits d'origine animale – Évaluation du risque – Fièvre aphteuse – Vaccination contre la fièvre aphteuse.

Bovinos, ovinos y porcinos vacunados contra la fiebre aftosa. ¿Existe riesgo de transmisión de la enfermedad por el comercio de estos animales y sus derivados?

A.J.M. Garland & K. de Clercq

Resumen
La situación sanitaria de un país o una región en relación con la fiebre aftosa influye sobremanera en su acceso a los mercados de exportación de animales vivos y productos de origen animal. Con arreglo a las normas internacionales de la Organización Mundial de Sanidad Animal (OIE), en los países no reconocidos como "libres de fiebre aftosa" se pueden imponer restricciones al comercio de animales, estén o no vacunados, y de sus derivados.
Los datos existentes dejan pensar que, a condición de que se cumplan ciertos criterios esenciales relativos a las vacunas, la vacunación y otras medidas zoosanitarias (principalmente la cuarentena y la inspección *ante* y *post-mortem*), el riesgo de propagación de fiebre aftosa por la importación de bovinos, ovinos y porcinos vacunados es extremadamente bajo. Los productos obtenidos a partir de esos animales vacunados presentan un nivel de riesgo aún menor, siempre y cuando se apliquen medidas adecuadas de mitigación del riesgo. Para determinar el riesgo es indispensable conocer la situación zoosanitaria del país exportador, aunque a veces resulta difícil verificarla.
Aunque los datos empíricos y la experiencia apuntan a todas luces a un bajo nivel de riesgo, no es posible afirmar que los animales vacunados o sus derivados no presentan absolutamente ningún riesgo. A falta de ciertos datos factuales básicos sólo cabe proceder a un análisis del riesgo de carácter cualitativo o semicuantitativo. Sin embargo, un nivel de riesgo muy bajo resulta a la vez inevitable y aceptable si se desea proceder a este tipo de transacciones comerciales.

Palabras clave
Análisis del riesgo – Animales – Comercio internacional de animales – Comercio internacional de productos de origen animal – Determinación del riesgo – Fiebre aftosa – Mitigación del riesgo – Vacunación contra la fiebre aftosa.

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