FOOT AND MOUTH DISEASE VACCINE PRODUCTION FOR USE IN THE UNITED STATES

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FMD Vaccine Production for Use in the United States

The enormous economic impact to the United States that would result from an outbreak of Foot and Mouth Disease (FMD) has been well documented. Regulatory authorities and animal industries alike support the shift in U.S. strategy to employ vaccination as a primary tool early in an outbreak. This revised strategy came about largely in response to the 2001 FMD outbreak in the United Kingdom resulting in the destruction of more than 6 million animals with an estimated cost of $34.5 billion (2017 dollars). However, the impact from this FMD outbreak in the UK cannot be measured in economic terms alone; the negative public reaction to the widely publicized destruction of so many animals was severe and global in scope. In contrast, a concurrent outbreak of FMD in Uruguay in 2001 that affected approximately the same number of premises and number of cattle, was controlled through vaccination in a shorter time frame and at a cost of only about $550 million (2017 dollars). More recent outbreaks in Japan (2010) and Korea (2010-2011) could only be brought under control and eliminated with the use of vaccination, again confirming the wisdom of the revised U.S. strategy. Secretary of Agriculture Sonny Perdue confirmed his support for an expanded FMD vaccine bank in testimony before the U.S House of Representatives Committee on Agriculture on May 17, 2017. Perdue said he sees vaccine as "insurance" and "priceless" since the agriculture sector cannot afford the fallout from an FMD outbreak in this country.

This reliance on vaccine as the backbone for the U.S. response to an FMD outbreak has unequivocally established the necessity for a greatly expanded FMD vaccine bank. This need is succinctly explained in a 2014 white paper prepared by the Center for Food Security and Public Health at Iowa State University:

> "Foot and mouth disease presents the greatest economic threat to U.S. animal agriculture and is viewed as the most important transboundary animal disease in the world. An outbreak of FMD in the U.S. would have a devastating impact on the U.S. economy extending far beyond animal agriculture. Work on the Secure Milk Supply and Secure Pork Supply Projects by federal and state officials, industry and academia has made it clear that an FMD outbreak in livestock dense areas cannot be effectively controlled without the rapid use of tens of millions of doses of FMD vaccine."[1]

It is important to note that there are 7 distinct types of FMD virus recognized worldwide. Each type of FMD virus has numerous unique subtypes and most of these subtypes do not produce cross immune protection. That means that the FMD vaccine to be used in the control of an outbreak has to precisely match the type and subtype of the FMD virus present in the field at the time.

The number of doses of vaccine needed in an outbreak will depend on several factors, including the number of animals, premises, and jurisdictions affected. Even in a Type 2, moderate regional FMD outbreak, up to 10 percent of the U.S. livestock population would be vaccinated, commencing approximately 4 days after the initial detection is confirmed and lasting for approximately 6 months.[2]

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[1] CFSPH, *FMD Vaccine Surge Capacity for Emergency Use in the United States* (Ames, IA: Jan 9, 2014), p.3

[2] An explanation of the phases and types of FMD outbreaks is found in CFSPH, *FMD Vaccine Surge Capacity for Emergency Use in the United States* (Ames, IA: Jan 9, 2014), pp.11-12 and can be found here: www.cfsph.iastate.edu/pdf/phases-and-types-of-an-fmd-outbreak

For the U.S. to be prepared for such an event, millions of doses of vaccine against the specific causative type/subtype of FMD virus will be needed within days - with an ongoing demand likely to continue for several months. Although the U.S. currently participates in the North American Foot and Mouth Disease Vaccine Bank (NAFMDVB), the need for a vaccine bank dedicated to the U.S livestock industry is clear. The number of different vaccine antigen concentrates (VAC)[3] in the NAFMDVB is restricted to only those thought to be most likely to enter the U.S. Even if VAC against the specific causative type/subtype of virus in an outbreak happens to be available in the Bank, the quantities of VAC on hand are limited and, at best, would only yield enough vaccine to respond to a small, confined outbreak.

Currently available commercial FMD vaccine production methods require culturing enormous quantities of live, virulent FMD virus. The capacity to produce sufficient quantities of vaccine or VAC for multiple types/subtypes of FMD virus does not exist in the United States. In fact, due to the risk of an accidental release of the virus, current law[4] does not permit live, virulent FMD virus to be held in the United States other than at the federal Plum Island Animal Disease Center (PIADC) and at its successor facility, the National Bio- and Agro-Defense Facility (NBAF), presently under construction in Manhattan, Kansas. A number of accidental releases of the FMD virus from high security facilities around the world confirms the wisdom of, and continuing need for, this law. In a May 2008 Government Accountability Office report evaluating the relative safety of moving the functions of PIADC to a mainland location, 14 accidental releases of FMD virus from high security facilities around the globe were listed.[5] These include a 2007 outbreak apparently caused by faulty decontamination and leakage from drainage pipes at the Pirbright Institute, a federal high security research facility in the United Kingdom. This facility is located on the same site with a private pharmaceutical laboratory operated by Merial Animal Health (now Boehringer Ingelheim), and either entity could have been responsible for the accidental release; the virus strain in question was being held at the Pirbright laboratory, and was also the same strain Merial had used in the production of a batch of vaccine shortly before the incident in question. By the time it was fully eradicated, the outbreak caused by this accidental release of FMD virus had spread to eight separate farms in geographical proximity to the Pirbright laboratory.

Similarly, there was an accidental release of live FMD virus from the PIADC in 1978, affecting cattle being held in pens on the island but outside of the containment facility. One can only speculate what might have happened if such a release had occurred on the U.S. mainland rather than an isolated island.

It is noteworthy that high security facilities holding pathogens of human significance are not immune from such accidents. In 2014, our own Centers for Disease Control and Prevention (CDC) was responsible for failing to properly inactivate batches of anthrax bacteria before sending them to other

[3] In lieu of finished vaccines which have a limited shelf-life, vaccine banks usually store concentrated antigens, called vaccine antigen concentrates, or VAC. These VAC can be stored at ultra-low temperatures extending the shelf-life for many years. In an outbreak, banks can rapidly formulate stored VAC into complete, finished vaccines.

[4] 21 U.S.C. 113a, as amended.

[5] GAO, *High-Containment Biosafety Laboratories, DHS Lacks Evidence to Conclude that Foot-and-Mouth Disease Research Can Be Done Safely on the U.S. Mainland*, GAO-08-821T, p. 14.

locations. The same year, a Department of Defense laboratory inadvertently sent live anthrax cultures to laboratories in 9 states.

The incidents above demonstrate that there can be no guarantee that live FMD virus will not be released accidentally, especially from a commercial vaccine production facility that would be generating enormous quantities of live FMD virus using conventional vaccine production methods. Even holding live FMD virus, and producing very limited quantities of the virus for research purposes, carries some risk of an accidental release. Nevertheless, it is recognized that ongoing research on FMD virus, particularly for the purpose of creating the next generation of vaccines, is essential. Only when the virus is held in a state-of-the-art high security facility, such as the facility planned for the NBAF, is the risk mitigated to an acceptable level for a U.S. mainland location.

Even if possession of live, virulent FMD virus was legalized in the U.S., it would take several years to build the biologically secure infrastructure required to produce the quantity of vaccine and VAC needed to stock a U.S. vaccine bank with sufficient capacity to meet the demand in the event of an outbreak. Because FMD could find its way into the U.S. today or tomorrow, the need for such an expanded FMD vaccine bank is critically urgent, leaving animal agriculture extremely vulnerable during the interim. There are multinational corporations with offshore facilities that are currently producing FMD vaccine for use in countries where the disease is endemic or controlled with vaccination. One or more of these facilities could more quickly and economically increase existing capacity in order to meet the U.S. demand for an adequately stocked, vendor-managed vaccine bank. By rotating stock and selling stockpiles of finished vaccine to its regular customers prior to vaccine or VAC expiration dates, the vendor could further reduce the cost as compared to a U.S. government-managed vaccine bank that would require destruction and replacement of expired vaccine. Further, by having the vaccine bank managed by the offshore vaccine vendor/manufacturer, there would be no time wasted shipping VAC to the vendor in order to convert it into finished vaccine. This would save precious time during the very early, critical period of an outbreak, and ensure an ongoing supply of vaccine when the initial stockpiles of finished vaccine are exhausted. Most importantly, this offshore option eliminates completely the concern of a costly accidental release of FMD virus from a vaccine manufacturer located within the continental U.S.

Having an adequately stocked FMD vaccine bank will provide for vaccine needs in the initial phases of an outbreak response. To meet the ongoing need for vaccine required in all but a Type 1 outbreak, one or more of these offshore firms could be contracted to maintain sufficient surge capacity. This would meet the ongoing demand for production of a specific strain of FMD vaccine that would be necessary for several months in a Type 2 or larger U.S. outbreak.

Clearly, the long term solution is to develop and commercialize one or more of the next generation vaccines that could be safely manufactured in the U.S.[6] While creating these new vaccines and bringing them into commercial production will take years, a number of promising novel vaccines are already under development. Each of these new vaccines is unique, employing a number of different

[6] For those interested in more information on these new vaccines, a detailed explanation can be found in *NAHEMS Guidelines: Vaccination for Contagious Diseases, Appendix A: Foot-and-Mouth Disease*, (May 2015), Section 6, pp. 24-34. The document can be downloaded from this site: http://lib.dr.iastate.edu/vmpm_reports/2/

technologies. What they all have in common is that none necessitates the use of live, virulent FMD virus in their production. Evaluating and incentivizing the development of these next generation vaccines is strongly encouraged.

Conclusions

1. The U.S. response strategy for an outbreak of FMD is heavily dependent on rapid and extensive use of vaccination. History has repeatedly shown that stamping out, without the benefit of vaccination, is ineffective in all but the most limited outbreak situations. The current stockpile of FMD vaccine and vaccine antigen concentrate is woefully inadequate to meet the anticipated demand, both initially and for an ongoing disease response.

2. The capacity to manufacture FMD vaccines in the continental U.S. does not currently exist. Even if live FMD viruses were to be allowed in commercial facilities in the U.S., producing enormous quantities of live, virulent FMD virus needed for large scale vaccine production increases the risk of an accidental release exponentially. The limited benefit of having such a vaccine production facility in the U.S. simply does not outweigh the enormous risks, given the expected loss of export markets that would result from even a very limited and quickly contained outbreak caused by the accidental release of FMD virus from a vaccine production facility.

3. The U.S. should contract with one or more corporations for the offshore production and stockpiling of sufficient quantities of FMD vaccine and VAC, most immediately for those types/subtypes of FMD virus with the highest likelihood of entering the U.S. Further, the U.S. government should enter into contracts with one or more of these firms to have sufficient surge capacity to allow for the production of adequate quantities of a specific type/subtype of FMD vaccine in the event of an ongoing U.S. outbreak.