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Review

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 toward FMD eradication.

1. 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–$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 drives 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].

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.

2. 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

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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].

3. 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 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 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 1950s, 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.

4. 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 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, 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

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