Transmission Dynamics and Emergency Control in an **FMDV-Free** Country with **Pasture-Based** Livestock Production Systems

María Victoria Iriarte Barbosa



Propositions

1. Misinformation about vaccination poses a greater threat to foot-and-mouth disease virus (FMDV) control than the virus itself (this thesis).

2. Global FMDV eradication efforts should better incorporate the lessons learned from South America (this thesis).

3. Blaming cows for environmental warming overlooks the potential contribution of pasture-based systems to sustainability.

4. English language dominance in science shapes what counts as scientific knowledge.

5. Science-based trade is impossible when countries demand measures beyond WTO standards.

6. Gender inequality in decision-making persists not because women fail to reach positions of authority, but because authority itself remains gendered.

Propositions belonging to the thesis entitled

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María Victoria Iriarte Barbosa

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Transmission Dynamics and Emergency Control in an FMDV-Free Country with Pasture-Based Livestock Production Systems

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Transmission Dynamics and Emergency Control in an FMDV-Free Country with Pasture-Based Livestock Production Systems

María Victoria Iriarte Barbosa

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Chapter 1

General Introduction

María Victoria Iriarte Barbosa

LEARNING FROM EPIDEMICS TO PREPARE FOR THE FUTURE

Foot-and-mouth disease (FMD) is a global disease that has affected most countries over time (Sutmoller et al., 2003) and remains one of the most important livestock diseases worldwide, limiting international trade in animals and animal products, causing productivity losses, and imposing substantial control costs (James & Rushton, 2002). Although it is among the most studied animal diseases, important knowledge gaps persist and limit the effectiveness of global control and eradication efforts (Humphreys et al., 2025).

Understanding foot-and-mouth disease virus (FMDV) transmission is essential because control succeeds only when it reduces transmission sufficiently. FMDV is endemic in some regions, while others remain free and at risk of introduction. Patterns of spread differ by context. Endemic areas experience frequent contact-driven transmission, whereas FMDV-free countries face rare seeding events such as contaminated fomites (Paton et al., 2018). In this context, FMDV transmission can be quantified at multiple levels to address different questions, within herds, between farms, and at regional and global scales.

This thesis focuses on transmission following introductions into FMDV-free settings, with particular emphasis on between-farm transmission, using Uruguay as a case study. Mathematical models provide a formal framework to represent transmission dynamics by integrating pathogen characteristics, host population structure, and interaction patterns among farms (Hagenaars et al., 2011). However, most modelling studies of FMDV introduction and spread in FMDV-free regions have been developed and applied in intensive production systems, leaving transmission dynamics in pasture-based livestock production systems comparatively underexplored. While the biological mechanisms of FMDV transmission are shared across systems, key structural determinants of between-farm spread, such as farm density, herd size, species composition, contact patterns, and animal movements, differ substantially between intensive and pasture-based livestock production systems. These differences are expected to affect the relative contribution of transmission routes as well as the spatial and temporal dynamics of FMDV spread. The 2001 FMD epidemic in Uruguay, which occurred when the country was FMDV-free without vaccination, provides a well-documented case to characterise transmission in pasture-based livestock production systems. In addition, the subsequent implementation of mass cattle vaccination to control the epidemic enables the assessment of vaccination effectiveness using population-level field data.

This thesis analyses farm-level data from the 2001 FMD epidemic in Uruguay to address a set of specific research questions. For example, it is well established that movements of infected animals during the High-Risk Period (HRP), defined as the interval between virus introduction and detection, contribute to FMDV spread (Gibbens et al., 2001), but the magnitude of that contribution is not always available. The role of animal movements during the HRP is therefore analysed and quantified, providing empirical estimates to inform the parameterisation of transmission models.

In addition, this thesis examines how farm-level heterogeneity, in terms of geographical location, species composition, herd size, and the density and characteristics of surrounding farms, shapes between-farm transmission potential and the generation of

secondary outbreaks. While experimental studies have provided estimates of the contribution of sheep to FMDV transmission (Bravo De Rueda et al., 2014), field-based quantification remains limited, particularly in pasture-based livestock production systems with co-grazing of species. The 2001 epidemic in Uruguay provides a suitable context to quantify the role of sheep in transmission under real production conditions.

Similarly, larger herds are often associated with increased between-farm transmission (Ferguson et al., 2001b), yet estimates of the effect of farm size on infectiousness (outward risk) and susceptibility (inward risk) remain scarce, especially in pasture-based livestock production systems. The marked heterogeneity in herd size in Uruguay provides the variation required to identify these size-specific effects. In this framework, this thesis quantifies how herd size shapes both infectiousness and susceptibility at the between-farm scale.

Moreover, the 2001 epidemic in Uruguay represents a valuable case study of large-scale emergency vaccination with commercial vaccines in a previously FMDV-free country without vaccination. While experimental studies have provided essential information on within-herd transmission and vaccine-induced protection under controlled conditions, field-based estimates of vaccine effectiveness for FMD remain limited. Although field-based analyses are inherently subject to greater uncertainty, they offer the opportunity to assess vaccine performance at the population level, where transmission occurs between farms under real-world conditions. In this sense, field data provide complementary evidence to support vaccine effectiveness parameters used in epidemiological models. Finally, scenario analyses were conducted to inform contingency planning, comparing cattle-only implementations with measures applied to all FMDV-susceptible species (cattle, sheep, pigs). Evaluated measures included culling of detected herds only, 1-km pre-emptive culling, ring vaccination at three radii, and preventive vaccination targeted by risk or by herd size.

Overall, complementary quantitative epidemiological methods were applied to identify the drivers of transmission during the 2001 FMD epidemic in Uruguay and to assess the effectiveness of alternative control measures. This improved understanding turns a past crisis into knowledge that can guide surveillance, preparedness, and control.

Before outlining the structure of the thesis, this chapter provides essential background on FMDV, the global epidemiological context, the Uruguayan setting, and the 2001 epidemic.

1. The Epidemiological Complexity of Foot-and-Mouth Disease

FMD is caused by the FMDV, which belongs to the genus Aphthovirus within the family Picornaviridae. The virus contains a genome made up of a single strand of RNA, and is divided into seven distinct serotypes, which do not provide cross-protection (Belsham, 1993). Serotypes O and A were the first identified, followed by serotype C, and later the Southern African Territories serotypes SAT 1–3 and Asia 1, as reviewed by Sutmoller et al., (2003). FMDV serotypes exhibit a wide range of topotypes, which are distinct genetic lineages within a serotype. These topotypes further diversify into multiple strains, each with unique genetic characteristics. This variation results from the virus' rapid evolution, leading to different strains that circulate in specific regions and require tailored vaccines

for effective control (Brito et al., 2017). Serotype C was last reported in 2004, with detections in both Kenya and Brazil, and is considered to be possibly eradicated (Paton et al., 2021).

FMDV affects a wide range of cloven-hoofed animals, including domesticated livestock such as cattle, pigs, sheep, and goats, as well as wild species like deer and African buffalo (Alexandersen, Zhang, et al., 2003; Grubman & Baxt, 2004). FMDV is most commonly transmitted through direct contact between susceptible and infected animals or indirectly through contaminated environment (Colenutt et al., 2020; Paton et al., 2018). Additionally, airborne transmission has been proposed, particularly when environmental and management conditions are favourable, such as high pig density (since pigs are major emitters of virus aerosols), the presence of large numbers of susceptible livestock (notably cattle due to their high susceptibility), stable atmospheric conditions with gentle winds, high relative humidity (≥55%), moderate or low temperatures, and proximity to infected premises (Brown et al., 2022; Gloster et al., 2005). However, its relative contribution to overall spread remains controversial.

FMD is characterized by acute fever accompanied by the formation of vesicles, particularly around the mouth and feet, leading to pain, lameness, and reluctance to move. Clinical manifestations vary across species. In cattle, symptoms typically include severe drooling and oral lesions, whereas pigs often exhibit acute lameness and vesicular lesions on the feet. In contrast, sheep and goats tend to show milder or even inapparent clinical signs (Clavijo VM & Kitching, 2003). Comprehensive descriptions of this clinical variability are provided in several detailed reviews (Kitching, 2002; Kitching & Alexandersen, 2002; Kitching & Hughes, 2002a). From an epidemiological perspective, species also differ in their contribution to virus excretion and transmission. While pigs are well known for producing large amounts of viral aerosols at the individual-animal level, cattle may also excrete substantial quantities of virus. Importantly, virus excretion by cattle, pigs, and sheep often peaks before the onset of clinical signs. As a result, FMDV can spread rapidly among susceptible animals, primarily through direct contact, but also indirectly via contaminated fomites or environmental exposure (Sutmoller et al., 2003).

Although FMDV generally has a high morbidity rate, mortality remains uncommon in adult animals, typically below 5% (Mardones et al., 2010). Mardones et al. (2010) performed an analytical review and meta-analysis to study the duration of different stages of serotype O FMDV infection. They showed that these stages vary across species, with cattle, pigs, and small ruminants each displaying distinct timelines. For instance, the latent period in cattle averages around 3.6 days, while pigs exhibit a shorter duration of approximately 3.1 days. The incubation period in cattle is about 5.9 days, longer than in pigs but shorter than in small ruminants, which can extend to 6.6 days. The infectious period ranges from 4.4 days in cattle to 5.7 days in pigs. The duration of these stages is influenced by factors such as the route of exposure (direct or indirect contact), the species of the infected and exposed animals, and the specific strain of the virus. Some virus strains are host-adapted. For example, some strains are less virulent in cattle but remain virulent in pigs such as the specific strain of FMDV that caused an outbreak in Taiwan in 1997 (Dunn & Donaldson, 1997) or vice versa, FMDV strains less adapted to pigs, as the Asia1 strain which predominantly affects cattle and sheep rather than pigs (X. Yang et al., 2011).

In addition, FMDV can cause a long-term, asymptomatic carrier state in ruminants following the initial acute infection. This persistent infection can occur in both animals that have recovered and those that have been vaccinated and subsequently exposed to the virus. This understanding has significantly influenced FMD control strategies. For example, policies like “stamping out”, which involve culling all susceptible animals on infected premises, or the strategic slaughter of vaccinated animals during an emergency, aim to prevent the potential spread of the virus from carriers (Alexandersen, Zhang, et al., 2003). It is widely accepted that the likelihood of FMDV transmission from carrier cattle is very low. Studies have consistently shown that despite the persistence of the virus in some animals, the risk of these carriers transmitting the disease to susceptible individuals remains minimal (Stenfeldt & Arzt, 2020).

The complex epidemiology of FMDV, characterized by its high transmissibility, ability to affect multiple species, and spread through various routes, combined with the presence of numerous serotypes each requiring specific vaccines that do not provide cross-protection, poses substantial challenges for effective control and eradication. As a result, FMDV continues to be a global threat to farmers and livestock industries.

2. Global Pressures on FMD-Free Regions: Risk and Impact

FMD is a disease listed by the World Organisation for Animal Health (WOAH) and is subject to mandatory reporting to the organization, as outlined in the Terrestrial Animal Health Code. The interconnectedness of the global livestock trade and movement of animals and animal products, has generated the development of standards for international trade by WOAH that have had an impact on animal health policies of countries in terms of FMD control and eradication programs. The WOAH recognizes two categories for FMD free status, "FMD-free without vaccination" and "FMD-free with vaccination", which has implications for animal and animal products international trade (Perry et al., 2020). Some countries may only allow the importation of animals and products from countries that are FMD-free without vaccination. Others may permit trade with countries that are FMD-free with vaccination but subject to certain conditions.

Countries where FMDV is endemic or occurs sporadically are categorized into seven regional pools based on the genetic and antigenic analysis of circulating FMDV strains, shaped by ecological similarities, livestock exchange, and cultural practices (Brito et al., 2017; Paton et al., 2009; Rweyemamu et al., 2008). This ongoing presence poses a risk to countries that are FMDV-free, as the virus can potentially spread through trade, animal movement, illegal transport, and contaminated materials or equipment.

FMD is considered one of the most economically devastating animal diseases. According to Knight-Jones & Rushton (2013), the economic impact of FMD arises from two main sources: direct losses in production, such as reduced fertility and lower yields of milk and meat, and indirect losses, including high costs of disease control and restricted access to international markets. These authors estimated that annual economic losses in endemic regions range between US$6.5 and 21 billion, with outbreaks in FMD-free countries and zones result in annual losses exceeding US$1.5 billion. They also highlighted that the economic burden is particularly severe in poorer regions, where communities rely heavily on livestock for their livelihoods. The presence or risk of FMDV limits trade opportunities, and outbreaks in free zones lead to costly efforts to regain disease-free

status. This is especially important for Uruguay, which economy heavily relies on the export of livestock products, representing about 30% of the country's total export value (OEC, 2022).

Regional cooperation is crucial for controlling transboundary animal diseases like FMD. In South America, countries have long collaborated through The Pan American Centre for Foot-and-Mouth Disease and Veterinary Public Health (PANAFTOSA/PAHO/WHO) (Naranjo & Cosivi, 2013; Rivera et al., 2023). Similarly, Europe has the European Commission for the control of FMD (EuFMD), and Southeast Asia benefits from the activities of the WOAH Sub-Commission for FMD Control in Southeast Asia and China (SEACFMD). On a global scale, the Global Framework for the Progressive Control of Transboundary Animal Diseases (GF-TADs) has promoted the development of regional roadmaps for FMD control. These roadmaps encourage countries within the same virus "pools", regions where specific FMDV strains are endemic, to coordinate activities and hold joint meetings, thereby enhancing the epidemiological relevance and effectiveness of control strategies.

Despite the global efforts to control and eradicate FMDV, it is still present in many parts of the world, impacting 77% of the global livestock population, especially in Africa, the Middle East, and Asia. In South America, the disease remains only in Venezuela (World Organization of Animal Health (WOAH), 2024).

In recent years, there have been several significant global events related to FMD. One key area of concern is North Africa, with the emergence of SAT-2 in Algeria and O/EA-3 in Libya. Additionally, in South Africa, there has been a loss of FMD-free status due to SAT-2 and SAT-3 infections of domestic animals. A notable event has been the introduction of SAT-2 and more recently SAT-1 into the Middle East, likely through livestock imports from the Horn of Africa. In Asia, the Middle East–South Asia lineage of the O strain (O/ME-SA-Ind-2001e lineage) has spread extensively, reaching Indonesia, China, Korea, Kazakhstan, Mongolia, and Russia (FAO, 2024). The 2022 FMDV outbreak in Indonesia, which re-emerged after 32 years of being FMD-free, highlights the ongoing threat of FMDV incursions even in regions that have maintained FMD-free status (Susila et al., 2023; Sutawi et al., 2023). One surprising development was the detection of FMD viruses of South American origin in Egypt, with genetic sequencing revealing close ties to Venezuelan strains. The route of this virus remains unclear, raising concerns about possible undetected circulation in Venezuela or Egypt and pointing to gaps in global FMD surveillance (Hagag et al., 2023).

Recent reports from the World Reference Laboratory for FMD highlight that Europe is not exempt from the threat of FMDV incursions. In early 2025, outbreaks were confirmed in Germany, Hungary, and Slovakia after many years without cases. In Germany, serotype O (O/ME-SA/SA-2018 lineage) was detected in water buffalo near Berlin, while in Hungary and Slovakia, a distinct serotype O lineage (PanAsia-2PUN-16) caused multiple outbreaks in cattle.

In sum, FMDV-free countries remain at ongoing risk of incursion as a result of global livestock trade, transboundary virus circulation, and the recurrent emergence of new FMDV lineages. Sustained prevention, risk-based surveillance, and robust emergency

preparedness are therefore essential to minimise health and economic impacts. This thesis contributes field-based evidence and parameter estimates to help strengthen these efforts.

3. A Historical Overview of FMDV Control

The control of FMD has a long history, with early recognition in Europe dating back to the 16th century. The development of vaccines after World War II enabled large-scale vaccination campaigns, although early understanding of vaccine-induced protection and its impact on transmission was limited. Systematic vaccination in Europe controlled and eradicated the disease until the 1990s when vaccination ceased for trade reasons (Sutmoller et al., 2003). Subsequently, experimental studies generated evidence of vaccine efficacy in reducing transmission and clarified species-specific differences in vaccine performance (Barnett, Cox, et al., 2002; Barnett, Garland, et al., 2002; Bouma et al., 2004; Bravo De Rueda et al., 2015; S. Cox et al., 1999; S. J. Cox et al., 2005; De Jong & Kimman, 1994; P. Eblé et al., 2006; P. L. Eblé et al., 2004; Orsel, de Jong, et al., 2007; Orsel, Dekker, et al., 2007; Orsel et al., 2005; Orsel & Bouma, 2009).

FMDV was introduced into North and South America in 1879 by the importation of animals and animal products from Europe, yielding distinct consequences in each region. While in North America, the occurrence of sporadic outbreaks was addressed through an eradication approach involving stamping-out, in South America the infection had spread among cattle populations across all affected countries and, therefore, could only be controlled using systematic vaccination of the cattle population. South American countries followed to the European non-vaccination policy between 1994 and 1999 to maintain their meat export status (Sutmoller et al., 2003).

In the first decade of the 21st century, FMDV raised global concerns by emerging in regions that were previously free from the virus. This happened in the United Kingdom in 2001, leading to its spread to other European Union countries, including France, Ireland, and the Netherlands (Bouma et al., 2003; Gibbens et al., 2001). Other large epidemics also occurred in FMDV-free countries in South America, one of those countries being Uruguay, leading most of these countries of South America to resume their mass cattle vaccination campaigns (Bergmann et al., 2005; Iriarte Barbosa et al., 2023; Naranjo & Cosivi, 2013; Sutmoller et al., 2003).

In 2001, European and South American countries implemented distinct strategies to control their respective epidemics. In the UK, the preferred approach was stamping out without the use of vaccination (Gibbens et al., 2001). By contrast, the Netherlands adopted a strategy that combined the standard EU control measures with emergency vaccination in the affected area, followed by the slaughter of all vaccinated animals (Bouma et al., 2003). The extensive use of stamping out of infected herds, pre-emptive culling of neighbouring farms, and the slaughter of vaccinated animals across the EU sparked considerable debate over these policies. In response to these concerns, the "vaccination-to-live" strategy emerged as a potential alternative for future outbreaks. For example, the Dutch government adopted emergency vaccination, with the goal of allowing vaccinated animals to live, as a preferred control policy (Backer, Engel, et al., 2012; Backer, Hagenaars, et al., 2012).

Japan and the Republic of Korea, both previously FMD-free without vaccination, faced major outbreaks in 2010 (Knowles et al., 2012). Japan initially applied stamping out, movement restrictions and disinfection in Miyazaki Prefecture, then adopted emergency vaccination when these measures proved insufficient (Muroga et al., 2012). Korea combined a nationwide vaccination campaign with extensive culling, ultimately affecting ~3,700 farms and culling 3.48 million animals (Park et al., 2013; Yoon et al., 2015). More recently, Korea has managed repeated incursions (2019, 2023, 2025), In 2023, the rapid deployment of antigenically matched serotype O vaccines, together with intensive active surveillance, successfully contained virus spread (Ryoo et al., 2024).

Recent FMD outbreaks in the European Union in 2025 were managed under the Animal Health Law, primarily through rapid stamping out, cleaning and disinfection, movement restrictions, and zoning, including the establishment of protection (≥3 km) and surveillance zone (≥10 km). In Hungary and Slovakia, suppressive emergency vaccination was additionally applied on selected high-risk farms prior to depopulation to limit further spread. In Germany, vaccination was not implemented; however, authorities activated the vaccine bank and prepared contingency plans, as stamping out and zoning measures were sufficient to contain the outbreak (European Commission, 2025).

Overall, control measures for FMD epidemics have varied across regions, shaped by economic constraints, production systems, and trade policies. Management strategies have typically balanced stamping out (culling) and vaccination, with countries adapting this mix to their specific epidemiological, logistical, and policy contexts. As a result, a wide range of control responses has been implemented, contributing to an evolving evidence base.

This thesis contributes field-based estimates of the effectiveness of emergency vaccination with commercial vaccines in pasture-based livestock production systems, providing evidence to support preparedness and model-based decision-making in FMD-free countries with similar epidemiological and production contexts. These parameters also facilitate the evaluation of alternative strategies, such as preventive vaccination, which may be more sustainable in pasture-based systems where veterinary culling capacity is limited and public concern about culling is high. Such concerns include animal welfare, environmental risks associated with carcass disposal, and impacts on food security and rural livelihoods. Because FMDV introduction and spread depend on population structure, species composition, herd-size distribution, and farm density, control strategies based solely on culling are highly context-dependent and may not produce comparable epidemiological outcomes across settings. Understanding the transmission processes underlying observed epidemics is therefore critical for selecting appropriate control strategies.

4. FMD in Uruguay: From the 2001 Epidemic to the Current Landscape

4.1. Brief history

FMD was endemic in Uruguay until 1961 when the control of the disease was declared mandatory. In 1987, the control programme was integrated into a regional framework between Argentina (Entre Ríos, Corrientes and Misiones), Brazil (Rio Grande do Sul), Uruguay and The Pan American FMD Centre (PANAFTOSA) (Dias, 2008).

In 1993, Uruguay was first recognised by WOAH as a FMD free country where vaccination is practiced. Later, in 1994, the country established actions to gain a status of free without vaccination. These actions were the suppression and prohibition of vaccination, regulation of culling in the presence of an outbreak as a control strategy, destruction of virus stock present in laboratories, and application of strict regulations for the importation of animals and products of animal origin. Later, in 1996 the WOAH recognised Uruguay as a FMD free country without vaccination. In 2000, an incursion of FMDV serotype O in the north, on the border with Brazil, caused a minor outbreak that was eradicated under a non-vaccination policy through culling of infected and contact animals, cleaning and disinfection, movement bans and zoning.

In April 2001, a new introduction, this time of FMDV serotype A, triggered a large epidemic. Eradication was achieved only after, in addition to standard control measures (including a ban on animal movements and enhanced biosecurity), a nationwide mass vaccination of the cattle population was implemented. On 22 May 2003, WOAH recognised Uruguay as FMD-free with vaccination, a status the country has maintained since. The 2001 epidemic caused a large economic and social impact in Uruguay, with an estimated cost of more than 730 million dollars (OPYPA-MGAP, 2004).

4.2. The 2001 FMD epidemic

On 23 April 2001, a suspicion of FMD occurrence was reported. The Veterinary Services investigated and clinically confirmed the disease on 24 April 2001. The official laboratory (DILAVE) confirmed the diagnosis by serology, identifying antibodies against type A virus on 25 April 2001. On 3 May, serotype A was confirmed by The Pan American Centre for Foot-and-Mouth Disease (PANAFTOSA)(OIE, 2001).

The index case was confirmed in Soriano which is a department located southwest of Uruguay at the border with Argentina. The most probable hypothesis established by the Official Veterinary Services was that FMDV was introduced by fomites from Argentina. This hypothesis was supported by the fact that the virus type identified was the same in both countries and no live animal movements from Argentina to Uruguay were observed during or shortly before the high-risk period (HRP), which is the period between the virus introduction and the index case detection. The border administrative departments of Soriano and Colonia (southwest of Uruguay) involve intense cross-border movement of tourists, hunters and people related to the agriculture sector (Figure 1). Subsequent epidemiological analyses suggested that multiple introductions during the HRP cannot be excluded.

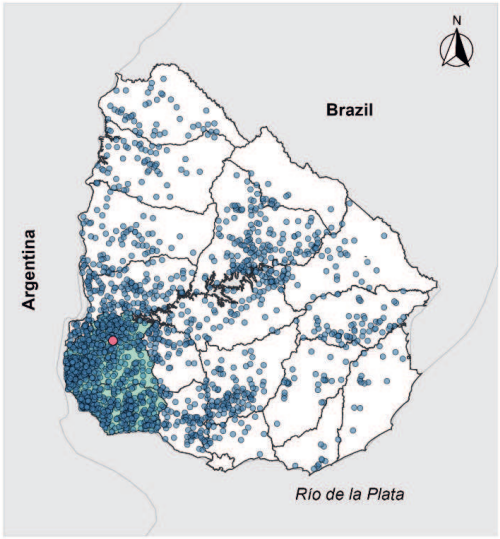


Figure 1 Locations of outbreak farms (blue points) and the index case (pink point) in Uruguay (2001). The departments of Soriano and Colonia are shaded in light blue in the southwest, along the border with Argentina.

First, authorities sought to control the disease without vaccination, implementing measures such as ban of animal, animal products and people movements, culling the clinically affected and in contact FMDV susceptible animals within the outbreak and the application of biosecurity measures. In addition, a ring vaccination within a 10 km radius around outbreaks was implemented on 26 April. The ban of animal movements was enforced locally for 3 days, but then on 27 April 2021 this measure was extended at a national scale. On 30 April the measures changed, stamping out was stopped and emergency vaccination within an extensive buffer zone was enforced, which aimed to stop the FMDV spread from southwest to northeast. Later in the epidemic, infection appeared to keep spreading and on 5 May 2001 a mass vaccination of the entire national cattle population was adopted, which was completed on 7 June. The ban on animal movements was in place until June 7 after completing the first round of vaccination. Animal movements were authorized under certain defined conditions and requirements, which were lifted after completing the second round of vaccination. The second round of mass vaccination was implemented from 15 June to 22 July 2001 (Figure 2).

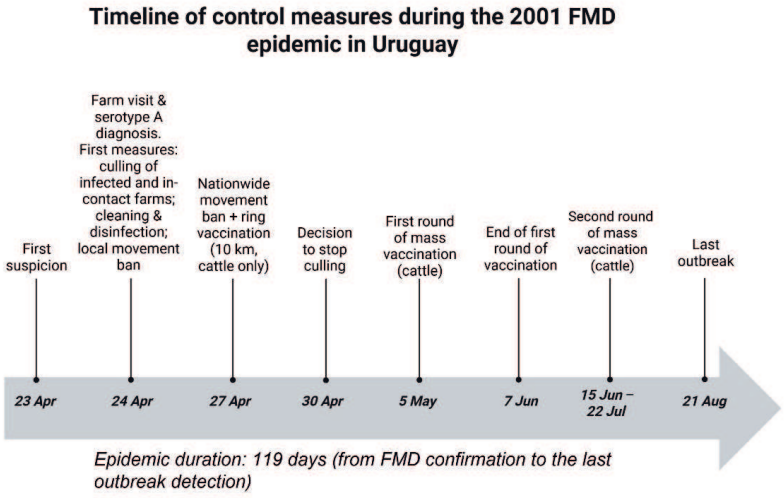


Figure 2 Timeline of control measures implemented during the 2001 foot-and-mouth disease (FMD) epidemic in Uruguay. Key events include detection and confirmation, initial culling and movement restrictions, nationwide movement ban, and the first and second rounds of mass cattle vaccination. The epidemic lasted 119 days from confirmation.

The epidemic lasted 119 days, with the last outbreak visit recorded on 21 August 2001. At the end of the epidemic, the total number of FMDV infected farms (outbreaks) was 2,057. The epidemic curve, i.e., the distribution of outbreaks over time, has a steep increase and a long tail (Figure 3).

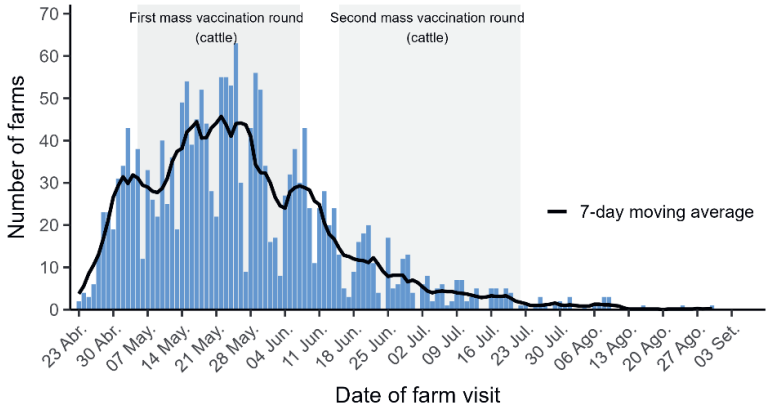


Figure 3 Epidemic curve of the 2001 foot-and-mouth disease (FMD) epidemic in Uruguay by date of farm visit. Bars show the number of farms visited per day; the black line is the 7-day moving average. Grey bands indicate the first and second rounds of mass cattle vaccination. "Date of farm visit" denotes the date when official veterinary services visited a farm following notification or tracing.

Figure 4 and Table 1 describe the composition of farms in Uruguay during the 2001 epidemic. Figure 4 summarizes farm composition and size by infection status, highlighting differences between infected and uninfected farms across cattle, sheep, and pig holdings. Table 1 complements this information by detailing the national distribution of farm types according to species composition, including single-species and mixed-species farms. Together, these descriptive summaries illustrate the predominance of cattle-based and mixed cattle–sheep farms in Uruguay.

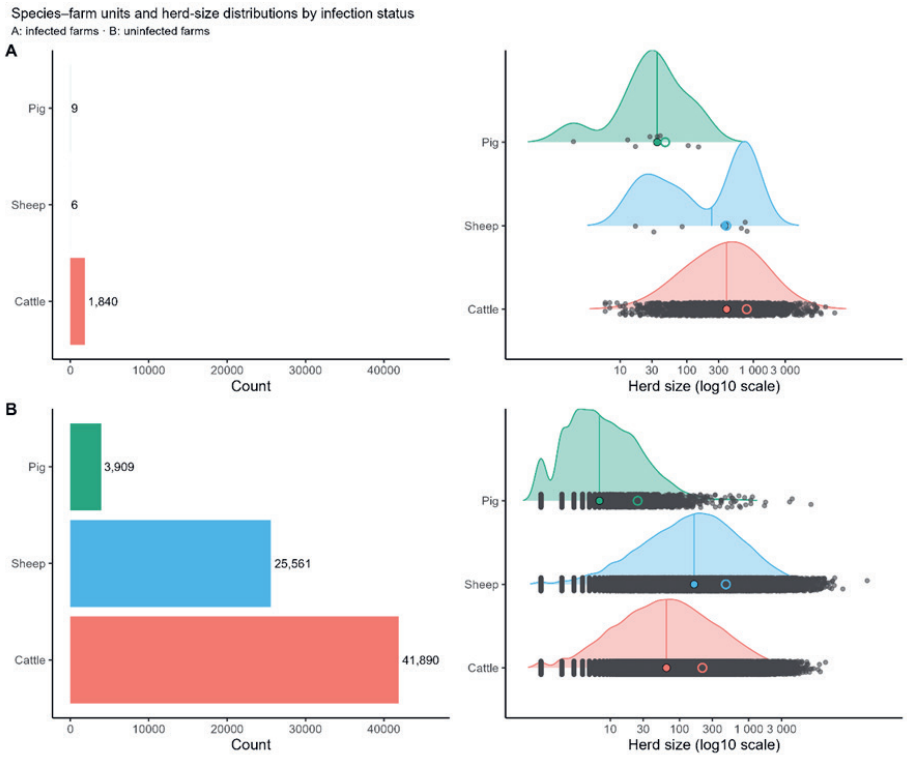


Figure 4 Farm composition and size by infection status. Row A: infected farms; Row B: uninfected farms. Left column: number of farms by species (Cattle, Sheep, Pig). Right column: farm-size distributions by species (log10 x-axis); vertical line marks the median; filled dot = median, open dot = mean. Note: among infected farms, sheep (n = 6) and pigs (n = 9) have small samples—interpret their distributions with caution.

Table 1 Species composition of farms in Uruguay in 2001. Distribution of farms (n and %) by farm type (single-species; mixed, two species; mixed, three species) and species combination. Percentages are expressed relative to the national total (N = 44,934). Data on single-species pig farms were not available in this dataset.

Type	Species combination	Farms 2001	
		n	%
Single species	Cattle	17,671	39.3
	Sheep	1,167	2.6
	Pigs	NA	NA
	Total	18,838	41.9
Mixed (2 species)	Cattle+Sheep	22,178	49.4
	Cattle+Pigs	1,696	3.8
	Sheep+Pigs	37	0.1
	Total	23,911	53.2
Mixed (3 species)	Cattle+Sheep+Pigs	2,185	4.9
Total		44,934	

In addition to differences in farm composition and size, livestock production in Uruguay also exhibits marked spatial heterogeneity. To complement the descriptive summaries presented in Figure 4 and Table 1, Figure 5 illustrates the spatial distribution of cattle and sheep across the country in 2001. These maps show that cattle and sheep are not uniformly distributed but instead concentrate in distinct areas. Together, the farm-level composition, national distribution of farm types, and spatial density patterns provide a comprehensive overview of Uruguay's livestock production system, which is essential for understanding subsequent patterns of disease spread and control.

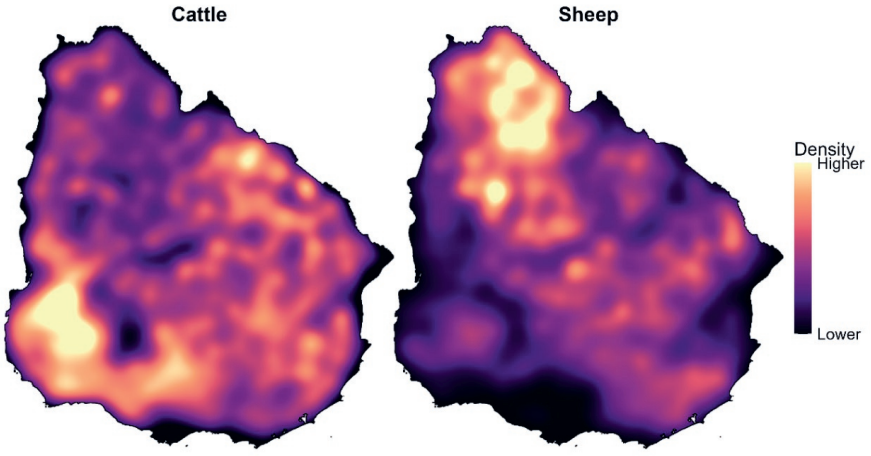


Figure 5 Spatial distribution of cattle (left) and sheep (right) density in Uruguay in 2001, showing regional heterogeneity in livestock production systems.

5. Scope and structure of the thesis

5.1. Scope of the Thesis

This thesis uses the 2001 FMD epidemic in Uruguay to improve understanding of FMDV transmission dynamics and the effectiveness of control measures in order to enhance emergency response strategies for future outbreaks. While much of the existing literature focuses on the 2001 epidemic in the UK, this research provides a complementary perspective based on a pasture-based livestock production system. Additionally, the use of cattle vaccination to control the epidemic offers valuable insights into the effectiveness of vaccination in emergency scenarios that are relevant beyond the Uruguayan context.

The scope of this thesis encompasses an in-depth analysis of the 2001 FMD epidemic in Uruguay, focusing on assessing the key factors associated with farm infection, examining the role of animal movements in the spread of FMDV between farms during the high-risk period, estimating between-farm transmission parameters, assessing the effectiveness of vaccination, and using simulation models to evaluate the effectiveness of different intervention scenarios.

The evidence generated supports improved preparedness by informing risk-based surveillance, guiding decisions on control measures, and contributing to contingency planning in regions with production systems similar to Uruguay, such as South America, Australia, and comparable settings.

5.2. Structure of the Thesis

Chapter 2: ***Main factors associated with foot-and-mouth disease virus infection during the 2001 FMD epidemic in Uruguay.***

In this chapter, we identified the main risk factors associated with FMDV infection during the 2001 epidemic in Uruguay. To address uncertainty in infection timing, farm-level dates of virus introduction were reconstructed and used throughout the analysis. The epidemic was divided into four periods: (1) the high-risk period (HRP), between virus introduction and detection of the index case; (2) the local control measures period (LCM), covering the initial control actions before mass vaccination; (3) the first mass vaccination round; and (4) the second mass vaccination round. Risk factors for infection and spread were evaluated across these periods.

Chapter 3: ***Animal Movements and FMDV Transmission during the High-Risk Period of the 2001 FMD Epidemic in Uruguay***

In the 2001 FMD epidemic in Uruguay, many farms were infected before the first outbreak was detected and a movement ban imposed. Prior movements of infected animals likely contributed significantly to disease spread. The aim of this study was to describe, visualize, and analyse the network of livestock movements between livestock premises during the initial phase of the 2001 FMD epidemic in Uruguay and gain insight into the risk of transmission by estimating the between herd basic reproduction number (R_H) before a ban on animal movements was implemented. Additionally, we analysed the current (2022) network of livestock movements in Uruguay, for the same period as in 2001, and estimated R_H assuming the same probability of infection as in 2001.

Chapter 4: Effectiveness of emergency vaccination in controlling a foot-and-mouth disease epidemic in a previously FMD-free country without vaccination

Vaccination has played a critical role in FMD control in Europe and South America and is among the options considered for outbreaks' control in previously FMD-free countries. While mathematical models help to evaluate emergency vaccination strategies, accurate vaccine effectiveness data is essential. Experimental studies confirm that FMD vaccines, especially in cattle, are effective, yet data on their effectiveness when used during emergency responses in FMDV-free areas are limited. In our study, we conducted a retrospective analysis to assess the effectiveness of commercial vaccines applied as an additional measure to control the 2001 epidemic in Uruguay. This was done by evaluating the reduction in the transmission rate parameter for between-farm transmission. Our research provides data for parameterizing and refining outbreak response models, supporting the design of effective control strategies. By improving the accuracy of transmission models, these findings contribute to enhancing preparedness and decision-making in FMDV-free regions facing potential incursions.

Chapter 5: Evaluating FMDV control strategies with a kernel-based transmission modelling approach: A case study in Uruguay

The 2001 FMDV epidemic in Uruguay, which at the time was FMDV-free without vaccination, provides field data to characterise between-farm transmission in pasture-based livestock production systems and to evaluate control strategies. Using these data, we estimated competing phase-specific spatial transmission kernels for the pre-vaccination (Phase 1) and post-vaccination (Phase 2) periods and quantified the effects of farm size and species on the probabilities of transmitting infection (infectiousness) and becoming infected (susceptibility). We used the selected kernels to compute farm-specific reproduction numbers ($R_{h,i}$) and construct risk maps for 2001 and 2023. In addition, the kernels were used to parameterise an individual-farm stochastic model to compare 13 scenarios that combined different control approaches. These included culling of infected farms only, pre-emptive culling within 1 km, emergency ring vaccination within 1, 3, or 10 km, preventive risk-based vaccination targeting farms with $R_h \geq 0.8$, and preventive vaccination stratified by farm size. These results provide model-ready parameters to support preparedness in FMD-free regions.

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Chapter 2

Main factors associated with Foot-and-mouth disease virus infection during the 2001 FMD epidemic in Uruguay

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Abstract

Large epidemics provide the opportunity to understand the epidemiology of diseases under the specific conditions of the affected population. Whilst foot-and-mouth disease (FMD) epidemics have been extensively studied in developed countries, epidemics in developing countries have been sparsely studied. Here we address this limitation by systematically studying the 2001 epidemic in Uruguay where a total of 2,057 farms were affected. The objective of this study was to identify the risk factors (RF) associated with infection and spread of the virus within the country. The epidemic was divided into four periods: (1) the high-risk period (HRP) which was the period between the FMD virus introduction and detection of the index case; (2) the local control measures period (LCM) which encompassed the first control measures implemented before mass vaccination was adopted; (3) the first mass vaccination, and (4) the second mass vaccination round. A stochastic model was developed to estimate the time of initial infection for each of the affected farms. Our analyses indicated that during the HRP around 242 farms were probably already infected. In this period, a higher probability of infection was associated with: (1) animal movements [OR: 1.57 (95% CI: 1.19–2.06)]; (2) farms that combined livestock with crop production [OR: 1.93 (95% CI: 1.43–2.60)]; (3) large and medium farms compared to small farms (this difference was dependent on regional herd density); (4) the geographical location. Keeping cattle only (vs farms that kept also sheep) was a significant RF during the subsequent epidemic period (LCM), and remained as RF, together with large farms, for the entire epidemic. We further explored the RF associated with FMDV infection in farms that raised cattle by fitting another model to a data subset. We found that dairy farms had a higher probability of FMDV infection than beef farms during the HRP [OR: 1.81 (95% CI: 1.12–2.83)], and remained as RF until the end of the first round of vaccination. The delay in the detection of the index case associated with unrestricted animal movements during the HRP may have contributed to this large epidemic. This study contributes to the knowledge of FMD epidemiology in extensive production systems.

KEYWORDS: foot-and-mouth disease (FMD), risk factors, epidemic, high risk period, FMDV infection

1. Introduction

Foot-and-mouth disease (FMD) is a transmissible viral disease that globally affects cloven-hoofed animals, including domesticated and wildlife species [1,2]. FMD continues to be one of the most important diseases of livestock worldwide as it limits international trade in animals and animal products, causes productivity losses and is costly to control [3]. In short, a foot-and-mouth disease virus (FMDV) outbreak in a FMDV free country that produces livestock for export has enormous economic consequences for that country. This is certainly true in the case of Uruguay, which is recognized as an FMD free country with vaccination by the World Organization for Animal Health (WOAH, formally known as OIE), and for which the exports of livestock products represent around the 30% of the country's total value exports [4].

During the first decade of the 21st century, FMDV has caused concern worldwide as it has appeared in previously FMDV-free territories. This occurred in the United Kingdom (UK) in 2001, which led to introductions in other countries of the European Union (EU), such as France, Ireland and The Netherlands [5,6]. Other large epidemics also occurred in free countries in South America, one of those countries being Uruguay, which was considered a FMDV-free country without vaccination since 1996 by the WOAH. However, in October 2000 Uruguay experienced a minor and localized outbreak of FMDV type O, which was controlled by stamping out, movement restrictions and disinfection [7]. The country achieved eradication and regained the FMDV-free status without vaccination by WOAH in January 2001. In April 2001 a new epidemic of FMDV type A started in Uruguay. This epidemic followed an ongoing FMDV type A epidemic in Argentina, which started some time before January 2001 [8]. During this epidemic, 2057 farms were affected in Uruguay.

Large epidemics provide the opportunity to understand the epidemiology of diseases under the specific conditions of the affected population. The identification of disease risk factors from data generated during epidemics can be useful to generate recommendations for future outbreaks and to guide effective surveillance systems as well.

Several researchers have reported risk factors associated with FMDV infection. Cattle herds and large farms were more strongly associated with outbreaks during the 2001 epidemic in UK [9]. The structure and density of the production sector in a country are also likely to be risk factors for infection. For example, most infected herds in the 2001 epidemic in the Netherlands were dairy farms [6], whilst beef farms, in a region of high density of cattle and pig farms, were the most affected farms during the 2010 epidemic in Japan [10]. Yang et al, [11] observed that high density areas of pig herds were the most affected in the 1997 FMD epidemic in Taiwan. The variable most strongly correlated with the spatial risk of outbreaks during the 2001 FMD epidemic in Argentina was cattle herd density [12]. Similarly, it was shown that high farm density areas in The Netherlands would remain high risk areas if EU standard interventions are taken during a FMD epidemic [13]. The relevance of farm density was also considered during the localized FMD outbreaks detected in UK in 2007. This minor epidemic involved eight outbreaks. Analysis of this epidemic led to the conclusion that the low density of cattle herds of the affected area combined with effective control measures, may explain why the virus did

not spread more widely [14]. In addition, some variables related with indirect transmission were reported as FMDV risk factors in the 2007 FMD epidemic in the UK. The risk of inadequate biosecurity was measured by indicators such as: location of car parking in relation to livestock areas, the presence of gates or physical barriers and whether farms were located next to public roads [14]. Likewise, during the 2010 FMD epidemic in Japan [10] it was observed that physical barriers were found to be a protective factor, whereas the movement of people, vehicles and farm equipment were risk factors.

Whilst FMD epidemics have been extensively studied in developed countries, epidemics in developing countries have been sparsely studied. Here we address this limitation by systematically studying the historic 2001 epidemic in Uruguay. This paper aims to contribute to the knowledge of the epidemiology and transmission of FMDV in extensive production systems. The objective of this study was to identify the risk factors associated with infection and spread of the virus within the country.

2. Materials and methods

2.1. The epidemic

The description of the epidemic was provided by the Epidemiology Department of the General Directorate of Livestock Services of the Ministry of Livestock, Agriculture and Fisheries of Uruguay [15].

On 23 April 2001, a suspicion of FMD occurrence was reported. The Veterinary Services investigated and clinically confirmed the disease on 24 April 2001. The official laboratory (DILAVE) confirmed the diagnosis by serology, identifying antibodies against type A virus on 25 April 2001. On 3 May, serotype A was confirmed by The Pan American Center for Foot-and-Mouth Disease (PANAFTOSA) [16].

The index case was confirmed in Soriano which is a Department located southwest of Uruguay at the border with Argentina. The most probable hypothesis established by the Official Veterinary Services was that the FMDV was introduced by fomites from Argentina. This hypothesis was supported by the fact that the virus type identified was the same in both countries and no live animal movements from Argentina to Uruguay were observed during or shortly before the high-risk period (HRP), which is the period between the virus introduction and the index case detection. The border administrative departments of Soriano and Colonia (southwest of Uruguay) involve intense cross-border movement of tourists, hunters and people related to the agriculture sector.

First, authorities sought to control the disease without vaccination, implementing measures such as ban of animal, animal products and people movements, culling the clinically affected and in contact FMDV susceptible animals within the outbreak and the application of biosecurity measures. In addition, a ring vaccination within a 10 km radius around outbreaks was implemented on 26 April. The ban of animal movements was enforced locally for three days, but then on 27 April 2021 this measure was extended at a national scale. On 30 April the measures changed, stamping out was stopped and emergency vaccination within an extensive buffer zone was enforced, which aimed to stop the FMDV spread from southwest to northeast. Later in the epidemic, infection appeared to keep spreading and on 5 May 2001 a mass vaccination of the entire national cattle population was adopted, which was completed on 7 June. The ban on animal movements was in place until June 7 after completing the first round of vaccination.

Animal movements were authorized under certain defined conditions and requirements, which were lifted after completing the second round of vaccination. The second round of mass vaccination was implemented from 15 June to 22 July 2001.

The epidemic duration was 119 days, with the last outbreak being reported on 21 August 2001. At the end of the epidemic, the total number of FMDV infected farms (outbreaks) was 2057. The epidemic curve, i.e. the distribution of outbreaks over time, has a steep increase and a long tail. The number of newly detected outbreaks increased from the first outbreak until the 25 of May, when the number of detected outbreaks reached the peak (65 farms/day). The declining phase was longer than the initial growth and reached a steady one to eight outbreaks per day for two months from 29 June (Figure 1).

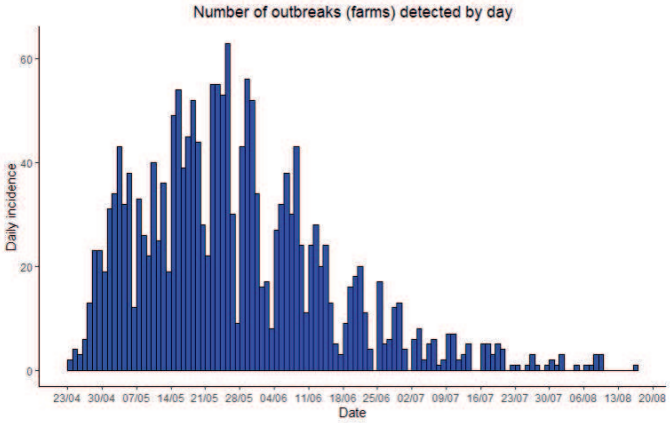


Figure 1 Time series of the number outbreaks (farms) detected per day in the 2001 epidemic by date of report

2.2. Data source

In this study, the start of an FMDV epidemic was defined as an infected herd officially diagnosed either clinically or serologically. During the epidemic, the Veterinary Services gathered the information for each infected herd. It consisted of a farm unique identifier, the geographical location, and farm´s stock and production information, such as animal numbers, animal species kept, the number of animals identified as infected by clinical inspection per species present, and the day of FMD/FMDV detection in the farm. The data also contained an assumed day of the onset of symptoms for each infected premise, which was estimated by the veterinary officer during the outbreak visit. These official reports were merged with the data on the location and livestock composition for all Uruguayan farms that kept cattle or sheep in 2001 (DICOSE Annual Affidavit, 2001). Only those records that had complete information were considered for the analysis.

2.3. Data analysis

2.3.1. FMDV introduction model

Preliminary investigation of the available data indicated some limitations. One was uncertainty about a more exact date of onset of symptoms in each farm based on age of FMD lesions. For several reports onset of symptoms was reported as the first day of the visit to an infected farm which was unlikely as there were already large numbers of clinically infected animals. This observation may indicate a longer period of infection in

the farm than was reported. Therefore, a mathematical model was developed to estimate each farm's infection dates.

A simple stochastic susceptible-exposed-infectious-removed (SEIR) model considering only the cattle population was used to describe the transmission of FMDV within herds [17-20] The model and its parameters are presented in supplementary information (S1, Table S2).

For simplification, we only considered the cattle population based on the fact that cattle was the most affected species during this epidemic (attack rate cattle: 5%, attack rate sheep: 0.02%). The stochastic model was performed for six scenarios that were set based on three different farm sizes of dairy and beef farms. By using these scenarios, the difference in the within farm transmission of FMDV between dairy and beef production systems was considered. Subsequently, we explored the time distribution for different accumulated numbers of clinical infectious bovines (CI), since the goal was to estimate the time of FMDV introduction based on the number of diseased animals. Finally, the mean time for each scenario was used to create general rules that were applied to the dataset to estimate each farm's infection dates. These analyses were performed in R version 4.0.4. [21].

2.3.2. Identification of risk factors

For this part of the study, the epidemic was divided into four periods in terms of the control measures implemented: 1) The high-risk period (HRP) corresponded to the period between the FMDV introduction and the index case detection when control measures were not yet taken. 2) The local control measures period (LCM) referred to the period between the first outbreak detection and the mass vaccinations implementation. 3) First (dose) mass vaccination round and 4) Second (dose) mass vaccination round.

First, the association between the FMD status of the farms (infected/not infected) and potential risk factors was assessed using a multivariable logistic regression model for the HRP. Our model building and variable selection approach started from formulating a hypothesis based on prior knowledge of FMD epidemiology, followed by careful control for confounders. To control confounding, we mainly considered the biological interpretation taking into account the causal structure underlying the hypothesis. First, an univariable analysis was performed and variables with a P value <0.20 were eligible for inclusion into the multivariable model. The assumption of linearity of continuous variables included in the analysis (herd density, farm size, and cattle young stock proportion) was assessed by plotting the midpoints of the quartiles vs. the logit for infection. To account for deviations in linearity, natural cubic splines or categorization on continuous variables were used. Additionally, biologically significant variables were evaluated as effect modifiers and were retained in the model if the P value was <0.05. Variable significance was assessed using the Likelihood Ratio Test (LRT). The overall fit of the model was evaluated by the Hosmer–Lemeshow goodness-of fit test [22] and the area under the ROC (Receiver Operating Characteristic) curve. Correlation between continuous variables were examined using the Pearson´s coefficient, while chi-squared were used to assess the relation between categorical predictors.

The following eight variables were selected to build the multivariable model for the HRP: (1) cropping farms as a categorical variable (no/yes: farms that combine livestock

production with cropping); (2) herd density as a continuous variable (total number of farms divided by the police section area[1] (in km2)); (3) farm size representing the number of cattle and sheep as a categorical variable (<36/ 36-134/134-463/>463); (4) species as a categorical variable (mixed:cattle&sheep/only cattle/sheep only); (5) animal movements as a categorical variable (no/yes) ; (6) the distance from farms to main routes as a categorical variable (<100 m/ >=100m); (7) the presence of pig as a categorical variable (no/family(<19 pigs)/company(>19 pigs)); and (8) the geographic coordinates (x and y) as natural cubic splines. Interaction terms between herd density and farm size, cropping and species, cropping and farm size, cropping and pigs, species and farm size, species and pig, pig and farm size were also investigated.

A multivariable model including the same variables as the HRP model was applied for each of the epidemic periods: LCM, first and second round of mass vaccination.

Finally, we created a subset of data to explore the risk factors associated with infection in those farms with at least one bovine i.e. cattle only herds and cattle and sheep herds. We considered two extra variables for this model: (1) the production system including beef, dairy and mixed categories, and (2) the proportions of cattle under two years of age as a continuous variable. A higher proportion of young stock (cattle between 12 and 24 months) in a herd was previously reported as high risk of increasing the susceptibility to infection by FMDV [14,20]

All analysis were conducted in R version 4.0.4. by using the following main packages: “car”, “ROCR”, “rms“, “splines” and “tidyverse” [21,23-26].

3. Results

3.1. Summary description of the data

We analyzed a dataset with 1,867 outbreaks (farms) and 43,068 uninfected farms. Although 2057 farms were affected during the epidemic, we considered only those records that had complete information. The dataset only considered farms that had at least one cattle or one sheep, i.e. it was not including those farms that raised only pigs. Farms that kept pigs only were not affected during the 2001 FMD epidemic.

In Uruguay, in 2001, there were more than 10.7 million cattle in 43,724 farms, around 12 million sheep in 25,594 farms, and almost 100,000 pigs in 3,461 farms (DICOSE Annual Affidavit, 2001). Most of the farms produced beef with cattle raised on grazing land under natural conditions. Generally, this type of farms (beef) raised cattle and sheep (mixed). Pigs were less relevant in terms of number of animals and farms (Table 1).

[1] The police section is an area that corresponds to the police precinct to which jurisdiction the farm is subject. It is used as the smallest administrative area in Uruguay.

Table 1 Number of outbreaks and uninfected farms during the entire epidemic considering the species kept, the farm size distribution and the production system within them.

Species	Outbreak	Number of farms	Farm size med (IQR)	Number of animals	Production System (farms)		
					Beef	Dairy	Mixed
Cattle	Yes	1,859	491 (199-969)	1,768,054	1,519	170	170
	No	41,865	65 (21-201)	8,951,367	37,353	3,024	1488
					Mixed[a]	Sheep only	
Sheep	Yes	1,145	449 (113-1,243)	1,149,094	1,138	7	
	No	24,449	159 (50-444)	11,000,000	23,246	1,203	
					Family	Company	
Pig	Yes	190	10 (4-23)	4,341	134	56	
	No	3,271	7 (3-19)	89,053	2,468	803	
Total farms[b]	Yes	1,867		2,921,489			
	No	43,068		20,040,420			

[a] *When we considered the species kept by farms there are 3 categories: mixed, sheep only and only cattle. In the table cattle only is not shown because it overlaps with production system (beef, dairy and mixed). Only cattle: num. of farms: (yes=722, no=18619).*

[b] *The sum of the number of farms that keep each species do not match the total farms because there were mixed farms that kept more than one species.*

During the epidemic 1,861 farms presented clinical diseased cattle, whereas only six and nine farms also showed diseased sheep and pigs, respectively. On the other hand, clinical disease was detected in all species (cattle, sheep and pig) only in one farm. The proportion of the variables of interest among outbreak farms and uninfected farms for each epidemic period are presented in supplementary information (Table S9-12).

3.2. Time of introduction of infection in each farm

We created general rules by using the results of the FMDV introduction model that were applied to the original dataset to estimate each farm's infection date (Table 2).

Table 2 General rules created by using the results of the FMDV introduction model, which were used to estimate approximate each farm´s infection dates. A simple stochastic susceptible-exposed-infectious-removed (SEIR) model considering only the cattle population was used to describe the transmission of FMD virus within herds.

Number of diseased animals	Estimated time of FMDV introduction (days before recorded visit)	
	Dairy	Beef
< 5	7	8
5 – 15	10	10
15 – 39	12	12
>39	13	14

The results for each scenario are presented in supplementary information (Table S3-8). These new estimated approximate dates of infection were applied to the dataset, and outbreaks were assigned to four consecutive epidemic periods (Table 3).

Table 3 Number of outbreaks and negatives farms for each epidemic period in Uruguay in 2001, including its duration and the number of outbreaks per day.

	HRP	LCM	FirstVAC	SecVAC
Uninfected farms	44693	44306	43205	43068
Outbreaks	242	387	1101	137
Duration (days)	15	10	33	44
Outbreaks/day	16	39	33	3

The results showed that probably around 242 farms were already infected by the time the first outbreak was confirmed (Figure 2).

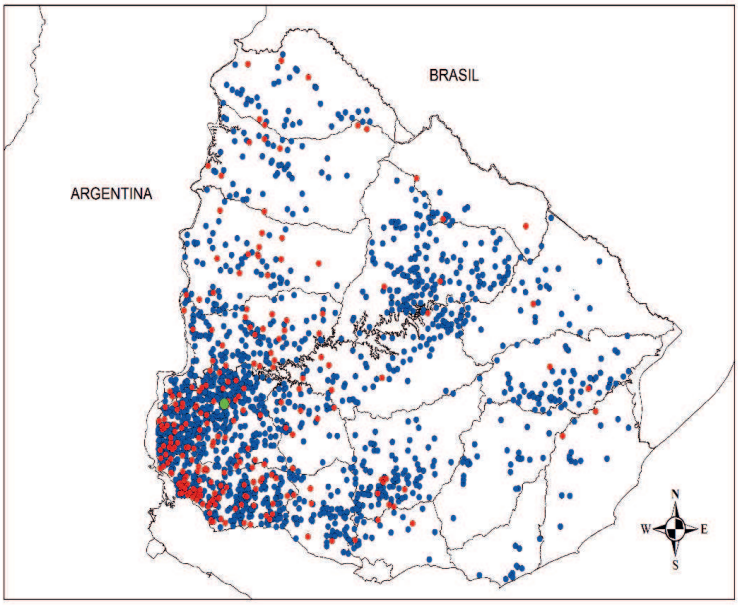


Figure 2 Spatial distribution of outbreaks. Farms that were infected during the high-risk period (HRP) are represented by red dots, while those infected in the

3.3. Risk factors for FMDV infection

We first analysed the HRP; the results of the univariable analysis are presented as supplementary information (Table S9-12). The following six variables were kept in the model for the HRP: (1) cropping; (2) herd density; (3) farm size; (4) species; (5) animal movements; (6) the geographic coordinates (x and y). The variables "distance from farms to main routes" and the presence of pig were removed from the model because there was no significant evidence of the contribution of these factors to the farm infection status. Only the interaction between herd density and farm size was considered in the model due to its epidemiological importance even though its level of significance (Chisq= 7.703, Df = 3, $p = 0.053$) was at the limit of the significance threshold $p < 0.05$.

The odds ratio (OR) of being infected with FMDV for each variable after controlling for all variables included in the model for the HRP are presented in Table 4. The odds of being infected was higher for larger farms compared to small farms, and the size of this difference is dependent on the herd density of the area that the farms were located. It can

be seen that, if the interaction between these variables is not considered, the probability of infection decreases for each farm size strata as herd density increases (Figure 3, A). However, by including the interaction term between herd density and farm size, the direction of the relationship between the probability of infection and herd density changes for the intermediate strata (36-134 and 134-463), showing a higher probability of infection as farm density increases (Figure 3, B). On the other hand, for large farms the probability of being infected decreases as herd density increases.

Table 4 Multivariable logistic regression output (OR: odds ratio) for the high-risk period (HRP).

Predictors	Odds Ratios	CI (95%)	Pr(Wald)	Pr(LRT)
(Intercept)	0.02	0.00 – 0.09	<0.001	
Cropping				<0.001
yes	1.93	1.43 – 2.60	<0.001	
Herd density	0.57	0.03 – 1.71	0.671	0.412
Farm size				<0.001
36-134	2.46	0.46 – 10.74	0.3	
134-463	6.53	1.27 – 27.98	0.029	
>463	48.56	9.39 – 210.18	<0.001	
Species				0.042
cattle	1.24	0.90 – 1.70	0.177	
sheep	0	0	0.96	
Movements				0.001
yes	1.57	1.19 – 2.06	0.001	
Latitude				<0.001
ns1[a](lat_y)	0.02	0.00 – 0.09	<0.001	
ns2[a](lat_y)	0.11	0.04 – 0.27	<0.001	
Longitude				<0.001
ns1[b](lon_x)	0.0003	1.03E-04 - 9.59E-04	<0.001	
ns2[b](lon_x)	0.03	0.004 – 0.12	<0.001	
Interaction				0.053
hd_km2:Farm_size(36-134)	2.11	0.38 – 47.61	0.575	
hd_km2:Farm_size(134-463)	1.97	0.33 – 45.01	0.615	
hd_km2:Farm_size(>463)	0.36	0.05 – 9.04	0.473	
Hosmer–Lemeshow GOF test	X-squared = 2.904, df = 8, p-value = 0.940			
Area under ROC	0.9258			

[a] Knots for natural spline (ns) effects with 2 degrees of freedom (ns(latitude, df = 2)): 6287201

[b] Knots for natural spline (ns) effects with 2 degrees of freedom (ns(longitude, df = 2)): 487821

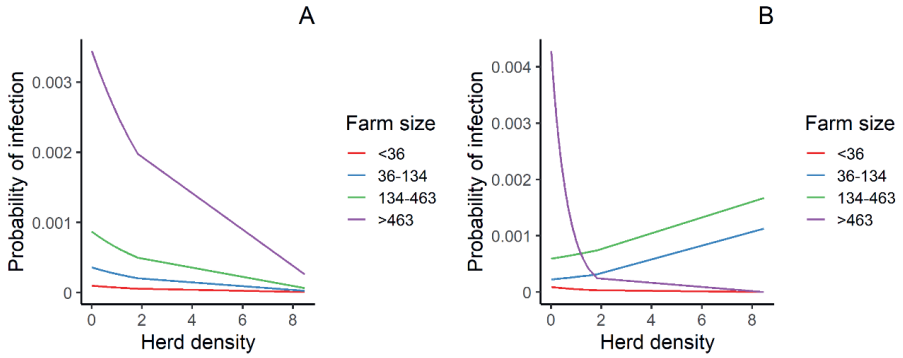


Figure 3 Predicted probability of FMDV infection for herd density across the farm size strata. (A) Model without interaction. (B) Model with interaction.

The odds of being infected for farms that combined livestock with crop production was 93% higher compared to those that did not have cropping as an activity. The odds of being infected was 24% higher for farms that raised cattle only compared to mixed farms (cattle and sheep). On the other hand, the chance of infection was almost zero for farms that raised sheep only compared to mixed farms. Interestingly, those farms with animal movements had 57% higher odds of infection than those farms without animal movements. Finally, the risk of FMDV infection was higher in the southwest and it decreases as longitude and latitude increase, from west to the east and from south to north, respectively (Figure 4).

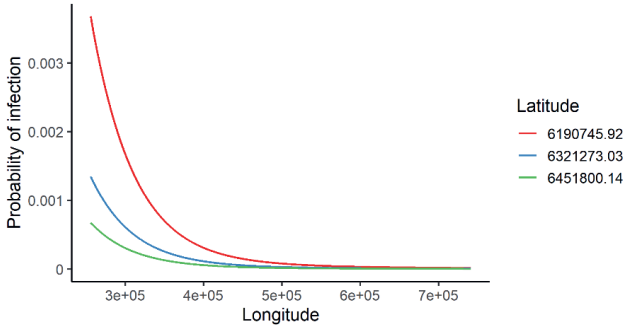


Figure 4 Predicted probability of FMDV infection during the high-risk period

For the following three periods of the epidemic multivariable models including the same variables as the HRP model were applied and the results are graphically shown in Figure 5. The findings indicated that animal movements were significantly associated with FMDV infection only during the HRP. Large farms and farms that kept cattle only remained as risk factors during the whole epidemic. Cropping farms remained at high risk over the HRP, the LCM and first vaccination periods. Finally, the risk of infection continued to decrease as the latitude increased (from south to north) throughout the entire epidemic, while for longitude (from east to west) the same effect was observed until the first vaccination period.

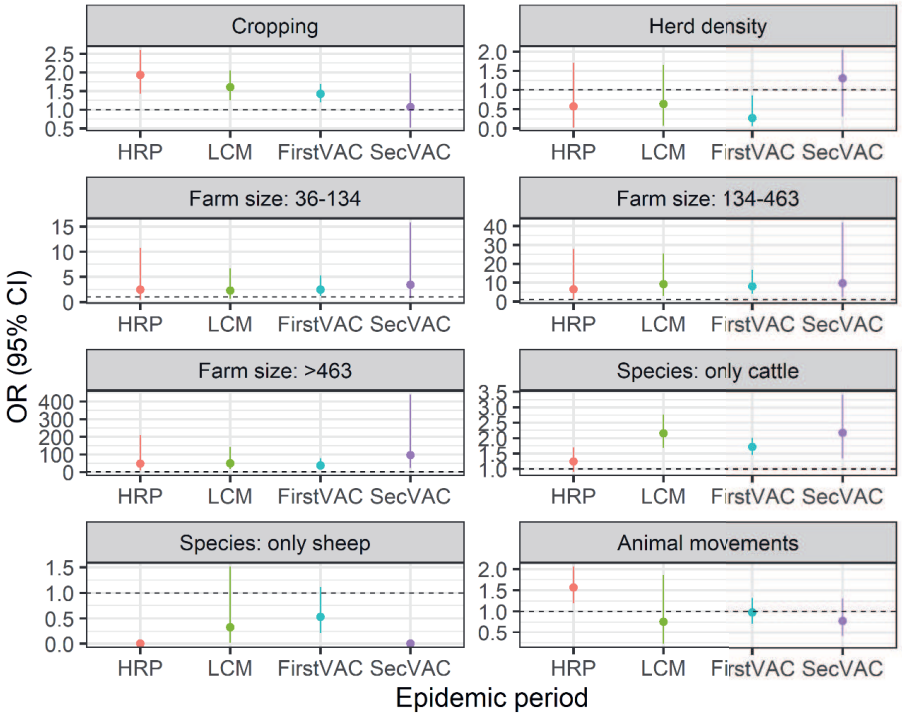


Figure 5 Odds ratio (OR) of each explanatory variables for consecutive epidemic periods. HRP, the high-risk period; LCM, local control measures period; FirstVAC and SecVAC are the first (dose) mass vaccination round and second (dose) mass vaccination round. Reference levels for categorical variables are: (1) Cropping: Farms that did not combine livestock with crop production; (2) farm size: <36 animals; (3) species: Farms that kept cattle and sheep (mixed); (4) animal movements: Farms without animal movements recorded. Regarding farm size variable, the estimated OR of "36–134" category was not significant for the HRP, LCM, and SecVAC periods, whereas was significant for the entire epidemic for categories "136–463" and ">463".

As cattle farms were at higher risk of being infected, we fitted a model using only data from cattle farms for which we considered two extra variables: (1) the production system as a categorical variable including beef, dairy and mixed (beef and dairy) categories, (2) the proportion of cattle under two years of age as a continuous variable. Both variables were significantly associated with farm FMD status in an univariate analysis. However, only the production system remained significant after controlling for other variables in the multivariable logistic regression model. During the HRP, the odds of being infected was 81% higher for dairy farms (OR= 1.81 [95%CI: 1.12 – 2.83]) and 66% higher for mixed farms (OR= 1.66 [95%CI: 1.08 – 2.49]) compared to beef farms. Moreover, dairy and mixed farms remained at high risk of infection until the first vaccination period (Figure 6).

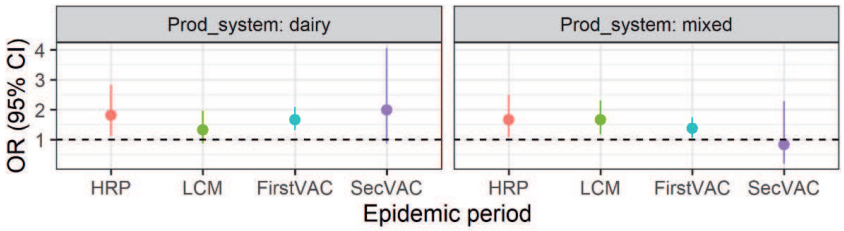


Figure 6 Odds ratio (OR) of production system being "beef" the reference, after controlling for all variables included in the model for each epidemic period. HRP, the high-risk period; LCM, local control measures period; FirstVAC and SecVAC are the first (dose).

4. Discussion

The objective of this study was to identify risk factors associated with the becoming an FMDV outbreak farm on farms during the epidemic in Uruguay in 2001.

We acknowledge some limitations. First, the date when the FMDV infects each herd, on which all epidemiological outputs were based, was not available for this epidemic. Our estimation of these dates was based on the number of cattle showing FMD-like clinical signs rather than the number of truly infected animals. The veterinary officer recorded the number of clinical diseased animals during the first visit of each infected farms. The need to implement the control measures as rapidly as possible, together with the risk of within herd transmission during animal inspection, may be the reason not to do a whole herd examination, leading to some inaccuracy in the estimation of the within herd incidence. Nevertheless, assuming that bias in this estimation were non-differential, the outputs of the analysis are unlikely to have been considerably biased. Moreover, if we had followed the approach used by Bouma et al. [6] in the analysis of FMD epidemic in the Netherlands in 2001 and assume that when only a few animals (<10) were diseased the infection started one week earlier; and when more than 10 animals were clinically affected the infection started two weeks earlier, we would have obtained similar results (data not shown). The diagnosis based on clinical signs raise another important point of discussion due to the difficulty in making clinical diagnosis in sheep as this species show less evident clinical signs when is infected with FMDV [27]. However, the veterinary services of Uruguay carried out a sero-epidemiological survey at the end of the epidemic (August 2001) to estimate the prevalence of FMDV in sheep within the outbreaks, which showed a 1.9% prevalence of antibodies against FMDV infection-associated antigen (VIAA). In addition, they tested sheep, sampling farms by geographical strata based on distance from the nearest FMD outbreaks (between 5 and 10 km, and greater than 10 km), which showed a 0.4% and 0.3% of antibodies respectively. These results support the clinical diagnosis made by veterinary officers during this epidemic (Epidemiology Department (DGSG-MGAP), personal communication, 2021).

Our analysis presented here showed that 242 farms were likely already infected at locations spread throughout the country by the time the first outbreak was confirmed. This delay in the detection of the index case probably hampered the efficacy of the first locally implemented measures and played a key role in determining the development of a large epidemic in Uruguay. The movements of animals, animal products, vehicles and

people at the time that FMDV was already introduced in the country, could have contributed to FMDV spread over long distances. A failure in early detection was reported in all other major epidemics that occurred in previously FMD-free countries [5,8,28,29]. Several factors can be related to the delay in the FMD detection such as the lack of awareness of clinical signs being the cause of suspicion of FMD in free countries, the need of high within herd prevalence to detect the disease, fear and discouragement of reporting, etc., illustrating a need to continuously improve surveillance and awareness systems.

During the HRP, the probability of being an outbreak herd was significantly associated with animal movements, farm size, the geographical location, and whether farms combined livestock with crop production. Some of these variables may be associated with the introduction of infection in the country. Since an FMD epidemic had been already ongoing in Argentina before January 2001 [8], there was no animal movement recorded between Argentina and Uruguay, and given that the virus type identified in Uruguay was the same as the one circulating in Argentina, it was hypothesized that the virus was introduced by fomites from this country. The illegal movement of animals from Argentina should be considered as other possible source for FMDV introduction. This pathway was less probably than the introduction from fomites since the border between Argentina and Uruguay consist of the Uruguay River, which functions as a natural barrier for the movement of animals. Our analysis provides some additional evidence to this hypothesis by confirming that those farms situated near the border were at higher risk of infection (higher risk observed in coordinates closer to Argentina) and by finding an association between infection and cropping activity. The latter reflects the intense cross-border movement during the HRP of people and cropping equipment and may provide an indication of indirect exposure of livestock in those farms to contaminated equipment.

Several researchers have reported high herd density as a risk factor associated with FMD [10-13]. We found that the direction and the size of the association between herd density and the probability of infection depended on farm size. We observed that high herd density was associated with FMDV infection only for medium farm size (36 – 463 animals). In contrast, we observed higher probabilities of infection for large farms (>463 animals) which were situated in low farm density areas. This may reflect that in extensive livestock production systems, where cattle are mainly raised in grazing areas, farm size is much related to land size. Therefore, farms located in high farm density areas in Uruguay are mainly small farms (< 36 animals), which did not contribute to FMDV transmission during this epidemic (less than 3% of the infected farm were small farms). On the other hand, large (>463 animals) and medium-size farms (134-463 animals) had been more affected during this epidemic. These kinds of farms may involve frequent movements of people, farm equipment and vehicles such as feed transport vehicles, which could be routes of FMDV transmission. A similar conclusion was reached in studies of the FMD epidemic in Japan in 2010 [10,30]. These results are also partially consistent with findings from studies of the epidemic in Argentina, which showed that the density of outbreaks was most strongly correlated with the distribution of large farms during and after the mass vaccination campaign [12].

The delay in the detection of FMD as well as in the enforcement of the nationwide livestock movement ban likely allowed infected animals to move between farms and to

be traded through livestock markets, contributing to the transmission of FMDV. As expected, the movements of animals were no longer a risk factor after the HRP probably due to the control measures implemented, such as banning of movement and the official control and vehicles disinfections for those movements that were officially authorized. Further research is planned to study the role played by animal movements in the FMDV spread during the HRP.

We found that cattle farms were at higher risk of infection from the end of the HRP compared to mixed farms, which kept cattle and sheep, and sheep farms. This finding is consistent with that of Bravo De Rueda et al. [31], who indicated that in this kind of mixed populations sheep play a more limited role in the FMDV transmission compared to cattle. These authors found that infectivity of sheep is lower than infectivity of cattle, while their susceptibility to FMDV is similar.

Regarding the production system of cattle herds, dairy and mixed farms, which combined beef and milk production, remained at higher risk of infection than beef farms until the end of the first mass vaccination period. This is probably related to the fact that higher frequency of different contacts between dairy herds is expected such as lorries for milk collection, veterinarian´s visits, farm equipment, people, feed transport vehicles, etc., leading to higher probabilities of transmission between these types of production. These results are in line with findings from the study of the 2001 FMD epidemic in the Netherlands [6] in which 23 of the 26 affected farms were dairy herds, and with the 2001 FMD epidemic in Argentina [12].

The presence of pigs in farms was not significantly associated with FMDV infection during the entire epidemic. Pigs are much less relevant in terms of the number of producers and animals in Uruguay compared to cattle and sheep. There were only around 100,000 pigs in Uruguay in 2001, while the cattle and sheep population stock were almost 10.6 and a 12.1 million heads, respectively (DICOSE Annual Affidavit, 2001). During the 2001 FMD epidemic in Uruguay, 112 pigs were affected in only nine of 2057 outbreaks. Therefore, the effect of high virus excretion by pigs when they are infected with FMDV and their ability to infect other animal species in [32], which was reported in the 2010 epidemic in Japan [28] could not be observed during this epidemic in Uruguay. The pig swill-feed practice could be a risk factor for introduction of FMDV and was the most likely source of infection of the index case in the 2001 FMD epidemic in the UK [5] and the FMDV type O introduction in Uruguay in 2000 [7]. The feeding of swill might be more frequently in pig´s familiar production systems (few animals) in Uruguay in 2000. However, we did not find an association between pig´s familiar production systems (defined here as farms with less than 19 pigs) and FMDV infection during the 2001 epidemic after controlling for the other variables of interest.

Researchers that analyzed the 2007 outbreak in the UK concluded that infection of secondary farms appeared to be driven mainly by biosecurity and environmental risk [14]. In our study, information regarding biosecurity measures implemented at herd level was not available and the assessment of risk factors related to fomite transmission was limited. However, we found a significant association between FMDV infection and the following factors such as cropping, farm size and production system that may indirectly indicate the contribution of lack of biosecurity, through indirect contacts, in FMDV transmission. We

also explored the role of farm distance from main routes as a factor of increasing the risk in contact between FMDV and susceptible animals but it was not significant. This may reflect the effectiveness of the measures implemented after the detection of the index case. These measures consisted of the ban of animal movements, the disinfection of vehicle wheels at farm entrances and exits, and strategic points of disinfection on routes.

Large farms that kept cattle remained at higher risk of infection during the epidemic. Similarly to the epidemic in Argentina [12], this may reflect that it is more difficult to achieve effective immune protection in such large herds compared to small herds where it is easier to achieve full vaccination of the animals. Furthermore, this may indicate the need for second rounds of mass vaccination to control large epidemics in extensive management systems.

In conclusion, our results suggest that the 2001 FMD epidemic was large as a result of a combination of factors including the delay in the detection of the index case, the movements of infected animals during the HRP, more difficult vaccination in large farms and insufficient biosecurity measures at the herd level. Large farms that kept cattle remained as risk factors for the entire epidemic, suggesting that these types of farms would need more rigorous biosecurity measures to control future FMD epidemics, and should be targeted for surveillance in surveillance systems that aim to enhance early detection of FMDV infection

The main practical contribution of our study is a better understanding of the risk factors associated with FMD infection of farms, which in combination to other epidemiological information provides support to inform surveillance and control strategies for future FMD epidemics.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Confidential database that contains exact farm location and other private information. Requests to access these datasets should be directed to unepi@mgap.gub.uy.

Author contributions

JG, MJ, AG, and MI contributed to conception and design of the study. MI organized the database and wrote the first draft of the manuscript. MI and EFC performed the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2023. 1070188/full#supplementary-material

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SUPPORTING MATERIALS

FMDV introduction model

A simple stochastic susceptible-exposed-infectious-removed (SEIR) model considering only the cattle population was used to describe the transmission of FMD virus within herds. We only considered the cattle population because this specie, together with sheep, is the most relevant livestock species in Uruguay, and cattle were the most affected during the 2001 FMD epidemic. This SEIR model is an extension of the SIR model well described by de Jong (1995), with an additional compartment that corresponds to the latent period of FMD. Briefly, susceptible animals (S) become infected after directly or indirectly contacting an infectious animal. The susceptible animals then move into a latent stage (Exposed) until they become infectious. The infectious period is split into two phases: subclinical infectious (SI) and clinical infectious (CI). As the latent period of FMD is shorter than the incubation period, spread of infection can happen before animal show clinical symptoms (Orsel, Bouma, Dekker, Stegeman, & Jong, 2009). After the clinical infectious period, individuals recover (R).

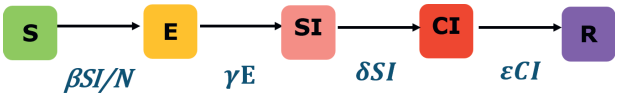


Figure S1 Schematic representation of the within-herd SEIR model with additional compartments to differentiate subclinical and clinical infectious individuals.

The parameters of the model were taken from the literature (Gonzales et al., 2014; Mardones, Perez, Sanchez, Alkhamis, & Carpenter, 2010) and are shown in Table 1. The stochastic model was performed for six scenarios that were set based on three different farm sizes of dairy and beef farms. By using these scenarios, the difference in the transmission rate of FMDV between dairy and beef production systems was considered. Subsequently, the time distribution was investigated for different accumulated numbers of CI, since the goal was to estimate the time of FMDV introduction from the number of sick animals. Finally, the mean time for each scenario was used to create general rules (see results) that were applied to the dataset to estimate each farm's infection date.

Table S1 Parameters of the FMDV introduction model.

Parameter			Source
β	transmission rate parameter R/T	Beef 0.61 Dairy 0.84	*Gonzalez et al., 2014.*
γ	1/duration of latent phase	1/3.6	*Mardones et al., 2010.*
δ	1/duration of the subclincial infectious phase	1/2	*Mardones et al., 2010.*
ε	1/duration of the clinical infectious phase	1/2.4	*Mardones et al., 2010.*

The simulation was implemented using Gillespie's algorithm. Instead of checking at each time-step if each event takes place, the Gillespie algorithm determines which of the possible events takes place and at what time (Vestergaard & Génois, 2015). The total rate (λ) is the sum of each event rates, and determines the time until the next event take place. The probability that an event happen is given by the rate of the event divided by the total

rate. Therefore, taking a random probability allows one to determine which event take place at the time given by λ.

The objective was to estimate the time of FMDV introduction based on the number of diseased animals detected by field veterinarians during visit to the infected farms. The stochastic model was performed for six scenarios that were set based on three different farm sizes of dairy and beef farms. By using these scenarios, the difference in the transmission rate of FMDV between dairy and beef production systems was considered. Subsequently, the time distribution was investigated for different accumulated numbers of CI. Finally, the mean time for each scenario was used to create general rules (see results) that were applied to the dataset to estimate each farm's infection dates.

Results

SCENARIO 1: Dairy farm, N=100

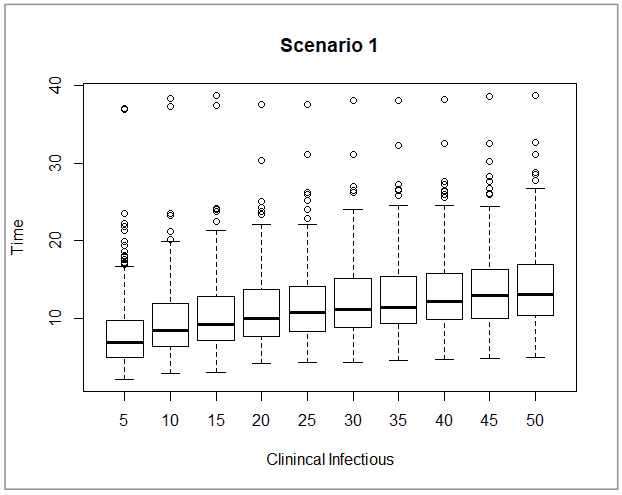


Figure S2 Boxplot summarizing the results of Scenario 1

Table S2 Summary statistics of Scenario 1

sick animals	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
5	2.093	4.972	6.892	8.035	9.719	37.121	604
10	2.868	6.424	8.431	9.529	11.883	38.319	671
15	3.083	7.133	9.256	10.483	12.847	38.816	704
20	4.176	7.694	9.936	11.147	13.700	37.540	716
25	4.327	8.344	10.792	11.762	14.129	37.546	725
30	4.361	8.850	11.178	12.285	15.193	38.148	732
35	4.601	9.408	11.378	12.765	15.442	38.148	738
40	4.755	9.841	12.197	13.268	15.757	38.214	743
45	4.816	10.063	12.901	13.721	16.349	38.677	746
50	4.901	10.383	13.095	14.122	17.005	38.705	750

SCENARIO 2: Dairy, N=200

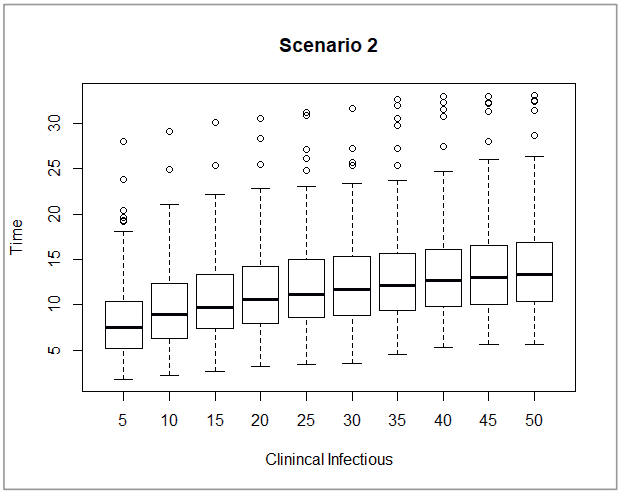


Figure S3 Boxplot summarizing the results of Scenario 2

Table S3 Summary statistics of Scenario 2

sick animals	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
5	1.757	5.200	7.483	8.175	10.365	28.016	558
10	2.195	6.248	8.923	9.644	12.356	29.149	637
15	2.705	7.373	9.725	10.646	13.324	30.163	671
20	3.203	8.001	10.634	11.483	14.267	30.570	687
25	3.469	8.582	11.159	12.136	14.980	31.243	694
30	3.571	8.901	11.684	12.572	15.327	31.703	704
35	4.487	9.401	12.170	13.080	15.677	32.615	709
40	5.295	9.778	12.738	13.426	16.123	32.963	719
45	5.610	10.073	13.025	13.805	16.566	32.970	725
50	5.622	10.391	13.355	14.198	16.854	33.148	726

SCENARIO 3: Dairy, N =405

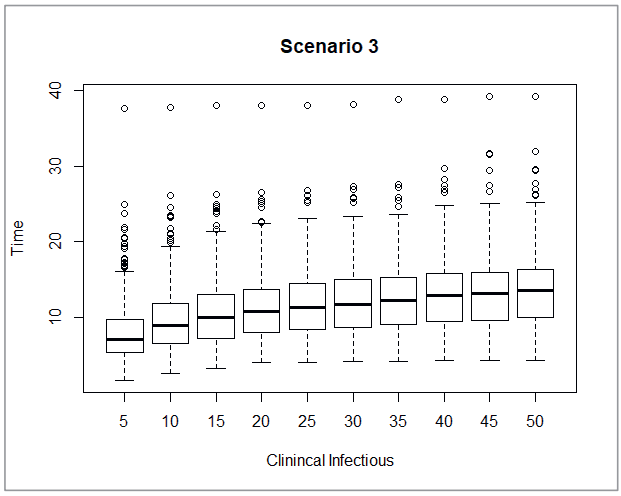


Figure S4 Boxplot summarizing the results of Scenario 3

Table S4 Summary statistics of Scenario 3

sick animals	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
5	1.566	5.289	7.049	8.033	9.706	37.604	596
10	2.482	6.437	8.886	9.578	11.731	37.740	667
15	3.240	7.208	10.001	10.603	12.927	37.979	691
20	3.977	7.897	10.703	11.292	13.714	38.031	705
25	4.020	8.317	11.239	11.846	14.435	38.078	713
30	4.102	8.676	11.717	12.326	14.974	38.184	719
35	4.129	9.016	12.224	12.759	15.264	38.807	719
40	4.188	9.390	12.882	13.206	15.742	38.852	722
45	4.194	9.583	13.118	13.565	15.958	39.166	724
50	4.224	9.998	13.462	13.935	16.359	39.268	728

SCENARIO 4: Beef, N =170

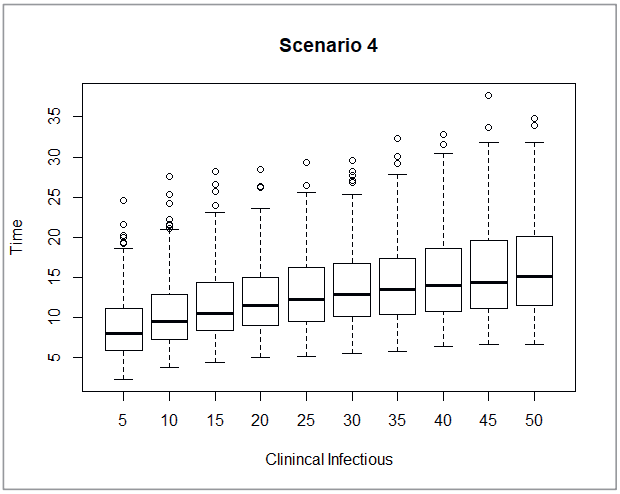


Figure S5 Boxplot summarizing the results of Scenario 4.

Table S5 Summary statistics of Scenario 4

sick animals	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
5	2.223	5.890	7.965	8.787	11.124	24.613	699
10	3.771	7.289	9.473	10.436	12.812	27.511	771
15	4.397	8.298	10.441	11.728	14.305	28.149	801
20	4.942	9.018	11.476	12.477	14.984	28.424	822
25	5.177	9.497	12.241	13.201	16.143	29.303	832
30	5.479	10.076	12.826	13.866	16.747	29.592	839
35	5.725	10.415	13.475	14.404	17.398	32.346	843
40	6.377	10.777	13.974	15.146	18.629	32.763	846
45	6.601	11.096	14.353	15.783	19.528	37.721	848
50	6.603	11.525	15.096	16.139	20.071	34.842	854

SCENARIO 5: Beef, N=456

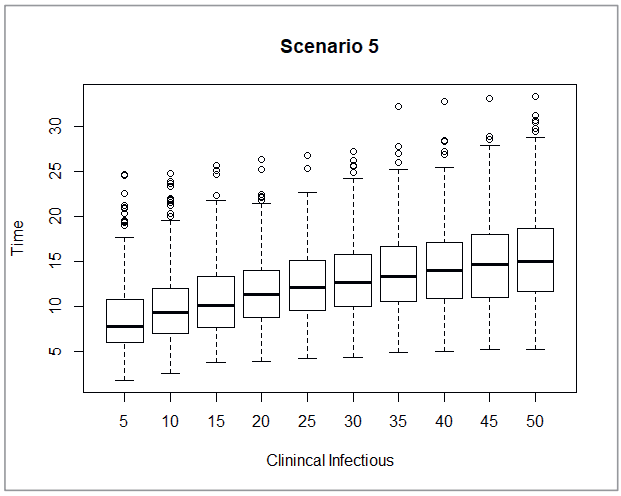


Figure S6 Boxplot summarizing the results of Scenario 5

Table S6 Summary statistics of Scenario 5

sick animals	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
5	1.732	5.999	7.772	8.632	10.761	24.607	656
10	2.551	6.923	9.280	10.069	11.957	24.729	739
15	3.707	7.676	10.083	10.975	13.256	25.632	772
20	3.861	8.787	11.299	11.780	13.950	26.359	795
25	4.226	9.489	12.075	12.486	15.050	26.719	801
30	4.326	10.007	12.614	13.266	15.700	27.219	806
35	4.877	10.522	13.362	13.917	16.630	32.220	814
40	4.978	10.825	13.981	14.496	17.085	32.789	822
45	5.180	10.985	14.676	15.118	17.923	33.145	824
50	5.195	11.619	14.945	15.676	18.665	33.356	828

SCENARIO 6: Beef, N=1050

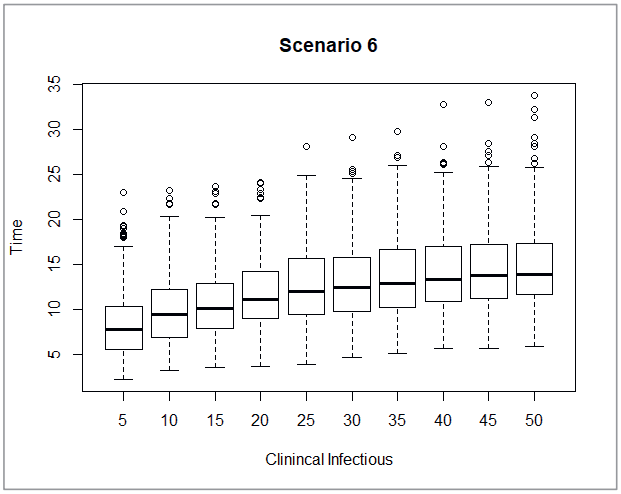


Figure S7 Boxplot summarizing the results of Scenario 6

Table S7 Summary statistics of Scenario 6

sick animals	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.	NA's
5	2.164	5.480	7.708	8.499	10.346	23.001	683
10	3.240	6.868	9.378	9.916	12.248	23.214	769
15	3.497	7.902	10.134	10.832	12.837	23.618	796
20	3.596	8.961	11.061	11.765	14.180	24.137	812
25	3.807	9.406	11.948	12.592	15.564	28.083	822
30	4.611	9.833	12.457	13.172	15.674	29.099	828
35	5.126	10.234	12.845	13.754	16.653	29.778	836
40	5.581	10.890	13.309	14.253	16.900	32.737	844
45	5.608	11.206	13.778	14.702	17.165	32.974	847
50	5.895	11.631	13.894	15.112	17.293	33.808	851

General rules

From the mean time for each scenario, we created these general rules presented in Table 8 that were applied to the dataset to estimate each farm's infection dates.

Table S8 General rules about dates of FMDV introduction created by using the results of the FMDV introduction model

Number of diseased animals	Time of FMDV introduction (days before recorded visit)	
	Dairy	Beef
< 5	7	8
5 – 15	10	10
15 – 39	12	12
>39	13	14

UNIVARIABLE MODELS

HRP

Table S9 Univariable analysis for the high-risk period (HRP)

Potential RF	Farms negatives N= 44693 n (%)	outbreaks N=242 n (%)	OR (95% IC)	ANOVA, LRT Pr(>Chi)
Herd density (cat.)				<0.01
<0.20	25.3	26.4	***Ref.***	
0.20-031	24.6	19.8	**0.772** (0.528 - 1.12)	
0.31-0.54	25.5	41.30	**1.55** (1.13 - 2.13)	
>0.54	24.6	12.4	**0.481** (0.308 - 0.736)	
Cropping				<0.01
No	92.2	55.8	***Ref.***	
Yes	7.8	44.2	**9.37** (7.24 - 12.1)	
Coordinates (splines)				<0.01
ns(lat_y, df = 2)1			**3.25** (1.40 - 7.73)	

ns(lat_y, df = 2)2			**0.04** (0.0012 - 0.0115)	
ns(lon_x, 2)1			**0.00034** (0.00012 - 0.000865)	<0.01
ns(lon_x, 2)2			**0.021** (0.0027 - 0.011)	
Distance from main routes				<0.01
>100m	87.8	76	***Ref.***	
<=100m	12.2	24	**2.26** (1.67 - 3.02)	
Animal movement (each period)				
No	80.1	50.4	***Ref.***	<0.01
Yes	19.9	49.6	**3.95** (3.069 -5.09)	
Farm size (cattle + sheep)				<0.01
<36	24.8	2.5	***Ref.***	
36-134	25.2	10.4	**4.09** (1.79 - 11.0)	
134-463	25.1	21.1	**8.39** (3.90 - 21.8)	
>463	24.9	66	**26.4** (12.8 - 67.2)	
Species				<0.01

only cattle	43.1	38.8	***Ref.***	
mixed	54.2	61.2	**1.25** (0.967 - 1.62)	
only sheep	2.7	0	**0.000000651** (8.66e-63- 9.08e-65)	
Pig				<0.01
No	92.3	85.1	***Ref.***	
family	5.8	11.2	**2.10** (1.37 - 3.08)	
company	1.9	3.7	**2.12** (1.01 - 3.91)	
Youngstock proportion				<0.01
			6.08 (3.51 - 10.4)	
Production system				<0.01
Beef	89.0	76.1	***Ref.***	
Dairy	7.3	11.1	***1.78*** *(1.15 - 2.64)*	
mixed	3.7	12.8	**4.00** (2.66 - 5.82)	

LCM PERIOD

Table S10 Univariable analysis for the local control measures period (LCM)

Potential RF	OR (95% IC)	P	ANOVA, LRT Pr(>Chi)	AIC
Herd density (cat.)			<0.01	4409
<0.20	***Ref.***			
0.20-031	**0.622** (0.461 - 0.834)	<0.01		
0.31-0.54	**1.20** (0.942 - 1.54)	0.139		
>0.54	**0.497** (0.360 - 0.680)	<0.01		
Cropping			<0.01	4214
No	***Ref.***			
Yes	**6.62** (5.35 - 8.17)	<0.01		
Coordinates (splines)			<0.01	4288
ns(lat_y, df = 2)1	**9.17** (4.46 - 19.2)	<0.01		
ns(lat_y, df = 2)2	**0.0077** (0.0025 - 0.0216)	<0.01		
ns(lon_x, 2)1	**0.0012** (0.0006 - 0.0022)	<0.01	<0.01	3908

ns(lon_x, 2)2	**0.099** (0.035 - 0.245)	<0.01		
Distance from main routes			<0.01	4426
>100m	***Ref.***			
<=100m	**1.94** (1.51 - 2.47)	<0.01		
Animal movement (each period)			0.370	4450
No	***Ref.***			
Yes	**1.63** (0.50 -3.85)	0.33		
Farm size (cattle + sheep)			<0.01	4113
<36	***Ref.***			
36-134	**3.04** (1.59 - 6.30)	<0.01		
134-463	**8.77** (4.92 - 17.4)	<0.01		
>463	**22.7** (13.03 - 44.17)	<0.01		
Species			<0.01	4437
only cattle	***Ref.***			
mixed	**0.918** (0.751 - 1.12)	0.402		
only sheep	**0.0881** (0.00501 - 0.392)	0.015		

Pig			0.014	4444
No	***Ref.***			
family	**1.46** (0.988 - 2.07)	0.046		
company	**2.00** (1.11 -3.30)	0.012		
Youngstock proportion			<0.01	4412
	4.20 (2.69 - 6.50)	<0.01		
Production system			<0.01	4306
Beef	***Ref.***			
Dairy	***1.26*** *(0.85 - 1.79)*	0.23		
mixed	***3.69*** *(2.66 - 5.00)*	<0.01		

FirstVAC PERIOD

Table S11 Univariable analysis for the first vaccinarion period (FirstVAC)

Potential RF	Farms negatives N= 43205 n (%)	outbreaks N=1101 n (%)	OR (95% IC)	P	ANOVA, LRT Pr(>Chi)	AIC
Herd density (cat.)					<0.01	10153
<0.20	25	34.2	***Ref.***			
0.20-031	24.6	24.3	**0.724** (0.614 - 0.849)	<0.01		
0.31-0.54	25.3	31.20	**0.902** (0.777 -1.05)	0.174		
>0.54	25.1	10.4	**0.302** (0.244 - 0.372)	<0.01		
Cropping					<0.01	10024
No	92.9	76.1	***Ref.***			
Yes	7.14	23.9	**4.08** (3.53 - 4.70)	<0.01		
Coordinates (splines)					<0.01	10009
ns(lat_y, df = 2)1			**11.6** (7.58 - 17.8)	<0.01		
ns(lat_y, df = 2)2			**0.054**(0.033 - 0.087)	<0.01		

ns(lon_x, 2)1			**0.0076**(0.0054 - 0.0107)	<0.01	<0.01	9477
ns(lon_x, 2)2			**0.158** (0.099 - 0.244)	<0.01		
Distance from main routes					<0.01	10269
>100m	88	80.8	***Ref.***			
<=100m	12	19.2	**1.74** (1.49 - 2.03)	<0.01		
Animal movement (each period)						
No	97.31	95.73	***Ref.***		<0.01	10306
Yes	2.69	4.27	**1.61** (1.18 - 2.14)	<0.01		
Farm size (cattle + sheep)					<0.01	9402
<36	25.6	2.6	***Ref.***			
36-134	25.7	10.9	**4.11** (2.78 - 6.28)	<0.01		
134-463	25.1	25.7	**9.93** (6.90 - 14.88)	<0.01		
>463	23.6	60.8	**24.96** (17.54 - 37.06)	<0.01		
Species					<0.01	10267
only cattle	43.2	37.4	***Ref.***			

mixed	54	62	**1.32** (1.17 -1.50)	<0.01		
only sheep	2.8	0.6	**0.226** (0.0892 - 0.462)	<0.01		
Pig					0.157	10313
No	92.4	91.1	***Ref.***			
family	5.7	6.3	**1.11** (0.859 -1.41)	0.409		
company	1.9	2.6	**1.43** (0.961 - 2.04)	0.062		
Youngstock proportion					<0.01	10249
			3.12 (2.38 - 4.08)	<0.01		
Production system					<0.01	10014
Beef	89.2	81.9	***Ref.***			
Dairy	7.2	9.66	***1.46*** *(1.18 - 1.78)*	<0.01		
mixed	3.6	8.45	***2.59*** *(2.06 - 3.22)*	<0.01		

SecVAC PERIOD

Table S12 Univariable analysis for the second vaccinarion period (SecVAC)

Potential RF	Farms negatives N= 43068 n (%)	outbreaks N=137 n (%)	OR (95% IC)	P	ANOVA, LRT Pr(>Chi)	AIC
Herd density (cat.)					<0.01	1821
<0.20	25	40.9	***Ref.***			
0.20-031	24.6	33.6	**0.834** (0.562 - 1.23)	0.363		
0.31-0.54	25.3	15.30	**0.370** (0.219 - 0.60)	<0.01		
>0.54	25.1	10.2	**0.248** (0.133 - 0.433)	<0.01		
Cropping					0.693	1854
No	92.9	92	***Ref.***			
Yes	7.14	8.03	**1.14** (0.577 -2.01)	0.688		
Coordinates (splines)					<0.01	1819
ns(lat_y, df = 2)1			**34.5** (9.92 - 131)	<0.01		
ns(lat_y, df = 2)2			**0.31** (0.11 - 0.86)	<0.01		

ns(lon_x, 2)1			**1.23** (0.384 - 4.30)	0.738	0.945	1856
ns(lon_x, 2)2			**0.998** (0.439 - 2.13)	0.995		
Distance from main routes					0.357	1853
>100m	88	85.4	***Ref.***			
<=100m	12	14.6	**1.25** (0.76 - 1.97)	0.344		
Animal movement (each period)						
No	94.18	89.05	***Ref.***		0.022	1849
Yes	5.82	10.95	**1.99** (1.11 - 3.29)	0.012		
Farm size (cattle + sheep)					<0.01	1701
<36	25.6	2.9	***Ref.***			
36-134	25.8	8.1	**2.73** (0.93 - 9.86)	0.085		
134-463	25.1	17.5	**6.12** (2.36 - 20.82)	<0.01		
>463	23.5	71.5	**26.76** (11.21 - 87.45)	<0.01		
Species					<0.01	1829
only cattle	43.2	26.3	***Ref.***			
mixed	54	73.7	**2.25** (1.55 - 3.33)	<0.01		

only sheep	2.8	0	**0.00000165** (6.25e-59 - 0.0317)	0.966		
Pig					0.673	1855
No	92.4	92	***Ref.***			
family	5.7	5.1	**0.896** (0.379 - 1.78)	0.777		
company	1.9	2.9	**1.57** (0.482 - 3.74)	0.373		
Youngstock proportion					0.362	1853
			1.44 (0.652 - 3.12)	0.359		
Production system					0.640	1825
Beef	89.2	91.1	***Ref.***			
Dairy	7.2	6.67	***0.90*** *(0.43 - 1.68)*	0.770		
mixed	3.6	2.22	***0.61*** *(0.15 - 1.62)*	0.401		


Chapter 3

Animal Movements and FMDV Transmission during the High-Risk Period of the 2001 FMD Epidemic in Uruguay

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Abstract

During the 2001 FMD epidemic in Uruguay, many farms were already infected and FMDV had spread throughout the country by the time the first outbreak was detected and a ban on animal movements was implemented. Before this ban, movements of infected animals between livestock premises were probably one of the main factors contributing to the spread of the disease. Understanding and quantifying this contribution allows identifying risk premises or risk areas to help policy makers to implement effective interventions and enhance targeted surveillance. The aim of this study was to describe, visualize and analyse the network of livestock movements between livestock premises during the initial phase of the 2001 FMD epidemic in Uruguay, and gain insight into the risk of transmission by estimating the between herd basic reproduction number (R_H) before a ban on animal movements was implemented. Here, we derived R_H from the average number of out contacts of infected premises and the average probability that a contact leads to infection. Additionally, we analysed the current (2022) network of livestock movements in Uruguay, for the same period as in 2001, and estimated R_H assuming the same probability of infection as in 2001. We found that the movements of infected animals during the high-risk period of this epidemic– i.e., the period between FMDV introduction and the detection of the index case – had an important contribution to the virus spread among premises (R_H=1.48). Livestock markets and highly connected farms were responsible for the early long-distance spread of FMDV. The analysis of the 2022 network shows that this network is similar to that of 2001 and highlights the importance of targeting highly connected premises, particularly livestock markets, for surveillance, target early detection and implement interventions during epidemics.

1. Introduction

Foot-and-mouth disease (FMD) is a contagious viral disease that affects cloven-hoofed animals. Susceptible animals can be infected by the direct contact with an infectious animal or by indirect contact via a contaminated environment [1-3]. The main route of transmission between farms is by the movement of infected animals. Foot-and- mouth disease virus (FMDV) also can be spread by contaminated animal products (particularly important in pigs) and by fomites such as transport vehicles, farming tools, milking machines, etc. [4,5].

In April 2001, a FMD major epidemic affected Uruguay. A previous study showed that during the high-risk period (HRP) – i.e., the period between FMDV introduction and the detection of the index case – of this epidemic, probably more than 200 farms were already infected [6]. During the HRP, between farms transmission could have taken place through movement of animals or contaminated fomites since control measures had not yet been implemented and farming activities remained unchanged.

The movement of infected animals between farms is probably one of the main factors contributing to the spread of diseases before interventions are implemented. For example, the long-distance movement of infected sheep to markets before FMDV was first diagnosed in the UK in 2001 has been reported as a determinant of the size of the epidemic, highlighting the role that livestock markets and dealers played in FMDV early spread [7].

Livestock movements can be analysed by using network analysis and graph theory, providing valuable information on the contact structure among livestock premises, on which infectious diseases can [8,9]. Knowledge of this structure allows disease dynamics modelling, which is an important tool to interpret epidemic data and to predict future scenarios to inform policy making [10,11].

Network analysis in veterinary epidemiology has been performed to assess the risk of disease spread through livestock movements and the identification of targets for surveillance and interventions [12-14]. Application of network analysis to data from epidemics can be used to gain insights in the role of animal movements in the spread of infection [15,16].

In Uruguay, a livestock stock and movement control system was established by law in 1973. Therefore, the movements of animals between farms have been recorded since many years before 2001. The availability of these data has been used by the Veterinary Services as a crucial piece of information during outbreaks investigations to trace potentially infected animals. More recently, the data of cattle movements from 2008 to 2013, was also used by researchers to analyse its patterns [17]. This study provided valuable information to identify risk farms for infection and spread of infectious diseases, and to guide the development of targeted surveillance and control interventions. However, the analysis of livestock movements during the 2001 FMD epidemic in Uruguay has not yet been performed. The analysis of this data provides the opportunity to better understand specifically the role of animal movements in the transmission of FMDV, and thus contribute to the development and parameterisation of epidemiological models of its spread.

The aim of this study is to describe, visualize and analyse the network of livestock movements between livestock premises during the initial phase of the 2001 FMD epidemic in Uruguay, and gain insight into the risk of transmission by estimating the between herd basic reproduction number (R_H) before a ban on animal movements was implemented. For this analysis, R_H is the average number of new infected farms that were caused by a typical infected farm through the movements of infected animals. This study will contribute to the parameterization of FMDV spread models that consider the contact structure among premises through animal movements, and it will provide a better understanding of the role of livestock networks during the initial phase of an epidemic.

2. Materials and Methods

2.1. Data source

The Livestock Control Office (DICOSE) under the Ministry of Livestock, Agriculture and Fishery (MGAP) manages the livestock stock and movements control system of Uruguay, which was established by law in 1973. In short, this system keeps a register of livestock owners, by assigning them a unique registration number, and who are then obliged to update their livestock stock record annually. In addition, there is an ownership and movement form for registration of livestock movements. This form contains information about livestock ownership, type of operation, the source and the recipient farm, the livestock species moved, the number of animals, the animal identification, the means of transport used, the places where the cattle will be moved from and to, who is responsible for moving the animals, and when the movement will be done. The movements can be audited at anytime and anywhere in the national territory [18].

In addition to the animal movements database, we used the database gathered by the Veterinary Services of Uruguay during the 2001 FMD epidemic to determine which farm was infected with FMDV during the HRP. These official reports were merged with the data on the location and livestock composition for all Uruguayan farms that kept cattle or sheep in 2001 (DICOSE Annual Affidavit, 2001). The 2001 data of pig only farms was not available.

2.2. Study population

In Uruguay, the farming of cattle and sheep is distributed throughout the country while pigs are less relevant in number of animals and farms. In 2001, the stocks of cattle, sheep and pigs were around 10.7 million heads of cattle kept in 43,724 farms, 12 million heads of sheep kept in 25,594 farms and almost 100,000 pigs kept in 3,461 farms (DICOSE Annual Affidavit, 2001). For this study, farms that raised cattle were classified regarding its production purpose as beef (38,872), dairy (3,194) and mixed (dairy and beef) (1,658) farms. In addition, farms were categorized into four herd size categories from the quartiles (<36 heads, 36-134 heads; 134–463 heads; and >463 heads).

For the purpose of this study, we considered the movements of life cattle and sheep during the initial phase of the 2001 FMD epidemic in Uruguay. The initial phase of this epidemic refers to the period between the estimated date of FMDV introduction (09/04/2001) and the enforcement of animal movements restrictions (27/04/2001), which occurred three days after the detection of the index case. Based on a previous study [6], the population consisted of 44,693 uninfected farms and 242 farms that were infected during the HRP.

2.3. Analysis

2.3.1. Description of livestock movements' network during the initial phase of the epidemic

First, a general directed network of cattle and sheep movements was constructed for the initial phase of the epidemic, which was named the General Network (GN). Each node represented a livestock operation (farm, livestock market or slaughterhouse) listed as a source or recipient in the animal movement database. The directed link between nodes represented the movement of livestock from source to recipient livestock operations on a specific date. Then, another network was developed after removing slaughterhouses as they were considered end points of FMDV transmission, which was named the General Network Without Slaughterhouses (GNWS). Finally, we defined a network called the Transmission Network (TN), which included all links from or to farms that were infected before the ban of animal movements was enforced. The geographical distances of livestock movements between premises were analysed for all the networks.

A more in-depth network analysis, stratified by production purpose and herd size, was limited due to the low number of movements involving dairy farms in the Transmission Network, and missing of demographic data for approximately 7% of farms that moved animals during the study period. Therefore, we only computed basic summary statistics of animal movements for these strata.

The connectivity of each farm was measured by its in-degree and out-degree. In this study, the in-degree represented the number of contacts that provide animals to a specific livestock holding (i.e., inwards livestock movements). On the other hand, the out-degree was the number of contacts that received animals from a specific livestock holding (i.e., outwards livestock movements). We further measured the betweenness for each premise of the General Network WS. The betweenness measures how frequently a vertex lies on the shortest paths between any two vertices in the network [19].

In addition, other metrics were estimated to assess the level of connectedness of the General Network WS. We estimated the average path length, which refers to the average shortest paths (number of steps) among reachable pairs of nodes in the network. This metric was compared to the average path length of 1000 random networks of same size and density as our network generated by using the algorithm developed by Erdös & Renyi [20]. We also estimated the number of nodes that can be reached in two steps from each node of the network.

We used the igraph package in R Statistical Software (v4.2.2) for these analyses [21].

2.3.2. Estimation of the basic reproduction number (R_H)

The basic reproduction number (R_0) is the average number of secondary infections caused by a typical infectious individual in a population where all other individuals are susceptible [22]. The infection process implies that susceptible individuals must have contact with an infectious individual or with infectious material of infectious individuals. In our study, we considered herds (premises) as the units of analysis. For the estimation of R_H, we assumed that susceptible premises only had contact with an infectious premise through the movements of infected animals. By definition, any infected premise through animal movements has been first infected by receiving infected animals itself before transmitting infection to other susceptible farms. This means that such a farm had at least

one inward and one outward movements [23] and its distribution of outward movements is not the distribution of outward movements in the whole population. Here we derived the reproduction number from the average number of out contacts of infected premises ($\bar{y}'$) and the probability that a contact leads to infection ($\bar{q}$) based on the approach of Diekmann et al. [23]. For the derivation details, please refer to Appendix 1.

The average number of out contacts of infected premises using that approach is:

$$\bar{y}' = \frac{cov(x,y)}{\bar{x}} + \bar{y} \quad (1)$$

Where x is the in-degree and y is the out-degree variable with the observed covariance ($cov(x,y)$) and averages ($\bar{x}$ and $\bar{y}$).

The probability that a contact leads to an infection ($\bar{q}$) was estimated from the number of farms that got infected before the movements restrictions were implemented, divided by the total number of farms included in the Transmission Network described above.

The expected number of secondary cases per primary case in the initial phase of the epidemic equals:

$$R_H = \bar{q}(\frac{cov(x,y)}{\bar{x}} + \bar{y}) \quad (2)$$

Due to the possible uncertainty around the date of infection of each farm, we also estimated R_H assuming that the virus was introduced one week earlier.

The mean of in- and out-degree and covariance between them were estimated for livestock premises in the three networks of livestock movements in 2001 (GN, GNWS and TN). Additionally, we estimated these metrics for the current network of livestock movements in Uruguay for the period between 09/04/2022 to 27/04/2022, which corresponds to the same period as the HRP of the 2001 FMDV epidemic. R_H was also estimated for current networks assuming the same probability of infection as that observed during the HRP.

3. Results

3.1. Description of animal movements during the initial phase of the epidemic

The General Network, containing all cattle and sheep movements during the initial phase of the epidemic consisted of 6,535 nodes and 7,695 links among them, with an average of 1.2 links per node, and a median of 22 animals (cattle and sheep) and a median distance of 64.9 km per link. Most of the movements involved cattle only (86%), while 11% of them were sheep only and 3% included both species. Of the total movements from farms, 48.7% were to slaughterhouses with a median of 30 animals and a median distance of 125 km, 26.5% to livestock markets with a median of 11 animals and a median distance of 49.3 km, and 24.8% to other farms with a median of 30 animals and a median distance of 45 km. (Figure 1).

From the total of farms that acted as source of animals, 89% of them corresponded to beef farms, 5.5% to dairy farms and 5.5% to mixed farms. With respect to farm size, these farms were mostly (56.2%) large farms (>463 animals). Additionally, out of the total of farms that acted as recipients of animals, 90.6% comprised beef farms, 4.6% dairy farms and 4.5% mixed farms, and mostly (49.7%) large farms (Table S1).

Regarding the overall number of livestock premises that had recorded movements during the initial phase of the epidemic, 74 were infected and 6,456 were uninfected during the HRP.

The General Network Without Slaughterhouses consisted of 4,590 nodes and 4,505 links with an average of 1.02 links per node and a median of 16 animals and a median distance of 48.3 km per link. Similarly to the General Network, 81% of the movements involved cattle only, while 15% of them were sheep only and 4% were mixed movements (cattle and sheep). Of the total of movement from farms, 47.9% were movements between farms and 52.1% from farms to livestock markets. Regarding the production purpose and the farm size, the proportion of farms of different production types and herd sizes were similar to its proportion in the General Network (Table S1). Figure 1 shows that the movements of animals between farms and from farms to livestock markets mostly comprised relative short distances and a few include long distances, being the median of the distance 45 km and 49.3 km respectively.

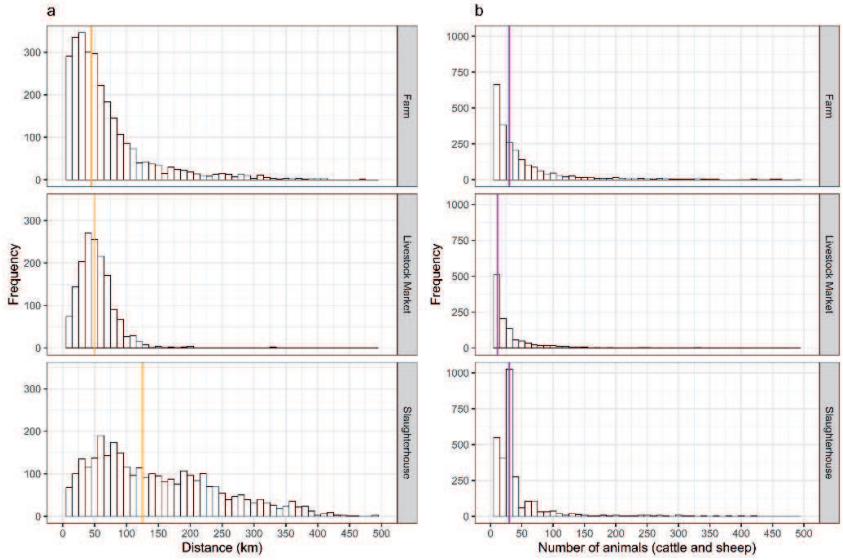


Fig. 1 (a) Distance (km) distribution of livestock movements from farms split by the type of recipient premise (farm, livestock market and slaughterhouse). (b) Distribution of the number of animals of livestock movements from farms split by the type of recipient premise. The vertical lines show the median of the distance and number of animals respectively.

We used two measures of centrality to characterise nodes that are central or important in the network: the in- and out-degree and the betweenness. A high heterogeneity in the number of contacts was found, in both in-degree and out-degree, where most premises had few links and a few had a large number of connections. Figure 2 shows the in- and out-degree distributions of premises in the General Network WS. When we considered all movements in the General Network, inwards and outwards animal movements were slightly correlated (ρ= 0.27 [95% CI (0.25 - 0.29)]). After removing slaughterhouses, inwards and outwards movements were highly correlated (ρ= 0.78 [95% CI (0.77 - 0.80)]).

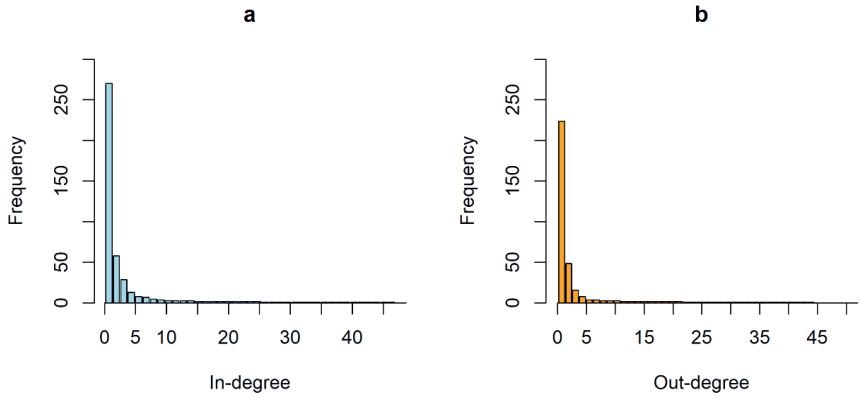


Fig.2 Degree distribution of premises after removing slaughterhouses. (a) In-degree; (b) Out-degree. In order to improve the visualization, only frequency <1500 were included.

Table 1 presents the betweenness, the in- and out-degree and the number of premises reachable in two steps for the ten premises with the highest betweenness of the General Network WS, and helps to identify the most influential vertices. It also shows the type of premise, either farm or livestock market, and the infection status during the initial phase of the epidemic (infected/uninfected). It can be seen that three of the ten premises with the highest betweenness became infected during the HRP.

Table 1 Connectedness metrics of the ten premises with the highest betweenness of the network without slaughterhouses. Type refers to the premise type, whether it is a farm or a livestock market, and the infection status indicates if the premise was infected or not during the high-risk-period.

N	Type	Betweenness	In-degree	Out-degree	Number of premises reachable in 2 steps	Infection status
1	Livestock market	40575	60	42	58	uninfected
2	Livestock market	36569	48	37	47	infected
3	Livestock market	29617	34	30	42	uninfected
4	Farm	22919	1	1	41	infected
5	Livestock market	22859	1	39	48	infected
6	Livestock market	22832	148	77	86	uninfected
7	Livestock market	20966	35	15	18	uninfected
8	Livestock market	20003	22	20	25	uninfected
9	Farm	19249	1	1	44	uninfected
10	Livestock market	18902.5	21	23	29	uninfected

Other measures were estimated to assess the level of connectedness of the General Network WS and are presented in a supplementary material. We found that 50% of

premises can only reach one or two premises in two steps, whereas the upper 25% can reach between 22 and 119 premises (Figure S1). Additionally, the average path length, which corresponds to the mean of the lengths of the shortest paths between all pairs of vertices in the network, was 4.66. This value was compared to the average path length of 1000 random graphs that were generated with the same number of vertices and the same density as the observed network. The average path length of the General Network WS was lower than the average path length of network randomizations, suggesting that the observed network is more interconnected and may facilitate the spread of the disease between premises (Figure S2).

3.2. Description of the Transmission Network

The Transmission Network consisted of premises that were infected during the HRP and all premises connected to them by animal movements between 09/04/2001 and 27/04/2001 (Figure 3). Out of the 242 farms that were infected during the HRP [6], only 34 had movements recorded during this period and are nodes of the Transmission Network. Therefore, there were no movements recorded for 208 of them. Slaughterhouses were removed as they are considered endpoints for FMDV transmission. Five livestock market were considered as infected because they received animals from infected farms. The Transmission Networks contained 320 nodes (313 farms and 7 livestock markets) and 327 links among them (1.04 links per node).

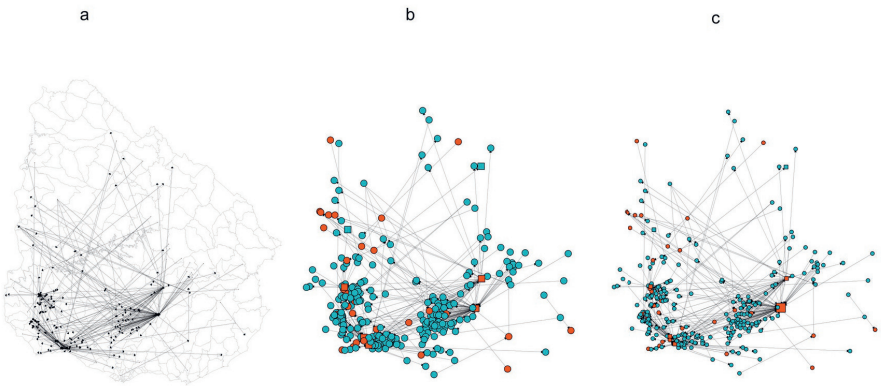


Fig. 3 Transmission Network (TN) of livestock movements during the high-risk period (HRP) of the 2001 FMDV epidemic in Uruguay (09/04/01-27/04/01). The TN consisted of premises that were infected during the HRP and all premises connected to them by animal movements during the HRP. (a) Visualization of the network by using Uruguay´s map as the layout. (b) Farms are represented by circles and livestock markets by squares. The infectious status is shown by colour; being orange, those infected premises during the HRP and light blue the uninfected ones. (c) The betweenness score determine the vertex size.

Most of the movements of the Transmission Network comprised cattle only (87.8%), whereas 9.2% sheep only and 3% involved both species (cattle and sheep). The 327 links among operations consisted of 133 (40.7%) from farms to livestock markets, 153 (46.8%) from livestock market to farms and 41 between farms (12.5%). Of the total movements from farms, 76.4% were to livestock markets with a median of nine animals and a median distance of 33.7 km, and 23.6% to other farms with a median of 33 animals and a median of 124 km of distance (Figure 4).

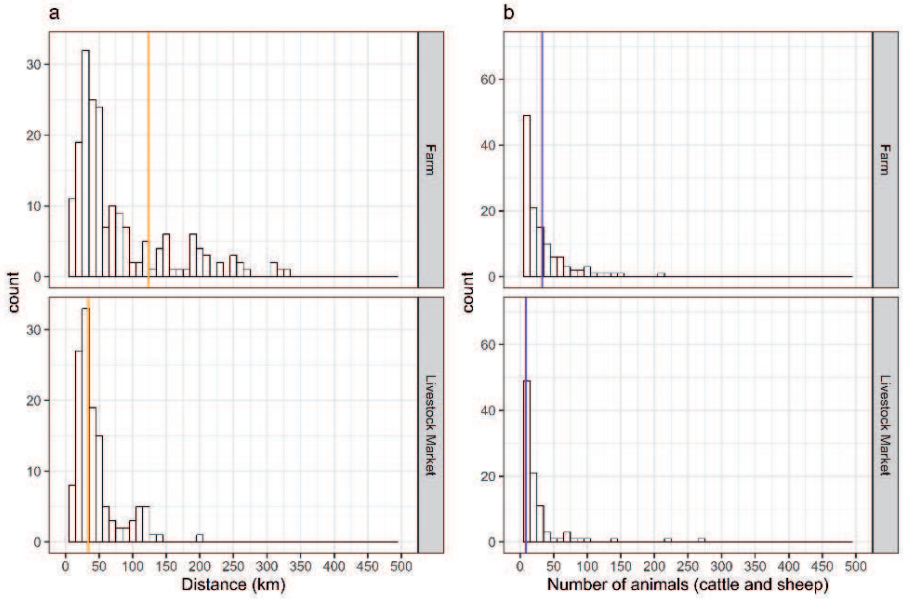


Fig. 4 (a) Distance (km) distribution of livestock movements from farms split by the type of recipient premise (farm, livestock market) in the Transmission Network. (b) Distribution of the number of animals of livestock movements from farms split by the type of recipient premise of the Transmission Network. The vertical lines show the median of the distance and number of animals respectively.

The proportion of dairy and mixed farms in the Transmission Network increased compared to the General Network and the General Network WS when farms were either source and recipients of animals. This increase was around 8% for dairy farms and around 14% for mixed farms when they acted as source of animals, and around 12% for dairy farms and around 14% for mixed farms when they were recipient farms (Table S1). As was mentioned above, the most frequent destination of animal movements from farms were livestock markets (76.4%), with this proportion within each stratum being higher for dairy farms (85.7%) than for beef farms (75%). When it came to movements towards farms, dairy farms exclusively received animals from livestock markets, whereas the movements to beef farms consisted of 25% from other farms and 75% from livestock markets (Table S2).

The in-degree and out-degree distributions of the Transmission Network are presented in Figure 5. The mean of the in- degree and out degree was 1.02 and the covariance was 11.41 (Table 2).

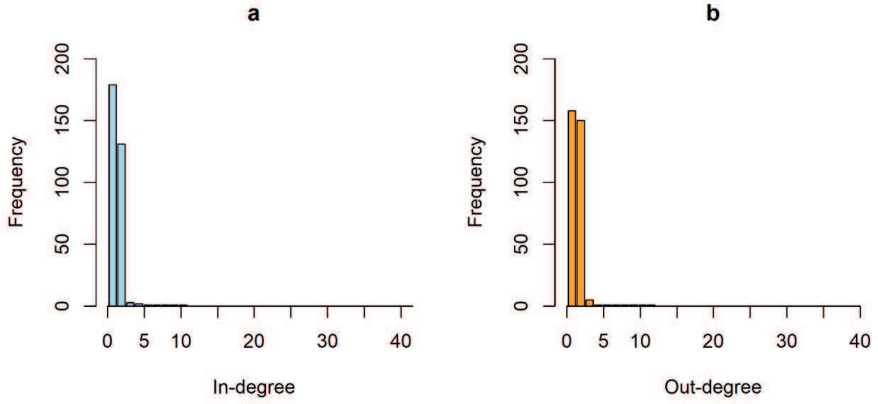


Fig. 5 (a) In-degree distribution of premises in the Transmission Network; (b) Out-degree distribution of premises in the Transmission Network.

3.3. Estimation of the herd Reproduction number (R_H)

Here we derived the Reproduction number from the average number of out contacts of infected premises ($\bar{y}'$) and the average probability that a contact leads to infection ($\bar{q}$).

The average number of out contacts of infected premises was 12.19 (Eq. 1)

The average probability that a contact leads to an infection ($\bar{q}$) was estimated from the number of farms that were infected before the movement´s restrictions enforcement (n = 39 out of the 242 farms that were infected during the HRP), divided by the total number of farms included in the Transmission Network (n = 320). The average probability that a contact leads to an infection was 0.12. The average number of new infected farms that were caused by a typical infected farm through animal movements was $R_H = 1.48$ (Eq. 2).

We found that if the virus was introduced one week earlier, the number of infected farms involved in animal movements would be 60 (out of the 242 infected farms of the HRP), and the total number of farms included in the Transmission Network would be 411, resulting in a probability of infection 0.15. In this scenario, the average number of out contacts of infected premises would be 14.8, and the estimated R_H = would be 2.16. Considering a three-week period instead of a two-week period, resulted in an increase in the number of infected farms (out of the 242 farms that were infected during the HRP) which contact other farms through animal movements, leading to a higher average of out contacts of infected premises and a higher probability that a contact leads to infection.

Table 2 Mean of in- and out-degree and covariance between them for networks of livestock movements in 2001 and current livestock movements (2022). General Network 2001 include all livestock movements in the period between 09-04 and 27-04 in 2001, which was the high-risk period (HRP) during the 2001 FMD epidemic in Uruguay. The same period of the year was considerate to define the General Network in 2022. Networks without slaughterhouses did not include movements to slaughterhouses. The Transmission Network 2001 consisted of premises that were infected during the HRP and all premises connected to them by animal movements during the HRP. The Transmission Network 2001 without livestock markets did not include the movements that involve livestock markets as source or recipients. The R_H was estimated for all networks by using Eq. 2 and assuming the same probability of infection as that in the Transmission Network (p=0.12).

Networks	Mean in-degree ($\bar{x}$)	Mean out-degree ($\bar{y}$)	$cov(x, y)$	R_H
2001				
General	1.18	1.18	7.50	0.91
General WS[a]	0.98	0.98	9.52	1.28
Transmission	1.02	1.02	11.41	1.48
Transmission WLM[b]	0.68	0.68	-0.31	0.03
2022				
General	1.23	1.23	7.06	0.84
General WS[a]	1.07	1.07	8.8	1.11
General WLM[b]	0.88	0.88	-0.09	0.09

[a] WS: without slaughterhouses. [b] WLM: without livestock markets

Discussion

The movements of infected animals played a key role in FMDV spread among premises during the HRP of the 2001 FMD epidemic in Uruguay. The similarities found between the 2001 and the current (2022) livestock networks in terms of contact heterogeneity, underscore the importance of targeting highly connected premises, particularly livestock markets, for enhanced surveillance and implement fast control measures during epidemics.

Similar to the observed livestock movement networks in the initial phase of the 2001 FMD epidemic in the UK, the network of livestock movements during the initial phase of the 2001 FMD epidemic in Uruguay has shown a high heterogeneity of contacts among premises [15]. A right-skewed distribution of both in- and out-degree was observed, where most of the premises had few connections and a few were highly connected. This high heterogeneity of contacts among premises was a pattern that has also been observed in other networks of livestock movements [14,17,24] as well as in the Uruguayan network of current livestock movements. In general, premises that have many inwards connections are at higher risk of being infected, while those with frequent outgoing movements have the potential to spread infectious agents widely. Therefore, it is important to identify

highly connected premises in advance of FMDV introduction, so they can be targeted for surveillance and education in peacetime, and for fast intervention during epidemics.

Premises that had both high in- and out-degree also tend to have high betweenness, and are likely important controlling the flow from one part of the network to another part. In other words, individuals with high betweenness have an important role by connecting different parts of a network that could otherwise be less connected. Of the ten premises with the highest betweenness of the General Network WS, eight were livestock markets and two were farms. In addition, three of these premises (two livestock markets and one farm) became infected during the HRP and played a crucial role in the spread of FMDV during the 2001 FMD epidemic in Uruguay. A similar finding was reached by Ortiz-Pelaez et al. [15] in the analysis of animal movements during the initial phase of the 2001 FMD epidemic in UK. The authors found that three of the ten premises with the highest betweenness were farms, highlighting the importance of this type of farms in the virus spread in addition to livestock markets. Intervention measures targeted to those premises with high betweenness could reduce the size of future epidemics.

The inwards and outwards movements were slightly correlated in the General Network (Pearson´s ρ= 0.27 [95% CI (0.25 - 0.29)]), and after removing the slaughterhouses this correlation substantially increased (ρ= 0.78 [95% CI (0.77 - 0.80)]) indicating that those highly connected farms were not only more likely to become infected but also to spread FMDV to other farms.

In this study, we estimated FMDV transmission through livestock movements by estimating the basic reproduction number (R_H). The high covariance between incoming and outgoing movements may explain that R_H was above one, confirming the high-risk animal movements played in sustained transmission of FMDV during the epidemic in Uruguay. Previous studies have evaluated the potential for transmission for an infection that may spread through the contact network by looking at the contribution of covariance between contact rates [25,26]. In this sense, we estimated the mean rates of contacts and the covariance between them for the network of livestock movements after removing livestock markets either as source or as recipients, to illustrate the key role that livestock market played in spreading FMDV during the initial phase of the epidemic. As expected, when we removed livestock markets, the magnitude of the covariance between contact rates resulted in a sharp decrease of R_H from 1.48 to 0.03 (Table 2). We also estimated the contact rates and covariance between them for the network of the current livestock movements in Uruguay (2022). No significant differences were found in terms of the mean contact rates and the covariance between the networks of 2001 and 2022. This suggests that if FMDV is introduced to Uruguay, finds its way to a livestock market and is not detected early, several farms may be already infected only through animal movements by the time the first outbreak is detected leading to a large epidemic as that in 2001.

While the majority of the movements (95%) occurred over a range of 37 to 129 km, 5% of them happened at 285 to 490 km. These long-distance movements may explain the large geographical spread of FMDV throughout the country during the HRP [6]. Most of the farms involved in animal movements were beef farms (around 90%) and more than half were large farms (>463 animals). However, we observed that the proportion of dairy

and mixed farms was higher in the Transmission Network compared to its proportions in the General Network and the General Network WS. This shows that dairy farms contributed to FMDV transmission through the movement of animals during the initial phase of this epidemic. This contribution may be mainly explained by the fact that dairy farms carried out more animal movements through livestock markets compared to beef farms in the Transmission Network.

We acknowledge some of the limitations of this study, which fall into two categories: related to the dataset and assumptions made for the analyses. Regarding the first, some omissions may exist in the movement dataset due to lack of movement declaration by livestock owners. These omissions may occur with very low frequency and usually comprise neighbours' farms trading, which likely involve few animals. Although these omissions, our results do provide an overall structure of the livestock movement networks and its implication in the FMDV transmission during the initial phase of the 2001 epidemic in Uruguay. In addition, uncertainty around the date of infection of the herd may also exist. For this reason, we also estimated the basic reproduction number assuming that the virus was introduced one week earlier. In this case, R_H was higher than our estimation (2.16 vs 1.48), which means that our assumed time of introduction results in a more conservative assessment of the contribution of livestock movements to FMDV spread during this epidemic. More confidence in the estimation of the time of infection would allow us to estimate a more precise probability of transmission from pairs of contacts and therefore, estimate a more accurate R_H. Regarding the assumptions made, we assumed that premises included in the transmission network were infected via livestock movements during the HRP, omitting other links between farms where infection can spread such as shared employees and equipment, the milk collection and feed transport vehicles, veterinarian´s visits and neighbouring.

Our study can contribute to a better understanding of the role of livestock movements in the spread of FMDV during the initial phase of the 2001 FMD epidemic in Uruguay when the virus was yet undetected. However, many farms that were infected during this period had not livestock movements recorded, so the movements of animals did not explain the whole transmission. This highlights the importance of other routes of transmission that involve contact links among premises that are hard to record, and reflects the need of using models able to capture it to analyse FMDV transmission between premises. Further research is planned in order to understand the overall transmission during this epidemic.

Conclusions

In conclusion, the movements of infected animals during the HRP of the 2001 FMD epidemic in Uruguay had an important contribution to the virus spread among premises. Livestock markets and highly connected farms were responsible for the early long-distance spread of FMDV before a ban on animal movements had been implemented. The analysis of the 2022 network shows that this network is similar to that of 2001 and highlights the importance of targeting highly connected premises, particularly livestock markets, for surveillance, target early detection and implement interventions during epidemics.

Appendix 1

Each premise has a certain number of contacts k (0,1,2,3 …), each number k with probability distribution P_k.

The average number of contacts is, thus, by definition $\bar{k} = \sum_{k=0}^{\infty} kP_k$, and the variance is $var\ k = \sum_{k=0}^{\infty}(k-\bar{k})^2 P_k$.

Infected premises have more contacts than other premises, i.e. k' number of contacts, with distribution $P_{k'} = \frac{kP_k}{\bar{k}}$. This is the (in)famous question why your friends on a social network site will have more friends than the average person on that site (so typical on average more than you).

For one thing, when $k = 0, P_{k'} = 0$, and premises cannot get infected.

If $k = 1, P_{k'} = \frac{P_1}{\bar{k}}$, and premises can get infected but they never will infect other premises.

The average number of contacts of an infected premise is $\bar{k'} = \sum_{k=0}^{\infty} k\ \frac{kP_k}{\bar{k}} = \sum_{k=0}^{\infty} \frac{k^2 P_k}{\bar{k}}$

Note: $var\ k = \sum_{k=0}^{\infty} k^2 P_k - (\sum_{k=0}^{\infty} kP_k)^2$

The average number of contacts of an infected premise can be expressed as

$\bar{k'} = \frac{var\ k}{\bar{k}} + \bar{k}$

As one contact is needed for infection so, the average number of contacts of an infected premise is $\bar{k'} = \frac{var\ k}{\bar{k}} + \bar{k} - 1$.

If x is the in-degree with distribution P_x ; and y de out-degree with distribution P_y. For each premise with x in-degree and y out-degree the probability is $P_{x,y}$.

For infected premises, the average number of out-contacts is given by:

$$\bar{y} = \sum_{x=0}^{\infty}\sum_{y=0}^{\infty} y \frac{x\ P_{x,y}}{\bar{x}}$$

Note: $cov(x,y) = \sum_{x=0}^{\infty}\sum_{y=0}^{\infty} xyPx,y - \sum_{x=0}^{\infty}\sum_{y=0}^{\infty} xP_x \sum_{y=0}^{\infty}\sum_{x=0}^{\infty} yP_y$

The average number of out contacts of infected premises can be expressed as (because we do not need to account for the one incoming contact in the number of outgoing contacts):

$$\bar{y}' = \frac{cov(x,y)}{\bar{x}} + \bar{y}$$

Data Availability

The data used to support the findings of this study were supplied by the Official Veterinary Services (Dirección General de los Servicios Ganaderos, DGSG) of the Ministry of Livestock, Agriculture and Fisheries of Uruguay (Ministerio de Ganadería,

Agricultura y Pesca, MGAP). It is confidential as it contains private information of livestock owners of Uruguay and so cannot be made freely available. Requests for access to these data should be made to the DGSG, MGAP, Uruguay, dgsg@mgap.gub.uy.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Acknowledgments

The authors acknowledge colleagues from the Department of Epidemiology of the Veterinary Services of Uruguay and colleagues from the Department of Epidemiology of WBVR for their scientific input for the discussions.

Supplementary Materials

Supplementary 1. Table S1: number of animal movements and proportion expressed as percentage of farms of different production purposes (beef, dairy, and mixed (beef and dairy)) and different herd sizes (463), either as source and recipient of animals, for livestock networks of the initial phase of the 2001 epidemic in Uruguay.

Supplementary 2. Figure S1: number of premises reachable in k≤2stepsfor all premises included in the general network without slaughterhouses. Figure S2: average path length of 1,000 randomly generated networks with the same number of vertices and density as the general network without slaughterhouses (GNWS) and the average path length for the observed network. Table S2: number of animal move ments and proportion expressed as percentage of farms of different production purposes (beef, dairy, and mixed (beef and dairy)) by destination of movements when farms were source, and by origin when farm were recipients, in the livestock networks of the initial phase of the 2001 epidemic in Uruguay. A text file with the R code was used for the analyses.

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Supplementary material

Table S1 Number of animal movements, and proportion expressed as percentage, of farms of different production purpose (beef, dairy and mixed (beef and dairy) and different herd size (<36, 36-134, 136-463, >463), either as source and recipient of animals, in the livestock networks of the initial phase of the 2001 epidemic in Uruguay. GN=General Network. GNWS=General Network Without Slaughterhouses. TN= Transmission Network. The GN includes all livestock movements in the period between 09-04 and 27-04 in 2001. The GNWS did not include movements to slaughterhouses. The Transmission Network 2001 included all links from or to farms that were infected during the high-risk period.

	Source				Recipient			
Production type	**Beef**	**Dairy**	**Mixed**		**Beef**	**Dairy**	**Mixed**	
	n (%)	**n (%)**	**n (%)**		**n (%)**	**n (%)**	**n (%)**	
GN	4983(89)	308 (5.5)	308 (5.5)		2352(90.6)	126(4.6)	117(4.5)	
GNWS	2496(89.8)	136(4.9)	146(5.3)		2352(90.6)	126(4.6)	117(4.5)	
TN	112 (68.3)	21(12.8)	31(18.9)		115(64.6)	30(16.9)	33(18.5)	
Farm size	**<36**	**36-134**	**134-463**	**>463**	**<36**	**36-134**	**134-463**	**>463**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
GN	294(5.2)	728(12.9)	1446(25.7)	3168(56.2)	242(9.2)	440(16.7)	642(24.4)	1309(49.7)
GNWS	166(5.9)	418(14.9)	862(30.8)	1357(48.4)	242(9.2)	440(16.7)	641(24.4)	1308(49.7)
TN	14(8.5)	43(26)	43(26)	65(39.5)	22(12.1)	42(23.1)	42(23.1)	76(41.8)

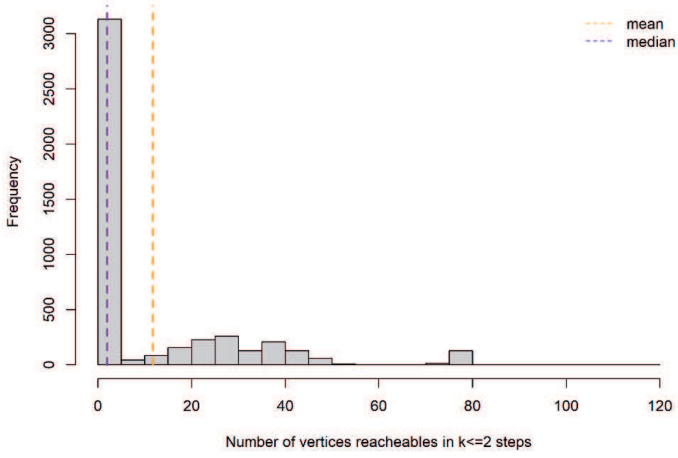


Fig. S1 Number of premises reachable in k<=2 steps for all premises included in the network after removing slaughterhouses (GNWS). The mean (12 premises) is shown in orange, while the median (2 premises) in purple.

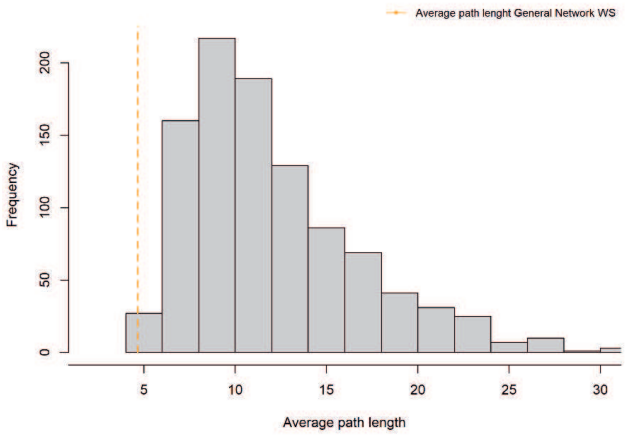


Fig. S2 Average path length of 1000 randomly generated networks with the same number of vertices and density as the General Network without Slaughterhouses (GNWS). The vertical line in orange represents the average path length for the network observed network.

Table S2 Number of animal movements, and proportion expressed as percentage, of farms of different production purpose (beef, dairy and mixed (beef and dairy) by destination of movements (when farms were source) and origin when farm were recipients, in the livestock networks of the initial phase of the 2001 epidemic in Uruguay. GN=General Network. GNWS=General Network Without Slaughterhouses. TN= Transmission Network. The GN includes all livestock movements in the period between 09-04 and 27-04 in 2001. The GNWS did not include movements to slaughterhouses. The Transmission Network 2001 included all links from or to farms that were infected during the high-risk period.

		Farm as source of animals						***Farm as recipient of animals***					
		GN		**GNWS**		**TN**		**GN**		**GNWS**		**TN**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Beef	farm	1189	23.9	1189	47.6	28	25	1249	53.1	1249	53.1	28	24.3
	livestock market	1307	26.2	1307	52.4	84	75	1103	46.9	1103	46.9	87	75.7
	slaughterhouse	2487	49.9										
		4983		2496		112		2352		2352		115	
Dairy	farm	69	22.4	69	50.7	3	14.3	40	31.7	40	31.7	0	
	livestock market	67	21.8	67	49.3	18	85.7	86	68.3	86	68.3	30	100
	slaughterhouse	172	55.8										
		308		136		21		126		126		30	
Mixed	farm	52	16.9	52	35.6	6	19.4	44	37.6	44	37.6	8	24.2
	livestock market	94	30.5	94	64.4	25	80.6	73	62.4	73	62.4	25	75.8
	slaughterhouse	162	52.6										
		308		146		31		117		117		33	

3


Chapter 4

Effectiveness of Emergency Vaccination in Controlling a Foot-and-Mouth Disease Epidemic in a Previously FMD-Free Country Without Vaccination

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Abstract

Foot-and-mouth disease (FMD) vaccines are key tools for controlling and eradicating FMD virus (FMDV) and are often used as a control measure during epidemics. Emergency vaccination decisions in previously FMD-free countries should be supported by evidence on vaccine effectiveness (VE) against transmission. Mathematical models help assess vaccination strategies but require accurate effectiveness parameters. While experimental studies have shown that FMD vaccination, particularly in cattle, effectively controls transmission, there is limited information on its effectiveness during emergency vaccination in formerly FMD-free countries. We assessed the effectiveness of emergency FMD vaccination implemented alongside other control measures such as ban on animal movements and enhanced biosecurity, estimating VE at one, two-, and three-weeks post-vaccination. VE was estimated by assessing the reduction in the between farm transmission rate parameter (β) following vaccination of the farms with commercial bivalent vaccines containing the O1 Campos and A24 Cruzeiro strains. To estimate β, we prepared the data within an SIR modelling framework and fitted a Generalized Linear Model with a complementary log-log link (cloglog). Since vaccination was implemented by zones during the epidemic, analyses were performed separately for each zone. It was observed that VE increased over time across all vaccination zones. Notably, even within the first week post-vaccination, VE was high, with estimates of 77.65% [70.53–82.94] in zone Pre, 71.05% [21.13–87.59] in zone A, 78.50% [75.44–81.21] in zone B, 68.80% [59.55–75.83] in zone C, and 59.75% [47.68–69.12] in zone D. Evaluating vaccine performance in fully susceptible livestock populations under high-risk conditions is key to improving control strategies and preparedness. Our findings indicate that emergency vaccination, as an additional measure, effectively contributed to control the epidemic in Uruguay. These VE estimates can parameterise and refine outbreak-response models and strengthen preparedness in previously FMD-free regions.

1. Introduction

Foot-and-mouth disease (FMD) is a global viral disease that has impacted numerous countries across the world throughout its history. FMD virus (FMDV) was introduced into South and North America by the end of the 19th century through the importation of animals and animal products from Europe, yielding distinct consequences in each region. While in North America, the occurrence of sporadic outbreaks was addressed through an eradication approach involving stamping-out, in South America the infection had spread widely among cattle across affected countries and, therefore, could only be controlled through mass vaccination of the cattle population (Bergmann et al., 2005; Iriarte Barbosa et al., 2023; Naranjo & Cosivi, 2013; Sutmoller et al., 2003).

After vaccines became available in the 1960s, they have played a critical role in FMD control efforts. For example, in the early 1990s, mass vaccination of cattle helped eradicate FMDV in most European countries. Once the disease was controlled, Europe discontinued vaccination for trade reasons (Sutmoller et al., 2003). Similarly, in South America, countries such as Argentina, Brazil, Chile, Paraguay, and Uruguay achieved FMD-free status through mass vaccination campaigns (Bergmann et al., 2005; Naranjo & Cosivi, 2013; Sutmoller et al., 2003). However, after following Europe's non-vaccination policy to maintain export positions between 1994 and 1999, these countries faced new outbreaks in 2000-2001, prompting them to resume mass vaccination. This decision had significant trade implications. According to the World Organisation for Animal Health (WOAH, formerly OIE) standards, regaining FMD-free status with vaccination requires a longer waiting period compared to achieving the same status without vaccination. These extended timelines can delay market access and pose economic challenges for countries reliant on livestock exports. In the case of Uruguay, after the 2001 epidemic, regaining FMD-free status with vaccination took 21 months (Office International des Epizooties (OIE), 2003), illustrating the prolonged recovery period and its economic consequences. In contrast to South American countries, the UK implemented a stamping-out policy without vaccination during the 2001 FMD epidemic (Gibbens et al., 2001). Meanwhile, the Netherlands adopted a different approach, combining standard EU control measures with emergency vaccination in affected areas, followed by the slaughter of all vaccinated animals for trade reasons (Bouma et al., 2003). The extensive use of culling of infected animals and slaughter of the vaccinated ones raised debate over control policies, leading to the emergence of a "vaccination-to-live" strategy as an alternative tool for future epidemics. While vaccination strategies have varied across regions, ranging from routine preventive programs to emergency measures, all approaches rely on the use of effective vaccines in inducing herd immunity to interrupt virus transmission.

The effect of vaccination in individuals can be categorized into clinical protection, reduced susceptibility to infection, and decreased infectivity after infection. Reduction in susceptibility and infectivity contribute to herd immunity, which lowers the overall rate of infection within a population. The objective of vaccination in the context of eradication is to reduce the basic reproduction ratio (R) below 1 by decreasing susceptibility, infectivity, and overall transmission within the population. When $R < 1$, each average infected individual generates, on average, fewer than one secondary infection, leading to the eventual extinction of the pathogen. This principle underlies the concept of herd immunity, where vaccination can effectively halt disease spread when a sufficient

proportion of the population is immunized. To quantify the impact of vaccination, various methods are employed, including experimental studies and field trials (De Jong & Bouma, 2001).

Many experimental studies have been conducted to assess the efficacy of FMD vaccines using the method developed by De Jong & Kimman (1994). For example, experimental studies have examined the transmission of FMDV serotype O in groups of vaccinated and unvaccinated cattle (Orsel, de Jong, et al., 2007; Orsel et al., 2005), sheep (Orsel, Dekker, et al., 2007), and pigs (Orsel, de Jong, et al., 2007). These transmission experiments on vaccine efficacy in groups of cattle, pigs, and sheep concluded that vaccination was effective to stop sustained transmission ($R < 1$) in cattle and sheep, but less effective in pigs. Although experimental conditions do not fully replicate field complexity, these studies have yielded important evidence on species-specific vaccine efficacy. Moreover, their results have been extrapolated to the herd level and incorporated into simulation models, contributing to the design of emergency preparedness plans (Backer, Hagenaars, et al., 2012; Kahn et al., 2002).

Evaluations of efficacy of vaccines in South America, have been limited to assess the efficacy against development of generalized infection (Duque et al., 2016). This assessment provides no information on the efficacy of the vaccines against transmission. Duffy et al., 2020 did investigate the impact of vaccinating cattle with a commercial vaccine containing four FMDV strains O1 Campos, A24 Cruzeiro, A/Argentina/2001, and C3 Indaial, commonly used in systematic vaccination campaigns in Argentina, 7 and 14 days prior to challenge with the A/Argentina/2001 FMDV strain. The findings demonstrated that early vaccination provided full clinical protection and effectively prevented viral transmission within a herd as indicated by an R value < 1 (Duffy et al., 2020). Translating this efficacy to field settings requires that the vaccine is antigenically matched to the outbreak strain, that vaccination is implemented rapidly and correctly, and that high population coverage is achieved. All these requirements can be challenging during emergencies, under field conditions.

However, there is limited literature available on the effectiveness of FMD vaccination when applied as an emergency measure during epidemics in formerly FMDV-free countries. One contribution is from Brito et al. (2011), who analysed observational data from the 2001 FMD epidemic in Argentina. These authors estimated the within-herd transmission rate parameter (β) and used a logistic regression model to identify factors associated with high transmission rate parameters, comparing vaccinated and unvaccinated herds. They found that vaccinated herds had a lower median transmission rate parameter ($\beta = 0.17$ day^{-1}) compared to unvaccinated herds ($\beta = 0.26$ day^{-1}). This analysis was limited to the assessment of the effect of vaccination at within herd level, but quantitative knowledge of the effectiveness of emergency vaccination at the population level (between herd/farm level) is not yet available.

Understanding vaccine performance in fully susceptible livestock populations, when emergency vaccination must be deployed under high-pressure conditions, is crucial for optimizing control strategies and improving emergency preparedness. In this scenario, emergency vaccination is expected to be applied as an additional measure to basic recommended measures such as rapid culling of infected animals, increased biosecurity,

ban on animal movements and enhanced surveillance (World Organisation for Animal Health (WOAH)., 2024).

In our study, we conducted a retrospective analysis to assess the effectiveness of vaccination as an additional measure to control the 2001 serotype A FMDV epidemic in Uruguay. This was done by evaluating the reduction in the transmission rate parameter for between-farm transmission. Our research provides essential data for parameterizing and refining outbreak response models, supporting the design of effective control strategies. By improving the accuracy of transmission models, these findings contribute to enhancing preparedness and decision-making in FMDV-free regions facing potential incursions.

2. Materials and Methods

2.1. Data source

During the 2001 epidemic, the Veterinary Services of Uruguay collected detailed information for each reported infected herd. This data included a unique farm identifier, geographical location, and livestock and production details, such as the number and species of animals, the count of clinically identified infected animals per species, the date of FMD/FMDV detection on the farm, and the vaccination and re-vaccination date. We used the estimated farm infection dates (date of FMDV introduction) from Iriarte Barbosa et al. (2023) rather than reported onset dates, because the onset day reported was often the first inspection date—when many animals were already affected—indicating delayed reporting and uncertain lesion ages. The epidemic dataset was then merged with data on the location and livestock composition of all Uruguayan farms that kept cattle or sheep in 2001 (DICOSE Annual Affidavit, 2001, Curtesy of The Ministry of Agriculture).

The control of the 2001 serotype A FMDV epidemic in Uruguay is well described by Sutmoller et al. (2003) and Iriarte Barbosa et al. (2023). Briefly, following detection of FMDV on 24/04/2001, the country tried to control the epidemic by a stamping-out policy without the use of vaccination. To prevent further spread of the virus, a nationwide ban on animal movements was enforced starting on 27 April. Concurrently, ring vaccination was initiated within a 10 km radius around infected farms and later expanded to a broader area to establish a protective barrier (Zone “pre” in Figure 1). One week later, a mass vaccination of the whole cattle population in Uruguay was established since the virus had already spread throughout the country.

The Veterinary Services established the timetable of the first round of vaccination based on zones comprised of police sections (the smallest administrative region in Uruguay), which correspond to the police precinct under whose jurisdiction the farm falls. The farm’s ID indicates the police section where the farm is located, ensuring proper administrative control and alignment with vaccination planning. The first vaccination zone, where vaccination started, attempted to function as a protective barrier (zone Pre: 01/05/2001). Next, vaccination was done in the farms located in police sections adjacent to Brazil (zone A: 05/05/2001) to avoid the virus’ spread to the neighbouring country. Vaccination in farms located in zones B, C and D were subsequently implemented (10/05/2001, 15/05/2001 and 21/05/2001 respectively) (Figure 1).

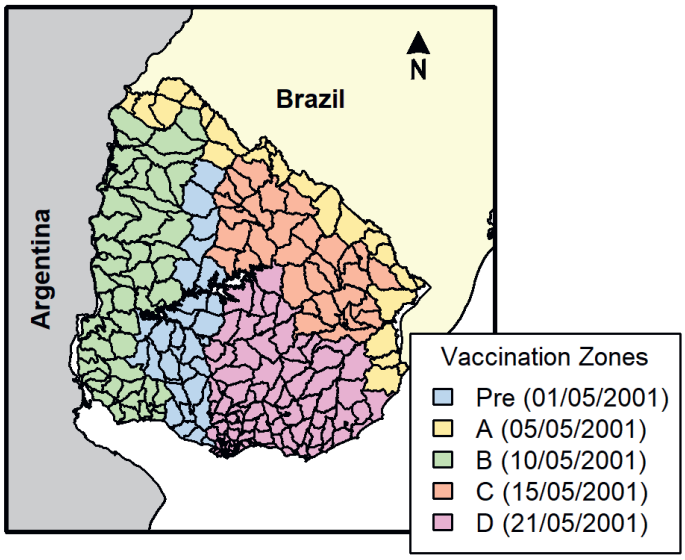


Fig 1 Timetable of the first-round mass vaccination against Foot and Mouth Disease in 2001, Uruguay.

The Official Veterinary Services coordinated the distribution of vaccines through police stations, schools, veterinarians, and farmers' associations, with farmers responsible for administering the vaccines under their supervision. Farmers whose farms were located within each police section were required to collect their vaccines on the designated date and begin vaccination immediately. The official Veterinary Services played an active role in supervising the vaccination procedures at the farm level by providing both oral instructions through local veterinarians and written guidelines to vaccinators. Most of the vaccinations were done by farmers and in some cases, they were performed by private veterinarians. The first vaccination round ended by June 7th and the second vaccination round lasted from June 15th to July 22nd.

2.2. Vaccines used

At the beginning of the epidemic, vaccines were not available in Uruguay. To address this, the Uruguayan Air Force transported vaccines from neighbouring countries. The primary source was Brazil, with additional imports from Paraguay, Colombia, and Argentina. The vaccines included trivalent formulations (O1 Campos, A24 Cruzeiro, and C3 Indaial strains) from Brazil and Paraguay, and bivalent formulations from Colombia (O1 and A24 strains) and Argentina (O1 and A24 strains, including strain A2000 Argentina). Most of the vaccines used were bivalent, containing the O1 Campos and A24 Cruzeiro strains. Trivalent vaccines were used only during the first vaccination round. These commercial vaccines, which had a potency of PD_{50} = 3, were approved and certified by the competent authorities in their countries of origin. Safety and efficacy tests in all cases adhered to the protocols established by the Regional Reference Laboratory, the Pan-American Centre for Foot-and-Mouth Disease (PANAFTOSA-PAHO/WHO).

In the Quarterly Report (October–December 2024), the World Reference Laboratory for FMD (WRLFMD) reported vaccine matching results for historical South American field isolates received from PANAFTOSA/OPS, Brazil, including the Uruguayan field strain from 2001. For the A24 Cruzeiro vaccine strain produced by Biogénesis Bagó®, the results indicated an r_1 value of 0.12 and a heterologous neutralisation titre of 1.95 (World Reference Laboratory for Foot-and-Mouth Disease, 2024). The r_1 value represents the ratio between the neutralisation titre of a vaccine reference serum against a field virus and its titre against the homologous vaccine virus, when tested using a virus neutralisation test (VNT) under standardised conditions (typically using 100 $TCID_{50}$ of virus). It serves as an indicator of the antigenic relationship between the vaccine strain and the field isolate. According to WOAH guidelines, r_1 values above 0.3 suggest that the vaccine strain is likely to confer protection against the field virus, whereas values below 0.3 indicate a poor antigenic match and potentially insufficient protection, unless compensated by high vaccine potency or additional doses.

2.3. Analysis

Vaccine effectiveness (VE) was estimated following the approach described by Halloran et al. (1997). Here, we estimated VE as one minus the reduction of the between farm transmission rate parameter (β) in the vaccinated group compared to the unvaccinated group.

To quantify the transmission rate parameter (β), we used a Susceptible-Infectious-Recovered (SIR) model, as described by De Jong and Kimman (1994), where S represents the total number of susceptible farms, I the total number of infectious farms, and R the total number of recovered farms. In the model, farms were classified as infectious (I) if they exhibited clinical signs or tested positive. We assumed that each infected farm remained in the infectious state for 26 days before transitioning to the recovered (R) compartment. This was the average infectious period estimated using a stochastic model presented in Iriarte et al. (2023), which simulates the within-farm dynamics of FMD using the Gillespie algorithm by taking into account average farm (cattle) sizes representative of the farm population during the epidemic. In addition, a sensitivity analysis was performed to evaluate the impact of the assumed infectious period on the estimation of vaccine effectiveness (VE). Estimates were compared using infectious periods of 21 and 31 days, representing ±5 days from the baseline assumption of 26 days.

2.3.1. Data preparation

The application of the SIR model for the estimation of the transmission rate parameter requires the preparation of the data, which includes structuring the dataset into discrete time steps, quantifying the number of susceptible, infectious and recovered farms and newly infected farms at each interval, and calculating the time increments between successive steps. Furthermore, it requires the classification of vaccination status for each farm. We prepared the data and performed this calculation for each vaccination zone (Figure 1), considering only the police sections with reported cases and accounting for the different vaccination dates.

2.3.2. Estimation of the transmission rate parameter (β)

To estimate the transmission rate parameter (β), we fitted a Generalized Linear Model (GLM) with a complementary log-log (cloglog) link function, to the prepared data. This method assumes that the probability of infection for each farm follows from a Poisson process over small time interval, Δt. Therefore, the probability that a susceptible farm became infected during Δt is given by:

$$p = 1 - e^{-\beta \frac{I}{N} \Delta t} \qquad (1)$$

Where β represents the transmission rate parameter, I the number of infectious farms, N is the population size (total number of farms).

The GLM uses a binomial distribution to represent the expected number of cases, with parameter p (Equation 1) and binomial total being equal to S, which corresponds to the total of susceptible farms at the start of the period. The cloglog transformation ($log(-log(1-p))$ is used to linearize the model (Velthuis et al., 2007):

$$cloglog\left(E\left(\frac{C}{S}\right)\right) = \log(\beta) + \log\left(\frac{I}{N}\Delta t\right) \qquad (2)$$

The term $\log\left(\frac{I}{N}\Delta t\right)$ of the Equation 2 corresponds to the offset, allowing the model to control for the proportion of infectious individual farms and the length of each time interval. This offset ensures that the estimated transmission rate parameter β reflects the rate parameter for one infectious farm during one time unit.

Given that vaccination was carried out immediately after the delivery of vaccines to the police section within each zone, vaccination coverage was assumed to reach 100% within a few days. Therefore, the vaccination status of each study zone was included in the model as a covariate, represented by a dummy variable (0 for unvaccinated and 1 for vaccinated), to assess its effect on the transmission rate parameter and thereby estimate the total effect of vaccination on transmission. The analysis was conducted by categorizing zones into unvaccinated and vaccinated groups according to their status during specific time periods. The unvaccinated group comprised farms present during the period following the national movement ban and the first week after vaccination in that zone, as it was assumed that vaccinated herds were not yet protected during this week (Figure 2). In contrast, the vaccinated group was analysed by creating variables that included all vaccinated farms at one week, two weeks, and three weeks post-vaccination. This framework, along with the temporal classification, is illustrated in Figure 2.

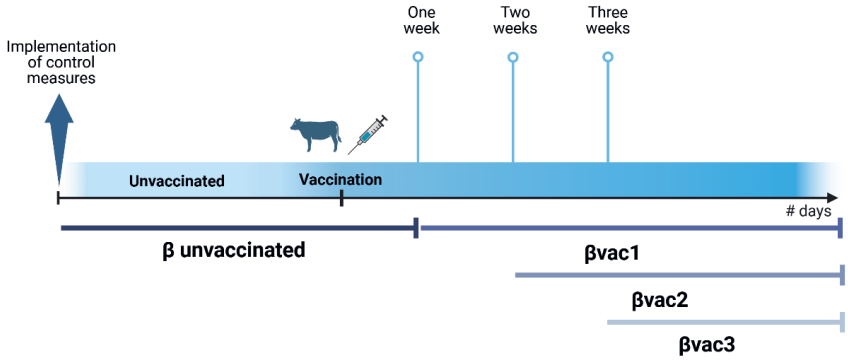


Fig 2 Classification of farms into unvaccinated and vaccinated groups over time. Three models were fitted to assess the effect of vaccination. In all models, the unvaccinated group remained consistent, representing farms from the start of the movement ban until one week after vaccination (prior to the onset of vaccine-induced protection). Vaccinated farms were categorized based on the time elapsed since vaccination into three groups: one, two-, and three-weeks post-vaccination.

2.3.3. Estimation of Vaccine Effectiveness

VE was estimated for each vaccination zone as one minus the reduction of the transmission parameter (β) in the vaccinated group relative to the unvaccinated group.

$$VE = \left(1 - \frac{\beta vaccinated_i}{\beta unvaccinated}\right) * 100 \quad (3),$$

where i represents the week after vaccination.

All analyses were performed using R Statistical Software version 4.2.2 (R Core Team, 2021).

3. Results

3.1. Descriptive statistics

A summary of the total number of police sections, the number with recorded cases (included in the analysis), the total number of farms, and the number of infected farms at the end of the epidemic is provided in Table 1.

Table 1 Number of police sections and farms within vaccination zones.

Zone	Number of police sections	Number of farms	Police sections with cases	Number of farms in police sections with cases	Infected farms
pre	34	6114	27	5288	221
A	26	4260	10	2016	27
B	60	9728	51	9479	935
C	35	7952	30	7289	241
D	99	16653	43	10257	226

Epidemic curves for each vaccination zone, showing the number of cases over time and indicating when vaccination was implemented, are presented in Supplementary Figure S1.

3.2. Estimated transmission rates and Vaccine Effectiveness (VE)

Table 2 presents the estimated transmission rate parameter (β) for unvaccinated and vaccinated groups in terms of weeks after vaccination (one, two and three) for each vaccination zone. The parameter β represents the daily rate at which a typical infectious farm transmits the infection to a typical susceptible farm. The results are presented with 95% confidence intervals to represent the uncertainty in the estimates.

Table 2 Estimated transmission rate parameters (β (day-1)) [95% confidence intervals] for unvaccinated and vaccinated groups for weeks one, two, and three after vaccination across vaccination zones.

zone	β unvaccinated	β vaccinated 1	β vaccinated 2	β vaccinated 3
pre	0.122 [0.098 - 0.151]	0.027 [0.023 - 0.032]	0.021 [0.017 - 0.026]	0.019 [0.015 - 0.024]
A	0.120 [0.048 - 0.244]	0.035 [0.022 - 0.052]	0.028 [0.016 - 0.044]	0.027 [0.014 - 0.045]
B	0.092 [0.085 - 0.100]	0.020 [0.018 - 0.022]	0.015 [0.013 - 0.018]	0.011 [0.009 - 0.014]
C	0.088 [0.072 - 0.107]	0.028 [0.023 - 0.032]	0.026 [0.021 - 0.031]	0.024 [0.020 - 0.030]
D	0.063 [0.053 - 0.075]	0.025 [0.021 - 0.031]	0.018 [0.014 - 0.024]	0.016 [0.011 - 0.022]

Overall, β values were lower in vaccinated groups compared to unvaccinated ones, with a statistically significant reduction ($p < 0.05$) already observed from the first week after vaccination for all zones. This reduction continued over the following weeks, indicating an increasing protective effect over time.

Interestingly, a decreasing trend in β was also observed among unvaccinated groups, particularly in Zones B, C, and D, which appears to correlate with the time of vaccination of each zone with respect to zone Pre (the first vaccinated zone). Zone D exhibited the lowest β value among the unvaccinated groups, and was the last zone where vaccination was implemented. This reduction may reflect indirect protection from vaccinated farms in adjacent zones. For instance, Zone D shares extensive borders with Zones Pre and C (Figure 1), both of which were vaccinated earlier (three and one week prior, respectively), potentially reducing the risk of virus transmission between farms in Zone D.

Figure 3 shows the vaccine effectiveness (VE) across different vaccination zones, which were derived using equation 3. VE was calculated for weeks one, two, and three after vaccination, with corresponding 95% confidence intervals.

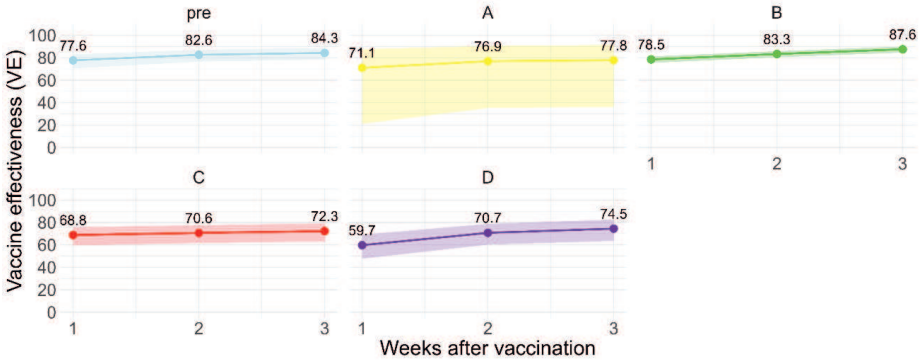


Fig 3 Vaccine effectiveness (VE) across different vaccination zones

It can be observed that VE increased over time across all vaccination zones. Notably, even within the first week post-vaccination, VE was high, with mean estimates [95% confidence intervals] of 77.65% [70.53–82.94] in zone Pre, 71.05% [21.13–87.59] in zone A, 78.50% [75.44–81.21] in zone B, 68.80% [59.55–75.83] in zone C, and 59.75% [47.68–69.12] in zone D.

A sensitivity analysis was performed to evaluate the impact of the assumed infectious period on the estimation of VE. The analyses compared results obtained using infectious periods 5 days shorter (21 days) and 5 days longer (31 days) than the baseline assumption of 26 days. In all cases, the differences in estimated transmission parameters and relative risks were not statistically significant ($p > 0.93$ for all zones and comparisons). These results indicate that the estimated VE is robust to moderate variations in the assumed infectious period.

In addition to estimating VE through the transmission rate parameter, we also explored an alternative approach based on the reduction in the attack rate (AR). This method was considered given that many epidemiological datasets report case counts, making it a widely used approach for evaluating VE. The rationale for prioritizing the transmission rate parameter approach is addressed in the Discussion section, while the results of the AR-based VE estimation are presented in the Supplementary Information.

4. Discussion

This study aimed to evaluate the vaccination effectiveness (VE) against FMDV transmission during the serotype A FMDV 2001 epidemic in Uruguay at three time points post-vaccination: one, two and three weeks. VE was measured by assessing the reduction in the transmission rate parameter (β) following vaccination of the farms with commercial vaccines available in South America containing a FMDV serotype A strain within their formulation (mainly A24 Cruzeiro strain). Despite the low r_1 value (0.12) observed between the vaccine strain and the field strain (World Reference Laboratory for Foot-and-Mouth Disease, 2024), vaccination contributed to controlling the epidemic in

Uruguay when implemented alongside culling of infected animals in the early stages, movement standstills, and biosecurity measures. This underscores that vaccination remains a valuable tool that can be effectively combined with other control strategies, even in the presence of suboptimal antigenic matching.

It was observed that vaccination significantly reduced the transmission rate parameter, with a significant effect already observed one-week post-vaccination. Consequently, VE was high even within the first week post-vaccination, with mean VE estimates [95% confidence intervals] of 77.65% [70.53–82.94] in zone Pre, 71.05% [21.13–87.59] in zone A, 78.50% [75.44–81.21] in zone B, 68.80% [59.55–75.83] in zone C, and 59.75% [47.68–69.12] in zone D. The large confidence interval observed for zone A is likely due to the low number of infected farms in this zone, leading to greater uncertainty in the VE estimate. As shown in Table 1 only 27 farms were recorded as infected in zone A, compared to substantially higher case counts in other zones.

On average, VE increased by approximately 6% from week one to week two and by approximately 2% from week two to week three. The larger increase observed between the first and second weeks, aligns with immune-kinetic data, as antibody levels reach their peak from day 14 post-vaccination (Doel, 2003), suggesting that most improvement occurs as animals approach peak immunity. Additionally, herd immunity likely plays a role. As more farms achieve protective immunity, the overall risk of virus transmission between farms declines. By week three, fewer susceptible farms remain, limiting additional gains in VE.

In the context of an FMD epidemic in a previously virus-free country, the primary interest lies in evaluating vaccination effectiveness to interrupt virus transmission. Mass vaccination within a population can lower transmission and confer indirect protection, benefiting even unvaccinated individuals (Halloran et al., 1997). This effect depends on herd immunity, which is achieved when a sufficient proportion of the population is protected, reducing the effective reproduction ratio (R_e) to a value below 1. The herd immunity threshold can be calculated using the formula: $1 - \frac{1}{R_0}$ (De Jong & Bouma, 2001). Given that R_0 was estimated to range between around 1.5 and 2.2 for the 2001 FMD epidemic in Uruguay (Iriarte et al., 2023), this implies that between 33% and 54.5% of farms need to be protected (measured as the proportion of farms vaccinated times the vaccine effectiveness) to reduce R_e below 1 and control the spread of the virus. Notably, in most zones these protection levels were likely reached as early as the first week post-vaccination. This suggests that the vaccination strategy rapidly contributed to herd immunity among the population of farms, significantly reducing the potential for further transmission and helping to control the epidemic more effectively. Despite its limitations, which will be discussed later, the method we used allows us to assess the overall effect of vaccination. This includes, implicitly, both the reduction in susceptibility of vaccinated farms and a potential reduction in their infectivity. Since vaccine effectiveness (VE) was estimated from observed transmission in vaccinated areas, the resulting estimate reflects the combined impact of both mechanisms, without distinguishing between them.

We also explored the estimation of VE using the reduction in the attack rate (AR) (Supplementary information). A key limitation of using AR (based on cumulative incidence) to estimate VE is that it does not account for the dynamics of transmission

over time and the resulting differences in exposure between vaccinated and unvaccinated individuals. This can lead to biased VE estimates, especially when exposure to infection varies between groups, as occurs in our study where comparisons are made at different time points during the course of the epidemic. This resulted for example in higher VE estimates for the first week post-vaccination for Zone B (VE = 69.2%), where the epidemic was already in decline (lower exposure to infection), compare to Zone Pre (VE = 23.8%) where the epidemic was still in the growing phase (higher exposure to infection) (Figures S1 and S2). In contrast, the estimation of VE using the transmission rate parameter takes into account heterogeneous exposure levels on transmission probabilities, resulting therefore in similar estimates among the different Zones. Although the SIR model makes simplifying assumptions (de Jong, 1995), it allows for a more realistic representation of how vaccination modifies the risk of infection between farms, rather than just comparing cumulative incidence between vaccinated and unvaccinated groups at different time points. Our assumptions are that all farms within each vaccination zone have homogeneous random contacts, which does not fully reflect reality. Additionally, we assumed that the infection rate remains constant throughout the infectious period and that farms moving to the Recovered compartment are fully immune. While these assumptions introduce some limitations, we consider that using this approach provides a more accurate representation of VE against transmission than the AR approach. Furthermore, the VE estimation using the transmission rate parameter incorporates the total effect of vaccination, by accounting for how vaccination lowers both susceptibility and infectivity, thereby reducing onward transmission within the population. In this way, vaccinated farms contribute to a lower risk of infection for both vaccinated and unvaccinated individuals. This effect is evident in the estimation of β for unvaccinated farms in each zone, showing a decreasing trend over time. For example, in Zone D, where vaccination was administered last, β is the lowest, likely due to the indirect protection provided by vaccinated farms in adjacent zones.

To counteract the limitations in both approaches, we sought to keep similar conditions between groups as much as possible. For instance, we excluded outbreaks that occurred before the ban on animal movements, focusing instead on the period when control measures were consistently applied across both vaccinated and unvaccinated groups. The vaccination strategy in Uruguay involves livestock owners vaccinating their herds simultaneously within designated zones. Therefore, considering vaccination zones in the analysis helps minimize time-related confounding factors, thereby reducing bias and enhancing the accuracy of VE estimates.

It should be noted that the VE estimates here provided, reflect the effectiveness of vaccination when used as a complementary control measure during an epidemic where basic minimal measures such as ban on animal movements, increased biosecurity, and enhanced surveillance are already in place. These VE estimates are by no means representative for scenarios where animal movements are still allowed, as is the case for example in endemic situations.

Moreover, the method of detecting infected vaccinated farms could introduce bias, as vaccination may reduce clinical signs or lead to minor outbreaks that go undetected or underreported. This could result in an overestimation of VE, as the number of infections in vaccinated farms would be underestimated. Despite the limitations, we believe that the

results do provide valuable information on VE that can be used as parameters for models aiming to evaluate emergency vaccination during a FMD epidemics.

The results highlight key considerations and potential implications. One is regarding the time to implement vaccination and different vaccination schedules. Two main aspects may be related to the delay in implementation during the 2001 epidemic, and should be key learning points from this epidemic. First, the delay in the decision to vaccinate was primarily driven by the goal of quickly restoring FMD-free status as recognized by WOAH in 2001 (OIE, 2001). However, this should no longer pose such a significant issue today due to changes in WOAH's Terrestrial Code, which now includes new tools that facilitate a faster recovery of FMD-free status (WOAH, 2024). It is crucial to assess vaccination strategies in advance to be better prepared for emergencies. Mathematical models can be used as valuable tool for emergency preparedness, and our study provides parameters to support such assessments. Second, when mass vaccination was considered as a control measure to control the 2001 FMD epidemic in Uruguay, the required number of doses to vaccinate the entire cattle population was not immediately available. The acquisition of vaccines from Brazil also conditioned the proposed vaccination timetable, starting in farms located in police sections adjacent to Brazil to avoid the virus' spread to the neighbouring country, instead of prioritizing the cessation of transmission in the country guided by epidemiological information. This highlights the critical need for national or regional vaccine banks capable of supplying South American countries with high-potency emergency vaccines. Further research is planned to evaluate various vaccination scenarios in Uruguay, aiming to identify the most effective strategies for controlling future outbreaks and improve emergency preparedness.

5. Conclusion

Vaccination with commercial vaccines, containing A24 Cruzeiro strain in their formulation, during the serotype A-2001 FMD epidemic in Uruguay demonstrated high effectiveness against transmission, significantly contributing to bring the effective reproduction ratio (R_e) below 1, which was critical for controlling the epidemic.

Our results provide evidence of vaccine performance in the field during an epidemic, when vaccination is implemented alongside other control measures such as animal movement restrictions and biosecurity protocols. These VE estimates can be used to parameterize mathematical models to forecast disease spread, optimize and develop control strategies, perform economic evaluations, and support the decision-making process, while also strengthening preparedness efforts in FMDV-free regions.

Data availability

The data are owned by Uruguay's Ministry of Livestock, Agriculture and Fisheries (MGAP) and are confidential and therefore not publicly available.

The R code used for data preparation and analysis is openly available at GitHub: https://github.com/victoriairiarte/FMD_VaccineEffectiveness_Uruguay2001/tree/main.

A simulated dataset with the same structure is provided in the repository's /data directory for demonstration purposes.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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SUPPLEMENTARY INFORMATION

Introduction

This section presents the results of the alternative estimation of vaccine effectiveness (VE) based on the reduction in the attack rate (AR). These findings complement the main analysis in the manuscript, where VE was primarily estimated through the transmission rate parameter. As discussed in the main text, the AR-based approach presents limitations and should be interpreted with caution.

Methods

Data preparation

We retrospectively estimated the cumulative incidence of infected farms in each police section by grouping the number of cases based on the time period post vaccination (variable "group"): (1) unvaccinated, (2) one to two weeks after the first vaccination, (3) two to three weeks after the first vaccination, (4) three to four weeks after the first vaccination, (5) four to five weeks after the first vaccination, and (6) more than one week after the second vaccination. To ensure consistency in the conditions across different groups, we focused on outbreaks that occurred after the implementation of control measures, including the ban on animal movements, biosecurity measures, and vaccination. This approach minimized differences in contact rates and the probability of transmission between infectious and susceptible farms, which might otherwise complicate interpretation. By excluding outbreaks that occurred prior to these interventions, we aimed to reduce potential biases arising from inconsistent control efforts across groups. During the epidemic, detection of infected farms was mainly based on clinical signs. As vaccination can reduce these signs, measures were implemented to maintain high detection sensitivity. These included contact-tracing by the official veterinary service, routine farm visits, and mandated daily observation and reporting by farmers, all aimed at ensuring a high probability of detection despite the potential reduction in observable symptoms.

For the analysis only police sections within each zone with recorded cases were included, in addition, we assumed that all farms within each police section were vaccinated on the same day. During the epidemic, the Veterinary Services implemented a detailed vaccination timetable by zones, each of which was composed of specific police sections. Farms within each police section were required to collect their vaccines on the designated date and begin vaccination immediately.

Analysis: Estimation of Vaccine Effectiveness

Vaccine effectiveness (VE) was estimated using the method described by Halloran et al. (1997), which defines VE as one minus the relative risk (RR) of infection in the vaccinated group compared to the unvaccinated group.

To estimate the RR, three Poisson regression models were fitted to the data. The first model aimed to estimate the crude VE, where the dependent variable was the number of infected farms in each police section, the independent variable was the vaccination group, and the log of the total number of farms in each police section was used as the offset. The

offset adjusts the model to account for population size, ensuring that the model predicts the incidence rate. The unvaccinated group was set as the reference group.

A second Poisson model also included the police section as a random effect. By incorporating this random effect, the model accounts for unobserved heterogeneity between police sections. This approach assumes that each police section may have unique characteristics—such as differences in management practices, environmental conditions, or local disease pressure—that are not directly captured by the fixed effects and could influence the number of infected farms.

A third Poisson model was fitted to estimate the RR, adjusting for the vaccination zone as a fixed effect and including an interaction term. This method controls for differences between zones and captures how the effect of vaccination may vary across zones.

Finally, VE was estimated for each vaccination zone, incorporating the police section as a random effect.

By exponentiating the model's coefficients, we estimated the relative risk (RR) for each vaccination group, allowing for a direct comparison of their risk of infection relative to the unvaccinated group. Vaccine effectiveness (VE) for each group was then estimated as one minus the RR.

We used the Akaike Information Criterion (AIC) to compare the goodness of fit among the three models (Akaike, 1974). All analyses were performed in RStudio version 4.2.2, using the packages broom (Robinson et al., 2023), lme4 (Bates et al., 2015) and broom.mixed (Bolker & Robinson, 2022).

Results

Before presenting the vaccine effectiveness (VE) results, we first provide insights into the data by examining the epidemic curves for each vaccination zone: pre, A, B, C, and D (Figure S1). Dashed black vertical lines indicate the timing of the first vaccination, while coloured lines represent the weeks following vaccination: purple for one-week, light blue for two weeks, green for three weeks, and olive for four weeks in each zone. It can be observed that most cases occurred in Zone B, while Zone A, which borders Brazil, experienced only a few cases. The number of cases began to decline as time progressed after vaccination.

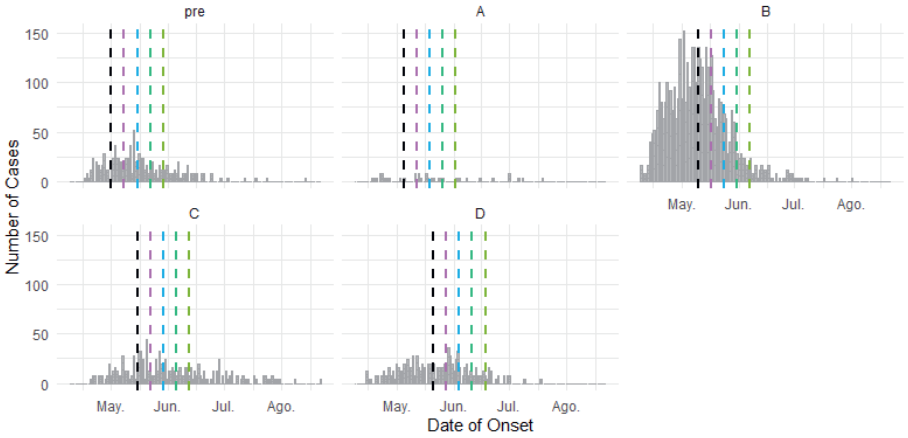


Figure S1 Epidemic curve for each vaccination zone: pre, A, B, C, D, and E. Dashed black vertical lines represent the timing of the first vaccination. Coloured lines indicate the weeks following vaccination: purple for one-week, light blue for two weeks, green for three weeks, and olive for four weeks in each zone.

Additionally, we present descriptive statistics for each vaccination zone, including the total number of police sections, police section with recorded cases, number of farms and number of infected farms (Table S1). These preliminary observations offer context before delving into the results of the Poisson models and the estimation of VE.

Table S1 Number of police sections and farms within vaccination zones

Vaccination Zones	Total number of Police sections	Police sections with cases	Police sections without cases*	Total number of farms	Infected farms
Pre	34	27	7	6114	221
A	26	10	16	4260	27
B	60	51	9	9728	935
C	35	30	5	7952	241
D	99	43	56	16653	226

** Police sections without recorded cases were excluded from the analysis.*

Table S2 presents the relative risks (RR) for each vaccination group compared to the unvaccinated group for two Poisson regression models, and the estimated vaccine effectiveness (VE). The first model is an unadjusted or crude model, while the second model includes the police section as a random effect.

Table S3 Poisson regression models outputs used to estimate the relative risk (RR) of infection in each vaccination group and estimated Vaccine efficacy (VE).

Time after vaccination	**RR [CI 95%]**	**VE = (1-RR)% [CI 95%]**	**RR [CI 95%]**	**VE = (1-RR)% [CI 95%]**
Unvaccinated	*ref.*		*ref.*	
One week	0.45 [0.39-0.51]	55.19 [48.73-60.97]	0.38 [0.33-0.44]	62.03 [56.37-66.95]
Two weeks	0.32 [0.27-0.38]	67.53 [61.83-72.54]	0.27 [0.23-0.32]	72.98 [68.03-77.16]
Three Weeks	0.24 [0.2-0.3]	75.73 [70.25-80.44]	0.2 [0.16-0.25]	79.59 [74.72-83.52]
Four weeks	0.19 [0.15-0.24]	81.36 [76.49-85.46]	0.19 [0.15-0.24]	81.08 [75.81-85.2]
One week (after second round)	0.12 [0.08-0.18]	87.83 [82.06-92.19]	0.16 [0.1-0.25]	83.76 [74.55-89.64]
Model	$e^{b_0+b_1 group}$		$e^{b_0+b_1 group+r_e sp}$	
AIC	2738.7		1798.7	

**group= time period post vaccination: (1) unvaccinated, (2) one to two weeks after the first vaccination, (3) two to three weeks after the first vaccination, (4) three to four weeks after the first vaccination, (5) four to five weeks after the first vaccination, and (6) more than one week after the second vaccination.*
**$r_e$sp= the police section as a random effect.*

The third model ($e^{b_0+b_1 group+b_3 zone+b_4(zonexgroup)}$), presented a significant interaction between the vaccination group and the vaccination zone. Therefore, the RR and the VE were estimated for each vaccination zone separately.

Figure S2 presents the VE for each vaccination zone. The outputs of zone A were not presented here because the number of cases (Figure S1 and Table S1) observed in that zone were too low, hindering the ability of the model to detect significant differences.

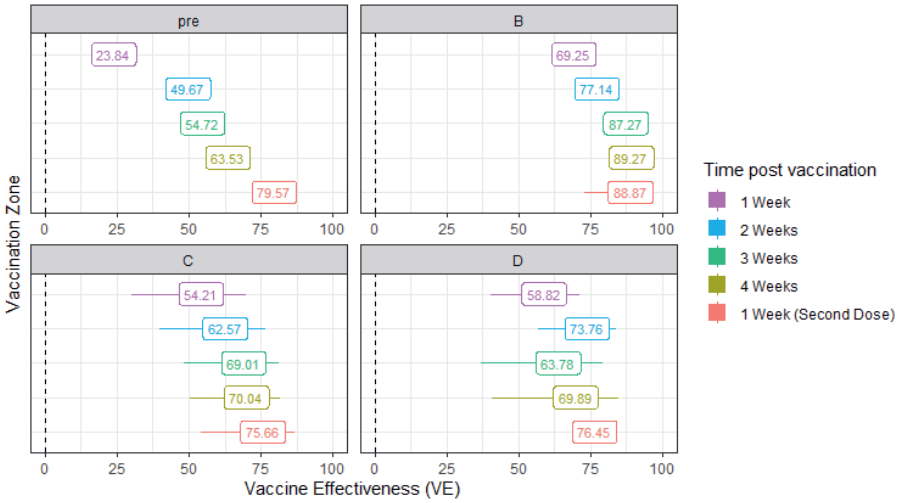


Figure S2 Vaccine effectiveness estimation per vaccination zone.


Chapter 5

Evaluating FMDV Control Strategies with Kernel-Based Transmission Modelling: A Case Study in Uruguay

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ABSTRACT

Recent outbreaks of foot-and-mouth disease virus (FMDV) in previously FMD-free European countries underscore the continuous risk FMD represents worldwide. Preparedness for infectious-disease outbreaks is, therefore, critical to minimise their impact. The 2001 foot-and-mouth disease virus (FMDV) epidemic in Uruguay, which was FMD-free without vaccination, provides an opportunity to characterise farm-to-farm transmission in pasture-based livestock production systems and to design targeted, effective control measures. Using data from this specific epidemic, we estimated competing phase-specific transmission kernels for two epidemic phases, pre-vaccination (Phase-1) and post-vaccination (Phase-2), and assessed the effect of farm size and livestock species on transmission. The phase-specific kernels distinguish the high-risk period, in which long-distance spread can occur via movement of infected animals, from the post-detection period, dominated by local farm-to-farm transmission. At the farm level, cattle farms have both the highest relative susceptibility and the highest relative infectiousness compared with sheep and pig farms. Because infections in sheep and pigs were few, species effects are imprecise and should be treated as adjustment covariates rather than as robust between-species contrasts. Larger farms increased transmission via both susceptibility and infectiousness, with a stronger effect on infectiousness. We used the selected phase-specific kernels to compute each individuals' between-farm reproduction number ($R_{h,i}$) and construct risk maps for 2001 and 2023. We then parameterised an individual farm-based stochastic model with these kernels to simulate FMDV spread and compare alternative control strategies. We observed a 76% relative reduction in R_h from Phase-1 to Phase-2, indicating the effectiveness of the control measures implemented. Overall, estimated R_h were higher in 2023 than in 2001, with higher frequency of farms with $R_h > 1$ likely reflecting demographic shifts (more cattle-only farms, fewer mixed cattle–sheep farms), implying a greater probability of sustained transmission following an FMDV introduction, all else equal. Epidemic outcomes would still depend on timeliness of detection and the implementation of effective control measures. In simulations, cattle-focused control was as effective as all-species control for epidemic duration and for infected and culled herds. In emergency vaccination scenarios, targeting cattle alone achieved similar outcomes while vaccinating fewer animals, and with a 10-km ring, the cattle-only strategy performed better (shorter epidemics, fewer infected and culled herds). Preventive risk-based vaccination targeting farms with ($R_h \geq 0.8$) was the most effective strategy.

Our results provide model-ready parameters to support preparedness in FMD-free regions, especially those with pasture-based, extensive systems like those in Uruguay.

1. INTRODUCTION

Numerous epidemics in history have demonstrated that being prepared to respond to outbreaks of infectious diseases is crucial to minimize their impacts. Foot-and-mouth disease (FMD), an infectious viral disease that mainly affects cloven-hoofed livestock but also cloven-hoofed wild animals, is a notable example of that. Recently, FMDV outbreaks in Germany, Hungary and Slovakia, free countries without vaccination, underscored the continuous risk FMDV represents worldwide. Whilst these outbreaks involved few farms, large epidemics in previously FMDV-free territories occurred in 2001 in Europe, including the United Kingdom and the Netherlands, (Bouma et al., 2003; Gibbens et al., 2001), and in South America, including Uruguay (Iriarte Barbosa et al., 2023) and Argentina (Perez et al., 2004). These large epidemics highlight how severe the economic consequences of an outbreak in a FMDV-free country can be, with the economic impact totalling US$730 million for Uruguay (OPYPA-MGAP, 2004) and US$9,204 million for the UK (Knight-Jones & Rushton, 2013). Apart from the huge damage brought by these epidemics, each epidemic offers also an opportunity to better understand the epidemiology of FMDV, which is crucial for tailoring preparedness and response efforts to the specific characteristics of the livestock population affected. Whilst the epidemics in Europe were managed under a non-vaccination, stamping-out policy, with the Netherlands as a notable exception using emergency vaccination-to-kill, South America relied on mass vaccination-to-live.

Uruguay was recognized as FMDV-free without vaccination by the World Organisation for Animal Health (WOAH) until the 2001 epidemic. That year, the country experienced a large outbreak of FMDV serotype A, which was only controlled after the implementation of emergency mass vaccination of the cattle population, in addition to standard biosecurity measures (Iriarte Barbosa et al., 2023). Following the eradication of the virus, Uruguay adopted a policy of preventive mass vaccination and has since maintained official recognition as FMDV-free with vaccination. This status remains essential for ensuring continued access to export markets for livestock products.

In case of an FMDV incursion, a country should be able to detect it early and to effectively control the outbreak to rapidly recover its FMD-free status. To be better prepared to respond to FMDV incursions, countries need to optimise contingency planning, updating their contingency plans, in which strategies to control and eradicate FMDV are established. These strategies often involve a combination of different control measures such as quarantine and enhanced biosecurity measures, livestock movement banning, culling of infected animals, pre-emptive culling of in-contact susceptible farms with potential infectious animals, emergency vaccination and risk-based preventive vaccination. Mathematical modelling of FMDV transmission, and other pathogens as well, is a powerful tool to assess the effect of control measures to inform policy makers on disease control and contingency planning (Hagenaars et al., 2011).

Mathematical modelling of infectious diseases involves building a model that represents the transmission dynamics within a population, considering the characteristics of the pathogen, the animal population, and the interactions between individuals (animals or

farms). The complexity of the models is directly related to the number of parameters needed, which are estimated by fitting outbreak data or from transmission experiments (Hagenaars et al., 2011). Therefore, it is essential to build the model according to the model´s purpose and the availability of the data to estimate the parameters. Different approaches have been used to model FMDV transmission according to the purpose, ranging from simple to more complex. For example, during the 2001 FMD epidemic in the UK, different mathematical models were used to guide control polices, each one with its advantages and limitations, which were reviewed by Kao (2002) and Keeling (2005). In addition, mathematical models have been used to make extrapolation to new scenarios, to test a wide range of control strategies and outbreak scenarios (Backer, Engel, et al., 2012; Backer, Hagenaars, et al., 2012; Boender et al., 2010; Hayama et al., 2013; Keeling et al., 2001).

Mathematical modelling of FMDV transmission between farms requires that the spatial feature of its transmission is considered, which can be addressed by using a transmission kernel. The transmission kernel for FMDV is a mathematical function used to describe the probability of disease transmission between infectious and susceptible farms as a function of the distance between them and can incorporate other heterogeneous factors such as animal species and farm size (Boender et al., 2010, 2014; Ferguson et al., 2001; Keeling et al., 2001). The kernel combines multiple transmission mechanisms into a distance-dependent function, and its parameters are typically inferred from the spatiotemporal pattern of new cases (Keeling, 2005). This modelling approach has also been used to model other important infectious diseases such as highly pathogenic avian influenza (Boender et al., 2007) and classical swine fever (Boender et al., 2014).

Most of the described mathematical models have been developed and applied for countries with intensive production systems. Work also exists in endemic settings, for example, a dairy district in Thailand with routine vaccination and no culling (Chanchaidechachai et al., 2021). Our study contributes a South American perspective, where pasture-based livestock production systems predominate, and presents one of the first kernel-based analyses of between-farm transmission in the region. The large 2001 FMDV epidemic in Uruguay offers the possibility to better understand the epidemiology of FMDV in these pasture-based production systems and allows for developing more targeted and effective measures to control and mitigate outbreaks.

Here, we estimated a set of candidate transmission kernels for two phases of the 2001 epidemic and used the best-supported kernel to compute the between-farm reproduction number R_h for each farm and construct risk maps for 2001 and 2023 following Boender et al. (2007, 2014). Finally, we used the transmission kernel in an individual farm-based stochastic model to simulate the spatial spread of FMDV in Uruguay and evaluate alternative control strategies.

2. METHODS

2.1. Data

The 2001 FMD epidemic in Uruguay began with a suspected case on April 23. The official Veterinary Services confirmed FMDV on April 24, and serotype A was confirmed the following day. Early control relied on a non-vaccination strategy, movement bans covering animals, animal products, and personnel, culling of affected and at-risk livestock, and reinforcement of biosecurity. This was followed by ring vaccination within a 10-km radius of outbreaks and later expanded to emergency vaccination within a broader buffer to limit north-eastward spread. As transmission persisted, mass vaccination of the entire cattle population was implemented on 5 May. The epidemic lasted 119 days and involved 2,057 infected farms (Iriarte Barbosa et al., 2023).

During the epidemic, Veterinary Services collected data on infected farms, including farm ID (DICOSE number), geographical location, livestock details, the number of clinically identified infected animals by species, and detection dates. We used the estimated farm infection dates (date of FMDV introduction) from Iriarte Barbosa et al.(2023), rather than reported onset dates, because initial data checks showed that onset was often recorded as the first visit date, even when many animals were already affected, indicating uncertain lesion-age estimates and reporting delay. The epidemic dataset was merged with the 2001 DICOSE Annual Affidavit, a census of all farms nationwide (IDs (DICOSE number), location, and species-specific stock), retaining only complete records for analysis.

We used the 2023 DICOSE Annual Affidavit (MGAP, 2023) to represent the current farm population for both the risk map and the simulations.

2.2. Transmission model and kernel parameterisation

2.2.1. Transmission model

A Susceptible-Exposed-Infectious-Removed (SEIR) model was used, incorporating a spatial kernel to account for between-herd transmission dynamics. This model is based on the methodology of Boender et al. (2007) and was extended to include dependencies on farm size and type (Boender et al., 2014; Chis Ster et al., 2009; Ferguson et al., 2001).

Briefly, an SEIR model is a compartmental model that describes the transition of individuals (animals, herds, farms, etc.) through different stages of an infectious disease (de Jong, 1995). The SEIR model divides the population into four compartments: Susceptible (S), Exposed (E, individuals who have been infected but are not yet infectious), Infectious (I, individuals who are infected and can transmit the disease to susceptible individuals), and Removed (R, individuals who have either recovered from the disease and gained immunity or removed by control measures such as culling or vaccination).

We used the farm as the unit of analysis. On multispecies holdings, each species was treated as a separate farm/herd sharing the same geographic coordinates (x and y) (e.g., cattle, sheep, and pigs on the same holding were analysed as three farms).

2.2.2. Data preparation

To estimate spatial transmission kernels before and after the implementation of emergency vaccination, we divided the epidemic on 15 May 2001. Mass vaccination began on 5 May and was implemented by zones, but effective protection was not expected to take place before 14 May. We therefore refer to Phase 1 as "pre-vaccination" (from first introduction to 14 May 2001) and Phase 2 as "post-vaccination" (15 May 2001 onward). We fitted phase-specific spatial transmission kernels rather than a single average kernel.

We organized the data in a discrete-time SEIR state matrix $C = (c_{ij})$ of size $n \times t_{max}$, where $c_{ij} \in \{S, E, I, R\}$ is the state of farm i on day j. For the Uruguayan 2001 epidemic, $n = 73{,}215$ species-specific farms (herds) (from 49,078 holdings) and $t_{max} = 119$ days. Each day, farms were classified as susceptible (S), exposed (E), infectious (I), or removed (R). We assumed a fixed 5-day latent period, meaning that a susceptible farm infected on day t moved to E on day t and became infectious on $t + 5$. Farms culled during the initial control phase were considered infectious until the cull date, after which they moved to R. In Phase 1, no vaccine-based removal rules apply. In Phase 2, removal from infected farms, was determined by vaccine timing at the time of infection, assuming total vaccine-induced protection is reached 30 days post-vaccination. If infection occurred < 30 days after the first dose, removal was set to 30 days after the first dose. If infection occurred ≥ 30 days after the first dose but < 30 days after the second dose (first-dose failure), removal was set to 30 days after the second dose. If infection occurred ≥ 30 days after the second dose (second-dose failure), farms remained infectious until the end of follow-up (t_{max}). In Phase 1 (pre-vaccination), susceptible farms could only move to E upon infection and otherwise remained in S. In Phase 2 (post-vaccination), uninfected vaccinated farms were moved from S to R 30 days after first vaccination (considered protected).

Each farm location was represented as a two-dimensional Euclidean vector $r_i = (x_i, y_i)$. From these vectors, an $n \times n$ distance matrix D was constructed, containing the pairwise distances between farms.

2.2.3. Kernel parameterisation

Transmission between farms was described using a discrete-time framework, following Boender et al. (2007, 2014). The central component of the model is the transmission kernel, which describes the transmission intensity between farms i (infectious) and j (susceptible) as a function of the distance between them and their characteristics (farm sizes and species composition: cattle, sheep, and pigs).

We parameterised the transmission kernel as:

$$h\left(r_{ij}, N_i, N_j, \tau_i, \tau_j\right) = \frac{h_0}{1+\left(\frac{r_{ij}}{r_0}\right)^{\alpha}}\left(1 - \exp\left(-\frac{N_i}{\phi_1}\right)\right)\left(1 - \exp\left(-\frac{N_j}{\phi_2}\right)\right)\iota_{\tau_i}\sigma_{\tau_j} \quad (1),$$

where $\tau_i, \tau_j \in \{c, s, p\}$, in which "c", "s" and "p" stand for cattle, sheep, and pig. The parameter h_0 determines the amplitude of the kernel, which corresponds to its maximum value (when $r_{ij} = 0$); r_{ij} is the distance between the infectious farm i and the susceptible farm j; r_0 is the between-farm distance for which the kernel value is at half of its maximum, and parameter α determines the shape of the kernel, which corresponds to the rate of decline at long distances. N_i and N_j represent the number of animals in farm i and farm j respectively. ϕ_1 and ϕ_2 are scaling parameters that determine how infectiousness and susceptibility vary with farm size, respectively. $\iota_{\tau_i}\sigma_{\tau_j}$ denotes the mixing term, where ι_{τ_i} is the infectiousness of farm type (τ) for infectious farms i, and σ_{τ_j} is the susceptibility of farm type (τ) for susceptible farms j. For example, if infectious farm i has cattle and susceptible farm j has pig, then $\iota_{\tau_i}\sigma_{\tau_j} = \iota_{\mathrm{c}}\sigma_{\mathrm{p}}$.

Because cattle accounted for most affected herds in Uruguay's 2001 FMD epidemic, we set cattle as the reference category and fix their infectiousness and susceptibility at 1. Accordingly, in equation (1), the parameters ι_{τ_i} and σ_{τ_j} for sheep and pigs are expressed relative to cattle.

Given the transmission kernel, the daily force of infection experienced by a susceptible farm j on day t is defined as the cumulative contribution from all infectious neighbouring farms:

$$\lambda_j(t) = \sum_{i \neq j} h(r_{ij}, N_i, N_j, \tau_i, \tau_j) \times 1[i \; infectious \; at \; t], \qquad (2)$$

where $1[\cdot]$ is an indicator function equal to 1 if farm i is infectious on day t.

The force of infection determines both the probability of infection on a given day (equation 3), the probability of remaining uninfected up to day t (equation 4) and the probability that a farm remains uninfected throughout the observation period.

$$q_j(t) = 1 - e^{-\lambda_j(t)}, \qquad (3)$$

$$r_j(t) = e^{-\sum_{s=1}^{t-1}\lambda_j(s)}, \qquad (4)$$

Parameters were estimated by maximum likelihood. In the discrete-time model, each day farms either remain uninfected or become infected. Those probabilities define the likelihood, and we choose the values that maximize it. For infected farms, the likelihood contribution is, therefore, the probability of escaping on all prior days and becoming infected on day t. For farms that remained uninfected or were censored, the contribution is the probability of remaining uninfected over the observed at-risk period, ending on the vaccination-based removal date. For full derivations and implementation details, see Boender et al. (2007, 2010).

We compared four alternative kernel parameterisations across the two phases. Kernel 1 depends only on between-farm distance: $h(r_{ij}) = \frac{h_0}{1+\left(\frac{r_{ij}}{r_0}\right)^{\alpha}}$, with phase-specific parameters.

Kernels 2 to 4 derive from Eq. (1) and differ only in which parameters were held constant across phases or estimated separately by phase. In Kernel 2, the parameters ($\iota_{\tau_i}, \sigma_{\tau_j}$, ϕ_1, ϕ_2) were held fixed across phases, while the estimated core kernel parameters (h_0, r_0, α) were phase-specific. In Kernel 3, species parameters were held equal across phases, but farm-size effect parameters (ϕ_1, ϕ_2) and core kernel parameters were allowed to vary by phase. In Kernel 4 (full), all parameters were estimated separately by phase. Based on the Akaike information criterion (AIC), Kernel 2 was the best-fitting model (AIC = 27,015.9), outperforming the distance-only baseline kernel (31,143.2), Kernel 3 (27,019.2), and the full phase-specific model (27,022.7) (see Supplementary Table S1).

2.3. $R_{h,i}$ estimation and risk maps

The between-farm reproduction number $R_{h,i}$ for farm i was computed under both phase-specific kernels (Phase 1 and Phase 2) fitted to the epidemic data. Here, $R_{h,i}$ is the expected number of secondary farm infections generated by farm i if it were infectious for its full infectious period while all other surrounding farms remained susceptible. It thus quantifies that farm's potential for between-farm transmission if infected.

For a specific distribution of farms, the reproduction number $R_{h,i}$ of farm i is given by:

$$R_{h,i} = E\left[\sum_{j \neq i} P\left(r_{ij}, N_i, N_j, \tau_i, \tau_j, T_i\right)\right] \quad (5)$$

where the index j runs across all farms in the population except the infected farm.

All possible infection routes are represented by a single probability function:

$$P\left(r_{ij}, N_i, N_j, \tau_i, \tau_j, T_i\right) = 1 - \exp\left(-h\left(r_{ij}, N_i, N_j, \tau_i, \tau_j\right)T_i\right) \quad (6)$$

where T_i is the infectious period of farm i.

We derived species-specific infectious periods from the data and used the median as a fixed infectious duration for the source farm in $R_{h,i}$, cattle $T_i = 26.0$ days, sheep $T_i = 16.5$ days and pigs $T_i = 16.0$ days.

Using estimated $R_{h,i}$ we constructed risk maps for the 2001 epidemic and for the contemporary distribution of Uruguayan livestock farms (using 2023 data). For mixed-species farms, we aggregated species-specific estimates by taking the largest R_h per location, typically the cattle estimate when present.

2.4. Assessment of interventions

We simulated farm-to-farm spread using a discrete-time SEIR model parameterized with phase-specific kernels. We assumed a 14-day high-risk period (HRP). For the first 14 days we used the fitted Phase 1 spatial kernel (pre-vaccination). From day 15 onward, after FMDV detection in the model, we switched to the Phase 2 kernel. Newly infected farms passed through a 1-day latent period and then remained infectious for a fixed, species-specific duration derived from the 2001 data (cattle 26.0 days; sheep 16.5 days; pigs 16.0 days). We assumed that emergency vaccination began 18 days after the initial detection, approximately 3 days for epidemiological assessment and 15 days for vaccine

availability. Protection was assumed to begin 15 days post-vaccination for all species (PANAFTOSA, personal communication). The culling capacity of the Veterinary Services of Uruguay was two farms/day, as provided by its Epidemiology Department. Each day, culling priority was infected farms first, high-risk farms (higher R_h) second, and other eligible farms at random last. The vaccination capacity was 3,000 farms/day, reflecting long-standing national delivery capacity (most doses administered by farmers, sometimes by private veterinarians, with Veterinary Services supervision). For vaccination scenarios, we conservatively assumed 60% farm-level protection, the probability that a vaccinated farm is effectively protected after immunity onset, based on our field estimate from the 2001 Uruguay epidemic (Iriarte et al., submitted). The index case for each simulation was randomly selected among the farms located within the identified areas with high-risk of between-herd transmission.

Table 1 presents 13 different scenarios based on a combination of interventions being assessed. For each scenario, we simulated 10,000 epidemics to compare key outcomes such as epidemic duration, cumulative infected farms, culled farms, and vaccinated farms. All scenarios assumed a common baseline of compulsory measures, including establishment of surveillance zones, movement bans, and enhanced biosecurity.

S_0 was the baseline scenario, which consisted of culling only on infected farms. Two scenarios (S_1 and S_2) did not include vaccination. While S_1 included culling on infected farms and preventive ring culling of all cloven-hoofed animals (cattle, sheep, pigs) within a 1-kilometer radius, S_2 applied the same measures as S_1 but only to cattle herds.

Three scenarios included emergency ring vaccination of all species within 1-kilometer (S_3), 3-kilometer (S_4), and 10-kilometer radii of infected farms (S_5). Additionally, scenarios S_6, S_7, and S_8 tested emergency ring vaccination only of cattle herds within the same radii, respectively.

S_9 and S_{10} apply preventive vaccination to cattle on farms at the highest risk of between-farm transmission ($R_h \geq 0.8$). To account for delayed case detection in vaccinated populations, S_9 assumes a 3-week HRP and S_{10} a 4-week HRP. All other scenarios assume a 14-day HRP. Additionally, we tested two size-based targeting rules (S_{11} and S_{12}), vaccinating all cattle farms with ≥ 300 animals and ≥ 100 animals, respectively, as a pragmatic alternative to these risk-based scenarios.

Table 1 Control scenarios evaluated. All scenarios are implemented on top of baseline measures: movement control, enhanced biosecurity, and 3-km protection and 10-km surveillance zones. Unless stated otherwise, the high-risk period (HRP) is 2 weeks; scenarios explicitly noting a different HRP use that value.

Scenario	Strategy type	Action	Applies to
S_0	Baseline	Cull infected farms only	Cattle, Sheep, Pigs
S_1	Pre-emptive ring culling	Cull farms within 1 km of infected farms	Cattle, Sheep, Pigs
S_2	Pre-emptive ring culling	Cull farms within 1 km of infected farms	Cattle

S_3	Emergency ring vaccination	Vaccinate farms within 1 km of infected farms	Cattle, Sheep, Pigs
S_4	Emergency ring vaccination	Vaccinate farms within 3 km of infected farms	Cattle, Sheep, Pigs
S_5	Emergency ring vaccination	Vaccinate farms within 10 km of infected farms	Cattle, Sheep, Pigs
S_6	Emergency ring vaccination	Vaccinate farms within 1 km of infected farms	Cattle
S_7	Emergency ring vaccination	Vaccinate farms within 3 km of infected farms	Cattle
S_8	Emergency ring vaccination	Vaccinate farms within 10 km of infected farms	Cattle
S_9	Preventive targeted vaccination	Vaccinate high-risk farms ($R_h \geq 0.8$), assuming a 3-week HRP	Cattle
S_{10}	Preventive targeted vaccination	Vaccinate high-risk farms ($R_h \geq 0.8$), assuming a 4-week HRP	Cattle
S_{11}	Preventive targeted vaccination	Vaccinate farms with ≥ 300 animals, assuming a 3-week HRP	Cattle
S_{12}	Preventive targeted vaccination	Vaccinate farms with ≥ 100 animals, assuming a 3-week HRP	Cattle

3. RESULTS

To contextualise the results, we first described the epidemic data. We summarised the number and species composition of infected farms and farms that escaped infection in Phase 1 and Phase 2, and characterised their farm-size distributions. These summaries informed interpretation of the transmission-kernel parameters and the scenario comparisons (Table 2).

Table 2 Counts and species composition of infected and escaped-infection farms in Phases 1 and 2, with herd-size distributions.

Type	Phase 1-case	Phase 2-case	Escape infection
Cattle	959 (2.2%); median=440, mean=864	881 (2%); median=350, mean=710	41,890 (95.8%); median=65, mean=214
Sheep	0 (0%)	6 (<0.1%); median=371, mean=390	25,561 (99.9%); median=163, mean=468
Pigs	4 (0.1%); median=26, mean=40	5 (0.1%); median=36, mean=53	3,909 (99.8%); median=7, mean=25

Note: Counts are number of farms (percent of farms within species). Medians and means are herd size (animals).

3.1. Transmission kernel

Of the four kernels assessed, Kernel 2 minimized the AIC and was therefore selected. Relative to the basic kernel (dependent only on distance between farms i and j), Kernel 2 adds farm-size dependence and species heterogeneity for infectious farm i and susceptible farm j, with parameters ϕ_1, ϕ_2, $\iota_{\tau_i}, \sigma_{\tau_j}$ shared across phases, while core parameters h_0, α, r_0 are estimated separately for Phase 1 and Phase 2. Table 3 reports the parameter estimates for Phase 1 (pre-vaccination) and Phase 2 (post-vaccination) for the selected kernel. Parameter estimates for all four kernel specifications are provided in the Supplementary Information (Table S1).

Table 3 Spatial transmission kernel parameters for Phase 1 (pre-vaccination) and Phase 2 (post-vaccination). Estimates are shown with 95% confidence intervals (CIs) in brackets. The selected specification keeps herd-size dependence and species heterogeneity (relative infectiousness and susceptibility of sheep and pigs to cattle) constant across phases and estimates phase-specific λ (amplitude), α (shape), and r_0 (half-kernel distance)).

Description	Description	Phase 1 (pre-vaccination) [95% CI]	Phase 2 (post-vaccination) [95% CI]
$h_0\ (day^{-1})$	Amplitude (height)	0.0078 [0.0053-0.0104]	0.0053 [0.0042-0.0073]
$\boldsymbol{\alpha}$	Shape	1.9928 [1.8998-2.095]	2.0777 [1.9991-2.1652]
$r_0\ (km)$	Half kernel distance	6.0876 [4.9242-8.0335]	3.409 [2.7498-4.0365]
$\boldsymbol{\phi_1}$	Infectiousness farm-size dependence	1101.8 [938.181-1294.78]	1101.8 [938.181-1294.78]
$\boldsymbol{\phi_2}$	Susceptibility farm-size dependence	109.204 [80.2977-157.847]	109.204 [80.2977-157.847]
ι_c	Infectiousness of cattle (reference)	1	1
ι_s	Relative infectiousness sheep	0.0099 [0.0046-0.0152]	0.0099 [0.0046-0.0152]
ι_p	Relative infectiousness pig	0.0002 [0.0001-0.0003]	0.0002 [0.0001-0.0003]
σ_c	Susceptibility of cattle (reference)	1	1
σ_s	Relative susceptibility sheep	0.0037 [0.0025-0.0055]	0.0037 [0.0025-0.0055]
σ_p	Relative susceptibility pig	0.2272 [0.1612-0.3085]	0.2272 [0.1612-0.3085]

Cattle exhibit the highest relative susceptibility as well as the highest relative infectiousness.

The shape of the transmission kernel is shown in Figure 1.

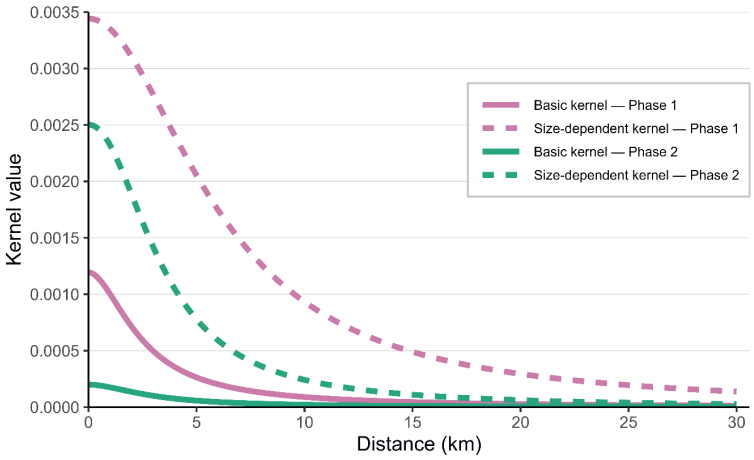


Figure 1 Spatial transmission kernels by phase and model specification. Phase 1 (pre-vaccination, purple) and Phase 2 (post-vaccination, green) are shown for the basic kernel (solid) and the herd-size-dependent kernel (dashed). Herd-size effects and species heterogeneity are held constant across phases. Phase-specific parameters are λ (amplitude), α (shape), and r_0 (half-kernel distance). Curves are evaluated at $N_i = 790$ animals and $N_j = 214$, the mean herd sizes computed from the data for infectious and susceptible cattle farms, respectively. For display, we show the cattle–cattle case only, fixing $\iota_c \sigma_c = 1$.

Figure 2 shows how herd size shapes both infectiousness (source farm i) and susceptibility (recipient farm j) in cattle farms. For visualization, we fixed the inter-farm distance at 5 km and varied the infectious-farm size (N_i) while holding the susceptible-farm size at its mean (N_j =214). Conversely, we varied N_j while holding the infectious-farm size at its mean (N_i =790). It can be seen that infectiousness increases with N_i but approaches a plateau around 3,000 animals, whereas susceptibility also rises with N_j and plateaus around 300 animals. Therefore, larger infectious farms are more likely to transmit, and larger recipient farms are more likely to become infected. However, while the probability of transmission keeps rising with the size of the source farm, the probability of getting infected plateaus around 300 cattle. Beyond this threshold, adding animals contributes little additional susceptibility.

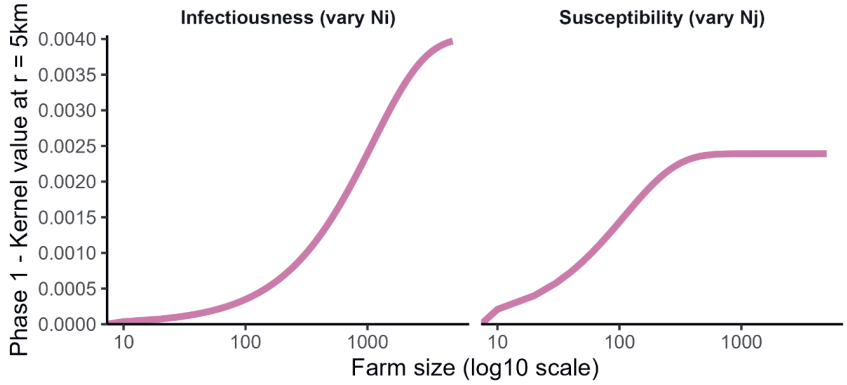


Figure 2 Farm-size effects on the transmission kernel at fixed distance (r = 5 km). Left panel (infectiousness): N_i varies, susceptible size held constant at N_j=214. Right panel (susceptibility): N_j varies,

infectious size held constant at N_i=790. Curves show the size-dependent kernel; shaded ribbons indicate pointwise 95% uncertainty obtained via parametric bootstrap from the parameter CIs. For display, we fix the species-pair to cattle–cattle, setting $\iota_c\sigma_c = 1$.

3.2. Risk maps

Figure 3 presents high-risk areas in Uruguay in 2001 derived from the between-herds reproduction numbers R_h. Farms were classified as high risk when $R_h \geq 0.8$ and low risk when $R_h < 0.8$. This threshold represents a conservative approach, accounting for variations in the mean R_h estimates. The left panel displays the map based on estimates computed with the Phase 1-kernel, and the right panel displays the map based on estimates obtained with the Phase 2-kernel.

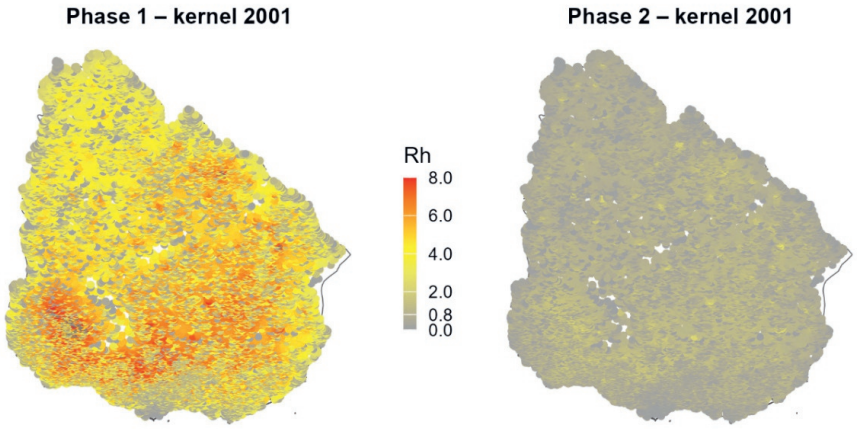


Figure 3 Risk maps for 2001 using two transmission kernels: left, between-farm R_h estimated with the Phase 1 (pre-vaccination) kernel; right, estimated with the Phase 2 kernel. Grey–red gradient indicates increasing between-farm R_h.

To quantify changes in farm-level reproduction numbers R_h between Phase 1 (pre-vaccination) and Phase 2 (post-vaccination), we computed the absolute difference between R_h estimated with the Phase 1 and Phase 2 kernels for each farm ($\Delta R_h = |R_{h,1} - R_{h,2}|$), and the relative reduction ($(1-R_{h,2}/R_{h,1})$ *100). Across 46,191 locations, the mean absolute decrease was 2.24 R_h units (SD 1.70), and the mean relative reduction was 76.29% (SD 4.26%).

Figure 4 shows the spatial distribution of farm-level reproduction numbers (R_h) across Uruguay for 2001 and 2023. The distribution of R_h values differed between 2001 and 2023. In 2023, a larger fraction of farms had $R_h > 1$ compared with 2001 (53.5% vs 45.8%). The median R_h increased from 0.67 (Q1–Q3: 0.03–3.51) in 2001 to 1.42 (Q1–Q3: 0.03–4.36) in 2023, indicating a shift of the distribution towards higher values.

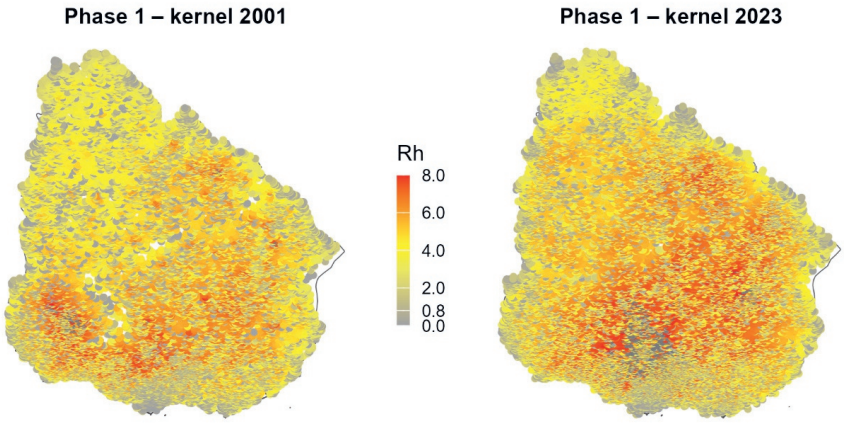


Figure 4 Risk maps for 2001 (left) and 2023 (right), Phase 1 kernel; grey–red gradient indicates increasing between-farm R_h.

3.3. Control measures assessment

For this study, a major epidemic was defined as an event in which 10 or more farms were affected. Here we present summary statistics on epidemic duration and on the numbers of infected, culled, and vaccinated farms, conditional on major epidemics (≥10 affected farms).

Once FMD is confirmed on a holding, all FMDV susceptible species on that holding are culled, regardless of which species is affected. In our dataset the epidemiological unit is the farm, defined as a species-specific farm. Therefore, multispecies holdings are represented as separate records per species (e.g., one cattle-farm, one sheep-farm, one pig-farm) that share the same coordinates. Consequently, when any species on a multispecies holding becomes infected, culling applies to all co-located species-farms, so the number of culled farms can exceed the number of infected farms. This is expected because around 46% of holdings are multispecies (42% with two species; 4% with three).

Over 10,000 simulations per scenario, the proportion of major epidemics (≥10 affected herds) was lower for the preventive targeted vaccination scenarios (S_9: 37.5%, S_{10}: 38.2%, S_{11}: 48.0%, S_{12}: 41.9%) compared with the other scenarios (mean 54.5%, range 53.8–55.0%).

The baseline scenario (S_0) showed the highest median number of infected farms and the longest epidemic duration. For this scenario, the estimated median number of detected farms was 11,382 [IQR 8478–14529] for cattle farms, 19 [IQR 13–28] for sheep farms and 30 [IQR 21–44] for pig farms, and the predicted median outbreak duration was 284 [IQR 220–398] days (Table S2).

Applying measures to all species versus cattle-only yielded similar outcomes at 1 km and 3 km (for both preventive culling at 1 km and ring vaccination at 1 and 3 km) in terms of

epidemic duration and total infected farms. At a 10-km radius, cattle-only ring vaccination (S_8) reduced the total number of infected farms compared with all-species vaccination (S_5). We therefore focus subsequent analyses on cattle-only measures. Results for all scenarios are provided in Table S2, Figure S1 and Figure S2 (Supplementary Information).

Relative to baseline, preventive 1-km culling of cattle farms (S_2) shortened epidemics and reduced the number of infected farms. Vaccination of cattle at 1 km (S_6) performed worse than preventive culling at the same radius, but expanding the ring to 3 km (S_7) and especially to 10 km (S_8) markedly shortened epidemics and reduced the epidemic size. Compared to emergency 10-km vaccination, targeted vaccination of farms with $R_h \geq 0.8$ (S_9 vs S_8) yielded many fewer infected farms with only a slight increase in epidemic duration (2–4 days). The preventive vaccination scenario (S_9) results in the lowest number of infected farms 113 [IQR 48–236] (Figure 5).

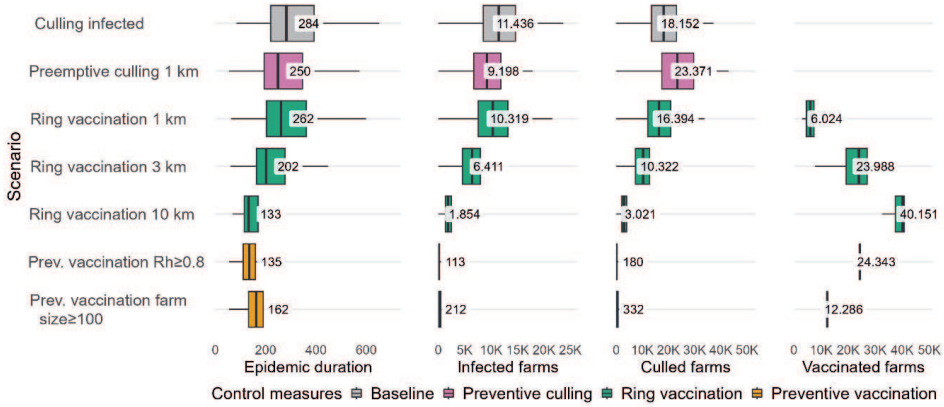


Figure 5 Outcomes of cattle-only FMDV control scenarios. Boxplots summarise the distribution across simulations (major outbreaks only; ≥10 infected herds). Panels, left to right: epidemic duration (days), infected farms, culled farms, and vaccinated farms. Numeric labels indicate medians. Interventions are applied only to cattle; once infection is detected on a holding, all susceptible species on that holding are culled. Fill colours denote control measures: Baseline (grey), Pre-emptive culling (purple), Ring vaccination (green), and Preventive vaccination (orange).

4. DISCUSSION

In this study, the phase-specific estimated transmission kernels from the 2001 FMDV epidemic in Uruguay was used in an individual farm-based stochastic model to simulate FMDV spread in Uruguay, and to assess a variety of control measures. The epidemiological parameters for FMDV quantified using data from the 2001 epidemic in Uruguay can provide useful information for other countries that have not experienced large epidemics and have a livestock farming system similar to Uruguay, where cattle rearing on natural pastures predominates. We were able to improve our understanding of FMDV transmission and its dependence on farm size and livestock species, which has

important implications in developing species-specific control strategies in mixed livestock populations.

The spatial transmission kernel integrates all potential routes of spread, which is advantageous because it avoids relying on route-specific parameters that are often unavailable. However, this aggregate structure prevents us from quantifying the contribution of each route, limiting how precisely we can target control measures. To partially address this, we fitted phase-specific kernels, allowing kernel shape to change across epidemic stages. The distance at which the transmission probability is half of the maximum (r_0) decreased from 6.1 km [95%CI 4.9-8.0] in Phase 1 to 3.4 km [95%CI 2.8-4.0] in Phase 2. This pattern is consistent with longer-range processes (movement of animals, people, and vehicles) contributing more early in the epidemic, and local transmission by proximity or airborne spread contributing more later. These findings underscore the need for rapid detection to prevent long-distance movement before identification of the index case and for strengthened biosecurity to reduce indirect transmission. Nevertheless, because the kernel aggregates routes, we cannot attribute transmission to specific pathways. Integrating movement and contact data would be required to do so.

Overall, the results suggest that cattle played a dominant role in transmission during the epidemic in Uruguay. For pigs and sheep, estimates indicate lower susceptibility and infectiousness relative to cattle. Species effects should be interpreted in the context of Uruguay's livestock composition (Table S3). Farms keeping cattle are the overwhelming majority, cattle were present on 97.4% of farms in 2001. Sheep were also common, 57.0% of farms in 2001, while pigs were present in 8.8% of farms. The two dominant holding types were cattle-only (39.3%) and mixed cattle–sheep (49.4%), together accounting for 88.7% of farms in 2001. Approximately 50% of infected farms in 2001 were mixed cattle–sheep farms (Iriarte Barbosa et al., 2023), which typically co-graze. However, only six of these farms reported clinically affected sheep. Under-ascertainment in sheep could have occurred because clinical signs are often mild (Kitching & Hughes, 2002). Nevertheless, a national post-epidemic serosurvey (unpublished) reported animal-level seroprevalence of antibodies against the FMDV infection-associated antigen (VIAA) of 1.9% in sheep within the focal area (≤5 km from the focus), showing that infection among sheep was limited in this epidemic. The low number of infections in sheep and pigs limits precision and comparability, so these terms function primarily as adjustment covariates in the model rather than as robust between-species inferences.

In addition, our estimates reflect context-specific susceptibility and infectiousness rather than intrinsic species traits from controlled experiments that often rank pigs as more infectious than cattle due to higher virus shedding (Orsel, de Jong, et al., 2007) and from estimates suggesting similar cattle–sheep susceptibilities (Bravo De Rueda et al., 2014). Our data suggest transmission was predominantly cattle-driven in Uruguay 2001. In addition to livestock structure, the potential strain-dependent host differences should be taken into account. For example, some strains are less virulent in cattle but remain virulent in pigs such as the specific strain of FMDV that caused an outbreak in Taiwan in 1997 (Dunn & Donaldson, 1997), or vice versa, FMDV strains less adapted to pigs, as the Asia1 strain which predominantly affects cattle and sheep rather than pigs (P. C. Yang et al., 1999). Ferguson et al. (2001) reported that during the 2001 epidemic in Great Britain,

cattle-type farms had the highest susceptibility, whereas pig-type farms had the lowest. They also found that smaller farms were markedly less infectious and less susceptible than larger farms, in line with our results on herd size.

Different effects of herd size on infectiousness and susceptibility were observed. Herd size strongly scaled infectiousness but had less influence on susceptibility, which remained nearly constant across sizes higher than approximately 300 animals (Figure 2). Above this threshold, additional animals contribute negligibly to the probability of becoming infected. Consistent with this pattern, the distribution of cattle-farm sizes was shifted toward larger herds among cases compared with farms that escaped infection (Table 2).

By estimating the between-farm reproduction numbers (R_h) for each farm in Uruguay, transmission risk-maps were generated for years 2001 and 2023. In contrast to countries such as the Netherlands (Boender et al., 2010) or Japan (Hayama et al., 2013), no localized high-risk areas were detected. High-risk farms are broadly dispersed nationwide, largely because the transmission probability scales with cattle herd size. This diffuse pattern suggests that geographically narrow measures, such as ring vaccination, may be less effective in these settings than in contexts with strong spatial clustering.

Farm-to-farm transmission risk (represented by the estimated R_h) fell on average by 76% between the first phase and the second phase of the epidemic. This gives an indication of the overall effectiveness of the control measures implemented. Estimating the same effect via the reduction in the amplitude of the phase-specific kernels yields a similar estimate of approximately 83% effectiveness, calculated as: $\left(1 - {\mathrm{h}_{0,2}}/{\mathrm{h}_{0,1}}\right) * 100$, where $\mathrm{h}_{0,1}$ and $\mathrm{h}_{0,2}$ are phase-specific estimates for pre- and post-vaccination, respectively. A comparable magnitude of impact was observed in the simulation analysis. In the simulations, emergency vaccination of cattle within a 10 km radius, the strategy most closely resembling that applied in 2001, reduced epidemic duration by approximately 53% and the number of infected farms by approximately 84%.

An increase in the proportion of farms with $R_h > 1$ was observed in 2023 (Figure 4), likely due to changes in livestock demographics. Farm-type composition differed between 2001 and 2023 ($\chi^2 = 284.6, p < 2.2 \times 10^{-16}$). The proportion of cattle-only farms increased from 39% to 50%, whereas two-species farms declined from 53% to 42%. Within the latter, cattle–sheep holdings decreased from 49% to 40% (Table S3). Overall, the sheep population decreased significantly from around 12 million to 6 million head, while the cattle population increased by approximately 2 million head. Farm-size distributions changed by species, the median increased slightly for cattle (8 heads), but with a heavier right tail decreased markedly for sheep (100 heads), with a narrower spread, and changed minimally for pigs (1 head). See Supplementary Figure S3. These demographic shifts, together with the higher proportion of farms with R_h>1 estimated for 2023, indicate that an FMDV introduction today would have a higher probability of sustained transmission than in 2001. Outcomes would still depend on timely detection and on the coverage, geographic extent, and speed of the selected control measures.

Our study indicates that focusing control on cattle achieves similar (or better, at 10 km) outcomes than all-species measures at the same radius while requiring fewer farms to be

vaccinated. At small radii, pre-emptive culling outperforms emergency vaccination, but vaccination gains efficacy as the radius increases. Consistent with previous studies (Hayama et al., 2013), culling infected farms is often the most effective option because it shortens the infectious period. However, under Uruguayan production conditions this is operationally challenging as the mean herd size is around 400 heads. Moreover, our results indicate that larger farms are more likely to become infected further constraining the practicality of culling. Consequently, the Official Veterinary Service have a culling capacity of only two farms per day, which probably hinder the effectiveness of culling strategies for controlling FMD spread. By contrast, vaccination capacity is far greater, approximately 3,000 farms per day, because most vaccinations would be carried out by farmers, who have extensive experience from systematic campaigns since the 2001 epidemic (Iriarte Barbosa et al., 202; Sutmoller et al., 2003). In our simulations, preventive vaccination targeted to high-risk farms ($R_h \geq 0.8$) was the most effective strategy, reducing epidemic duration by approximately 53% and the number of infected farms by approximately 99% relative to the base scenario. Implementing this approach would require vaccinating approximately 24,000 farms, about half of all farms in Uruguay.

Compared with the risk-based scenario (S_9: vaccinate farms with $R_h \geq 0.8$), the size-based scenario (S_{12},: vaccinate farms with ≥100 animals) required approximately 50% fewer vaccinations (median 12,286 vs 24,343) but produced worse outcomes. The median epidemic lasted 27 days longer (162 vs 135), 100 more farms became infected (211 vs 111), and around 150 more farms were culled (332 vs 180). This highlights a clear trade-off between operational simplicity (vaccinate farms with ≥100 animals) and epidemiological performance (vaccinate farms with $R_h \geq 0.8$).

We extended the assumed HRP (the interval from infection to detection) for the preventive-vaccination scenarios by one week in S_9, S_{11} and S_{12}, and by two weeks in S_{10}, compared with the other scenarios, to reflect that vaccination can mask clinical signs and thereby reduce the sensitivity of passive surveillance. Strengthening detection during preventive campaigns, for example through farmer education and awareness activities, could enhance the effectiveness of these preventive-vaccination scenarios. When preventive vaccination is undertaken (e.g., because the risk of FMDV introduction is elevated due a regional outbreak), targeted active surveillance can also be implemented to shorten detection times and thereby further improve effectiveness. Moreover, we assumed a conservative vaccine effect. An 18-day lag to start vaccination (15 days to vaccines supply), 60% protection, and effective immunity beginning on day 15 post-vaccination. These parameters provide lower-bound estimates of the effectiveness of vaccination scenarios. In practice, higher-potency formulations and better antigenic match may accelerate the onset of protection and raise effectiveness. Access to antigen or vaccine banks can further improve outcomes by shortening time to availability, enabling rapid deployment of strain-matched and high-potency vaccine. Optimizing implementation (coverage, timeliness, cold-chain integrity, correct dosing) would increase effectiveness beyond the estimates reported here. Consequently, all scenarios that include vaccination would be expected to perform better than reported here, with additional reductions in the number of infected farms and in epidemic duration.

Our results can contribute to inform decision-makers about control measures to take in the event of an increased risk or an introduction of the FMDV into the country. While the decision will depend on the epidemiological scenario, we consider that this study, by identifying high-risk farms, provides an excellent tool for emergency preparedness in Uruguay, with the potential for implementing targeted surveillance and/or control measures on these farms.

5. CONCLUSION

This study advances understanding of between-farm FMDV transmission in pasture-based livestock production systems, a relatively understudied setting. During the 2001 FMD epidemic in Uruguay, cattle drove the spread and were both more susceptible and more infectious than other species. Farm size increases the overall risk of transmission, with a greater effect on infectiousness than on susceptibility. Demographic changes in Uruguay since 2001 have raised the overall risk, indicating that a new introduction could sustain a longer epidemic unless control is rapid. Therefore, early detection is pivotal, and strengthening Uruguay's surveillance and reporting is essential. During periods of elevated regional risk, preventive vaccination of farms with ≥100 head of cattle is a pragmatic, high-impact strategy. Effective preparedness in Uruguay depends on rapid access to strain-matched, high-potency vaccines, which supports maintaining and using antigen and vaccine banks. Finally, our results provide model-ready parameters to support preparedness in FMDV-free countries that have not experienced large epidemics and have livestock production systems similar to Uruguay's, where cattle rearing on natural pastures predominates.

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Supplementary information

Table S1 Parameter estimates for four spatial transmission kernels fitted across Phase 1 and Phase 2. ***Kernel 1*** *(basic kernel): phase-specific core parameters* (λ_0, r_0, α). ***Kernel 2****: adds farm-size dependence and species heterogeneity, which parameters* $\phi_1, \phi_2, \iota_{\tau_i}, \sigma_{\tau_j}$ *shared across phases; core parameters remain phase-specific.* ***Kernel 3****: species parameters shared across phases* ($\iota_{\tau_i}, \sigma_{\tau_j}$)*; farm-size dependence* (ϕ_1, ϕ_2) *and core parameters differ by phase.* ***Kernel 4*** *(full kernel): all parameters differ by phase. Best-fitting model by AIC is highlighted.*

		Kernels					
	Parameter	**Basic kernel**	**final kernel**: same (size, infectiousness, susceptibility) rate for pre- and post-vaccination			**Different size**	**Full kernel**
			Lower CI	**mean**	Upper CI		
Phase 1 (pre-vaccination)	$\lambda_0\ (day^{-1})$	0.00119566	0.0053065	**0.00782903**	0.0103639	0.0120817	0.0090302
	$\boldsymbol{\alpha}$	1.80469	1.89976	**1.99284**	2.09499	1.92516	1.97152
	$r_0\ (km)$	2.48183	4.92415	**6.08759**	8.03345	4.58095	5.63609
	$\boldsymbol{\phi_1}$		938.181	**1101.8**	1294.78	1307.53	1250.53
	$\boldsymbol{\phi_2}$		80.2977	**109.204**	157.847	69.1112	78.2825
	I_s		0.00458159	**0.00992625**	0.0152163	0.00786551	0.0107213
	I_p		0.000133463	**0.000217749**	0.000315173	0.00085534	0.0007367
	σ_s		0.00248782	**0.00366849**	0.00545727	0.00373372	0.0013784
	σ_p		0.161178	**0.227179**	0.308496	0.18074	0.136649
Phase 2 (post-vaccination)	$\lambda_0\ (day^{-1})$	0.00019961	0.00421266	**0.00525916**	0.00725332	0.00479736	0.0052681
	$\boldsymbol{\alpha}$	1.7922	1.99912	**2.07769**	2.16518	2.10719	2.0885
	$r_0\ (km)$	3.02304	2.74983	**3.40895**	4.03646	3.66846	3.39881
	$\boldsymbol{\phi_1}$		938.181	**1101.8**	1294.78	990.399	977.572
	$\boldsymbol{\phi_2}$		80.2977	**109.204**	157.847	156.064	156.227
	I_s		0.00458159	**0.00992625**	0.0152163	0.00786551	0.0002025
	I_p		0.000133463	**0.000217749**	0.000315173	0.00085534	0.119245
	σ_s		0.00248782	**0.00366849**	0.00545727	0.00373372	0.0060767
	σ_p		0.161178	**0.227179**	0.308496	0.18074	0.232448
	AIC	**31143.2**	**27015.9**			**27019.2**	**27022.7**

Table S2 Summary by scenario. Values shown as median [IQR: Q1–Q3].

Scenario	Epidemic duration (days)	Infected cattle farms	Infected sheep farms	Infected pig farms	Farms culled	Farms vaccinated
s0	284 [220–398]	11382 [8478–14529]	19 [13–28]	30 [21–44]	18152 [13527–23089]	0 [0–0]
s1	253 [196–358]	9063 [6601–11614]	16 [11–23]	22 [15–33]	27804 [20734–34910]	0 [0–0]
s2	250 [195–351]	9157 [6682–11780]	18 [11–27]	26 [17–40]	23371 [17446–29626]	0 [0–0]
s3	259 [201–360]	10353 [7620–13228]	18 [12–27]	27 [18–40]	16530 [12210–21059]	9260 [7087–11401]
s4	204 [163–281]	6335 [4522–7898]	13 [8–20]	16 [10–25]	10246 [7319–12765]	36849 [29444–41835]
s5	136 [123–170]	2219 [1319–3832]	7 [3–12]	9 [4–19]	3556 [2154–6041]	58370 [55245–59647]
s6	262 [204–365]	10268 [7547–13093]	19 [13–28]	30 [20–44]	16394 [12084–20888]	6024 [4612–7404]
s7	202 [164–278]	6362 [4546–7894]	19 [10–29]	27 [15–44]	10322 [7378–12824]	23988 [19295–27036]
s8	133 [115–170]	1810 [1327–2422]	17 [7–31]	22 [9–41]	3021 [2192–4001]	40151 [37442–40662]
s9	135 [111–159]	111 [48–236]	0 [0–1]	0 [0–1]	180 [78–386]	24343 [24276–24412]
s10	151 [128–173]	185 [77–374]	1 [0–1]	1 [0–2]	299 [123–602]	24341 [24277–24412]
s11	254 [220–299]	1067 [397–2192]	2 [1–5]	4 [1–10]	1678 [621–3410]	6118 [6084–6152]
s12	162 [132–190]	211 [82–474]	0 [0–1]	1 [0–3]	332 [131–744]	12286 [12239–12334]

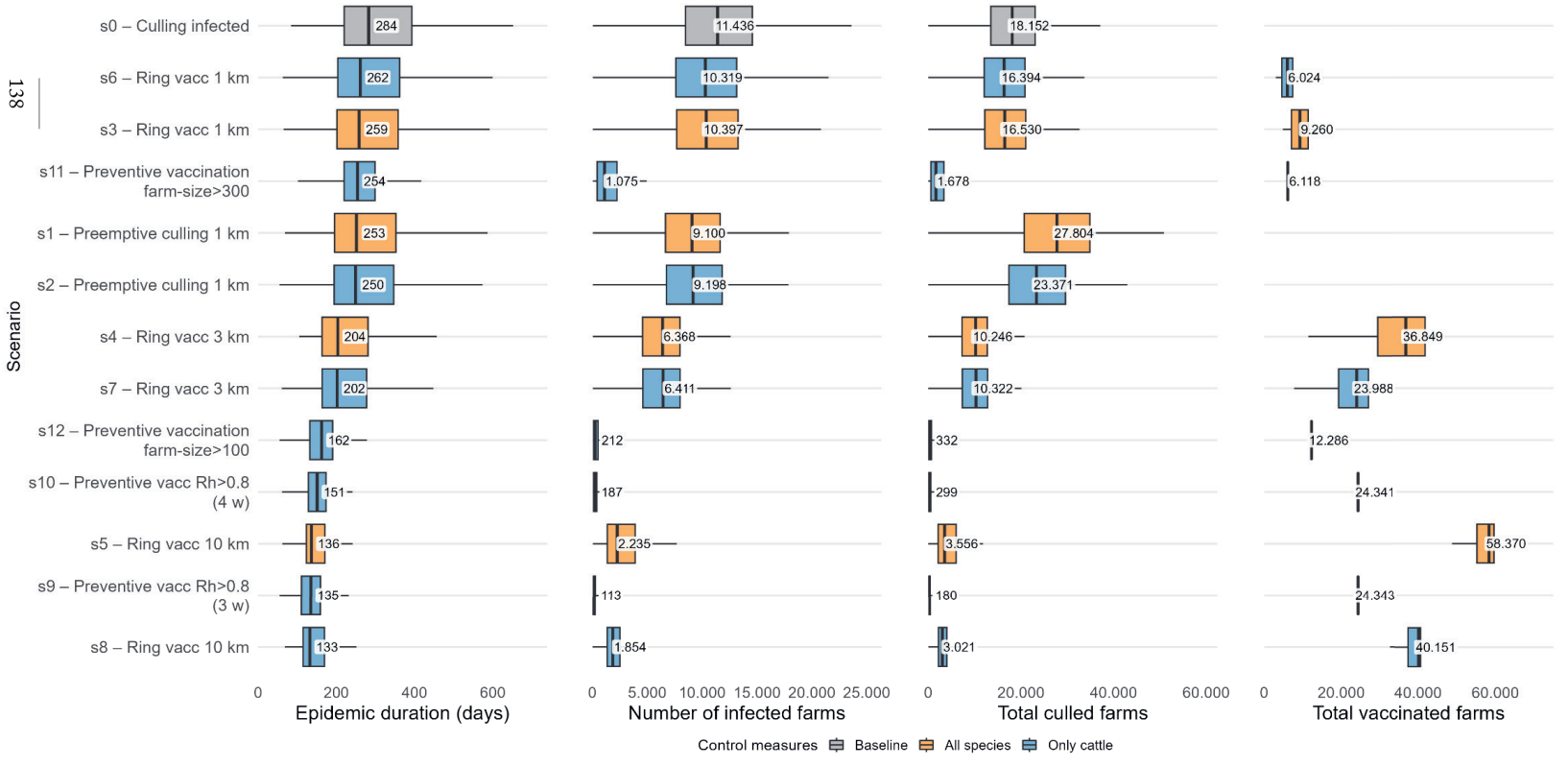


Figure S1 Outcomes of FMDV control scenarios simulated. Boxplots summarise the distribution across simulations for each scenario (only "major" outbreaks are shown; ≥10 infected herds). Panels display, from left to right: epidemic duration (days), number of infected herds, total culled herds, and total vaccinated herds. Scenarios on the y-axis are ordered by median epidemic duration; numeric labels indicate medians. Fill colours denote control measures: Baseline (culling of detected herds only, grey), All species (measures applied to all cloven-hoofed animals, orange), and Only cattle (blue).

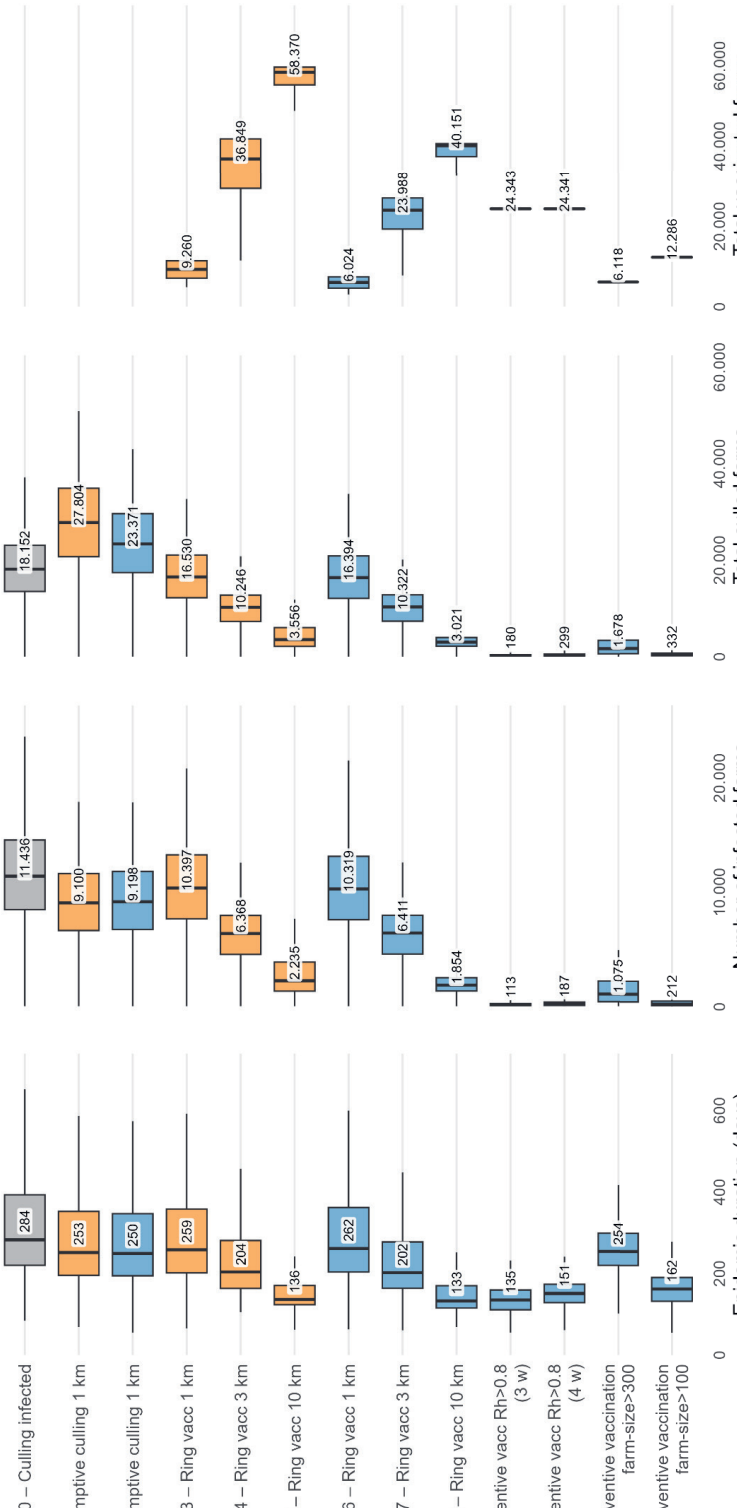


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Table S3 Farm species composition in Uruguay (2001 vs 2023). Counts of farms and percentages by species combination, stratified by composition type (single species; mixed: two species; mixed: three species). "Within type (%)" uses, as denominator, the total farms in that composition type for the given year; "Of all farms (%)" uses all farms in that year. Note: Data for pig-only farms in 2001 were not available (NA).

Type	Species combination	2001			2023		
		Farms	Within type (%)	Of all farms (%)	Farms	Within type (%)	Of all farms (%)
single species	Cattle	17,671	93.8	39.3	24,518	91.9	50.0
	Sheep	1,167	6.2	2.6	1,947	7.3	4.0
	Pigs	NA	NA	NA	228	0.9	0.5
	Total	*18,838*		*41.9*	*26,693*		*54.4*
mixed: 2 species	cattle+sheep	22,178	92.8	49.4	19,500	94.9	39.7
	cattle+pigs	1,696	7.1	3.8	890	4.3	1.8
	sheep+pigs	37	0.2	0.1	160	0.8	0.3
	Total	*23,911*		*53.2*	*20,550*		*41.9*
mixed: 3 species	cattle+sheep+pigs	2,185		4.9	1,835		*3.7*
Total		44,934			49,078		

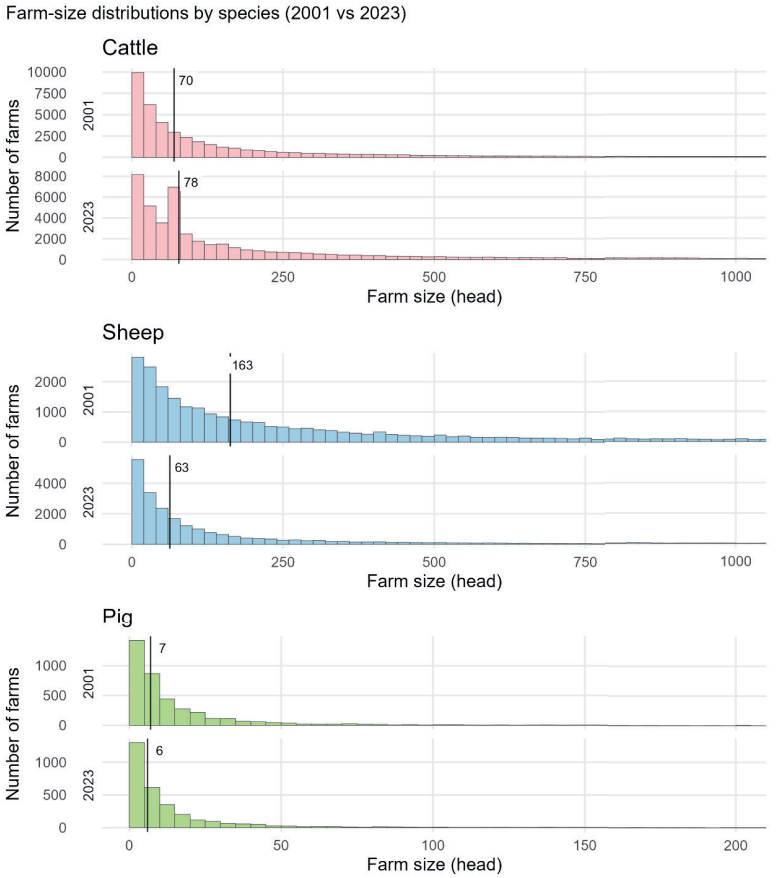


Figure S3 Histograms of farm size (head) by species (Cattle, Sheep, Pig) in 2001 (top row of each panel) and 2023 (bottom row). Bars show the number of farms. The vertical line indicates the median for each year. Axes are truncated to improve readability: 0–1000 head for cattle and sheep, 0–200 for pigs (farms above these limits are not displayed but are included in statistics). Bin widths: 20 head for cattle and sheep, 5 head for pigs.


Chapter 6

General Discussion

María Victoria Iriarte Barbosa

FROM EVIDENCE TO PREPAREDNESS

The main objective of this research was to advance understanding of foot-and-mouth disease virus (FMDV) transmission following its introduction into a previously FMDV-free country with pasture-based livestock production system. Understanding transmission is essential because control succeeds only when it reduces transmission sufficiently, meaning that the effective reproduction number (R_e) falls below one. Transmission is driven by context-specific factors that vary across settings. These drivers include the spatial distribution of farms, farm size, species composition, and the structure of animal movement networks, and have been studied extensively in developed countries with intensive production systems, particularly after the 2001 epidemic in the United Kingdom (UK). By contrast, quantification of transmission in countries with pasture-based production systems remains under-documented. The large 2001 FMD epidemic in Uruguay provided a valuable opportunity to improve understanding in such systems, by estimating key transmission parameters and assessing the factors that influenced between farm transmission. These estimates were subsequently used to inform simulation models of FMDV spread in Uruguay and may also support preparedness modelling efforts in other countries. Therefore, the resulting insights are particularly relevant for settings with similar production conditions and may become increasingly important as sustainable livestock production shifts toward more extensive systems in other regions.

In addition, the 2001 FMDV epidemic in the UK provided an important reference for evaluating the effectiveness of control strategies on transmission. However, control of that epidemic relied on stamping-out measures and did not include emergency vaccination. In contrast, the Netherlands implemented emergency vaccination as part of the control strategy, followed by the culling of vaccinated animals (Bouma et al., 2003). In endemic contexts, including Thailand (Chanchaidechachai et al., 2024), vaccination has also been applied as a control measure. Experimental studies have shown that emergency vaccination can substantially reduce transmission between cattle, lowering the within-herd reproduction number to values below one (Orsel, de Jong, et al., 2007; Orsel et al., 2005). When transmission between animals within a herd is effectively interrupted, sustained infection within the farm cannot be maintained. Consequently, transmission between farms is also prevented. These experimental estimates have subsequently been incorporated into transmission models to assess the potential impact of vaccination on between-farm spread (Backer, Hagenaars, et al., 2012; Tildesley et al., 2006). In contrast to experimental studies, field-based evaluations of vaccine effectiveness capture the combined effect of the vaccine (potency or antigenic match) and the broader implementation context, introducing additional determinants of the observed effectiveness. These include characteristics of the vaccination programme (e.g. coverage, cold-chain maintenance, and the act of vaccination itself), as well as concurrent control measures such as movement restrictions and biosecurity interventions. Nevertheless, the effect of emergency vaccination on between-farm transmission has not been widely studied using field data. The 2001 epidemic in Uruguay represents a particularly valuable case study, as mass vaccination with commercial vaccines was implemented in a previously FMDV-free country without vaccination. Our results provide additional field-based evidence that, even in emergency situations where high-potency vaccines may not be readily available, the use of a good-quality commercial vaccine, combined with

complementary control measures such as movement restrictions and enhanced biosecurity, can be sufficient to interrupt transmission between farms.

Taken together, this thesis provides a framework to interpret the dynamics observed during the 2001 epidemic. The large scale of the 2001 FMD epidemic in Uruguay can be largely explained by delayed detection of FMDV incursions. By the time the index farm was recognised, infection had likely already reached more than 200 farms throughout the country. In addition, the timing and geography of the earliest foci are consistent with multiple introductions from Argentina (**Chapter 2**). During the high-risk period (HRP), which is the interval between virus incursion and detection, animal movements spread the virus across regions (**Chapter 3**), limiting the effectiveness of early, localised control measures. Control was achieved once emergency mass vaccination of cattle was added to the movement ban and strengthened biosecurity, reducing transmission sufficiently, and bringing R_e below one. The livestock population structure of Uruguay, characterised by a cattle-dominant system with many large farms, shaped transmission dynamics and helped sustain spread (**Chapter 5**).

This chapter synthesizes the main findings, identifies remaining uncertainties, and discusses their implications for preparedness.

Epidemiological Implications of Detection Delay

An initial review of the epidemic data showed uncertainty in farm-level onset of clinical signs dates, as it was often recorded at the first official visit, when many animals were already clinically affected. Because infection timing is central to all subsequent analyses, we reconstructed farm-level infection dates (**Chapter 2**) using a simple stochastic within-herd SEIR (Susceptible-Exposed-Infectious-Removed) model for cattle. The analysis indicated that, when the first outbreak was confirmed, infection had probably already reached 242 farms distributed nationwide (Figure 1).

The geographically widespread epidemic likely reflects a combination of factors, notably at least two-week detection delay that allowed infected animals to move during the HRP, especially through highly connected nodes such as livestock markets, thereby enabling long-distance spread (**Chapter 3**). Similarly, delayed detection has also been identified as a major factor contributing to the scale of other large FMD epidemics, such as the 2001 outbreak in the United Kingdom, where the HRP lasted about 20 days before the first diagnosis (Gibbens et al., 2001). In the 2001 outbreak in the Netherlands, the interval between virus introduction and detection of the index case was estimated at approximately three weeks (Bouma et al., 2003). In Japan, during the 2010 FMD epidemic, the virus was estimated to have been introduced nearly one month before the first detection (Muroga et al., 2012). Taken together, these comparisons suggest that the true HRP in Uruguay may have exceeded two weeks, indicating that our two-week estimate is likely conservative.

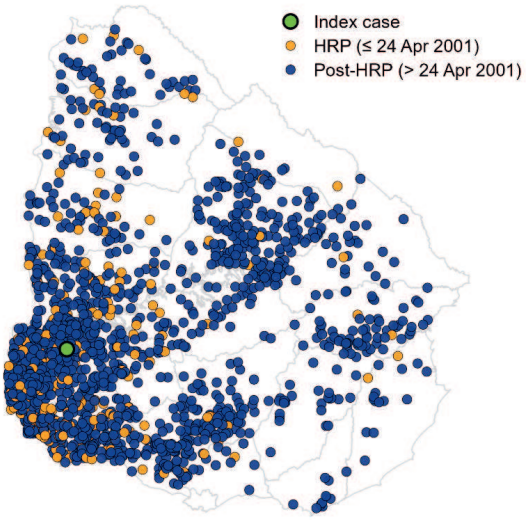


Figure 1 Spatial distribution of infected farms by FMDV introduction date during the 2001 epidemic in Uruguay. Each dot represents a farm, classified by its estimated infection date: index case (green), high-risk-period (HRP) (≤ 24 Apr 2001) (orange), and post-HRP (> 24 Apr 2001) (blue). Department boundaries are shown in grey for reference.

Furthermore, multiple introductions from Argentina likely occurred. At the time, Argentina was experiencing an FMDV serotype A epidemic that had begun before January 2001 (Perez et al., 2004). The concurrence of early infections across distant regions, in the absence of traceable movement connections, is more consistent with repeated introductions than with spread from a single source. In this context, the Uruguayan departments along the Argentine border experience intense cross-border movement of tourists, hunters, and people involved in agriculture. These movements provide potential opportunities for indirect virus introduction. The most plausible pathway of FMDV introduction is therefore via fomite rather than live-animal movement as there were no recorded legal livestock movements across the border, the Uruguay River acts as a natural barrier that limits illicit crossings, and farms closer to the border had higher infection risk (**Chapter 2**).

Several findings suggest that indirect transmission pathways such as movements of vehicles and people may also have contributed to FMDV spread before detection. During the HRP, farms that combined livestock and crop production had higher odds of becoming infected [OR 1.93 (95% CI 1.43–2.60)], consistent with greater indirect exposure to contaminated equipment and personnel (**Chapter 2**). In addition, of the 242 farms infected during the HRP, only 34 had recorded animal movements, meaning that no livestock movements were documented for 208 infected farms (**Chapter 3**), further supporting the contribution of transmission routes other than animal movements.

Our results highlight the need to continuously strengthen surveillance and awareness systems to enable early detection in the event of an FMDV introduction. Detection lag, and the resulting delay in implementing control measures, critically shapes epidemic size, and therefore eradication feasibility and economic impact. For example, a study in California, USA, using a simulation model showed that extending detection from 7 to 22

days increased epidemic size from 15 to 745 infected farms, and costs from US$2.3 billion to US$69 billion (Carpenter et al., 2011). Early detection of FMD can be delayed by multiple factors, from the limited sensitivity of passive surveillance to producer reluctance to report due to concerns about restrictions, costs, and stigma. To shorten these delays, authorities must address both technical and behavioural barriers. Behavioural work underscores the role of risk perception, trust, and perceived consequences in under-reporting (Elbers et al., 2010). Complementing these insights, a modelling study in Victoria, Australia showed that the most effective path to earlier detection is investing in producer education and reporting, strengthening the passive surveillance system more than adding active surveillance such as saleyard screening or bulk-milk testing (Garner et al., 2016). However, in modelling analyses of the 2010 Japan FMD epidemic (Hayama et al., 2013), a two-week reduction in the detection delay substantially decreased the epidemic size, yet large epidemic still occurs in 35% of iterations. This underscores that early detection is necessary but not sufficient. Epidemic magnitude is also determined by which control measures are adopted and how rapidly they are implemented.

Quantifying between- farm transmission and its drivers

The epidemic curve, which represents the distribution of cases over time, is presented in Figure 2. In contrast to the epidemic curve shown in the General Introduction (**Chapter 1**), which was based on the date of farm visit, this curve is constructed using the estimated date of infection. It shows a rapid rise followed by an extended tail. Newly infected farms increased from the first case until May 10, peaking at 55 farms per day.

This temporal pattern provided the basis for defining the epidemic phases used in the transmission modelling. In **Chapter 5**, between-farm transmission was quantified using a spatially explicit Susceptible–Exposed–Infectious–Removed (SEIR) model, with transmission described by a distance-based kernel that incorporates farm type and farm size. Kernel parameters were inferred from observed incidence, farm locations, farm type, and farm size across two epidemic phases: pre-vaccination (Phase 1) and post-vaccination (Phase 2) (Figure 2).

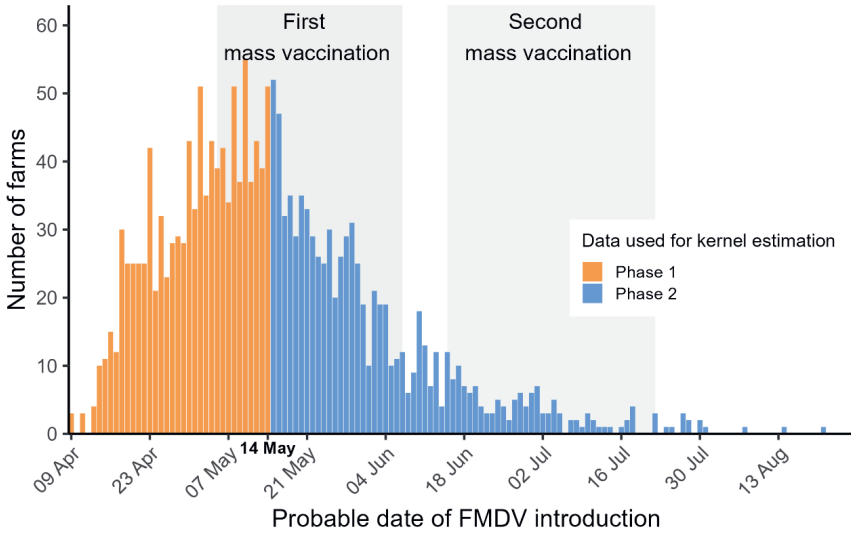


Figure 2 Epidemic curve of the 2001 foot-and-mouth disease (FMD) epidemic in Uruguay, plotted by the probable date of FMD virus (FMDV) introduction. Orange bars correspond to data used for estimating kernel 1(pre-vaccination), and blue bars correspond to data used for estimating kernel 2 (post-vaccination). Grey shaded areas denote the first and second rounds of mass cattle vaccination implemented for epidemic control.

From these phase-specific kernels, we computed the between-farm reproduction number for each farm $R_{h,i}$, the expected number of secondary farm infections generated by farm i if it were infectious during the average infectious period, assuming all surrounding farms remained susceptible (Boender et al., 2007). It represents the farm-level potential to generate secondary outbreaks given its location, species composition and size, and surrounding density, type and size of susceptible farms.

By incorporating the effect of farm size into the transmission kernel, cattle density becomes a central determinant of between-farm transmission potential. While the transmission kernel describes how infection pressure declines with distance, the overall magnitude of transmission is strongly influenced by the density of cattle in the surrounding area. In pasture-based production systems such as Uruguay, herd density and cattle density do not necessarily coincide. Regions with relatively few farms may nonetheless hold large numbers of animals, whereas areas with many small farms may contain comparatively fewer animals. Our results indicate that cattle density, rather than farm density alone, is the more relevant determinant of transmission potential. This is reflected in the spatial distribution of the estimated farm-level reproduction numbers ($R_{h,i}$), which closely follow the national pattern of cattle density presented in Figure 5 of the General Introduction (Chapter 1). This extension of the kernel-based approach based on Boender et al.(2014), explicitly incorporates farm-size effects and is particularly important in pasture-based livestock systems, where substantial heterogeneity in herd size means that farm density alone is insufficient to capture spatial variation in transmission risk.

When interpreted in a broader epidemiological context, the estimated transmission kernel for Uruguay highlights how production systems and applied control strategies shape the spatial structure of between-farm transmission. Comparative analyses of transmission kernels show differences across epidemiological contexts (Table 1). In endemic settings without culling and applying vaccination, such as the 2016 outbreak in Thailand, transmission is characterized by high local intensity but a very limited spatial range, reflected by a small half-kernel distance (r0= 0.2 km) and lower values of the scaling exponent α, both indicating predominantly local spread (Chanchaidechachai et al., 2021). In contrast, epidemic outbreaks in intensive production systems that were previously FMDV-free, such as the Netherlands 2001 and Japan 2010, exhibit lower transmission intensity at short distances but broader spatial kernels (r0=0.6-1.2 km), consistent with high farm density and rapid implementation of control measures (Boender et al., 2010; Hayama et al., 2013). In the present study, the estimated transmission kernel for Uruguay displayed a markedly wider spatial scale, with values ranging from approximately 3 to 6 km and α values close to 2, indicating intermediate- to long-range transmission (Boender & Hagenaars, 2023).

Table 1 Comparison of estimated transmission kernel parameters across different foot-and-mouth disease (FMD) epidemic contexts. The table summarises the baseline transmission rate (k_0), spatial scale parameter (r_0), and distance decay exponent (α) for endemic and epidemic settings under different production systems and control strategies

Country	Epidemiological context	k_0 (day^{-1})	r_0 (km)	α
Thailand 2016 (Lamphaya Klang subdistrict)	Endemic, no culling	0.0054 (0.0023–0.012)	0.19 (0.07–0.35)	1.56 (1.29–1.84)
Netherlands 2001	Epidemic, intensive system, stamping-out	0.0018 (0.0004–0.0063)	1.22 (0.67–3.35)	2.8 (2.3–4.1)
Japan 2010	Epidemic, intensive system, rapid control	0.00074	0.58	2.47
Uruguay 2001 – pre-vaccination	Epidemic, pasture-based production system, delayed control	0.0078 (0.0053–0.0104)	6.09 (4.92–8.03)	1.99 (1.90–2.10)
Uruguay 2001 – post-vaccination	Epidemic, pasture-based production system control with mass vaccination	0.0053 (0.0042–0.0073)	3.41 (2.75–4.04)	2.08 (2.00–2.17)

Note: Parameter values are shown for the distance-dependent component of each model. The Uruguayan model incorporates farm size and species composition.

These differences are likely influenced by viral characteristics, but also reflect differences in production systems, spatial farm distribution, and dominant transmission pathways. In pasture-based livestock production systems, neighbouring farms are often located at substantially larger distances compared with intensive systems, meaning that even routine contacts such over-fences transmission or local interactions may occur over several

kilometres. As a result, between-farm transmission can operate across broader spatial scales.

It was observed that larger farms contributed to higher transmission via both susceptibility and infectiousness, with a stronger effect on infectiousness **(Chapter 5)**. This pattern is consistent with the associations observed in **Chapter 2**. During the HRP, the probability of FMDV infection increased markedly with farm size, with higher odds of infection with increasing farm size (36–134: OR 2.46 (ns); 134–463: OR 6.53 (p=0.029); >463: OR 48.56 (p<0.001), relative to farms with <36 animals) (**Chapter 2**). Larger farms tend to have more contacts than smaller ones. This occurs through several mechanisms, including more direct contacts via animal movements and more indirect contacts due to increased movements of people working on the farm and higher traffic of vehicles such as feed trucks. In addition, large farms in Uruguay generally have more neighbouring farms. Farm area, which, in pasture-based production systems, correlates with farm size, showed a strong, monotonic association with the number of neighbours (Spearman's $\rho = 0.64$, $p < 0.001$) and a sublinear (concave) pattern (Pearson's $r = 0.47$). Larger farms therefore border more neighbours and face more contact opportunities, increasing both the probability of becoming infected (susceptibility) and the probability of transmitting infection (infectiousness). These multiple contact pathways increase both the probability of becoming infected (susceptibility) and the probability of transmitting infection (infectiousness). The estimated kernel parameters for farm size showed a stronger effect on infectiousness than on susceptibility, a pattern that is biologically plausible. A farm can become infected after a single effective exposure, so increases in susceptibility with herd size are modest. In contrast, larger herds sustain more infected animals with higher levels of viral shedding and generate more within-farm transmission and environmental contamination, thereby amplifying infectiousness. Thus, while susceptibility may rise with herd size because more animals are at risk, the increase in outward transmission potential is comparatively greater. As large farms are at greater risk of infection and onward transmission, they should be prioritised for risk-based surveillance and targeted control, with the aim of enabling early detection and containing spread following an introduction. They may also be considered priority candidates for preventive actions, particularly when regional risk is elevated.

Transmission was also influenced by species composition (farm type), with cattle farms as the main driver during this epidemic, consistent with findings from the 2001 UK epidemic reported by Keeling et al. (2001) and Chis Ster & Ferguson (2009; 2007). In **Chapter 2**, we found that cattle-only farms (vs mixed cattle–sheep) had higher odds of FMDV infection after the HRP and, together with large farms, remained at high-risk throughout the epidemic. Within cattle population, dairy farms had higher odds of infection than beef farms (OR 1.81, 95% CI 1.12–2.83 in the HRP), and remained as a risk factor until the end of the first vaccination round. This production-type effect likely reflects differences in contact structure between systems, including milk-collection lorries, veterinary visits, shared equipment, staff movements, and feed deliveries, which increase transmission opportunities. In Uruguay, dairy production systems are more intensive than beef production systems, with higher contact rates between animals within farms. This increases within-herd transmission, leading to a larger number of infected animals and higher levels of viral shedding, which in turn can amplify between-herd transmission. Although production type was not explicitly incorporated into the

transmission kernel, future work could explore the inclusion of production system (e.g., dairy versus beef) as an additional farm-level covariate to better capture management-related heterogeneity in between-farm transmission.

The species-specific extension of the transmission kernel (**Chapter 5**) indicates that cattle played the dominant epidemiological role during the 2001 epidemic. Although sheep and pigs showed lower estimated susceptibility and infectiousness, these effects should be interpreted cautiously given the limited number of infected farms in these species. Despite their widespread presence in 2001, sheep contributed little to transmission. The low number of clinically affected sheep during the epidemic could reflect both reduced infectiousness and potential under-ascertainment due to mild clinical signs (Kitching & Hughes, 2002). However, available serological evidence suggests that infection in sheep was indeed limited. Together, these findings indicate that, under the pasture-based and co-grazing conditions of Uruguay, sheep did not act as major drivers of between-farm transmission. This is also consistent with analyses of the 2001 UK epidemic (Chis Ster & Ferguson, 2007) and experimental studies of Pan Asia O, which found limited sheep-to-sheep transmission (Streftaris & Gibson, 2004). This may differ under other production systems or viral strains

Given the diversity of possible transmission pathways, a kernel-based approach to quantifying FMDV transmission risk implicitly captures all transmission mechanisms, avoiding the need to model specific pathways when these are poorly understood. (Boender & Hagenaars, 2023; Keeling, 2005). In Uruguay, the available data supported this kernel approach, but a more detailed quantification of transmission by individual contact routes would require high-quality tracing information for each pathway (Hagenaars et al., 2011), which is difficult to collect in sufficient depth under epidemic conditions. If such detailed route-specific data were available, they would allow quantification of the contribution of each transmission route and enable more precise targeting of prevention and control measures towards those routes that contribute most to spread. However, incorporating route-specific parameters inevitably increases model complexity and the amount of parameterisation required, reinforcing the general trade-off between biological realism and model tractability when choosing the appropriate level of detail for transmission models as discussed by Hagenaars et al. (2011).

In addition to the spatial kernel analyses, in **Chapter 3** we previously quantified the contribution of livestock movements to transmission during the high-risk period (HRP) of the 2001 epidemic. Using the livestock movement network, the between-herd reproduction number (R_h) was estimated by combining the average number of out-contacts of infected premises with the probability that a contact resulted in infection. For the estimated two-week HRP, this yielded $R_h = 1.48$, indicating that animal movements alone were sufficient to sustain transmission before movement restrictions were enforced. When the HRP was extended to three weeks, as a way to reflect uncertainty in the initial date of introduction, both the number of infected farms involved in movements and the probability of transmission increased, resulting in a higher estimated $R_h = 2.16$. These findings highlight the critical role of early detection and rapid implementation of movement restrictions. Even modest extensions of the undetected infectious period substantially increase transmission potential, reinforcing the importance of minimizing the HRP to prevent sustained spread through the movement network.

Effectiveness of Control Measures on Transmission

When FMDV re-emerges in a previously FMD-free country, control strategies are guided by a formal epidemiological assessment (e.g., spatial extent, estimated number of infected holdings at detection) and are further shaped by national legislation and policy. Typical contingency plans integrate stamping out of infected premises; delineation of protection and surveillance zones (approximately 3 km and 10 km) with intensified surveillance and movement restrictions; forward and backward contact tracing. Some include pre-emptive culling around infected holdings (e.g., ≥1 km) and emergency ring vaccination at context-appropriate radii.

During the 2001 FMD outbreak in Uruguay, several control measures were implemented within a short time frame, limiting the ability to estimate their individual effects. Together, these interventions reduced transmission and brought the epidemic under control. Early actions included movement restrictions, culling of infected and in-contact animals, and disinfection of affected premises. Ring vaccination within 10 km of outbreaks began three days after detection. About one week after detection, stamping out ceased and emergency vaccination was applied across an extended buffer zone. As the epidemic progressed, a nationwide mass vaccination of the cattle population was decided and carried out in two rounds, accompanied by strict movement controls and strengthened biosecurity measures (**Chapter 2**).

On average, the combined control measures resulted in a mean absolute decrease of 2.24 in R_h (SD 1.70) and a mean relative reduction of 76.29% (SD 4.26%) between Phase 1, corresponding to the period before mass vaccination, and Phase 2, corresponding to the period after vaccine-derived immunity was assumed to be established (See Figure 3 in **Chapter 5**). When assessed via the relative reduction in the phase-specific amplitude (h_0) of the simple distance-based kernel, the decrease corresponds to an apparent reduction of approximately 83% in overall transmission intensity (Supplementary Information of Chapter 5).

To explore how the implemented control measures influenced transmission over time, the effective reproduction number $R_e(t)$ was estimated using a standard time-varying approach. Estimates were obtained following the method proposed by Cori et al. (2013), as implemented in the *EpiEstim* R package. The analysis was based on daily incidence data by estimated date of infection, assuming a discrete gamma distribution for the generation interval. Two alternative mean generation times were evaluated to assess the sensitivity of the estimates: 8.5 days and 15 days. Under both assumptions, $R_e(t)$ showed a decline following the implementation of control measures after detection of the first outbreak. Notably, $R_e(t)$ was observed to fall below the epidemic threshold (<1) approximately 14 days after the start of mass vaccination under the 8.5-day assumption and 16 days under the 15-day assumption (Figure 3).

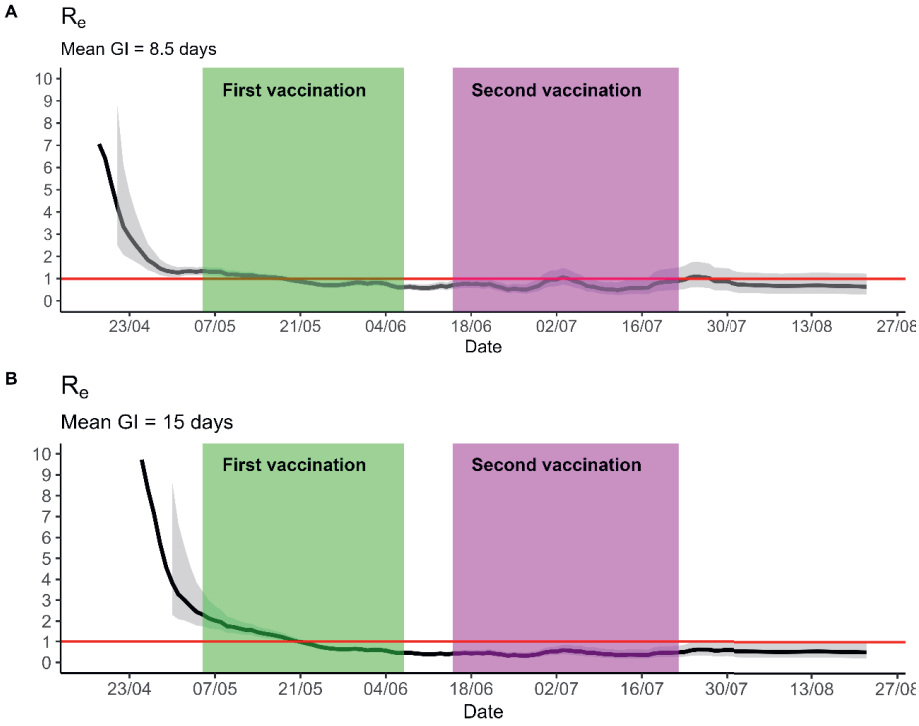


Figure 3 Time-varying effective reproduction number (R_e) estimated during the 2001 FMD epidemic in Uruguay under two generation-interval assumptions. Panel A assumes a discrete gamma generation interval with mean 8.5 days and panel B assumes 15 days. The black line represents the median $R_e(t)$, and the grey shaded area shows the 95% credible interval. The red horizontal line indicates the epidemic threshold (R = 1). Green and purple shaded periods correspond to the first and second vaccination campaigns, respectively.

The 2001 FMD epidemic in Uruguay provided a rare opportunity to evaluate the effectiveness of emergency vaccination under field conditions. To assess, as far as possible, the specific effect of vaccination independently of other control measures, vaccine effectiveness (VE) for emergency FMD vaccination during this epidemic was quantified by estimating the reduction in the between-farm transmission rate β after vaccination with commercial bivalent vaccines containing O_1 Campos and A_{24} Cruzeiro (**Chapter 4**).

The results indicate that emergency vaccination rapidly reduced between-farm transmission, with substantial effectiveness already evident within the first week following vaccination across all zones (zone Pre 77.65% (95% CI 70.53–82.94), zone A 71.05% (21.13–87.59), zone B 78.50% (75.44–81.21), zone C 68.80% (59.55–75.83), and zone D 59.75% (47.68–69.12)). This rapid onset of protection is consistent with the temporal decline in transmission observed at the epidemic level (Figure 3), suggesting that vaccination likely contributed to reducing transmission once movement restrictions and enhanced biosecurity were in place. Importantly, these estimates reflect vaccine impact under field conditions, where vaccination was implemented in the context of

ongoing transmission and heterogeneous exposure, providing population-level evidence that complements experimental studies conducted under controlled settings.

In this analysis, the total effect of vaccination on transmission was assessed. A more detailed decomposition of vaccine effects on infectiousness and susceptibility was not undertaken in this thesis due to time constraints. Disentangling these components remains an important area for future research, as it would allow a more refined understanding of how vaccination modifies transmission dynamics and would support more informed decision-making during outbreak response. This would require estimating transmission parameters (β) stratified by the vaccination status of infectious and susceptible farms, for example, β_{VN}(vaccinated to non-vaccinated) to quantify the effect of vaccination on infectiousness, β_{NV} (non-vaccinated to vaccinated) to quantify its effect on susceptibility, and β_{VV} (vaccinated to vaccinated) to quantify the combined effect when both infectious and susceptible farms are vaccinated.

The estimates generated in this thesis are particularly relevant in the current international context of FMD control. After the 2001 European FMD crisis, the extensive use of pre-emptive culling prompted debate and renewed interest in vaccination. In addition, operational experience has shown that culling capacity is limited, timely depopulation becomes increasingly difficult as the number of infected farms grows. These constraints have not been observed only in Uruguay. Experiences in the Netherlands (Bouma et al., 2003c) and Japan (Hayama et al., 2013) similarly demonstrated that maintaining rapid culling became progressively more challenging as outbreaks expanded.

Historically, the use of vaccination was associated with longer times to regain FMD-free status compared with stamping-out (Cabezas et al., 2022). Recent revisions introduced by the World Organisation for Animal Health (WOAH) have shortened the timelines for regaining FMD-free status following emergency vaccination under defined surveillance conditions, thereby enhancing the practical feasibility of vaccination-based control strategies. Together, these developments have reinforced the role of vaccination as a key component of contemporary FMD control. In this context, robust and context-specific estimates of vaccine effectiveness are essential for preparedness planning, calibration of outbreak-response models, and evidence-based decisions on when and how to deploy emergency vaccination. Several countries have therefore evaluated emergency vaccination as part of their preparedness strategies, employing mathematical models to assess the performance of alternative control options across a range of epidemiological and operational scenarios. In many of these modelling studies, vaccine effectiveness has been parameterised using estimates derived from experimental studies. One representative example, the work of Backer et al. (2012), is discussed later in this chapter.

Our results add field-based evidence indicating that, the use of a good-quality commercial vaccine, when combined with complementary measures such as movement restrictions and enhanced biosecurity, can be sufficient to interrupt between-farm transmission.

Relevance of 2001 Transmission Estimates for Assessing Current and Future FMD Risk

The transmission kernel estimated from the 2001 FMD epidemic in Uruguay provides a quantitative description of how infection pressure declines with distance between farms (**Chapter 5**). Importantly, by extending the kernel to include farm-level covariates such as herd size and species, the estimated transmission parameters are not limited to the specific spatial configuration observed in 2001. This approach separates the effect of spatial proximity from heterogeneity in farm infectiousness and susceptibility, allowing the kernel to be applied to contemporary livestock data. As a result, the model can be used to assess current and future FMD transmission risk using contemporary farm distributions, livestock densities, and population structures, assuming that the underlying transmission mechanisms remain comparable.

Comparison of livestock demographics between 2001 and 2023 indicates structural changes that may increase current FMD transmission risk (**Chapter 5**). In particular, the cattle population has increased while the sheep population has declined, and cattle-only farms now represent a larger proportion of holdings. Consistent with these changes, a higher proportion of farms with $R_h > 1$ was estimated for 2023, suggesting that an FMDV introduction under present conditions would have a greater potential for sustained transmission than in 2001. Nonetheless, epidemic outcomes would remain strongly dependent on early detection and the timeliness, scale, and effectiveness of implemented control measures.

Other countries that have experienced FMD epidemics have adopted similar kernel-based modelling approaches. For example, Hayama et al. (2016) applied a transmission kernel parameterized using data from the 2010 FMD epidemic in Miyazaki (Hayama et al., 2013) to livestock areas with differing species composition and farm densities in order to evaluate potential epidemic spread and the performance of alternative control strategies. This approach illustrates how kernels estimated from historical outbreaks can be used beyond the original epidemic context. In addition, by explicitly incorporating farm size and species composition, the transmission kernel used in this thesis can accommodate changes in the livestock production system through updated demographic inputs, thereby maintaining its relevance for current and future FMD risk assessment without re-estimation of transmission parameters.

In **Chapter 3**, we also analysed the livestock movement network for 2022 and compared it with the network observed during the same calendar period in 2001. This comparison showed similar structural characteristics between the two networks, including heterogeneous connectivity patterns and the presence of highly connected premises. The observed similarity suggests that, if an FMDV introduction were to occur, patterns of movement-mediated spread comparable to those observed in 2001 could be expected during the HRP. In addition, in periods of elevated risk, enhanced surveillance targeting highly connected premises may be particularly relevant. Prioritising these premises may therefore contribute to earlier detection and reduce the likelihood of widespread transmission.

Implications for Preparedness. How to strengthen response capacity in future outbreaks.

Preparedness for future FMDV outbreaks is shaped not only by the existence of contingency plans, but also by the ability to evaluate, in advance, how alternative control strategies may perform under realistic epidemiological and operational conditions. In this context, simulation models play a central role in outbreak-response planning, and their value depends strongly on how well transmission parameters reflect field conditions (Hagenaars et al., 2011).

In this thesis two phase-specific kernels were estimated: a first kernel, representing transmission during Phase 1, which mainly covers the high-risk period (HRP) and a short interval after the implementation of initial control measures, and a second kernel representing transmission once FMDV has been detected and broader control measures are in place including mass vaccination. The Phase 1 kernel is suited for estimating the expected number of outbreaks during the HRP, whereas the Phase 2 kernel is more appropriate for simulating transmission dynamics and assessing alternative control strategies following FMDV detection, when animal-movement bans and biosecurity measures have been implemented. The spatial risk maps show that the risk of farm-level transmission greater than the threshold ($R_h \geq 0.8$) is not confined to a few localized areas. In contrast to the clear hot spots reported for countries such as the Netherlands (Boender et al., 2010), high transmission risk in Uruguay is more widely distributed across the country (see Figure 4 in **Chapter 5**). As a consequence, the probability of a large epidemic remains high under many of the control scenarios evaluated in **Chapter 5**. In this context, preventive vaccination emerges as an attractive strategy, particularly given constraints in culling capacity and issues related to social acceptance, animal welfare and environmental impact, as well as the shorter time to recovery of WOAH status associated with the use of vaccination compared with past practice.

During periods of elevated regional risk, preventive measures can be implemented before FMDV introduction. For example, preventive vaccination can be targeted to farms at higher risk of transmission $R_h \geq 0.8$. This strategy is feasible given the availability of purified, high-potency vaccines and validated DIVA assays that detect antibodies to non-structural proteins and thereby distinguish infection from vaccination (Barnett et al., 2015). A size-based vaccination scenario was included to provide a more operationally feasible alternative to risk-based targeting. This approach was motivated by the relationship observed between herd size and susceptibility, which increases up to approximately 300 animals, after which additional animals have little effect on infection risk (susceptibility). From an implementation point of view, regulations based on herd size (e.g., vaccinating all holdings with more than 100 or 300 cattle) can be communicated and enforced more easily during an emergency than criteria based on epidemiological metrics such as R_h. Thus, although vaccinating farms with $R_h \geq 0.8$ performs better epidemiologically, vaccinating farms with ≥ 100 animals reduce the number of vaccinations required and may represent a pragmatic alternative. A size-based rule could also be used to prioritise the initial deployment of emergency vaccination when vaccine supplies are limited. Vaccination-to-live strategies were explored in detail by Backer et al. in the Netherlands (Backer, Engel, et al., 2012; Backer, Hagenaars, et al., 2012), where the 2001 epidemic prompted interest in alternatives to large-scale culling. Vaccination-

to-live also has the potential to increase acceptability of control measures among farmers. However, it requires robust final screening to ensure that no vaccinated animals remain infected, and it has implications for how rapidly a country can recover its FMD-free status under WOAH regulations. Their analyses showed that when an adequate final screening protocol is implemented, vaccination-to-live can achieve a level of safety comparable to pre-emptive culling, with similarly low numbers of undetected infected animals at the end of the outbreak.

In outbreak preparedness, decision-making often take place under conditions of uncertainty and limited information. While economic cost–benefit analyses provide an essential framework for evaluating control strategies, such an analysis was not conducted in this thesis due to time constraints and should be addressed in future research. Nevertheless, to support a structured comparison of alternative intervention strategies, a simplified decision-support approach was explored, combining epidemiological impact with operational considerations.

This approach combines epidemiological effectiveness with an approximate indicator of how demanding each intervention strategy is to implement, allowing strategies to be compared in terms of both impact and practical feasibility. Epidemiological effectiveness was quantified as the relative reduction in epidemic size (infected farms) and epidemic duration compared with the baseline scenario (S_0):

$$E_I = 1 - {}^{I_{S_x}}\!/_{I_{S_0}} ,$$

$$E_D = 1 - {}^{D_{S_x}}\!/_{D_{S_0}} ,$$

Where I stand for the number of infected farms, D for epidemic duration (days) S_x for each scenario from 1 to 12.

These measures were combined into a single effectiveness metric (E_{total}) using two weighting schemes: equal weights (50–50) for epidemic duration and number of infected farms, and an alternative scheme giving greater weight to infected farms (30-70).

$$E_{total} = wD \times E_D S_x + wI \times E_I S_x ,$$

$$wD + wI = 1$$

In addition, the epidemiological benefit of each intervention was quantified in terms of infections averted and epidemic duration averted relative to the baseline scenario.

$$Infections\ Averted\ (IA)_{S_x} = I_{S_0} - I_{S_x} ,$$

$$Duration\ Averted\ (DA)_{S_x} = D_{S_0} - D_{S_x} ,$$

Operational effort was approximated using an indicator termed Labor Effort Units (LEU), defined as a weighted sum of control actions. Culling was assigned a higher effort weight than vaccination (1 for culling and 0.01 for vaccination), reflecting the substantially greater operational and economic burden associated with culling.

$$LEU_{S_x} = N_{cull} + 0.01 \times N_{vac} \,,$$

Where N_{cull} and N_{vac} are the number of culled and vaccinated farms, respectively.

This weighting scheme was primarily informed by farm-level cost estimates reported by Bates et al. (2003), who quantified the direct costs of culling and vaccination during the 2001 FMD epidemic in the UK. In that study, culling costs were dominated by indemnification payments, complemented by slaughter and cleaning and disinfection activities, whereas vaccination costs were largely driven by vaccine purchase and delivery. The authors reported marked differences by farm type, while for dairy farms, the ratio between vaccination and culling costs was approximately 0.001, for non-dairy farms this ratio was substantially higher (0.023). These estimates showed that culling was substantially more resource-intensive than vaccination, with the relative magnitude depending on farm type.

The plausibility of the selected weighting for the Uruguayan context was subsequently assessed using national-level information from Perry et al. (2020). Although that analysis does not report farm-level culling or vaccination costs, it provides estimates of total annual expenditure on FMD vaccination programmes in Uruguay. When expressed on a per-farm basis, these programme-level vaccination costs remain small relative to plausible farm-level indemnification values, supporting the use of a markedly lower weight for vaccination in the LEU formulation.

Taken together, the estimates from Bates et al. (2003) indicate that plausible vaccination-to-culling ratios span more than one order of magnitude depending on production system. In this context, the value of 0.01 was selected as an intermediate and conservative approximation. Moreover, LEU is intended to capture overall operational effort rather than direct financial costs alone.

The Efficiency Ratio (ER) was then calculated as the ratio between operational effort (LEU) and the epidemiological benefit, such that lower values indicate more efficient strategies.

$$ER, I_{S_x} = {LEU_{S_x}}\Big/{IA_{S_x}},$$

$$ER, D_{S_x} = {LEU_{S_x}}\Big/{ID_{S_x}} \,,$$

Based on this framework, the results for intervention strategies applied to cattle only are presented in Table 1.

Table 2 Effectiveness and operational efficiency of alternative FMD control strategies relative to the baseline scenario (S_0: culling of infected farms only). Effectiveness is measured as reductions in epidemic duration (ED) and number of infected farms (EI), combined into total effectiveness indices using equal (50–50) and weighted (30–70) approaches. Operational effort is expressed as Labor Effort Units (LEU), and efficiency is summarized using Efficiency Ratios (ER).

Scenario	Effectiveness in epidemic duration reduction (E_D)	Effectiveness in infected farms reduction (E_I)	Etotal = $0.5E_D + 0.5E_I$	Etotal= $0.3E_D + 0.7E_I$	Labor Effort Unit (LEU) = $1*N_{cull}+0.01*N_{vac}$	Infections averted (IA)	ER_I= LEU/IA	Days averted (DA)	ER_D =LEU/DA
S_0: Cull infected farms only					18152				
S_2: Ring culling 1 km	12.0	19.5	15.8	17.3	23371	2225	10.504	34	687.382
S_6: Ring vaccination 1 km	7.7	9.8	8.8	9.2	16454.24	1114	14.770	22	747.920
S_7: Ring vaccination 3 km	28.9	44.1	36.5	39.5	10561.88	5020	2.104	82	128.803
S_8: Ring vaccination 10 km	53.2	84.1	68.6	74.8	3422.51	9572	0.358	151	22.666
S_9: Targeted vaccination ($R_h \geq 0.8$, 3-week HRP)	52.5	99.0	75.7	85.1	423.43	11271	0.038	149	2.842
S_{10}: Targeted vaccination ($R_h \geq 0.8$, 4-week HRP)	46.8	98.4	72.6	82.9	542.41	11197	0.048	133	4.078
S_{11}: Targeted vaccination (≥300 cattle, 3-week HRP)	10.6	90.6	50.6	66.6	1739.18	10315	0.169	30	57.973
S_{12}: Targeted vaccination (≥100 cattle, 3-week HRP)	43.0	98.1	70.6	81.6	454.86	11171	0.041	122	3.728

ER_I: Efficiency Ratio for infections, representing the operational effort required per infected farm averted.

ER_D: Efficiency Ratio for epidemic duration, representing the operational effort required per unit of epidemic duration averted.

Reactive measures, including ring culling (S_2) and small-radius ring vaccination (S_6), resulted in limited reductions in epidemic size and duration (**Chapter 5**) while requiring relatively high operational effort, leading to poor efficiency scores.

Expanding the vaccination radius (S_7 and S_8) substantially improved epidemiological outcomes and yielded clear gains in operational efficiency compared with reactive strategies. However, these approaches still required considerably more effort than preventive targeted vaccination strategies. Their higher LEU values mainly reflect a larger number of infected farms and the associated need for culling, rather than increased operational effort related to vaccination.

Preventive targeted vaccination strategies ($S_9 - S_{12}$) consistently outperformed reactive interventions achieving the largest reductions in infected farms (except S_{11}), and substantial reductions in epidemic duration while requiring markedly lower operational effort. Among these, the risk-based strategy targeting farms with high transmission potential (S_9) (with a 3-week HRP), achieved the most favourable balance between epidemiological impact and operational effort, resulting in the lowest combined Efficiency Ratios (ER). As indicated by the ER values, reducing epidemic duration was consistently more operationally demanding than reducing the number of infected farms, highlighting the higher effort required to shorten epidemics compared with limiting their overall size. Under the culling capacity assumed in this model (two farms per day), none of the evaluated strategies achieved large reductions in epidemic duration. Increasing culling capacity could represent a potential alternative to accelerate epidemic control. However, such an approach would need to be carefully evaluated in light of additional considerations, including social acceptance, animal welfare implications, and potential environmental impacts.

To assess the robustness of the results to the relative weighting of control measures, a sensitivity analysis was performed using alternative weights for vaccination (0.001, 0.03 and 0.1), while keeping the weight for culling fixed at 1. The overall patterns and main conclusions were consistent across the range of values explored. When vaccination effort was assumed to be very low (weights of 0.001, 0.01–0.02 relative to culling), the risk-based strategy (S_9) achieved the highest efficiency. However, from a vaccination effort weight of approximately 0.03 onwards, the size-based strategy targeting farms with ≥100 cattle (S_{12}) became more efficient, and remained dominant across higher vaccination effort assumptions up to 0.1.

Overall, these findings highlight a trade-off between epidemiological performance, operational effort, and implementation simplicity. They suggest that preventive targeted vaccination can offer a highly efficient and operationally feasible alternative to purely reactive control strategies.

From a preparedness perspective, further refinement of modelling frameworks could strengthen the evaluation of alternative response strategies. In particular, some simplifying assumptions were necessary in the present analysis. One key assumption is that farm-level infectiousness is treated as constant over the infectious period, whereas in reality infectiousness is expected to increase over time as the number of infected animals within a farm grows, resulting in a larger amount of virus being shed prior to detection and intervention. Therefore, more detailed modelling frameworks, such as the approach

used by (Backer, Hagenaars, et al., 2012), which integrates within-herd and between-herd dynamics, or the AADIS model in Australia (Bradhurst et al., 2015), which couples a deterministic within-herd model with a stochastic, spatially explicit between-herd model, could be applied. However, in such cases, within-herd parameters would need to be taken from the literature or experimental studies because the available data of Uruguay did not allow estimation of within-herd transmission parameters. Another important simplifying assumption is that vaccinated infected farms were considered equally infectious as non-vaccinated infected farms, which may underestimate the potential reduction in infectiousness conferred by vaccination.

Finally, much of what was learned from the 2001 epidemic remains directly applicable to the virus that predominantly affected cattle in that epidemic (serotype A). However, future risk is not restricted to the repetition of a cattle-dominated scenario. If, for example, a virus more strongly adapted to sheep were introduced into Uruguay, a species of longstanding relevance for the country, the resulting transmission dynamics could differ substantially. This underscores the importance of maintaining continuous preparedness, strengthening surveillance systems, and systematically updating emergency response plans, so that the country is equipped to respond to different epidemiological profiles of FMDV and other transboundary animal diseases.

Overall, this thesis illustrates how quantitative epidemiology and mathematical modelling can be used to analyse field data and characterise transmission processes relevant for preparedness. By providing empirical evidence from an FMD-free country with a pasture-based livestock production system, a context that has been less studied than intensive production systems, it advances understanding of between-farm transmission dynamics and the impact of emergency vaccination. The estimation of phase-specific transmission kernels, complemented by a network-based assessment of transmission via animal movements during the high-risk period, yields parameters that are directly applicable to outbreak-response modelling in similar settings.

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Summary

Foot-and-mouth disease (FMD) remains one of the most economically damaging livestock diseases globally, constraining trade and imposing major control costs. Despite long-standing control efforts and the achievement of FMDV-free status in many regions, recent incursions into previously free countries demonstrate that the risk of introduction persists and that preparedness remains essential. Although extensively studied, important gaps persist in how transmission unfolds in different production systems and how control measures perform under field conditions.

This thesis advanced understanding of foot-and-mouth disease virus (FMDV) transmission following introduction into a previously FMDV-free country, with a focus on between-farm spread in pasture-based livestock systems. Using Uruguay's 2001 epidemic as a case study, key drivers of transmission were quantified, the contribution of livestock movements during the high-risk period (HRP) was evaluated, between-farm transmission parameters were estimated, and the effectiveness of emergency mass vaccination was assessed when implemented alongside movement restrictions and enhanced biosecurity measures. The resulting estimates support outbreak preparedness modelling and contingency planning in Uruguay and in other regions with similar livestock production systems, and are likely to become increasingly relevant as livestock sustainability goals drive a shift from intensive toward more extensive production systems.

The 2001 Uruguay epidemic occurred when the country was FMDV-free without vaccination. By the time the index case was detected, infection had already spread widely. Because accurate infection timing is central to transmission inference, farm-level infection dates were reconstructed using a within-herd SEIR framework, enabling analyses based on likely introduction dates. Results indicate that when the first outbreak was confirmed, infection had likely already reached over 200 farms distributed nationwide. The spatial pattern of early infections is consistent with a detection delay of at least two weeks and suggests that multiple introductions from Argentina via indirect pathways cannot be excluded. During the HRP, livestock movements, especially through highly connected premises such as markets, enabled long-distance dissemination, limiting the impact of early local control measures.

Between-farm transmission was then quantified using complementary approaches. First, network analysis of animal movements during the HRP showed that movement-mediated transmission alone could sustain spread, estimated at $R_H = 1.48$ for a two-week HRP and $R_H = 2.16$ for a three-week HRP. Second, a spatially explicit kernel-based modelling framework was developed to estimate phase-specific transmission kernels. A pre-vaccination phase capturing the HRP and early response (culling, ban of animal movements), and a post-vaccination phase representing transmission after detection and the establishment of vaccine-derived immunity. Incorporating herd size and species composition into the kernel allowed separation of distance effects from farm-level heterogeneity in infectiousness and susceptibility. In Uruguay's pasture-based livestock production system, where farms may be farther apart and herd sizes vary markedly, cattle density emerged as a key determinant of transmission potential, and the estimated kernels exhibited a broader spatial scale than those reported for intensive systems.

Farm heterogeneity strongly shaped transmission. Larger farms were more likely to become infected and contributed to onward spread, with herd size showing a stronger effect on infectiousness than on susceptibility, consistent with biological expectations. Species composition also mattered. Transmission during the epidemic was overwhelmingly driven by cattle holdings. Sheep and pig farms were rarely infected, and species-specific kernel terms suggested that sheep and pigs were less infectious and less susceptible than cattle and in this field context, though these estimates are imprecise due to small numbers and should be interpreted cautiously. Together, these findings identify large, cattle farms and highly connected through animal movement as priorities for risk-based surveillance and early detection.

The thesis also evaluates how control measures reduced transmission over time. Uruguay implemented movement restrictions, biosecurity enhancement, initial culling and ring vaccination, followed by emergency mass vaccination of cattle nationwide. Estimation of time-varying $R_e(t)$ showed a clear decline after detection and a drop below the epidemic threshold roughly two weeks after mass vaccination began (depending on the assumed generation interval), consistent with control taking effect once vaccination was added to movement bans and biosecurity. Vaccine effectiveness was quantified using field data by estimating the reduction in the between-farm transmission rate (β) after vaccination with commercial bivalent vaccines (A_{24} cruzeiro y O_1 campos). Substantial reductions in transmission were evident within the first week post-vaccination across zones, providing population-level evidence that good quality commercial vaccines, combined with complementary measures, can interrupt between-farm transmission even when high-potency vaccines may not be available.

Finally, the estimated kernels were used to compute farm-specific reproduction numbers $R_{h,i}$ and generate risk maps, and to parameterize a stochastic individual-farm simulation model to compare alternative control strategies. Fourteen scenarios were evaluated, including culling of detected farms only, pre-emptive culling, emergency ring vaccination at different radii with comparisons between cattle-only versus multi-species application, and preventive cattle vaccination targeted by transmission risk ($R_h \geq 0.8$) or herd size (farms with >300 and >100 heads of cattle). Results showed that reactive small-radius interventions had limited impact and poor operational efficiency under constrained culling capacity. In contrast, preventive targeted vaccination, especially risk-based targeting of farms with high transmission potential, consistently achieved the largest reductions in epidemic size with much lower operational effort.

Overall, this thesis demonstrates how quantitative epidemiology and the modelling of field data can translate lessons from a major epidemic into evidence-based insights that directly inform outbreak preparedness and response planning. It shows that delayed detection and HRP movements can drive widespread dissemination before control begins. Transmission in pasture-based production systems is shaped by cattle density and by farm-size heterogeneity, with larger cattle farms contributing more to onward spread. Furthermore, emergency vaccination with commercial vaccines can rapidly reduce between-farm transmission when integrated with movement bans and biosecurity measures.

By providing phase-specific transmission estimates, evidence on movement-mediated spread, and field-based estimates of vaccine effectiveness, this work strengthens the

empirical basis for risk-based surveillance, outbreak-response modelling, and contingency planning for future FMD incursions in Uruguay and comparable settings.

Resumen

La fiebre aftosa (FA) continúa siendo una de las enfermedades del ganado con mayor impacto económico a nivel mundial, ya que restringe el comercio e impone elevados costos de control. A pesar de los esfuerzos sostenidos durante décadas y del logro del estatus libre de virus de la fiebre aftosa (VFA) en muchas regiones, las incursiones recientes en países previamente libres demuestran que el riesgo de introducción persiste y que la preparación sigue siendo esencial. Aunque ha sido ampliamente estudiada, aún existen vacíos importantes en la comprensión de cómo se desarrolla la transmisión en distintos sistemas productivos y cómo se desempeñan las medidas de control en condiciones de campo.

Esta tesis profundiza en la comprensión de la transmisión del virus de la fiebre aftosa (VFA) tras su introducción en un país previamente libre, con énfasis en la propagación entre predios en sistemas ganaderos basados en pasturas. Utilizando la epidemia de Uruguay en 2001 como estudio de caso, se cuantificaron los principales determinantes de la transmisión, se evaluó la contribución de los movimientos de animales durante el período de alto riesgo (en inglés HRP), se estimaron parámetros de transmisión entre predios y se evaluó la efectividad de la vacunación masiva de emergencia cuando se implementó junto con restricciones de movimiento y medidas reforzadas de bioseguridad. Las estimaciones resultantes aportan parámetros clave para la modelización orientada a la preparación ante emergencias y la planificación de contingencia en Uruguay y en otras regiones con sistemas productivos similares, y probablemente adquirirán mayor relevancia a medida que los objetivos de sostenibilidad impulsen una transición desde sistemas intensivos hacia sistemas más extensivos.

La epidemia de 2001 ocurrió cuando el país era libre del VFA sin vacunación. Para el momento en que se detectó el caso índice, la infección ya se había diseminado ampliamente. Dado que la estimación precisa del momento de infección es central para inferir la transmisión, se reconstruyeron las fechas de infección a nivel predial utilizando un modelo SEIR intrapredial, lo que permitió realizar análisis basados en fechas probables de introducción. Los resultados indican que, cuando se confirmó el primer foco, la infección probablemente ya había alcanzado más de 200 predios distribuidos en todo el país. El patrón espacial de las infecciones tempranas es consistente con un retraso en la detección de al menos dos semanas y sugiere que no puede descartarse la existencia de múltiples introducciones desde Argentina por vías indirectas. Durante el período de alto riesgo, los movimientos de animales, especialmente a través de establecimientos altamente conectados como las ferias de ganado, facilitaron la diseminación a larga distancia, limitando el impacto de las primeras medidas locales de control.

Luego, la transmisión entre predios se cuantificó mediante enfoques complementarios. En primer lugar, el análisis de redes de movimientos durante el período de alto riesgo mostró que la transmisión mediada por movimientos podía sostener por sí sola la propagación, con un R_H estimado de 1,48 para un período de alto riesgo de dos semanas y de 2,16 para un período de alto riesgo de tres semanas. En segundo lugar, se implementó un modelo espacial explícito basado en kernels de transmisión para estimar kernels específicas por fase: una fase pre-vacunación que capturó el período de alto riesgo y la

respuesta temprana (sacrificio sanitario, prohibición de movimientos), y una fase post-vacunación que representó la transmisión tras la detección y el establecimiento de la inmunidad inducida por la vacuna. La incorporación del tamaño del rodeo y la composición de especies en el kernel permitió separar el efecto de la distancia de la heterogeneidad a nivel predial en infecciosidad y susceptibilidad. En el sistema ganadero extensivo de Uruguay, donde los predios pueden estar más distantes y los tamaños de rodeo varían marcadamente, la densidad de bovinos emergió como un determinante clave del potencial de transmisión, y los kernels estimados mostraron una escala espacial más amplia que la reportada en sistemas intensivos.

La heterogeneidad entre predios moldeó fuertemente la transmisión. Los predios más grandes tuvieron mayor probabilidad de infectarse y de contribuir a la propagación, mostrando el tamaño del rodeo un efecto más fuerte sobre la infecciosidad que sobre la susceptibilidad, en línea con las expectativas biológicas. La composición de especies también fue relevante. La transmisión durante la epidemia estuvo impulsada principalmente por predios bovinos. Los predios ovinos y porcinos se infectaron raramente, mientras que ovinos y porcinos fueron menos infecciosos y menos susceptibles que los bovinos en este contexto de campo, aunque estas estimaciones son imprecisas debido al bajo número de casos y deben interpretarse con cautela. En conjunto, estos hallazgos identifican a los grandes predios bovinos y a los establecimientos altamente conectados por movimientos de animales como prioridades para la vigilancia basada en riesgo y la detección temprana.

La tesis también evalúa cómo las medidas de control redujeron la transmisión a lo largo del tiempo. Uruguay implementó restricciones de movimiento, refuerzo de la bioseguridad, sacrificio sanitario inicial y vacunación en anillo, seguidos por vacunación masiva de emergencia de bovinos a nivel nacional. La estimación del número reproductivo efectivo en el tiempo $R_e(t)$ mostró un descenso claro tras la detección y una caída por debajo del umbral epidémico aproximadamente dos semanas después del inicio de la vacunación masiva (dependiendo del intervalo generacional asumido), consistente con la efectividad del control una vez que la vacunación se sumó a las restricciones de movimiento y a la bioseguridad. La efectividad vacunal se cuantificó utilizando datos de campo mediante la estimación de la reducción en la tasa de transmisión entre predios (β) tras la vacunación con vacunas comerciales bivalentes (A_{24} cruzeiro y O_1 campos). Se evidenciaron reducciones sustanciales en la transmisión dentro de la primera semana posterior a la vacunación en distintas zonas, proporcionando evidencia a nivel poblacional de que vacunas comerciales de buena calidad, combinadas con medidas complementarias, pueden interrumpir la transmisión entre predios incluso cuando no se dispone de vacunas de alta potencia.

Finalmente, los kernels estimados se utilizaron para calcular números reproductivos específicos por predio ($R_{h,i}$), generar mapas de riesgo y parametrizar un modelo estocástico de simulación entre predios para comparar estrategias alternativas de control. Se evaluaron catorce escenarios, incluyendo sacrificio sanitario únicamente de predios detectados, sacrificio preventivo, vacunación en anillo de emergencia con distintos radios y comparación entre aplicación solo en bovinos versus en múltiples especies, y vacunación preventiva de bovinos dirigida según el riesgo de transmisión ($R_h \geq 0.8$) o según el tamaño del rodeo (predios con más de 300 y más de 100 bovinos). Los resultados

mostraron que las intervenciones reactivas de pequeño radio tuvieron impacto limitado y baja eficiencia operativa bajo capacidad restringida de sacrificio sanitario. En contraste, la vacunación preventiva dirigida, especialmente aquella basada en el riesgo de transmisión de predios con alto potencial de propagación, logró consistentemente las mayores reducciones en el tamaño epidémico con un esfuerzo operativo mucho menor.

En conjunto, esta tesis demuestra cómo la epidemiología cuantitativa y la modelización basada en datos de campo pueden traducir las lecciones de una gran epidemia en evidencia que informa directamente la preparación y la planificación de la respuesta ante brotes. Muestra que la detección tardía y los movimientos durante el período de alto riesgo pueden impulsar una diseminación amplia antes de que comiencen las medidas de control. La transmisión en sistemas productivos basados en pasturas está determinada por la densidad de bovinos y por la heterogeneidad asociada al tamaño de los predios, con una mayor contribución a la propagación por parte de los establecimientos bovinos de mayor tamaño. Asimismo, la vacunación de emergencia con vacunas comerciales puede reducir rápidamente la transmisión entre predios cuando se integra con la prohibición de movimientos y medidas de bioseguridad.

Al proporcionar estimaciones de transmisión específicas por fase, evidencia sobre la propagación mediada por movimientos y estimaciones de efectividad vacunal basadas en datos de campo, este trabajo fortalece la base empírica para la vigilancia basada en riesgo, la modelización de respuesta ante brotes y la planificación de contingencia frente a futuras incursiones de fiebre aftosa en Uruguay y en contextos productivos comparables.

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Publications

This thesis

Main factors associated with foot-and-mouth disease virus infection during the 2001 FMD epidemic in Uruguay
María V. Iriarte, José L. Gonzáles, Eduardo de Freitas Costa, Andrés D. Gil, Mart C. M. de Jong
Front. Vet. Sci., 01 February 2023
Sec. Veterinary Epidemiology and Economics
Volume 10 - 2023 | https://doi.org/10.3389/fvets.2023.1070188

Animal Movements and FMDV Transmission during the High-Risk Period of the 2001 FMD Epidemic in Uruguay
María V. Iriarte, José L. Gonzáles, Andrés D. Gil, Mart C. M. de Jong
Transboundary and Emerging Diseases (2023), 2023, 1-11, 10.1155/2023/8883502
2023-11-11

Effectiveness of emergency vaccination in controlling a foot-and-mouth disease epidemic in a previously FMD-free country without vaccination
María V. Iriarte, José L. Gonzáles, Andrés D. Gil, Mart C. M. de Jong
The Veterinary Journal (under review) - Date of submission: 22nd September 2025

Other

Shifting to foot-and-mouth disease-free status without vaccination: Application of the PROMETHEE method to assist in the development of a foot-and-mouth national program in Uruguay
Luis Gustavo Corbellini, Federico Fernández, Edgardo Vitale, Cyntia Moreira Olmos, Pablo Charbonnier, María Victoria Iriarte Barbosa, Franklin Riet-Correa
Preventive Veterinary Medicine, Volume 181, 2020, 105082, ISSN 0167-5877, https://doi.org/10.1016/j.prevetmed.2020.105082.

Review on ecological interactions of the Cochliomyia hominivorax fly and assessment of the possible impacts of its eradication in Uruguay
Etchevers, I., Iriarte, M. V., Marques, L., Ferenczi, A., Dalla Rizza, M., Marzaroli, J., Saravia, A., Fresia, P. (2022). Review on ecological interactions of the Cochliomyia hominivorax fly and assessment of the possible impacts of its eradication in Uruguay. Agrociencia Uruguay, 26(2), e1056. https://doi.org/10.31285/AGRO.26.1056

Non-typhoidal Salmonella in food animals in Paraguay: predominant serovars and resistance phenotypes
Rossana Irrazábal, María V. Iriarte, Julio Alvarez
Front. Vet. Sci., 24 March 2025.
Sec. Veterinary Epidemiology and Economics. Volume 12 - 2025 |
https://doi.org/10.3389/fvets.2025.1521469

Training and Supervision Plan (TSP)

Graduate School WIAS

Section 1. GENERAL INFORMATION AND LEARNING GOALS

Name PhD candidate	María Victoria Iriarte Barbosa	
Project title	FMD transmission and effective emergency response in Uruguay	
Group	Infectious Disease Epidemiology	
Supervising team:		
	Name:	Daily supervisor?
Intended (co)promotor	José Luis Gonzales	☐
Intended promotor	Mart de Jong	☑
Intended (co)promotor	Andrés Gil	
PhD study advisor	Martin Lankheet	
Project term	from 01/11/2019	until 01/04/2025
Submitted	13/2/2025	certificate

EDUCATION AND TRAINING (minimum 30 credits)

A. The Basic Package	year	credits *
WIAS Introduction Day **(mandatory)**	2021	0.3
WGS Scientific Integrity course **(mandatory)**	2020	0.6
WGS Ethics in Animal Sciences course **(mandatory)**	2020	0.8
Introduction course on Personal Effectiveness *(recommended)*	2021	1.2
Subtotal Basic Package		**2.9**

B. Disciplinary Competences	year	credits
Writing research proposal	2020	6.0
Management of Infections and Diseases in Animal Populations	2020	6.0
Basic statistics	2022	1.5
DataCamp courses	2019-22	2.8
Workshop: Using transmission models to simulate FMD epidemics and the implementation of control actions	2022	1.0
Subtotal Disciplinary Competences		**17.3**

C. Professional Competences	year	credits
Scientific writing	2021	1.8
Scientific Publishing	2021	0.3
Searching and Organising Literature	2022	0.6
Efficient writing	2023	1.3
Final Touch	2023	0.6
Subtotal Professional Competences		**4.6**

D. Societal Relevance	year	credits
Societal Impact of your Research	2020	1.5
Subtotal Societal Relevance		**1.5**

E. Presentation Skills		year	credits
Main factors associated with FMDV introduction and infection spread during the high risk period of the 2001 FMD epidemic in Uruguay, Global Foot-and-Mouth Disease Research Alliance (GFRA2001), Scientific Meeting, Buenos Aires-Argentina (online)	Oral	2021	1.0
Animal movements and FMD virus transmission during the initial phase of the 2001 FMD epidemic in Uruguay, "Digitalization and innovation applied to the prevention and control of FMD And Similar Transboundary animal diseases (FAST)" Open Session-European Commission for the Control of Foot-and-Mouth Disease (EUFMD),Marseille-France	Poster	2022	1.0

Main factors associated with FMDV introduction and infection during the 2001 epidemic in Uruguay, 16th International Symposium of Veterinary Epidemiology and Economics (ISVEE 16 or ISVEE2022) Halifax-Canada	Oral	2022	1.0
Assessing interventions by using data from the 2001 FMD epidemic curve of Uruguay, 16th International Symposium of Veterinary Epidemiology and Economics (ISVEE 16 or ISVEE2022), Halifax-Canada	Poster	2022	1.0
Foot-and-mouth disease vaccination effectiveness during the 2001 epidemic in Uruguay, 17th International Symposium on Veterinary Epidemiology and Economics, Sydney-Australia	Oral	2024	
Subtotal presentations			**4**

F. Teaching competences	year	credits
Contributed to undergraduate teaching materials by writing two chapters ("Risk Analysis" and "Outbreak Investigation") for a lecture guide.	2023	2.0
Lectures on Veterinary Epidemiology course for undergraduate students at the Faculty of Veterinary Medicine, University of the Republic (Uruguay).	2024-25	2.0
Lectures on Epidemiology and the Uruguayan Official Veterinary Services workshop for undergraduate students at the Faculty of Veterinary Medicine, University of the Republic (Uruguay).	2024-25	2.0
Subtotal Teaching competences		**6**

Education and Training Total (minimum 30 credits)* **One ECTS credit equals a studyload of approximately 28 hours*	**36**

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About the author



María Victoria Iriarte was born in Montevideo, Uruguay, on November 30, 1984. She grew up in the Department of Artigas, in northern Uruguay, on the border with Brazil, where her early life was closely connected to livestock production systems.

In 2006, she began her studies in Veterinary Medicine at the Faculty of Veterinary Medicine, Universidad de la República (Montevideo, Uruguay). She graduated in December 2011 and received the Academic Excellence Award. Following graduation, she returned to Artigas, where she worked on her family's farm and as a private practicing veterinarian.

In 2014, she joined the Ministry of Livestock, Agriculture and Fisheries (MGAP) of Uruguay as a field veterinarian in the Department of Artigas. While working in the field, she decided to resume her academic training, despite the structural difficulties of accessing postgraduate education outside the capital city at that time. She enrolled in the Master's programme in Animal Health at the Faculty of Veterinary Medicine, Universidad de la República.



In 2018, she moved to Montevideo to work at the Epidemiology Unit of the Official Veterinary Services of Uruguay (the General Directorate of Livestock Services of MGAP). She obtained her Master's degree in August 2019, with distinction (Master's thesis: "Evaluation of Foot-and-Mouth Disease Surveillance Systems in Uruguay during the period 2016–2018."). In November of the same year, she began her PhD studies at Wageningen University & Research, the Netherlands.

In 2023, she was appointed Technical Advisor within the Official Veterinary Services of Uruguay. In parallel, she serves as a teaching assistant in the Epidemiology Unit at the Faculty of Veterinary Medicine, Universidad de la República. Her professional and academic work focuses on veterinary epidemiology, infectious disease surveillance and control, and preparedness and response to transboundary animal diseases, particularly foot-and-mouth disease.

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