LAWRENCE
LIVERMORE
NATIONAL
LABORATORY

LLNL-PROC-401095

Foot & Mouth Disease & Ulcerative/Vesicular Rule-outs: Challenges Encountered in Recent Outbreaks

P. Hullinger

February 7, 2008

American College of Vererinary Ineternal Medicine
San Antonio, TX, United States
June 4, 2008 through June 7, 2008

Disclaimer

206. **Foot & Mouth Disease & Ulcerative/Vesicular Rule-outs: Challenges Encountered in Recent Outbreaks**
June 6th, 2008, 2:15-3:05 pm
P. Hullinger

Foot and mouth disease and response overview
Foot and mouth disease (FMD) is a highly infectious and contagious viral disease affecting bovidae (cattle, zebus, domestic buffaloes, yaks), sheep, goats, swine, all wild ruminants and suidae. Camelidae (camels, dromedaries, llamas, vicunas) have low susceptibility. Foot and mouth disease is caused by a RNS virus of the family Picornaviridae, genus *Aphthovirus*. There are seven immunologically distinct serotypes: A, O, C, SAT1, SAT2, SAT3, Asia 1. Foot and mouth disease causes significant economic loss both to countries who manage it as an endemic disease (with or without vaccination), as well as those FMD free countries which may become infected. The mortality rate is low in adult animals, but often higher in young due to myocarditis.

Foot and mouth disease is endemic in parts of Asia, Africa, the Middle East and South America (sporadic outbreaks in free areas). The Office of International Epizootics (OIE), also referred to the World Organization for Animal Health maintains an official list of free countries and zones.[1] The OIE *Terrestrial Code* (Chapter 2.2.10) provides detailed information on the categories of freedom that can be allocated to a country as well as guidelines for the surveillance for foot and mouth disease (Appendix 3.8.7). In short, countries may be completely free of FMD, free with vaccination or infected with foot and mouth disease virus (FMDV).

Source of FMDV include incubating and clinically affected animals with virus present in breath, saliva, faeces, urine, milk and semen. In experimental settings virus has been detected in milk several days before the onset of clinical signs[2]. Additional sources of virus are meat and by-products in which pH has remained above 6.0 as well as persistently infected carrier animals. Carrier animals may include cattle and water buffalo; convalescent animals and exposed vaccinates (virus persists in the oropharynx for up to 30 months in cattle or longer in buffalo, 9 months in sheep). Pigs do not become carriers. It has been shown that the African Cape buffalo are the major maintenance host of SAT serotypes.

FMDV transmission can occur by either direct or indirect contact. Indirect transmission can occur via contaminated animate vectors (humans, etc.), inanimate vectors (vehicles, implements) or airborne transmission. Indirect disease transmission via animate or inanimate vectors can play a major role in disease transmission. Good biosecurity can significantly reduce this type of transmission. Airborne transmission is often debated and is known to be serotype and species specific as well as require specific environmental conditions to occur. Airborne transmission is favored in temperate zones and has been postulated to occur over distances of up to 60 km overland and 300 km by sea.

Foot and mouth disease virus is an unenveloped virus which is preserved by refrigeration and freezing and progressively inactivated by temperatures above 50°C. FMDV is highly sensitive to pH change and is inactivated by pH <6.0 or >9.0. There are many disinfectants which are effective against FMDV including sodium hydroxide (2%), sodium carbonate (4%), and citric acid (0.2%). FMDV is resistant to iodophores, quaternary ammonium compounds, hypochlorite and phenol, especially in the presence of organic matter. The virus can survive in lymph nodes and bone marrow at neutral pH, but is destroyed in muscle when is pH <6.0 i.e. after *rigor mortis*. FMDV can persist in contaminated feed/commidities and the environment for over to 1 month, depending on the temperature and pH conditions.

The incubation period for FMD is 2-14 days. Animals transition through latent (infected but not infectious), subclinically infected (infectious but lacking clinical signs) clinically infected and recovered disease states. In cattle clinical signs include pyrexia, reluctance to eat, bruxism, drooling, lameness, treading or stamping of the feet and decreased milk production. Most clinical signs are related to the development and subsequent rupturing of vesicles at the coronary band and in the oral cavity. Vesicles and ulcerations can also occur on the mammary gland. Recovery in adult animals usually occurs in 8-15 days. Clinical signs for most serotypes are less dramatic in sheep and goats. Swine can develop very severe coronary band lesions and high mortality in piglets has been observed.

One of the challenges of diagnosing FMD is that it may be clinically similar to several other vesicular or ulcerative diseases. FMD is clinically indistinguishable from Vesicular stomatitis, Swine vesicular disease and Vesicular exanthema of swine. It may also resemble Bovine viral diarrhea, Mucosal disease, Infectious bovine rhinotracheitis, Bluetongue, Bovine papular stomatitis, Bovine mammillitis and Rinderpest.

If FMD is suspected (even if it is not the primary differential), a state or federal animal health official should be contacted to initiate a foreign animal disease investigation. This will include the collection of in-depth herd/flock history, a clinical exam and the collection of diagnostic specimens for expedited testing at the foreign animal disease lab at Plum Island. Diagnostic tests focus on identification of the agent (virus isolation, PCR, ELISA and compliment fixation) and serological tests (ELISA and virus neutralization). There are several new, novel diagnostic assays in various stages of development and validation which may be available in addition to the traditional battery of tests. Examples are ulcerative /vesicular rule out panels for both bovine and porcine species. These assays are

targeting nucleic acid and have been developed on a Luminex bead-based assay platform. The bovine panel consists of 23 signatures which detect FMD, Malignant Catarrhal Fever (MCF), Rinderpest, Bluetongue, Infectious Bovine Rhinotracheitis (IBR), Bovine Viral Diarrhea (BVD), Parapox and Vesicular Stomatitis. The porcine panel is comprised of 19 signatures that test for a total of five viral diseases including FMD, Swine Vesicular Disease (SVD), Vesicular Exanthema of Swine (VES), Vesicular Stomatitis and Porcine Reproductive and Respiratory Syndrome (PRRS). These assays are still in the process of validation, but could in the future be used for targeted FMD surveillance programs. A second assay in development is a pen-side test which utilizes an isothermal loop amplification process to allow for sensitive and specific detection of FMDV in approximately 30 minutes using a disposable, self contained testing device. If successful, this may allow for cost effective on farm FMD diagnosis during an FMD outbreak response.

A presumptive or confirmed positive FMD case in the US would trigger a response from the Federal and State animal health officials. Measures would include quarantine of infected premises and movement restrictions, enhanced biosecurity, determining the extent of the outbreak via tracing and surveillance, and activation of response activities to carry out control and eradication activities. The exact response strategy implemented would depend on the characteristics of the outbreak and may include stamping out (culling diseased and exposed animals) and or vaccination in addition to regional movement controls.

Responsive FMD vaccination, if utilized, would be implemented strategically with several possible outcomes for the vaccinated animals. Vaccinates could be killed (and carcasses disposed of), slaughtered (following proper withdrawal for the vaccine) or possibly allowed to live (although they would be permanently identified and subject to movement restrictions). While use of vaccination with or without subsequent culling may have potential benefits, especially in the short term, there are several issues relative to the timely eradication of FMD and return to the classification of an FMD free country where vaccination is not practiced. Vaccination prevents clinical illness caused by infection with FMD virus, but does not prevent infection. This means that vaccinated animals may be a source of infection for other animals. If a vaccinated animal (cattle and sheep) is infected, either before or after vaccination, that animals can become a carrier of FMD virus. Immunity produced in animals by vaccination, or by natural infection, lasts for only 6 to 12 months. Animals continuing to live beyond 6 months may require re-vaccination. Vaccination against one FMD virus subtype gives no (or very limited) cross protection against illness caused by other FMD virus subtypes. Vaccinates must be permanently identified. When an animal is found to have antibodies to FMD virus it is important to know that the animal was previously vaccinated and that the antibodies may not be due to natural infection with FMD virus. Differentiating infected from vaccinated animals ("DIVA") is not yet possible in individual animals with current FMD vaccines. Because vaccinated animals are not necessarily protected against infection with FMD virus, the presence of FMD antibodies in a previously vaccinated animal does not preclude the possibility that the animal was also naturally infected. Recent work done by Arnold suggests that strategies in which individual animals tested post vaccination can optimize carrier detection and allow for positive animals vs. herds to be culled.[3]

The ideal foot and mouth vaccine is not currently available. The ideal FMD vaccine would be able to be manufactured in the United States, possess the ability to allow for differentiating vaccinated from vaccinated then infected (DIVA) animals on an individual animal basis, provide multi-serotype protection, induce fast protection 24 to 96 hours post vaccination and be readily available in sufficient quantities for immediate deployment in the event of an FMD outbreak. The Department of Homeland Security in collaboration with the United States Department of Agriculture is supporting research to develop the next generation of FMD vaccines and immunomodulators. The goal is to have adenovirus vectored vaccines which would induce both the production of immunomodulators and antibodies against FMD. These vaccines once developed would become part of the National Veterinary Stockpile.

2007 Foot and mouth disease outbreak in the United Kingdom

The recent outbreak of foot and mouth disease first reported on August 3rd, 2007 was an excellent reminder of the challenges that the United States may face if FMD was intentionally or naturally introduced here. The virus causing the outbreak was determined to be type O1BFS which was the same virus which caused the 1967 outbreak. Epidemiological investigations lead to the conclusion that the virus originated from a site near where the Pirbright diagnostic laboratory and a commercial vaccine plant are co-located. The most likely cause of the contamination was escape of live virus from the drainage system that connected the vaccine production plant to the sodium hydroxide treatment tanks.

Having dealt with a major outbreak of foot and mouth disease in 2001 the United Kingdom (UK) was prepared to respond in a expedient, efficient, effective and well-coordinated manner. The index case was investigated and conclusive test results obtained with in 24 hours of reporting. Also impressive, the UK had an electronic reporting and permitting system in place within two days of confirmation. This website was updated daily and served as an effective means of communicating with the industry and the media.

There are several important lessons to be learned from this most recent UK outbreak. The index case was a small, family run beef operation which had stock on three premises (IP1). The stock were checked daily from a distance. By the time the producer recognized his animals were diseased 38 of 38 cattle had clinical signs of FMD. The oldest lesions were 9 days old and 30/38 had lesions which were 6-8 days old. This highlights the point that FMD may go undiagnosed for some period of time, even in cattle which usually have more dramatic clinical disease. The fortunate thing in this situation was that like many small beef cattle operations, the direct and indirect movements on and off this farm were minimal and thus the spread from this premise was limited.

Like the index case, the second premises discovered had advanced clinical disease (IP2). This was a beef suckler herd run on 300 acres where the sucklers calves were reared, fattened and sent directly to slaughter. Forty-four of the 49 cattle had typical FMD lesions in their mouths and on their feet.

It was almost a month later, on September 12, 15 and 18th, that three further cases of FMD were confirmed approximately 16 km north of Pirbright. The farm detected on September 11th, was primarily a beef cow-calf/suckler herd (IP3). At the time of reporting 40% of the animals had clinical signs and lesions were judged to be one to five days old. The farm detected on September 15th (IP3) was likely the source of infection for IP3. All cattle (54) had lesions 6-10 days old at slaughter, none of the 743 pigs kept on a separate premises by the same farmer had evidence of disease. It was determined that the failure of the producer to identify the diseased animals sooner was related to the fact that the owner had been on vacation and stock inspections while he was away were very limited. An additional four cases were detected in this second focus area. It was determined that the most likely source of virus transmission to the first infected premises in this area was via fomites (trucks and personnel) contaminated with soil from the initially contaminated area near Pirbright. Then spread from that farm infected the additional five in that cluster.

Even though FMD was present for a significant time prior to discovery, the limited movement from the infected facilities while they were infectious limited the distribution of the disease. An important take home message was that in this case disease spread undetected in beef cattle for up to ten days. If one of these facilities were a dairy, with significantly higher daily movements or if there had been a shipment of infectious animals through a sale yard or auction, the disease could have become much more wide spread and the outbreak much larger. It is also important to note that as the UK has a national system for premises and animal identification the collection of tracing information and investigation of the traces occurred in an expedient manner. As there is not a national system for animal or premises ID in the United States, we would be severely challenged to collect, manage and act upon the epidemiological tracing information in a timely manner.

The recent outbreak of FMD in the UK was a reminder that continued prevention, planning and vigilance by both veterinarians, the livestock industry and government is needed to assure that we are best prepared to detect, confirm and respond in a timely and efficient manner to mitigate the impacts of a foot and mouth disease occurrence in the United States.

1. OIE Website (http://www.oie.int/eng/info/en_fmd.htm). Accessed 1/27/08.
2. Reid S, et al. **Vet. Res.** 2006;37:121.
3. Arnold M E, et al. **Proc of the Royal Society**. 2007;10:1154

This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. LLNL-PROC-401095