Vaccination against foot-and-mouth disease: the implications for Canada

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Abstract — Vaccination of susceptible animals against foot-and-mouth disease (FMD) is a well established strategy for helping to combat the disease. Traditionally, FMD vaccine has been used to control a disease incursion in countries where the disease has been endemic rather than in countries considered free of the disease. In 2001, the use of vaccine was considered but not implemented in the United Kingdom (1), whereas vaccine was used to help to control FMD in The Netherlands (2,3). Canadian contingency plans provide for the use of vaccine; Canada is a member of the North American Foot-and-Mouth Disease Vaccine Bank, which could supply vaccine if needed. This article explains why Canada might use FMD vaccine to combat an outbreak and the factors that are relevant to the disposal of vaccinated animals and their products. It concludes that vaccination is an important mechanism in Canada's preparedness for an outbreak of FMD and that products from vaccinated animals are safe for human consumption.

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Introduction

This article discusses Canadian planning to combat an outbreak of foot-and-mouth disease (FMD), with particular reference to the rationale for and the implications of using vaccination as part of the response. Current international norms classify countries as FMD-free, FMD-free with vaccination, or FMD-infected, and identify strict risk management measures for trade in animals and animal products from FMD-infected countries and those that vaccinate against FMD to prevent the spread of the disease (4). Consistent with international standards, Canada would slaughter vaccinated animals as soon as possible so that the country could regain its FMD-free status quickly. Products, including meat, from animals vaccinated against FMD could be safely consumed by the public.

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The role of FMD vaccine in Canadian contingency plans

The Canadian Food Inspection Agency (CFIA) is responsible for the development and regular updating of contingency plans to combat foreign animal diseases. For FMD and many other foreign diseases, the objective is to contain and eradicate an incursion as quickly as possible. Canada has a "stamping-out" policy. Stamping-out refers to the slaughter of affected and in-contact susceptible animals, followed by disposal of the carcasses by burial, burning, or rendering. The premises are cleaned, disinfected, and not restocked with susceptible animals for a defined period (5). The CFIA policy for FMD specifies a minimum period of 60 d: 30 d without animals followed by 30 d during which sentinel animals are resident on the farm (6). Stamping-out is the best way to rapidly regain country disease-free status according to international norms established by the Office International des Épizooties (OIE) (4).

Rapid slaughter and disposal of livestock, consistent with a stamping-out policy, may be significantly impeded by technical and logistic problems or by the application of legal restrictions. The policy adopted by the United Kingdom during the 2001 outbreak of FMD required that animals on infected and dangerous contact premises be slaughtered within 24 and 48 h of diagnosis, respectively (7). However, in the 2001 outbreak, veterinary authorities frequently were unable to meet these targets (8). In their 2001 outbreak, the Dutch authorities used vaccination, because the capacity for preemptive culling and destruction was insufficient (9).

Current Canadian policy provides for vaccination of susceptible species in designated vaccination buffer

zones. In practice, it is likely that this would be done with the objective of slowing the spread of disease until it was possible to slaughter and dispose of all infected and at-risk animals (6).

Contingency plans for the use of FMD vaccine in North America have been developed in consultations between the veterinary authorities of Canada, the United States, and Mexico, all of which are FMD-free countries. They incorporate written protocols for decision making and the acquisition and distribution of vaccine under the auspices of the North American Foot-and-Mouth Disease Vaccine Bank (The Bank). Protocols specify that all animals vaccinated for FMD will be permanently identified, placed under movement restrictions, and slaughtered as soon as is practicable, so that that country can regain FMD-free status without vaccination (10).

The "North American Decision Tree for FMD Vaccine Use" sets out the factors that are relevant to a decision to use vaccine (6). Rapid disease spread, or a high probability of spread, and the involvement of swine or multiple animal species are factors that favor the use of vaccine. A recent study of the 2001 outbreak in The Netherlands demonstrated that the economically optimal control strategy (which may or may not include vaccination) was dependent on animal density, the course of the epidemic, animal culling, and rendering capacity (11). This study concluded that ring vaccination (susceptible animals in a zone surrounding an infected area are vaccinated to contain the virus within that area) is the economically optimal strategy for densely populated livestock areas because of the limitations imposed by culling and rendering capacity.

In Canada, as in other countries, personnel shortages and scarcity of rendering and other equipment for the disposal of carcasses are key limitations to rapid slaughter and disposal. It is in this situation that vaccination might be used. However, the availability of personnel to administer the vaccine would also be a problem (6).

It is important to guard against the risk of disease spread as an unwanted consequence of vaccination. In the past, this occurred in Europe because of live virus in incompletely inactivated vaccine (12). However, producers of vaccines for The Bank must enforce strict quality control measures. All vaccines held by The Bank must have passed a rigorous assessment of safety, including virus inactivation, which is equivalent to the normal requirements for licensing (13). An inadequate immune response to vaccination in a small percentage of vaccinated animals also poses a risk. This is largely influenced by the antigenic match of the vaccine to the field virus and the timing of vaccination relative to the exposure of animals to infection, as discussed below. Vaccination teams must adopt strict biosecurity measures to prevent inadvertent spread of disease on fomites.

How would Canada obtain FMD vaccine?

Under a contractual agreement established in 1982, the governments of Canada, the United States, and Mexico established The Bank to provide rapid access to killed vaccines of proven safety and potency, should vaccine be needed to deal with an outbreak of FMD. Each country contributes to a total revenue for The Bank of US$0.5 million per year. The Bank, which is physically located in the United States, holds viral antigens of several strains of FMD virus, which are reevaluated periodically in relation to global developments.

If an outbreak of FMD occurred in North America, the chief veterinary officers of the 3 countries would activate The Bank. The strain of virus involved in the outbreak would be compared with antigens held in The Bank. If an antigen was judged to be protective against the field strain, the concentrate would be sent to a contracted company for finishing (dilution of concentrate to final doses of vaccine, addition of adjuvant, bottling, and labeling), with the view to supplying a predetermined number of vaccine doses within 3 wk.

If the vaccines held by The Bank were judged not to be protective, The Bank could send the field virus to a commercial contractor for development of a suitable vaccine. In this case, finished vaccine for use in the field would not be available within 3 wk.

International standards

The OIE provides guidelines to support the safe international trade of live animals and animal products between countries of different zoosanitary status (4). The OIE recognizes countries that are FMD-free with vaccination and those that are FMD-free without vaccination. Countries such as Canada, the United States, Mexico, and The Netherlands, which are FMD-free without vaccination, enjoy a significant advantage in the export of animals and their products. These countries can export live animals and animal products to all other countries of the world, both FMD-free and infected, vaccinating and nonvaccinating. A recent study indicated that, in the United Kingdom, an FMD-free status is worth £1.2 billion per annum, relating to export trade alone (14). For exporting countries, the current OIE norms encourage the rapid slaughter and disposal of animals vaccinated against FMD.

The use of vaccine during an outbreak of FMD may be suppressive or protective. Suppressive vaccination is used to reduce potential FMD virus production in herds and flocks that may already have been exposed to infection, but in which possibly only a few of the animals are incubating disease (2). By vaccinating all of the exposed animals, it is hoped that those not already infected will develop sufficient immunity to provide at least partial protection against clinical disease. It is accepted, however, that infection is probably present and, when time and resources permit, these animals will be slaughtered. Protective vaccination is used on herds and flocks that are in the vicinity of an outbreak but are thought not to have been exposed to live virus (3). Once vaccinated, these animals present a barrier to the further spread of the disease. While animals exposed to infection and those that are diseased will be eliminated, animals vaccinated for protective purposes could be tested to confirm the absence of viral activity and, if they are free of infection, allowed to live for the term of their productive lives.

Veterinary authorities in some European countries recently proposed that the international norms be

modified to allow vaccinated cattle to be kept for their productive life and their products to be traded under specified conditions (15). If accepted by the international community, this would help to mitigate the economic losses associated with the use of vaccine and could provide for the maintenance of vaccinated animals. However, exporting countries would need to demonstrate that they were free from infection. Measurement of antibody to nonstructural proteins has been used as an indirect estimate of viral activity in a vaccinated population (16).

Immune response to FMD

An FMD vaccine stimulates a predominantly humoral immune response in the vaccinated animal and, in cattle, there is a good correlation between antibody level and protection against live virus challenge by the same strain of FMD virus from which the vaccine was produced (17). There are 7 serotypes of FMD virus; namely, O, A, C, SAT1, SAT2, SAT3, and Asia-1, which are immunologically distinct (18). An animal that has recovered from infection with a strain of one serotype of FMD virus is still fully susceptible to infection with any of the other 6 serotypes. But, even within each serotype, there are a large number of strains with their own antigenic characteristics, so there may be only partial cross-immunity between strains of the same serotype. This is particularly true of serotype A, in which there is considerable antigenic diversity (18). Therefore, in order to achieve maximum advantage from an FMD vaccine, it is necessary to ensure that the FMD virus strain used to produce the vaccine shares as many antigenic characteristics as possible with the outbreak strain it is intended to protect against.

Characteristics of FMD vaccines

While some countries have used live FMD vaccine, only killed vaccines that have been evaluated for purity, potency, safety, and efficacy according to established criteria would be used in Canada (13). All FMD vaccines are derived from viruses that have been grown in tissue culture and inactivated, and have had an adjuvant added (17,19,20). Inactivation is achieved by treatment with binary ethyleneimine, which has been shown to be highly effective for this purpose (21). An animal could not be a source of live FMD virus as a consequence of vaccination with properly inactivated vaccine, unless it had been exposed to infection before vaccination, under which circumstances administration of vaccine could not be expected to prevent virus amplification (22,23). Thus, it is important that animals are vaccinated before they have been exposed to infection. This is best achieved by following protocols that specify appropriate circumstances for vaccination (6).

The FMD vaccine contains an equal volume of FMD antigen suspended in an aqueous buffer with an adjuvant, either aluminium hydroxide with saponin or an inert mineral oil. Both adjuvants can be used in vaccines administered to ruminants; in countries that vaccinate routinely, aluminum hydroxide, which boosts the immune response, is commonly used (22). However, the efficacy of this adjuvant in pigs has not been clearly demonstrated (22,24), and manufacturers recommend that oil-adjuvant FMD vaccines be used in swine (22,25). For emergency vaccination in Canada, oil-adjuvant vaccines, which would be effective in both ruminants and swine, would be used.

Published data on the oil adjuvants used in FMD vaccines support the conclusion that these adjuvants have no major deleterious effects in food-producing animals (26). They are also used in other animal vaccines that are currently registered and used in Canada. The oil-adjuvant vaccines may be either a single-oil emulsion, in which the suspension of antigen is mixed with the oil adjuvant, or a double-oil emulsion, in which the aqueous antigen mixed with oil is emulsified again in an aqueous solution.

In pigs, the vaccine is administered IM, usually behind the ear. In ruminants, single-oil emulsion vaccines are also given IM, but double-oil vaccines can be given SC or IM.

Oil can be detected at the site of inoculation for many months, particularly in cattle that have been vaccinated repeatedly (some countries routinely vaccinate cattle twice yearly for prophylactic purposes). Injection site lesions have been documented in carcasses as a result of vaccination with different types of vaccines in Canada (27,28). The use of FMD vaccine could cause similar lesions, which would be detected and removed at slaughter, resulting in some losses. The economic impact of such lesions could be reduced by injecting the vaccine into less valuable parts of the carcass (the neck rather than the hindquarters). According to public health inspection requirements, injection site lesions in carcasses (that could result from FMD vaccination) would be detected and removed at slaughter (29).

The duration of immunity following a single dose of high-potency vaccine in a previously naive animal is usually less than a few months against homologous challenge, and shorter for heterologous challenge. A booster dose given 3 to 4 wk after the initial dose will prolong the immunity for up to 6 mo, but this can be dependent on the level of exposure of the vaccinated animals to live virus challenge. Normally, when a number of animals are vaccinated, some animals fail to develop immunity. Should these animals become infected and develop clinical FMD, they can excrete large amounts of virus, which may overcome the vaccinal immunity of the other animals in the group. It is almost impossible to provide pigs with complete protection by vaccination if they are in direct contact with clinically infected animals (30).

Canadian controls over veterinary vaccines and the use of FMD vaccines

Vaccines against FMD are not registered for use nor are they produced in Canada or the United States, as both countries have enjoyed long-term freedom from FMD (the most recent outbreaks occurred in 1952 [Canada] and 1929 [California]).

Most food-producing animals raised in Canada are vaccinated to prevent or control endemic diseases, such

as pneumonia, enteritis, and foot rot, during their lifetime. More than 450 vaccines are registered in Canada for use in cattle, swine, poultry, sheep, goats, and fish (31). In order to obtain an import permit (foreign manufacturer) or a product licence (Canadian manufacturer) for distribution of a veterinary vaccine in Canada, the manufacturer must submit to the CFIA a dossier containing information on the manufacturing process and master seeds; data on experimental results; and verification of the efficacy, safety, purity, and potency of the vaccine (32). All label claims must be supported by scientific data.

Manufacturers of vaccines must satisfy the CFIA that products of animal origin used in the preparation of master seeds and vaccines are at minimal risk of being contaminated with prions (33). They may also be required to submit samples of master seeds and prelicensing serials for testing by the CFIA. Similarly, records and processes relevant to prion contamination of FMD vaccines in The Bank have been inspected and verified (34).

The CFIA also maintains a system for postrelease surveillance, based on a requirement to report all major adverse reactions observed in vaccinated animals to ensure that any required corrective measures are implemented (35).

Disposition of vaccinated animals

When considering the disease risk presented by vaccinated animals, differentiation of vaccinated animals that are infected from those that are vaccinated but free of infection is of critical importance. Since cattle that are exposed to infection can become persistently infected, whether vaccinated or not, all seropositive animals are considered a risk (5), which explains, in part, the distinction established by the OIE (4). The objective of improved serological tests, therefore, must be to reliably detect animals that have been infected with FMD, regardless of whether they have also been vaccinated. A serological test that detects antibodies to the nonstructural polyprotein 3-ABC can be used on a herd basis to detect viral circulation in vaccinated populations (16,36). However, there is evidence that not all animals that have been vaccinated and are infected seroconvert to nonstructural proteins. Further research is needed to develop an approach that combines measuring antibody to nonstructural proteins with detecting the agent by polymerase chain reaction (PCR), so that reliable identification of all infected animals, whether vaccinated or not, can be done rapidly (16). It is anticipated that international norms will be modified in light of these developments, but new test methods will need to be validated first by the OIE.

Economic factors are important in deciding the disposition of vaccinated animals. As previously stated, countries that are FMD-free without vaccination enjoy significant economic benefits relative to those that are FMD-free with vaccination. A recent study of the 2001 outbreak of FMD in The Netherlands demonstrated that if animals were destroyed immediately after vaccination, the livestock industry would experience losses of 0.5% of income and 1340 person-years of employment annually (15). If vaccinated stock were kept alive, extending export bans from a period of 4 mo to at least 1 y, the livestock industry would lose 2% to 3% of income and 7000 person-years of employment. Thus, the immediate slaughter of vaccinates, which allowed the country to quickly regain FMD-free without vaccination status, delivered a significant economic advantage (15).

Public expectations also influence decisions on the disposal of vaccinated animals. Dutch veterinary authorities reported that destruction of vaccinated animals was seen as abhorrent and a wanton waste of valuable protein (37). The Federation of Veterinarians of Europe reported that the veterinary profession would not support the killing of healthy animals for disease control where vaccination was seen as "an appropriate alternative" (37). On the other hand, large retailers in the United Kingdom were unwilling to market products derived from vaccinated animals, owing to concerns that consumers would reject these foods. A recent survey showed that 45% of consumers in the United Kingdom believe that eating meat presents too many risks, despite advice from the British Food Standards Agency to the effect that eating products from animals vaccinated against FMD presents no health risk (38).

While there is a continuing incentive for destruction of vaccinated animals, vaccination cannot be regarded as a means of reducing the total number of animals destroyed. In The Netherlands, some 268 000 animals (including vaccinates) were destroyed for 26 cases of disease, giving an average of 10 000 animals destroyed per case in a period of 10 wk (9). The outbreak in the United Kingdom involved 2030 cases and a total of more than 4 million animals destroyed, for epidemic control purposes, over a period of 32 wk, for an average of 2000 animals destroyed per case (7). In comparison, the 1967 outbreak of FMD in the United Kingdom involved 2364 cases and the destruction of less than half a million animals (18), for an average of approximately 200 animals destroyed per case. Clearly, factors other than vaccination determine the course of an epidemic and influence the number of animals destroyed.

Human health implications of FMD

The FMD virus has been studied extensively and is known to be easily destroyed by heat treatment, low humidity, or when placed in an acid or alkaline environment (18,39). Cases of human infection with FMD virus have occurred rarely in the past 50 y, the sole association with food products being the ingestion of unpasteurized dairy products (40,41). The symptoms of human infection with FMD virus are mild and transient. They include fever; sore throat; and blisters on the tongue, mouth, hands, and feet (42–44). The human illness known as "hand, foot and mouth disease" has similar symptoms but is caused by an unrelated virus (coxsackievirus). Thus, FMD is not considered to be a significant zoonotic pathogen and an outbreak of FMD in Canada would have no significant human health implications.

Vaccination of food-producing animals is common in Canada. Some 20 different licensed bacterial and viral antigens (inactivated or live) may be administered to

cattle in vaccines in Canada (45) and Canadians have been consuming products from these vaccinated animals without any detectable adverse effects for many years. Government regulations ensure the safety of these vaccines in food-producing animals (46). Antibodies produced as a result of vaccination occur in meat and milk, but no detrimental health effect has been reported. Vaccines are used similarly in swine and poultry.

Canada imports meat and meat products from countries, such as Brazil, which routinely vaccinate animals against FMD, and Canadians travel in these countries and consume animal products produced locally. Consumption of meat from vaccinates has not been associated with any negative impact on human health in Canada or overseas.

There is extensive experience and an established safety record with the use of both aluminum hydroxide and oil emulsion adjuvants in human vaccines (the former in commercial production; the latter in experimental vaccines) (47–49). Although there is no evidence of public health risk, for esthetic reasons, many countries that use vaccines with oil adjuvant in livestock require a withdrawal period between vaccination and slaughter to allow for dispersal and excretion of the oil. Canadian regulations impose a withdrawal period of 60 d for animals vaccinated with vaccines containing oil adjuvants and 21 d for vaccines with or without other adjuvants, as stipulated in the outline of production for each of these vaccines (50).

If meat from vaccinated animals was intended for human consumption, the animals would have to satisfy public health requirements, including antemortem and postmortem inspections by relevant authorities. Animal products that pass inspection are considered safe for human consumption.

Conclusions

Vaccination is considered as a potentially important tool that could help Canadian authorities faced with impediments to rapid slaughter and disposal of susceptible animals to gain control of an outbreak. Prompt slaughter and disposal of vaccinated animals would ensure that Canada's FMD-free status would be quickly regained, in accordance with current international standards.

Future development of tests that can reliably distinguish animals that are vaccinated and infected from those that are vaccinated and uninfected would make it possible for vaccinated animals to be kept for their productive life without delaying recognition of FMD-free country status.

Products derived from vaccinated animals are safe for human consumption. The use of meat and other products from vaccinates offers a viable and cost-effective means of handling of these animals and should be considered in the management of a disease outbreak. CVJ

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