Foot-and-Mouth Disease: Technical and Political Challenges to Eradication

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Abstract

Foot-and-mouth disease (FMD) is a highly-contagious livestock disease with global socioeconomic ramifications. The disease negatively impacts both individual farmers through reduced herd viability and nations through trade restrictions of animals and animal derivatives. Vaccines for FMD prevention have existed for over 70 years, yet the disease remains enzootic in a large percentage of the globe. FMD persistence is due in part to technical limitations of historic and current vaccine technologies. There also exist many socioeconomic and political barriers to global FMD eradication. Here we highlight the barriers to eradication and discuss potential avenues towards FMD eradication.

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Introduction

Foot-and-mouth disease (FMD) is a highly contagious viral disease affecting both domesticated and wild cloven-hoofed animals worldwide [1-3]. The disease has global ramifications, costing an estimated $6 to $21 billion USD each year in prevention expenditure and agricultural damage [4]. The significant portion of this cost is shouldered by the world's poorest countries, who are financially unable to proactively protect themselves against the virus and are therefore subject to uncontrolled outbreaks [5]. Further compounding the issue, many countries experience additional economic loss from trade restrictions imposed by the World Organization for Animal Health (*Office International des Epizooties* or OIE)[6]. In addition, FMD-free countries are under constant threat of infection and must actively prevent introduction of FMD. The worldwide negative economic impact of FMD drive the desire for global eradication of the disease [1].

As mentioned above, the interest in potential eradication of FMD is not limited to countries who suffer frequent outbreaks of the disease. The ease of transmission leaves FMD-free countries with the perpetual risk of accidental or deliberate infection of their respective herds with potentially devastating effects to agriculture. For example, in 1997, Taiwan had been considered FMD-free for 68 years when an outbreak arose and quickly spread to virtually the entire nation [7]. This forced the introduction of a vaccination program, which resulted in international trade restrictions and generally devastated Taiwan's pork industry [8].

Divergent opinions are held around the world as to how FMD outbreak and prevention should be approached due to the social, economic and political ramifications of the disease. This compounds the complexity of an already difficult problem and these complications must be considered when pursuing global scale eradication [9, 10].

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Many excellent articles have discussed the nature of the FMD virus (FMDV) [11, 12] and limitations of FMD vaccine technologies [3, 13, 14]. Here we highlight the technical and political challenges of FMD eradication and how these challenges exacerbate one another. Finally, we consider approaches for methodical global eradication that will potentially satisfy the technical, social, economic and political challenges surrounding FMD.

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FMD Virus and Related Challenges

Foot-and-mouth disease virus belongs to the family picornaviridae – small, non-enveloped viruses with a single positive-sense RNA molecule. The viral genome encodes for 4 structural proteins (VP1, VP2, VP3, and VP4) and several non-structural proteins that play roles in virus replication, assembly of the virus particle, and control of the host innate and adaptive immune response [2]. FMDV is genetically diverse, with seven distinct serotypes: type O, A, C, SAT 1, SAT 2, SAT 3, and Asia 1 [15]. Furthermore, subtypes within each serotype contain a large spectrum of genetic diversity due to high mutation rates during genome replication and many of these mutations can be accommodated while maintaining virulence [16]. The broad genetic diversity between and within serotypes complicates identifying and protecting against disease [17]. Specifically, the variability in the antigenic regions can reduce or effectively eliminate cross-subtype or -serotype protection from previous infection or vaccination as occurred in Iran in 2005 [18].

Disease Traits and Related Challenges

In addition to the significant genetic diversity of the virus, FMDV infects diverse hosts, affecting over 70 species of wild and domestic cloven-hoofed species such as cattle, sheep and swine [2]. The variety of hosts and diversity of serotypes synergistically complicates disease prevention. Furthermore, signs and disease severity may significantly differ from species to species. Generally, cattle have obvious oral and pedal lesions, while swine primarily have pedal lesions [19]. Sheep show milder signs - 25% of infected sheep develop no lesions and a further 25% develop only one lesion - making visible diagnosis difficult or impossible [20]. In addition a number of other viral diseases including vesicular stomatitis, swine vesicular disease, and

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vesicular exanthema of swine cause disease signs similar to FMD [2]. Incubation periods from exposure to first signs vary by initial infection dose, route of transmission, and animal species ranging from as little as 1 day to up to 14 days [1]. Therefore, some animals may remain asymptomatic and act as carriers of the virus while others are misdiagnosed [21]. Such cases increase the possibility of accidental transmission from primary or secondary contact between herds.

The ability of the virus to infect cross-species through sundry routes increases transmission opportunities, particularly where livestock agriculture is densely populated [22]. Cattle and sheep are primarily infected through respiration of the virus in aerosol form, while swine are more likely to be infected through ingestion or subcutaneous wounds [1]. Shedding of the virus may occur through multiple routes including in aerosol form, urine, feces, and bodily fluids [23]. Excreted virus can retain infectivity for significant durations in aerosol form, with examples of some strains naturally traveling as far as 300 km [1]. The extent of FMD transmission can be further amplified by incidental transport on vehicles, humans, water, and animal products [1, 24]. The diverse routes of shedding and transmission coupled with the diversity of host species provide myriad opportunities for spread of the disease.

In certain hosts, including cattle and buffalo, the virus can persist and these asymptomatic, persistently infected animals can remain potentially contagious for up to 5 years [17, 21]. Infected animals are thought to reach a maximum transmission potential within 12 days of infection [25]. In a dead host, the virus may remain stable, and persist in an infectious form for as long as 11 days in muscle tissue, and 4 months in the liver [24]. Also, infectious virus can persist within many other animal products such as milk and cheese for differing durations [24]. Some experts suspect that the longevity of the virus in animal products is what led to the 2001

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outbreak in the UK. The outbreak is thought to have started when a farmer purportedly fed his animals FMDV-contaminated imported food scraps, which were insufficiently heat treated to remove the possibility of infection [26].

The complexities of this highly infectious and persistent disease complicate strategies of eradication. Although an inactivated FMD-vaccine was developed and successfully used on large numbers of animals in the 1950's, FMD is still prolifically spread through the world [27, 28]. Below, we will discuss the attributes of the predominant vaccine technology and the economic, social and political barriers that have hindered global eradication to this point.

Predominant Vaccine Technology

The predominately utilized FMD vaccine is based on inactivated FMDV [29]. This vaccine is typically produced from live FMDV amplified in baby hamster kidney-21 cells, chemically inactivated, partially purified by some manufacturer's, and subsequently formulated with an adjuvant [3]. Throughout the process, a sterile environment and meticulous management of temperature and pH is essential to ensure production of an effective, noninfectious vaccine [30]. This vaccine technology comes with the inherent risk of live virus release from production facilities or insufficient inactivation of the virus during vaccine preparation [3]. Indeed, it is thought that the 2005 FMD outbreak in China initiated when insufficiently inactivated virus was used to vaccinate, resulting in an outbreak that spread throughout China and into Russia and Mongolia [18]. In addition, the 2007 outbreak in the UK was caused by inadvertent release of virus from the Pirbright vaccine and research institute [23].

The risk of virulent virus contamination or insufficient inactivation during vaccine production requires that production facilities maintain rigorous biosafety standards. This restricts

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the locations where production facilities can be successfully constructed, maintained, and operated. Furthermore, these facilities must operate at a high level of containment. The distance between production facilities and regions of FMD infections presents a logistical challenge of distribution, particularly where international borders are concerned. To help alleviate this challenge, in some parts of the world FMD vaccine banks have been established to increase vaccine accessibility [31, 32].

FMD vaccine banks decide how much vaccine they will store for any given serotype, and regularly test these stored vaccines for efficacy [33, 34]. These tests are essential as a concern with the current technology for inactivated virus vaccine production is the possible selection of antigenic variants during virus replication [35, 36]. It has been found that the selected variants for vaccines may not always be protective against current virus strains circulating in the field. In addition, the choice of which vaccines to store is complicated by limited cross-subtype and cross-serotype protection, requiring individual vaccines against each subtype that is currently circulating for effective protection [33, 37]. Vaccines must also be periodically replaced due to a shelf life of 1-2 years for conventional FMD vaccines [17]. Storage of vaccines as concentrated antigens in liquid nitrogen improves shelf life [38]. However, these concentrated antigens must be shipped to manufacturers for formulation with an adjuvant when needed, thus delaying their use in the field.

Administration of the vaccine also presents its own set of complexities such as proper handling, correct dosage, and optimal time of vaccination. All of these variables can significantly impact the efficacy of the vaccine [3, 39]. For example, a higher dosage of vaccine generally results in increased number of animals protected and reduces the time from administration to protection [3]. As a consequence, during outbreaks in previously disease-free countries,

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emergency vaccination of animals with 6 protective dose 50 (PD50) is recommended by the OIE. Complexities of administration make it desirable for trained persons to administer the vaccine. Also, persons administering vaccines to multiple herds may inadvertently act as disease carriers [40]. Furthermore, regions with inadequate veterinary services face the added challenge of increasing competency among those administering vaccination [41].

Other vaccine technologies are becoming available that are attempting to address the shortcomings of inactivated virus vaccines discussed above. These include empty capsid vaccines, DNA vaccines, recombinant protein vaccines and peptide vaccines, among others [13, 29, 39, 42, 43]. An example of a novel vaccine technology is the recent development of a replication-defective human adenovirus vector containing the FMDV capsid protein coding region for serotype A24 Cruzeiro [44]. This vaccine has been granted a conditional license by the Center for Veterinary Biologics, Animal Plant and Health Inspection Service, USDA. This license allows the vaccine to be included in the U.S. National Veterinary Vaccine Stockpile to be used in cattle in the event of an emergency situation [45]. Recent reviews have described the benefits and limitations of this and other novel vaccine technologies [29, 43, 46].

Vaccine production technologies must also become more efficient and economical, as is being pursued with emerging technologies involving production of virus-like particle FMD vaccines produced in *E. coli*, in insect cells infected with recombinant baculoviruses, and in cell-free systems [2, 3, 47, 48]. To be successful for eradication, vaccine technologies and systems must avoid the pitfalls of inactivated viruses and be sufficiently inexpensive as to be economically viable for developing countries.

Economic Considerations for FMD-Free Regions

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One concern with the use of inactivated-virus vaccines is the inability to differentiate infected animals from vaccinated animals (DIVA) [3]. However, more recently some FMD vaccine manufacturers have partially purified their vaccines thus presumably eliminating or mitigating this problem. Nevertheless, as discussed below, FMD-free countries still have generally resisted using vaccination to control the disease in the event of an outbreak. The OIE classifies nations and regions as FMD-free without vaccination, FMD-free with vaccination, Suspended with or without vaccination or Unrecognized (Figure 1) [49]. Typically, only regions designated "FMD-free without vaccination" are unburdened by trade restrictions on animals and animal products [18]. Although regions can achieve the status "FMD-free with vaccination," the lack of DIVA vaccines puts the true disease status of vaccinated animals into question and trade restrictions remain imposed [3]. Such was the case in 1977 in Morocco when an outbreak resulted from importation of "vaccinated" South American animals, costing an estimated $3.3 million USD to eradicate [6].

The classifications established by the OIE and their ramifications on animal commerce incentivize the use of preventative measures other than vaccination to avert outbreaks. Many FMD-free regions rely on expensive preventative measures such as border control and animal movement restrictions [50, 51]. Import restrictions on animals and animal products are also employed [18]. While effective, there is still a risk of virus introduction due to illegal animal movement as occurred in Chile in 1984 and 1987, causing outbreaks after disease status was declared FMD-free in 1981 [52].

At times, the risk of outbreak overcomes the best prevention efforts. Once an outbreak is confirmed, there are three primary courses of action that have been used by FMD-free countries

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to prevent further spread of the disease: 1) isolate and vaccinate-to-live, 2) isolate, vaccinate, and slaughter or 3) isolate and slaughter (Figure 2) [3].

For the isolate and vaccinate response policies, samples of virus are collected from outbreak sites, analyzed to determine serotype and subtype, and then matched with vaccines contained in storage to determine which will be most potent [3]. Once vaccinated, animals may become immunologically protected from the disease within days or weeks, depending on the vaccine's efficacy [53]. Delays in time-to-protection and the imposition of trade restrictions are major reasons the vaccinate-to-live policy is problematic in regions previously free of the disease and rarely employed. Therefore, most FMD-free countries have preferred the isolate and slaughter policy or the isolate, vaccinate, and slaughter policy during outbreaks [7, 54, 55]. A further impetus for FMD-free countries to utilize slaughter-based policies rather than vaccinate-to-live is that the former policy allows countries to regain FMD free status more quickly according to OIE guidelines.

When outbreaks occur in regions historically free of the disease, slaughtering is often vigorously pursued to prevent further transmission [54-56]. Indeed, this approach tends to be somewhat indiscriminate and many uninfected animals may be killed as a precaution [54]. The 2001 outbreak in Great Britain resulted in the slaughter of 4 million animals on over 10,000 farms [26]. Of those 10,000 farms, 8,000 of them contained animals that were only potentially exposed to disease [26].

The disposal or destruction of slaughtered animals poses a significant logistical hurdle. Due to the persistence of the virus even in dead tissue, carcasses must be disposed of in such ways that prevent further transmission. This is typically accomplished by burial in a remote

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location or burning. In either case, success of disposal is dependent on trained personnel and the existence of sufficient facilities.

When facilities are unavailable to slaughter and dispose of large amounts of animals, a policy of isolation, vaccinating and slaughtering can be employed. In the 2001 outbreak in the Netherlands, this technique was used until animals were sufficiently protected by vaccination and able to be transported to central culling facilities [54].

Destroying animals can be economically painful for individual farmers, unless they are compensated for their loss. Incentivizing surveillance and reporting through compensation is commonly used to make up for the loss but can also have unintended consequences. During the 1997 outbreak in Taiwan, the government was offering more than market price for infected animals, purportedly incentivizing farmers to infect their own herds and increase marginal profits [57, 58]. Therefore, incentives must be carefully crafted to avoid similar outcomes.

Economic Considerations for FMD-Enzootic Regions

Left untended, regions of disease outbreak could become FMD-enzootic regions. At such a juncture, the method of slaughter and destroy used in FMD-free countries is not considered economically feasible [59]. In places such as Mexico, sustained slaughter and burn eradication techniques in 1947 quickly led to food shortages and general devastation of livestock agriculture until a vaccination policy was implemented [56].

Quarantining infected animals is also difficult, as many of the FMD enzootic regions have limited governmental infrastructure to impose a quarantine [60]. Even if a quarantine is imposed, without thorough testing and surveillance at the end of the quarantine, FMD positive animals can be released back into the population as occurred in Zimbabwe in 1987. Infected

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cattle which had been quarantined for 6 months and then placed on another farm were the cause of the 1989 Zimbabwe outbreak [61]. Also, many enzootic regions are rural in nature, increasing the potential of wild-domestic herd interaction and transmission [22]. These interactions can result in FMD persistence and spread, but the significance of such interactions on propagating FMD is unclear [22][62].

If the rate of outbreaks exceeds 4 outbreaks every 10 years, prevention through methodical vaccination becomes economically preferable to slaughter and more effective than long term quarantine [6, 56]. Thus, vaccination is currently considered the most plausible plan for FMD eradication in enzootic areas [59].

Although vaccines are currently available, they can be cost prohibitive and be limited in availability for many enzootic regions [18]. In a cost-benefit summary of FMD eradication in Sudan it was estimated that 81% of the eradication costs were attributed to purchasing the vaccine [50]. The price of a current vaccine hinders economically developing countries from disease eradication efforts because each vaccine cost between $0.40 and $3.00 USD to manufacture and ship [4]. It is a challenge to reduce the cost of the traditional vaccine due to the stringent conditions needed to prevent contamination or insufficient inactivation and costs associated with testing, distribution, and storage. Future developments in vaccine technology must consider cost when attempting to produce alternative candidates for developing countries.

Regions striving to obtain FMD-free status face the costs of vaccination as well as trade restrictions and animal production losses [6]. These regions also shoulder similar burdens that FMD-free regions face such as restricting imports and animal movement control in order to prevent disease reintroduction from bordering countries [4]. Some nations may have the resources to deal with these problems. However, many FMD enzootic nations are too

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impoverished to take meaningful steps towards eradication and may need outside sources to fund programs that overcome this challenge (Figure 3) [63]. Procuring initial funding for vaccine based eradication through the World Bank has become increasingly more difficult due to policy changes forcing developing countries to depend on other sources [59]. Even after initial aid is secured and vaccinations are underway, the lack of continued economic support can result in reemergence of the disease [60]. However, there are success stories where countries such as Turkey, Georgia, and Armenia receive continued foreign financial support funding vaccination due to their proximity to FMD-free European countries [18]. Although the disease is still present in these countries, vaccination has reduced disease incidence within these countries [64]. Thus, sustained financial investment from developed countries is perhaps the only way in which global FMD eradication could occur.

Global FMD eradication would remove a primary barrier preventing global animal commerce. Freedom from trade restrictions has the potential to improve national economies. More importantly, livestock agriculture is considered a viable path from poverty and eradication of FMD would help individuals rise out of poverty in developing countries [6, 59].

Social and Political Challenges Surrounding Eradication

Globalization of animal trade and animal product commerce further amplifies the difficulty to contain FMD. Both legal and illegal animal trade and animal product commerce have FMD outbreaks in the past. This was epitomized by outbreaks occurring in Albania in 1996 due to lax trade policy and outbreaks in the island nation of Taiwan in 1997 where the suspected origin of the outbreak was illegally imported feed or pigs [2, 41]. Taiwan's and Albania's outbreak, as well as other outbreaks, suggests that there is inadequate education on the threat of

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disease transmission. The lack of education leads to ineffective FMD prevention and eradication programs. Providing proper information regarding FMD transmission and convincing skeptical populations to take proper precautions is no small task. This is especially challenging when a short-term individual economic gain could be realized by ignoring proper precautions [65].

Lack of effective education, surveillance, and reporting programs have undermined eradication and exacerbated outbreaks. In the 2001 UK outbreak, the farm where the outbreak began failed to report the disease until 3 weeks post infection [26]. In this time, the diseased animals were able to travel to FMD-free France, Netherlands and Ireland [54, 66, 67]. This outbreak cost the UK an estimated $9 billion USD [68]. Educating both local authorities and local farmers on FMD could have mitigated the outbreak extent and cost.

To entice countries to work toward disease freedom, the OIE and the UN Food and Agriculture Organization (FAO) will work with a given country to establish multiple zones with separate FMD designations [69]. These zones allow countries to increase the export of animal products from FMD-free regions of the country while working toward disease freedom in other regions. Countries with multiple FMD designated regions include Argentina, Brazil, Peru and the Philippines among others (Figure 1) [70].

In the past 6 years, the OIE and FAO have established a Progressive Control Pathway for FMD eradication [71, 72]. This tool aims to aid entire regions in controlling and eradicating FMD by providing clearly defined outcomes for each stage of control. The outcomes can be achieved through a variety of means, allowing each country inside the control region discretion to progress within the stages as they choose. The progressive control pathway has helped control and combat multiple outbreaks [73]. However, individual countries must still sort out the logistics of how outcomes are obtained.

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India, one such country working toward disease freedom, faces many social challenges to disease eradication. These challenges stem from lack of cooperation between officials and livestock owners as well as a lack of cooperation between departments [74]. . This exemplifies the necessity of cooperation within a country in order to achieve disease free status.

The lack of cross-governmental cooperation has also played a role in delaying eradication efforts. The ease of transmission and variety of hosts promotes transmission across borders. Therefore, the spread of an outbreak is better controlled when bordering countries communicate and cooperate [75]. Failure of international cooperation can undermine eradication programs through cross-border reintroduction of FMD. Cross-border spread of the disease is further stimulated by burdensome trade restrictions imposed on countries who report FMD within their borders. To avoid these trade restrictions, countries with outbreaks will delay reporting in order to privately stamp it out and continue trade [41]. These delays in reporting increase the risk of disease spread and transmission [76]. Although challenging, cross-governmental cooperation has proven effective in the past resulting in eradication or minimizing FMD outbreaks in places such as the US, Mexico Argentina, Venezuela, Brazil, the UK, and parts of Asia [56, 77].

Proper education and cooperation between government and locals in Argentina provided the foundation for a successful vaccine-based eradication program. Suffering from yearly outbreaks of FMD since 1870, Argentina began the Argentine National FMD Control Programme from 1990 to 1997 which resulted in over 85% of cattle being vaccinated, the disease eradicated, and the designation of FMD-free without vaccination [78]. Due to bordering countries maintaining disease status, Argentina currently has effectively partitioned off their northern border with a disease status of free with vaccination, and their southern border as free without vaccination, as seen in Figure 1 [49].

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Conclusion

The global eradication of FMD is fraught with many challenges. However, vaccine-based eradication has been demonstrated to be a feasible strategy regionally and could be expanded to global application. To do so, multiple significant challenges must be overcome. First, education and logistical organization must be arranged to properly incentivize and execute eradication measures. For example, developing countries have very little veterinary infrastructure and must rely on support from developed countries to establish a veterinary service system trained to recognize FMD signs and perform serosurveillance. Some of these measures are currently being pursued in Iraq and many other countries [63]. Second, development of effective surveillance methods such as on-site diagnostic tests available for use on animals crossing borders or within a countries borders could aid in the more rapid detection of FMD outbreaks [79]. Third, vaccines and vaccine production technology must be significantly less expensive while becoming more flexible for deployment of vaccines. Also, the development of safe vaccine technologies that remove the possibility of accidental outbreak and enable rapid differentiation between infected and vaccinated animals (DIVA) would simplify the eradication effort. Recent developments have begun to address some of these concerns, such as the replication deficient adenovirus-vectored FMD DNA vaccine and the *E. coli*-produced FMD-SUMO fusion vaccine [29, 80]. A subsidized coordinated global effort to methodically vaccinate with an effective and inexpensive vaccine appears to be one of the most viable pathways to global eradication of FMD.

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Figure Captions

Figure 1: Worldwide FMD Status

The FMD Status as defined by the OIE in November 2013. Recognized OIE status is dependent on OIE membership. South Africa, South Korea, and Taiwan are areas currently under suspension. South America has large areas currently FMD-free with vaccination. Continued vaccination programs have progressively stamped out the disease in the majority of South America. FMD Status map used with permission courtesy of OIE and can be found online at http://www.oie.int/en/animal-health-in-the-world/official-disease-status/fmd.

Figure 2: Response to FMD Outbreak and in FMD Enzootic Regions

Possible response routes to an FMD outbreak in regions free of FMD and possible response routes in regions enzootic with FMD. Response option limitations must be weighed against the ultimate goal of FMD eradication.

Figure 3: FMD Disease Cycle

Many FMD enzootic countries are unable to economically afford the technology or the response routes necessary to completely eradicate FMD, thus they remain trapped in a cycle of FMD infection. If a response reaction and surveillance are not maintained, FMD will persist in those countries.

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References

[1] Alexandersen S, Zhang Z, Donaldson AI, Garland AJM. The Pathogenesis and Diagnosis of Foot-and-Mouth Disease. J Comp Pathol. 2003;129:1-36.

[2] Grubman MJ, Baxt B. Foot-and-mouth disease. Clin Microbiol Rev. 2004;17:465-93.

[3] Parida S. Vaccination against foot-and-mouth disease virus: strategies and effectiveness. 2009.

[4] Knight-Jones TJD, Rushton J. The economic impacts of foot and mouth disease – What are they, how big are they and where do they occur? Prev Vet Med. 2013;112:161-73.

[5] Jonathon Rushton TK-J. The Impact of Foot and Mouth Disease. 2012.

[6] James AD, Rushton J. The economics of foot and mouth disease. Revue scientifique et technique-Office international des épizooties. 2002;21:637-41.

[7] Yang PC, Chu RM, Chung WB, Sung HT. Epidemiological characteristics and financial costs of the 1997 foot-and-mouth disease epidemic in Taiwan. Vet Rec. 1999;145:731-4.

[8] Blayney DP, Dyck J, Harvey D. Economic effects of animal diseases linked to trade dependency. Amber Waves. 2006;4:23-9.

[9] Parent K, Miller G, Hullinger P. Triggers for foot and mouth disease vaccination in the United States. Revue Scientifique et Technique-OIE. 2011;30:789.

[10] Haydon DT, Kao RR, Kitching RP. The UK foot-and-mouth disease outbreak—the aftermath. Nature Reviews Microbiology. 2004;2:675-81.

[11] Arzt J, Juleff N, Zhang Z, Rodriguez L. The Pathogenesis of Foot-and-Mouth Disease I: Viral Pathways in Cattle. Transbound Emerg Dis. 2011;58:291-304.

[12] Morelli MJ, Wright CF, Knowles NJ, Juleff N, Paton DJ, King DP, et al. Evolution of foot-and-mouth disease virus intra-sample sequence diversity during serial transmission in bovine hosts. Vet Res. 2013;44:1-15.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[13] Uddowla S, Hollister J, Pacheco JM, Rodriguez LL, Rieder E. A safe foot-and-mouth disease vaccine platform with two negative markers for differentiating infected from vaccinated animals. J Virol. 2012;86:11675-85.

[14] Haixue Z, Jianhong G, Ye J, Fan Y, Jijun H, Lv L, et al. Engineering Foot-and-Mouth Disease Viruses with Improved Growth Properties for Vaccine Development. PLoS One. 2013;8:1-9.

[15] Reid SM, Ferris NP, Hutchings GH, Zhang Z, Belsham GJ, Alexandersen S. Detection of all seven serotypes of foot-and-mouth disease virus by real-time, fluorogenic reverse transcription polymerase chain reaction assay. J Virol Methods. 2002;105:67-80.

[16] Domingo E, Escarmis C, Martinez M, Martinez-Salas E, Mateu M. Foot-and-mouth disease virus populations are quasispecies. Genetic Diversity of RNA Viruses: Springer; 1992. p. 33-47.

[17] Foot and Mouth Disease. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2009.

[18] Keith Sumption JP, Juan Lubroth, Subhash Morzaria, Tom Murray, Stephane De La Rocque, Feliz Njeumi. Foot-and-Mouth Disease Situation worldwide and major epidemiological events in 2005-2006. 2007. p. 11.

[19] Yoon H, Yoon S, Wee S, Kim Y, Kim B. Clinical Manifestations of Foot-and-Mouth Disease During the 2010/2011 Epidemic in the Republic of Korea. Transbound Emerg Dis. 2012;59:517-25.

[20] Kitching R, Hughes G. Clinical variation in foot and mouth disease: sheep and goats. Revue Scientifique Et Technique-Office International Des Epizooties. 2002;21:505-10.

[21] Salt J. The carrier state in foot and mouth disease—an immunological review. Br Vet J. 1993;149:207-23.

[22] Morgan ER, Lundervold M, Medley GF, Shaikenov BS, Torgerson PR, Milner-Gulland EJ. Assessing risks of disease transmission between wildlife and livestock: The Saiga antelope as a case study. Biol Conserv. 2006;131:244-54.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[23] Cottam EM, Wadsworth J, Shaw AE, Rowlands RJ, Goatley L, Maan S, et al. Transmission pathways of foot-and-mouth disease virus in the United Kingdom in 2007. PLoS Pathog. 2008;4:e1000050.

[24] Ryan E, Mackay D, Donaldson A. Foot-and-Mouth Disease Virus Concentrations in Products of Animal Origin. Transbound Emerg Dis. 2008;55:89-98.

[25] Charleston B, Bankowski BM, Gubbins S, Chase-Topping ME, Schley D, Howey R, et al. Relationship between clinical signs and transmission of an infectious disease and the implications for control. Science. 2011;332:726-9.

[26] Scudamore J. Origin of the UK foot and mouth disease epidemic in 2001. Department of Environment, Food and Rural Affairs, London, United Kingdom. 2002.

[27] Lombard M, Pastoret P, Moulin A. A brief history of vaccines and vaccination. Revue Scientifique et Technique-Office International des Epizooties. 2007;26:29.

[28] Mahy BW. Introduction and history of foot-and-mouth disease virus. Foot-and-Mouth Disease Virus: Springer; 2005. p. 1-8.

[29] Rodriguez LL, Grubman MJ. Foot and mouth disease virus vaccines. Vaccine. 2009;27, Supplement 4:D90-D4.

[30] Bank IWoFV. Requirements for Vaccines and Diagnostic Biologicals FMD and CSF Coordination Action. Pirbright, United Kingdom2006. p. 51-7.

[31] Barnett P, Bashiruddin J, Hammond J, Geale D, Paton D. Toward a global foot and mouth disease vaccine bank network. Revue scientifique et technique (International Office of Epizootics). 2010;29:593-602.

[32] Lombard M, Füssel A. Antigen and vaccine banks: technical requirements and the role of the european antigen bank in emergency foot and mouth disease vaccination. Revue scientifique et technique (International Office of Epizootics). 2007;26:117-34.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[33] Guidelines for International Standars for Vaccine Banks. OIE Terrestrial Manual 2008. 6th ed. Paris, France: Office International des Epizooties; 2008. p. 115-9.

[34] Forman A, Garland A. Foot and mouth disease: the future of vaccine banks. Revue scientifique et technique-Office international des épizooties. 2002;21:601-8.

[35] Rieder E, Henry T, Duque H, Baxt B. Analysis of a foot-and-mouth disease virus type A24 isolate containing an SGD receptor recognition site in vitro and its pathogenesis in cattle. J Virol. 2005;79:12989-98.

[36] Bolwell C, Brown A, Barnett P, Campbell R, Clarke B, Parry N, et al. Host cell selection of antigenic variants of foot-and-mouth disease virus. J Gen Virol. 1989;70:45-57.

[37] Doel T. Natural and vaccine induced immunity to FMD. Foot-and-mouth disease virus: Springer; 2005. p. 103-31.

[38] Barnett P, Statham R. Long term stability and potency of antigen concentrates held by the International Vaccine Bank. European Commission for the Control of Foot-and-Mouth Disease Research Group of the Standing Technical Committee, Aldershot (United Kingdom), 14-18 Sep 1998: FAO; 1998.

[39] Liu F, Ge S, Li L, Wu X, Liu Z, Wang Z. Virus-like particles: potential veterinary vaccine immunogens. Res Vet Sci. 2012;93:553-9.

[40] Sáiz M, Núñez JI, Jimenez-Clavero MA, Baranowski E, Sobrino F. Foot-and-mouth disease virus: biology and prospects for disease control. Microbes and Infection. 2002;4:1183-92.

[41] Kitching RP. Foot-and-mouth disease: current world situation. Vaccine. 1999;17:1772-4.

[42] Zheng H, Guo J, Jin Y, Yang F, He J, Lv L, et al. Engineering Foot-and-Mouth Disease Viruses with Improved Growth Properties for Vaccine Development. PLoS One. 2013;8:e55228.

[43] Hua Tang X-SL, Yu-Zhen Fang, Li Pan, Zhong-Wang Zhang, Peng Zhou, Jian-Liang LV, Shou-Tian Jiang, Wen-Fa Hu, Pan Zhang, Yong-Lu Wang, Yong-Guang Zhang. Advances in Studies on Vaccines of Foot-and-mouth Disease. Asian J Anim Vet Adv. 2012:1245-54.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[44] Grubman MJ, Moraes MP, Schutta C, Barrera J, Neilan J, Ettyreddy D, et al. Adenovirus serotype 5-vectored foot-and-mouth disease subunit vaccines: the first decade. Future Virol. 2010;5:51-64.

[45] Grubman MJ, Diaz-San Segundo F, Dias CC, Moraes MP, Perez-Martin E, de los Santos T. Use of replication-defective adenoviruses to develop vaccines and biotherapeutics against foot-and-mouth disease. Future Virol. 2012;7:767-78.

[46] Zhang L, Zhang J, Chen H-t, Zhou J-h, Ding Y-z, Liu Y-s. Research in advance for FMD novel vaccines. Virol J. 2011;8:268.

[47] Smith MT, Varner CT, Bush DB, Bundy BC. The incorporation of the A2 protein to produce novel Qβ virus-like particles using cell-free protein synthesis. Biotechnol Prog. 2012;28:549-55.

[48] Bundy BC, Franciszkowicz MJ, Swartz JR. Escherichia coli-based cell-free synthesis of virus-like particles. Biotechnol Bioeng. 2008;100:28-37.

[49] World Organization for Animal Health. 2013.

[50] Barasa M, Catley A, Machuchu D, Laqua H, Puot E, Tap Kot D, et al. Foot-and-Mouth Disease Vaccination in South Sudan: Benefit–Cost Analysis and Livelihoods Impact. Transbound Emerg Dis. 2008;55:339-51.

[51] Paton DJ, Sinclair M, Rodríguez R. Qualitative Assessment of the Commodity Risk for Spread of Foot-and-Mouth Disease Associated with International Trade in Deboned Beef. Transbound Emerg Dis. 2010;57:115-34.

[52] Sutmoller P, Barteling SS, Olascoaga RC, Sumption KJ. Control and eradication of foot-and-mouth disease. Virus Res. 2003;91:101-44.

[53] Cox SJ, Barnett PV. Experimental evaluation of foot-and-mouth disease vaccines for emergency use in ruminants and pigs: a review. Vet Res. 2009;40:1.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[54] Pluimers F, Akkerman A, Van Der Wal P, Dekker A, Bianchi A. Lessons from the foot and mouth disease outbreak in the Netherlands in 2001. Revue scientifique et technique-Office international des épizooties. 2002;21:711-21.

[55] Thompson D, Muriel P, Russell D, Osborne P, Bromley A, Rowland M, et al. Economic costs of the foot and mouth disease outbreak in the United Kingdom in 2001. Revue scientifique et technique-Office international des epizooties. 2002;21:675-85.

[56] Blackwell JH. Internationalism and survival of foot-and-mouth disease virus in cattle and food products. J Dairy Sci. 1980;63:1019-30.

[57] Whiting TL. Foreign animal disease outbreaks, the animal welfare implications for Canada: Risks apparent from international experience. The Canadian Veterinary Journal. 2003;44:805.

[58] Kenyon S. Foot and Mouth Disease. 2011.

[59] Perry B, Sones K. Poverty reduction through animal health. Science. 2007;315.

[60] Garabed RB, Johnson WO, Gill J, Perez AM, Thurmond MC. Exploration of associations between governance and economics and country level foot-and-mouth disease status by using Bayesian model averaging. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2008;171:699-722.

[61] Vosloo W, Bastos A, Sangare O, Hargreaves S, Thomson G. Review of the status and control of foot and mouth disease in sub-Saharan Africa. Revue Scientifique Et Technique-Office International Des Epizooties. 2002;21:437-45.

[62] Thomson G, Vosloo W, Bastos A. Foot and mouth disease in wildlife. Virus Res. 2003;91:145-61.

[63] BenYoussef A. Internationally supported FMD projects in the World: Regional and interregional activities. 80th Session of the EuFMD Executive Committee. Vienna, Austria2010.

[64] Knight-Jones T, Bulut A, Gubbins S, Stärk K, Pfeiffer D, Sumption K, et al. Retrospective evaluation of foot-and-mouth disease vaccine effectiveness in Turkey. Vaccine. 2014;32:1848-55.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[65] Cai C. The risk of foot and mouth disease entering China through the movement of animals from Upper Mekong region countries: Murdoch University; 2012.

[66] Chmitelin I, Moutou F. Foot and mouth disease: lessons to be learned from the experience of France. Revue scientifique et technique (International Office of Epizootics). 2002;21:731-7, 23-30.

[67] Costelloe J, Gaynor M, Gaynor S, McAteer W, O'REILLY P. Control of foot and mouth disease: lessons from the experience of Ireland. Revue scientifique et technique-Office international des épizooties. 2002;21:739-50.

[68] Cheung Y-K, Cheng SC-S, Sin FW-Y, Xie Y. Plasmid encoding papillomavirus Type 16 (HPV16) DNA constructed with codon optimization improved the immunogenicity against HPV infection. Vaccine. 2004;23:629-38.

[69] Scott A, Zepeda C, Garber L, Smith J, Swayne D, Rhorer A, et al. The concept of compartmentalisation. Revue Scientifique et Technique-Office International des Epizooties. 2006;25:873-907.

[70] World Organization for Animal Health. 2013.

[71] FAO: Progressive control pathway for foot-and-mouth disease control (PCP-FMD). Food and Agriculture Organization of the United Nations. Rome, Italy2011.

[72] Sumption K, Domenech J, Ferrari G. Progressive control of FMD on a global scale. The Veterinary record. 2012;170:637.

[73] Jamal SM, Belsham GJ. Foot-and-mouth disease: past, present and future. Vet Res. 2013;44:116.

[74] Rajput DS, Tripathi H. Constraints perceived by field veterinarians for providing animal health services in arid zone of Rajasthan. Vet Pract. 2010;11:158-61.

[75] Forman S, Le Gall F, Belton D, Evans B, François J, Murray G, et al. Moving towards the global control of foot and mouth disease: an opportunity for donors. Revue scientifique et technique-Office international des épizooties. 2009;28:883-96.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

[76] Valarcher JF, Leforban Y, Rweyemamu M, Roeder P, Gerbier G, Mackay D, et al. Incursions of Foot-and-Mouth Disease Virus into Europe between 1985 and 2006. Transbound Emerg Dis. 2008;55:14-34.

[77] Thomson GR. Foot and mouth disease: facing the new dilemmas: OIE; 2002.

[78] Mattion N, König G, Seki C, Smitsaart E, Maradei E, Robiolo B, et al. Reintroduction of foot-and-mouth disease in Argentina: characterisation of the isolates and development of tools for the control and eradication of the disease. Vaccine. 2004;22:4149-62.

[79] Dukes J, King D, Alexandersen S. Novel reverse transcription loop-mediated isothermal amplification for rapid detection of foot-and-mouth disease virus. Arch Virol. 2006;151:1093-106.

[80] Guo H-C, Sun S-Q, Jin Y, Yang S-L, Wei Y-Q, Sun D-H, et al. Foot-and-mouth disease virus-like particles produced by a SUMO fusion protein system in Escherichia coli induce potent protective immune responses in guinea pigs, swine and cattle. Vet Res. 2013;44:48.

Please Cite this work as: Smith MT, Bennett AM, Grubman MJ, Bundy BC. 2014. Foot and Mouth Disease: Technical and Political Challenges to Eradication. Vaccine. 32(31):3902-3908.

Figure 1

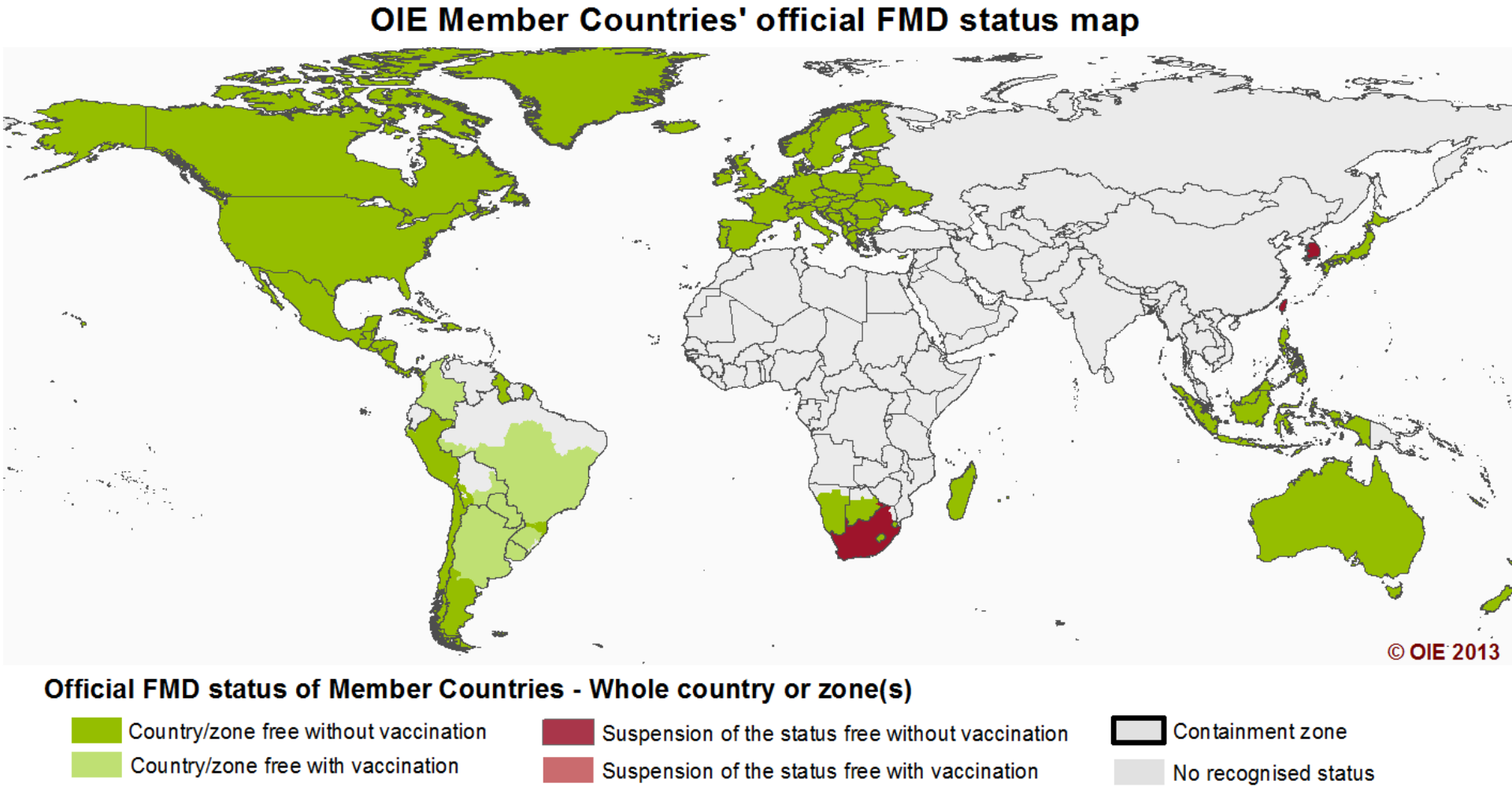

OIE Member Countries' official FMD status map
© OIE 2013
Official FMD status of Member Countries - Whole country or zone(s)
Country/zone free without vaccination
Country/zone free with vaccination
Suspension of the status free without vaccination
Suspension of the status free with vaccination
Containment zone
No recognised status

Figure 2

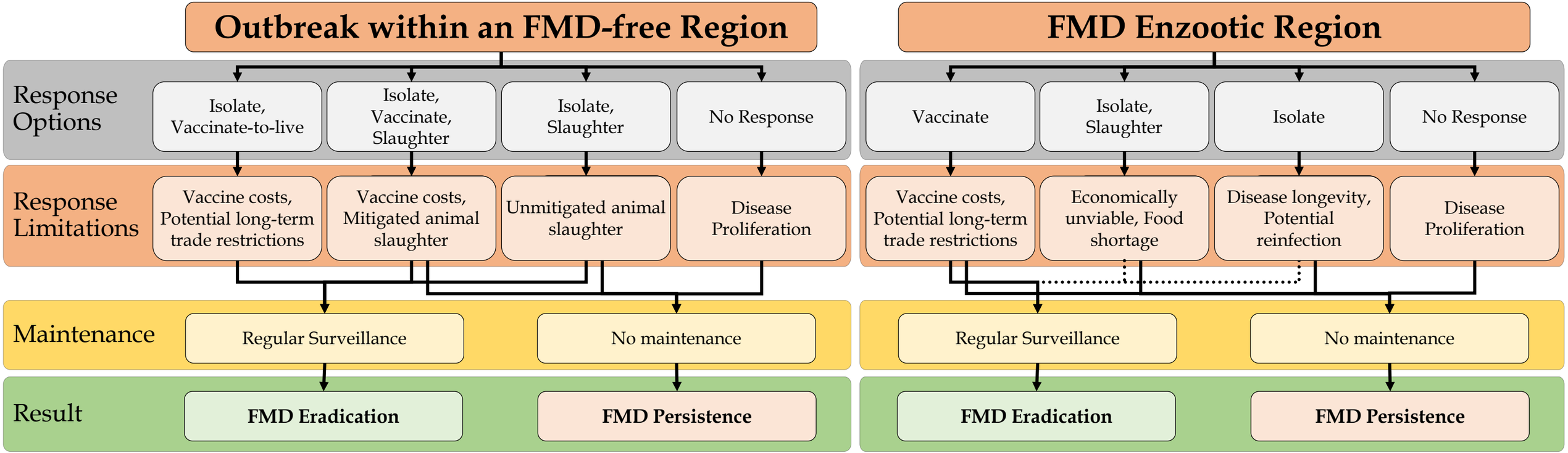
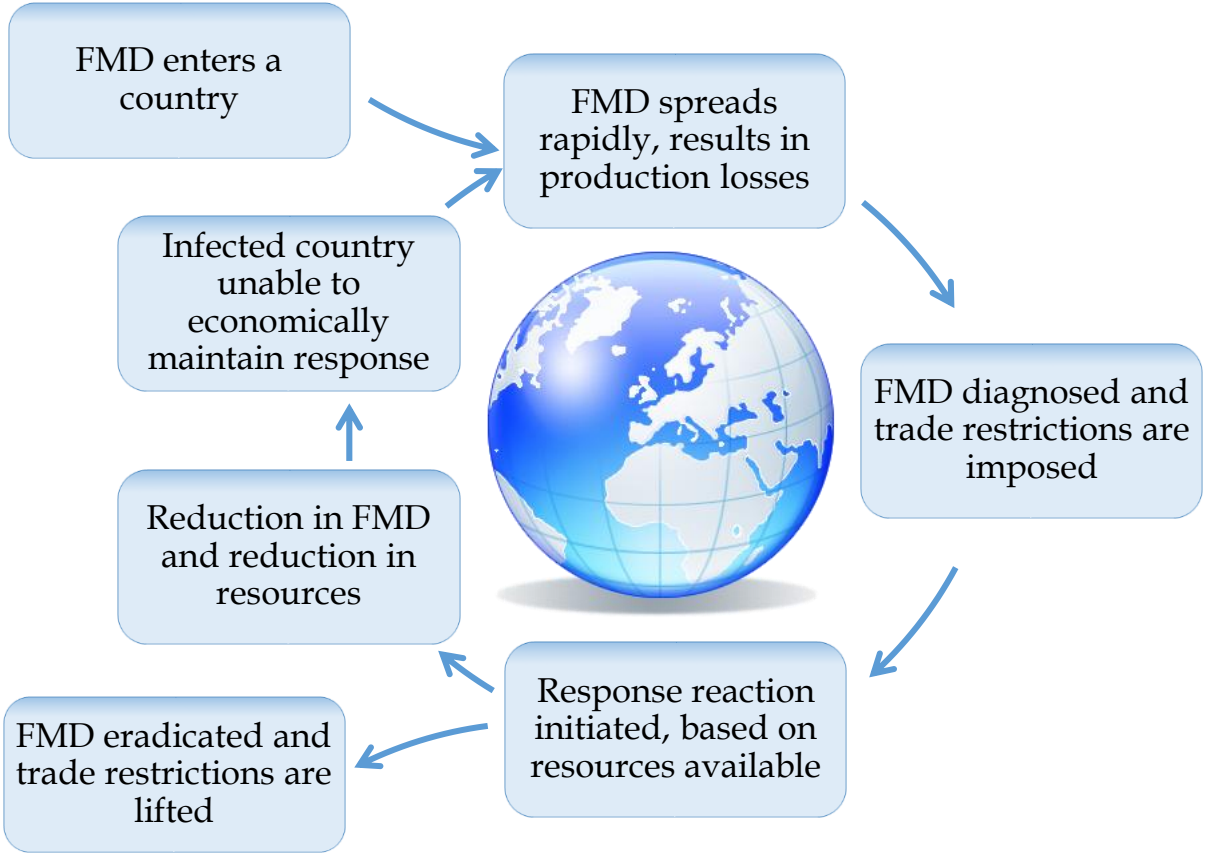

Outbreak within an FMD-free Region
FMD Enzootic Region
Response Options
Isolate, Vaccinate-to-live
Isolate, Vaccinate, Slaughter
Isolate, Slaughter
No Response
Vaccinate
Isolate, Slaughter
Isolate
No Response
Response Limitations
Vaccine costs, Potential long-term trade restrictions
Vaccine costs, Mitigated animal slaughter
Unmitigated animal slaughter
Disease Proliferation
Vaccine costs, Potential long-term trade restrictions
Economically unviable, Food shortage
Disease longevity, Potential reinfection
Disease Proliferation
Maintenance
Regular Surveillance
No maintenance
Regular Surveillance
No maintenance
Result
FMD Eradication
FMD Persistence
FMD Eradication
FMD Persistence

Figure 3


FMD enters a country
FMD spreads rapidly, results in production losses
FMD diagnosed and trade restrictions are imposed
Response reaction initiated, based on resources available
Reduction in FMD and reduction in resources
Infected country unable to economically maintain response
FMD eradicated and trade restrictions are lifted