

Mathematical modeling and social network analysis applications in foot-and-mouth disease transmission and livestock movements in U.S. production types

by

Aurelio Hugo Cabezas Murillo

DVM, Universidad de las Americas, 2012

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Department of Diagnostic Medicine and Pathobiology
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Abstract

The U.S. has been FMD-free since 1929. The U.S. has a large beef industry with over 45% of cattle on-feed concentrated in feedlots with a one-time head capacity $\geq 32,000$ cattle. The country has a complex production system in which there is a continuous flow of livestock. An incursion of FMD could be devastating, so an understanding of the dynamics of a hypothetical outbreak in these large operations is needed. Also, an understanding of movement patterns to identify areas at-risk that can be targeted during disease response is needed.

Mathematical modeling is the only tool available to study epidemics of infectious diseases such as FMD while Social Network Analysis (SNA) is an approach that helps to understand movement patterns. Parameterization of mathematical models is challenging due to the variability of the FMDv and the lack of specific data to U.S. beef populations. We developed an FMD expert survey to collect key parameter values of FMD natural history and transmissibility in beef U.S. feedlots. Data synthesized, used in combination with experimental and outbreak investigation data, will help to parameterize FMD-transmission models to evaluate implications of epidemics in U.S. beef feedlots.

We developed a meta-population model to study FMDv transmission and evaluate interventions strategies within U.S. beef feedlots. We found that the projected outbreak duration was shorter for those feedlots with over 12,000 cattle population that operated with one hospital-pen compared to those feedlots that operated with two hospital pens. Restriction of movements of cattle from home pens to hospital pens within the feedlots was found to prolong the projected outbreak duration but did not interrupt FMDv transmission in feedlots modeled. Partial depopulation interventions were not found to be highly efficient in controlling FMDv transmission or required depopulation of a large proportion of cattle in feedlots modeled.

We used social network analysis to describe inter-state movements of beef cattle, dairy cattle, swine, and small ruminants, and identify trade-communities within the contiguous U.S. for each livestock type network. We found that outputs generated resemble the nature of the beef feedlot industry (cow-calf to feedlot) while areas with large animal counts in the swine and dairy cattle networks were found to have high degree centrality. We also found between 1 to 2 largest communities in the beef cattle, dairy cattle, and swine networks which accounted for up to 65% of arcs in each network. The outputs of these networks could be useful to parameterize network models to assess disease transmission such as FMD at a national scale and evaluate the application of intervention strategies.

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Approved by:

Major Professor
Michael W. Sanderson

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Chapter 1 - Literature Review: Epidemiology of foot-and-mouth disease (FMD) and the application of simulation modeling to assess foot-and-mouth disease virus (FMDv) transmission and control strategies

Introduction

Foot and mouth disease (FMD) is a highly infectious disease that affects mainly livestock species such as cattle, swine, and small ruminants; but it has also been shown to infect over a 100 wild, feral, laboratory, and domesticated species although their role in the overall disease ecology is not well understood (Weaver et al., 2013). FMD is one of 117 diseases notifiable to the OIE (World Organization for Animal Health) and one of six diseases for which official disease status is recognized by the OIE (OIE, 2018c). It has been suggested that FMD was first documented in the 16th century when an outbreak with similar characteristics was described in Italy (Fracastorius, 1546) cited by Bachrach (1968); Grubman and Baxt (2004); Mahy (2005) but the viral agent was not discovered until 1898 by Loeffler and Frosch (Coetzer and Tustin, 2004). There are 7 serotypes, and multiple subtypes within serotypes exist.

FMD has never occurred in New Zealand, and in Australia the last outbreak occurred in 1872 (Bachrach, 1968). The European Union achieved eradication in 1992 (Coetzer and Tustin, 2004) but outbreaks in the early 2000s affected the United Kingdom, The Netherlands, and France (Anderson, 2002; Bouma et al., 2003; Chmitelin and Moutou, 2002; Ellis-Iversen et al., 2011). In South America, major outbreaks occurred in 2000-2001 in Uruguay, in 2000 and 2006 in Argentina, in 2002 and 2011 in Paraguay (Clavijo et al., 2017). An aggressive eradication

campaign lead to most of the continent being FMD-free with or without vaccination with the exception of Venezuela where there is no recognition of the current status of the disease (Clavijo et al., 2017). FMD focalized outbreaks were reported in Colombia in 2017 and 2018 but they were effectively controlled. The South American goal is to achieve FMD elimination on the continent by 2020 (Naranjo and Cosivi, 2013). In North America, the United States, Canada and Mexico have been free of FMD since 1929, 1952 and 1953, respectively (Graves, 1979; Mohler, 1930). The disease remains endemic in Asia and Africa, and large outbreaks have affected Japan and South Korea between 2000 and 2011 (Nishiura and Omori, 2010; Park et al., 2014; Yoon et al., 2015).

The socio-economic consequences of outbreaks reported in developed countries with large livestock populations have raised concerns in FMD-free countries such as New Zealand, Australia, Canada, and the U.S. to understand and evaluate the risk and impacts of FMDv introduction as well as effective control options. Mathematical modeling is the only tool available to study FMD spread and control strategies to mitigate potential epidemics in non-endemic countries; however, parameterization of FMD transmission models in non-endemic settings is challenging due to incomplete knowledge of the characteristics of the FMDv in the specific production systems and the virus behavior in a naïve livestock populations. Simulations models in combination with standard epidemiological methods can provide a strong foundation for policymaking for disease surveillance and FMD-outbreak preparedness plans.

Etiology

FMDv is part of the *Aphovirus* genus within the *Picornaviridae* family. Seven immunologically distinct serotypes have been identified: A, O, C, SAT 1, SAT 2, SAT 3, and

ASIA 1. The 7 serotypes were identified between 1922-1954 and since then no other serotypes have been identified (Brown, 2003). There is no cross-protection between serotypes and multiple subtypes exist within serotypes. FMDv has high mutation, selection, and recombination rates which induce the generation of new antigenic variants and the need for careful selection of strains during vaccine development and continual monitoring to assure vaccine efficacy (Coetzer and Tustin, 2004).

Pathogenesis

Infection occurs generally via the respiratory route by inhalation of aerosolized virus in cattle and via the oral route by consumption of contaminated feed in pigs (Alexandersen et al., 2003; Donaldson, 1987). The minimal dose to cause clinical disease has been reported to be 10 bovine thyroid tissue culture infectious dose (TCID₅₀) via respiratory route for cattle and sheep, and higher than 800 TCID₅₀ for swine. The oral TCID₅₀ has been reported to be 10⁴ to 10⁶ for all three species (Alexandersen et al., 2003). The nasopharynx and the soft palate have been demonstrated to be the primary sites of infection in cattle (Arzt et al., 2011b), however it is less understood in pigs and small ruminants (Arzt et al., 2011a; Stenfeldt et al., 2016a).

The onset of infectiousness occurs before the onset of clinical signs in cattle, swine, and small ruminants. Experimental studies confirmed FMDv transmission in pigs, cattle, and sheep at least 24 hours before the clinical signs were identified (Arzt et al., 2019; Orsel et al., 2009) although one study suggests that cattle become infectious on average 0.5 days after the onset of clinical signs (Charleston et al., 2011). The incubation period for FMD from the time of effective exposure until the onset of clinical signs, is highly variable between 2 to 14 days but generally between 2-6 days (Kitching and Mackay, 1995). Experimental studies have shown onset of signs

may be as early as 1-2 days in cattle inoculated with FMDv and between 2-5 days in susceptible cattle housed with inoculated FMD infectious cattle in controlled environments (Christensen et al., 2011; Fowler et al., 2014; Maddur et al., 2008; Maddur et al., 2009; Oem et al., 2008; Onozato et al., 2014; Orsel et al., 2009; Pacheco et al., 2015; Pacheco et al., 2016; Stenfeldt et al., 2011; Zhang and Alexandersen, 2004). Generalization of these results is difficult due to the differences in experimental designs between experiments.

Clinical presentation of the disease varies with species, dose of infection, and virulence of the strain (Kitching et al., 2005; Sobrino and Domingo, 2004). Morbidity can reach 100% but it has a very low mortality in adults; high mortality has been shown in neonates due to myocarditis (Kitching, 2002). Cattle and pigs are more likely to develop severe disease whereas in small ruminants the clinical presentation is generally mild and difficult to identify (Alexandersen et al., 2002b; Barnett and Cox, 1999; Donaldson and Sellers, 2000; Hughes et al., 2002). There is also evidence that some strains have a predilection for specific species such as the Taiwanese outbreak during 1997 which was caused by the strain TAW 9/97 (serotype O) and only affected pigs and no other species. Early non-specific clinical signs are depression, fever, loss of production, and anorexia. Specific signs of the disease are vesicles in the hoofs, mouth, udder and teats along with salivation and lameness. Eventually, vesicles rupture resulting in substantial erosions. Long term effects include depressed production and weight loss. Secondary infections are likely during the clinical phase of the disease and complete recovery in terms of productivity is not likely (Kitching, 2002). Ageing of the lesions is done by visual assessment of the appearance of lesions, and complete healing of lesions occurs on average by day 7 after the onset of clinical signs (DEFRA, 2005; Kitching and Mackay, 1995; Sobrino and Domingo, 2004).

Rapid immune response occurs in naturally infected or vaccinated animals and antibodies can be detected within 3-5 days after the onset of clinical signs (Alexandersen et al., 2003). Protective immunity can develop between day 7 and 14 after either natural infection or vaccination (Grubman and Baxt, 2004). Cattle are resistant to re-infection with strains from the same serotype after natural infection for up to 3 years (Bachrach, 1968), but the period might be dependent on the serotype as it has been shown that immunity for the SAT serotypes is shorter compared to the other serotypes (Coetzer and Tustin, 2004).

Epidemiology

Distribution

Six of the seven serotypes (A, O, C, SAT 1, SAT 2, and SAT3) have been found in Africa while serotypes A, O, C, and ASIA-1 have occurred in Asia. In South America, serotypes A, O, and C have occurred (Grubman and Baxt, 2004; Rweyemamu et al., 2008). A more up to date review of the global distribution by Brito et al. (2017) has proposed a distribution based on FMDv pools of similar viruses due to ecological similarities and livestock exchange movements. The review was conducted based on the FMD situation in endemic areas and outbreaks during 2007-2014. Seven pools have been identified and various serotypes and genotypes classified within each pool. Three pools are restricted to Asia including strains in serotypes A, O, and ASIA 1. Three pools map to Africa with serotypes O, A, SAT 1, SAT 2, and SAT 3. One pool is in South America with strains within serotypes A, and O. A graphical distribution and more detailed classification of these FMDv pools can be found in Paton et al. (2009) and Brito et al. (2017).

Host range

The disease affects all cloven-hoofed animals (Coetzer and Tustin, 2004). Mahy (2005) distinguished 3 different categories in terms of the role the species play in the epidemiology of FMDv:

1. Species that play an active role in the epidemiology of the disease such as bovine, swine, and small ruminants. These species are susceptible to infection, develop clinical disease, and can transmit the virus to other susceptible animals.
2. Species that can be infected under controlled environments, develop disease, and might represent a risk under certain conditions such as deer, camel, alpacas, wild boar, and buffalo subspecies. Wernery and Kaaden (2004) studied the role of camelids in FMDv transmission. They suggest that llamas and alpacas can be infected by direct contact with an infectious animal but do not represent a risk for other susceptible camelids or livestock and they clear the virus after 14 days post-infection. They concluded the same about dromedaries in the Middle East. Infection of white-tailed deer was studied by Moniwa et al. (2012); deer were inoculated intranasally and all animals developed disease 1-2 days post-infection. Also, the same study housed a group of deer in the same room with cattle and FMDv transmission was confirmed from deer to cattle under experimental conditions. Wild boar have been found seropositive to FMDv in areas in Bulgaria, but the role of this species in FMD transmission is highly dependent on population density and environmental conditions (Alexandrov et al., 2013). The Cape buffalo (*Syncerus caffer caffer*) is a demonstrated maintenance host for the SAT serotypes (Vosloo et al., 1996). Also, studies conducted in West, Central, and South Africa confirm circulation of multiple FMDv serotypes in buffalo subspecies (*Syncerus*

caffer aequinoctalis, *Syncerus caffer brachyceros*) (Di Nardo et al., 2015; Jori et al., 2016; Sikombe et al., 2015). The role of the buffalo subspecies into the epidemiology of FMDv is not well-understood although transmission from African buffalo to cattle has been demonstrated under field and experimental conditions (Dawe et al., 1994; Hedger and Condy, 1985).

3. Species susceptible to experimental infection that might develop disease but that do not represent a risk of transmitting infection in field conditions such as mice, hedgehogs, guinea pigs, etc.

A review by Weaver et al. (2013) found that there are more than 100 species (wild, captive wild, feral, and domesticated) susceptible to FMDv infection. The study found that 49% of the species reported in studies (experimental or natural infection) developed mild to severe clinical disease, 19% of them did not develop disease, and no data related to clinical disease was reported in 32% of the species studied. FMD in humans has been reported in one case during the FMD outbreak in the UK in 1966 who developed vesicles in mouth, hands, and feet. It was later confirmed that infection was the same strain that caused the outbreak (Armstrong et al., 1967). During the 2001 FMD UK outbreak, there were 13 human cases suspected but all of them were negative by laboratory analyses (Mayor, 2001). It has been suggested that humans can carry the virus in the respiratory tract for 24 hours (Sellers et al., 1970), but there is no evidence that humans play a role in the epidemiology of FMD .

Transmission

FMDv can spread via direct or indirect contact or aerosol spread. Spread occurs mainly via direct contact between infectious and susceptible animals; aerosol and indirect contact

transmission depends on the viral load shed by an infectious animal, the survival of the virus in the environment, and the exposure dose (Coetzer and Tustin, 2004; Sellers, 1971). Cattle and small ruminants are more susceptible to natural infection via the nasal route while pigs are more susceptible to oral routes (Alexandersen et al., 2003). Infectious animals excrete the virus in all secretions and excretions, but the amount of virus and survival in contaminated materials varies depending on the virus strain and environmental conditions as demonstrated by Alexandersen et al. (2003); Bartley et al. (2002); Sellers (1971). The peak of viral shedding coincides with the onset of the clinical stage in cattle and swine whereas in small ruminants the peak of viral shedding occurs during the subclinical stage (Coetzer and Tustin, 2004). It is suspected that sheep were responsible for the spread of FMD during the silent phase of the 2001 UK outbreak as they develop mild disease and detection is difficult (Anderson, 2002). Pigs excrete a higher amount of virus compared to cattle and small ruminants (Donaldson and Alexandersen, 2002; Sellers and Parker, 1969) although that difference varies in literature due to the experimental design used in studies (Coetzer and Tustin, 2004). An analysis reported by Bravo de Rueda et al. (2014) suggests that type of secretion (saliva) and excretion (feces or urine), days post infection, animal species, stage of the disease, and FMDv serotype are factors associated with the amount of virus shed by infectious animals.

Indirect transmission can occur due to exposure of susceptible animals with contaminated materials such as drinking water, milk, carcasses, hay, soil, wood, vehicles, and farm personnel (Bachrach, 1968). FMDv is stable within pH range 7-8.5 (Alexandersen et al., 2003). The virus can be inactivated by the decrease of pH in meat during rigor mortis in cattle. The virus can survive for long periods in bone marrow and lymph nodes where pH does not decrease during rigor mortis and might be a potential cause for outbreaks if susceptible animals, particularly pigs

are exposed to unheated waste food (Donaldson, 1987). FMDv has been demonstrated to be stable in aerosols within 55-60% relative humidity (RH) (Barlow, 1972). The survival of FMDv in the environment depends on several factors such as temperature, pH, RH, strain, and the material hosting the virus. FMD transmission via water and other fluids has been less investigated. One study investigated the potential risk for FMDv infection via consumption of contaminated water. The study used the experience from the 2001 outbreak in the Netherlands in which, due to the transport prohibition instituted, farmers illegally discharged milk produced by their FMD infected dairy cows into the sewerage. The quantitative risk assessment found that there is a high risk of FMDv transmission to susceptible cattle grazing in near areas to FMD infected farms where they could drink the water contaminated with the infected milk (Schijven et al., 2005). FMDv has been reported to be viable for 14 days in feces, 36 days in urine, and 6 months in slurry during the cold season. FMD survived 3 days in the ground during the hot season, and 28 days during the fall (Alexandersen et al., 2003). Other studies have reviewed FMDv survival in other animal excretions and secretions, and their FMD viral load Alexandersen et al. (2003), as well as in fomites (Bartley et al., 2002); however, it should be considered that these estimates have been done based on experimental methods under different procedures, so application to field setting is challenging. Nevertheless, despite the research conducted it is worthwhile to highlight that the virus can be easily inactivated by ensuring standard practices in the processing of animal by-products, and via common disinfection methods at the farm level. The OIE in its terrestrial animal health code recommends a series of procedures to deactivate the FMDv (OIE, 2018b).

Airborne transmission has been a subject of concern although specific environmental conditions must occur for the virus to remain viable and travel for prolonged distances. After the

FMD UK epidemics in 1967-1968, the contribution of atmospheric conditions into the FMDv transmission has been considered (Gloster et al., 1982; Henderson, 1969; Hugh-Jones and Wright, 2009). The risk of airborne transmission varies between strains, species infected, and species at risk (Donaldson et al., 2001). This study used an atmospheric dispersion model to estimate the risk of airborne transmission and found that 1 infectious animal (cattle/sheep/pig) could infect any susceptible animal within less than 0.1 km, and less than 6 km if there were 1,000 infectious animals. On the other hand, another atmospheric dispersion model by Sørensen et al. (2000) suggests that strains such as the C Noville strain might have the potential to infect susceptible animals over a 300 km distance. Longer distances of potential FMDv transmission can be expected when pigs are the source of infection because they shed higher quantities of FMDv to the environment compared to ruminants (Sutmoller et al., 2003). Recently, a study by Hagerman et al. (2018) investigated the potential implications of weather conditions and livestock population in FMDv airborne transmission within the U.S., they found that years with moderate environmental conditions were more likely to contribute to FMDv spread compared to years with more extreme weather conditions. Also, higher risks of FMDv spread were found in areas with large pig populations. Interpretation and analysis of conclusions drawn by the application of atmospheric models into FMDv spread should be cautiously done and not generalized due to the lack of data and the variability of FMDv strains.

Transmission to susceptible farms can occur via movement of animals from infected farms or through direct contact between infectious and susceptible animals in markets or exhibition shows (Fevre et al., 2006; Sutmoller et al., 2003). Movement of infected sheep was the main cause of FMD spread during the UK 2001 FMD epidemic being responsible for introduction of the virus into 9 major geographical areas before the movement ban was put in

place (Gibbens et al., 2001). Introduction of FMDv in 2001 to the Netherlands and France was confirmed to happen through movement of calves originating in the UK (Bouma et al., 2003; Chmitelin and Moutou, 2002). In a similar way, the incursion of an FMDv serotype O in Vietnam in 2015 is hypothesized to have happened through movement of cattle from Laos where outbreaks of the same serotype were previously reported (Vu et al., 2017). Also, fomites carrying the virus such as motorized vehicles, veterinarians, farmers, or contaminated feed can be responsible for introducing the virus into susceptible farms (Bachrach, 1968; Suttmoller et al., 2003). For instance, trace-back investigations during the 2001 FMD UK outbreak found FMDv in swill in a pig fattening unit suggesting it was the possible source of infection (Gibbens et al., 2001). Similarly, FMDv contaminated wheat straw was suggested to be the likely route of FMDv introduction that caused the 2000 epidemic in Japan (Sugiura et al., 2001). The 2007 FMD outbreak in Surrey is suspected to have been caused by FMDv virus escape from deficient drains from a laboratory facility and carried in mud/soil by motorized vehicles (Ellis-Iversen et al., 2011). Milk and movements of milk through tankers were found to be responsible of 22 secondary outbreaks during the 1967-1968 UK FMD outbreak (Dawson, 1970; Hedger and Dawson, 1970). International travel of owners from a pig-farm complex was considered to be the likely route of FMDv introduction that caused the 2010-2011 FMD epidemic in South Korea (Yoon et al., 2015). In addition, during the 15 days that passed between infection to detection during the South Korean epidemic, transport of FMD contaminated feed was responsible to spread the virus between farms.

Carriers

FMD persistently infected animals commonly known as carriers are a substantial topic of debate in terms of their role as a potential route of FMD spread and consequently in terms of trade regulations (Gareth Davies, 2002; Sutmoller and Casas Olascoaga, 2002). A carrier is defined as an animal in which the virus can be recovered from the oropharynx for at least 28 days after infection (Salt, 1993; Sutmoller et al., 1968). A literature review of the role of carriers in the transmission of FMD found evidence that the carrier state in cattle can last up to 42 months and up to 12 months in sheep while pigs were not found to become carriers (Thomson, 1996). On the other hand, the persistent infection in the African buffalo can last up to 5 years and the prevalence under field conditions ranges from 50 to 70% (Condy et al., 1985). Either naturally infected or vaccinated animals can become carriers; however, the viral load in vaccinated carrier animals has been shown to be lower compared to those naturally infected, and the proportion of carriers in vaccinated populations decrease when total vaccination of the cattle population is achieved (Anderson et al., 1974). Experimental studies in cattle are not consistent in demonstrating transmission from carriers to susceptible animals. For instance, Parthiban et al. (2015) housed 2 groups of sero-negative non-vaccinated cattle (2 cattle per group) with 9 and 3 carriers for 75 and 63 days, respectively, and no evidence of FMDv transmission was found. On the other hand, Dawe et al. (1994) confirmed transmission in an experiment in which three FMD carrier African buffaloes were housed together with four sero-negative non-vaccinated cattle. The four cattle developed FMD 5 months later. The authors suggested that the virus might have persisted for that time in one of the African buffaloes. A field study conducted by Bertram et al. (2018) in Vietnam failed to confirm transmission in field settings from carrier cattle to sero-

negative non-vaccinated cattle during a follow-up period of 6 months. Despite the extensive research conducted about the role of carriers in the epidemiology of FMD (Alexandersen et al., 2002a; Arnold et al., 2008; Bronsvort et al., 2016; Moonen and Schrijver, 2000; Parthiban et al., 2015; Salt, 1993; Stenfeldt et al., 2016b; Tenzin et al., 2008; Thomson, 1996), the risk of transmission from carriers to susceptible species in field settings is still uncertain.

Outbreaks

From 1992 to 2003, McLaws and Ribble (2007) identified 24 outbreaks in non-endemic areas. The authors reported four major outbreaks during that period with more than 2,000 premises infected in each (Taiwan 1997, Argentina 2000, Uruguay 2001, and UK 2001), and less than 150 infected premises in each of the remaining 20 outbreaks described.

The 1997 epidemic in Taiwan was caused by a strain of serotype O (O TAW 9/97), the epidemic spread over the entire country infecting only pigs and lasted about 4 months (Dunn and Donaldson, 1997). After identification of FMD, depopulation of all pigs in infected premises and vaccination of pigs in farms at high-risk of infection was implemented. Later in the epidemic the policy changed to vaccination of all pigs in the country. After completion of vaccination, depopulation of clinical animals (only) in infected farms was put in place. Approximately 6,100 farms were affected during the epidemic and the total financial cost due to slaughter, vaccination, carcass disposal, loss of market value, and compensation was approximately \$378 million (Yang et al., 1999).

In the early 2000's Argentina had 2 outbreaks. In 2000, 124 bovine herds were affected by a strain of serotype A (A/Arg/2000) and a strain of serotype O (O/Arg/2000) which was controlled by early 2001 after movement restriction and depopulation (Brito et al., 2011). In

2001, a new strain of serotype A (A/Arg/2001) caused a larger epidemic infecting around 2,500 bovine herds which represented an attack rate of less than 1% (Perez et al., 2004b); movement restriction and vaccination of animals in farms surrounding infected farms was implemented at the beginning of the epidemic which then changed to a mass vaccination program (Perez et al., 2004a). The epidemic lasted until January 2003 (Perez et al., 2004a, b). A focalized outbreak was reported in February 2006 which was eventually controlled a month later the same year (Clavijo et al., 2017).

In Uruguay 2000, an outbreak by a strain of serotype O was reported in one pig farm that consumed infected feed and then spread to cattle. Approximately 20,000 animals were destroyed to control the outbreak (OIE, 2001). In 2001, the strain of serotype A that affected Argentina spread to Uruguay and caused an epidemic that affected 2,057 bovine farms. Around 7,000 cattle were destroyed and 12 million animals were vaccinated (OIE, 2001).

In February 2001, the PanAsia O strain affected the UK; some suggested that the virus was introduced to the country in swill that was eventually fed to pigs (Anderson, 2002; G. Davies, 2002). It is also thought that movements of infected sheep, susceptibility of sheep to the PanAsia strain, time of the year the FMDv was introduced, and the delay in notifications contributed to the widespread of the virus before it was detected (Gibbens et al., 2001). Movement restrictions were put into place and then followed by two depopulation strategies (culling of all animals in infected premises within 24 hours and culling of all animals in farms classified as dangerous contacts within 48 hours). The strategic management of the outbreak was informed by three mathematical models (Kao, 2002). The epidemic lasted for 6 months and infected around 2,000 farms (G. Davies, 2002). Approximately 4 million animals were

depopulated, and the approximate the total financial cost due to slaughter, carcass disposal, loss of market value, and compensation was around £2.7bn (Anderson, 2002; G. Davies, 2002).

France and The Netherlands were also affected due to the FMD 2001 UK outbreak. France adopted pre-emptive slaughter of animals imported from the UK during the risk period; however, 2 outbreaks were reported after the pre-emptive slaughter and eventually around 63,000 animals were slaughtered due to the control plan (Chmitelin and Moutou, 2002). The Netherlands also traced back animals imported from the UK and France and depopulated all small ruminants imported from those countries. This did not prevent introduction of the virus; animals imported from a farm in France were the cause of the spread of the virus into The Netherlands (Bouma et al., 2003). A total of 26 premises were affected by the outbreak and the main control strategies adopted were emergency vaccination of all susceptible animals in farms around the infected farms, ring vaccination of all animals within 2 km of infected farms, and eventual culling of all vaccinated animals (Pluimers et al., 2002). The epidemic lasted for approximately 2 months and around 260,000 animals were destroyed in the control strategies (Bouma et al., 2003).

In 2007, a small-scale outbreak affected 8 premises in the UK. The virus escaped from the Pirbright Institute in damaged drains and spread through vehicles but it was soon controlled and did not spread further in the country (Ellis-Iversen et al., 2011).

In March 2010, a strain of serotype O caused a large-scale epidemic in Japan. After detection, early control strategies adopted in the country were culling of animals in infected premises, movement bans, closure of markets, and surveillance of those farms surrounding infected premises. Emergency ring vaccination of all susceptible animals in farms within 10 km of infected premises was later implemented (Nishiura and Omori, 2010). The epidemic infected a

total of 292 farms and around 300,000 animals were destroyed. The outbreak lasted until July 4 when the last case was detected (Muroga et al., 2013).

South Korea was also affected during 2010/2011 by an FMDv lineage endemic to SEA (Yoon et al., 2015). The index case was reported to be a pig farm in GyeongBuk province and the epidemic lasted for 145 days (Park et al., 2013; Yoon et al., 2015). Movement restrictions, culling of animals, disinfection of infected premises, and a vaccination-to-live policy were the main control strategies implemented during the epidemic (Park et al., 2013; Yoon et al., 2015). One-hundred and fifty three farms were confirmed to be infected by the virus and around three million animals were destroyed during the epidemic (Yoon et al., 2012).

Molecular Epidemiology

Molecular epidemiology is an important tool in the study of the epidemiology of FMDv which can help to trace the origin of FMDv strains and their global distribution. For instance, two publications (Knowles and Samuel (2003); Knowles et al. (2005) used molecular techniques to describe the spread of the PanAsia strain that caused the 2001 FMD UK epidemic. The authors described the movement of the strain since 1990 when it was first detected in India through Saudi Arabia, east Asia, South Africa, and finally into Europe in the early 2000s. Interestingly, they were also able to assess how the strain has adapted to its geographical locations in endemic areas and replaced the other circulating strains, and managed to reach FMD-free areas with strict surveillance and control measures in the importation of animals and animals by-products (Samuel and Knowles, 2001). Molecular tools have also been used during outbreak investigation to identify transmission pathways as shown by Cottam et al. (2006); Cottam et al. (2008) during the FMD UK 2001 and 2007 outbreaks.

Other studies conducted in Bangladesh (Loth et al., 2011; Nandi et al., 2015; Siddique et al., 2018), Afghanistan (Jamal et al., 2011; Schumann et al., 2008), Pakistan (Brito et al., 2013; Jamal et al., 2011), India (Mohapatra et al., 2011; Sanyal et al., 2004), China (Bai et al., 2011), South East Asia (Abdul-Hamid et al., 2011), Egypt (El-Shehawy et al., 2014; Elhaig and Elsheery, 2014), Uganda (Dhikusooka et al., 2016), Cameroon (Bronsvort et al., 2004), West Africa (Gorna et al., 2014; Sangare et al., 2004), South America (Konig et al., 2007; Malirat et al., 2012), and Turkey (Klein et al., 2006) used molecular techniques to describe the circulating groups in their respective areas, but also the emergence of novel subgroups within different serotypes and demonstrated how they have established and replaced other circulating subgroups. The studies highlighted the importance of the identification of these novel subgroups in their respective countries for the appropriate selection of strains in the development of effective vaccines as control strategies, and evidence to implement more strict regulations for animal movements with neighbor countries. Other studies have examined the application of molecular tools to develop simpler and faster diagnostic methods that can be used as an alternative to conventional methods which lack an optimum degree of sensitivity (Le et al., 2012; Longjam et al., 2011).

Diagnosis and control

Detection methods

Diagnosis of FMD is based on primary examination of clinical signs followed by laboratory confirmation. In acute cases, collection of fluids from vesicles is the method of choice because vesicles contains high concentrations of FMDv (Coetzer and Tustin, 2004). Diagnosis of

FMDv can be done by identification of the FMD viral agent or by detection of antibody response (Jamal and Belsham, 2013; Knight-Jones et al., 2016).

Identification of the FMD viral agent can be done by Enzyme-linked immunosorbent assays (ELISA), virus isolation, complement fixation test (CFT), lateral flow devices (LFD), and real time reverse-transcriptase polymerase chain reaction (RT-PCR). Virus isolation and RT-PCR can evaluate epithelium, probang-samples, milk and serum samples whereas ELISA, CFT, LFD can evaluate epithelial suspension, vesicular fluids or cell culture supernatants (OIE, 2018a). Detection of antibody response can be done by ELISA for antibodies against nonstructural proteins (NSP Ab ELISA), ELISA for antibodies against structural proteins (SP Ab ELISA), virus neutralization test (VNT), and agar gel immunodiffusion (AGID) (OIE, 2018a). The main objectives of the use of serological test are for certification of trade animals, confirmation of suspected cases, confirmation of absence of infection, and demonstration of vaccine efficacy (OIE, 2018a). One of the main use of tests against non-structural proteins is the differentiation between natural infections which induce production of antibodies against both structural and non-structural proteins and vaccinated animals which only induce antibodies against structural proteins (Jamal and Belsham, 2013). Finally, Knight-Jones et al. (2016) suggests the need to develop pen-side tests which can facilitate early detection during outbreaks. The authors reviewed several studies with encouraging results however more investigation and validation of these devices is needed.

Another important issue in the application of non-invasive sampling methods in combination with RT-PCR is surveillance strategies in non-endemic countries. A recent study in an endemic area investigated the use of environmental sampling; swab samples were collected in households and milk collection points with active FMD infection (Colenutt et al., 2018). The

study demonstrated successful identification of FMDv in the samples collected in FMD infected sites with animals at different stages in the disease progression (pre-clinical, clinical, and recovery stage). Another study evaluated the feasibility to detect FMDv during the pre-clinical stage in experimental settings (Nelson et al., 2017). The study reported the possibility to use sampling of saliva from baits and ropes in farms, and aerosol sampling in closed environments such as milking parlors which can be easily conducted by farm personnel. Other experimental studies have also evaluated saliva sampling in baits in wild boar populations (Mouchantat et al., 2014) and oral fluid sampling using cotton ropes in swine populations (Vosloo et al., 2015) to evaluate their efficacy to identify FMDv. While studies mentioned above have demonstrated this approach to be an important alternative to consider in the future as a surveillance strategy in non-endemic areas, there is still a need of further investigation of its applicability to field settings.

Control strategies

Rapid implementation of control interventions during an outbreak is important in order to stop transmission, minimize losses, and rapidly recover FMD-free status. The main strategies employed are movement restrictions, stamping-out, biosecurity measures, and vaccination (Sutmoller et al., 2003).

Movement restrictions are the first line of defense after detection of infection. The main objective of this measure is to delay spread of infection and/or prevent contact between infected and susceptible animals. Movement bans have been applied during all outbreaks already discussed above in the *Outbreaks section* in combination with other control strategies such as stamping-out/vaccination or both. Implementation of movements bans in countries with a large flow of animals such as the U.S. will not be an easy task. A study by Delgado et al. (2014)

targeted cow-calf producers in Texas and surveyed beliefs about movement restrictions under a hypothetical FMD outbreak. The study suggests that producers were concerned about potential consequences of movement restrictions such as lack of human labor to handle animals, shortage of feed for the animals, loss of value of their animals, and animal suffering. The FMD preparedness plan for a potential FMD outbreak in the U.S. and recent continuity of business planning describes the implementation of biosecurity protocols and movement restrictions in infected zones (zone that immediately surrounds an infected premise) and buffer zones (zone that immediately surrounds an infected zone or a contact premise) (USDA, 2014). Secure Food Supply plans are available for swine, cattle and milk (<http://www.cfsph.iastate.edu/Secure-Food-Supply/index.php>). These strategies aim to allow continuity of the business in other areas which might not be affected by the infection or are at-low risk of infection.

Stamping-out can be applied as a pre-emptive measure—culling of all animals in farms that had previous contact with farms or areas in which infection has been confirmed. This strategy was implemented in France (Chmitelin and Moutou, 2002), The Netherlands (Bouma et al., 2003), and Ireland (Costelloe et al., 2002) and when the disease was confirmed in the UK during the FMD 2001 epidemic. The success of this strategy relies on the possibility to trace those farms or areas at high risk of infection (Sutmoller et al., 2003). During the 2001 FMD UK epidemic, stamping-out of infected premises and dangerous contacts was applied (Anderson, 2002; G. Davies, 2002; Kao, 2002). Japan and South Korea also implemented immediate depopulation of infected farms during the outbreaks in 2010-2011 (Park et al., 2013; Sugiura et al., 2001). Stamping out strategies have proven to be successful if conducted during a short period of time, and also favor the faster recovery of FMD-free status issued by the OIE. On the other hand, it is a challenging task when applied on large-scale outbreaks because of the logistics

in densely populated livestock areas, the possible risk of indirect transmission due to handling and disposal of carcasses, and the elevated costs (Sutmoller et al., 2003). In the U.S., McReynolds and Sanderson (2014) investigated the possibility to implement depopulation in a large feedlot during an FMD outbreak. The authors surveyed feedlot producers, feedlot consulting veterinarians, veterinary pharmacologists, and veterinary toxicologists about different methods of depopulation such as the use of captive bolt, toxic agents via injection or in the feed, sharpshooters, and carbon monoxide gas in an enclosed area. The study results demonstrated that there was no consensus between the experts about an acceptable method for a rapid depopulation of a large feedlot. All potential methods had substantial drawbacks related to safety, welfare, disposal or efficacy. In addition, an important issue to consider is the public perception of the implementation of these stamping out strategies and their consequences at the social level as shown during the UK 2001 epidemic (G. Davies, 2002). For instance, the stamping-out policy implemented during the UK 2001 epidemic has been highly criticized. It has been suggested that culling of animals in infected premises within 24 hours of detection was an effective control measure while culling of animals in dangerous contacts within 48 hours of detection did not provide any advantage in controlling the infection spread (Thrusfield et al., 2005).

Another control method that has been used in conjunction with strategies described above is emergency vaccination where the main objectives are to increase resistance of susceptible animals and reduce the shedding levels in infected animals (USDA, 2014). Emergency vaccination is done under two policies: vaccination-to-kill which implies rapid culling of vaccinated animals after vaccination, and vaccination-to-live in which vaccinated animals are not culled. Vaccination along with other strategies have been implemented in previous outbreaks in Argentina (Perez et al., 2004a), South Korea (Park et al., 2013), and Japan (Nishiura and Omori,

2010). Uruguay used mass vaccination without culling of vaccinated animals to effectively control their outbreak in 2001; the vaccination rate per day achieved was on average 360,000 animals and it was only applied to the bovine population (Sutmoller et al., 2003). In other areas in South America, mass vaccination of animals has proven to be successful in eliminating clinical disease. Most of the continent is FMD-free with or without vaccination and the goal is to achieve eradication by 2020 (Clavijo et al., 2017; Naranjo and Cosivi, 2013). In other endemic areas such as Africa the use of mass vaccination for eradication purposes is complicated due to the circulation of multiple FMD strains, and the wildlife population which can act a reservoir of the virus (Smith et al., 2014).

A principal factor that drives the decision on the implementation of response plans are the OIE guidelines for recovery of free status. In FMD-free countries where vaccination is not practiced OIE (2018b) guidelines for restoration of free without vaccination status after an outbreak are as follows:

- a. Three months after the last animal has been disposed in a contingency plan in which stamping-out was implemented without emergency vaccination.
- b. Three months after the last animal has been disposed in a contingency plan in which stamping-out was implemented with vaccination-to-die policy.
- c. Six months after the last animal has been disposed in a contingency plan in which stamping-out was implemented with vaccination-to-live policy.

Guidelines for recovery of free status in FMD-free countries where vaccination is practiced imposed by the OIE (2018b) are as follows:

- a. Three months after the last animal has been disposed in a contingency plan in which stamping-out was implemented with emergency vaccination and

surveillance and serological surveillance based on detection of antibodies against the non-structural proteins provides no evidence of FMDv transmission.

- b. Twelve months after detection of the last case where stamping-out is not applied, but emergency vaccination and serological surveillance against the non-structural proteins provided no evidence of FMDv transmission.

In an emergency vaccination scenario, a pre-established plan for vaccine allocation is important to increase the likelihood of success of vaccination. Uruguay controlled and eradicated FMD during the 2001 outbreak by vaccination of cattle (only) and without implementation of stamping-out (Sutmoller et al., 2003); other modelling studies suggest that targeted vaccination in infected areas with high bovine density (Backer et al., 2012), and/or those farms with high contact rates with other farms could increase the efficiency of vaccination. In the U.S., a modeling study suggests that implementation of emergency vaccination (either vaccination-to-kill or vaccination-to-live policy) targeting cattle in large feedlots to control an outbreak in the Midwest could reduce losses approximately from \$188 billion to \$56 billion (Schroeder et al., 2015).

Vaccines

FMD inactivated vaccines are the current formulation used worldwide and within them there are 2 main groups: standard potency vaccines which have a minimum potency level of 3 PD₅₀ (50% protective dose), and high potency vaccines which have a minimum potency level of 6 PD₅₀ (OIE, 2018a). Standard potency vaccines are mainly used during eradication programs while high potency vaccines in the case of outbreak situations. Vaccines are monovalent or multivalent (including more than one serotype) but they are more efficient against strains of

similar serotypes (Cao et al., 2016). High potency vaccines are used during outbreak situation because of the ability to induce immune response as early as 4 days post-vaccination (Rodriguez and Gay, 2011). However, experimental studies in pigs (Barnard et al., 2005) and cattle (Horsington et al., 2017) have shown that effective immunity was achieved in animals vaccinated 7 days pre-challenge. On the other hand, sheep vaccinated 4 days pre-challenge demonstrated protection against clinical disease (Horsington et al., 2015). The development of NSPs-based ELISAs has greatly contributed to the success of inactivated vaccines that allows the differentiation of infected from vaccinated animals (DIVA vaccines); however, some limitations of the current vaccines available are the short duration of the immune response (~6 months), the need of cold chains, and the need of high containment facilities for production (Cao et al., 2016). There are several new experimental vaccines platforms under study (Cao et al., 2016; Rodriguez and Gay, 2011) however to be considered as a candidates to replace inactivated vaccines, these have to be produced safely, induce long-lasting immunity, be DIVA-compatible, and be cost-effective. The latter criteria represents a serious challenge to fill for a single vaccine so Cao et al. (2016) suggest the development of fit-for-purpose vaccines which means that the type of vaccine used will depend on the FMD status of the country (endemic or non-endemic) or purpose of vaccination (eradication program or emergency vaccination).

FMD simulation modeling

Epidemiological models

Models are a simplified representation of a complex system. In epidemiology, there are 3 types of models that have been used to study infectious diseases: animal models, mechanical

models, and mathematical models (Vynnycky and White, 2010). Mathematical models are a powerful tool that allows researchers to use data available related to pathogen and host-factor dynamics build epidemiological models which are linked through algebraic formulae to represent disease transmission (Garner and Hamilton, 2011; Vynnycky and White, 2010). Epidemiological models are a powerful technique to understand the main factors associated with the spread of disease, and the only tool available to study the potential consequences of the introduction of highly infectious diseases such as FMD in naive populations.

There is no single basis to classify epidemiological models although Vynnycky and White (2010) and Garner and Hamilton (2011) propose three different classifications based on modeling method (deterministic or stochastic), modeling structure (SI, SIS, SIR, SIRS, SLIR, and SLIRS where S represents susceptible, L latent, I infectious, and R recovered), and contact structure (homogenous or heterogeneous mixing). Deterministic models use fixed estimates for parameters included to obtain an average outcome while stochastic models allow the outcome to vary through chance by including a range of possible values for parameters included in the model (Aron, 2001; Garner and Hamilton, 2011; Vynnycky and White, 2010). Homogenous mixing models assume that every individual in the population of interest has the same probability of contact with every other individual while heterogeneous mixing models take into consideration multiple factors to estimate the probability of contact (Pomeroy et al., 2015). An example of a heterogenous model is network modeling which requires previous information about patterns of contacts to predict the spread of disease in a population (Dubé et al., 2011). The choice of the type of model to use depends on the system/disease modeled, the research question, and the data available to parameterize the model (Grassly and Fraser, 2008).

Mathematical modeling of FMDv transmission in territories other than the U.S.

Outbreaks described above in developed countries with large livestock populations have stimulated the development and use of simulation models to understand the dynamics of epidemics and to assess potential intervention strategies to mitigate the consequences. During the FMD 2001 UK epidemic, 3 mathematical models were developed: the Ferguson model (Ferguson et al., 2001), the Keeling model (Keeling et al., 2001), and the Morris model (Morris et al., 2001). The three models were used to support recommendations for contingency plans during the epidemic, the Ferguson model used a deterministic ordinary differential equations approach while Keeling and Morris used a stochastic approach, they all suggested that the 24/48 policy (described above in *outbreaks* section) was the right approach to control the epidemic (Kao, 2002). Other studies have used data gathered during the outbreak in the UK in 2001 (Keeling et al., 2003), The Netherlands 2001 (Boender et al., 2010), France 2001 (Le Menach et al., 2005), Japan 2010 (Hayama et al., 2013), and South Korea 2002 (Yoon et al., 2006) to parameterize models and evaluate alternative intervention scenarios for the control of the epidemics.

The individual-based model developed by Keeling et al. (2003) suggests that mass prophylactic vaccination (vaccination of all individuals to build antibodies to prevent potential infection) targeting high-risk groups (farms with large number of cattle) significantly decreases the size and duration of an epidemic in the UK compared to mass prophylactic vaccination of farms selected at random. They also investigated the use of mass reactive vaccination (vaccination of all individuals after detection of the outbreak) which also was found to be effective although it required high vaccination uptake and highly efficient logistics to be rapidly implemented

Boender et al. (2010) described the spatial FMDv spread in The Netherlands and evaluated the standard EU (European Union) control methods (movement bans, bio-security measures, and culling of infected and dangerous contacts) along with ring culling (culling of animals within a determined radius) and vaccination. The authors suggest that standard control methods are not efficient to control epidemics in areas with large density of animals, and ring culling and vaccination policies can help to improve the efficiency of the standard interventions in those areas. Large livestock populated countries like the U.S. can benefit from ring culling and vaccination along with standard interventions in areas with high density of cattle; however, practical issues regarding the implementation of these strategies and the political and social impact of them might compromise their application.

Le Menach et al. (2005) developed a stochastic farm-based model applying the approach by Keeling et al. (2003) to evaluate the impact of an FMDv re-introduction in France and the implementation of pre-emptive culling (culling of farms with recent contact or proximity to infected farm) and ring vaccination. They found that pre-emptive ring culling within a 1.5 km radius and ring vaccination within 3 to 10 km decreased the number of cases by 80% compared to the baseline scenario (no intervention strategies modeled). They also found that the introduction of FMDv in areas with high density of ruminants had a larger impact on the epidemic size and duration compared to areas with less density of ruminants.

Yoon et al. (2006) used the InterSpread Plus model, a stochastic spatial model, to simulate epidemics of FMD in 8 counties in South Korea. They evaluated alternative strategies such as ring culling and vaccination compared to the reference strategies used during the 2002 epidemic (movement bans, surveillance, and pre-emptive culling) and found that early detection and implementation of reference strategies had an impact on the size and duration of the

outbreak. The same conclusions were reached when ring vaccination within a radius of 5 km was conducted with extended pre-emptive depopulation (depopulation of farms that had contact or are at proximity to infected pens within 3 km).

Hayama et al. (2013) used data from the 2010 epidemic in Japan to assess 10 control strategy scenarios including prompt culling (culling of infected farms within 24, 48, or 72 hours), pre-emptive culling (culling of farms within 0.5 and 1 km of an infected farm within 48 hours), vaccination, and early detection. They found that culling infected farms within 24 hours after detection had the shortest epidemic period reducing the total infected farms by 30% compared to the baseline model where the required time for culling infected farms after detection ranged from 3 to 16 because the increase numbers of detected farms during the epidemic. Pre-emptive culling scenarios resulted in smaller epidemics compared to prompt culling although the authors discussed the practical application of pre-emptive culling in densely populated areas due to the resources necessary to implement the intervention. Ring vaccination within 10 km was the most efficient scenario within vaccination strategies, reducing the number of infected farms by 40% comparing to the baseline model. Early detection scenarios were found to decrease the duration of the epidemic compared to the baseline scenario. Another model that used the 2010 epidemic data (Hayama et al., 2015) found that the highest risk of infection was found in those areas within the country with a large number of cattle and pig farms.

Other authors have studied different modeling approaches to mimic FMD epidemics and the implementation of control strategies. For instance, Gerbier et al. (2002) used a linking point approach to model FMDv spread between farms. The authors states that network modeling is a useful method to capture heterogeneities in the population modeled; however, when there is limited data to parameterize a network model their approach is an alternative option. Martinez-

Lopez et al. (2010), developed a spatial stochastic transition model to simulate an FMD epidemic in the Castile-and-Leon region which is an area with high density of livestock in Spain. The authors used the model to estimate the size and duration of the epidemic, and the impact of control strategies such as depopulation and vaccination. They found that preventive depopulation (depopulation of premises that received shipments from infected and detected premises) within a radius of 1km around an infected premise, and vaccination within 3 km of an infected farm were more efficient in controlling the spread of infection. A dynamic model based on differential equations was developed by M. Kobayashi et al. (2007) to evaluate the most efficient control strategy for an FMD outbreak in a three-region county in California (Mimako Kobayashi et al., 2007). Scenarios of preemptive depopulation and vaccination were modeled accounting for different vaccine availability and a depopulation capacity of 4,000 cattle per day. Results found that vaccination of dairy operations were the optimal interventions. Thornley and France (2009) used a deterministic differential equation model and suggest that early detection, implementation of movement bans, and rapid culling are efficient to reduce the R_0 sufficiently to control an epidemic. However, the authors acknowledge the fact that early detection will be highly dependent on the contribution of farmers and veterinarians as it has already been shown by the experience during the 2001 UK epidemic (Anderson, 2002).

Different models to evaluate the potential introduction of FMDv in non-endemic countries have also been developed. Halasa et al. (2013) used a the DTU-DAS model which is a dynamic spatial simulation model and data based on Bates et al. (2003a) to estimate the number of detected farms within the first 14 days after detection as a predictive factor for the course of the epidemic in Denmark. The study found that the number of detected farms within 14 days after detection is a good predictor for the epidemic size and the economic costs, and also to

predict the number of infected herds after 14 days post-detection. A study by Boklund et al. (2013) used the DTU-DAS and the InterSpread Plus models to simulate hypothetical outbreaks in Denmark and evaluate different control strategies and associated costs. The InterSpread Plus model predicted outbreaks starting in a high-cattle density would last around 80 days compared to 56 days that was predicted by the DTU-DAS model. Suppressive vaccination (emergency vaccination in conjunction with stamping-out policy) was more cost-effective; however, protective vaccination (emergency vaccination to protect susceptible animals against FMDv) resulted in fewer farms being depopulated. The DTU-DAS model was also used to simulate potential outbreaks in Sweden and assess control strategies (Dorea et al., 2017). Simulations suggested that, when detected within 4-5 weeks, outbreaks in Sweden are not likely to spread quickly and that they would be controlled easily by promptly implementing movement restrictions and culling of animals in infected and dangerous contact farms. Every week delay in detection doubled the number of infected farms by the time the outbreak was controlled; however, outbreak duration was only increased by 3 to 4 days.

Mathematical models of FMDv transmission in the U.S.

The U.S. has been FMD-free since 1929 when the last outbreak occurred in California (Mohler, 1930); however, FMDv remains a serious threat due to the trade of animals and animal products (Graves, 1979). Several simulation models have been developed to investigate the potential incursion of FMDv into the country. Bates et al. (2003a) developed a model which considered the size of the farm, spatial location, and direct and indirect contact rates to study the impact of culling infected farms and restriction of movements in 3 counties in California. The model also analyzed alternative strategies such as ring vaccination, ring culling, and culling of

high-risk herds. Results in the simulated area suggest that culling of high-risk farms which were defined by the model based on rates of direct and indirect contacts, and vaccination of farms around an infected farm decrease the number of infected herds by 48% and 41%, respectively (Bates et al., 2003b). S. W. McReynolds et al. (2014) used the North American Disease Spread Model (NAADSM) which is a farm-based spatial stochastic model (Harvey et al., 2007) to estimate the impact of vaccination strategies on the duration of the outbreak and number of farms depopulated in the Central United States. Seventeen scenarios were modeled and those scenarios with larger vaccination zones had the larger impact on the outbreak durations and number of farms depopulated.

Tildesley et al. (2012) used the model developed by Keeling et al. (2001) during the 2001 UK epidemic to simulate a hypothetical outbreak in Pennsylvania. The model was formulated and parameterized based on the UK 2001 outbreak data. They found that the outbreak size was dependent on the county where the outbreak was initiated; counties with high livestock density generated in larger epidemics which is consistent with results by Boender et al. (2010); however, interpretation of outcomes presented by Tildesley et al. (2012) should be done cautiously due to the differences in livestock production systems in both territories. The authors also stated that results were dependent on the extensive local spread and resources available for control. The AusSpread Plus model was used by Ward et al. (2009) to assess the spread of FMDv in an 8-county region of the Texas Panhandle. Herds depopulated, vaccination, and surveillance (passive or active) were the control strategies modeled. They found that the durations of the outbreaks were larger when they were initiated in company feedlots which were defined as an operation with a one-time head capacity larger than 50,000 cattle. The authors do not discuss in detail the reason for the prolonged outbreaks when outbreaks were initiated in this operation type

although based on the results it seemed that it was perhaps the time of depopulation of these farms which was on average 28 days and was significantly longer than the other farms modeled. In addition, the time to detection was also influential in the length of the epidemic. Schoenbaum and Disney (2003) developed a stochastic model to simulate epidemics in 3 counties in targeted areas in the U.S.: 1 county in the south-central region with an area of 31,398 km², 0.36 herd per km², and an average of 33 animals per herd; 1 county in the north-central region with an area of 44,096 km², 0.157 herd per km², and an average of 1857 animals per herd, and 1 county in the western region with an area of 60,391 km², 0.069 herd per km², and an average of 670 animals per herd. Movement restrictions, culling, vaccination and surveillance were evaluated along with the human capacity to vaccinate and cull infected animals during simulations. The median duration of outbreaks was 30 to 109 days and all mitigation strategies decreased duration. Overall, they concluded the demographics of the area can have a large impact in the model outputs. Early ring vaccination decreased the duration of the outbreaks although it was more expensive to conduct than applying only culling strategies.

Auction markets and state fairs might play a significant role if an infectious animal is present. Carpenter et al. (2007) developed two stochastic models to simulate intra-herd infection within a state fair, and a state-level model to simulate between herd infection in California if infection was released from their state fair. They found that due to the short period that animals spend in the state fair (5 days), detection of infection was not likely. The simulation indicated approximately 13 animals were already infected by the end of the simulation period that would be potentially leaving the state fair prior to detection. For the statewide model which included outputs from the state fair model, the duration of the outbreak ranged from 111 to 115 days with a median number of infected premises of 33 to 244.

Another important issue to consider is the large concentration of animals in U.S. operations. For instance, over 44% of the cattle on-feed population is concentrated in farms with a one-time head capacity equal or larger than 32,000 animals (USDA-NASS, 2017). Carpenter et al. (2004) simulated a hypothetical FMD outbreak in a 1,000-cow dairy farm in California modeled as a single group and assuming transmission was only possible via direct contact between susceptible and infectious cattle. They assume that detection could occur once 5% (50 cows) of the herd showed clinical signs. The model predicted that over 60% of the herd would be infected by the time the infection was detected which seems unrealistic because of the contact structure in a dairy farm is certainly non-homogenous, but also detection is likely to occur more rapidly because cows are more likely to be detected by farm personnel compared to other production systems. Other models have also attempted to describe within-herd FMDv transmission in cattle farms although in settings different than in the U.S. (Chis Ster et al., 2012) and to simulate within-herd FMDv spread in swine populations (farrow to finish, and farrow to wean commercial farms) (Kinsley et al., 2018). Large feedlots in the U.S. have a unique environment in terms of production system in which cattle are grouped within pens but might also have contact with cattle from other pens either by fence line contact or by mixing in hospital pens. Modeling all the potential routes of transmission and the contact structure within these feedlots is important to correctly capture the FMDv transmission dynamics in these environments and should be the aim of future models.

A limitation to increase the granularity of FMD models is the natural variability of FMDv and the lack of data available to parameterize these models. Despite the extensive experimental studies conducted, extrapolation of experimental data to field conditions is difficult. Pomeroy et al. (2015) reviewed FMD models published until 2015 and found that only 30% of those models

incorporated disease data and over half of those models used the 2001 UK data to parameterize their models. Data available to parameterize FMD models for different species and under different production settings are limited. Other studies have used different approaches to gather and synthesize data regarding FMD such as meta-analysis (Mardones et al., 2010) and expert opinion surveys (Cabezas et al., 2018; Kinsley et al., 2016; Ward et al., 2009). However, these data must be combined with experimental and outbreak investigation data to produce robust models.

Models described above have used various methods to model contact structure such as homogenous mixing, local-spread mixing, or kernel transmission to model FMDv spread. Livestock industries in developed countries with large populations are complex systems in which the contact structure is influenced by other factors such as seasonality, distance to markets or slaughterhouses, proximity to areas with large feeding capacities, etc. Those heterogeneities need to be captured when modeling FMD spread at larger levels of aggregation such as county, state, or national level. Knowledge regarding animal movements is critical to effectively describe disease transmission and implement control strategies (Dubé et al., 2009, 2011; Martinez-Lopez et al., 2009). Recent research in social network analysis of contact networks are useful for understanding livestock contact networks at the individual animal and herd level. Movement and contact network datasets are more available in countries with advanced livestock tracking systems. The U.S. data on livestock movements are only partially recorded and fragmented into individual states making collection and analysis challenging.

Social network analysis

Introduction

Social network analysis (SNA) refers to the study of relationships or interactions between individuals within population groups (Dubé et al., 2011; Martinez-Lopez et al., 2009) and the implications of those interactions (Newman, 2010). In SNA, the study units are called *nodes* which can be a cell, an animal, a farm, a county, a state, etc. The relationships between nodes are represented by links which are called *arcs* if they are directed, or *edges* if they are undirected.

There are 2 main measures to describe networks:

- a) Measures of centrality to determine the importance of nodes in the network.
Examples of these are degree, betweenness, closeness/farness, eigenvector/page rank centrality.
- b) Measure of cohesiveness to evaluate is the connectivity of the network. Examples are density, fragmentation, average path length, transitivity, reciprocity, and sub-groups such as giant and weak components.

The use of the metrics mentioned above will depend on the objective(s) of the study; a detailed review of network representation and terminology can be found in (Dubé et al., 2009, 2011; Martinez-Lopez et al., 2009)

Application of SNA in veterinary science

In human medicine, SNA has been used since the early 90s while it was only during the early 2000s when it started to be applied in veterinary sciences (Dubé et al., 2011; Martinez-

Lopez et al., 2009). The first two published studies in veterinary sciences used SNA to model patterns of social behavior of wild brushtail possums to predict the spread of tuberculosis (*Mycobacterium bovis*) (Corner et al., 2003), and to explore the contacts between racehorse trainers in the UK to evaluate the potential for disease spread (Christley and French, 2003). After the events of highly pathogenic avian influenza during the first decade of the 21st century, SNA has also been used to study poultry trade networks to identify risk factors for potential infection spread and implications for control strategies and surveillance in New Zealand , China (Martin et al., 2011; Sun et al., 2018), and Bangladesh (Moyen et al., 2018).

The experience of the FMD 2001 UK epidemic demonstrated the importance of understanding the contribution of movement patterns in the spread of infection. As mentioned above in the *Mathematical modeling for FMDv transmission* section, movements of sheep during the silent phase of the epidemic may have been largely responsible for the spread of the infection in the UK FMD outbreak. Webb (2005, 2006) studied the roles of local sheep farm proximity and farm-to-show sheep contacts to evaluate the potential risk for disease transmission. Both studies demonstrated that the networks consisted of one large component and few isolated farms. The authors found that distances as far as 600 km were traveled by farmers to exhibition shows; however, they also highlighted the fact that shows are only a single component of the sheep industry and that markets (not considered in the study) might play a more important role in the disease. One of the limitations of both studies described above (Webb, 2005; Webb 2006) was the source from which data were collected. The authors used questionnaires to record movements and the response rates in both studies were approximately 60%. This limitation was overcome by Kiss et al. (2006) by collecting sheep movements from official national databases in the UK to describe and identify characteristics of the sheep network in the UK during 2003-2004. They

found seasonal patterns with an increase of movements during August and October in both years which were also associated with a higher risk of disease transmission. These results suggest that elevated biosecurity during high movement periods may be valuable to control transmission risk. Volkova et al. (2010) studied the role of sheep movements in Scotland from 2003 to 2007 to estimate the size of the giant components, and the approximate magnitude of the basic reproduction number to identify which characteristics of the farm network, and which farms contribute the most to the spread of infection through the network. Approximately 50% of farms were part of the giant strong component (strong component: the largest number of nodes that can be reached when the direction of links is considered), and approximately 99% of farms were part of the weak component (weak component: the largest number of nodes that can be reached when the direction of links is not considered). They also estimated the farm-to-farm basic reproduction number for cattle networks could be reduced by 90% if the top 20% of farms (in relation to contribution to movements) were removed. The latter is in agreement with the 20-80 rule applied by Woolhouse et al. (2005) in the study of a cohort of beef farms in Scotland.

Ortiz-Pelaez et al. (2006) investigated cattle and sheep movements before movement bans were put in place during the 2001 UK FMD epidemic. Markets and dealers had high betweenness (betweenness: the extent to which a node is in the path between any pair of nodes in the network) which suggest the large role of these nodes in the spread of infection. In addition, a few other farms were identified with high degree (degree: the number of incoming and outgoing links a node has) and betweenness suggesting a similar pattern of movements compared to markets, and the need to target those nodes when implementing control strategies. Robinson and Christley (2007) explored the impact of auction markets in cattle movements during 2002-2003; they were able to capture over 90% of actual movements during the study period. They found

that auction markets behaved as hubs (hubs: nodes with high degree centrality) for the cattle network during the study period as suggested in previous studies for sheep networks in the UK (Ortiz-Pelaez et al., 2006). Finally, Brennan et al. (2008) used a cross-sectional study to investigate direct and indirect contacts between cattle farms in North-west England. The study showed high heterogeneity in the frequency and type of contacts, and that farms that are closely located tend to have a larger number of direct/indirect contacts.

Other countries in Europe have applied SNA to study the patterns of livestock movements. For instance, the cattle network in Italy during 2007 was studied by Natale et al. (2009). They found that control strategies targeted to nodes based on betweenness and eigenvector centrality (eigenvector: measures the connectivity characteristics of the node but also the connectivity of its neighbors) could be more efficient compared to interventions targeted based on degree centrality. Another study by Natale et al. (2011) used the movement of cattle data during 2007-2009 and proposed a new method called Disease Flow Centrality to estimate centrality measures. They found that measures estimated varied considerably to the standard centrality measures and that they can be unstable through time but also suggested that might be a useful method to predict at-risk areas in the network. Swine movements and cattle trade patterns have been studied in Denmark ((Bigras-Poulin et al., 2007; Bigras-Poulin et al., 2006), respectively). The swine network was found to be a large finite scale-free directed graph with at least one large component and a low herd-to-herd contact rate. The authors discussed that networks with these characteristics can have a low R_0 and still be able to maintain the pathogen in the population even in low prevalence which make challenging to eliminate certain pathogens. On the other hand, the cattle network in Denmark was characterized by a large number of nodes, low number of connections between nodes, and few large components. For both Danish

networks, the authors also addressed limitations such as missing data and misclassification of movements due to gaps in the movement record databases and the need to combine several databases to construct the network. Finally, the authors also discussed the limitation of their conclusions because heterogeneities in contact structure between premises was not considered for both swine and cattle Danish networks. Other studies have also assessed the pig trade networks in Europe. Relun et al. (2016) described the spatial distribution of the pig trade in Bulgaria, France, Italy, and Spain. Networks in Spain and France were found to have high degree centrality which was expected due to the large number of commercial farms in both countries. In developing countries, the application of SNA is challenging due to the availability and quality of data. Kukielka et al. (2017) used a semi-structured questionnaire to study the pig trade in Georgia. The study estimated centrality measures for 4 of the 9 regions in the country. Backyard production systems are predominant in Georgia, so local trade (movements within regions) was found to be the main trade pattern. However, the authors emphasized that results should be cautiously interpreted as 5 regions were omitted from the study because of the lack of data.

Social network analysis in U.S. production systems

The U.S. has one of the largest livestock populations around the world with over 93 million cattle (dairy and beef) and over 71 million pigs (USDA-NASS, 2017), and by consequence there is a large flow of animals within the country. The only traceability system in the country are the Certificates of Veterinary Inspection (CVI) which are issued by accredited veterinarians after inspection of animals to be transported. A CVI is required when animals are transported across state borders, and they do not go directly to an auction market or a slaughter plant (Forde et al., 1998). These documents may be recorded electronically or in paper form.

The proportion of electronic and paper vary from state to state as do sometimes even in the fields to be collected in the document. They are, however, only data source to study livestock movements (Forde et al., 1998; Portacci et al., 2013). Some authors have used alternative methods (questionnaires and surveys) to estimate direct and indirect contact rates in some areas of the U.S. such as Colorado and Kansas (S. W. McReynolds et al., 2014), and 3 counties in California (Bates et al., 2001). While both studies mentioned above provide useful information in terms of movements between production types in the study areas, they do not capture specific geographic connections to allow network analysis. Further, the livestock network in the country is very complex and requires a detailed data from the local to the national level to fully understand trade patterns.

Buhnerkempe et al. (2013) conducted the first national level study of cattle movements in the U.S. by collecting a systematic sample of 10% of CVI export records during 2009 from 47 states of the contiguous U.S. (New Jersey did not participate). They developed movement networks at the county and state level and estimated measures of centrality and cohesiveness for both networks. The authors found that heterogeneities within the country were well captured by the county-to-county network, and as expected the central plains (states with more feeding capacity) had high in-degree. Over 60% of nodes were included in the giant strong connected component while 99% of nodes were included in the weakly connected component. Unfortunately, CVIs do not capture movements to and from auction markets which is highlighted by the authors. Auction markets play a significant role in the U.S. cattle industry, but such data is not available.

Most of the studies described above in this review have focused on estimating measures of centrality and/or cohesiveness to understand movement patterns; however, a more powerful

approach to understand interactions within a network is the phenomena of trade communities. Trade communities are defined as group of nodes which have a higher number of connections within the group and lower number of connections between groups, but communities can also may be grouped into a hierarchical structure in which a group of links are identified as a community rather than a group of nodes (Newman, 2010). Communities are identified by computer algorithms; several methods have been proposed depending on the nature of the network described and they can be found in (Newman, 2010). Gorsich et al. (2016) used the CVI network developed by Buhnerkempe et al. (2013) to identify trade communities by modularity maximization method within the beef and dairy cattle networks. Modularity compares the observed number of edges within groups vs the number of such edges that can be expected by chance. Modularity values range from -1 to 1 in which larger modularity values occur when density of edges within communities is larger than the density of edges between community. The study identified 26 communities for the beef network, and 41 communities for the dairy network and 7 and 9 large communities were found in each network, respectively. Communities were geographically located within the country which suggest that local proximity is an important driver for cattle movements in both networks. The study also highlighted that the structure of trade communities was consistent at the monthly and annual movement patterns. The trade community detection approach has also been used for swine movements in Bulgaria, France, Italy, and Spain by Relun et al. (2016). The study suggested the presence of large communities in Bulgaria and France which included up to 30% of nodes, and less than 15% of nodes in Italy and Spain. In the UK, a study found that approximately 25% of all swine premises are present within the ten largest communities (Guinat et al., 2016). A limitation of the community detection algorithms applied in these studies is that they are meant to be applied to undirected networks.

Livestock networks by nature are directed networks in which animals commonly move across specific production types during their different production stages. However, algorithms available for directed networks are computationally very intensive and are not applicable to large networks (Relun et al., 2016). The application of trade community detection is an important feature of network analysis to inform risk-based strategies for disease control and disease surveillance programs (Gorsich et al., 2016; Relun et al., 2016).

Some other limitations for the U.S. networks described above are: the incomplete nature of the movement data to develop networks, the fact that most of the research in this area have been conducted in cattle populations, and the fact that only a subset of interstate movements are captured by CVIs. Studies have applied other methods to fill the gaps mentioned above, for instance, Lindstrom et al. (2013) used a Bayesian approach to scale-up a partially observed network from Buhnerkempe et al (2013). Kinsley et al. (2019) developed the first description of the swine movements in 3 multi-site production systems in the U.S. to identify premises that would be more likely to be targeted to increase the efficacy of intervention strategies implemented during potential outbreaks of infectious diseases. Finally, Beck-Johnson et al. (2019) conducted an expert elicitation survey to investigate differences between inter- and intra-state movements across regions within the U.S.

Finally, the ultimate objective of network analysis is the application of network modeling on the study of transmission of highly infectious diseases (Dubé et al., 2009). Some authors have already applied network theory to simulate the spread of infection in populations (Buhnerkempe et al., 2014; Lebl et al., 2016; Relun et al., 2017; Wiratsudakul and Sekiguchi, 2018).

Conclusion

FMD is a highly infectious disease that affects mainly livestock species and is present in all continents around the world. The infection spreads mainly by direct contact between infectious and susceptible animals but also by indirect contacts via contact with contaminated materials, and via airborne under some circumstances.

The devastating outbreaks during the past two decades in developed countries with large livestock populations raised concerns for FMD-free countries such as the U.S. to prepare contingency plans for an unexpected introduction of the FMDv into the country. Issues related with the costs of vaccination and problems related to vaccine allocation and labor and record keeping requirement to conduct vaccination need to be explored in future studies. In addition, the feasibility of depopulation and its implication at the public level needs to be evaluated to be considered as a viable alternative of control in countries such as the U.S. with large concentration of animals within farms. *Mathematical modeling* is a powerful tool that allows researchers to simulate FMD spread and study the implementation of different intervention scenarios. *Social network analysis* is a useful technique to understand the implications of patterns of animal movements into the risk of the spread of disease. Both techniques require models have accurate parameters and accurately reflect the structure of the production systems they intend to model.

The lack of data to parameterize FMDv transmission models is a data gap barrier to production of more robust models. Computational resources are available to develop complex models, so efforts to conduct studies under controlled environments and target disease parameters or indicators needed to model disease transmission are needed. Also, patterns of

movements of livestock species other than bovine need to be investigated because they also play an important role in the transmission of FMDv as shown by previous studies. Finally, more efficient traceability systems for animal movements are needed to be able to capture a more realistic picture of the livestock network in the country.

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Chapter 2 - Clinical and infection dynamics of foot-and-mouth disease in beef feedlot cattle: an expert survey Your Chapter Title

Aurelio H. Cabezas^{a,b}, Michael W. Sanderson^{a,b}, Majid Jaber-Douraki^c, Victoriya V. Volkova^{a,b}

^aDepartment of Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States

^bCenter for Outcomes Research and Epidemiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States

^cInstitute of Computational Comparative Medicine, Department of Mathematics, Kansas State University, Manhattan, KS 66506, United States

*Corresponding authors

Phone: +1 (785) 706-3074. e-mail: aureliocm@vet.k-state.edu (A.H. Cabezas).

Phone: +1 (607) 220-8687. e-mail: yv88@vet.k-state.edu (V.V. Volkova).

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Abstract

Parameterizing mathematical models of foot-and-mouth disease virus (FMDv) transmission is challenging due to knowledge gaps on the variable dynamics in susceptible populations. Expert opinion surveys are an approach to gather data on topics where no data have been reported. The objective of this study was to collect—via an expert-opinion survey—key parameter values of the potential FMD natural history and transmissibility in beef feedlot cattle in the U.S. Experts with experience working with FMD in endemic and non-endemic settings were targeted. Parameters surveyed were: duration of infection and disease stages, proportions of animals with specific clinical manifestations, duration and extent of the reduction in feed consumption, and probabilities of severe clinical disease and FMDv transmission. We surveyed the parameter values for infections by strains of different virulence, different infection doses, and routes of transmission. Twenty-seven experts from around the world agreed to participate and 16 (59%) completed the survey. The expert responses to individual questions were resampled via Monte Carlo simulations; to the resulting distributions, candidate theoretical distributions were fitted using the maximum likelihood method and the sought parameter values estimated based on the best-fit distributions. Of the infection stages, the estimates of the expected FMD latent period in beef feedlot ranged from 1.7 to 5.3 days and the infectious period from 5.6 to 10.9 days. Of the disease stages, the estimated incubation period ranged from 2.9 to 6.1 days, subclinical period from 1.2 to 2.8 days, and clinical period from 4.2 to 7.5 days. Probability of developing clinical disease after infection varied from 82% (IQ range 90-70%) with high-virulent to 63% (IQ range 89-60%) with low-virulent strains. Reduction in feed consumption was estimated to last 5 (SD +/-2) days in cattle infected by a low-virulent FMDv strain and 7 (SD +/-2) days for high virulent strains. The study results can be used in combination with experimental and

outbreak investigation data to parameterize FMDv-transmission models to evaluate intervention responses during hypothetical FMD epidemics in beef feedlot populations in the U.S.

Keywords: foot-and-mouth disease, expert survey, clinical FMD, infectious disease dynamics, feed consumption, beef feedlot

Introduction

Foot-and-mouth disease (FMD) is one of the most contagious diseases of livestock and wildlife. It is one of 117 animal diseases notifiable to the OIE – World Organization for Animal Health (OIE, 2018). The disease is endemic in some countries while others maintain FMD-free status. In the past two decades, there have been several major outbreaks in previously FMD-free countries with large livestock populations, including the United Kingdom, Netherlands, France, South Korea, Japan, Uruguay, and Argentina (Gibbens et al., 2001; Chmitelin and Moutou, 2002; Correa et al., 2002; Davies, 2002; Pluimers et al., 2002; Bouma et al., 2003; McLaws and Ribble, 2007; Nishiura and Omori, 2010; Brito et al., 2011; Ellis-Iversen et al., 2011; Madin, 2011; Park et al., 2014; Yoon et al., 2015). Mathematical models of FMD virus (FMDv) transmission were developed to evaluate control strategies used during those outbreaks (Keeling et al., 2001; Kao, 2002; Keeling et al., 2003; Yoon et al., 2006; Boender et al., 2010; Hayama et al., 2013). Given the large size and value of the beef industry in the U.S., an introduction of FMD would be devastating to the industry due to the animal welfare, disease-control logistics, and trade restriction consequences. The majority of cattle fed for slaughter in the U.S. are fed in large feedlots of greater than 8,000 head (USDA, 2011). Two modeling studies have reported potential losses due to outbreaks in the U.S. Schroeder et al. (2015) reported between \$56-118 billion losses for a regional, central U.S. outbreak while Pendell et al. (2015) reported potential losses between \$16-140 billion for an outbreak in the Midwestern U.S. if the virus was released from a high containment facility located locally. These studies included economic impact from lost international trade which would be suspended and not reestablished until OIE requirements for freedom are met and trading partners are confident in the safety of US products (USDA,

2015). Mathematical modeling of potential FMD transmission and manifestation on feedlots can be used to simulate and evaluate outbreak control strategies. Modelling FMD spread and control is challenging due to the data needed to parameterize the models (*i.e.*, assign values to the model parameters). A review by Pomeroy et al. (2015) of published FMDv transmission models indicated that out of 106 studies ~80% used data specific to production practices of the food-animal host, while only 30% used data specific to FMD natural history in the host, to parameterize the models. Thus, to produce more robust models, it is necessary to generate the host specific FMD natural history (*i.e.*, time-line and pathobiology of the infection and disease stages) parameters. Specifically, such parameters are important for robust modeling of the outbreak detection and control strategies.

A description of the FMD natural history in species affected has rarely been included in the published reports of the recent outbreaks. Only Yoon et al. (2012) summarized the proportion of infected farms— beef and dairy cattle, pigs, deer, and goats— having animals with specific clinical signs during the 2010-2011 outbreak in South Korea. Parameterization of the models of the recent outbreaks (Keeling et al., 2001; Kao, 2002; Keeling et al., 2003; Yoon et al., 2006; Boender et al., 2010; Hayama et al., 2013) has been mostly based on the FMD natural history parameter estimates from *in vivo* studies in experimental conditions. For example, Nelson et al. (2017) estimated durations of the disease and infection stages in cattle (Holstein Friesian calves) based on two FMDv inoculation experiments. The estimates were employed to parameterize a model assessing the likelihood of detecting FMD during the pre-clinical disease in typical dairy and beef farms in the UK and Netherlands (100 head per farm) (Nelson et al., 2017). Mardones et al. (2010) performed a meta-analysis of the experimental data published from 1960 to 2007 to estimate durations of the disease and infection stages for FMD in cattle experimentally

inoculated with FMDv strains of serotype O. However, extrapolations of the experimental results to field conditions are difficult due to dissimilar conditions (*e.g.*, animal housing and density) and factors such as the animal species affected, FMDv strain, exposure dose, and routes of exposure. Moreover, not all data generated in the experiments may be reported in the manuscripts.

An alternative approach to generate data on the FMD natural history in field conditions is a questionnaire for those with applicable experience. In epidemiology, questionnaires are an efficient tool to collect data when no published records are available (Dohoo et al., 2009), or data are difficult to obtain or are incomplete (Vose, 2008). Two recent studies have estimated the FMD natural history parameters for specific livestock species based on a literature review or a literature review and expert-opinion survey. Kinsley et al. (2016) estimated durations of the disease and infection stages in swine, using a meta-analysis of published literature combined with a survey of expert opinion on the incubation period, mortality rates, probability of transmission, and most likely proportion of infected animals before a vesicular disease is suspected in a typical swine herd (farrow-to-finish and farrow-to-wean). Ward et al. (2009) estimated durations of the infection stages in infected herds (beef, dairy, swine, and small ruminant operations), between-herd FMDv transmission rates, time to FMD detection in the index herd, expected vaccine effectiveness, and other parameter values pertinent to a regional FMD outbreak affecting multiple livestock species using an expert questionnaire. These estimates were employed to parameterize a model of FMD spread within the livestock systems (beef, dairy, swine, and small ruminant) in eight counties of Texas (Ward et al., 2009). Surveys of expert opinion have also been used to assess the risks of FMDv introduction into the Netherlands (Horst et al., 1998) and New Zealand (Forbes et al., 1994). Moreover, Garabed et al.

(2009) evaluated differences in expert opinions and relative accuracy of the opinion synthesis compared to another method for assessing the probability of occurrence at least one FMD-case at a country-level between 1996 to 2004 and for predicting FMD presence during 2009 to 2014.

The objective of this study was to collect expert opinion about key parameter values of the potential FMD natural history and FMDv transmissibility in immunologically naïve beef cattle of the age, body weight, and health status common in feedlot production systems. The comparative parameter values were sought for virus strains of high or low virulence, transmission via airborne or direct contact, and infections by a high or low virus dose. The study was implemented using a structured on-line questionnaire completed by invited experts with first-hand experience with FMD outbreaks in the field or *in-vivo* FMD experimentation in livestock. The data were gathered for usage in modeling potential FMD outbreaks and control strategies in the U.S. beef feedlots.

Material and methods

Survey design

The literature review summarized above indicated a paucity of data on the FMD natural history in immunologically naïve beef cattle of feedlot age and health status. Relevant parameters for data collection through the expert-opinion survey were identified (**Table 2-1**). In the survey, respondents were asked to provide the minimum, most likely, and maximum values for each of these parameters:

- Durations of disease stages (incubation, subclinical, and clinical periods) and infection stages (latent and infectious periods) in cattle infected by a low or high virulent FMDv strain at a low or high virus dose and via an airborne or direct-contact transmission.
- Probability of virus transmission via direct contact to immunologically naive cattle from the clinically diseased cattle infected by a low or high virulent FMDv strain at a low or high virus dose via direct contact.
- Probabilities of clinical FMD and severe clinical FMD in cattle infected by a low or high virulent FMDv strain.
- Proportions and duration (in days) of cattle showing specific clinical signs if infected by a low or high virulent FMDv strain at a low or high virus dose via an airborne or direct-contact transmission (only the most likely values were requested).
- Duration (in days) and percentage of reduction in feed consumption, and the day of the clinical stage when the peak reduction occurred, in the clinically diseased cattle infected by a low or high virulent FMDv strain.

In an optional section of the survey, opinions (qualitative descriptions) were gathered about the speed of the infection progression and clinical manifestation depending on the FMDv infection dose and route. Similarly, opinions were gathered about the relationship between the virulence and transmissibility of an FMDv strain.

Specific expertise on feedlot production systems from experts was not necessary, but instead, we prioritized the typical cattle population characteristics such as age, body weight, stocking density, and health and immunologically naïve status relating to FMD. A description of the target cattle population was provided in the survey:

“The target population is beef cattle in a commercial open-air feedlot in the Central U.S. Beef steers are the predominant population and their age ranges from 8 to 20 months, weighing from 200 kg at placement to 600 kg at harvest. The animals are well-conditioned and not vaccinated against FMDv. The feedlot is divided into pens. The animal groups are allocated to pens, with 100-200 cattle (of similar weight and age) per pen with 20-25 m² space per animal. All-in-all-out management is practiced in individual pens but not for the feedlot as a whole. At the feedlot level, animals from different pens do not generally mix but do have through the fence contact with neighboring pens. Other susceptible animal species are not generally kept within these feedlots and their surroundings.”

Pilot testing the questionnaire

Two pilot tests of the survey instrument were conducted, each with an individual expert. Each of the two experts has worked with FMD in controlled experimental conditions and in endemic and non-endemic settings in the field. The survey was refined based on the comments received to develop the final version. The two experts did not participate in the actual survey.

Expert selection

A list of potential participants was developed. A participant was included if she/he met the conditions (1)-(2) and also at least one of the conditions (3)-(6) listed below:

- (1) Participant must have a background in veterinary sciences, *e.g.*, be an epidemiologist, virologist, or practicing veterinarian.
- (2) Participant must have worked with FMD in a professional setting.

- (3) Participant has a strong publication record on FMD, including of experimental studies but preferably outbreak investigations.
- (4) Participant has worked at the OIE referent institutions for FMD.
- (5) Participant has experience investigating FMD outbreaks in the field in FMD endemic or non-endemic countries.
- (6) Participant has been referred by colleagues (including other participants) for their knowledge of FMD natural history in livestock.

All selected participants, hereafter – FMD experts, were contacted individually via email informing them of the purpose and overview of the survey. The experts who agreed to participate were then sent the invitation, an electronic version of the survey, and link to the on-line survey.

Survey delivery

The survey questionnaire was implemented in two formats: an online version in the Qualtrics software (Qualtrics Inc., Dallas, TX, USA), and a file version in Microsoft Word® 2013 (Microsoft Corporation, Redmond, WA, USA). Both versions were included in the email sent to each of the experts who agreed to participate. The experts had 30 days to complete the survey. The survey was anonymous for those who chose the on-line version. The survey was conducted in two rounds: the first round during September 2016 – November 2016 and the second round during December 2016 – February 2017. The same survey was administered in both rounds and each expert participated once.

Data analysis

For duration of clinical signs parameters (for which the minimum, maximum, and most likely values were requested in the survey), a Pert distribution was used to estimate the parameter values provided by each expert. Individual expert distributions were equally (unweighted) re-sampled via 1,000 Monte-Carlo simulations. Candidate theoretical distributions were fitted to the resulting combined simulated parameter-value distributions using the maximum likelihood methods. The best fit distribution was chosen based on the lowest Akaike Information Criteria (AIC) value. The probabilities of FMDv transmission, and of developing clinical disease and severe clinical disease were modeled similarly. For expected percentages of animals showing specific clinical signs and duration in days only a single estimate was requested. These percentages and durations in days were summarized with descriptive statistics (range, inter-quantile range, and modes) of the expert actual responses. For each of the parameters related to reduction in feed consumption, minimum, maximum, and most likely values were requested in the survey and the same Monte-Carlo simulation-based resampling described above was used and descriptive statistics (mean, median, and inter-quantile range) of the parameter distribution were computed. The Monte-Carlo simulations, fitting candidate distributions, and computing summary statistics were implemented in @Risk v.7.5 (Palisade Corp., Ithaca, NY, USA). **Figure 2-1** was developed in the OriginPro® 2017 software (OriginLab Inc., Northampton, MA, USA).

Results

Expert demographics

A total of 33 potential survey participants were identified. Twenty-seven agreed to complete the survey and 16 finished the survey (59% completion rate). Of the 27 experts that

agreed to participate: 100% ($n=27$) were veterinarians, and had worked with FMD; 52% ($n=14$) had a strong publication record relating to FMD; 48% ($n=13$) had worked at the OIE referent institutions for FMD; 56% ($n=15$) had experience working during FMD outbreaks in endemic or non-endemic settings; and 63% ($n=17$) were referred by other experts selected. All the responses were submitted via the on-line survey version and were anonymous. The survey respondents collectively had a variety of experience with FMD in different geographical locations, as detailed in **Table 2-2**.

Duration of FMD clinical and infection stages

The best-fit distributions and their descriptive statistics for the durations of the FMD infection and disease stages in beef feedlot cattle depending on the strain virulence, dose of infection, and route of infection are detailed in **Table 2-3**. The estimated mean infectious period for infections via direct contact transmission with high virulent strains ranged from 10.9 days with high dose to 9.1 days with low dose; for low virulent strains it was ~8.6 days for both high and low doses. For infections via airborne transmission with high virulent strains, the infectious period ranged from 10.0 days with high dose and 8.9 days with low dose; it was ~8 days for low virulent strains with both high and low dose. The estimated mean incubation period for infections via direct contact with high virulent strains increased from 3.2 days with high dose to 5.0 days with low dose; for low virulent strains it increased from 4.4 days with high dose to 6.1 days with low dose. For infections via airborne transmission with high virulent strains, the incubation period increased from 3.8 days with high dose to 5.4 days with low dose; for low virulent strains it increased from 5.0 days with high dose to 6.0 with low dose. The estimated mean clinical period ranged between 6.3 to 7.7 days for all the scenarios.

Clinical signs and their duration

Descriptive statistics of the expert estimated percentages of animals showing specific clinical signs are reported in **Table 2-4**. The percentages tended to decrease for low virulent strains compared to high virulent strains for a given infectious dose, and for strains with a given virulence from a high to low infection dose. This was similar for infections via direct contact and airborne, and consistent across different clinical signs and their duration in days. However, the interquartile ranges were wide and overlapped substantially between strains of different virulence, infection doses, and routes of infection (**Table 2-4**).

Probabilities of virus transmission, clinical disease, and severe clinical disease

The estimated median probability of FMDv transmission via direct contact ranged from 53% for cattle infected by low virulent strains in a low dose to 82% for cattle infected by high virulent strains in a high dose (**Figure 2-1**). However, a maximum probability of 100% was reported by the experts for all the scenarios. The minimum probability of transmission via direct contact decreased from 40% to 20% between the infections by high virulent strains at a high and low virus dose, respectively (**Figure 2-1**). For cattle infected by low virulent strains at a high or low infection dose the minimum probability of transmission via direct contact was less than 5%. The comparative probabilities of cattle developing clinical disease once infected were only requested in the survey for low vs. high virulent strains (irrespective of the infection dose). The estimated median probability of developing disease was 82% after infection with high virulent strains and 63% for low virulent strains (**Figure 2-1**). While the estimated median probability of

developing severe clinical disease after infection with high virulent strains was 68% and for low virulent strains it was 47% (**Figure 2-1**).

Reduction in feed consumption

Based on the expert responses summarized in **Table 2-5**, the expected mean reduction in feed consumption by cattle infected by high virulent FMDv strains was 63% compared to 50% for low virulent strains. The mean duration of this reduction in feed consumption was reported to be 7 days for high virulent strains and 5 days for low virulent strains. The peak reduction was reported to occur by day 2 of the clinical disease for both high and low virulent strains.

Discussion

We used an expert survey to collect data on the parameter values of natural history and transmissibility of FMDv that are not available in, or are difficult to extrapolate from published literature. The parameter values are relevant for simulation models of potential FMD outbreaks in production systems of young cattle confined in group pens such as a U.S. beef feedlot. We did not make a distinction between specific FMDv serotypes and strains even though differences in the pathobiology and clinical manifestation had been demonstrated (Arzt et al., 2011), and some strains have been observed to be species-specific in the field and controlled-environment conditions (Dunn and Donaldson, 1997; Yang et al., 1999; Joo et al., 2002; Oem et al., 2008). Instead, we elicited expert opinion on clinical manifestation and transmissibility of “generic” high and low virulence strains. The virus has not been detected in the U.S. since 1929 (Mohler, 1930) and introduction of any FMDv strain into the U.S. would cause devastating impacts on

welfare of the naive beef cattle population and on the industry's trade and business continuity. Thus, our main interest was to obtain the parameter values distinguishing between high and low virulent strains, dose of infection, and routes of transmission, to enable parameterizing mathematical models to simulate outbreak scenarios and evaluate control strategies for U.S. beef feedlots.

To our knowledge, this is the first study that aimed to estimate parameters of FMD natural history and FMDv transmissibility using only expert opinion. Due to the nature and variability in pathobiology of the infection and disease dynamics among FMDv strains (Kitching, 2002; Alexandersen et al., 2003b; Kitching et al., 2005; Arzt et al., 2011; Onozato et al., 2014), we conducted a worldwide survey seeking experts with collective experience with different FMDv strains in different geographical locations and from several areas of expertise.

A pilot of the survey was conducted with two FMD-experts to maximize the likelihood of gathering fit-for-purpose data. Van Teijlingen and Hundley (2001) state the importance of pilot studies before the survey questionnaire release to identify implementation problems and test the adequacy of the research methods. Next, potential respondents to our survey were asked to indicate an agreement to participate (electronic communication) prior to being sent the survey; the agreement was obtained in order to maximize completion rate due to the complexity of the survey. However, 41% of the respondents who agreed to participate did not complete the entire survey, citing lack of expertise about non-completed topics addressed in the survey. This highlighted the gaps in existing knowledge about the virus-host interactions for FMD, some of which have been discussed by Arzt et al. (2011). The survey results could have been affected by selection bias due to the non-response rate among the experts who had agreed to participate. However, all the 27 experts were chosen using the same criteria (see the expert selection rubric

above), and we were unable to identify systematic differences among the experts who completed and those who did not complete the survey. The number of expert responses for individual parameters surveyed ranged from 8 to 15, consistent with previously reported studies on diagnosing country-level FMD presence (Garabed et al., 2009) and FMD risk estimation (Horst et al., 1998). Moreover, our sample size should not be considered as small when compared to the number of FMD experts around the world, as discussed by Garabed et al. (2009). We prioritized the context of the health status of young immunologically naive and group housed cattle (See Materials and Methods – Survey Design) so the gathered data are applicable to beef feedlot populations.

Focus groups and Delphi techniques are other flexible tools used to collect expert opinion about a topic; the tools are especially suited when an agreement among the participants in the final estimates is desirable and clarifications of the study objectives to the participants during the study are needed (Hsu and Sandford, 2007; Dohoo et al., 2009). Kinsley et al. (2016) used a Delphi technique to survey expert opinion on values of parameters of FMDv transmission in farmed swine populations. McReynolds and Sanderson (2014) conducted an online Delphi study with veterinary pharmacologists, toxicologists, cattle welfare specialists, cattle veterinarians, and the feedlot industry to identify feasible methods to depopulate large commercial feedlots if infected by FMD. While the Delphi technique is an inexpensive method to gather focused expert opinion (Jones and Hunter, 1995; Green et al., 2007), it requires several rounds to reach an agreement between the participants (Jones and Hunter, 1995). In our case, the need to include experts from different geographical locations plus the length of the survey (time-to-complete the survey) precluded the use of the Delphi techniques. Although, this approach could be explored in

the future. In the present study, we instead utilized response resampling techniques to combine parameter estimates provided by individual experts into overall estimates.

Durations of the infection and disease stages were surveyed differentiating by strain virulence, routes of infection, and infection dose. It is known that FMDv spreads mainly by direct contact with infected animals (Arzt et al., 2011) but also, Alexandersen et al. (2003b) reports that under specific conditions virus can travel in the air and remain infectious. The dose of infection is believed to affect the length of the incubation period (Alexandersen et al., 2002; Alexandersen et al., 2003a). Indeed, the expert responses in our study demonstrated that the expected incubation period after a high infection dose is shorter compared to a low infection dose for infections via either direct contact or aerosol (Table 3). The distributions estimated in this study for the durations of the infection and disease stages in immunologically naïve to the infection, confined beef cattle are right skewed (Table 3). This is consistent with such distributions reported by Mardones et al. (2010) for the serotype O in unvaccinated cattle, small ruminants, and swine; and those reported by Kinsley et al. (2016) for unvaccinated swine, irrespective of the serotype. Mardones et al. (2010) and Kinsley et al. (2016) did not differentiate between high and low virulent strains, high and low infection dose, and direct contact and airborne transmission, as we did. However, the results of both the earlier studies (Mardones et al., 2010; Kinsley et al., 2016) suggest that the duration of the stages is influenced by the strain within a serotype. As reported by the experts in this survey, duration of the latent period for infections via direct contact was shorter than for airborne infections (**Table 2-3**) which is expected due the limited viability of the virus in the environment (Sørensen et al., 2000). The estimated infectious period in cattle for all the strain virulence, infection dose, and route of transmission scenarios was longer and the incubation period was shorter (**Table 2-3**) compared

to those estimated by Mardones et al. (2010). This could be due to the beef cattle production scenario presented to the experts in our survey (see Materials and Methods: Survey design); high viral loads could be expected in the environment after the early stages of the outbreak on a U.S. beef feedlot due to the large concentration of the animals. The duration of the clinical period of up to 8-9 days expected by the experts in our study (**Table 2-3**) was in agreement with that reported by Kitching and Mackay (1995) and DEFRA (2005), but the clinical signs may last up to 11 days (Kitching, 2002) and secondary infections are possible (Kitching and Mackay, 1995).

There were wide and overlapping interquartile ranges in the expected proportions of cattle with specific clinical signs between the FMDv strain virulence, doses of infection, and routes of transmission scenarios (Table 4). This signals a similarity in the expected clinical presentation of FMD in confined cattle regardless of the route of transmission, strain virulence, or dose. The data acquired in controlled *in vivo* experiments should be considered cautiously because of the differences in the animal housing and density as well as environmental conditions compared to field settings. The environmental conditions such as temperature and humidity would affect the viability of FMDv as shown by Barlow (1972) and thus the infection dose for airborne, water-borne, fomite-based, and environmental transmission within the feedlot. The animal housing and density would also affect transmission via those routes and direct contact.

The expert reported probabilities of FMDv transmission from infected to naïve cattle significantly overlapped between the strains of high and low virulence and the infection doses (**Figure 2-1**). The estimated median probabilities of developing clinical disease and developing severe clinical disease decreased for low virulent compared to high virulent strains, but also overlapped among the virulence and dose scenarios (**Figure 2-1**). Interpretation of these results should be done cautiously. While the experts in this study had extensive collective experience

with FMD in non-endemic and endemic settings in different geographical locations, there is a significant uncertainty in the estimates since multiple factors can affect FMDv transmission and FMD presentation in field settings. There is no real consensus for differentiating high from low virulent strains but it is known that strains within the SAT serotype are less virulent than those within serotypes A, O, C, and Asia-1 (Coetzer and Tustin, 2004). Christensen et al. (2011) inoculated the SAT1/Zimbabwe/1989 strain in naïve Holstein Friesian cattle and evaluated virus detection in serum, saliva, and air samples; however, other naïve animals were not exposed to the inoculated animals to assess transmission. All animals in this experiment developed clinical signs but severity of clinical manifestation was not reported (Christensen et al., 2011). The estimated median probability of FMDv-infected cattle developing clinical disease for infections with low virulent strains in our survey was 63% with a maximum of 98% (**Figure 2-1**).

Experimental studies (Burrows, 1968; Graves et al., 1971a; Graves et al., 1971b; Zhang and Alexandersen, 2004; Orsel et al., 2009; Pacheco et al., 2010; Stenfeldt et al., 2011; Onozato et al., 2014; Bravo de Rueda et al., 2015; Pacheco et al., 2016) have inoculated naïve cattle with strains of serotypes A, O, and C - which could be considered as high virulent strains - and directly exposed other naïve recipient cattle to those inoculated. The percentage of the recipients successfully infected ranged from 64 to 100%, and those developing disease out of the infected recipients ranged from 58 to 100%. Our estimates (**Figure 2-1**) are consistent with these experimental observations. Experimental assessment of the probabilities of transmission and developing clinical disease for high and low infection doses is complex because it is difficult to estimate the viral load transmitted between the donor and recipient animals. Moreover, the experimental design, breed, and age of the animals used in the studies mentioned above may have influenced the estimated transmission and clinical disease probabilities.

The results for the expected reduction in feed consumption by beef feedlot cattle suggest that the peak reduction is expected at day 2 after the onset of clinical FMD for both high and low virulent strains (**Table 2-5**). We asked the expert opinion on three parameters: percentage reduction in feed consumption, duration of that reduction, and day since onset of the clinical signs when this reduction is at its peak. A limitation of the design is that we did not ask about the reduction in feed consumption for each day during the clinical stage. A report by DEFRA (2005) shows that by day 2 of the clinical disease the vesicles in the mouth are ruptured which in theory might be when animals experience the peak reduction in feed consumption due to pain from the lesions. The reports by (DEFRA, 2005) and (Kitching and Mackay, 1995) also mention that complete healing of vesicles in steers occurs by day 7 since the onset of clinical signs which might be the day when the feed consumption could return to that pre-infection. Neither of the two reports accounts for the role of the strain virulence for the clinical manifestation, which complicates comparisons between the report data and our estimates (**Table 2-5**). Some experts in this study (data not shown) reported that virulence of the strain affects the incubation period but may not have an impact on clinical manifestation; once cattle develop clinical signs, the dynamics of clinical manifestation is the same regardless of the strain virulence. Data on feed consumption during clinical FMD are scarce or unfortunately have not been reported in most of the experimental studies. Only two relevant reports from experimental studies and none from outbreak investigations could be located. Orsel et al. (2005) mentioned that feed intake was minimally affected during the clinical FMD in Holstein Friesian calves that presented mild clinical signs. Alexandersen et al. (2003a) reported that pigs showed little or no interest in feed due to the severe clinical FMD. Observational surveillance of cattle health by pen-riders is practiced in U.S. beef feedlots. The main objective of this routine surveillance is to diagnose

endemic diseases and syndromes, particularly bovine respiratory disease (BRD) (Smith et al., 1994). The daily feed delivery to the pens of cattle is also routinely monitored. It is noted by Wolfger et al. (2015) that average feed intake per meal is a good indicator for cattle affected with BRD during the initial disease. In addition, Buhman et al. (2000) reported changes in feeding behavior such as time spent at feedbunk and number of visits to the feedbunk in cattle affected with BRD compared to those visually healthy. This highlights the importance and practicality to consider feed consumption in U.S. beef feedlots as a possible variable to monitor for identification of FMD-infected feedlots in the early stages of the disease in case of an FMD outbreak. Thus, further studies of the expected reduction in feed consumption by beef feedlot cattle during clinical FMD are warranted.

Conclusion

This is the first study estimating parameters of the natural history and transmissibility of FMDv in U.S. beef feedlot cattle using expert opinion and differentiating among infections by strains of different virulence, doses of infection, and routes of infection. The estimated duration of the infection and disease stages, proportions of cattle with specific clinical signs, and the extent and duration of reduction in feed consumption can be used in mathematical models to evaluate the probability to detect FMD, simulate outbreak progression in beef feedlots, and assess the impact of outbreak control strategies. The reported parameter values are strictly based on expert opinion; we targeted experts with different areas of expertise and from various geographical locations to improve the data quality. Nevertheless, due to the variable natural history of FMD, the data reported in this study should be combined with experimental and

outbreak-investigation data to produce more robust simulation models. In addition, reporting data regarding frequency of specific clinical signs as well as effects on feed and water consumption generated by FMD experimental studies and outbreak investigations is needed.

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Author contributions

The survey was designed by AHC, MWS, and VVV. The survey was implemented and the expert responses collated by AHC. The data were analyzed by AHC, MWS, VVV, and MJD. AHC, VVV, and MWS wrote the manuscript. All authors have read and approved the final version for publication.

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Table 2-1 Parameters of foot and mouth disease natural history in beef feedlot cattle and the infection scenarios that were surveyed

Description	Parameter	Strain virulence	Route of infection	Infection dose
Duration of each infection or disease stage	Latent	High Low	Airborne Direct contact	High Low
	Infectious			
	Incubation			
	Subclinical Clinical			
Transmission probability ¹	Probability of transmission	High Low	Direct contact	High Low
Clinical disease and severe disease probabilities	Probability to develop clinical disease	High	N/A	N/A
	Probability to develop severe disease	Low		
Proportion of cattle showing clinical signs and their duration	Ulceration	High Low	Airborne Direct contact	High Low
	Mouth vesicles			
	Hoof vesicles			
	Drooling			
	Lameness			
	Fever Depression			
Proportional reduction of feed consumption and its duration	Reduction in feed consumption	High Low	N/A	N/A

¹ Questions about airborne FMDv transmission were not included in the survey, because the airborne viral load, survival, and distribution are affected by local factors such as environmental temperature and humidity, and wind direction.

Table 2-2 Number of experts who completed the survey per area of expertise and geographical area where they acquired experience with foot-and-mouth disease (FMD)

Description	Background	Number of experts
FMD-expertise area ¹	Research: epidemiology, mathematical modeling	6
	Research: virology, vaccine development	2
	Research: <i>in-vivo</i> experiments	4
	Government, policy	1
	Practicing veterinarian: participation in outbreak investigation	0
	Other	3
Geographical area where experience with FMD was acquired ²	Africa	3
	Asia	7
	U.S., Canada	2
	Latin America (Mexico, Central America, South America)	5
	European Union, United Kingdom, rest of Europe	6
	Australia, New Zealand	0

¹ Each expert could only select one area of expertise.

² Each expert could select several geographical areas where he/she has acquired experience with FMD.

Table 2-3 The best-fit distributions based on the combined expert responses about the expected duration in days of the infection and disease stages of foot and mouth disease (FMD) in beef feedlot cattle for the infection scenarios that were surveyed

Clinical signs <i>Route of infection</i>	Virulence and infection dose ¹	Percentage of cattle showing these clinical signs				Duration of these clinical signs, day			
		<i>n</i> ²	Range ³	IQ range ⁴	Modes ⁵	<i>n</i>	Range	IQ range	Modes
Ulceration									
<i>Direct contact</i>	H vir – H dose	12	100-60	95-70	70, 90	11	15-3	14-4	4
	H vir – L dose	12	95-40	90-50	50	11	15-2	10-4	4
<i>Airborne</i>	L vir – H dose	12	95-20	90-40	90	11	15-2	7-3	3, 6, 7
	L vir – L dose	12	95-10	83-30	30	11	15-1	8-3	3, 7
	H vir – H dose	9	100-50	90-70	70	9	15-2	8-4	6
	H vir – L dose	9	100-20	90-40	90	9	15-2	8-5	5
	L vir – H dose	9	90-15	90-30	90	9	15-2	7-6	6
	L vir – L dose	9	90-8	80-30	30, 80	9	15-2	7-5	5, 6, 7
Mouth vesicles									
<i>Direct contact</i>	H vir – H dose	15	100-70	100-80	100	14	14-1	5-3	4, 5
	H vir – L dose	15	100-40	90-50	50, 80, 90	13	14-1	5-2	4
	L vir – H dose	15	95-10	90-50	50,90	14	7-1	5-2	2, 3, 5
	L vir – L dose	15	95-5	80-30	80	13	10-1	4-2	2, 3
<i>Airborne</i>	H vir – H dose	11	100-50	95-70	80	11	14-1	5-3	4
	H vir – L dose	11	100-30	90-50	50, 80, 90, 100	11	14-1	5-3	3, 4, 5
	L vir – H dose	11	90-25	90-40	90	11	7-1	5-2	2, 3, 4, 5
	L vir – L dose	11	90-15	80-20	20, 50, 80	10	7-1	5-2	2, 3, 4, 7
Hoof vesicles									
<i>Direct contact</i>	H vir – H dose	14	100-60	90-70	90	12	14-3	8-4	4, 5
	H vir – L dose	14	95-30	80-50	50	12	14-2	9-4	4
	L vir – H dose	14	95-10	80-30	30	12	13-2	7-3	2, 3, 7
	L vir – L dose	14	95-5	75-20	10, 30, 50	12	13-2	8-3	2, 3, 7
<i>Airborne</i>	H vir – H dose	10	95-30	90-60	90	10	14-3	7-4	4
	H vir – L dose	10	95-10	80-50	80	10	14-3	7-4	4
	L vir – H dose	10	95-7	90-30	30, 80, 90	10	8-2	7-3	6
	L vir – L dose	10	95-3	75-20	20, 90	10	8-2	7-3	2, 6, 7
Drizzling									
<i>Direct contact</i>	H vir – H dose	14	100-50	97-75	80, 100	13	14-1	4-2	4
	H vir – L dose	14	97-20	80-50	50, 80	13	14-1	4-2	4
	L vir – H dose	14	97-10	80-50	50	13	7-1	5-2	2
	L vir – L dose	14	97-5	65-35	10, 40, 50, 65	13	10-1	5-1	1
<i>Airborne</i>	H vir – H dose	10	100-50	90-70	70, 80	10	14-2	4-2	2, 4
	H vir – L dose	10	100-30	90-50	80	10	14-2	5-3	3
	L vir – H dose	10	100-20	90-30	50, 75	10	8-2	6-2	2
	L vir – L dose	10	100-10	90-20	65, 90	10	1-8	7-2	1, 2, 3, 7
Lameness									
<i>Direct contact</i>	H vir – H dose	14	100-20	80-50	80	12	21-2	11-4	2, 4, 7
	H vir – L dose	14	90-15	70-50	50	12	21-2	12-4	2, 7

	L vir – H dose	14	90-10	60-30	30	12	20-1	11-2	1, 2, 5, 7, 14
	L vir – L dose	14	90-5	60-10	10	12	20-1	12-1	1
<i>airborne</i>	H vir – H dose	10	90-20	90-30	90	10	14-2	7-4	7
	H vir – L dose	10	90-10	80-20	80	10	21-4	8-5	5
	L vir – H dose	10	90-7	80-20	30, 90	10	14-2	8-5	7
	L vir – L dose	10	90-3	70-10	10, 70	10	14-1	8-5	7
Fever ($\geq 40^{\circ}\text{C}$)									
<i>Direct contact</i>	H vir – H dose	15	100-40	100-50	100	15	6-1	5-2	2
	H vir – L dose	15	100-20	90-50	50, 80	14	10-1	4-2	2
	L vir – H dose	15	100-10	90-30	90	15	6-1	3-1	2
	L vir – L dose	15	97-5	70-10	10, 40, 70	14	10-1	3-1	1
<i>Airborne</i>	H vir – H dose	11	100-40	97-70	70, 90, 100	11	5-1	5-2	2
	H vir – L dose	11	100-40	95-40	40	11	5-1	5-2	2, 3, 5
	L vir – H dose	11	100-10	95-30	30, 70, 100	11	6-1	4-2	2
	L vir – L dose	11	100-10	75-20	10, 20, 70	10	7-1	4-1	2
Depression									
<i>Direct contact</i>	H vir – H dose	14	100-30	100-50	90, 100	12	30-1	7-2	2
	H vir – L dose	14	100-20	90-50	50, 90	11	15-1	8-2	2
	L vir – H dose	14	100-10	90-20	10, 90	12	60-1	6-2	1, 2
	L vir – L dose	14	100-5	90-10	5, 10, 40, 100	11	10-1	8-1	1
<i>Airborne</i>	H vir – H dose	11	100-40	90-65	90	10	15-1	7-2	2, 3
	H vir – L dose	11	100-35	90-50	50, 100	10	10-1	7-3	3, 5
	L vir – H dose	11	100-10	90-30	10, 30, 90, 100	10	8-1	6-2	2
	L vir – L dose	11	100-5	90-20	20, 50, 100	9	8-1	6-2	1, 2, 5

¹ Number of experts that provided the parameter values.

² The relative FMD virus strain virulence and dose by which the animal is infected: H vir – high virulent; L vir – low virulent; H dose – high dose; and L dose – low dose.

Table 2-4 Summary statistics for the expert responses of percentages of beef feedlot cattle expected to show specific clinical signs and their duration in days depending on the route of infection, strain virulence, and infection dose of foot-and-mouth disease virus (FMDv)

Clinical signs <i>Route of infection</i>	Virulence and infection dose ¹	Percentage of cattle showing these clinical signs				Duration of these clinical signs, day				
		<i>n</i> ²	Range ³	IQ range ⁴	Modes ⁵	<i>n</i>	Range	IQ range	Modes	
Ulceration										
<i>Direct contact</i>	H vir – H dose	12	100-60	95-70	70, 90	11	15-3	14-4	4	
	H vir – L dose	12	95-40	90-50	50	11	15-2	10-4	4	
<i>Airborne</i>	L vir – H dose	12	95-20	90-40	90	11	15-2	7-3	3, 6, 7	
	L vir – L dose	12	95-10	83-30	30	11	15-1	8-3	3, 7	
	H vir – H dose	9	100-50	90-70	70	9	15-2	8-4	6	
	H vir – L dose	9	100-20	90-40	90	9	15-2	8-5	5	
	L vir – H dose	9	90-15	90-30	90	9	15-2	7-6	6	
	L vir – L dose	9	90-8	80-30	30, 80	9	15-2	7-5	5, 6, 7	
	Mouth vesicles									
	<i>Direct contact</i>	H vir – H dose	15	100-70	100-80	100	14	14-1	5-3	4, 5
H vir – L dose		15	100-40	90-50	50, 80, 90	13	14-1	5-2	4	
L vir – H dose		15	95-10	90-50	50,90	14	7-1	5-2	2, 3, 5	
L vir – L dose		15	95-5	80-30	80	13	10-1	4-2	2, 3	
<i>Airborne</i>	H vir – H dose	11	100-50	95-70	80	11	14-1	5-3	4	
	H vir – L dose	11	100-30	90-50	50, 80, 90, 100	11	14-1	5-3	3, 4, 5	
	L vir – H dose	11	90-25	90-40	90	11	7-1	5-2	2, 3, 4, 5	
	L vir – L dose	11	90-15	80-20	20, 50, 80	10	7-1	5-2	2, 3, 4, 7	
Hoof vesicles										
<i>Direct contact</i>	H vir – H dose	14	100-60	90-70	90	12	14-3	8-4	4, 5	
	H vir – L dose	14	95-30	80-50	50	12	14-2	9-4	4	
	L vir – H dose	14	95-10	80-30	30	12	13-2	7-3	2, 3, 7	
	L vir – L dose	14	95-5	75-20	10, 30, 50	12	13-2	8-3	2, 3, 7	
<i>Airborne</i>	H vir – H dose	10	95-30	90-60	90	10	14-3	7-4	4	
	H vir – L dose	10	95-10	80-50	80	10	14-3	7-4	4	
	L vir – H dose	10	95-7	90-30	30, 80, 90	10	8-2	7-3	6	
	L vir – L dose	10	95-3	75-20	20, 90	10	8-2	7-3	2, 6, 7	
Drizzling										
<i>Direct contact</i>	H vir – H dose	14	100-50	97-75	80, 100	13	14-1	4-2	4	
	H vir – L dose	14	97-20	80-50	50, 80	13	14-1	4-2	4	
	L vir – H dose	14	97-10	80-50	50	13	7-1	5-2	2	
	L vir – L dose	14	97-5	65-35	10, 40, 50, 65	13	10-1	5-1	1	
<i>Airborne</i>	H vir – H dose	10	100-50	90-70	70, 80	10	14-2	4-2	2, 4	
	H vir – L dose	10	100-30	90-50	80	10	14-2	5-3	3	
	L vir – H dose	10	100-20	90-30	50, 75	10	8-2	6-2	2	
	L vir – L dose	10	100-10	90-20	65, 90	10	1-8	7-2	1, 2, 3, 7	
Lameness										
<i>Direct contact</i>	H vir – H dose	14	100-20	80-50	80	12	21-2	11-4	2, 4, 7	
	H vir – L dose	14	90-15	70-50	50	12	21-2	12-4	2, 7	

	L vir – H dose	14	90-10	60-30	30	12	20-1	11-2	1, 2, 5, 7, 14
	L vir – L dose	14	90-5	60-10	10	12	20-1	12-1	1
<i>airborne</i>	H vir – H dose	10	90-20	90-30	90	10	14-2	7-4	7
	H vir – L dose	10	90-10	80-20	80	10	21-4	8-5	5
	L vir – H dose	10	90-7	80-20	30, 90	10	14-2	8-5	7
	L vir – L dose	10	90-3	70-10	10, 70	10	14-1	8-5	7
Fever ($\geq 40^{\circ}\text{C}$)									
<i>Direct contact</i>	H vir – H dose	15	100-40	100-50	100	15	6-1	5-2	2
	H vir – L dose	15	100-20	90-50	50, 80	14	10-1	4-2	2
	L vir – H dose	15	100-10	90-30	90	15	6-1	3-1	2
	L vir – L dose	15	97-5	70-10	10, 40, 70	14	10-1	3-1	1
<i>Airborne</i>	H vir – H dose	11	100-40	97-70	70, 90, 100	11	5-1	5-2	2
	H vir – L dose	11	100-40	95-40	40	11	5-1	5-2	2, 3, 5
	L vir – H dose	11	100-10	95-30	30, 70, 100	11	6-1	4-2	2
	L vir – L dose	11	100-10	75-20	10, 20, 70	10	7-1	4-1	2
Depression									
<i>Direct contact</i>	H vir – H dose	14	100-30	100-50	90, 100	12	30-1	7-2	2
	H vir – L dose	14	100-20	90-50	50, 90	11	15-1	8-2	2
	L vir – H dose	14	100-10	90-20	10, 90	12	60-1	6-2	1, 2
	L vir – L dose	14	100-5	90-10	5, 10, 40, 100	11	10-1	8-1	1
<i>Airborne</i>	H vir – H dose	11	100-40	90-65	90	10	15-1	7-2	2, 3
	H vir – L dose	11	100-35	90-50	50, 100	10	10-1	7-3	3, 5
	L vir – H dose	11	100-10	90-30	10, 30, 90, 100	10	8-1	6-2	2
	L vir – L dose	11	100-5	90-20	20, 50, 100	9	8-1	6-2	1, 2, 5

¹ The relative FMDv strain virulence and dose by which the animal is infected: H vir – high virulent; L vir – low virulent; H dose – high dose; and L dose – low dose.

² Number of experts that provided the parameter values.

³ The maximum – minimum parameter value provided.

⁴ The upper quartile (75%) – lower quartile (25%) of the parameter values provided.

⁵ Parameter values provided by the experts most frequently.

Table 2-5 Summary statistics for the expert responses about the expected reduction in feed consumption by beef feedlot cattle during the clinical stage of foot-and-mouth disease depending on the virus strain virulence

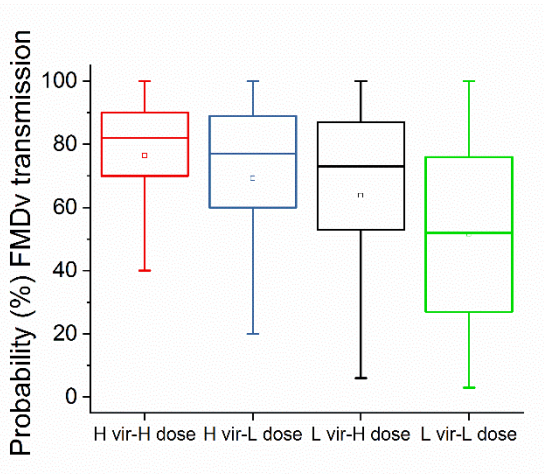
Parameter	<i>n</i> ¹	High virulent strains			Low virulent strains		
		Mean (SD) ²	Median	IQ Range ³	Mean (SD)	Median	IQ Range
Reduction in feed consumption, %	8	63 (22)	69	79-51	50 (21)	49	63-33
Duration of reduction in feed consumption, days	8	7 (5)	6	10-4	5 (2)	5	6-3
Day since onset of clinical signs of peak (maximum) reduction in feed consumption	9	2 (1)	2	4-2	2 (1)	2	3-2

¹ Number of experts that provided the parameter values.

² Mean and standard deviation of the mean of the parameter values provided.

³ The upper quartile (75%) – lower quartile (25%) of the parameter values provided.

a)



b)

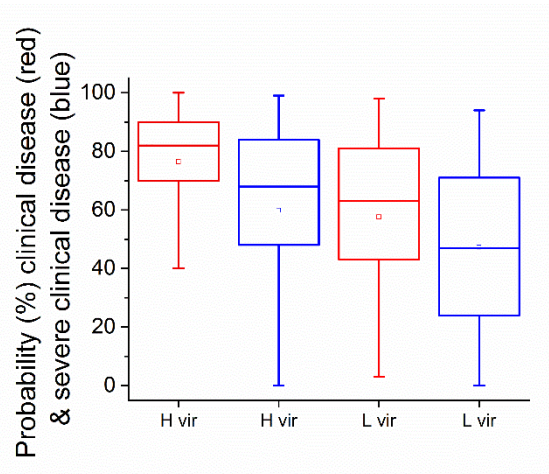


Figure 2-1 a) Estimated probability of foot-and-mouth disease virus (FMDv) transmission in confined cattle via direct contact to immunologically-naïve cattle from infected cattle depending on the strain virulence and infection dose: H vir – high virulent; L vir – low virulent; H dose – high dose; and L dose – low dose. b) Estimated probability of clinical disease (red boxplots) and severe clinical disease (blue boxplots) in confined cattle infected by an FMDv strain that is H vir – high virulent or L vir – low virulent

Chapter 3 - A meta-population model of potential foot-and-mouth disease transmission, clinical manifestation, and detection within U.S. beef feedlots

Aurelio H. Cabezas, Michael W. Sanderson^{*}, Victoriya V. Volkova^{*}

Department of Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States

Center for Outcomes Research and Epidemiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States

^{*}Corresponding authors:

Victoriya Volkova, Department of Diagnostic Medicine/Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States.

Phone: +1 (607) 220-8687. e-mail: vv88@vet.k-state.edu

Michael Sanderson, Department of Diagnostic Medicine/Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States.

Phone: +1 (785)-532-4264. e-mail: sandersn@vet.k-state.edu

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Abstract

Foot-and-mouth disease (FMD) has not been reported in the U.S. since 1929. Recent outbreaks in previously FMD-free countries raise concerns about potential FMD introductions in the U.S. Mathematical modeling is the only tool for simulating infectious disease outbreaks in non-endemic territories. In the majority of prior studies, FMD virus (FMDv) transmission on-farm was modeled assuming homogenous animal mixing. This assumption is implausible for a U.S. beef feedlot which is divided into multiple home-pens with no contact between pens except fence line with contiguous pens and limited mixing in hospital pens. To project FMDv transmission and clinical manifestation in a feedlot, we developed a meta-population stochastic model reflecting the contact structure. Within a home-pen, the dynamics were represented assuming homogenous animal mixing by a modified SLIR (susceptible-latent-infectious-recovered) model with four additional compartments tracing the cattle with subclinical or clinical FMD and infectious status. The virus transmission among home-pens occurred via cattle mixing in hospital-pen(s), cowboy pen rider (care-giver) movements between pens, airborne, and for contiguous home-pens fence-line and via shared water-troughs. We modeled feedlots with the one-time capacity of 4,000 (small), 12,000 (medium), and 24,000 (large) cattle. Common cattle demographics, feedlot layout, endemic infectious and noninfectious disease occurrence, and production management were reflected. The projected FMD-outbreak duration on a feedlot ranged from 49 to 82 days. The outbreak peak day (with maximum number of FMD clinical cattle) ranged from 24 for a small to 49 for a large feedlot. The detection day was 4 to 12 post FMD-introduction with projected 28%, 9%, or 4% of cattle already infected in a small, medium, or large feedlot, respectively. Depletion of susceptible cattle in a feedlot occurred by day 23 to 51 post FMD-introduction. Parameter-value sensitivity analyses were performed for the model

outputs. Detection occurred sooner if there was a higher initial fraction of latent animals in the index-pen. Shorter outbreaks were associated with a shorter latent period and higher bovine respiratory disease morbidity (impacting the in-hospital-pen cattle mixing occurrence). This first model of potential FMD dynamics on U.S. beef feedlots shows the importance of capturing within-feedlot cattle contact structure for projecting infectious disease dynamics. Our model provides a tool for evaluating FMD outbreak control strategies.

Keywords: Mathematical modeling, Foot-and-mouth disease, Transmission dynamics, Infectious disease dynamics, Meta-population, Environmental transmission, Waterborne transmission, Beef cattle, Beef feedlot

Running title: FMD transmission in beef feedlots

Introduction

Foot-and-mouth disease (FMD) is a highly contagious disease affecting livestock and over a hundred wildlife species (Weaver et al., 2013). Foot-and-mouth disease virus (FMDv) is of the genus *Aphovirus*, family *Picornaviridae*. There are 7 antigenically distinct FMDv serotypes: A, O, C, SAT-1, SAT-2, SAT-3, and ASIA-1. Serotypes O and A are most widely distributed world-wide according to a recent review (Brito et al., 2017). In the Americas, major FMD outbreaks have not occurred since an outbreak in Paraguay in 2012, in which FMDv strains of serotype O predominated. An on-going program is aimed at eradicating FMD in South America by 2020 (Clavijo et al., 2017). The disease has not been reported in the U.S. since 1929 when southern California was affected (Mohler, 1930). The last outbreak in North America occurred in 1952 in Saskatchewan, Canada (Graves, 1979). Economic impacts of an FMD outbreak in disease-free countries can be devastating due to export bans for susceptible animal species and their products, disease-associated animal losses, and outbreak control expenses. For example, the FMD outbreak in United Kingdom in 2001 resulted in the estimated overall costs over £8 billion (\$15 billion) (Anderson, 2002).

The U.S. beef industry is one of the largest in the world with over 30,000 feedlots, primarily concentrated in the Central U.S. (USDA-NASS, 2017). Almost 50% of the national fed cattle inventory are in large commercial feedlots, each with the on-time capacity $\geq 24,000$ head of cattle. Approximately 1,160 million kilograms of beef are exported by the U.S. producers each year (USDA Economic Research Service, 2017). Response by the world animal-health community to an FMD outbreak in the U.S. would likely involve a ban on beef exports. Schroeder et al. (2015) estimate that an FMD outbreak in the U.S. could result in \$188 billion overall costs without emergency vaccination and \$56 billion with high-capacity emergency

vaccination in the Midwest. (Pendell et al., 2015) estimated \$16 to \$140 billion costs for an outbreak if FMDv would be released from a high-security laboratory facility in the Midwest. Others estimated a decrease in farm income of \$14 billion, ~6% of the national gross farm income, in the U.S. for an outbreak assuming the outbreak characteristics were similar to the UK 2001 outbreak (Paarlberg et al., 2002)

For long-term FMD-free countries such as the U.S., mathematical modeling is the only tool for projecting dynamics of a potential FMD outbreak and evaluating control strategies. To simulate an FMD outbreak in the U.S. cattle population and evaluate control strategies, Tildesley et al. (2012) proposed a model of between-farm FMDv transmission similar to that in Keeling et al. (2001). The Tildesley et al. (2012) model was formulated and parameterized based on the UK 2001 outbreak data, and assumed an instantaneous infection of all animals on a farm. Ward et al. (2009) used the AusSpread model, a stochastic state-transition model of between-farm virus transmission, to simulate FMDv spread and evaluate control strategies in a region of Texas farming multiple livestock species. A spatial stochastic model of between-farm virus transmission was used to simulate an FMD outbreak in three counties of California farming multiple livestock species (Bates et al., 2003). Schoenbaum and Disney (2003) developed a stochastic model of between-farm virus transmission to compare control strategies during an FMD outbreak in 3 circular areas which size, cattle herd density, and mean number of cattle per herd corresponded to a county in the South Central U.S., a county in North Central U.S., and a county in Western U.S. An outbreak of FMD in California originating at a state fair was simulated (Carpenter et al., 2007) using a modified Reed-Frost model to simulate virus transmission within the state fair while a stochastic spatial model previously published by Bates et al. (2003) was used to simulate between-farm virus transmission. Finally, McReynolds et al.

(2014) used the spatial stochastic North American Animal Disease Spread Model (NAADSM) of between-farm virus transmission to simulate an FMD outbreak and compare vaccination vs. depopulation strategies for multiple livestock species in the Central U.S. All these models focused on projecting the impact on the outbreak of the virus transmission dynamics between farms. It was assumed that once one infected animal was introduced onto a farm, all animals on the farm were infected with FMD, *i.e.*, an instantaneous and homogenous animal mixing. A similar assumption has been made in models of FMD outbreaks in territories other than the U.S. (Boender et al., 2010; Hayama et al., 2013; Kao, 2002; Keeling et al., 2003; Keeling et al., 2001; Kobayashi et al., 2007; Thornley and France, 2009; Yoon et al., 2006).

In a U.S. beef cattle feedlot, the cattle are compartmentalized in multiple home-pens (*e.g.*, 200 head per home-pen). The home-pen subpopulations contact via multiple routes conducive to contagious agent transmission, forming the meta-population of cattle in the feedlot. There is a multi-route, complex, and heterogeneous in time and space contact structure among the home-pen subpopulations. The relevant contact routes include mixing of some cattle from different home-pens during short stays in hospital-pens, fence-line contact for contiguous home-pens, waterborne contact for contiguous home-pens sharing water-troughs, environmental due to the care-givers moving between the home-pens located in the same home-pen row (the rows are separated by feed-delivery alleys and drover alleys), and airborne across the feedlot. Thus, an assumption of a contagious virus transmission via an instantaneous and homogeneous mixing of all cattle present on a feedlot is implausible. Projecting the transmission among the home-pen subpopulations necessitates a more explicit model of the contact structure. Reflecting the meta-population contact structure when modeling infectious agent transmission is necessary because the agent temporal dynamics and likelihood of persistence in a meta-population are different

from in a homogenously mixing population (Lloyd and May, 1996; North and Godfray, 2017; Wang and Zhao, 2004).

Three teams have modeled within-farm FMDv transmission in cattle (Carpenter et al., 2007; Carpenter et al., 2004; Chis Ster et al., 2012). However, the animal contact structure, demographics, and production management represented were dissimilar to those in U.S. beef feedlots. One study (Kinsley et al., 2018) modeled within-farm FMDv transmission in swine. Models of potential FMDv transmission dynamics in the cattle meta-populations on U.S. beef feedlots have not been reported.

The aim of this study was to develop a mathematical model of potential FMDv transmission, infection, and FMD clinical manifestation dynamics in U.S. beef feedlots, reflecting the animal meta-population contact structure, animal demographics, and contemporary production management. The model was developed as a stochastic meta-population model. In the model, FMDv transmission within a home-pen occurred via homogenous cattle mixing. Relevant contacts among the home-pen subpopulations occurred via cattle mixing in hospital-pen(s), and through fence-lines, shared water-troughs, environment due to care-giver movements between the home-pens in a row, and airborne. The model reflected commercial U.S. beef cattle feedlot demographics and production management, including the incidence and control approaches to endemic infectious diseases and noninfectious diseases. We used the model to project FMDv infection dynamics and clinical manifestation in the absence of control measures on feedlots of several sizes and layouts typical for the U.S. We analyzed the model outputs to describe the projected outbreak characteristics. To our knowledge, this is the first model of potential FMD dynamics on commercial U.S. beef feedlots.

Material and methods

Host population and feedlot size and layout cases modeled

The model reflected the following assumptions. Beef finishing cattle in an open-air feedlot was the target population. No other FMD-susceptible animal species were included on the feedlot or in the surroundings. The cattle were not vaccinated against FMD. Cattle were housed 200 per home-pen, with 22 m² floor space per animal. Cattle morbidity due to production diseases including endemic infectious diseases and non-infectious diseases, *e.g.*, bovine respiratory disease (BRD) and lameness, determined the rate of pulling cattle from the home-pens to hospital-pen(s). Cattle mortality rates due to the production diseases and clinical FMD were incorporated. The model parameter definitions and values are listed in **Table 3-1**. We simulated the feedlot cattle meta-population as a closed one, with no cattle introduced or leaving the feedlot after FMD latent animals were introduced in the index home-pen. Five hypothetical feedlot size and layout cases were modeled: a small-size feedlot with 4,000 cattle in 20 home-pens in 4 rows and 1 hospital-pen (FS1); a medium-size feedlot with 12,000 cattle in 60 home-pens in 8 rows and 1 hospital-pen (FM1); a medium-size feedlot with 12,000 cattle in 60 home-pens in 8 rows and 2 hospital-pens, (FM2); a large-size feedlot with 24,000 cattle in 120 home-pens and 2 hospital-pens, the feedlot includes 2 sections each with 8 home-pen rows and 1 hospital-pen (FL1); and a large-size feedlot with 24,000 cattle in 120 home-pens and 4 hospital-pens, the feedlots includes 2 sections each with 8 home-pen rows and 2 hospital-pens (FL2). The feedlot layouts are detailed in Figures in the Supplementary Materials.

Model formulation

Two levels of FMDv transmission inside the feedlot cattle meta-population were modeled: within each home-pen (1 route of transmission: direct cattle contact) and between home-pens (5 routes of transmission detailed below).

FMD infection and clinical manifestation dynamics in a home-pen

The FMD infection and clinical disease dynamics in each home-pen were modeled using a modified SLIR (susceptible-latent-infectious-recovered) model. The model was modified to add four compartments for tracing the numbers of cattle that were subclinical low infectious (I_1 animals), subclinical high infectious (I_2 animals), clinical high infectious (I_3 animals), and clinical non-infectious (C). A schematic of the infection and clinical disease progression stages in individual cattle and how those were reflected in the model compartments is provided in **Figure 3-1**. Cattle started in the susceptible compartment (S) (equation 1). Susceptible cattle were infected via direct contact with infectious home-pen-mates at a rate reflecting homogenous cattle mixing and density-dependent transmission within the home-pen (the transmission parameter β_{wp} , equation 1) or due to between-home pen FMDv transmission (detailed below) and moved into the latent compartment (L) (equations 1-2). The cattle then moved into a subclinical low infectious compartment (I_1) at a rate $1/\delta$ (equations 2-3), proceeded into a subclinical high infectious compartment (I_2) at a rate $1/\theta$ (equations 3-4), then into a clinical high infectious compartment (I_3) at a rate $1/\varepsilon$ (equations 4-5), and then into a clinical non-infectious compartment (C) at a rate $1/\gamma$ (equations 5-6) where they were still manifesting clinical disease but no longer shed the virus. Finally, the cattle proceeded into a non-clinical non-infectious recovered compartment (R) at a rate $1/\tau$ (equations 6-7). Cattle mortality (*i.e.* culling) due to

endemic infectious diseases and noninfectious diseases occurred at a rate μ in all the compartments (equations 1-7). Cattle mortality (*i.e.* culling) due to clinical FMD in the compartments I_3 and C occurred at a rate ψ (equations 5 and 6). Definitions and values of the model parameters are given in **Table 3-1**.

The modified SLIR model of FMD infection and clinical manifestation dynamics in cattle in a home-pen on a beef feedlot

The modeled home-pen is denoted i . j is the contiguous home-pen proceeding i in the home-pen row. h is the contiguous home-pen following i in the home-pen row. k is any other home-pen than i . n is the number of home-pens in the feedlot. If the feedlot had more than one hospital-pen, cattle were always pulled to the hospital-pen nearest to their home-pen for either a production disease or clinical FMD treatment. The nearest hospital-pen, or the only hospital-pen if there was one on the feedlot, is denoted l . The other parameters are defined in the following sections on the FMDv transmission between home-pens. The time step was 1 day, $dt=1$ (all the rates in the equations including those with the values sampled from Binomial distributions are daily rates).

Susceptible:

$$\begin{aligned}
\frac{dS}{dt} = & -\beta_{wp}S(I_1+I_2+I_3) - \varphi S - \text{Bin}\left(\varphi_{(t-1)}S_{(t-1)}, p_{\text{inf_hp}}l_{(t-1)}\right) - \\
& \left\{ \begin{array}{l} S\beta_{bp}(I_1+I_2+I_3)_j; j \text{ present} \\ 0; \text{ otherwise} \end{array} \right\} - \left\{ \begin{array}{l} S\beta_{bp}(I_1+I_2+I_3)_h; h \text{ present} \\ 0; \text{ otherwise} \end{array} \right\} - \\
& \left\{ \begin{array}{l} \text{Bin}(S, 0.5); j \text{ present, shares water-trough with } i, \text{ and FMDv load in 1 L of the water } \geq ID_{50} \text{ per oral} \\ 0; \text{ otherwise} \end{array} \right\} - \\
& \left\{ \begin{array}{l} \text{Bin}(S, 0.5); h \text{ present, shares water-trough with } i, \text{ and FMDv load in 1 L of the water } \geq ID_{50} \text{ per oral} \\ 0; \text{ otherwise} \end{array} \right\} - \\
& \left\{ \begin{array}{l} \text{Bin}\left[\left(\frac{\text{FMDv_floor}_j \times \sigma}{ID_{50} \text{ per oral}}\right), 0.5\right]; j \text{ present and } \left(\frac{\text{FMDv_floor}_j \times \sigma}{ID_{50} \text{ per oral}}\right) \leq S \\ 0; \text{ otherwise} \end{array} \right\} - \\
& \left\{ \begin{array}{l} \text{Bin}(S, p_{\text{air}_i}); \sum_{k=1}^n I_3 \geq 0 \\ 0; \text{ otherwise} \end{array} \right\} - \mu S
\end{aligned}$$

(1)

Latent:

$$\begin{aligned}
\frac{dL}{dt} = & \beta_{wp}S(I_1+I_2+I_3) - \varphi L + \text{Bin}\left(\varphi_{(t-1)}S_{(t-1)}, p_{\text{inf_hp}}l_{(t-1)}\right) + \\
& \left\{ \begin{array}{l} S\beta_{bp}(I_1+I_2+I_3)_j; j \text{ present} \\ 0; \text{ otherwise} \end{array} \right\} + \left\{ \begin{array}{l} S\beta_{bp}(I_1+I_2+I_3)_h; h \text{ present} \\ 0; \text{ otherwise} \end{array} \right\} + \\
& \left\{ \begin{array}{l} \text{Bin}(S, 0.5); j \text{ present, shares water-trough with } i, \text{ and FMDv load in 1 L of the water } \geq ID_{50} \text{ per oral} \\ 0; \text{ otherwise} \end{array} \right\} + \\
& \left\{ \begin{array}{l} \text{Bin}(S, 0.5); h \text{ present, shares water-trough with } i, \text{ and FMDv load in 1 L of the water } \geq ID_{50} \text{ per oral} \\ 0; \text{ otherwise} \end{array} \right\} + \\
& \left\{ \begin{array}{l} \text{Bin}\left[\left(\frac{\text{FMDv_floor}_j \times \sigma}{ID_{50} \text{ per oral}}\right), 0.5\right]; j \text{ present and } \left(\frac{\text{FMDv_floor}_j \times \sigma}{ID_{50} \text{ per oral}}\right) \leq S \\ 0; \text{ otherwise} \end{array} \right\} + \\
& \left\{ \begin{array}{l} \text{Bin}(S, p_{\text{air}_i}); \sum_{k=1}^n I_3 \geq 0 \\ 0; \text{ otherwise} \end{array} \right\} - \delta L - \mu L
\end{aligned}$$

(2)

Subclinical low infectious:

$$\frac{dI_1}{dt} = \delta L - \theta I_1 - \varphi I_1 + \varphi_{(t-1)} I_{1(t-1)} - \mu I_1 \quad (3)$$

Subclinical high infectious:

$$\frac{dI_2}{dt} = \theta I_1 - \varepsilon I_2 - \varphi I_2 + \varphi_{(t-1)} I_{2(t-1)} - \mu I_2 \quad (4)$$

Clinical infectious:

$$\frac{dI_3}{dt} = \varepsilon I_2 - \gamma I_3 - (\varphi + \zeta) I_3 + (\varphi_{(t-1)} + \zeta) I_{3(t-1)} - (\mu + \psi) I_3 \quad (5)$$

Clinical non-infectious

$$\frac{dC}{dt} = \gamma I_3 - \tau C - (\varphi + \zeta) C + (\varphi_{(t-1)} + \zeta) C_{(t-1)} - (\mu + \psi) C \quad (6)$$

Recovered

$$\frac{dR}{dt} = \tau C - \varphi R + \varphi_{(t-1)} R_{(t-1)} - \mu R \quad (7)$$

FMDv transmission between home-pens

Transmission of FMDv between the home-pen subpopulations occurred via 5 routes: direct contact of cattle from different home-pens in hospital-pen(s) when they were pulled from the home pen for treatment in the hospital, fence-line direct contact of cattle from contiguous home-pens, environmental contact through pen-riders moving between home-pens in the same home-pen row (only from a preceding to the next home-pen in the row), waterborne between contiguous home-pens that shared a water-trough, and airborne.

Transmission via direct contact of cattle in hospital-pen(s)

An S-L (Susceptible-Latent) model was implemented in each hospital-pen l . The susceptible and infectious (I_1 - I_3) cattle originated from the home-pens when morbid cattle were

sent to this hospital-pen. The new latents infected in the hospital-pen and remaining susceptibles (as well as the prior infectious, prior clinical non-infectious, and prior recovered pulled to the hospital-pen) returned to their home-pens the next day (equations 1-7). Recall that cattle from a home-pen were always pulled to the nearest hospital-pen, except in the FS1 and FM1 feedlots where all cattle were pulled to the single hospital-pen.

From a home-pen, a number of cattle were daily pulled to the hospital-pen due to production diseases – endemic infectious and noninfectious diseases – and returned next day; the per-animal daily pull probability (ϕ) was equal for all cattle irrespective of their FMD status. This probability was a product of the expected production disease morbidity and the probability to be pulled to the hospital-pen for treatment depending on the disease. The expected production disease morbidity was the sum of the bovine respiratory disease (BRD) daily morbidity (π) during the first 30 days simulated (which corresponded to the first 30 days since cattle placement on the feedlot), and the aggregated daily morbidity for all other production diseases (ρ) such as lameness, digestive conditions, bullers, and central nervous system problems during the entire 200-day simulation (which corresponded to a 200-day feedlot period since cattle placement on the feedlot). The probability of cattle with BRD to be pulled to the hospital-pen for treatment was $brdtrt$ and with the other diseases it was $endtrt$. The total per-animal daily probability to be pulled due to the production diseases from a home-pen to the hospital-pen was $\phi = \pi * brdtrt + \rho * endtrt$. There was also a per-animal daily probability (ζ) to be pulled to the hospital-pen for cattle with clinical FMD.

In a hospital-pen, there was homogenous mixing of the cattle pulled from different home-pens that day. The susceptible cattle were infected via direct contact with infectious cattle (I_1 - I_3)

at a rate reflecting the homogenous mixing and density-dependent transmission (as in the home-pens), and with the same transmission parameter value, β_{hp} in the hospital-pen(s) = β_{wp} .

S-L Susceptible-Latent model of FMD infection dynamics in a hospital-pen l

$$\frac{dS_{hpl}}{dt} = \sum_{i=1}^m \varphi S_i - \beta_{hp} \sum_{i=1}^m \varphi S_i \left[\sum_{i=1}^m \varphi I_{1_i} + \sum_{i=1}^m \varphi I_{2_i} + \sum_{i=1}^m (\varphi + \varsigma) I_{3_i} \right]$$

$$\frac{dL_{hpl}}{dt} = \beta_{hp} \sum_{i=1}^m \varphi S_i \left[\sum_{i=1}^m \varphi I_{1_i} + \sum_{i=1}^m \varphi I_{2_i} + \sum_{i=1}^m (\varphi + \varsigma) I_{3_i} \right]$$

Where i is a home-pen, m is the number of home-pens from which cattle are pulled to the hospital-pen l , and φ and ς are defined in the preceding paragraph. All the parameters are also defined in **Table 3-1**. $m=n$ if the feedlot had one hospital-pen. The probability for a susceptible animal pulled to the hospital-pen l to be infected by FMD in the hospital-pen that day was:

$$p_inf_hp_l = \frac{\beta_{hp} \sum_{i=1}^m \varphi S_i \left[\sum_{i=1}^m \varphi I_{1_i} + \sum_{i=1}^m \varphi I_{2_i} + \sum_{i=1}^m (\varphi + \varsigma) I_{3_i} \right]}{\sum_{i=1}^m \varphi S_i}$$

The number of latent cattle returning to a home-pen i that were pulled a day earlier to the hospital-pen l while still susceptible and infected by FMD in the hospital-pen was

$$Bin\left(\varphi_{(t-1)} S_{i(t-1)}, p_inf_hp_{l(t-1)}\right).$$

i. Fence-line transmission via direct contact of cattle from contiguous home-pens

A fence-line contact between cattle from neighboring home-pens is typical on U.S. feedlots. Home-pens are separated by fences, which do not prevent animal nose-to-nose contact. The fence-line FMDv transmission between each two contiguous home-pens was modeled assuming a homogenous animal mixing and density-dependent transmission along the fence (equations 1 and 2). The effective contact rate fence-line was assumed to be 25% of that within the home-pens, $\beta_{bp} = \beta_{wp} \times 0.25$. Definitions and values of the parameters are given in **Table 3-1**. The number of cattle infected on a given day by FMD in a home-pen i via the fence-line transmission from a contiguous home-pen j (or home-pen h on the other side of i) was

$$S_i \beta_{bp} (I_1 + I_2 + I_3)_{j \text{ (or } h \text{)}}.$$

Environmental transmission due to pen-riders moving between home-pens

Beef feedlots in the U.S. employ personnel to visually monitor cattle health as an observational disease surveillance method; they are known as pen-riders, pen-checkers, or cowboys and move between the home-pens on foot or on horses. The home-pen floor materials attached to the pen-rider boots or horse hooves could serve as a fomite for FMDv transmission. Such environmental virus transmission between each two contiguous home-pens sequentially visited by a pen-rider in the same home-pen row was modeled (see Figures in Supplementary Materials for the feedlot layouts modeled). A possibility of such environmental transmission between the home-pen rows separated by feed-delivery or drover alleys was not modeled, assuming that majority of the floor materials picked up by a pen-rider in a home-pen are deposited in the next visited home-pen.

In the originating home-pen j we considered:

- The daily volumes of cattle secretions (saliva) and excretions (urine and feces) in which FMDv can be shed,
- The fractions of the secretions deposited into the home-pen environment and then on the floor (the excretions were assumed to be entirely deposited on the floor),
- The viral quantities shed per unit volume of each of the secretions and excretions by an animal in the clinical high infectious FMD stage (I₃),
- The floor size and floor top depth that can be contaminated by the secretions and excretions, and
- The daily viral decay in the floor materials were reflected to model the remaining viral load in the floor materials.

We assumed that only secretions and excretions from the I₃ cattle contributed to this transmission route. Each I₃ animal daily excreted *uri* urine and *fec* fecal volumes, and secreted *sal* saliva volume. We assumed that a fraction *fsal_env* of the daily saliva secreted by an animal was deposited into the home-pen environment and a fraction *fsal_env_floor* of that landed on the floor. The total daily volume of saliva deposited into the home-pen floor by the clinical high infectious cattle was $I_3 \times sal \times fsal_env \times fsal_env_floor$, of urine it was $I_3 \times uri$, and of feces it was $I_3 \times fec$. The virus quantity shed by a highly infectious animal with clinical FMD per unit volume of saliva was *salv*, per unit volume of urine it was *uriv*, and per unit volume of feces it was *fecv*. The deposited secretions and excretions from the I₃ were evenly distributed across the pen floor top in *j*. The viral decay in the resulting mixed floor materials occurred at a daily exponential rate *vir_dec_env*. The width of a home-pen was *w_pen*, the length was *l_pen*, and the contaminated floor top depth was *d_pen*. The remaining viral load in the contaminated floor-top materials in the home-pen *j* as

$$FMDv_floor_j = \left(\frac{I_{3_j} \times sal \times fsal_env \times fsal_env_floor \times salv + I_{3_j} \times uri \times uriv + I_{3_j} \times fec \times fecv}{w_pen \times l_pen \times d_pen} \right)^{-vir_dec_env}$$

We assumed that an amount σ of the virus-containing floor materials from the originating (visited by pen-riders first) home-pen j was transported on the boots of the pen-riders or hooves of the horses during each pen-rider round to the next – receiving – home-pen i in the same row. The pen-rider rounds through the home-pen row occurred twice per day. In the receiving home-pen i , we assumed that the maximum number of cattle that could be infected due to consumption of the transported contaminated materials was $\frac{FMDv_floor_j \times \sigma}{ID_{50} \text{ per oral}}$. The infections occurred on

the same day when the materials were introduced to i . The daily number of cattle in i infected via this route was modeled as $Bin \left[\left(\frac{FMDv_floor_j \times \sigma}{ID_{50} \text{ per oral}} \right), 0.5 \right]$ (equations 1 and 2). Definitions and

values of the parameters are given in **Table 3-1**.

Waterborne transmission

We assumed that only contiguous home-pens which shared a drinking water-trough were at risk of waterborne FMDv transmission (see Figures in Supplementary Materials for the feedlot layouts modeled). Potential waterborne transmission among home-pens that did not share a drinking water-trough was not modeled. Hospital-pens did not share drinking water-troughs with home-pens in feedlot layouts modeled. We assumed that a fraction ($fsal$) of the daily saliva secreted by an animal (sal) was deposited in the home-pen environment, of which a fraction $fsal_env_w$ was deposited in the drinking water-trough. We assumed that all the saliva deposited

into the home-pen environment was deposited in the water-trough or the floor, hence,

$fsal_env_w = 1 - fsal_env_floor$. We assumed that only saliva of the clinical high infectious cattle (I_3) contributed to this transmission route. Daily volume of saliva produced by an animal, the fraction of the daily saliva volume deposited into the home-pen environment and what fraction of that deposited in the shared water-trough(s) by the I_3 animals from the two home-pens that shared the water-trough, viral quantity shed per unit volume of saliva by an animal in the clinical high infectious FMD stage, volume of water in the shared water-trough, and viral decay in the water were reflected to model the remaining viral load in the water in the shared trough. A homogenous mixing of the deposited saliva with the water in the trough was assumed. The viral decay in the cattle drinking water occurred at a daily exponential rate vir_dec_w . The water volume in a shared trough was vol_watert . The home-pen i only shared a water-trough with one other home-pen j (here, either j or h could be on either side of i). If the home-pen i was at the end of the home-pen row in a row with odd number of home-pens, it did not share the water-trough with other home-pens and waterborne transmission was not modeled. The viral load per L of water in the water-trough shared by i and j was:

$$FMDv_watert_{i,j} = \left(\frac{(I_{3_i} + I_{3_j}) \times sal \times fsal \times fsal_env_w \times salv}{vol_watert} \right)^{-vir_dec_w}$$

We assumed an animal consumed at least 1 L of water every time they visited the water-trough. On each day when $FMDv_watert_{i,j}$ was $\geq ID_{50}$ of FMDv for oral exposure, the number of cattle infected by FMD in the home-pen i via consumption of contaminated water from that shared trough was modeled as a $Bin(S_i, 0.5)$ (equations 1 and 2). Definitions and values of the parameters are given in **Table 3-1**.

Airborne transmission

Airborne transmission was modeled using a kernel function that incorporated an exponential decay in the FMDv transmission probability with increasing Euclidian distance between home-pen centroids. Based on the feedlot layout detailed in the Supplementary Materials, we estimated the Euclidean distance between centroids of a home-pen i and k (where k is any other home-pen than i) and scaled it by the shortest Euclidean distance between any two home-pen centroids in the feedlot. The scaled distance between two home-pen centroids was $d_{i,k}$. The airborne transmission probability to a home-pen i depended on the distances to and proportions of FMD clinical highly infectious cattle (I_3) in the other home-pens. The proportion in a home-pen k was $\frac{I_{3,k}}{N_k}$. The probability of FMD infection of a susceptible animal in i via the

airborne transmission was $p_air_i = 1 - \left[\prod_{k=1}^n k \left(1 - \frac{I_{3,k}}{N_k} * e^{-\alpha * d_{i,k}} \right) \right]$, and the daily number of cattle

infected was $Bin(S_i, p_air_i)$ (equations 1 and 2). Value of the parameter α reflected the power of the kernel function (**Table 3-1**).

Outbreak characteristics analyzed

We defined the following characteristics of the projected FMD outbreaks, traced these outputs during the model simulations, and analyzed sensitivity of the outputs to the model structure and parameter values. The outbreak characteristics were:

- (1) Outbreak peak day defined as the day with the highest number of clinical cattle (those in the I_3 and C compartments) in the feedlot, counting from the day of introduction of FMD latent cattle into the index home-pen.

- (2) Number of clinical cattle in the feedlot on the outbreak peak day.
- (3) Day of outbreak detection in the feedlot, counting from the day of introduction of FMD latent cattle into the index home-pen. The detection was assumed to occur on the day when the proportion of clinical cattle in the index home-pen reached a detection threshold of 3%. (This detection threshold was chosen based on data provided via personal communication by veterinarians with experience of FMD investigation on cattle farms during the FMD outbreaks in South America in the 2000s)
- (4) Fraction of latent cattle in the feedlot on the day of outbreak detection.
- (5) Cumulative number of infected home-pens (a home-pen was counted on the day when FMD latent cattle occurred in it for the first time) in the feedlot throughout the outbreak.
- (6) Outbreak duration defined as the day when the last clinical infectious cattle became clinical non-infectious, counting from the day of introduction of FMD latent cattle into the index home-pen.

Model implementation, verification, and validation

The model was implemented in Vensim® PLE Plus Version 6.4a (Ventana Systems Inc., Harvard, MA, USA). The figures were made in R using the ggplot package and in Microsoft Office Power Point® 365 ProPlus (Microsoft, Redmond, WA, USA). The statistical analysis was done in STATA® 13 (StataCorp LP, College Station, TX, USA). Distances between home-pen centroids in each of the feedlot size and layout cases were estimated using Autodesk® Fusion 360 (Autodesk, Inc., San Rafael, CA, USA).

Model verification and validation were performed systematically during the model development and implementation process, *i.e.*, after adding each new component such as a virus

transmission route or a new module such as a section of the feedlot layout, and following recommended approaches (Garner and Hamilton, 2011; Reeves et al., 2011). Specifically, at each verification a dynamic approach described by Reeves et al. (2011) was used to confirm the model behavior and outputs were logical when giving extreme parameter value inputs. A population balance check was done for the total number of cattle in the feedlot on each day simulated. We conducted a conceptual validation that the model met the intended purpose which was to project FMDv transmission and clinical manifestation dynamics within the feedlot by capturing the effects of the different processes reflected in the model, and a face validation which consisted of an assessment of the system modeled and model outputs by experts in epidemiological models (Garner and Hamilton, 2011; Reeves et al., 2011).

Sensitivity analyses of the model outputs to the model structure and parameter values

i. Sensitivity analysis of the model outputs to the index home-pen location within the feedlot and time spent by individual cattle in the hospital pen per visit

Cattle with latent FMD were introduced into one home-pen; a proportion of cattle in the index home-pen were FMD-latent at the start of simulations on day 0. Three scenarios of the index home-pen location within the feedlot were modeled: S1 – index home-pen was located at the edge of the feedlot and shared a drinking water-trough with one contiguous home-pen; S2 – index home-pen was located at the edge of the feedlot and did not share a drinking water-trough with another home-pen; and S3 – index home-pen was located centrally within the feedlot and shared a drinking water-trough with one contiguous home-pen. In the base scenario individual cattle pulled to the hospital-pen on one day returned to the home-pen on next day (the beta

transmission parameter value for the FMD transmission via direct contact of cattle in the hospital-pen(s) per day was β_{hp}). In a comparative scenario, cattle spent a half day in the hospital-pen, returning to the home-pen same day when pulled (the transmission parameter value was $\beta_{hp}/2$). The model was simulated for each of the feedlot size and layout cases (detailed in Figures in the Supplementary Materials) with each of the three scenarios of the index home-pen location within the feedlot, and each of the two scenarios of the time spent by individual cattle in the hospital-pen per pull due to a production disease or FMD. For each case and scenario, 2,000 Monte Carlo simulations were performed and the FMD outbreak characteristics (listed in section 2.3) were traced during the simulations. After evaluating the model outputs and if there were no variations in the outputs, a base scenario of the index home-pen location and the time spent by individual cattle in the hospital-pen per visit was chosen based on closest representation to production systems. The base scenario was implemented in the remainder of the sensitivity analyses.

Sensitivity analysis of the model outputs to the parameter values

The model output sensitivity analysis to values of a set of target parameters was performed. Values from each of the target parameters were sampled for each of 2,000 Monte Carlo simulations of the model. The model was simulated for each specific feedlot size and layout case and the chosen base scenario of the index home-pen location and the time spent by individual cattle in the hospital-pen per visit. The sampled distributions of the target parameters are given in **Table 3-4**. For each of the remaining model parameters, a single value listed in **Table 3-1** was used for each of the 2,000 simulations. The target parameters included the FMD latent, infectious, and subclinical periods in individual cattle and cattle infectivity as a change in

the value of the beta transmission parameter within the home-pens, fence-line, and in the hospital-pen(s). The infection and disease temporal progression and infectivity could vary with the strain virulence (Cabezas et al., 2018). Thus, targeting these parameters in the sensitivity analysis allowed evaluating the model outputs for different FMDv strain virulence scenarios. The target parameter set also included the BRD morbidity in the first 30 days since the cattle placement in the feedlot. The morbidity increases the cattle pull rate to the hospital-pens, but it could vary depending on the feedlot production management and time of year. The target parameter set also included the initial proportion of FMD-latent cattle in the index home-pen, the fraction of daily saliva volume secreted by an animal that is deposited to the home-pen environment, the home-pen floor top depth contaminated by the animal secretions and excretions daily, the water intake per cattle visit to the drinking water-trough, the mortality rate for animals with BRD and other production diseases, the mortality rate for animals with clinical FMD, the urine volume produced by an animal, the saliva volume produced by an animal, the volume of feces produced by an animal, the virus quantity shed in urine by an animal in the FMD clinical high infectious status, the virus quantity shed in saliva by an animal in the FMD clinical high infectious status, the virus quantity shed in feces by an animal in the FMD clinical high infectious status, and the proportion of the cattle daily saliva volume deposited into the home-pen environment. (**Table 3-1**).

Sensitivity to the values of the target parameters was analyzed for outbreak peak day with highest number of clinical cattle and outbreak duration in the feedlot. Using the outputs of the 2,000 model simulations for each of the feedlot size and layout cases, statistical significance of a pair-wise association between the value of each of the target parameters and each the outbreak peak day or outbreak duration was tested with the Spearman rank correlation coefficient. The

pair-wise correlation was considered statistically significant if the p -value ≤ 0.05 . Also using the simulation outputs, a multivariable linear regression model was built to identify a parameter group most associated with each of outbreak peak day and outbreak duration. A predictor variable was excluded from the model if p -value > 0.05 for its association with the outcome variable. The predictor variable selection was performed using the backward stepwise regression and the final model was chosen based on largest adjusted R^2 value. The final multivariable linear regression model's adjusted R^2 statistic was partitioned to obtain the fractional contributions of the target parameters to the projected outcome variance.

An additional parameter-value sensitivity analysis was performed for the power (α) of the function of an exponential decay in the probability of airborne FMDv transmission with increasing distance between home-pens (see the Kernel function definition in the section 2.2, subsection v. Airborne transmission). The model simulations were performed similarly to that described above for the target parameter set; additionally to sampling the value of each of the target parameters, the value of α (the sampled values are given in **Table 3-4**) was sampled for each of the 2,000 Monte Carlo simulations of the model. The model was simulated for each of the feedlot size and layout cases for each of the three index home-pen location scenarios and assuming individual cattle spent one day in the hospital-pen pen visit. The outbreak duration distribution was summarized over the 2,000 simulated outbreaks with each value of α . The non-parametric Kruskal-Wallis test was used to test statistical significance of differences in the median outbreak duration with different values of α for a given scenario and for a given feedlot of size and layout case. If p -value ≤ 0.05 for the Kruskal-Wallis test, the Dunn's test with Bonferroni correction was conducted for the multiple comparisons.

Relative impact of the FMDv transmission routes on the outbreak duration

The model structure sensitivity analysis was focused on the relative impact of the five routes of FMDv transmission between home-pens on the outbreak duration. The five routes were the direct animal contact in the hospital-pen(s), fence-line direct contact, via shared drinking water-troughs, via environment by pen-riders, and airborne. The model was simulated for each of the feedlot size and layout cases for each of the three-index home-pen location scenarios and assuming individual cattle spent one day in the hospital-pen pen visit. The value of each of the target parameters (Table 3-4) was sampled for each of the 2,000 Monte Carlo simulations of the model, while setting to zero the parameter values related to one of the transmission routes. The outbreak duration distribution was summarized over the 2,000 simulated outbreaks for the full model and each of the reduced models with one of the routes of transmission excluded, for each feedlot size-layout case and index home-pen location scenario. The non-parametric Kruskal-Wallis test was used to test statistical significance of differences in the median outbreak duration between the full and reduced models and for a giving scenario for each of feedlot and layout cases. If $p\text{-value} \leq 0.05$ for the Kruskal-Wallis test, the Dunn's test with Bonferroni correction was conducted for the multiple comparisons.

Results

Characteristics of projected FMD outbreaks in feedlots of different sizes and layouts

There was no significant variation in the outbreak characteristics among the three scenarios of the index home-pen location within the feedlot, in any of the feedlot size and layout

cases modeled (detailed in Figures in the Supplementary Materials). There was also no significant variation in the outbreak characteristics when individual cattle were assumed to spend a full day vs. a half of day in the hospital-pen per visit, in any of the feedlot size and layout cases and index home-pen location scenarios. In the light of this, we chose the base scenario of the FMD latent cattle introduced in an index home-pen that was located centrally within the feedlot and shared a drinking water-trough with one contiguous home-pen (S3 scenario) and cattle spending a full day in the hospital-pen per visit. Under the base scenario, 2,000 Monte Carlo simulations of the model with sampling the values of the target parameters were performed for the feedlot of each size and layout modeled. The percentiles of the projected numbers of FMD susceptible, latent, subclinical, clinical, and recovered cattle on each day of the outbreak over the 2,000 model simulations in each of the feedlot size and layout cases are shown in Figure 3-3. The distribution of the projected number of cattle with clinical FMD on the outbreak peak day in the feedlot is shown in **Figure 3-4**. The percentiles of the projected cumulative number of home-pens with FMD-latent cattle in the feedlot on each day is shown in **Figure 3-5**. Characteristics of the projected outbreaks are also summarized in **Table 3-2**. The feedlot size refers to the number of home-pens and total cattle head count (200 cattle per home-pen in all the layouts). The layouts are detailed in the Supplementary Materials. In short, FS1 was a 4,000 cattle (20 home-pens) feedlot with 1 hospital-pen; FM1 was a 12,000 cattle (60 home-pens) feedlot with 1 hospital-pen; FM2 was a 12,000 cattle feedlot with 2 hospital-pens; FL1 was a 24,000 cattle (120 home-pens) feedlot with 2 hospital-pens; and FL2 was a 24,000 cattle feedlot with 4 hospital-pens.

The projected outbreak duration ranged from 49 days in the smallest FS1 to 82 days in the largest FL2 feedlot. The outbreak peak day ranged from 23 in FS1 to 49 days in FL2. The outbreak proceeded slower and lasted longer in a feedlot of a given size if more hospital-pens

were operated. The median outbreak duration was 16 days longer in a medium-size feedlot FM2 where 2 hospital-pens were operated compared to FM1 where 1 hospital-pen was operated (**Table 3-2**). In a large-size feedlot, the median outbreak duration was 9 days longer if 2 hospital-pens per section of home-pens were operated (4 hospital-pens total, FL2), compared to 1 hospital-pen per section (2 hospital-pens total, FL1) (Table 2). All home-pens were infected by day 15 following introduction of FMD latent cattle onto the feedlot in FS1, on day 22 in FM1 vs. day 40 in FM2, and on day 37 in FL1 vs. day 46 in FL2 case (Fig. 5). The number of clinical cattle on the outbreak peak day decreased with a larger number of hospital-pens (**Figure 3-4**). The median number of clinical cattle on the outbreak peak day was 1,760 (44%) in FS1, 5,520 (46%) in FM1 vs. 2,880 (24%) in FM2, and 6,240 (26%) in FL1 vs. 5,520 (23%) in FL2. Thus, a higher number of hospital-pens had a larger impact on the FMD outbreak dynamics – slowing the outbreak and decreasing the percentage of clinical cattle on the peak day – in a medium-size (12,000 cattle) than in a large-size (24,000 cattle) feedlot, for the layouts modeled.

FMD outbreak detection

The outbreak detection was assumed to occur on the day when the proportion of cattle with clinical FMD in the index home-pen reached 3%. The detection timeline was therefore similar for all the feedlot size and layout cases. The results presented are for the base scenario of FMD latent cattle introduced in an index home-pen that was located centrally within the feedlot, shared a drinking water-trough with one contiguous home-pen, and pulled cattle spent a full day in the hospital-pen per visit. The results are summarized over the 2,000 model simulations performed with sampling the values of the target parameters for each feedlot size-layout case. The day of detection ranged from 4 to 12 days since introduction of FMD latent cattle in the

index home-pen (**Table 3-2**). Detection on day 4 occurred in 12%, on days 5 and 6 in 60%, on day 7 in 11%, and between days 8 and 12 in 17% of the simulated outbreaks. Overall, the longer it took to detect the outbreak, the larger was the fraction of latent cattle in the feedlot at detection; however, the relative magnitude of this impact declined with the feedlot size. The fraction of latent cattle in the smallest FS1 feedlot increased from 2% at detection on day 4 to 28% on day 12. In both FM1 and FM2, the fraction of latent cattle increased from 1% at detection on day 4 to 9% on day 12, while in both FL1 and FL2 it increased from 1% on day 4 to only 4% on day 12. The median fractions of latent cattle on days 5 and 6 (when the outbreak was most commonly detected, in 60% of the simulated outbreaks) were 4% and 10% in FS1, 1% and 3% in both FM1 and FM2, and 1% and 2% in both FL1 and FL2 (**Table 3**).

Sensitivity of the projected outbreak characteristics to the model parameter values

Of the target parameters for the sensitivity analysis for the base scenario, the durations of the FMD infection stages in individual cattle were most influential on the outbreak duration and outbreak peak day in the feedlot (**Table 3-4** and **Figure 3-6**). Using the simulation outputs, a multivariable linear regression model was built for each the outbreak duration and peak day of outbreak variables with the target parameters as the predictor variables (**Table 3-4**). The duration of the FMD latent period was the most influential parameter. The fractional contribution of the latent period duration to the variance in the outbreak duration ranged from 53% in FS1 to 66% in FM1, and to the variance of the outbreak peak day it ranged from 4% in FM2 to 42% in FS1 (**Figure 3-6**). The duration of the FMD infectious period was the second most influential parameter. Its fractional contribution to the variance in the outbreak duration ranged from 25% in FS1 to 20% in FM1. The infectious period contribution to the outbreak duration variance

decreased with a larger feedlot size and for a feedlot of a given size decreased if more hospital-pens were operated. This contribution was 25% for FS1, 20% for FM1 vs. 5% for FM2, and 13% for FL1 vs. 9% for FL2 (**Figure 3-6**). The subclinical period was less influential compared to the latent and infectious periods with a fractional contribution of 5% or less for both outcomes in all feedlots modeled.

A larger value of the beta transmission parameter (β_{wp}) reflected a higher cattle infectivity for FMDv transmission via direct contact in the home-pens, fence-line, and in hospital pen(s). A larger value of this parameter was negatively correlated with each the outbreak duration and outbreak peak day (Table 3-4). This appears straightforward that a higher virus transmission rate via direct animal contact could lead to a faster outbreak progression. However, the relative contribution of β_{wp} to the total variance in either the outbreak duration or outbreak peak was $\leq 5\%$, low compared to that of the durations of the FMD infection stages in individual animals (Figure 3-6).

The initial fraction of FMD-latent cattle in the index home-pen had smaller fractional contributions to the variances in the outbreak duration and outbreak peak day compared to the parameters related to the FMDv durations of the infection stages and cattle infectivity via direct contact (Figure 3-6). The contribution of the initial FMD-latent fraction to the outbreak duration decreased with a larger feedlot size and in a medium-size feedlot was lower if more hospital-pens were operated. This contribution was 24% for FS1 and 11% for FM1, but it was $<4\%$ for FM2 and both FL1 and FL2 (Figure 3-6).

The morbidity rate of BRD during the first 30 days since cattle placement in the feedlot was weakly correlated with both outcomes in each of the feedlot size and layout cases (Table

3-4). The fractional contribution of the BRD morbidity to the variance in the outbreak duration ranged from 1% to at most 17% in FM1 (Figure 3-6).

Target parameters were those which values were initially assigned based on our judgment in the absence of data (Table 3-1). This included the fraction of daily saliva secreted by an animal that is deposited to the home-pen environment; the home-pen floor top depth daily contaminated by the animal secretions and excretions; and the water intake per cattle visit to the drinking water-trough. The values of each of these parameters had low correlations with the outbreak duration and outbreak peak day (Table 3-4), and low fractional contributions to the variances in these outcomes (Figure 3-6) across the feedlot size and layout cases. The remainder of investigated target parameters were found to be not influential to model outputs (results not shown) and are not discussed in the rest of the manuscript. These target parameters included: the mortality rate for animals with BRD and other production diseases, the mortality rate for animals with clinical FMD, the urine volume produced by an animal, the saliva volume produced by an animal, the volume of feces produced by an animal, the virus quantity shed in urine by an animal in the FMD clinical high infectious status, the virus quantity shed in saliva by an animal in the FMD clinical high infectious status, the virus quantity shed in feces by an animal in the FMD clinical high infectious status, and the proportion of the cattle daily saliva volume deposited into the home-pen environment.

Relative impact of individual routes of FMDv transmission between home-pens on the outbreak duration

The results presented are for the base. For each feedlot size-layout case, 2,000 model simulations were performed with sampling the values of the target parameters, and also setting to

zero the parameter values related to one of the between-pen FMDv transmission routes. Exclusion of the transmission via environment by pen-riders or the transmission via contaminated drinking water in the shared water-troughs did not result in a substantially different median outbreak duration or outbreak peak day (each $p > 0.05$ for the post-hoc multiple comparisons test) compared to that in the full models across the feedlot size and layout cases (Figure 3-7). Exclusion of the FMDv transmission via direct contact of cattle from different home-pens in the hospital-pen(s) resulted in a significantly longer median outbreak duration ($p < 0.001$ for the post-hoc multiple comparisons test) in FM1, FM2, and FL1 compared to the full models. The median outbreak duration in FM1 was 27 days longer, in FM2 it was 11 days longer, and in FL1 it was 10 days longer if the β_{hp} was set to 0 (Figure 3-7). Exclusion of the transmission via fence-line direct animal contact resulted in a significantly longer median outbreak duration ($p < 0.001$ for the post-hoc multiple comparisons test) in all the feedlot size and layout cases, with largest differences in FM2, FL1, and FL2. Specifically, the median outbreak duration in FM2 was 19 days longer, in FL1 it was 7 days longer, and in FL2 it was 12 days longer (Figure 3-7). Exclusion of the airborne transmission resulted in a significantly shorter or longer median outbreak duration ($p < 0.001$ for the post-hoc multiple comparisons test), depending on the feedlot size and layout. The median outbreak duration in FS1 was 6 days longer, in FM1 was 3 days shorter, but in FM2 it was 15 days shorter, in FL1 it was 11 days shorter, and in FL2 it was 23 days shorter (Figure 3-7). This occurred because in the FM2, FL1, and FL2 layouts (where 1-2 hospital-pens were operated for each of the home-pen sections) the airborne transmission was the only route of the FMDv transmission between the sections of the home-pens.

Impact of the power (α) of the function of an exponential decay in the probability of airborne FMDv transmission with increasing Euclidean distance between home-pen centroids on the outbreak duration

The results presented are for the base scenario. Additionally, for each simulation a different power [α , modified from Boender et al. (2010)] was specified for the Kernel function of an exponential decay in the probability of airborne FMDv transmission with increasing distance between home-pen centroids. The values of α modeled were: -3, -3.5 (baseline), -4, -4.5, and -5; higher values of α represents a higher intensity of airborne transmission. There were no significant differences in the median outbreak duration ($p > 0.05$ for the post-hoc multiple comparisons test) in FS1, FM1, and FM2 with a change in the value of α (Figure 3-8). In FL1 and FL2, a higher value of α decreased the projected duration of the outbreak. In FL1, the median outbreak duration was 68 days for the highest value of α (-3) and 82 days with a value of α of -5 (Figure 3-8). Similarly, in FL2 the median duration of the outbreak was 77 days for values of α -3 and 92 for values of α of -5 (Figure 3-8).

Discussion

The projected outbreak duration was shorter for those feedlots that operated with one hospital-pen and one section of home-pens because cattle from the whole feedlot mixed within a single hospital-pen. Our results suggest that reduction of interaction within the feedlot might help to decrease the speed of the outbreak; however, it should be noted that all home-pens were infected in all feedlots modeled despite the difference in population size, sections of home-pens per hospital-pen, or number of hospital-pens. If no intervention strategies are implemented, rapid

progression of infection/disease might be the best scenario to clear out disease and infection more rapidly from the population as this will also impact between-farm transmission.

The outbreak peak day was found to be earlier in the outbreak in feedlots with fewer cattle and with one hospital pen (FS1 and FM1) because the outputs suggested a more pronounced outbreak curve for clinical cattle compared to feedlots with more hospital pens (FM2, FL2, and FL1) which were found to have bi-modal curves; limiting differences in the number of cattle in the clinical stage during the outbreak. The number of clinical cattle at the outbreak peak day was lower in those feedlots with more hospital pens (FM2, FL1, and FL2) which can be a result of the spatial segregation of cattle to more areas within the feedlot and therefore the longer time the infection took to reach other sections in the feedlots

The day of detection was estimated to be day 4-12 and was highly associated with the initial number of latent animals at the beginning of the simulations. In available data on herd level detection of outbreaks, time to detection was estimated to be 21 days during the UK 2001 epidemic (Gibbens et al., 2001) and 13 days in bovine farms during the 2010/2011 Korean epidemic (Yoon et al., 2013). McLaws and Ribble (2007) reviewed the time to detection for outbreaks in non-endemic areas during 1992 to 2003; it varied from 7 to 24 days and reasons for delayed detections found were misdiagnosis of the disease, mild clinical signs (in small ruminants), laboratory confirmation, and deliberate underreporting by farmers. Other herd level modeling studies have suggested the mean time to detection to be around day 10-11 (McReynolds et al., 2014), day 6-7 (Schoenbaum and Disney, 2003), and day 10-13.5 (Carpenter et al., 2004). We modeled the day of detection based on identification of clinical signs by observational surveillance of pen-riders which are generally experienced in identifying diseased cattle in feedlots. It is important to consider the differential diagnosis as there are various

diseases with similar symptomatology as mentioned by Coetzer and Tustin (2004) which can delay the time to detection in the field. Nelson et al. (2017) suggests the possibility to use qPCR to identify FMDv during the pre-clinical stage. Modeling early detection with the use of a surveillance test in targeted situations could potentially decrease time to detection however no practical surveillance test for FMD in cattle is currently available. Our simulations suggest that proportion of latent cattle can substantially increase from day 4 to 12. This had a larger impact in small-size feedlots which in worst-case scenario (detection on day 12) we can expect up to 28% of the population already infected according to our simulations. Carpenter et al. (2004) modeled within-herd transmission within a 1,000-dairy farm; their simulations suggested that between 65% to 97% of cattle in the farm would be already infected by the day of detection using a 1% and 5% detection threshold. However, the contact structure in dairy farms differs compared to beef feedlots. Herd level FMD modeling studies has shown that early detection has a large impact on the scale of the outbreak and the success of intervention strategies (Thornley and France, 2009; Tildesley et al., 2012; Ward et al., 2009).

We found that the model was sensitive to changes in the latent and infectious periods which suggests that characteristics of the strain could impact the transmission dynamics within the feedlot. Our sensitivity analysis suggests that the latent period and fraction of latent animals at the beginning of simulations had an impact on the outbreak peak day. Longer latent periods were associated with delaying the outbreak peak day since animals took longer to become infectious and therefore the clinical stage was also delayed. Surprisingly, the fraction of latent cattle and the BRD morbidity rates were found to be poorly influential with the outcomes modeled. We modeled BRD as the main risk factor for animal mixing in the hospital-pen during the first 30 days post cattle arrival only which is on average the highest risk period to develop

BRD in beef feedlots (Cusack et al., 2003; Smith, 1998; Smith et al., 1994; Wolfger et al., 2015) although that risk can be affected by several other factors (Buhman et al., 2000; Cernicchiaro et al., 2012a; Cernicchiaro et al., 2012b; Sanderson et al., 2008) which we have not considered in our model.

To our knowledge, there is no other study that assess within-farm transmission for FMD in beef feedlots. A study conducted by Kinsley et al. (2018) evaluated within-farm dynamics in swine farms. They estimated a shorter day of peak of the outbreak compared to ours. They also estimated that the mean time of detection for within-herd FMD in swine farms based on observation of clinical signs ranged from 3 to 12 days. However, comparison between both studies are challenging due to differences in contact structure and the transmissibility via different routes in swine farms compared to beef feedlots. Also, swine are known to shed the virus in much larger quantities to the environment compared to cattle (Alexandersen et al., 2003a; Alexandersen et al., 2003b; Coetzer and Tustin, 2004) which can contribute to the rapid spread of the infection across the farm

For the indirect routes of transmission (waterborne, pen-rider, and airborne) we only considered the contribution of cattle at the clinical high-infectious stage because they shed the virus in all excretions and secretions (Coetzer and Tustin, 2004; Mahy, 2005; Nelson et al., 2017); the amount of virus shed to the environment by clinical diseased cattle has been previously reviewed (Alexandersen et al., 2003b; Bartley et al., 2002; Bravo de Rueda et al., 2014; Suttmoller and Vose, 1997). We attempted to model transmission of contaminated material by pen-riders within the feedlots. Pen-riders represent the first line of surveillance as they monitor cattle for endemic disease within the feedlot (Smith, 2017). We adopted the simplifying assumption that the FMDv containing animal secretions and excretions were evenly distributed

in the home-pen though this is unlikely. We modeled transmission via contaminated water-troughs in those contiguous home-pens that shared water-troughs only. Our aim was to model waterborne transmission from an infected home-pen to a susceptible home-pen. We simplified this transmission route by modeling exposure of cattle to contaminated water and not modeling specific factors related to drinking behavior; however, future models could incorporate drinking behavior of cattle as it has been shown to be highly variable (Shane et al., 2016). Nonetheless, feeding and drinking behavior during the progression of FMD infection not been sufficiently described in literature. The local sensitivity analysis showed that both transmission of contaminated materials by pen-riders and transmission via contaminated water-troughs did not substantially contribute to FMD transmission between home-pens as the projected duration of the outbreak was similar when compared to the models with all the routes of transmission.

The effect of airborne transmission had a larger impact on FS1 compared to the other feedlots which may be explained by the closer spatial proximity of the home-pens compared to the other feedlots modeled. In feedlots with more sections of home-pens (FM2, FL1, and FL2) airborne transmission was responsible for spreading infection between sections of home-pens. In the event of an outbreak in U.S. beef feedlots, additional routes of transmission such as equipment and personnel movement would likely contribute to spread within the farm. These were not captured in the current model due to the lack of data. Mixing in the hospital-pen(s) had a larger impact in those feedlots that operated one section of home-pens per hospital-pen which was expected due to the possibility of all home-pens moving cattle into the hospital-pen. Direct contact through fence-line was found to be influential in all feedlots modeled however we assumed an arbitrary value for decreased direct contact rate through fence-line compared to

within home-pen direct contact. Transmission via this route should be explored more carefully in future models.

On the other hand, it is important to point-out that we used a modified value for the power (α) of the function of an exponential decay in the probability of airborne FMDv transmission with increasing scaled distance between home-pens in our kernel function from Boender et al. (2010). They considered all routes of transmission in their kernel function while we only considered airborne transmission. For that reason, we investigated the impact of varying values for α on the projected duration of the outbreak. We found that even extreme values of α (-3 and -5) had only a modest impact on the projected duration of the outbreak suggesting our choice of α did not influence our conclusions. It is important to highlight that airborne transmission in U.S. beef feedlots might play a large role in spreading the infection because of the large concentration of cattle within a defined geographical area. For instance, a simulation study by Donaldson and Alexandersen (2002) suggested that 100 infected cattle at a source would be enough for the virus to travel up to one km and infect a susceptible host which might suggest that within a medium to large beef feedlot, airborne transmission by itself can be responsible to spread the infection to the entire population. On the other hand, environmental conditions can severely impact the viability of the virus in the environment. Moreover, other factors such as seasonality and geographical location of the feedlot within the country have to be taken into account as they have been suggested to increase the risk of FMD airborne transmission (Hagerman et al., 2018).

We used data mostly from Serotype O which is the most widely prevalent serotype (Brito et al., 2017; Grubman and Baxt, 2004), and it has been responsible for epidemics in developed countries with large livestock industries such as the UK, France, The Netherlands, South Korea,

and Japan (Bouma et al., 2003; Chmitelin and Moutou, 2002; Davies, 2002; Gibbens et al., 2001; Nishiura and Omori, 2010; Yoon et al., 2015); however, we performed a sensitivity analysis for the duration of the FMD stages of infection and disease progression, the beta transmission parameter, and also an analysis for the values of α for airborne transmission which allowed us to account for potential differences in the transmission characteristics of different FMD strains. Given that the last documented outbreak in the U.S. was in 1929 (Mohler, 1930), it is important to highlight that an introduction of any FMDv strain might severely impact the livestock sector in the U.S. due to costs related to restrictions of international trade, depopulation, and production losses (USDA, 2014).

We considered multiple compartments during the infectious stage (I_1, I_2, I_3) because it has been shown in experimental studies that shedding of the virus to the environment can start before the clinical stage (Alexandersen et al., 2003a; Burrows, 1968; Nelson et al., 2017; Onozato et al., 2014; Orsel et al., 2009; Pacheco et al., 2016). Although we parameterized the model with equal transmission parameters for the three infectious stages which might lead to an overestimation of the within-herd FMD transmission as suggested by Kinsley et al. (2018), we believe that was not the case in the outputs reported because the three stages were modeled within the length of the infectious period (subclinical + clinical infectious) used to parameterize the model. Moreover, as more data related to FMDv transmission parameters for the different infectious stages become available, our model can be used in the future to understand the contribution of each infectious stage to the transmission dynamics in U.S. beef feedlots. We modeled the feedlots as a closed system in which incoming and outgoing animals during the simulations were not considered. While U.S. feedlots generally have continuous turnover of cattle, once FMD was diagnosed quarantine would result in quarantine of the infected feedlot.

Finally, the presented model is consistent with data available to date but can be improved with better data on FMDv survival in within-feedlot environments (*e.g.*, in cattle manure and drinking water); FMDv infectious dose depending on the exposure route for beef feedlot cattle that are healthy or experience common production diseases; clinical presentation of FMD in such cattle depending on the strain virulence; potential for the virus airborne transmission in areas where the U.S. beef industry is concentrated; and sensitivity of the routine production disease surveillance system based on visual observation of large cattle populations to detect FMD introduction.

Conclusions

This is the first model projecting FMD transmission, infection, and clinical manifestation dynamics on contemporary U.S. beef cattle feedlots and accounting for the population structure. Our findings highlight the importance of understanding the complex contact structure in the cattle meta-populations within feedlots for projecting possible dynamics of FMD and other infectious diseases. The lack of such understanding limits the realism and granularity of current models of within farm transmission of foreign animal diseases if introduced to the U.S. The developed model will be used to project and compare impacts of FMD control such as cattle depopulation, within-feedlot movement restrictions, and vaccination strategies on the outbreak progression. Finally, we emphasize that although mathematical models are powerful tools to understand complex systems, they are simplified representations of real-life systems.

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Author contributions

VVV conceived the study. MWS and VVV designed the study. All authors contributed to the development, implementation, and analysis of the models and the output interpretation. AHC implemented the models and performed the sensitivity analyses. All authors wrote the manuscript, read and approved the final version for publication.

Conflict of interest

None.

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Table 3-1 Definitions and values of parameters used in modeling potential foot and mouth disease transmission, infection, and clinical manifestation dynamics on U.S. beef cattle feedlots

Parameter	Definition (units)	Mean value and distribution	References ¹
Within a home-pen			
<i>lat_initial</i>	Initial proportion of latent cattle in the index-pen	0.05, Vector (0.005, 0.105, 0.020)	Assumed
β_{wp}	Beta transmission parameter for virus transmission via direct animal contact in a home-pen (animal ⁻¹ day ⁻¹)	0.026, Triangular (0.020, 0.026, 0.031)	Derived from Chis Ster et al. (2012)
<i>lat</i>	Duration of latent period (days)	3.2, Weibull (α 1.782, β 3.974)	Mardones et al. (2010)
<i>sub</i>	Duration of subclinical period (days)	2.0, Gamma (α 1.222, β 1.672)	Mardones et al. (2010)
<i>inf</i>	Duration of infectious period (days)	4.0, Gamma (α 3.969, β 1.107)	Mardones et al. (2010)
<i>cli</i>	Duration of clinical period (days)	7.5, Fixed	(DEFRA, 2005)
<i>cliinf</i>	Duration of clinical infectious period (days)	(inf-sub) in each model simulation	
<i>clinon_inf</i>	Duration of clinical non-infectious period (days)	(cli-clininf) in each model simulation	
δ	Rate of progression to subclinical low infectious status (day ⁻¹)	1/lat	
θ	Rate of progression to subclinical high infectious status (day ⁻¹)	1/(sub/2)	
ε	Rate of progression to clinical high infectious status (day ⁻¹)	1/(sub/2)	
γ	Rate of recovery from being infectious (day ⁻¹)	1/cliinf	
τ	Rate of recovery from clinical disease after recovering from being infectious (day ⁻¹)	1/clinon_inf	
π	Morbidity rate for bovine respiratory disease (BRD) during the first 30 days since cattle placement in the feedlot	0.162, Vector (0.050, 0.300, 0.050)	(USDA, 2011)
ρ	Morbidity rate for other production diseases during the	0.1280, fixed	(USDA, 2011)

	200 days since cattle placement in the feedlot		
<i>brdtrt</i>	Probability for an animal with BRD to be pulled to a hospital-pen for treatment during the disease course (dmnl)	0.8750, fixed	(USDA, 2011)
<i>endtrt</i>	Probability for an animal with other than BRD production diseases to be pulled to a hospital-pen for treatment during the disease course (dmnl)	0.6908, fixed	(USDA, 2011)
$\varphi_{t=1 \text{ to } 30}$	Per-animal pull rate from a home-pen to hospital-pen due to BRD and other production diseases during the first 30 days since cattle placement in the feedlot (day^{-1})	0.0052	Calculated, $\left(\frac{\pi * brdtrt}{30}\right) + \left(\frac{\rho * endtrt}{200}\right)$
$\varphi_{t=31 \text{ to } 200}$	Per-animal pull rate from a home-pen to hospital-pen due to production diseases between the days 31 and 200 since cattle placement in the feedlot (day^{-1})	0.0004	Calculated, $\frac{\rho * endtrt}{200}$
ζ	Per-animal pull rate from a home-pen to hospital-pen due to clinical FMD (day^{-1})	0.02800	Expert opinion
μ	Mortality rate for animals with BRD and other production diseases (endemic infectious diseases and noninfectious diseases) (day^{-1})	Triangular (0.01, 0.03, 0.05)	Expert opinion
ψ	Mortality rate for animals with clinical FMD (day^{-1})	Triangular (0, 0.005, 0.010)	Expert opinion
Between home-pens			
In hospital-pen(s)			
β_{hp}	Beta transmission parameter for virus transmission via direct animal contact in a hospital-pen ($\text{animal}^{-1} \text{ day}^{-1}$)	Same as β_{wp}	Derived from Chis Ster et al. (2012)
Fence-line			
β_{bp}	Beta transmission parameter for virus transmission via fence-line direct animal contact ($\text{animal}^{-1} \text{ day}^{-1}$)	$\beta_{wp}/4$	Assumed (β_{wp} derived from Chis Ster et al. (2012))
Environmental by pen-riders			
<i>uri</i>	Urine volume produced by an animal (L/ day)	Uniform (8.8, 22.0)	(Alexandersen et al., 2003)
<i>sal</i>	Saliva volume produced by an animal (L/ day)	Uniform (98, 190)	(Alexandersen et al., 2003)

<i>fec</i>	Volume of feces produced by an animal (kg/ day)	Uniform (14, 45)	(Alexandersen et al., 2003)
<i>uriv</i>	Virus quantity shed in urine (plaque forming units (PFU)/mL) by an animal in the FMD clinical high infectious status	Uniform ($10^{2.5}$, $10^{5.5}$)	(Alexandersen et al., 2003)
<i>salv</i>	Virus quantity shed in saliva (PFU/mL) by an animal in the FMD clinical high infectious status	Uniform (10^6 , 10^8)	(Alexandersen et al., 2003)
<i>fecv</i>	Virus quantity shed in feces (PFU/mL) by an animal in the FMD clinical high infectious status	Uniform (10^2 , $10^{4.1}$)	(Alexandersen et al., 2003)
<i>fsal_env</i>	Proportion of the cattle daily saliva volume deposited into the home-pen environment (dmnl)	0.3, Vector (0.1, 0.5, 0.1)	Assumed
<i>fsal_env_floor</i>	Proportion of <i>fsal</i> that lands on the floor (dmnl)	0.33	Assumed
<i>vir_dec_env</i>	Virus decay rate in the home-pen floor environment (day^{-1})	0.28, Fixed	(Schijven et al., 2005)
σ	Amount of the home-pen floor materials moved daily to the next home-pen in the row by pen-riders (g/day) (300 g per pen-rider round, 2 rounds per day)	600, Fixed	Assumed
<i>w_pen</i>	Width of a home-pen (m)	61.0, Fixed	Typical Industry value
<i>l_pen</i>	Length of a home-pen (m)	75.2, Fixed	Typical Industry value
<i>d_pen</i>	Depth of a home-pen floor top contaminated with the animal fresh secretions and excretions (m)	0.02, Vector (0.02, 0.05, 0.03)	Expert opinion
<i>min_oral</i>	Minimum infective dose of FMDv via oral exposure in cattle (PFU/mL)	10^6 , Fixed	(Sellers, 1971)
Via shared water-troughs			
<i>fsal_env_w</i>	Proportion of <i>fsal</i> that lands in the water-trough (dmnl)	(1- <i>fsal_env_floor</i>)	Assumed
<i>vir_dec_w</i>	Virus decay rate in water (day^{-1})	0.12, Fixed	(Schijven et al., 2005)
<i>vol_watert</i>	Volume of the water trough shared between two home-pens (L)	6,000, Fixed	Expert opinion
<i>min_oral</i>	Minimum infective dose of FMDv via oral exposure in cattle (PFU/mL)	10^6 , Fixed	(Sellers, 1971)
Airborne			

α	Power of the exponential function of decay in the airborne transmission with increasing distance between home-pen centroids (dmnl)	-3.5, Fixed	(Boender et al., 2010)
$\frac{I_{3k}}{N_k}$	Proportion of clinical infectious cattle in a home-pen k	Modeled	
$d_{i,k}$	Scaled distance between centroids of a home-pen i and home-pen k (k is any other home-pen than i) (dmnl)	1.0 to 22.4, Fixed	Euclidean distance between each two home-pen centroids scaled by the shortest Euclidian distance between two home-pen centroids in the feedlot

¹ In the reference column: “Assumed” refers to parameter values assigned based on our knowledge/judgement. “Derived from [x]” refers to values that we estimated based on data in the cited references. “[x]” is the reference from which the value was adopted directly. “Expert opinion” refers to values obtained via personal communication with experts in the feedlot industry.

PFU, plaque forming units

Table 3-2 Characteristics of projected foot and mouth disease outbreaks on a U.S. beef cattle feedlot.

Feedlot	Number of home-pens	Total number of cattle	Number of sections of home-pens	Number of hospital-pens	Outbreak duration ¹ , days (10 th , 50 th , and 90 th percentiles of $n=2,000$ simulated outbreaks)	Outbreak peak day with highest number of cattle with clinical FMD (10 th , 50 th , and 90 th percentiles of $n=2,000$ simulated outbreaks)	Range of day of outbreak detection ² (based on $n=2,000$ simulated outbreaks)
FS1	20	4,000	1	1	39, 49, 59	21, 23, 27	4-12
FM1	60	12,000	1	1	46, 58, 69	25, 28, 33	4-12
FM2	60	12,000	1	2	61, 74, 89	26, 31, 43	4-12
FL1	120	24,000	2	2	60, 73, 86	33, 41, 48	4-12
FL2	120	24,000	2	4	68, 82, 95	42, 49, 57	4-12

¹ Outbreak duration was defined as the number of days since introduction of FMD latent cattle in the index home-pen on the feedlot until the last animal infected within the feedlot proceeded from the clinical high infectious stage to the clinical non-infectious stage.

² Outbreak detection was assumed to occur via routine visual surveillance of cattle health by the pen-riders, on the day when proportion of cattle with clinical FMD in the index home-pen reached 3%. This detection threshold was assumed to be independent of the feedlot size (cattle head count).

Table 3-3 Estimated percentage of cattle with latent foot-and-mouth disease on a U.S. beef cattle feedlot depending on the outbreak detection day since FMD introduction

Feedlot ¹	Percentage (%) of latent cattle in the feedlot on the day of FMD outbreak detection (10 th , 50 th , 90 th percentiles of $n=2,000$ simulated outbreaks) ²								
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
FS1	<1,2,3	<1,4,7	1,10,14	2,14,18	6,18,24	13,24,25	18,25,26	24,26,29	25,28,36
FM1	<1,1,1	<1,1,2	0,3,4	1,5,5	3,6,6	4,6,7	6,7,9	7,8,10	8,9,12
FM2	<1,1,1	<1,1,2	0,3,4	1,5,5	3,6,6	4,6,7	6,7,8	7,8,9	8,9,12
FL1	<1, <1, <1	<1,1,1	0,2,2	1,2,3	1,3,3	2,3,4	3,4,4	3,4,5	4,4,6
FL2	<1, <1, <1	<1,1,1	0,2,2	1,2,3	1,3,3	2,3,4	3,4,4	3,4,5	4,4,6

¹ Feedlot sizes and layouts modeled are detailed in Table 2 and Figure S1 in the Supplementary Materials.

Briefly, FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen).

² The outbreak detection occurred between day 4 and 12 post-introduction of FMD latent cattle in the index home-pen, when summarized for $n=2,000$ simulated outbreaks in every of the feedlot size and layout cases sampling the values of target parameters.

Table 3-4 Target parameters investigated for associations with the projected outbreak’s peak day with highest number of clinical cattle since foot-and-mouth disease introduction and the total outbreak duration on a U.S. beef cattle feedlot

Target parameter*	Parameter value distribution	Strength of the correlation (Spearman correlation coefficient value) between the model parameter value and outcome variable value for the feedlot of that size and layout									
		Peak day of the outbreak ¹					Duration of the outbreak				
		FS1 ²	FM1	FM2	FL1	FL2	FS1	FM1	FM2	FL1	FL2
Beta transmission parameter in home-pens (β_{wp})	Triangular (0.02, 0.026, 0.031)	$\bar{-}$ 0.14*	$\bar{-}$ 0.21*	$\bar{-}$ 0.09*	$\bar{-}$ 0.09*	$\bar{-}$ 0.10*	$\bar{-}$ 0.05*	$\bar{-}$ 0.08*	$\bar{-}$ 0.14*	$\bar{-}$ 0.09*	$\bar{-}$ 0.08*
Bovine respiratory disease morbidity during the first 30 days of cattle placement in the feedlot (π)	Vector (0.05, 0.30, 0.05)	-0.01	-0.05	0.03	$\bar{-}$ 0.10*	$\bar{-}$ 0.17*	$\bar{-}$ 0.05*	$\bar{-}$ 0.13*	$\bar{-}$ 0.15*	$\bar{-}$ 0.07*	$\bar{-}$ 0.05*
Depth of the home- pen floor top contaminated by fresh animal excreta (d_{pen}) (m)	Vector (2, 5, 3)	-0.06	-0.05	-0.01	-0.04	-0.03	-0.05	-0.05	-0.05	-0.06	-0.06
Initial proportion of latent cattle in the index home-pen ($lat_{initial}$)	Vector (0.005, 0.105, 0.020)	$\bar{-}$ 0.42*	$\bar{-}$ 0.29*	$\bar{-}$ 0.09*	$\bar{-}$ 0.15*	$\bar{-}$ 0.17*	$\bar{-}$ 0.11*	$\bar{-}$ 0.09*	$\bar{-}$ 0.08*	$\bar{-}$ 0.09*	$\bar{-}$ 0.09*
Fraction of saliva daily produced by the animal that is excreted into the home-pen environment (σ)	Vector (0.1, 0.5, 0.1)	0	-0.05	0.03	-0.05	-0.03	0.04*	0.03*	$\bar{-}$ 0.01*	$\bar{-}$ 0.01*	0.01*
Duration of FMD latent period (lat) (days)	Weibull ($\alpha = 1.782, \beta = 3.974$)	0.67*	0.62*	0.25*	0.48*	0.64*	0.75*	0.77*	0.77*	0.82*	0.83*
Duration of FMD infectious period (inf) (days)	Gamma ($\alpha = 3.969, \beta = 1.107$)	0.02	$\bar{-}$ 0.11*	-0.02	$\bar{-}$ 0.14*	$\bar{-}$ 0.12*	0.48*	0.42*	0.23*	0.35*	0.29*

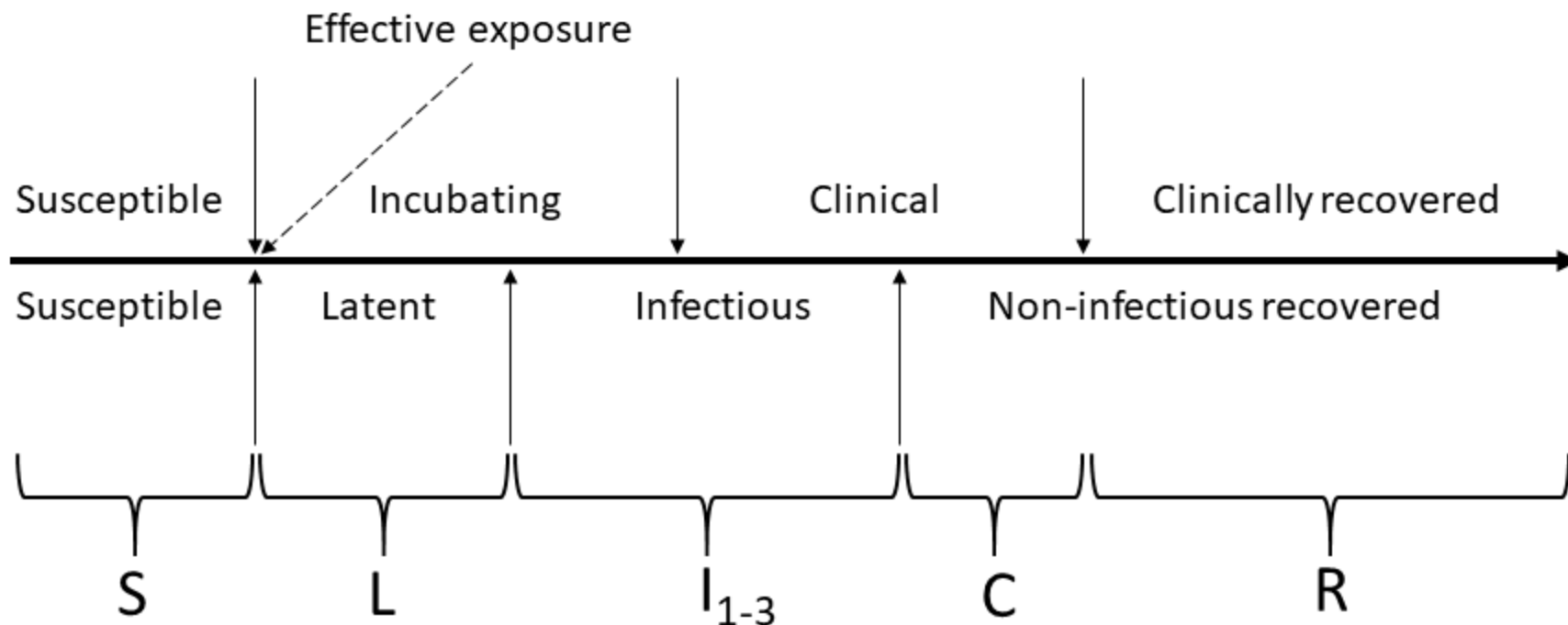
Duration of FMD subclinical period (<i>sub</i>) (days)	Gamma ($\alpha = 1.222, \beta = 1.672$)	0.19*	0.25*	0.07*	0.18*	0.22*	$\bar{}$ 0.21*	$\bar{}$ 0.17*	$\bar{}$ 0.03*	$\bar{}$ 0.09*	$\bar{}$ 0.06*
Water intake by the animal per visit to the water-trough in the home-pen (<i>wat int</i>) (l)	Vector (1, 5, 4)	-0.02	-0.08	0.01	-0.09	-0.10	0.01	-0.01	-0.05	-0.06	-0.06

¹ Bold coefficients with * indicate $p < 0.05$ for the correlation coefficient between the parameter value and outcome variable value.

² Feedlot sizes and layouts modeled are detailed in Table 2 and Figure S1 in the Supplementary Materials. Briefly, FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen).

* Results of the following target parameters were not included in the table above because were found to be not influential to model outputs: mortality rate for animals with BRD and other production diseases (endemic infectious diseases and noninfectious diseases) (day^{-1}) (μ), Mortality rate for animals with clinical FMD (day^{-1}) (ψ), urine volume produced by an animal (L/ day) (*uri*), saliva volume produced by an animal (L/ day) (*sal*), volume of feces produced by an animal (kg/ day) (*fec*), virus quantity shed in urine (plaque forming units (PFU)/mL) by an animal in the FMD clinical high infectious status (*uriv*), virus quantity shed in saliva (PFU/mL) by an animal in the FMD clinical high infectious status (*salv*), virus quantity shed in feces (PFU/mL) by an animal in the FMD clinical high infectious status (*fecv*), and the proportion of the cattle daily saliva volume deposited into the home-pen environment (*dmnl*) (*fsal_env*). Their distributions can be found in Table 1

Disease progression



Infection progression

Figure 3-1 Schematic of foot-and-mouth disease (FMD) infection and clinical disease progression in individual cattle. The compartments of the modified SLIR model of FMD dynamics are indicated by letters: S - susceptible, L - latent, I₁ – subclinical low-

infectious, I_2 – subclinical high-infectious, I_3 – clinical high-infectious, C - clinical but no longer infectious, and R – non-infectious clinically recovered

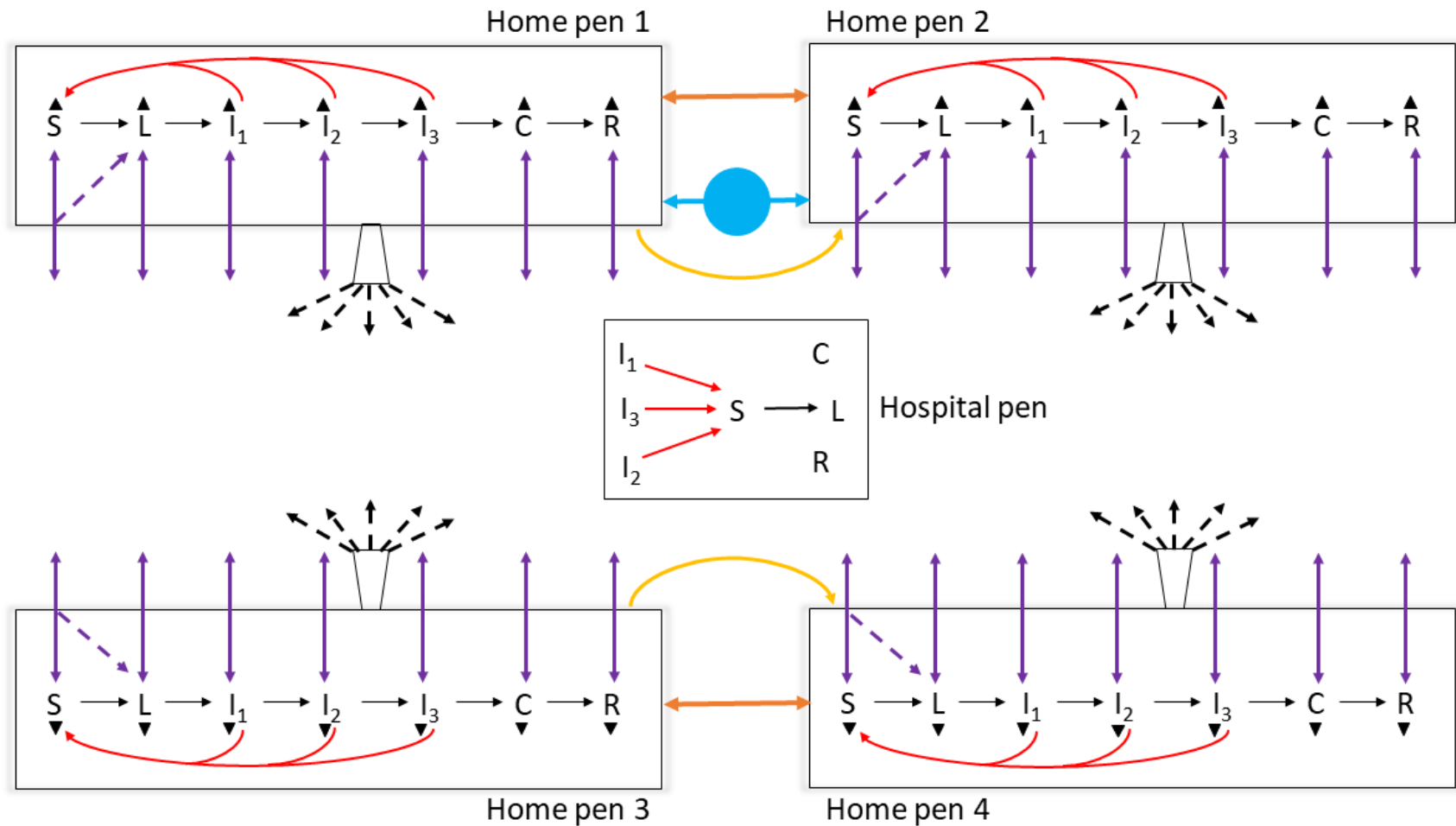


Figure 3-2 Schematic diagram of the model of foot-and-mouth disease (FMD) virus transmission and FMD clinical manifestation dynamics in cattle within home-pens and among home-pens in a beef cattle feedlot. S - susceptible, L - latent, I₁ – subclinical low-infectious, I₂ – subclinical high-infectious, I₃ – clinical high-infectious, C - clinical but no longer infectious, and R – non-infectious

clinically recovered. The black solid arrows show the home-pen subpopulation progression through the infection and disease stages. The red solid arrows show the virus transmission via direct contact between infectious to susceptible cattle in the home-pens and hospital-pen. The purple solid arrows show the animal movements from home-pens to the hospital-pen and back to the home-pens, and the purple dotted arrows show the possibility that susceptible animals moved acquired infection in the hospital-pen and returned as latent to the home-pens. The orange solid arrows show the virus transmission via animal direct contact fence-line. The yellow solid arrows show the virus contaminated material transmitted by pen-riders. The blue circle with solid arrows shows the virus transmission via contaminated water-troughs shared by home-pens. The buckets with black dotted arrows represent the airborne virus transmission. The black triangles represent animal mortality in each of the infection and disease stages

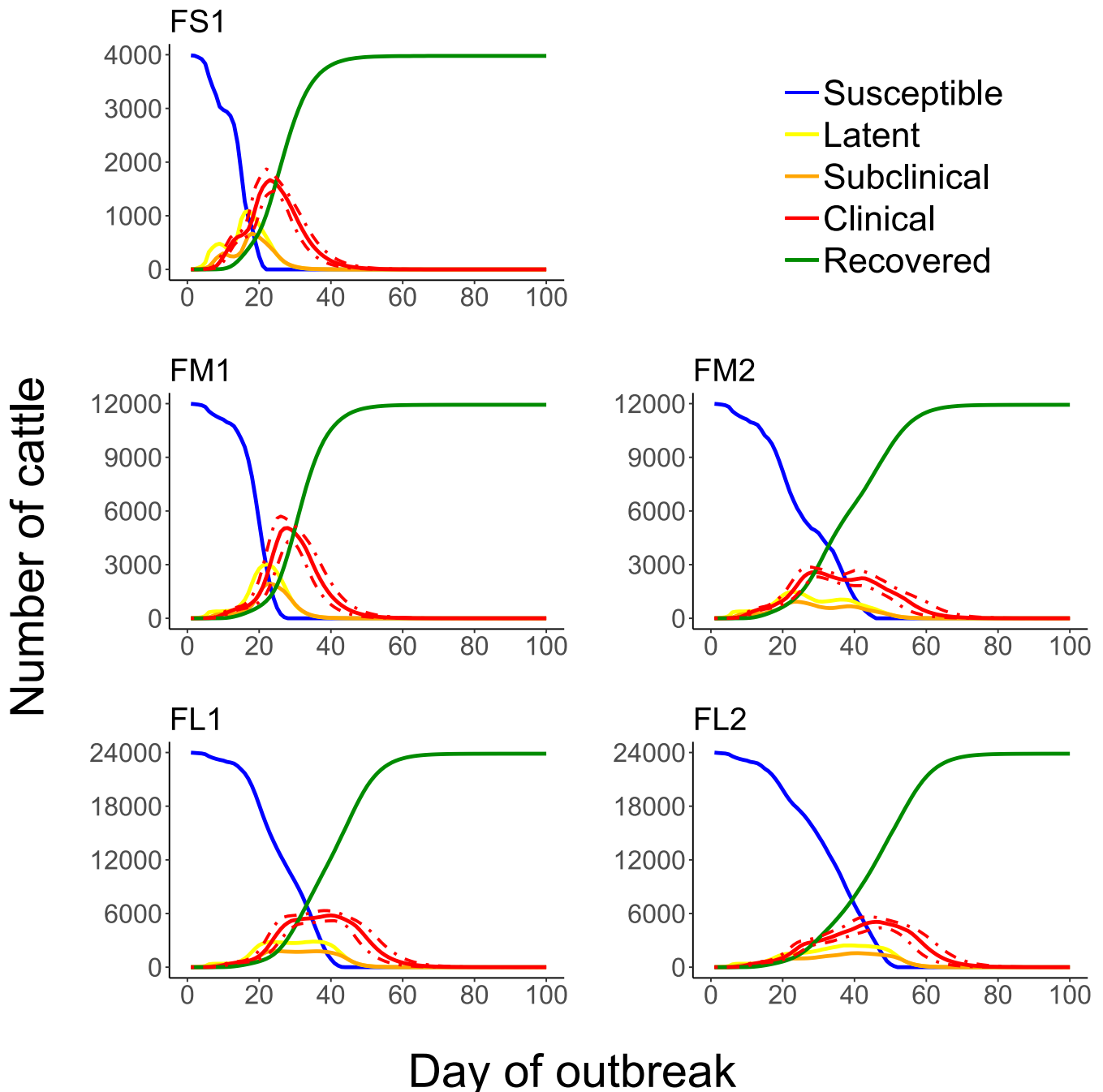


Figure 3-3 Numbers of cattle in each of the foot-and-mouth disease infection and disease stages during projected outbreaks on U.S. beef cattle feedlots. The solid lines represent the 50th percentiles for the cattle numbers in the infection stages and the red dotted lines represent the 25th and 75th percentiles for the number of cattle with clinical FMD (infectious and non-infectious clinical cattle) of n=2,000 simulated outbreaks in the feedlot of that size and layout sampling the values of the target parameters. Feedlot size and layout cases

modeled: FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

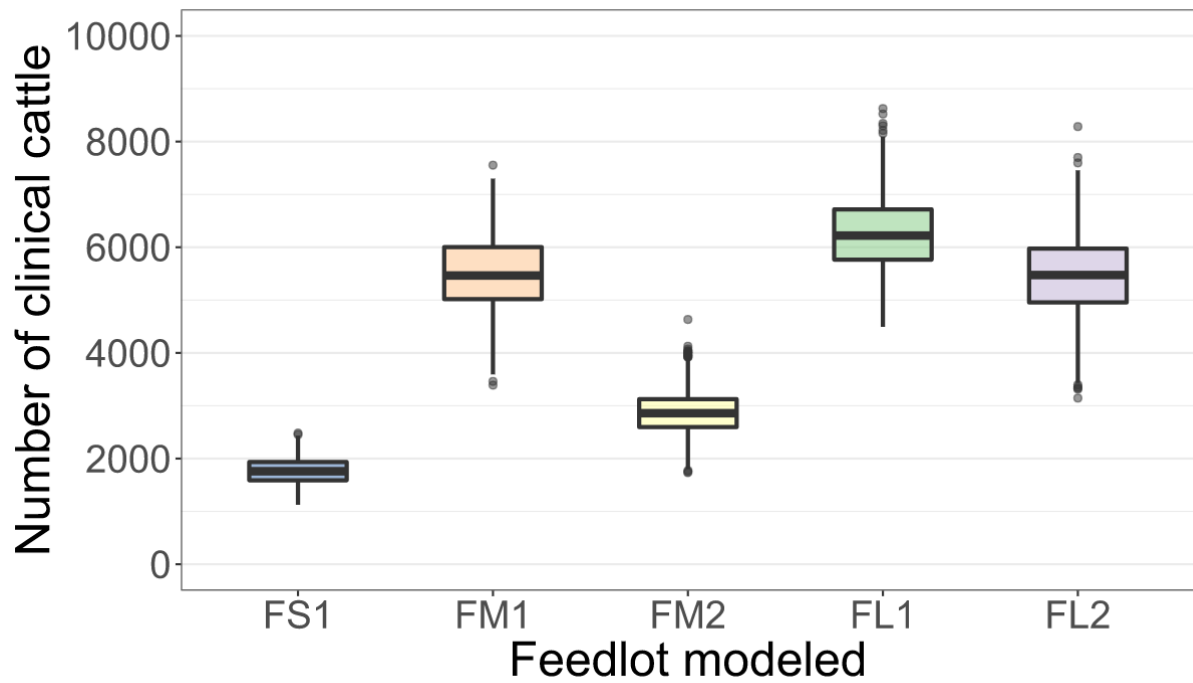


Figure 3-4 Boxplot of the projected number of cattle with clinical FMD on the outbreak peak day for each of the feedlot size and layout cases modeled. The outbreak peak day was defined as the day with the highest number of clinical cattle (infectious and non-infectious) since the FMD introduction in each of n=2,000 simulated outbreaks in the feedlot of that size and layout sampling the values of the target parameters. Feedlot size and layout cases modeled: FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts n=200 cattle per home-pen)

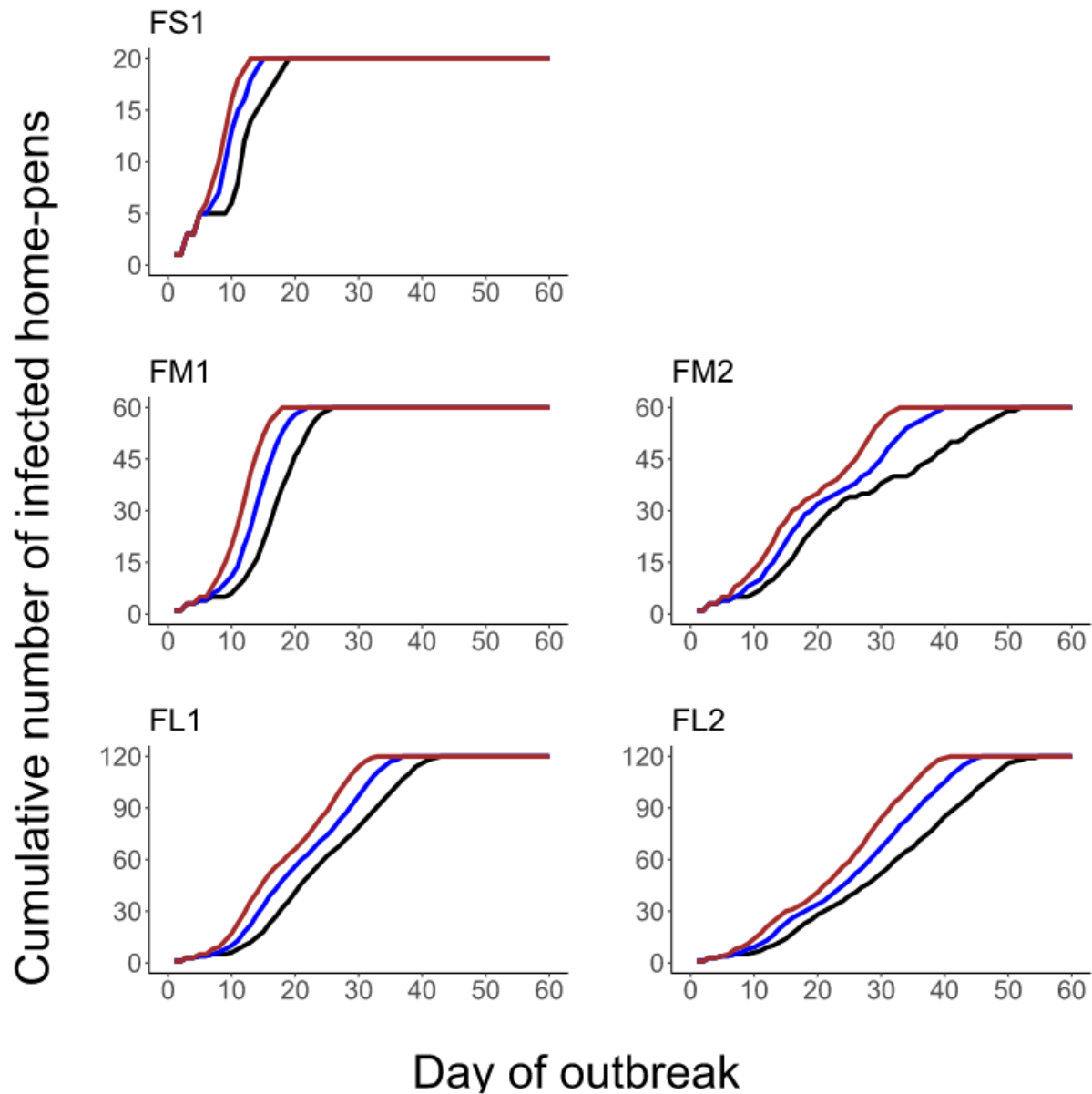


Figure 3-5 The cumulative number of the home-pens infected with foot-and-mouth disease during a projected outbreak on a U.S. beef cattle feedlot. The lines represent the percentiles for $n=2,000$ simulated outbreaks in the feedlot of that size and layout sampling the values of the target parameters. Feedlot size and layout cases modeled: FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

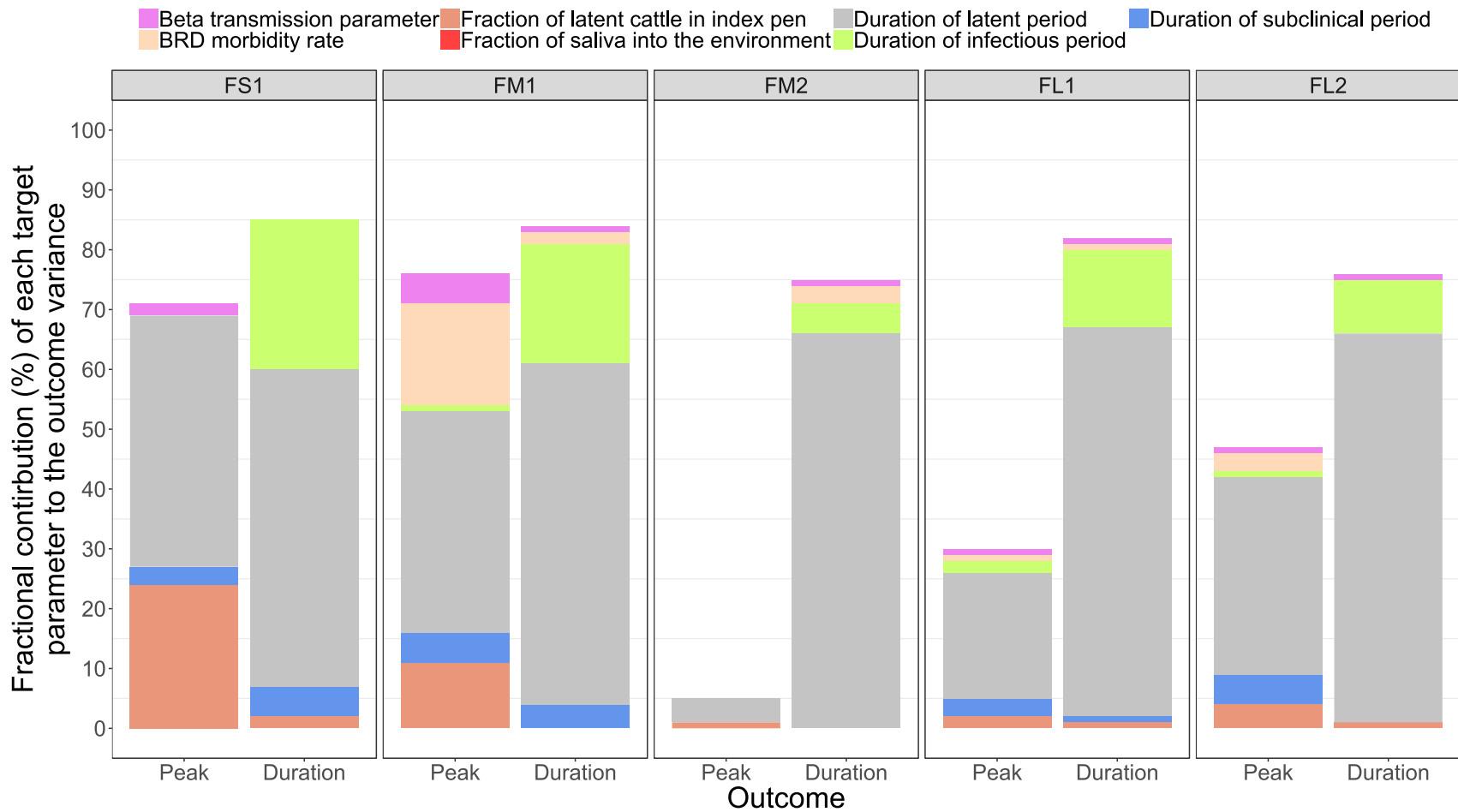


Figure 3-6 The fractional contributions of select target parameters to the variance in each the outbreak peak day with highest number of clinical cattle and the total outbreak duration in the feedlot since the foot-and-mouth disease introduction, estimated based on n=2,000 simulated outbreaks in each of the feedlot size and layout cases modeled. Multivariable linear regression models were developed for each of the outcome variables of the projected outbreak peak day and outbreak duration and the target parameters as the predictor variables. For each outcome, the final regression model adjusted R² statistic was partitioned to obtain the fractional contributions of the target parameters to the projected outcome variance. Outcomes: Peak

– outbreak peak day, Duration – duration of the outbreak. Target parameters: beta transmission parameter for FMD virus transmission via direct cattle contact [Beta transmission parameter]; morbidity rate of bovine respiratory disease (BRD) during the first 30 days since cattle placement in the feedlot [BRD morbidity rate]; initial fraction of FMD latent cattle in the index home-pen [Fraction of latent cattle in index pen]; fraction of the daily saliva volume produced by an animal that is deposited into the home-pen environment [Fraction of saliva into environment]; and the durations of the FMD latent period [Duration of latent period], infectious period [Duration of infectious period], and subclinical period [Duration of subclinical period] in individual cattle. Feedlot size and layout cases modeled: FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

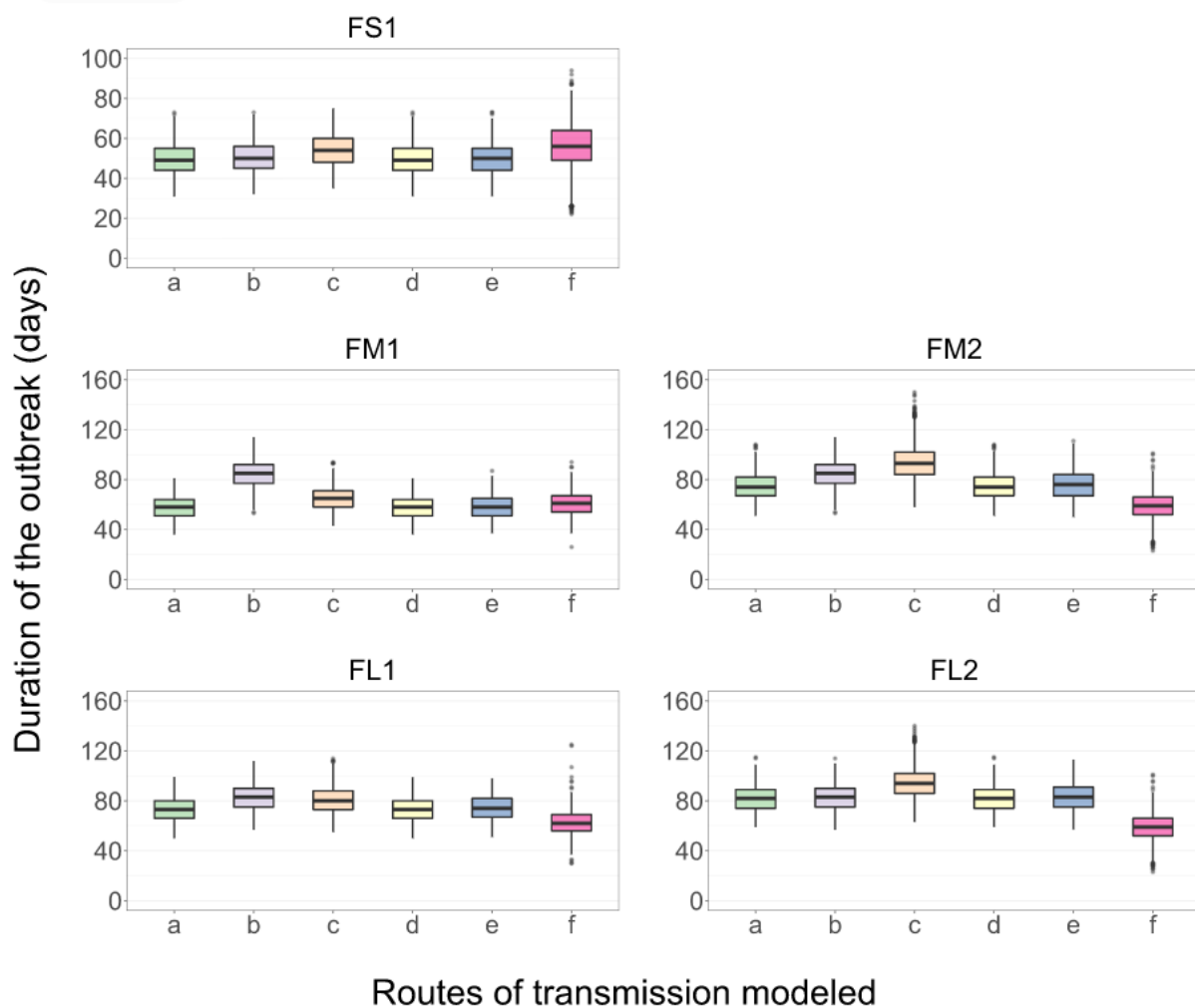
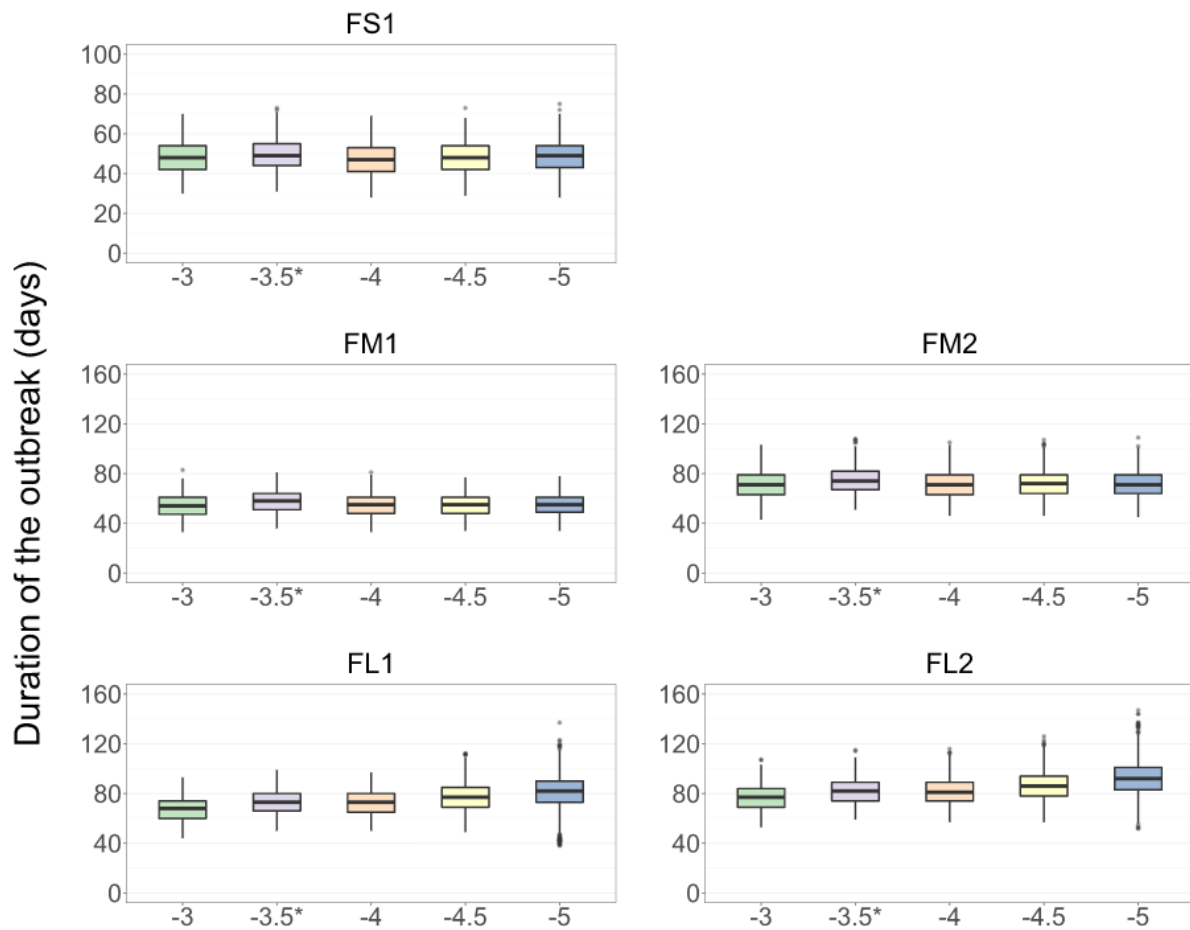


Figure 3-7 Boxplot of the projected duration of a foot-and-mouth disease outbreak on a U.S. beef cattle feedlot for n=2,000 simulated outbreaks in the feedlot of that size and layout sampling the values of the target parameters, when the full model incorporating all the routes of FMD virus transmission among the home-pens or a model with one of the transmission routes excluded was simulated. a – all the routes of FMD virus transmission among home-pens incorporated, b – transmission via direct contact of cattle in the hospital-pens excluded; c – fence-line transmission between cattle in neighboring home-pens excluded; d – transmission of virus contaminated material between home-pens by the pen-riders excluded; e – transmission via contaminated

water-troughs excluded; and f – airborne transmission excluded. Feedlot size and layout cases modeled: FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts n=200 cattle per home-pen)






Power of the decay with distance function for airborne FMDv transmission

Figure 3-8 Boxplot of the projected duration of a foot-and-mouth disease outbreak on a U.S. beef cattle feedlot for n=2,000 simulated outbreaks in the feedlot of that size and layout sampling the values of the target parameters, depending on the power (α) of the function of an exponential decay in the probability of airborne FMD virus transmission with increasing distance between home-pens. * - baseline value used to simulate the models for the other analyses. Feedlot size and layout cases modeled: FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a

24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts n=200 cattle per home-pen)

Supplementary materials

Supplementary Figure 1: Feedlot layouts modeled.

	Water trough
	Drovers alley (5 meters)
	Feed alley (8 meters)
a	61 meters
b	75.2 meters
c	30 meters
S1, S2, S3	Infection scenario

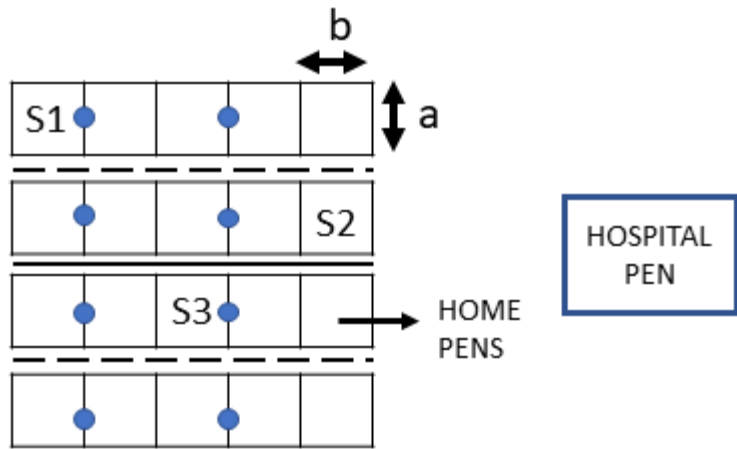


Figure S 3-A FS1 small-size feedlot with one hospital-pen

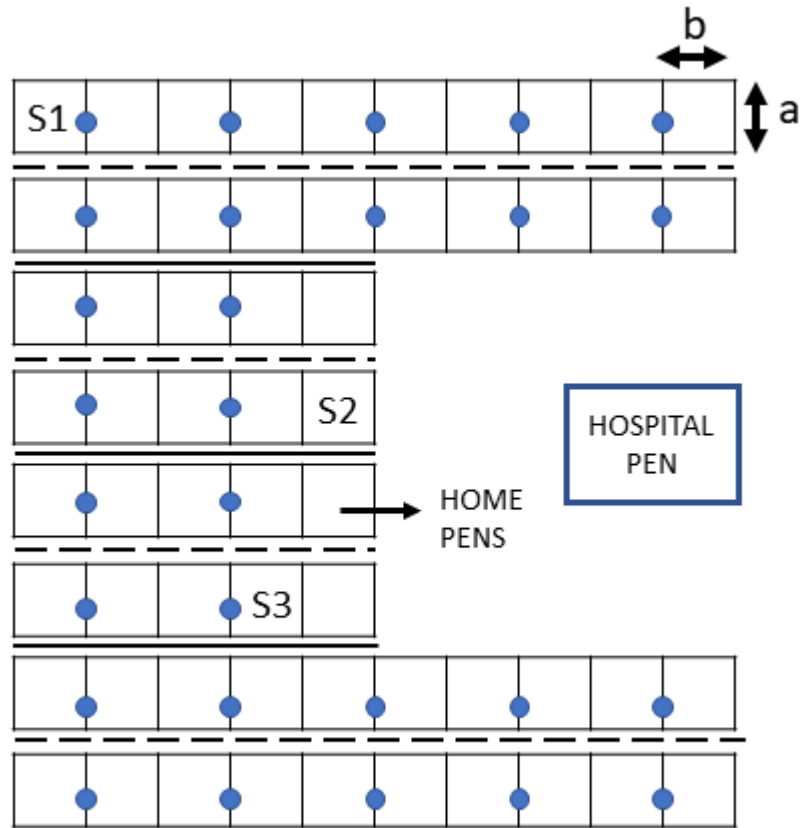


Figure S 3-B FM1 medium-size feedlot with one hospital-pen

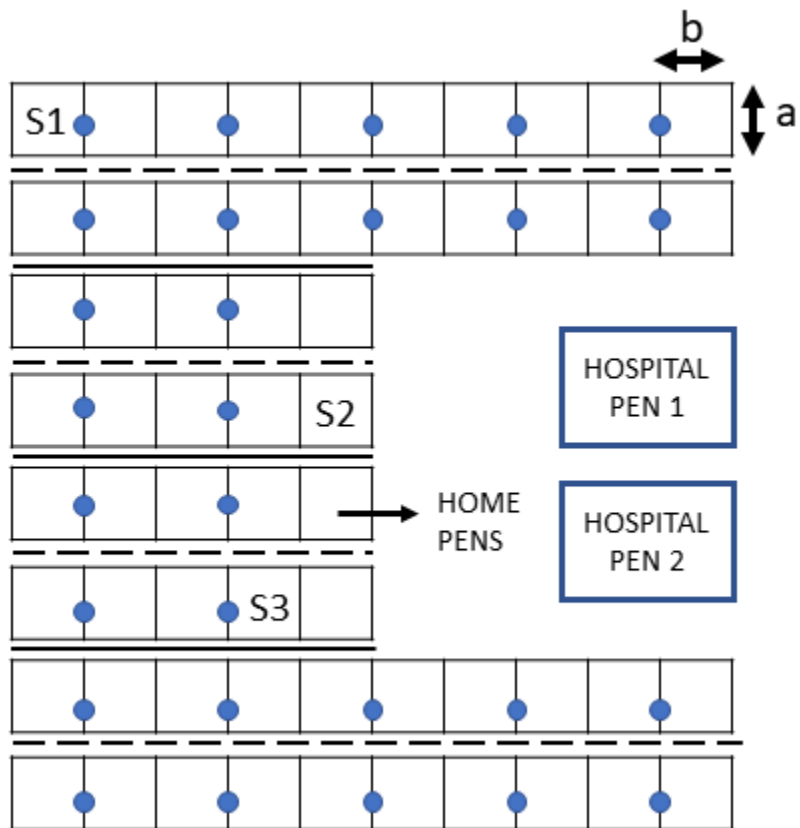


Figure S 3-C FM2 medium-size feedlot with one hospital-pen

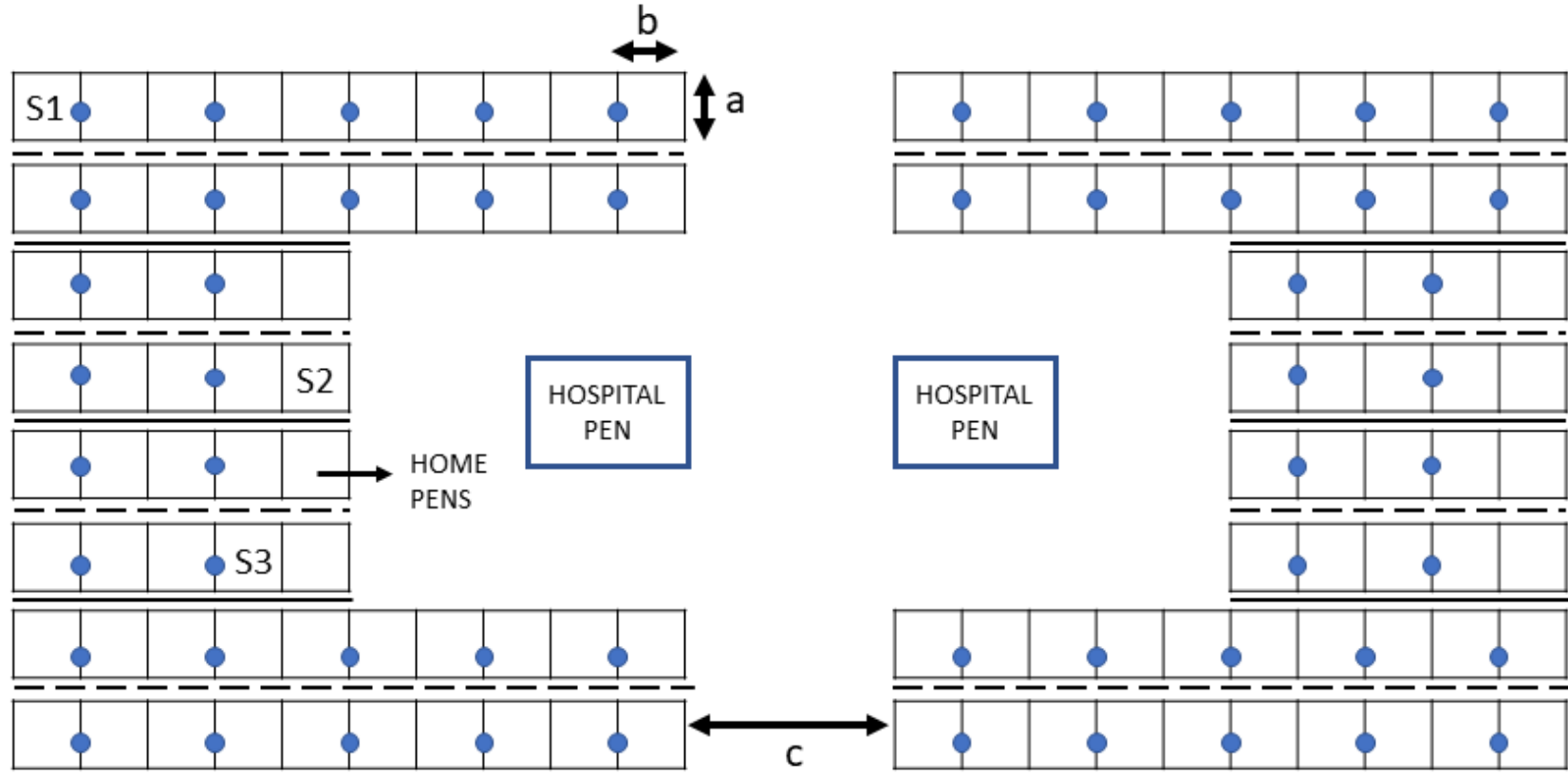


Figure S 3-D FL1 large-size feedlot with two sections and two hospital-pens

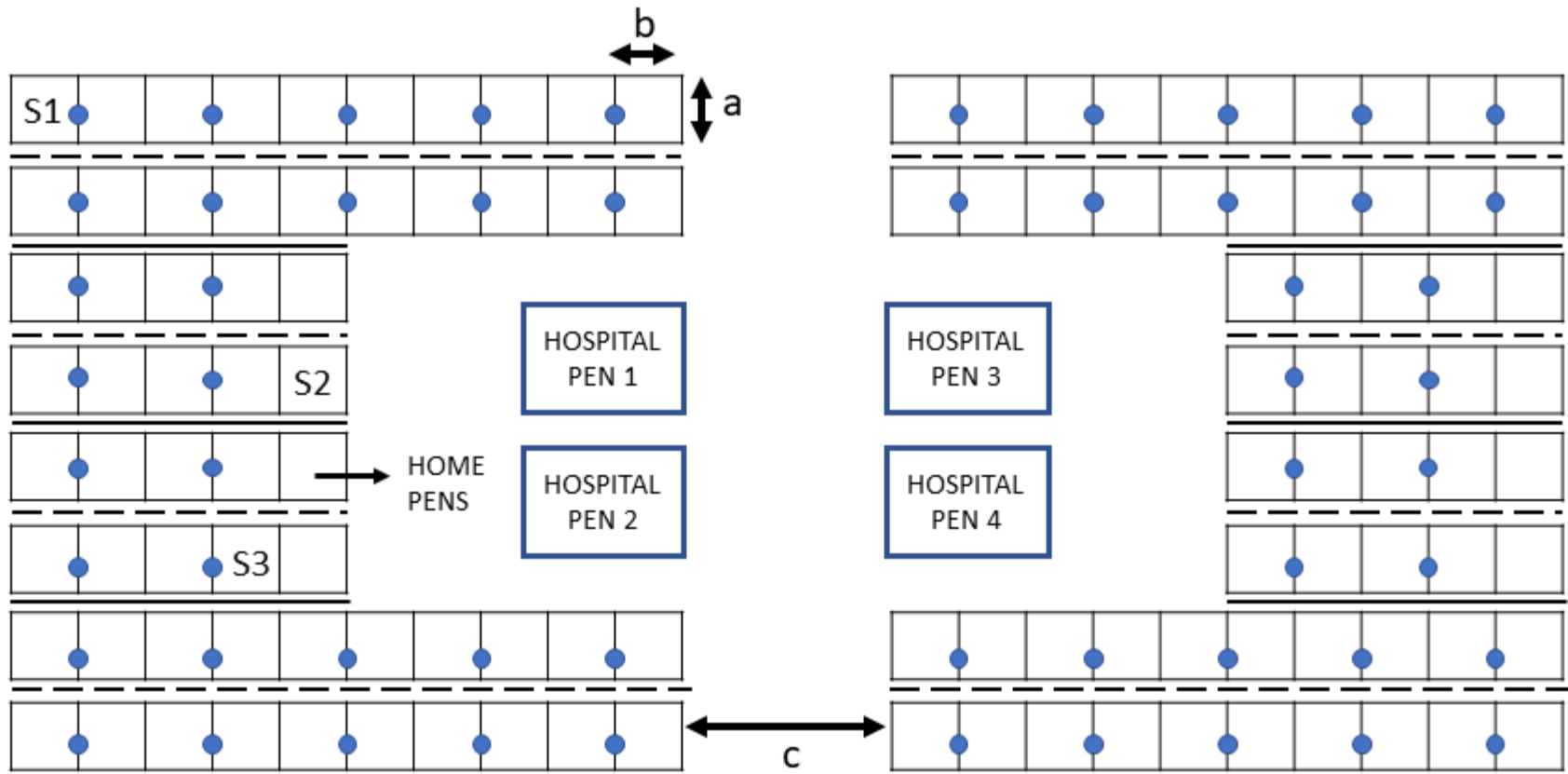


Figure S 3-E FL2 large-size feedlot with two sections and four hospital-pens

Chapter 4 - Models to simulate intervention scenarios during potential foot-and-mouth disease outbreaks within U.S. beef feedlots

Aurelio H. Cabezas, Michael W. Sanderson*, Victoriya V. Volkova

Department of Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States

Center for Outcomes Research and Epidemiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States

*Corresponding author: Michael Sanderson, Department of Diagnostic Medicine/Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States. Phone: +1 (785) 532-4264. e-mail address: sandersn@vet.k-state.edu (M.W. Sanderson).

Abstract

Foot-and-mouth disease is a highly infectious disease of livestock and has severely affected the livestock industry during the past two decades in previously FMD-free countries with large livestock populations. The disease was eliminated in North America in 1953 but remains a threat for re-introduction. Approximately 45% of the U.S. beef cattle on-feed population is concentrated in feedlots greater than 32,000 head but little information is available on behavior of FMD in a large feedlot. Therefore, there is a need to explore possible management and intervention strategies that might be implemented during potential FMD outbreaks. We used a within pen stochastic susceptible-latent-infectious-recovered (SLIR) nested in a meta-population model of pens previously developed to simulate foot-and-mouth disease virus (FMDv) transmission within U.S. beef feedlots. We evaluated three intervention strategies initiated on the day of FMD detection: stopping movements of cattle from home pens to the hospital pens(s) (S1), barrier depopulation combined with S1 (S2), and targeted depopulation combined with S1 (S3). Depopulation strategies were assumed to have a depopulation rate of 1,000 cattle depopulated per day. We evaluated the effectiveness of the interventions modeled by comparing them with a baseline (no-intervention) scenario previously reported. Feedlots modeled were a small-size feedlot (4,000 cattle), medium-size feedlots (12,000 cattle), and large-size feedlots (24,000 cattle). Implementation of S1 delayed the outbreak progression but it did not prevent infection of the entire feedlot. Implementation of S2 resulted in depopulation of 50% of cattle in small-size and medium-size feedlots, and 25% in large size feedlots, and the intervention prevented infection of the whole feedlot in only 40% of simulated outbreaks in medium-size feedlots, and in 8% simulations in large-size feedlots. Day of FMD detection was found to highly impact the success of S2. Implementation of S3 resulted in depopulation of up to

50% of home pens in small-size feedlots, 75% in medium-size feedlots, and 25% of home pens in large-size feedlots but only rarely prevented infection of the whole feedlot. Number of hospital pens in the feedlot was shown to weakly impact the success of S3. Overall, the outputs produced by our model suggest that the interventions proposed were not highly effective to interrupt FMD transmission within the feedlots modeled.

Keywords: Foot-and-mouth disease, meta-population model, beef feedlot, intervention strategies, cattle depopulation

Introduction

Foot-and-mouth disease (FMD) is a highly infectious disease that has affected several non-endemic countries in the past 20 years such as the United Kingdom, Japan, Uruguay, Argentina, The Netherlands, and France (Anderson, 2002; Bouma et al., 2003; Chmitelin and Moutou, 2002; Clavijo et al., 2017; Davies, 2002; Ellis-Iversen et al., 2011; Nishiura and Omori, 2010). In North America, the last outbreaks occurred in 1929 in the United States, 1952 in Canada, and 1946 in Mexico; FMD was eventually eliminated in North America in 1953 (Graves, 1979; Mohler, 1930). Nonetheless, FMD remains a threat for re-introduction to the U.S. due to the introduction of FMD infected animals or animal products infected with the foot-and-mouth disease virus (FMDv). The survival and infectivity of FMDv in fomites and excretions, and aspects of the spread of FMDv has been previously reviewed (Alexandersen et al., 2003; Bachrach, 1968; Bartley et al., 2002; Sellers, 1971). An FMD outbreak in the U.S. would cause catastrophic economic consequences as has been previously suggested by modeling studies (Paarlberg et al., 2002; Pendell et al., 2015; Schroeder et al., 2015).

At any given time the U.S. has approximately 13 million cattle on feed distributed in over 30,000 feedlots across the 48 states (USDA-NASS, 2017). Approximately 1% of those feedlots have a one- time capacity equal or greater than 32,000 head; however, they contain approximately 44% of the cattle on-feed population in the country (USDA-NASS, 2017). The main control strategies used during the course of an outbreak in non-endemic countries has been: movement bans, depopulation of infected and susceptible animals in affected and at-risk areas, sanitary/biosecurity measures, surveillance zones, and emergency vaccination (Bouma et al., 2004; Bouma et al., 2003; Chmitelin and Moutou, 2002; Davies, 2002; Kao, 2002; Nishiura and Omori, 2010; Park et al., 2013; Pluimers et al., 2002). To our knowledge, there are no studies

that evaluate the effectiveness of on-farm (within herd) intervention strategies during FMD outbreaks in U.S. beef feedlots. The large concentration of cattle in this type of operation might represent a challenge to the success of any of the control strategies mentioned above. For this reason, there is a need to investigate possible management and intervention strategies that might be implemented during potential FMD outbreaks—especially in large concentrated livestock operations.

Some authors have used models to simulate potential between-herd transmission in FMD outbreaks within the contiguous U.S., and to evaluate different intervention strategies such as movement bans, depopulation and vaccination (Bates et al., 2003; McReynolds et al., 2014; Schoenbaum and Disney, 2003; Tildesley et al., 2012; Ward et al., 2009). These models do not focus on within-herd transmission dynamics, which are necessary to assess within herd management and control in large compartmentalized feedlots. Others have used alternative methods to evaluate the potential use of control strategies at the farm level. For instance, the feasibility of depopulation within a large feedlot has been previously described by McReynolds and Sanderson (2014). They used a Delphi survey and facilitated expert discussion to investigate total depopulation methods in a large feedlot considering effectiveness, animal and human welfare, public perception, and availability of needed supplies. Given the difficulty of depopulation in large U.S. beef feedlots, alternatives to total depopulation of infected premises may be required. We evaluated alternative intervention strategies to investigate the impact of those strategies on outbreak progression. In this study, we used a metapopulation model, specifically developed to assess FMDv transmission within U.S. beef feedlots, to investigate the effectiveness of intervention strategies such as movement bans, and targeted depopulation of subpopulations of cattle after FMD detection during the outbreak.

Material and methods

Within-herd FMD model description

We modeled beef finishing cattle within 5 different feedlot layouts (Table 4-1). We used a stochastic within pen SLIR model nested in a meta-population of feedlot pens (described in Chapter 3). This is a modified SLIR (Susceptible-Latent-Infectious-Recovered) model. Two levels of FMDv transmission were modeled: within-pen and between pen. Within-pen transmission was modeled via direct contact assuming homogeneous cattle mixing inside the pen. Between pen transmission was modeled via direct contact of cattle in hospital pen(s), fence-line direct contact of cattle in contiguous pens, by pen-riders moving between pens, waterborne, and airborne. Simulations started with a proportion of FMD latent cattle in an index pen located centrally within the feedlot. See Chapter 3 for a detailed description of the formulation of the model.

We modeled 5 feedlots of different size and layouts: FS1 – small-size feedlot with 20 home pens and 1 hospital pen, FM1 – medium-size feedlot with 60 home pens and 1 hospital pen, FM2 – medium-size feedlot with 60 home pens and 2 hospital pens (30 home pens hospital pen), FL1 – large-size feedlot with 120 home pens and 2 hospital pens (60 home pens per hospital pen), and FL2 – large size feedlot with 120 home pens and 4 hospital pen (30 home pens per hospital pen). For those feedlots that operate with more than one hospital pen, the hospital pen receives cattle from the section of home pens that is in closest spatial proximity to the hospital pen. See Figures in Supplementary Materials for a graphical representation of the feedlots modeled.

Intervention scenarios modeled

Control scenarios were applied upon the day of FMD detection which was based on observational surveillance of clinical signs by pen-riders which are experienced personnel in feedlots to detect diseased cattle. FMD detection occurred when the proportion of clinical cattle in the index home-pen reached a 3% prevalence threshold. The intervention scenarios were applied by modifying some parameters from the baseline no intervention scenario models (list of parameters used in the model can be found in Table 3-1 in Chapter 3). We modeled 3 different on-farm intervention scenarios and compared them to a baseline no intervention scenario (results for the baseline no intervention scenario are reported in results section in Chapter 3).

In scenario 1 (S1) hospital movement restrictions were implemented to stop mixing of cattle from different home pens in the hospital pen(s) beginning the day after FMD detection. In scenario 2 (S2) S1 was combined with barrier depopulation. Upon the day of FMD detection, cattle in the row of home pens containing the index home pen and home pens in the surrounding rows were depopulated. No further depopulation was done following completion of the initial barrier. In scenario 3 (S3) S1 was combined with trace back and targeted depopulation. Upon the day of FMD detection, cattle in home pens that had contact with the hospital pen(s) within 7 days prior to FMD detection were traced-back, and those home pens were depopulated. No further depopulation was done following completion of the initial traceback. We assumed a baseline depopulation rate of 1,000 cattle (or 5 home pens), but also evaluated the impact of other depopulation rates. For FS1, we also modeled 2,000 depopulation rates: for FM1 and FM2, we also modeled 500 and 2,000 depopulation rates; and for FL1 and FL2, we also modeled 2,000

and 4,000 depopulation rates. See Figures in Supplementary Materials for a schematic representation of the intervention strategies in the feedlots modeled.

As mentioned above, we applied intervention scenarios upon the day of FMD detection. For S1, the daily pulling rate of cattle from home pens to the hospital pen (φ) was modified to 0 in all modeled compartments after the day of FMD detection to restrict mixing of cattle from different home pens in the hospital pen(s) (equation 1).

$$\left\{ \begin{array}{l} \text{if } \left[\frac{(I_3 + C)_x}{N_x} \right]_{t-1} \geq 0.03, \text{ then: } \varphi_{t-1} = 0 \\ \text{otherwise: } \varphi_{t-1} = \text{baseline no intervention scenario} \end{array} \right\} \quad (1)$$

Where I_3 is the number of clinical infectious cattle in the index home pen on a given day, C is the number of clinical non-infectious cattle in the index home pen on a given day, N is the total number of cattle in the index home pen on a given day, x represents the index home pen, and φ is the daily pulling rate from home pens to hospital pen.

For S2 (equation 2), the mortality rate (μ) was modified to 1 (or 100%) to represent depopulation in the index home pen, home pens in the row where the index home pen is located, and home pens in rows surrounding the index home pen upon the day of FMD detection. For S2, home pens were depopulated from inside-out starting with the row of home pens in the same row as the index home pen.

$$\left\{ \begin{array}{l} \text{if } \left[\frac{(I_3 + C)_x}{N_x} \right]_{t-1} \geq 0.03 \ \& \ \text{home pen} = y \ \& \ k = \text{yes}, \text{ then } \mu = 1 \\ \text{otherwise: } \mu = \text{baseline no intervention scenario} \end{array} \right\} \quad (2)$$

Where I_3 is the number of clinical infectious cattle in the index home pen on a given day, C is the number of clinical non-infectious cattle in the index home pen on a given day, N is the

total number of cattle in the index home pen on a given day, x represents the index home pen, and y means that the home pen is within the fixed boundaries established where the barrier depopulation was conducted (home pens containing the index home pen and home pens in the surrounding rows of the row containing the index home pen), and k represents whether cattle in home pen was selected for depopulation on the simulation day accounting the different depopulation rates (500 or 1,000 or 2,000 or 4,000 cattle depopulated per day).

For S3 (equation 3), the mortality rate (μ) was modified to 1 (or 100%) to represent depopulation in home pens that had contact with the hospital pen(s) within 7 days prior to the day of FMD detection in combination with S1.

$$\left\{ \begin{array}{l} \text{if } \left[\frac{(I_3 + C)_x}{N_x} \right]_{t-1} \geq 0.03 \ \& \ \text{home pen} = z \ \& \ k = \text{yes, then } \mu = 1 \\ \text{otherwise: } \mu = \text{baseline no intervention scenario} \end{array} \right\} \quad (3)$$

Where I_3 is the number of clinical infectious cattle in the index home pen on a given day, C is the number of clinical non-infectious cattle in the index home pen on a given day, N is the total number of cattle in the index home pen on a given day, x represents the index home pen, z means that the home pen had contact with the hospital pen(s) within 7 days prior to the day of FMD detection, and k represents whether cattle in home pen was selected for depopulation on the simulation day accounting the different depopulation rates (500 or 1,000 or 2,000 or 4,000 cattle depopulated per day). See Section 2.2 in Chapter 3 for a complete formulation of the model, Figure 3-2 in Chapter 3 for a schematic representation of the model, and Figures in Supplementary Materials for a schematic representation of both depopulation scenarios.

Outbreak metrics investigated

We evaluated the following metrics in each feedlot modeled:

- (1) The duration of the outbreak for S1 compared to the baseline no-intervention scenario defined as the time in days since the introduction of FMD latent cattle until the prevalence of infectious individuals within the feedlot is equal to 0.
- (2) Time to infection of all home pens for S1 compared to the baseline no-intervention scenario. A home pen was considered infected when at least one cattle become FMD latent throughout the outbreak.
- (3) The effectiveness of all the interventions implemented in preventing FMD spread.

We defined effectiveness of the intervention strategies as the percentage of simulations in which FMD transmission was interrupted for each feedlot and intervention modeled. We finally compared the results of the intervention strategies to those of the baseline no-intervention scenario described in results section in Chapter 3 to assess potential implications of the implementation of those strategies.

Model Implementation

The model was implemented in Vensim® PLE Plus Version 6.4a (Ventana Systems Inc., Harvard, MA, USA). The output figures were done in R using the ggplot package and the schematic representations of the depopulation interventions in Microsoft Office Power Point® 365 ProPlus (Microsoft, Redmond, WA, USA). The statistical analysis of the simulation outputs was done in STATA® 13 (StataCorp LP, College Station, TX, USA). The model was previously verified and validated (See Section 2.4 in Chapter 3).

Sensitivity analysis

We selected the influential target parameters described in Section 2.5 in Chapter 3 for inclusion in the sensitivity analysis: The target parameters included the FMD latent, infectious, and subclinical periods, and the beta transmission parameter within the home-pens (See Table 3-4 in Chapter 3 for a more detailed description). We simulated the model for each feedlot size and layout, for a scenario in which FMD latent cattle are introduced in an index home pen located centrally within the feedlot, and for each intervention scenario. The value of each target parameter was sampled for each of 2,000 Monte Carlo simulations of each model. For each of the other parameters in the model, a single value was used for each of the 2,000 simulations (See Table 3-1 in Chapter 3).

For S1, we investigated the effect of the target parameters and the day of FMD detection on the duration of the outbreak. Using the outputs of the 2,000 model simulations for the feedlot size and layout, we used the Spearman rank correlation coefficient to test statistical significance of the association between the target parameters values and the day of FMD detection with the outbreak duration. For S2 and S3, we investigated the effect of the target parameters along with the number of hospital pens in the feedlot, the day of FMD detection, and the number of pens depopulated (only in S3) on the effectiveness of the interventions. Using the outputs of the 2,000 model simulations for the feedlot size and layout, we used the Spearman rank correlation coefficient to test the association between the target parameters, the day of FMD detection, and the number of pens depopulated with the outbreak duration. We also estimated the proportion of simulations in which we found uninfected home pens at the end of simulations. For S2, a fixed number of home pens was depopulated for each feedlot modeled (10 in FS1, and 30 for the rest); then, if the remaining home pens were not infected during the simulations (10 in FS1, 30 for

FM1 and FM2, and 90 for FL1 and FL2), we considered the intervention successful. For S3, the number of home pens depopulated was variable depending on how many home pens had contact with the hospital pen prior 7 days of FMD detection. So, we consider the intervention successful if at least one home pen remained uninfected. Descriptive statistics for the number of depopulated and uninfected home pens during the simulations were summarized. Finally, we estimated the effect modeling different depopulation rates on the outcome described above. For FS1, FM1, and FM2 we modeled depopulation rates of 500 and 2,000 cattle per day while we modeled depopulation rates of 2,000 and 4,000 cattle per day for FL1 and FL2.

Results

Outbreak progression and duration of the outbreak

Results of this section are only compared between S1 and the baseline no intervention scenario in which depopulation was not implemented. The largest variation in the projected duration of the outbreak when S1 was implemented was seen in FM1. Implementation of this strategy was found to significantly increase the duration of the outbreak when compared to the baseline no intervention scenario (82 days compared to 58 days for the baseline no intervention scenario). For FM2 and FL1 the projected median duration of the outbreak for the baseline no intervention scenario was 73 for both and implementation of S1 increased it by 8 (FM2) to 11 days (FL1). For FS1 and FL2, there were no changes in the median projected duration of the outbreak when S1 was implemented compared to the baseline no intervention scenario (49 days for FS1 and 84 days for FL2). See Table 4-1 for more detail results.

Time to infection of all home pens

Results of this section are only compared between S1 and the baseline no intervention scenario. The time to infect all home pens since FMDv introduction when comparing S1 to the baseline no intervention scenario was longest for FM1. All home pens took a median of 22 days to become infected for the no intervention scenario compared to a median of 54 days when S1 was implemented. The second largest difference was for FL1 in which the median time for all home pens to become infected for the no intervention scenario was 37 days compared to 53 days for S1. For the rest of feedlots modeled the median time to infect all home pens was 40 days for the baseline scenario compared to 54 days for S1 (FM2), 46 days for the baseline scenario compared to 54 for S1 (FL2), and 15 days for the baseline scenario compared to 18 days for S1 (FS1).

Effectiveness of interventions implemented considering the different depopulation strategies and rates modeled

Implementation of S1 was found to be unsuccessful in preventing FMD infection in all feedlots modeled. S1 delayed the time to infect the entire population but eventually all cattle were infected in all feedlots modeled (See Figure 4-1, Figure 4-2 and Table 4-1 for more detailed information).

Barrier depopulation (S2) was the intervention with the highest probability of success in interrupting FMD infection after its implementation (Table 4-2). For feedlots FM1 and FM2 continued transmission FMDv of infection was interrupted in 16% of simulations when depopulation was set at 500 cattle per day. Continued transmission was interrupted in 38-40% of simulations if 1,000 or 2,000 cattle per day were depopulated in FM1 and FM2. For FL1 and FL2, continued transmission of FMDv infection was interrupted in 41-42% of simulations when

4,000 cattle were depopulated per day; 34-38% of simulations when depopulation was set at 2,000 cattle per day but decreased to only 7-8% when depopulation was set at 1,000 cattle per day. S2 was never successful in interrupting FMD transmission in FS1 for either depopulation rates modeled (1,000 or 2,000 cattle per day) (Table 4-2).

Targeted depopulation (S3) was less effective compared to S2 (Table 4-3). For FM1, if depopulation was set at 500 cattle per day, the percentage of successful simulations was 82%; however, 43 home pens (72%) were depopulated and a median number of 2 uninfected home pens remained after the intervention. The percentage of successful simulations increased to over 90% and a median of 15 (25%) and 18 (30%) home pens remain uninfected when 1,000 or 2,000 cattle were depopulated per day. For FM2, FL1, and FL2, the intervention was poorly effective with rare uninfected home pens after the intervention with a median number of 25, 33, and 27 home pens depopulated regardless the number of cattle depopulated per day. S3 was never successful in FS1 with a median number of 11 home pens depopulated in the intervention (See Table 4-3).

Sensitivity analysis

For S1, the sensitivity analysis showed that the duration of the latent period had a strong positive correlation (Spearman rank correlation coefficient ≥ 0.77 for all feedlots modeled) with the duration of the outbreak. The infectious period was moderately positively correlated (Spearman rank correlation coefficient was approximately 0.28 for FM1, FM2, FL1, and FL2 and 0.47 for FS1) with the duration of the outbreak. The subclinical period had a negative weak correlation with the duration of the outbreak in all feedlots modeled. The beta transmission

parameter did not have a significant association ($p\text{-value}>0.05$) with the duration of the outbreak for any of the feedlots modeled (See Table 4-4).

We summarized only the results of FM1, FM2, FL1, and FL2 for the sensitivity analysis for the depopulation scenarios because the interventions were never successful in interrupting FMDv transmission in FS1. For both S2 and S3, simulations showed that the duration of FMD stages (latent, infectious, and subclinical period) were weakly correlated with having uninfected home pens after the interventions for any of the feedlots and for any of the depopulation rates modeled. The number of hospital pens did not show a significant correlation ($p\text{-value}>0.05$) with having uninfected home pens after S2 was implemented, in contrast, it was weakly correlated (Spearman rank correlation coefficient at most 0.05 for any of the feedlots and for any of the depopulation rates modeled) with having uninfected home pens after S3 was implemented. The day of FMD detection was moderately and negatively correlated with having uninfected home pens after the interventions (S2 and S3) for all feedlots modeled for higher depopulation rates (Spearman rank correlation coefficient was around -0.60 for FM1 and FM2 for 1,000 and 2,000 cattle depopulated per day, and around -0.60 for FL1 and FL2 for 2,000 and 4,000 cattle depopulated per day). The Spearman rank correlation coefficient decreased to -0.23 for both FM1 and FM2 for 500 cattle depopulated per day, and to -0.26 for both FL1 and FL2 for 1,000 cattle depopulated per day) (See Table 4-5).

Discussion

To our knowledge, our model is the first to describe the application of on-farm intervention strategies in the face of a potential FMD outbreak in U.S. beef feedlots. Based on our knowledge of the feedlot production system and previous experience of FMD epidemics in

non-endemic countries, we evaluated the impact of movement restriction during the outbreak, and 2 partial depopulations strategies combined with movement restrictions on the outbreak progression.

The interventions modeled were found to have no effect on the projected duration of the outbreak and eventual infection of the entire feedlot (S1) or the number of remaining uninfected home pens (S2 and S3) in small sized FS1 feedlots. While feedlots with one-time head capacity of 4,000 or less represent approximately 27% of the cattle on-feed population, they represent up to 97% of the feedlots in the country (USDA-NASS, 2017), and partial or targeted depopulation may have little effect on disease in these feedlots. S1 was found to significantly decrease the outbreak progression in feedlots that operated with more home pens per number of hospitals such as FM1 and FL1 which operate with 60 home pens per hospital pen. In feedlots that operated with fewer? home pens per hospital such as FM2 and FL2 which operate with 30 home pens per hospital pen, the outbreak progression was delayed by S1 but not as much as for FM1 and FL1. However, it is important to emphasize that the entire population in these feedlots was infected. S1 may be a useful strategy in medium- and large-size feedlots to delay infection progression while preparing logistics for other intervention strategies such as vaccination, however this was not assessed by the current model. In reality, complete stoppage of mixing of cattle from different home pens in a hospital system might not be feasible. Any attempt to do so would likely require treatment within home pens or use of portable hospital facilities that could move between home pens. The impact of increased entry into home pens or the use of portable hospital pens on transmission within the feedlot was not assessed in this model. Also, complementary interventions to improve the success of movement restrictions such as well-defined biocontainment practices should be developed in advance as suggested by Brandt et al. (2008).

Temporary movement restriction during the period of targeted depopulation is also not assessed in this model but could be implemented.

Implementation of S2 (S1 combined with barrier depopulation) under our assumptions was partially effective on medium- (50% of home pens uninfected after the intervention) and large-size feedlots (25% of home pens uninfected after the intervention) when higher depopulation rates were implemented (1,000 or higher cattle per day for medium-size feedlots, and 2,000 or higher for large-size feedlots). However, this was following a depopulation of 50% of home pens. We used an inside-out strategy of depopulation which means that depopulation was conducted starting with the index home pen and then home pens surrounding the index pen. An outside-in strategy could be explored to assess if there is any advantage. S3 (S1 combined with targeted depopulation) was found to be poorly effective in all feedlots modeled. In FM1, the intervention was partially successful to prevent infection up to 30% of home pens in the feedlot when the depopulation rate was 1,000 or 2,000 head per day, although around 65 to 70% of home pens in the feedlot had to be depopulated. Approximately 50% of home pens were depopulated for FM2, and between 20-30% for FL1 and FL2 while only a few uninfected home pens were present at the end of the outbreak in successful simulations. We highlight that for all strategies we modeled an optimistic day of FMD detection of 3% clinical animals in the pen by observational surveillance of pen-riders. While pen-riders are experienced personnel in detecting diseased animals (Center for Food Security and Public Health et al., 2011; Smith et al., 1994), clinical signs of FMD are very similar to other diseases which may confuse detection (Coetzer and Tustin, 2004). Initial clinical detection will be followed by laboratory confirmation which can take up to several days depending on the logistics to collect and ship samples, and conduct the required tests to confirm FMDv suspicion as discussed by Suttmoller et al. (2003) in their

description of FMD outbreaks in the early 2000s. Other methods for early detection such as the use of a surveillance test are not currently available but could be explored in the future. Other authors have discussed the potential use of real-time polymerase chain reaction (Rt-PCR) to test the saliva of animal in ropes in pens as a surveillance method to detect FMDv during the pre-clinical stage (Nelson et al., 2017). Our model suggests that even with optimistic early detection of FMD within the feedlot, modeled methods are not sufficient to reliably stop an outbreak. Since interventions following our early detection were not sufficient, we did not model later detection times.

Depopulation strategies in previous outbreaks in Ireland, The Netherlands, and the UK attempted depopulation of affected cattle and/or susceptible cattle within 2 days (Costelloe et al., 2002; Pluimers et al., 2002; Scudamore and Harris, 2002). This might be feasible for these countries where the average herd size is <100 cattle (AHBD, 2016); however, the experience in the UK demonstrated that the implementation of this policy was difficult to achieve (Davies, 2002; Ferguson et al., 2001; Gibbens et al., 2001). A requirement to complete depopulation on a large feedlot in 2 days is likely unrealistic even for the partial depopulations modeled by the current model. McReynolds and Sanderson (2014) conducted a survey to investigate the feasibility of depopulation in large feedlots during a health emergency event such as an FMD outbreak and concluded that the methods explored were not viable to ensure a rapid depopulation.

We used a base depopulation rate of 1,000 cattle per day but also modeled higher depopulation rates than 1,000 cattle per day. We found that higher depopulation rates did not make larger differences in modeled outcomes compared to the base depopulation rate. In addition, implementing higher depopulation rates than 1,000 cattle per day could be difficult to

achieve, depending on available facilities. Hence, larger daily culling capacities modeled here may be optimistic. Moreover, facilities available in feedlots to dispose of depopulated carcasses might play a large role to limit rapid depopulation, however this limitation was not assessed in the current model. The cost of implementation should be explored in the future to make a more informed decision about the feasibility of implementation of partial or targeted depopulation strategies.

Another important factor to consider in our model is that for S3 we used a 100% accurate traceback prior to implementation of the depopulation strategies. Even good record-keeping in the feedlot likely will not achieve this level of trace-back accuracy. Since this level of accuracy was not effective, we did not explore less accurate traceback. There is only one report, to our knowledge, that addresses intervention strategies in a large feedlot (>14,000 cattle capacity) in South Africa (Bruckner et al., 2002). The authors reported that they adopted vaccination instead of depopulation due to the difficulties in maintaining bio-security measures during the depopulation of large number of animals. Other authors have suggested the potential implementation of selective depopulation which requires the culling of severely affected cattle by FMD. An expert survey of FMD related parameters and clinical manifestation suggested that approximately 50% to 70% of cattle with clinical FMD in U.S. beef feedlots might develop severe clinical FMD if infected by a high or low strain virulent strain, respectively (Cabezas et al., 2018).

In the sensitivity analysis, we found that the S1 models were sensitive to changes in the latent and infectious periods. This suggests that introduction of high or low virulence strains could have an effect in the outbreak progression within the feedlots modeled. However, for S2 and S3 models, the duration of latent, infectious, and subclinical stages were less influential and

other parameters had a higher effect on the outputs presented. For S2 and S3, the day of FMD detection was the most influential parameters on probability of success in all feedlots modeled. This is not surprising since increased time to detection results in more time for spread between pens prior to implementation of interventions. For future models, different values for sensitivity of the observational surveillance, and delay in implementation of intervention due to FMD laboratory confirmation should be explored. This model does not assess the potential effectiveness of vaccination as a control option and future work should evaluate this.

Conclusions

We believe we have captured the important structure and management aspects of U.S. feedlot systems and best estimates of FMD transmission parameters. Even with some optimistic assumptions, the three intervention strategies modeled were not highly effective in controlling the outbreak or required depopulation of a large proportion of cattle. Still, the results of our model should be interpreted with caution. Little data is available to inform the biological behavior of FMD in completely immunologically naïve cattle population in confined production systems. Refinement of the methods used to model shedding and transmission along with better quality of data is needed to produce more robust models. The strategies should also be measured with a financial component to evaluate the cost-effectiveness of their implementation. Restriction of cattle movements from home pens to hospital pen proved to considerably prolong the outbreak in larger feedlots. Strategies combining vaccination with such movement restriction or targeted depopulation should be investigated. Finally, the exploration of different intervention strategies is challenging in beef feedlots in the U.S. because there are few other countries in the world with a similar production system and the immunologically naïve cattle population, so there is

substantial uncertainty in how severe an FMD outbreak will be if the virus is introduced into the country.

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Author contributions

MWS and VVV conceived and designed the study. All authors contributed to the development, implementation, and analysis of the models and the output interpretation. AHC implemented the models and performed the sensitivity analyses. All authors wrote the manuscript, read and approved the final version for publication.

Conflict of interest

None

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Table 4-1 Description of the feedlot size and layout, and the projected duration of the outbreak for the baseline no intervention scenario and S1 ((hospital movement restrictions to stop mixing of cattle from different home pens in the hospital pen(s) beginning the day after FMD detection)

Feedlot modeled	Number of home pens	Total number of cattle	Number of hospital pens	Intervention scenario modeled ¹	Outbreak duration, days (10 th , 50 th , and 90 th percentiles of $n=2,000$ simulations) ²
FS1	20	4,000	1	None	39, 49, 59
				S1	37, 47, 57
FM1	60	12,000	1	None	46, 58, 69
				S1	68, 82, 95
FM2	60	12,000	1	None	61, 74, 89
				S1	69, 82, 95
FL1	120	24,000	2	None	60, 73, 86
				S1	70, 84, 97
FL2	120	24,000	4	None	68, 82, 95
				S1	70, 84, 97

¹ None – baseline no intervention scenario (Reported in Chapter 3) S1 – hospital movement restrictions to stop mixing of cattle from different home pens in the hospital pen(s) after the day of detection.

² The duration of the outbreak defined as the time in days between the introduction of FMD latent cattle and when the prevalence of infectious individuals within the feedlot is equal to 0.

Table 4-2 Results of the effectiveness of S2 (S1 combined with barrier depopulation) for the feedlot size and layout and the different depopulation rates modeled

Feedlot modeled ¹	Depopulation rate modeled	Number of home pens depopulated (based on $n=2,000$ simulated outbreaks)	Percent of successful simulations (%) ² (based on $n=2,000$ simulated outbreaks)	Number of non-infected remaining home pens in successful simulations (based on $n=2,000$ simulated outbreaks)
FS1	1,000 cattle per day	10	0	0
	2,000 cattle per day	10	0	0
FM1	500 cattle per day	30	16	30
	1,000 cattle per day	30	38	30
	2,000 cattle per day	30	38	30
FM2	500 cattle per day	30	16	30
	1,000 cattle per day	30	39	30
	2,000 cattle per day	30	40	30
FL1	1,000 cattle per day	30	7	90
	2,000 cattle per day	30	34	90
	4,000 cattle per day	30	41	90
FL2	1,000 cattle per day	30	8	90
	2,000 cattle per day	30	39	90
	4,000 cattle per day	30	42	90

¹ FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

² We defined effectiveness of the intervention strategies as the percentage of simulations in which FMD transmission was interrupted for each feedlot and intervention modeled

Table 4-3 Results of the effectiveness of S3 (S1 combined with targeted depopulation) for the feedlot size and layout and the different depopulation rates modeled

Feedlot modeled	Depopulation rate modeled	Number of home pens depopulated (25 th , 50 th , 75 th percentiles of $n=2,000$ simulated outbreaks)	Percent of successful simulations (%) ¹ (based on $n=2,000$ simulated outbreaks)	Number of non-infected remaining home pens in successful simulations (25 th , 50 th , 75 th percentiles $n=2,000$ simulated outbreaks)
FS1	1,000 cattle per day	10, 11, 11	0	0, 0, 0
	2,000 cattle per day		0	0, 0, 0
FM1	500 cattle per day	42, 43, 45	82	1, 2, 12
	1,000 cattle per day		91	2, 18, 18
	2,000 cattle per day		94	4, 15, 18
FM2	500 cattle per day	21, 25, 29	68	0, 2, 4
	1,000 cattle per day		68	0, 2, 4
	2,000 cattle per day		70	0, 2, 4
FL1	1,000 cattle per day	30, 33, 36	42	0, 0, 1
	2,000 cattle per day		46	0, 0, 1
	4,000 cattle per day		48	0, 0, 1
FL2	1,000 cattle per day	25, 27, 30	46	0, 0, 2
	2,000 cattle per day		47	0, 0, 2
	4,000 cattle per day		47	0, 0, 2

¹ FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

² We defined effectiveness of the intervention strategies as the percentage of simulations in which FMD transmission was interrupted for each feedlot and intervention modeled

Table 4-4 Target parameters investigated for associations with the projected duration of the outbreak after implementation of S1 (hospital movement restrictions to stop mixing of cattle from different home pens in the hospital pen(s) beginning the day after FMD detection) for the feedlot size and layouts modeled

Target parameter	Parameter value distribution ¹	Strength of the correlation (Spearman correlation coefficient value) between the model parameter value and the duration of the outbreak for the feedlot of that size and layout ²				
		FS1 ³	FM1	FM2	FL1	FL2
Beta transmission parameter in home-pens (β_{wp})	Triangular (0.02, 0.026, 0.031)	-0.05	-0.01	0.01	0.01	0.01
Duration of FMD latent period (<i>lat</i>) (days)	Weibull ($\alpha = 1.782, \beta = 3.974$)	0.80	0.77	0.83	0.87	0.88
Duration of FMD infectious period (<i>inf</i>) (days)	Gamma ($\alpha = 3.969, \beta = 1.107$)	0.47	0.28	0.29	0.28	0.28
Duration of FMD subclinical period (<i>sub</i>) (days)	Gamma ($\alpha = 1.222, \beta = 1.672$)	-0.19	-0.07	-0.07	-0.07	-0.06

¹ See Section 2.5 and Table 1 in Chapter 3 for a more detailed information of the target parameters

² Bold coefficients indicate $p < 0.05$ for the correlation coefficient between the parameter value and the duration of the outbreak

³ FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

Table 4-5 Target parameters investigated for associations with having uninfected home pens after implementation of S2 (S1 was combined with barrier depopulation) and S3 (S1 was combined with targeted depopulation) for the feedlot size and layouts modeled

Target parameters	Parameter value distribution ¹	Strength of the correlation (Spearman correlation coefficient value) between the target parameters and presence of uninfected home pens after implementation of S3 for the feedlot of that size and layout ²					
		FM1 & FM2 ³ (500 cattle/day) ⁴	FM1 & FM2 (1,000 cattle/day)	FM1 & FM2 (2,000 cattle/day)	FL1 & FL2 (1,000 cattle/day)	FL1 & FL2 (2,000 cattle/day)	FL1 & FL2 (4,000 cattle/day)
Beta transmission parameter in home-pens	Triangular (0.02, 0.026, 0.031)	0.03	0.01	0.01	-0.01	-0.01	-0.01
Duration of FMD latent period (days)	Weibull ($\alpha = 1.782, \beta = 3.974$)	-0.21	-0.14	-0.15	-0.03	-0.10	-0.13
Duration of FMD infectious period (days)	Gamma ($\alpha = 3.969, \beta = 1.107$)	-0.17	-0.14	-0.13	-0.07	-0.08	-0.09
Duration of FMD subclinical period (days)	Gamma ($\alpha = 1.222, \beta = 1.672$)	0.04	0.01	0.02	0.03	0.02	0.02
Number of hospital pens in the feedlot ⁵	Fixed	0.01	0.01	0.01	0.02	0.05	0.05
Day of FMD detection ⁶	Modeled	-0.23	-0.64	-0.65	-0.26	-0.62	-0.63

¹ See Section 2.5 and Table 1 in Chapter 3 for a more detailed information of the target parameters

² Bold coefficients indicate $p < 0.05$ for the correlation coefficient between the parameter value and the duration of the outbreak

³ FS1 is a 4,000 cattle feedlot with 1 hospital-pen; FM1 is a 12,000 cattle feedlot with 1 hospital-pen; FM2 is a 12,000 cattle feedlot with 2 hospital-pens; FL1 is a 24,000 feedlot with 2 hospital-pens; and FL2 is a 24,000 cattle feedlot with 4 hospital-pens (in all the layouts $n=200$ cattle per home-pen)

⁴ Depopulation rates modeled

⁵ FM1 has 1 hospital pen, FM2 has 2 hospital pens, FL1 has 2 hospital pens, and FL2 has 4 hospital pens

⁶ FMD detection occurred when the proportion of clinical cattle in the index home-pen reached a 3% prevalence threshold

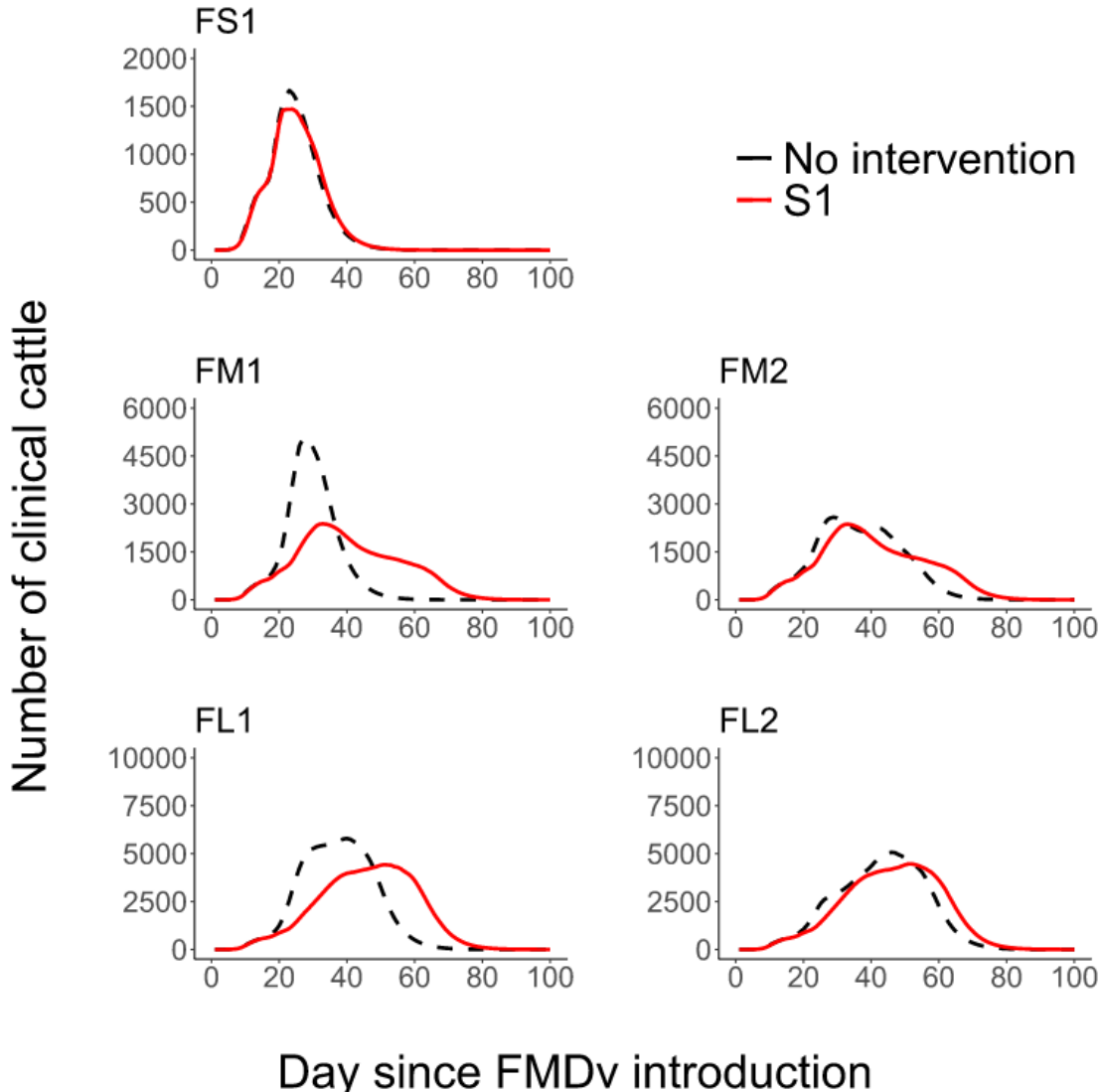


Figure 4-1 Line plots comparing the foot-and-mouth outbreak curves for clinical cattle (Y-axis) during each day since FMDv introduction (X-axis) between the baseline no intervention scenario (Reported in Chapter 3) and the hospital movement restriction (S1) scenario for each feedlot of size and layout. FS1 – small-size feedlot with 1 hospital pen, FM1 – medium-size feedlot with 1 hospital pen, FM2 – medium-size feedlot with 2 hospital pens, FL1 – large-size feedlot with 2 hospital pens; and FL2 – large-size feedlot with 4 hospital pens. The black solid lines represent the 50th percentile of n=2,000 simulated outbreaks for clinical cattle for the baseline no

intervention scenario for each feedlot size and layout (modeled in Chapter 3), red solid lines represent the 50th percentile of the simulations of n=2,000 simulated outbreaks for clinical cattle for S1 – hospital movement restrictions to stop mixing of cattle from different home pens in the hospital pen(s) after the day of FMD detection

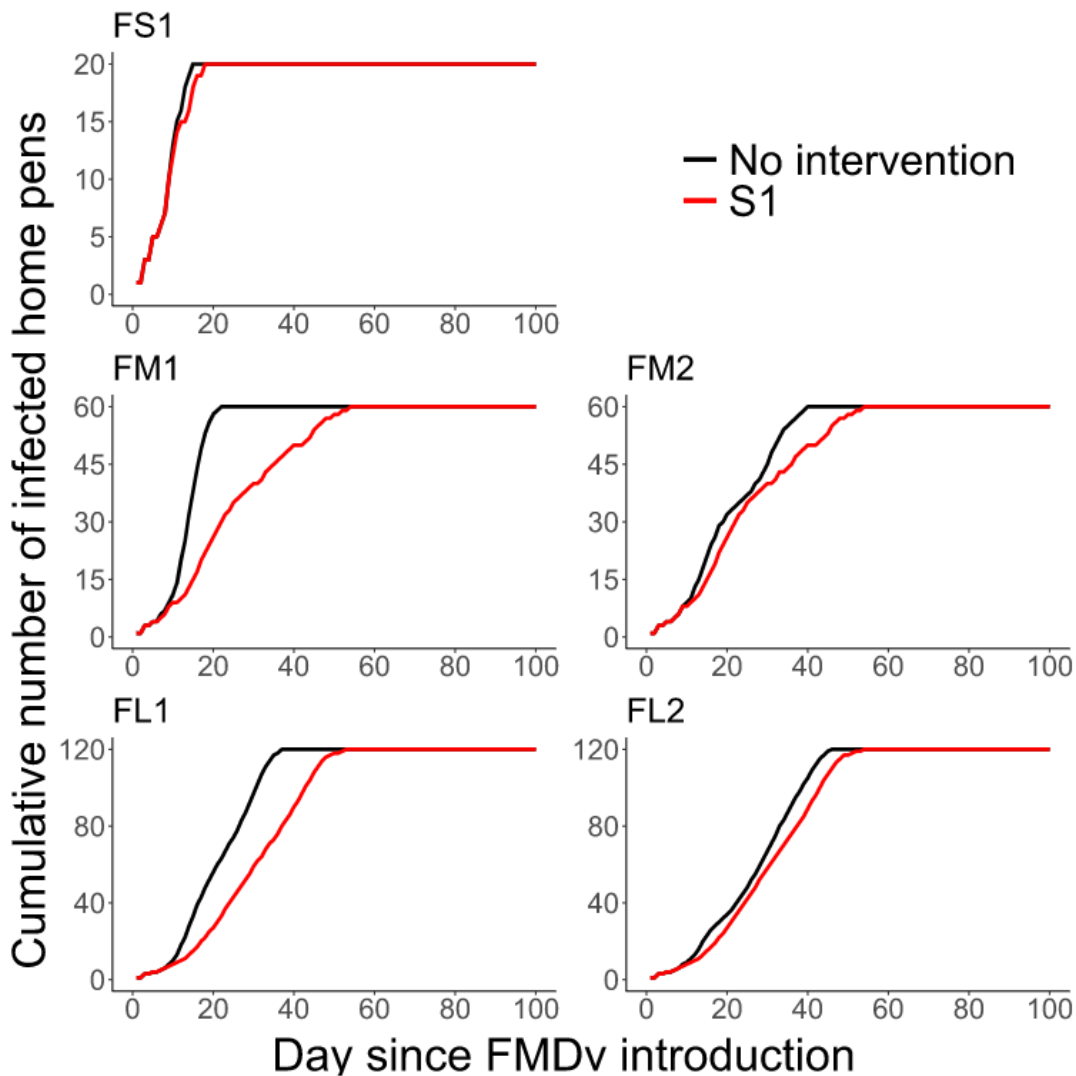


Figure 4-2 Line plots comparing the cumulative number of infected home pens (Y-axis) during each day since FMDv introduction (X-axis) between the baseline no intervention scenario (Reported in Chapter 3) and the hospital movement restriction (S1) scenario for each feedlot of size and layout. FS1 – small-size feedlot with 1 hospital pen, FM1 – medium-size feedlot with 1 hospital pen, FM2 – medium-size feedlot with 2 hospital pens, FL1 – large-size feedlot with 2 hospital pens; and FL2 – large-size feedlot with 4 hospital pens. The black solid lines represent the 50th percentile of n=2,000 simulated outbreaks for the cumulative number of infected home

pens for the baseline no intervention scenario for each feedlot size and layout (modeled in Chapter 3), red solid lines represent the 50th percentile of the simulations of n=2,000 simulated outbreaks for the cumulative number of infected home pens for S1 – hospital movement restrictions to stop mixing of cattle from different home pens in the hospital pen(s) after the day of FMD detection

Supplementary materials

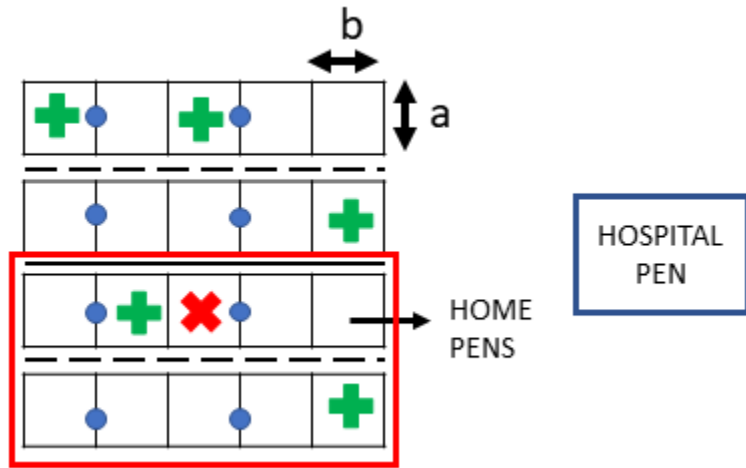


Figure S 4-A FS1 small-size feedlot with 4,000 cattle distributed in 20 pens (200 cattle per home pen), and one hospital-pen. Solid black lines – the drovers alley, dashed black lines – the feed alley, a – the width of the home pens (61 meters), b – the length of the home pens (75.2 meters), blue circle – the water troughs, red X – the index home pen, red rectangle – the area of the feedlot that was depopulated in scenario S2 (depopulation of the row of home pens containing the index home pen and the row on one side of the index home pen), green crosses show representative traced-back home pens that had contact with hospital pen up to 7 days before detection depopulated in scenario S3

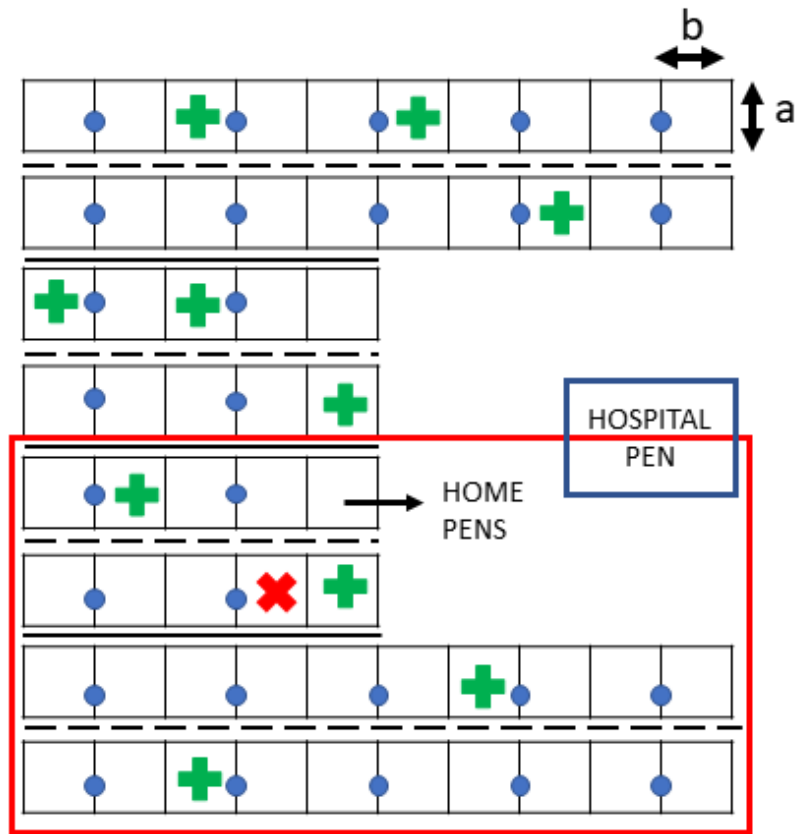


Figure S 4-B FM1 medium-size feedlot with 12,000 cattle distributed in 60 pens (200 cattle per pen), and one hospital-pen. Solid black lines – the drovers alley, dashed black lines – the feed alley, a – the width of the home pens (61 meters), b – the length of the home pens (75.2 meters), blue circle – the water troughs, red X – the index home pen, red rectangle – the area of the feedlot that was depopulated in scenario S2 (depopulation of the row of home pens containing the index home pen, one row on the upper side of the

index home pen, and two rows on the lower side on the index home pen), green crosses show representative traced-back home pens that had contact with hospital pen up to 7 days before detection depopulated in scenario S3

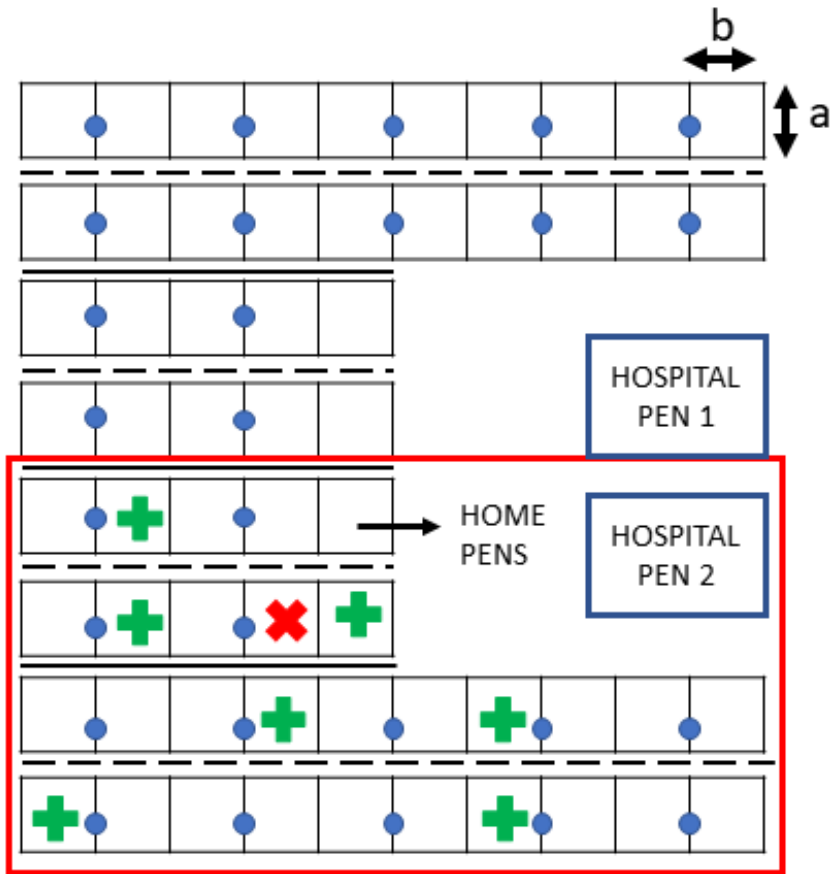


Figure S 4-C FM2 medium-size feedlot with 12,000 cattle distributed in 60 pens (200 cattle per pen), and two hospital-pens. Solid black lines – the drovers alley, dashed black lines – the feed alley, a – the width of the home pens (61 meters), b – the length of the home pens (75.2 meters), blue circle – the water troughs, red X – the index home pen, red rectangle – the area of the feedlot that was depopulated in scenario S2 (depopulation of the row of home pens containing the index home pen, one row on the upper side of the

index home pen, and two rows on the lower side on the index home pen), green crosses show representative traced-back home pens that had contact with hospital pen up to 7 days before detection depopulated in scenario S3

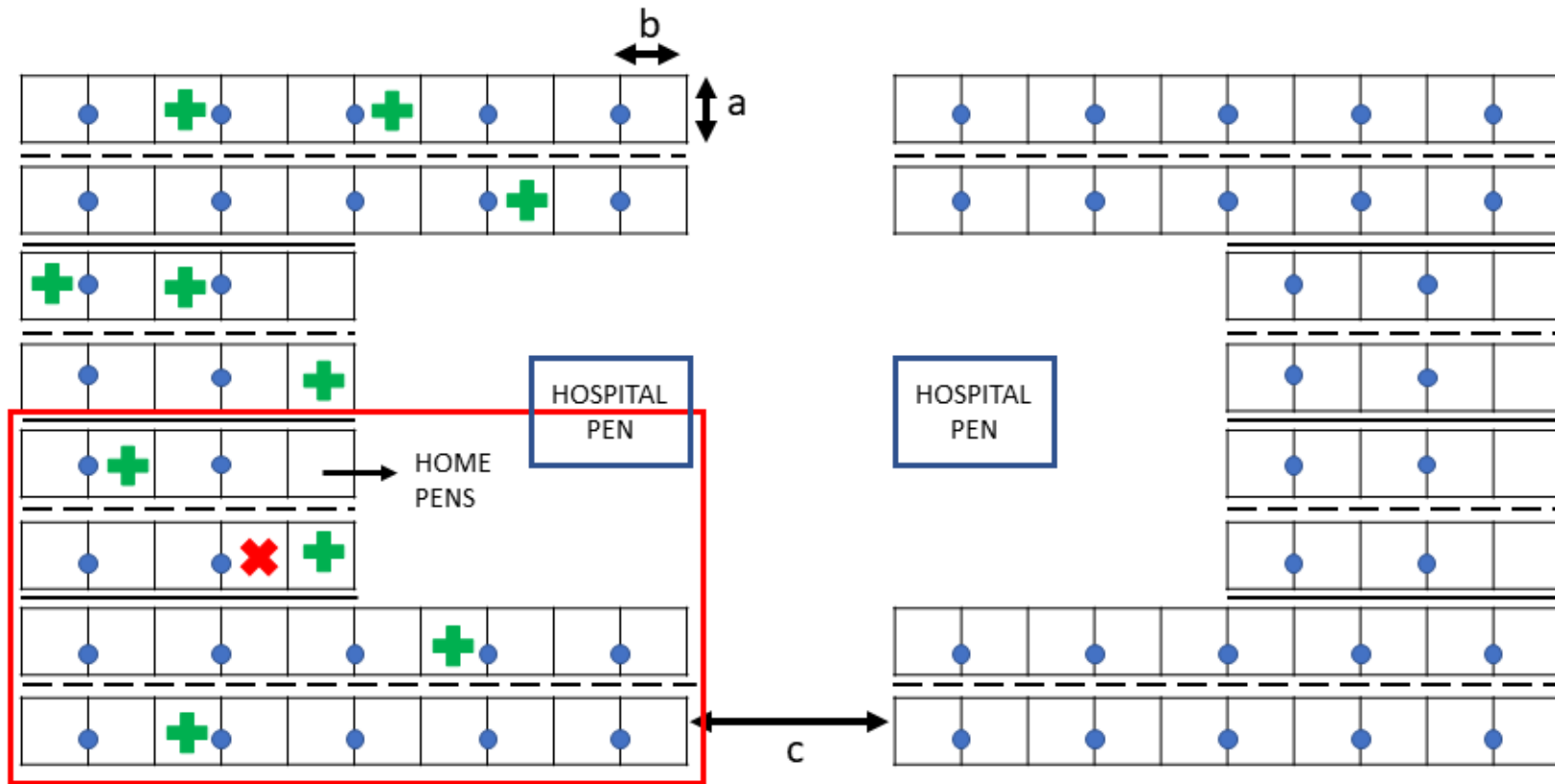


Figure S 4-D FL1 large-size feedlot with 24,000 cattle distributed in 120 pens (200 cattle per pen), and one hospital-pen. Solid black lines – the drovers alley, dashed black lines – the feed alley, a – the width of the home pens (61 meters), b – the length of the home pens (75.2 meters), c – the distance between section of home pens (30 meters), blue circle – the water troughs, red X – the index home pen, red rectangle – the area of the feedlot that was depopulated in scenario S2 (depopulation of the row of home pens containing the

index home pen, one row on the upper side of the index home pen, and two rows on the lower side on the index home pen), green crosses show representative traced-back home pens that had contact with hospital pen up to 7 days before detection depopulated in scenario S3

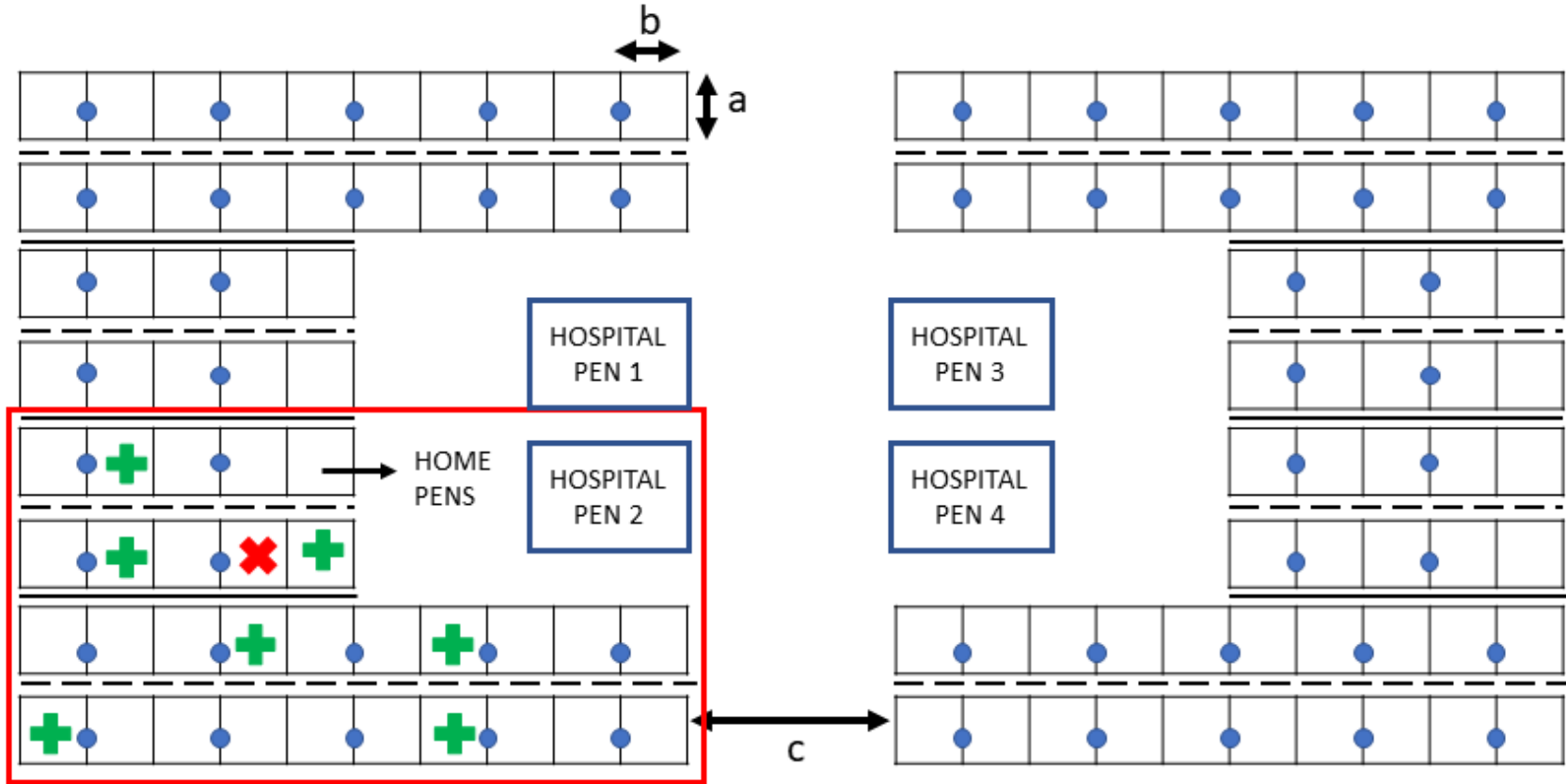


Figure S 4-E FL2 large-size feedlot with 24,000 cattle distributed in 120 pens (200 cattle per pen), and four hospital-pens. Solid black lines – the drovers alley, dashed black lines – the feed alley, a – the width of the home pens (61 meters), b – the length of the home pens (75.2 meters), c – the distance between section of home pens (30 meters), blue circle – the water troughs, red X – the index home pen, red rectangle – the area of the feedlot that was depopulated in scenario S2 (depopulation of the row of home pens containing the index home pen, one row on the upper side of the index home pen, and two rows on the lower side on the index home pen), green

crosses show representative traced-back home pens that had contact with hospital pen up to 7 days before detection depopulated in scenario S3

Chapter 5 - A Description of the U.S. Livestock Industry: Spatial and Network Analysis of Interstate Certificates of Veterinary Inspection Animal Movements

A.H. Cabezas^{1,2}, M.W. Sanderson^{1,2*}, C.Y. Lockhart³, K.A. Riley^{1,2,4}, C.J. Hanthorn^{1,2}

¹Department of Diagnostic Medicine and Pathobiology College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA.

²Center for Outcomes Research and Epidemiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA.

³Animal Health Service, Food and Agriculture Organization of the United Nations, Rome, Italy.

⁴Kansas Department of Agriculture, Division of Animal Health, Manhattan, KS, USA

*Corresponding author: Michael Sanderson, Department of Diagnostic Medicine/Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, United States.

Phone: +1 (785) 532-4264. e-mail: sandersn@vet.k-state.edu

Abstract

Livestock movements are an important mechanism to spread infectious diseases in a population. An understanding of livestock movement patterns is needed to understand national transmission risks of epidemics of highly infectious diseases. Social Network Analysis (SNA) is an approach that helps to describe the relationships among individuals and the implications of those relationships. We used SNA to describe the contact structure of farm-to-farm livestock movements throughout the contiguous U.S. from April 1st, 2015 to March 31st, 2016. We describe 4 network types: beef cattle, dairy cattle, swine, and small ruminant. Livestock movements were sourced from Interstate Certificates of Veterinary Inspection (ICVI) while county-level farm demographic data was from the National Agricultural Statistics Service (NASS). In the described networks, nodes are represented by counties and arcs by shipments between nodes; the networks were weighted based on the number of shipments between nodes. For the analyses, movement data were aggregated at the county level and on an annual basis. Measures of centrality and cohesiveness were computed and identification of trade-communities in all networks was conducted. During the study period, a total of 219,042 movements were recorded and beef cattle movements accounted for 63% of all movements. At least 70% of U.S. counties were present in each of the networks, but the density of arcs was less than 2% in all networks. In the beef cattle network counties with high out-degree were strongly correlated (0.8) with the number of beef cows per county while for the dairy cattle network a strong correlation (>0.86) was found with the number of dairy cattle per km² at the county level. All networks were found to have between 4 and 6 large communities (50 counties or more per community), and they were geographically clustered except for the communities in the small ruminant network. Outputs reported in these analyses can help to understand the contact structure patterns of the

contact networks for beef cattle, dairy cattle, swine, and small ruminants. They might also be used in conjunction with simulation modeling to evaluate spread of highly infectious disease such as foot-and-mouth disease at the national level and to evaluate the application of intervention strategies.

Keywords: U.S. livestock industry, Interstate certificate of veterinary inspection, Social network analysis, Livestock traceability.

Introduction

The U.S. has one of the largest livestock industries in the world with over 92 million cattle in the country (cattle, and calves), over 71 million hogs and pigs, and over 7 million sheep and goats which represents a value of production of approximately \$101 billion for the 4 species (USDA-NASS, 2017). The different production types (beef feedlot, cow-calf, dairy, farrowing-to-finish, farrow-to-feeder, finisher, and farrow-to-weaner) are geographically concentrated in different areas of the country. Texas, Nebraska, Kansas, Iowa, and Colorado are the top 5 states with largest number of cattle on feed and most cattle in feedlots are born in different premises from where they are fed out (Center for Food Security and Public Health et al., 2011a). Feedlot cattle originate mostly from cow-calf operations which are distributed throughout the nation but particularly in Texas, Oklahoma, Missouri, Nebraska, South Dakota and Kansas; they can be brought directly from these operations or from third parties such as stockers and/or auction markets (Center for Food Security and Public Health et al., 2012). Dairy premises also move cattle on and off premises for different purposes. For instance, a common practice is to place young heifers in other feeding operations until they reach the breeding stage (Center for Food Security and Public Health et al., 2011b). For swine, it is suggested that around 71% of pigs in the U.S. finish their production stage in different locations than where they were born. Many of these movements are within-state but there are also a large number of movements that occur between states; for instance, Iowa receives around 1.7 million pigs every month from other states (Center for Food Security and Public Health et al., 2011c). As described above, the livestock industry in the U.S is complex and involves large movement of animals during their different production stages.

Movements between states are mostly recorded by Interstate Certificates of Veterinary Inspection (ICVI) which are documents issued by an accredited veterinarian certifying that animals are visually healthy at the time of inspection (Portacci et al., 2013). Most animal shipments that cross state borders are required to be accompanied by an ICVI, but there are exceptions such as shipments that go directly to slaughter plants. Additionally, some interstate movements occur without an ICVI even if one is required. These certificates are however, the most accessible source of information regarding interstate animal shipments within the country (Forde et al., 1998; Portacci et al., 2013).

Attempts to capture shipment rates with other source of information than ICVIs have been previously done. Bates et al. (2001) estimated the rates of direct (animal movements) and indirect (personnel or vehicle movements) contact among farms in 3 counties in California. McReynolds et al. (2014) conducted a similar study to estimate direct and indirect contact rates between farms in Colorado and Kansas. Liu et al. (2012) developed a spatial agent-based simulator to summarize beef cattle movements in Kansas. In intensive bovine and swine production systems, alternatives sources of movement data are the database of large companies which own multi-sites in different parts of the country. This was the source of data Kinsley et al. (2019) used to characterize swine movements in an eastern seaboard state of the USA and the Great Plains; however, access to data from private companies might be difficult to obtain due to confidentiality and privacy concerns. Studies above used surveys, questionnaires, and/or private-company data as sources of information and while they provided useful data regarding animal movements in the study areas, there is a need to capture animal movements at a larger scale and not constrain them to a specific area due to the complex livestock production system in the country. The understanding of animal movements and its association with the spread of

infectious diseases in livestock populations is a key issue in order to efficiently implement surveillance programs and control strategies during potential outbreaks (Fevre et al., 2006).

The study of livestock movements requires an approach that allows researchers to capture networks of movements and factors that influence movements such as animal production stage, seasonality, distance to markets or slaughter plants, proximity to areas with large feeding capacities, etc. Social network analysis (SNA) is an approach that provides the tools to describe and characterize relationships or interactions between individuals and the ramifications of those interactions (Martinez-Lopez et al., 2009; Newman, 2010; Dubé et al., 2011). The first published SNA studies in veterinary sciences were conducted to predict tuberculosis (*Mycobacterium bovis*) transmission in wild brushtail possum (Corner et al., 2003) and to explore the contact network among race horse trainers in Great Britain (Christley and French, 2003). Since the FMD 2001 UK epidemic, SNA has been used to study the implications of livestock movements (cattle, swine, and sheep) to evaluate the risk for disease transmission in numerous countries (Webb, 2005; Bigras-Poulin et al., 2006; Kiss et al., 2006; Ortiz-Pelaez et al., 2006; Webb, 2006; Bigras-Poulin et al., 2007; Robinson and Christley, 2007; Brennan et al., 2008; Natale et al., 2009; Volkova et al., 2010; Relun et al., 2016; Kukielka et al., 2017).

In the U.S., Buhnerkempe et al. (2013) used SNA to describe patterns of livestock movements within the contiguous U.S. They collected a systematic sample of 10% of the ICVI export records during 2009 from all states to develop annual cattle networks at the county, state, or grid (50 and 500 km) level. While this was the first study to describe the national cattle network, it did not differentiate between beef or dairy cattle movements. Kinsley et al. (2019) described annual pattern movements between swine operations. They used data from 3 multi-site swine production company sources in 2 regions of the country which represents around 25% of

the sow population in the U.S. To our knowledge, there are no studies that describe patterns of movements in small ruminants (sheep or goats). The understanding of contact networks for the different livestock species should be explored because of the role each of them play in the spread of infectious diseases such as Foot-and-mouth disease (FMD). For instance, it is suggested that sheep were responsible for the spread of Foot-and-mouth disease virus (FMDv) during the initial phase of the 2001 UK epidemic (Anderson, 2002) as they only develop mild clinical signs and detection is difficult (Coetzer and Tustin, 2004).

A valuable tool within SNA is the use of trade-community detection to better characterize patterns of livestock movements. Newman (2010) defines a *community* as a group of nodes which have more interaction within groups and less interaction between groups. Trade-community detection has been previously used to describe pig trade patterns in Bulgaria, France, Italy, and Spain (Relun et al., 2016), and England and Wales (Guinat et al., 2016). In the U.S., Gorsich et al. (2016) used the cattle network developed by Buhnerkempe et al. (2013) to identify communities within the beef, and dairy cattle network. The application of trade-community detection can be useful to identify group of nodes (counties) with high frequency of interaction which can be targeted by surveillance systems or during the early implementation of intervention strategies during disease outbreaks (Gorsich et al., 2016).

In this study, we used SNA to describe patterns of interstate movements for livestock species (beef cattle, dairy cattle, swine, and small ruminants) during April 1, 2015 to March 31, 2016 within the contiguous U.S. (excluding Alaska, Hawaii, American Samoa, US Virgin Islands, Northern Mariana Islands, Guam, and Puerto Rico) which have been derived from ICVI import records. We also used the species-specific networks developed to characterize the trade structure by the application of community detection algorithms. We expect our results to

contribute to the investigation in cattle movements already conducted, but also to provide the first description of beef cattle, dairy cattle, swine and small ruminant movements at the national level which will be helpful to inform contingency plans for disease surveillance and control strategies, and to contribute to the development and parameterization of disease spread modelling.

Methods

Data collection

We contacted the Veterinary State Offices in each of the 48 states of the contiguous U.S. and requested the total bovine, swine, and small ruminant ICVIs imports—in digital form if possible—during April 1st, 2015 to March 31st, 2016. Paper form records were collected if the state could not provide digital record movements. The time period was selected because it matches the timeframe for the cooperative agreements that states receive from the US Department of Agriculture (USDA) for reporting the animal disease traceability program. Follow-up contact was initiated to maximize response. Fields of interest were county of origin and destination, date of movement, species (bovine, swine, ovine, and caprine), livestock type (beef cattle, dairy cattle, swine, small ruminants), production type (cow-calf, feedlot, dairy, all swine operations, ovine, and caprine) number of animals, and purpose of shipment (e.g. breeding, feeding, show). States were asked to provide data on specific county of origin to county of destination movements, or if this could not be provided, state of origin to state of destination movements.

Assembly of the database

Data provided by the veterinary state offices were variable and not consistent regarding the fields provided; some states provided movements that could be aggregated at the county level while others provided only movements at the state level (See section 3.1 for a more detailed description of the data received). It was common that states provided zip code and/or city of origin and destination, so we used a commercial database to match zip codes or cities of origin and destination with their respective counties. The distance between shipments was estimated based on the longitude and latitude of the centroids in each county. Records of movements with a large number of animals (e.g. records with movements of 10,000 animals or more) were split based on the average production shipment size in the state of destination on the assumption that they represented multiple movements.

For the analysis, movements were classified into 4 livestock types: beef cattle, dairy cattle, swine, or small ruminant. If a state did not differentiate the production type of movement for bovine, we used the purpose of shipment (if it was provided) to determine whether the movement was beef or dairy cattle (Figure S 5-A in Supplementary Materials for a classification tree to determine production type of movement for bovine). If the determination of beef or dairy cattle movement was not possible based on the purpose of shipment or purpose of shipment was not provided, we used a probability distribution based on the proportion of beef and dairy cattle in the county (if state provided county-to-county movements) or state (if state provided state-to-state movements) to infer the production type of movement. That is, the number of bovine records in which livestock type (beef or dairy cattle) could not be specified were defined as beef or dairy cattle based on the proportional distribution of beef or dairy cattle population in the county or state for both origin and destination. We used demographic data from the 2012 Census

of Agriculture to estimate the proportion of animals for each livestock type (beef or dairy cattle) at the county and state level. Caprine and ovine movements were combined into a single category (small ruminants).

Inference of data for missing states, and counties of origin and/or destination

Twelve states did not provide ICVI data (Arizona, Arkansas, Connecticut, Delaware, Georgia, Maine, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, Tennessee). For non-reporting states, we estimated the annual number of import shipments for each production type based on the state of origin specific production type shipment rates into bordering counties/states and adjusted those rates based on the number operations of each production type in the non-responding state to estimate the final number of shipments. Denoting N the annual

number of shipments into the non-reporting state, then $N_{(a,b)} = \left[\left(\frac{\sum X_{a,b}}{\sum Z_a} \right) \right] * \sum Y_b$ where a

represents the county/state of origin, b the county/state of destination, X the number of production type-specific shipments from the origin county/state into the neighboring county/state, Z the number of production type specific premises in the origin county/state, and Y the number of production type specific premises in the non-reporting state.

For states that county of origin/destination were not provided (non-county reporting states) (list), the zip code/city provided could not be matched to a county due to irregularities in the data, or only provided state-to-state movements; we inferred the county of origin/destination based on the proportional distribution of number of animals in each production type at the county level in the state of origin and destination. We used demographic data from the 2012 Census of Agriculture to estimate the proportion of animals in each production type at the county level.

Comparison with the USDA NASS annual in-shipments

We evaluated the accuracy of the ICVI data collected and inferred by comparing the reported number of animals imported into each state in the ICVI data with the 2015 number of in-shipments (animals imported into states for feeding or breeding purposes, excluding the animals imported for immediate slaughter) reported in the Meat Animals Production, Disposition, and Income 2015 Summary by USDA (2016). Based on our knowledge of the livestock industry we developed the following conditions after comparison of imported animals in both sources:

- For those states in which the annual number of imported animals in the ICVI data was higher than those reported by USDA (2016), we accepted the ICVI estimates.
- For those states in which the annual number of imported animals in the ICVI data was lower than those reported by USDA (2016), we generated new shipments based on that difference and those new generated shipments were allocated to production types and counties using the process already described above.
- For those states that did not provide any data, we used the annual number of in-shipments (animals imported into states for feeding or breeding purposes, excluding the animals imported for immediate slaughter) reported by USDA (2016) and compared with those already inferred in Section 2.3 above. We used the difference to generate new shipments and those new generated shipments were allocated to production types and counties using the process already described above.

Verification of method to infer county level movements for states that only reported state-to-state data and for non-reporting states

We evaluated our process to infer counties of origin or destination by selecting one of the states that provided only state-to-state movements. We simulated the process described above (to infer counties of origin and destination) 100 times and measured the number of times (in percentage) specific counties were included in the outputs for each production type (e.g. feedlot). We then compared those percentages simulated with the percentage of animals for that specific production type in each county reported by the Census of Agriculture 2012. We used a non-parametric Wilcoxon Signed-Rank Test to test the difference in both measures under the 5% level of significance.

We evaluated the accuracy of the methods we used to infer movements in non-reporting states by repeating the process in two states. We chose one state to evaluate inferred bovine movements and one state to evaluate inferred swine movements. Both states were chosen because their ICVI data matched the number of in-shipments reported by USDA (2016). The process was repeated 20 times in each state. We then compared the proportion of production type inferred movements per county with the observed ICVI data for both states.

Network analysis

Description of the networks

We described contact networks for beef cattle, dairy cattle, swine, and small ruminants. We considered counties as nodes and the shipments between nodes as the arcs in each network. Arcs were weighted based on the number of shipments between nodes. We aggregated

movements at the county level because data on a smaller scale of aggregation is not available due to privacy concerns and confidentiality.

We described 4 types of networks for each production type:

- Complete county: annual county-to-county inferred networks for the 48 states.
- Partial county: annual county-to-county network for the 36 states that provided data.
- Complete state: annual state-to-state networks for the 48 states.
- Partial state: annual state-to-state networks for the 36 states that provided data.

Descriptive statistics such as number of shipments between nodes, number of animals per shipment, and distance traveled between nodes were computed. We also estimated metrics related to the network size such as number of nodes and arcs present, centrality measures, and measures of cohesiveness for every network. We evaluated the network centrality measures estimated in the county-to-county networks with the demographic and production data at the county level by calculating Spearman rank correlation coefficients. Metrics estimated, and their definitions can be found in Table 5-1.

Detection of trade communities

We used the Walktrap algorithm developed by Pons and Latapy (2006) to identify trade communities within the complete and partial county networks for each production type. A community can be defined as a group of nodes with larger number of edges/arcs within the group compared to between groups (Newman, 2010). This is a computationally efficient method to identify communities in large networks based on random walks. The reasoning behind the approach is that “random walks tend to get trapped within densely connected parts corresponding to communities”; based on these random walks, the algorithm measures the structural similarity

between nodes and between communities; the random walks are then used to compute distances between nodes, and finally nodes are allocated to groups based on those distances computed (Pons and Latapy, 2006). The largest communities (communities with more than 50 counties) in each network were mapped and summary metrics such as number of nodes, number of links were estimated. Also, the number of isolated counties (counties that are not members of any community) were computed. The percentage of arcs (out of the total arcs in the networks) within the largest communities were computed in each network.

The cleaning process, assembly of the dataset, and statistical analyses were conducted in R (R Core Team, 2014) and STATA® 13 (College Station, Texas 77845, USA). Network analyses were done in R (R Core Team, 2014) using the “igraph” package (Csardi and Nepusz, 2006). Figures were made in R (R Core Team, 2014) using the “ggplot” package (Wickham, 2016).

Results

Descriptives of the ICVI data collected and verification methods

We received ICVI movements from 36 states. Twelve states (Arkansas, Arizona, Connecticut, Delaware, Georgia, Kentucky, Massachusetts, Maine, Maryland, Mississippi, New Jersey, and Nevada) did not provide any data due to inadequate personnel available to do the job or simply no response to our contact. Of the 36 states that provided data, 7 states provided movements only at the state to state level and the remaining 31 provided information (full address or city or zip code or county) that could be matched to county of origin/destination. One state did not provide date of movement and another state only provided the month in which the

movement occurred; they both provided an aggregated number of shipments and animal headcounts. Five states did not provide purpose of shipment and the information provided in the remaining states were highly variable.

The ICVI dataset for all reporting states and all species consisted of 190,254 movement records. County of origin and destination was provided in 67% and 84% of the ICVI data, respectively. Determination of livestock type for bovine (beef or dairy cattle) could be determined in 28% of the ICVI bovine data. In ICVI data where livestock type was reported, beef cattle movements accounted for 63% of the total ICVI data collected, dairy for 13%, swine for 19%, and small ruminants for 5%. Fifty percent of the ICVI import records consisted of shipments with 1 to 30 headcounts. The median headcount per shipment was largest for swine (549) and smallest for small ruminants (4). Median number of shipments between counties was 1 for all production types but beef cattle and dairy cattle had the largest range (up to 398 shipments). Swine was the species with shortest distance traveled per shipment (495 km), the distance for the other species was on average 600 km (See Table 5-2). After the inference of shipment data for those states that did not report livestock movements, and the approximation of the ICVI data to the number of in-shipments reported by NASS, the final dataset consisted 219,042 record movements which represented an increase of approximately 15% of the ICVI data collected.

We found that the method used to infer movements in non-reporting states was able to infer between 80 to 90% of movements compared to the observed ICVI data in the state selected for bovine movements and 60 to 85% compared to movements in the observed ICVI data in the state selected for swine movements. The process was repeated 20 times in each state and the results were always within the ranges mentioned above. For the verification of the process to

infer counties, the Wilcoxon Signed-Ranks Test indicated that there were no statistically differences ($p\text{-value}>0.05$) between the number of times out of the 100 simulations a county was selected (represented in percentage) for each production type and the percentage of animals in each production type in a specific county reported by the 2012 Census of Agriculture.

Description of the network level metrics

Metrics described below focus on the county-to-county complete networks. A detailed summary of the metrics investigated in the county-to-county partial networks and state-to-state complete and partial networks can be found in Table 5-3. All networks had more than 70% of counties present (of 3,053 total counties in the U.S), but the beef cattle network had the highest percent of counties with 96% of them sending/receiving at least 1 shipment during the study period. The density of arcs present in the networks was less than 2% for all networks. The proportion of arcs having bi-directional paths was highest for the beef cattle network with 12% and lowest for the small ruminant network with 3%. There was no evidence of preferential connections between nodes in any network as demonstrated by the low values of assortativity (between -0.14 to 0.08). When the direction of arcs was not considered, all networks became a single giant component with more than 99% of counties being members of the Giant Weakly Connected Component (GWCC). In contrast, when direction of the arcs was considered 88% of counties were present in the Giant Strongly Connected Component (GSCC) in the beef cattle network, 65% in the dairy cattle network, 57% in the swine network, and 48% in the small ruminant network.

Description of node-level metrics

In the beef cattle network, counties with highest in-degree were mainly found in the central states of the country (Colorado, Kansas, Nebraska, and Wyoming) while counties with high out-degree shifted towards the north central and west of the country. Counties with high in- and out-degree also had high betweenness centrality. In the dairy cattle network, counties mainly in California, Oregon, and Wisconsin were found to have high in- and out-degree. Counties in Pennsylvania, New York, and in the Central states were found to have high betweenness centrality in the dairy cattle network. In the Swine network, counties with high degree and betweenness centrality matched those with large swine population such as in Iowa, Illinois, and Minnesota. Counties in western states were found to have high degree and betweenness centrality in the small ruminant network. See maps in Figure 5-1, Figure 5-2, Figure 5-3, and Figure 5-4 for a more detailed picture of degree and betweenness centrality in county-to-county complete networks. We found that in general most counties in all networks had on average low degree and betweenness centrality but a few were found to have large values for both metrics. In- and out-closeness were consistent across all nodes in all networks but the low values suggest that counties do not reach other counties or are reached by other counties on a short path (See Figure S 5-B, Figure S 5-C, Figure S 5-D, and Figure S 5-E in Supplementary Materials). We also investigated the presence of hubs and authorities in the county-to-county complete network. In brief, identification of hubs and authorities accounts for the out-degree and in-degree centrality, respectively, but also accounts for the importance of a county ranked by the connections with other counties that also have high connectivity. In all networks, we found that counties with high in-degree were also identified as hubs and counties with high out-degree were also identified as authorities (See Figure S 5-F and Figure S 5-G in Supplementary Materials).

Centrality measures correlations with the demographic metrics

The highest correlation in the beef cattle network was the number of beef cows per county with the out-degree centrality (0.80). Beef cattle density per km² was only moderately correlated with out-degree centrality (0.67). In a similar way, the county number of cattle on-feed was moderately correlated with in-degree centrality. For the dairy cattle network, high positive correlations were found between out-degree and number of dairy cows per county (0.86) and dairy cattle density per km² (0.82). In the swine network, the swine density per km² was found to be highly correlated with out-degree (0.75) and moderately correlated with in-degree (0.64). Strong correlations were not found for any of the demographic metric in the small ruminant network. Overall, livestock demographic metrics in the beef cattle, dairy cattle, and swine network were better predictors for out-degree as compared to in-degree centrality. See Table 5-4 for a detailed description of correlations between demographic metrics and centrality measures investigated.

Trade-community detection

The trade-community detection was conducted in the county-to-county complete networks to represent a national picture in which all states participate (or potentially participate) in the livestock movements. The small ruminant network had the highest number of communities (724) identified by the algorithm and the largest number of isolated counties (510). The beef cattle network had the lowest number of communities (172) and the lowest number of isolated counties (148). All networks had between 4 and 6 large communities (more than 50 counties). The beef cattle network had two large communities with 1,079 and 867 counties each, they

accounted for 28% and 25% of total arcs, respectively, and were geographically located in the central and west region of the country. Two large communities with 767 and 683 counties were found in the dairy cattle network, they accounted for 25% and 28% of total arcs, respectively. One large community in the swine network with 682 counties was found which accounted for 64% of the total arcs. The communities identified in the small ruminant network had less than 500 counties, they were more spread out in the west of the country, and the largest community had 13% of total arcs. See maps in Figure 5-1, Figure 5-2, Figure 5-3, and Figure 5-4 for a geographical depiction of the largest communities in all networks and Table 5-5 for a more detailed description of the communities identified in all networks.

Discussion

The present study represents the second attempt to describe interstate livestock movements (Buhnerkempe et al., 2013) and identify patterns of trade communities in U.S cattle (Gorsich et al., 2016), and the first attempt to picture national movements in swine and small ruminants. Previously, Kinsley et al. (2019) described swine movements within two regions that represents approximately 25% of the sow population in the country.

Interstate Certificates of Veterinary Inspection are still the only traceability system for animal movements in the U.S. (Portacci et al., 2013). The ICVI data collected was variable between states and not all movements between states are captured either due to allowed exceptions or movements that should have an ICVI but do not.. Of note, the ICVI volume of import movements for some states varied from the in-shipments reported by the NASS. We conducted the approximation methods described above to infer missing data and represent the flow of livestock throughout the country. Our inference process for missing data underestimated

movements when used to infer movements in states that reported county to county movement data and then compared to the ICVI data for that state. As such our estimates of livestock movement may be best considered as a lower bound for interstate livestock movements. It should also be noted that the description of the networks in this study focused on interstate movements only. Intra-state movements are not captured here as there are no tracking systems in the U.S. that record those movements. A recent study by Beck-Johnson et al. (2019) describes the proportion of intra-state shipments by region in the U.S. in the beef cattle and dairy cattle sector via elicitation surveys. The study did not identify differences in intra-state shipment rates by region due to the small sample size but suggests that most of livestock movements occur within state boundaries and the importance of those movements to improve the understanding of national cattle movement. They also discussed the possibility to infer intra-state movements based on other variables such as proportion of premises in a county, presence of auction markets, and proximity to state borders in combination with ICVI data. This methodology has been used by Lindstrom et al. (2013) a study to scale-up partially observed networks. This can be a powerful method to explore and develop more complete networks than the ones described in here.

In the present study we mostly focused in the description of the county level networks because the study of networks at the state level overlook the heterogeneities within states as described by Buhnerkempe et al. (2013) who also conducted analysis at other aggregation levels such as grids of 50 and 500 km². They suggested that aggregation at the county-level is a good indicator of the movements patterns to capture heterogeneities within the country. These heterogeneities should be considered when developing surveillance or control strategies at the state level because in general there are few counties within states that dominate or are more responsible for livestock movements. In general, our results are in agreement with those

presented by Buhnerkempe et al. (2013); however, there were some differences in the network and node-level metrics. Such differences might be due to changes in the livestock industry during the time-frame in which studies were conducted, but also the separation of bovine movements by livestock type (beef or dairy cattle). There are marked differences in the geographical location within the country for dairy and beef cattle (cowcalf and feedlot) operations, and also there are on average 5 more times beef cattle than dairy cattle in the country (USDA-NASS, 2017).

A large proportion of counties within the country (more than 70% for all networks) were present in all networks although the density (less than 2%) suggest that only a few counties highly participated in livestock movements during the study period. The ratio of arcs between the beef cattle and the dairy cattle network (4.8:1) resembles the ratio of the beef cattle and dairy cattle population (4.8:1) which was also suggested in a previous description of the U.S. national network (Buhnerkempe et al., 2013). The low reciprocity found in all networks (less than 0.12) confirms the direct nature of livestock networks in which animals are normally moved from one farm to another according to their production stage and they do not normally return to the farms or counties where they were born. In all networks, when the direction was not considered, almost 100% of the counties were part of the GWCC while around 60% of counties were part of the GSCC in the dairy and swine network, 48% in the small ruminant network, and 88% in the beef cattle network. Previous work suggests that the GWCC and the GSCC can be considered as indicators of the lower and upper bound of the estimated epidemic size if an infectious disease is introduced in a population (Kao et al., 2006) although the outputs here are based on a static network aggregated at the annual level, so a temporal analysis should be conducted to analyze the potential epidemic size.

We found that counties with higher in-degree centrality in the beef cattle network were located in the central states where more feeding operations are present while counties with high out-degree were towards the northern and west states where large concentrations of cow-calf operations are present. This resembles the production system in the U.S. and is supported by the high correlation between number of beef cows per county and out-degree. This finding is consistent with the lower correlation for beef cattle density per km² with out-degree. Counties with high beef cattle per km² likely have a high population of cattle on-feed which would have a low out-degree since shipments to slaughter were not captured in this study. This would dilute any correlation between density and out-degree in high density counties.

In the dairy cattle network, counties with high out-degree were correlated with the number of dairy cattle per county. Counties with large number of dairy cattle per county would likely move many heifers for development and breeding in addition to animals not destined for breeding to get fed and finish their production life in a feeding operations. In the swine network, counties with high in- and out-degree were found in IA and states bordering IA which are the states with larger concentration of swine. In the swine network, interpretation of correlation metrics between demographics and centrality measures should be done with caution as we did not differentiate movements between specific production type (farrowing-to-finish, farrow-to-feeder, finisher, and farrow-to-weaner) for swine. The ICVI data collected only allowed us to identify whether a movement occurred between swine operations regardless the specific type of operation.

We also identified authorities and hubs to try to determine important nodes in the network. Overall we found that authorities matched those counties with high in-degree and hubs matched counties with high out-degree. This suggests that degree centrality is a good indicator of

the importance of counties in the networks described during the study period which can be targeted for disease surveillance or control programs. Modeling studies should be conducted to assess the impact of targeting counties with high degree centrality to evaluate interventions. A study in Italy (Natale et al., 2009) found that interventions are more efficient if nodes with high betweenness are targeted instead of nodes with high degree centrality. In a similar way, a study conducted in the UK demonstrated that nodes with high betweenness were identified to spread disease during the initial phase of the outbreak (Ortiz-Pelaez et al., 2006). One group of actors missing from this analysis and from previous analyses is auction markets through which a substantial portion of livestock move. Data including them are not available but they could have a substantial impact on the network and would likely have high betweenness.

We found that all networks consisted of 4 to 6 large and geographically defined communities during the study period. Further analyses have to be done to assess if there are seasonal variations in community structure in shorter periods although it has been previously described that community structure is consistent in monthly and annual shipments in the U.S. beef and dairy cattle industry (Gorsich et al., 2016). The community structure reported here appears more geographically clustered than the community structure reported by (Gorsich et al., 2016). Differences may be due to differences in ICVI collection. They collected a systematic sample of 10% of ICVI movement data from all states which may be more susceptible to small sample variation. Our study collected a census of ICVI movement data but with missing data from some states. Further, the method of community detection varied between the studies (modularity maximization vs walktrap algorithm) that may have resulted in differences. The community structure reported here is consistent with the distribution of the dairy cattle population in the country.

The estimated ratio of arcs within communities compared to between communities was 3:1 in the swine network which was expected due to swine being more concentrated in fewer areas of the country compared to beef and dairy cattle. This was supported by the fraction of arcs (64%) in the largest swine community which is geographically located in states with the largest swine population in the US. Other studies characterizing swine movements in Europe have also reported larger ratios of arcs within communities than between communities (Relun et al., 2016). The ratio of arcs within communities for the beef cattle, dairy cattle, and small ruminant network was not as high as for the swine network. In the the beef and dairy cattle networks, the two largest communities accounted for 1/3 of movements in each network. This supports that the beef and dairy network is more geographically dispersed but also that a few areas of the country tend to dominate the livestock movements in the US. An important application of identification of communities in networks might be when planing disease control implementation of a containment zone for recovery of disease free status during an outbreak of an infectious disease such as FMD. Currently, the US has FMD-free status where vaccination is not practiced. Incursion of FMDv would result in loss of FMD-free status which would severely affect the country financially. Knowledge of community structure within the US could help to sucesfully implement a containment zone, according to the provisions of Chapter 4.3 of the Terrestrial Animal Health Code (OIE, 2019), which could limit the suspension of FMD-free status of that containment zone only while the FMD-free status for the rest of the country could be resumed. Such a plan would require clear separation of the containment zone and traceable livestock movements (OIE, 2019).

One limitation of the Walktrap community algorithm is that it does not consider directionality which might limit the interpretation of our findings given that movements of

livestock between farms are generally considered directed due to the production system (Dubé et al., 2009). However, currently available algorithms for direct networks are computationally very intense and do not work well with large networks (Relun et al., 2016). The same authors also mentioned that they compared the Walktrap algorithm with an algorithm for directed networks for a country in their study and they found a good agreement between both outputs. Yang et al. (2016) investigated the accuracy of several algorithms (including the Walktrap) in artificial networks and found that the Walktrap had generally a higher level of accuracy when applied in small and large networks compared to other algorithms tested. They also mentioned that other algorithms tend to over or underestimate the number of communities in a network while the Walktrap was consistent in identifying the correct number of communities in the networks tested. However, exploration of other algorithms to identify communities in directed networks should be of further interest to apply in the networks reported here and compare to the outputs of the Walktrap algorithm.

Conclusion

Patterns of livestock movement at the national level is a key factor to understand implications for disease spread and therefore to inform policy for disease surveillance and disease control interventions. Our analyses helps to identify important nodes (counties) within the country and also trade communities for the main livestock types which can be targeted during disease reponse plans. We found that networks described resembled the distribution of production type systems of the livestock types in the country. However, we highlight that the outputs presented in this study are based on the study period and only apply to interstate livestock movements and not intra state movements. Also, it should be noted that data for 12

states were inferred, so overinterpretation of these results should be avoided. On the other hand, the results presented here can be used to generate hypotheses for future studies and might serve as basis for more complete analyses in the future. In addition, our network outputs might be used in conjunction with simulation modeling to evaluate spread of highly infectious disease such as foot-and-mouth disease at the national level and to evaluate the application of intervention strategies.

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Author contributions

MWS conceived and designed the study. KAR and CJH collected the movement data. AHC cleaned the ICVI data received and developed the datasets for network analysis. AHC, CYL, and MWS implemented, analyzed, and interpreted the outputs. All authors wrote the manuscript, read and approved the final version for publication.

Conflict of interest

None

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Table 5-1 Glossary of social network analysis metrics investigated

Metrics investigated	Definition¹
Nodes	The unit of interest (county or state)
Arcs	Directed links between nodes
Diameter	The maximum number of steps in the shortest path between any pair of nodes
Density	The proportion of links present in the network out of the maximum possible
Average path length	The shortest path between two pair of nodes averaged over all pair of nodes in the network
Reciprocity	The proportion of bi-directional arcs in the network
Transitivity	The proportion of a node's neighbors that are also neighbor of one another
Assortativity	The degree of interaction between nodes in the network
Giant weak component	The largest set of nodes that are reachable in the network when the direction of links is not considered (GWCC)
Giant strong component	The largest set of nodes that are reachable in the network when the direction of links is considered (GSCC)
In-degree	The number of links into a node
Out-degree	The number of links from a node
Betweenness	The frequency with which a node is in the shortest path between any pair of nodes in the network
In-closeness	Reciprocal of mean geodesic distance between incoming nodes
Out-closeness	Reciprocal of mean geodesic distance between outgoing nodes
Hubs	Nodes with high out-degree which have high interaction with nodes with high in-degree
Authorities	Nodes with high in-degree which have high interaction with nodes with high-outdegree
Community	A group of nodes that have a greater number of links within groups compared to between groups
Isolates	Nodes that are not part of any community

¹ Definitions of the metrics investigated were adapted from (Dubé et al., 2009; Martinez-Lopez et al., 2009;

Newman, 2010; Dubé et al., 2011)

Table 5-2 Descriptive statistics of the Interstate Certificates of Veterinary Inspection (ICVI) data collected

Network type	Headcount ¹		Number of shipments ²	Distance traveled (km) ³	
	Inter-quartile range (IQR) ⁴	Median	Range (min-max)	Inter-quartile range (IQR) ⁴	Median
Beef	22 – 65	55	1 – 398	388 – 968	626
Dairy	7 – 64	48	1 – 336	369 – 1,122	643
Swine	363 – 1092	549	1 – 137	322 – 797	495
Small ruminant	2 – 15	4	1 – 284	352 – 1,082	639

¹ Number of animals per shipment between any pair of nodes

² Total number of shipments between any pair of nodes

³ Distance traveled by animals between any pair of nodes

⁴ The lower quartile (25%) – upper quartile (75%) of the parameter

Table 5-3 Network-level metrics for the movement networks investigated

Network type	Number of nodes	Number of edges	Diameter	Density (%)	Average path length	Reciprocity	Transitivity	Assortativity	Number of nodes in the GWCC ⁵	Number of nodes in the GSCC ⁶
<i>County-to-county complete network¹</i>										
Beef	2,959	137,615	7	1.57	2.8	0.12	0.18	-0.14	2,959	2,631
Dairy	2,139	28,352	8	0.62	3.3	0.08	0.11	-0.13	2,139	1,396
Swine	2,101	42,597	11	0.97	3.5	0.11	0.18	0.08	2,095	1,195
Small ruminant	2,442	10,478	13	0.18	4.5	0.03	0.03	-0.09	2,425	1,173
<i>County-to-county partial network²</i>										
Beef	2,426	119,580	7	2.03	2.7	0.14	0.20	-0.17	2,426	2,140
Dairy	1,846	24,492	9	0.72	3.3	0.09	0.11	-0.14	1,844	1,202
Swine	1,721	38,127	11	1.29	3.3	0.13	0.20	0.07	1,713	1,025
Small ruminant	1,964	8,055	12	0.21	4.6	0.04	0.03	-0.11	1,946	969
<i>State-to-state complete network³</i>										
Beef	48	1,477	3	65.47	1.4	0.81	0.87	-0.04	48	48
Dairy	48	1,146	3	50.80	1.5	0.70	0.77	-0.12	48	48
Swine	48	918	3	40.69	1.6	0.64	0.72	-0.15	48	46
Small ruminant	48	1,139	3	50.49	1.5	0.61	0.78	-0.11	48	45
<i>State-to-state partial network⁴</i>										
Beef	36	930	3	73.81	1.2	0.88	0.91	-0.08	36	35
Dairy	36	735	4	58.33	1.5	0.76	0.82	-0.12	36	36
Swine	36	602	3	47.78	1.5	0.69	0.77	-0.19	36	34
Small ruminant	36	685	3	54.37	1.4	0.65	0.81	-0.09	36	33

¹ County-to-county networks with inferred data for the states we couldn't collect movement data

² County-to-county networks only for the states we collected movement data

³ State-to-state networks with inferred data for the states we couldn't collect movement data

⁴ State-to-state networks only for the states we collected movement data

⁵ GWCC refers to the giant weakly connected component which are all the nodes that can be reachable when direction of links is not considered

⁶ GSCC refers to the giant strongly connected component which are all the nodes that can be reachable when direction of links is considered

Table 5-4 Spearman correlation coefficients between the main centrality measures investigates for the county-to-county complete networks in the different species and livestock demographic metrics at the county level

Network type	In-degree	Out-degree	Betweenness	In-closeness	Out-closeness
<i>Beef cattle county-to-county complete network¹</i>					
Number of cattle on-feed	0.553	0.440	0.501	0.472	0.304
Number of beef cows	0.572	0.804	0.654	0.399	0.237
Number of feedlot operations	0.474	0.354	0.444	0.505	0.568
Number of cow-calf operations	0.375	0.557	0.537	0.325	0.366
Beef cattle density per km ²	0.518	0.661	0.665	0.479	0.482
<i>Dairy cattle county-to-county complete network¹</i>					
Number of dairy cows	0.422	0.857	0.689	-0.138	0.691
Number of dairy operations	0.322	0.612	0.513	-0.088	0.512
Dairy cattle density per km ²	0.373	0.818	0.644	-0.159	0.681
<i>Swine county-to-county complete network¹</i>					
Number of sows in farrow-to-feeder	0.259	0.265	0.294	0.081	0.063
Number of sows in farrow-to-finish	0.549	0.603	0.511	0.199	0.156
Number of sows in farrow-to-wean	0.463	0.513	0.435	0.093	0.072
Number farrow-to-feeder operations	0.249	0.255	0.288	0.120	0.107
Number of farrow-to-finish operations	0.534	0.568	0.516	0.237	0.192
Number of farrow-to-wean operations	0.456	0.501	0.434	0.173	0.148
Swine density per km ²	0.638	0.754	0.560	0.455	0.344
<i>Small ruminant county-to-county complete network¹</i>					
Sheep population	0.303	0.633	0.560	0.111	0.367
Goat population	0.081	0.278	0.336	0.002	0.184
Number of sheep operations	0.290	0.544	0.536	0.120	0.309
Number of goat operations	0.121	0.256	0.325	0.044	0.146
Small ruminant density per km ²	0.165	0.451	0.456	0.045	0.260

¹ County-to-county networks with inferred data for the states from which we did not receive ICVI data

Data Source: National Agricultural Statistics Service (NASS) 2012 Census of Agriculture

Table 5-5 Descriptive statistics of the trade-community detection for the county-to-county complete networks in the different species

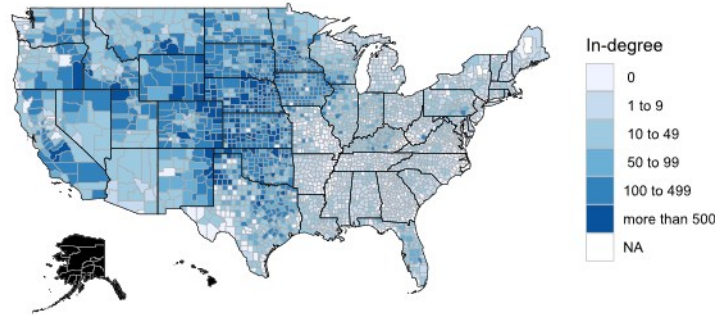
Network type	Number of communities (total, largest) ¹	Number isolated ²	Range (min-max) of node members of a community ³	Number of arcs within communities	Number of arcs between communities
Beef cattle	172, 6	148	2 – 1,079	77,771	59,844
Dairy cattle	314, 4	277	2 – 767	16,896	11,456
Swine	529, 4	403	2 – 682	31,446	11,151
Small ruminant	724, 5	510	2 – 447	4,730	5,748

¹ Total number of communities identified by the Waltrap algorithm, number of largest communities with 50 or more nodes

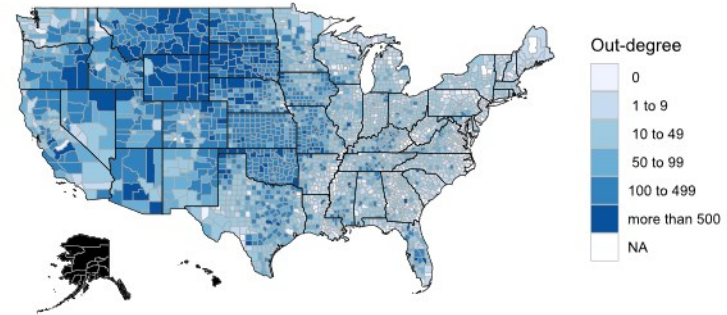
² Nodes that are not member of any community

³ Minimum and maximum number of nodes members in communities that have more than 1 node

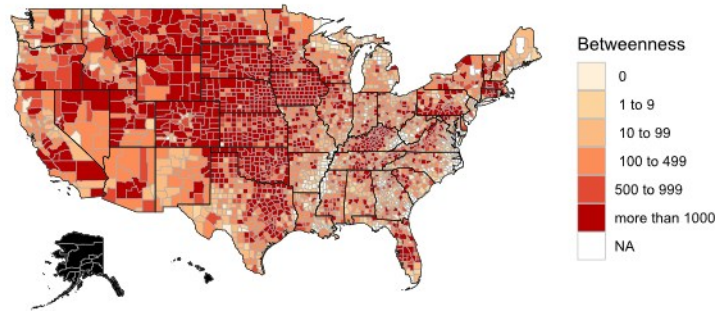
Beef cattle network in-degree



Beef cattle network out-degree



Beef cattle network betweenness



Largest communities in the beef cattle network

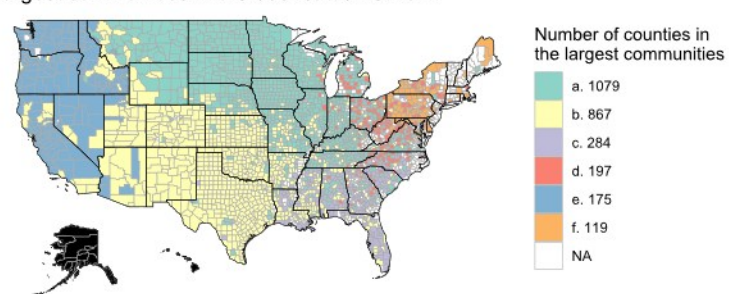
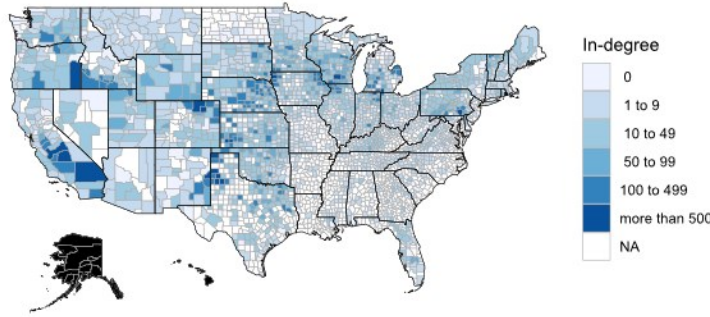
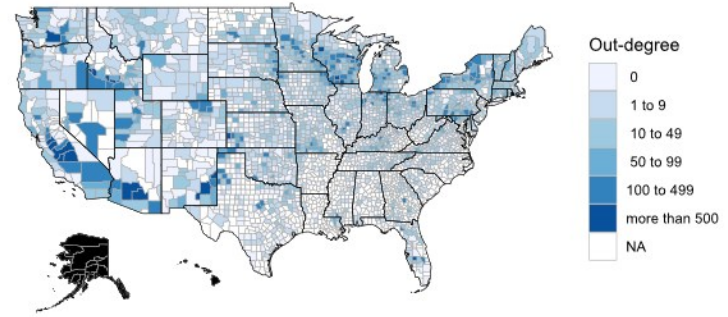


Figure 5-1 National maps for the in-degree (top left), out-degree (top right), betweenness (bottom left), and counties members of the largest communities identified by the Walktrap algorithm (bottom right) in the beef cattle county-to-county complete network

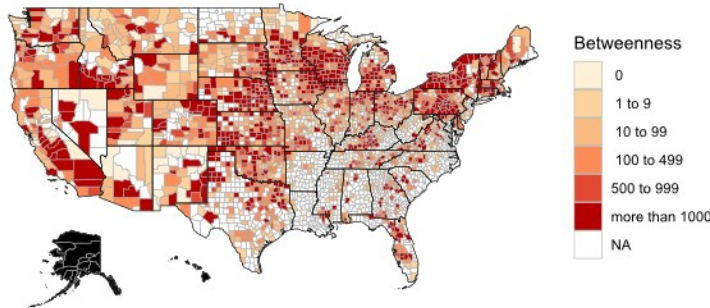
Dairy cattle network in-degree



Dairy cattle network out-degree



Dairy cattle network betweenness



Largest communities in the dairy cattle network

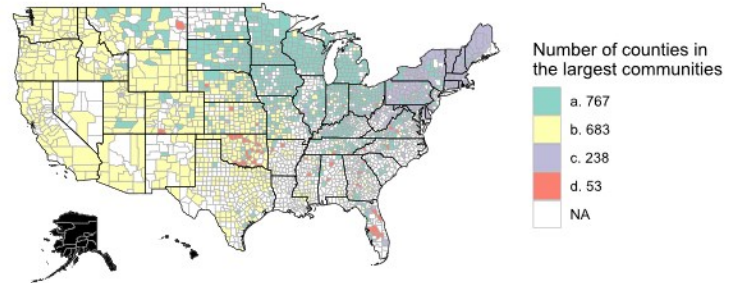
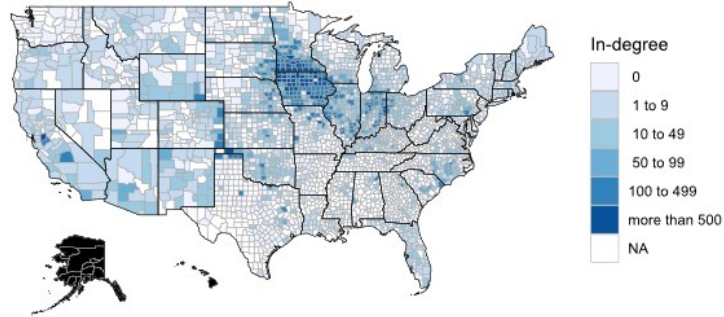
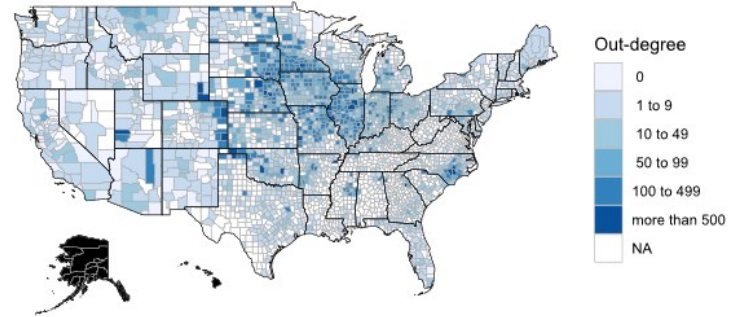


Figure 5-2 National maps for the in-degree (top left), out-degree (top right), betweenness (bottom left), and counties members of the largest communities identified by the Walktrap algorithm (bottom right) in the dairy cattle county-to-county complete network

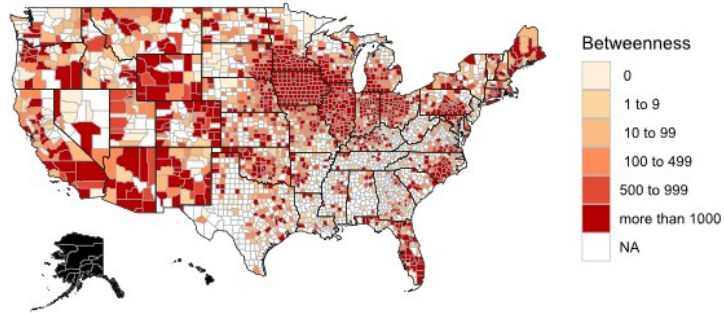
Swine network in-degree



Swine network out-degree



Swine network betweenness



Largest communities in the swine network

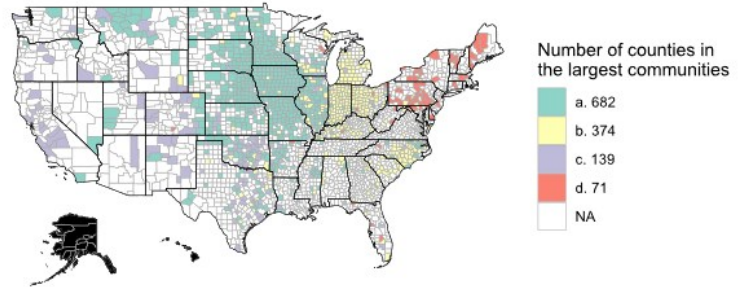
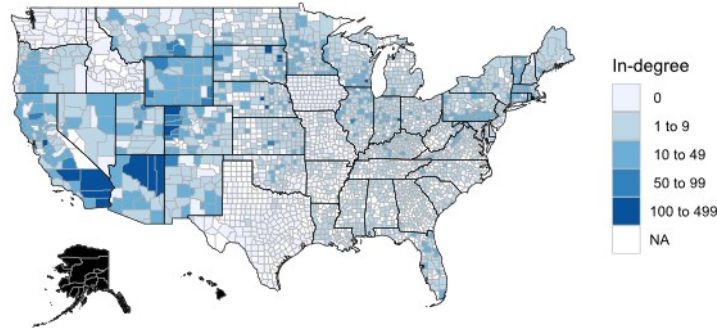
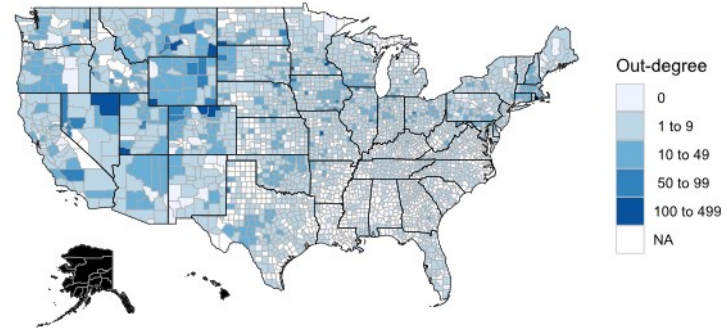


Figure 5-3 National maps for the in-degree (top left), out-degree (top right), betweenness (bottom left), and counties members of the largest communities identified by the Walktrap algorithm (bottom right) in the swine county-to-county complete network

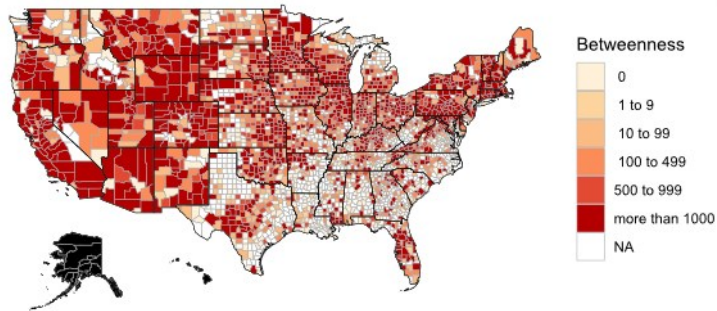
Small ruminant network in-degree



Small ruminant network out-degree



Small ruminant network betweenness



Largest communities in the small ruminant network

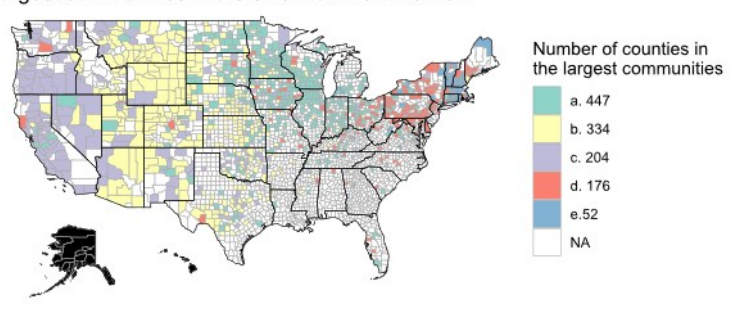


Figure 5-4 National maps for the in-degree (top left), out-degree (top right), betweenness (bottom left), and counties members of the largest communities identified by the Walktrap algorithm (bottom right) in the small ruminant county-to-county complete network

Supplementary materials

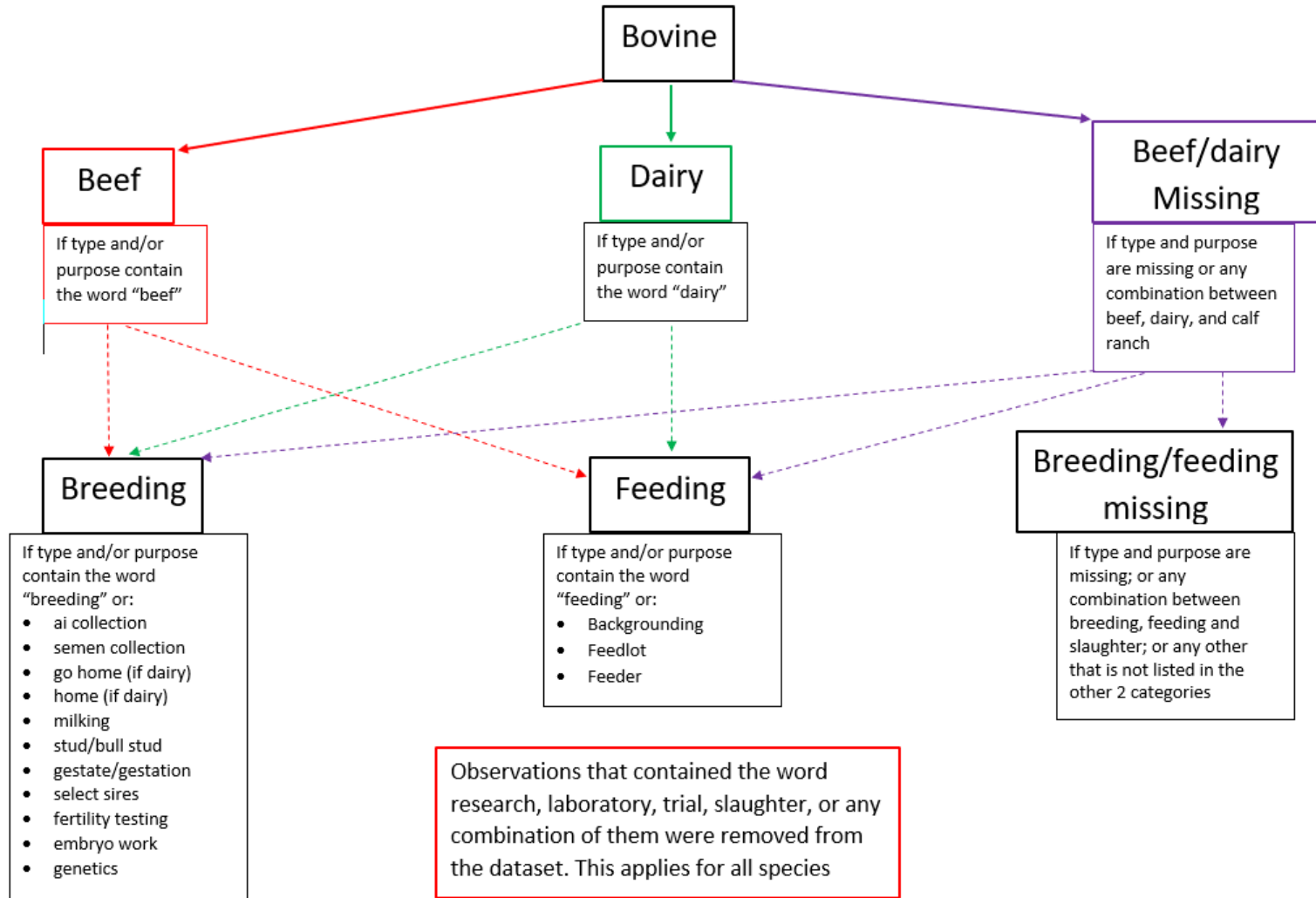


Figure S 5-A Classification tree to determine the livestock type for bovine movements provided in the ICVI data

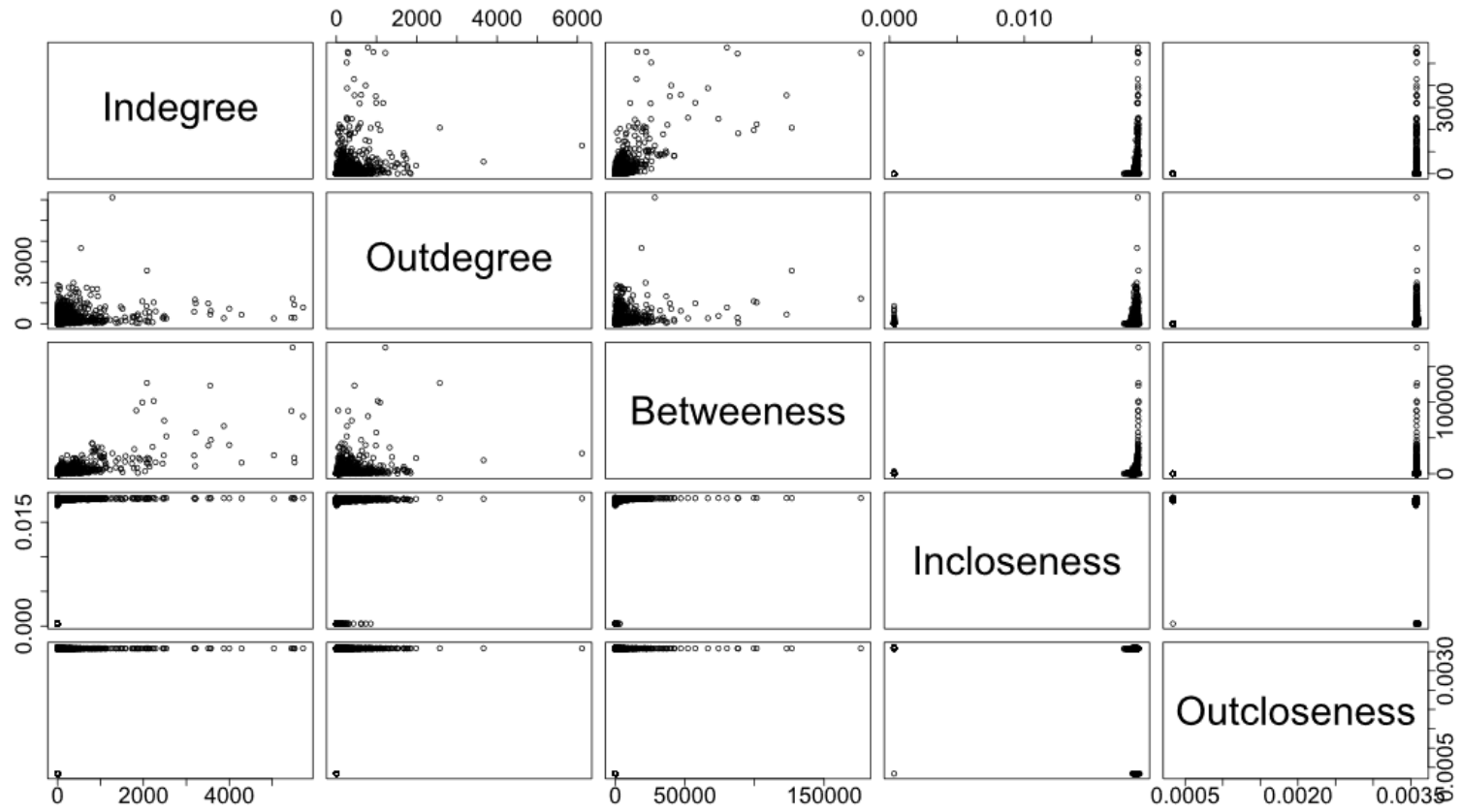


Figure S 5-B Scatter plots to evaluate the correlation between in-degree, out-degree, betweenness, in-closeness, and out-closeness for the beef cattle network

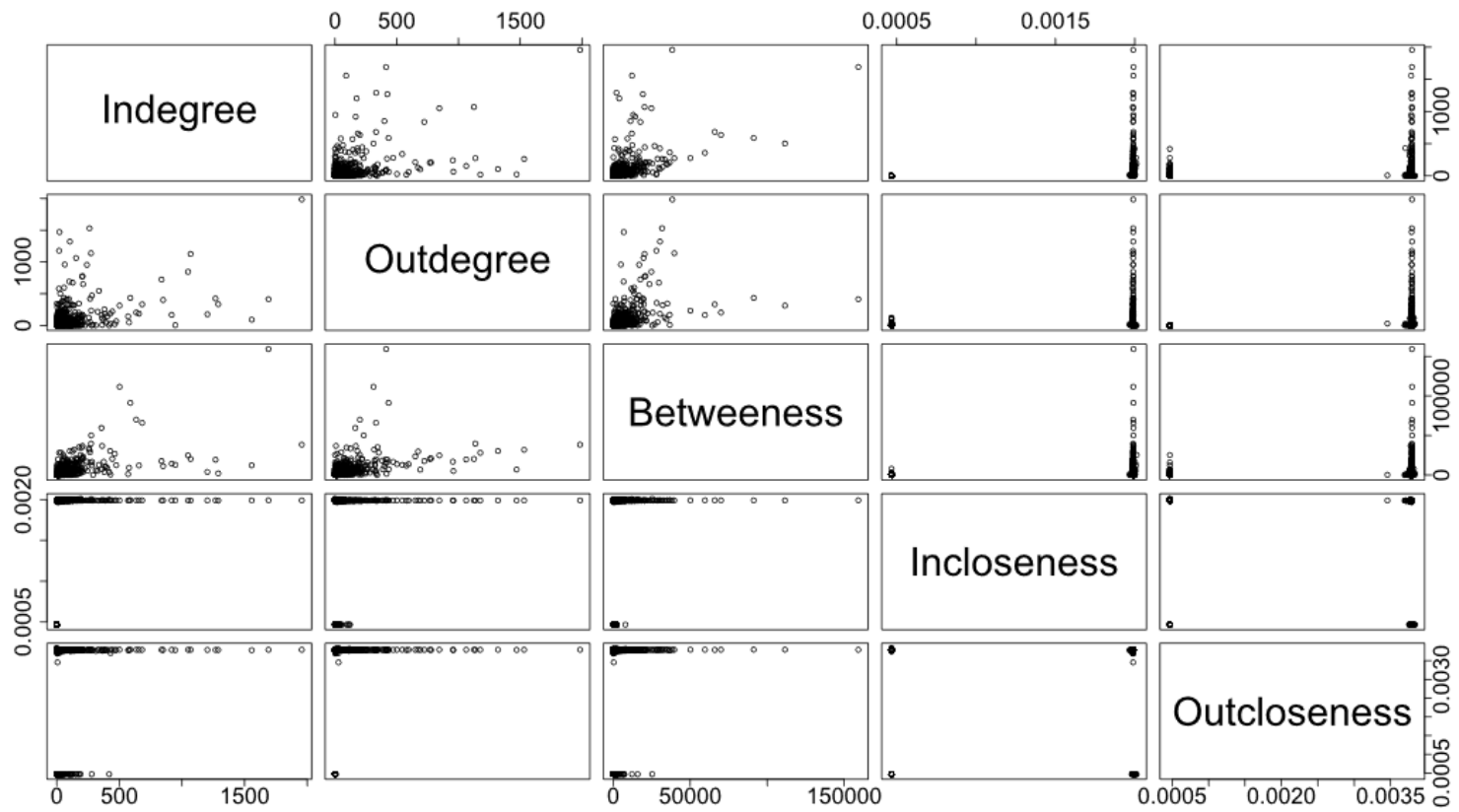


Figure S 5-C Scatter plots to evaluate the correlation between in-degree, out-degree, betweenness, in-closeness, and out-closeness for the dairy cattle network

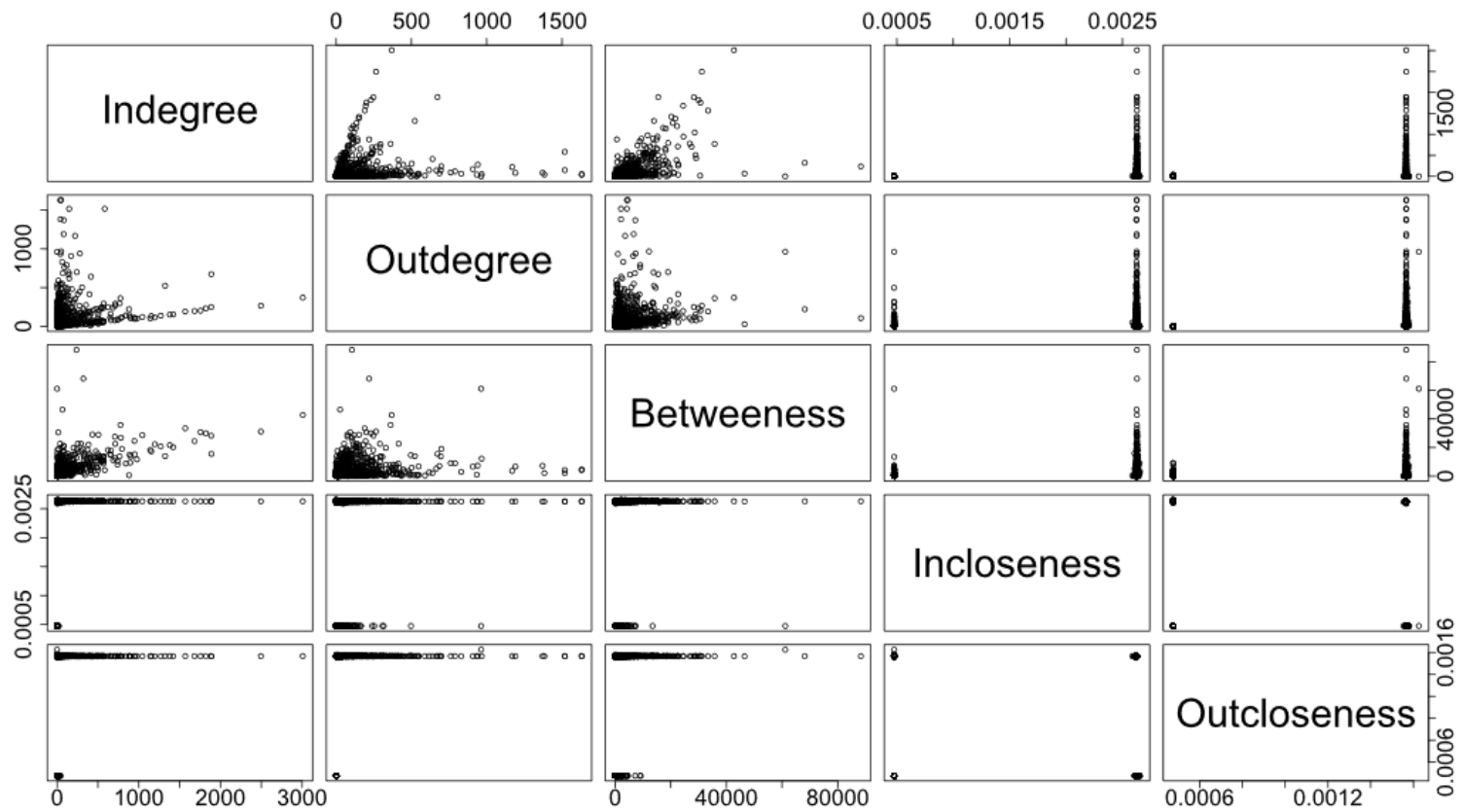


Figure S 5-D Scatter plot to evaluate the correlation between in-degree, out-degree, betweenness, in-closeness, and out-closeness for the swine network

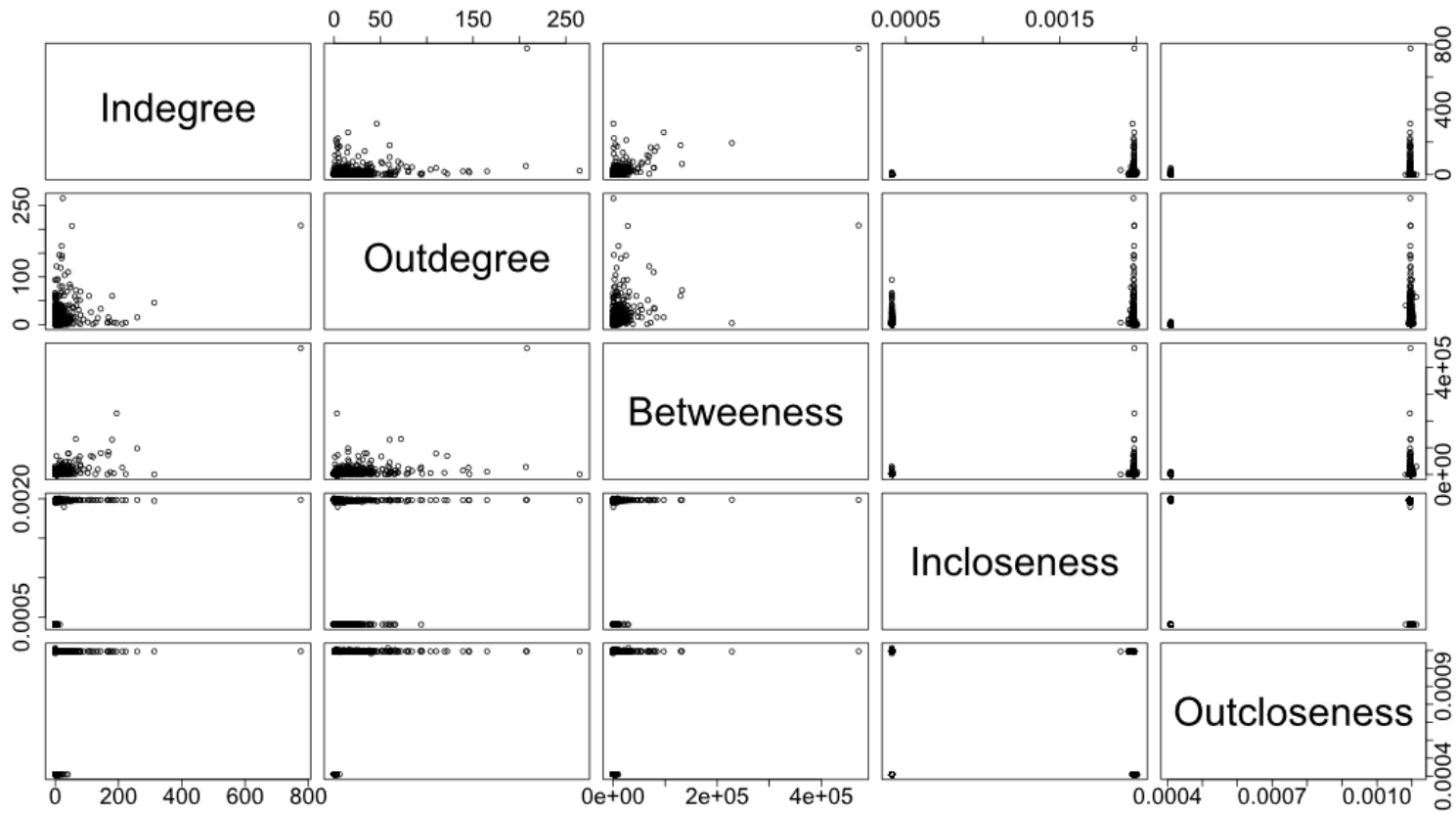
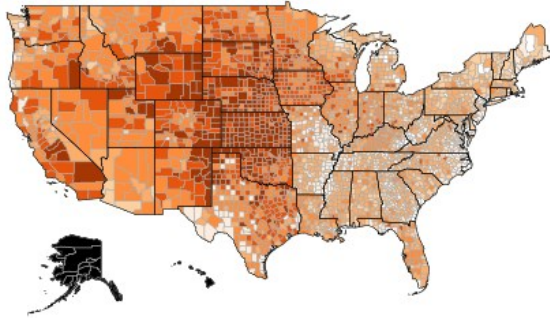
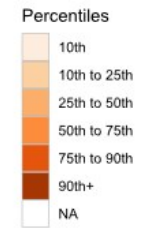
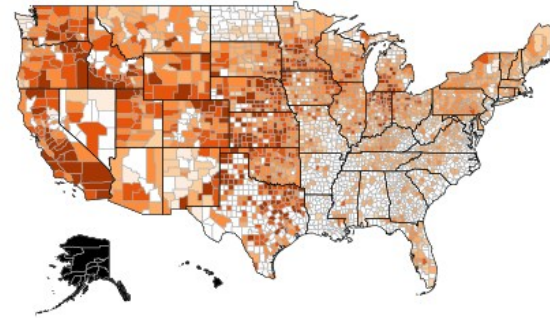


Figure S 5-E Scatter plot to evaluate the correlation between in-degree, out-degree, betweenness, in-closeness, and out-closeness for the small ruminant network

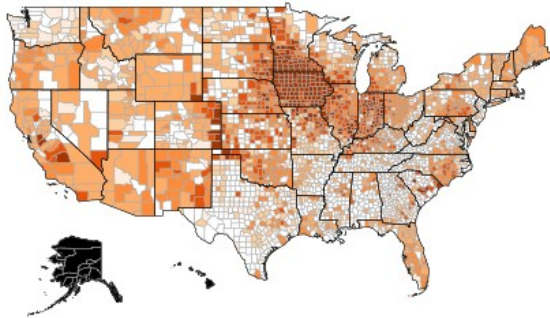
Beef cattle network authorities



Dairy cattle network authorities



Swine network authorities



Small ruminant network authorities

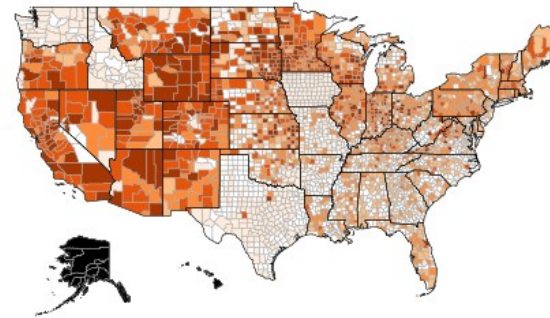
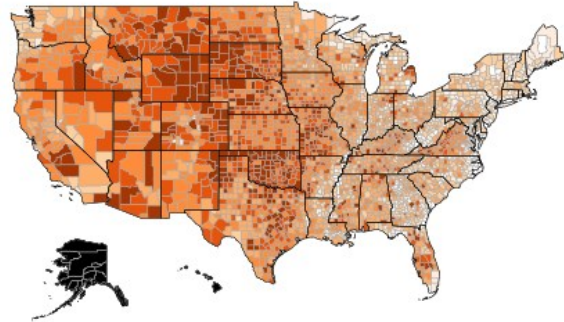
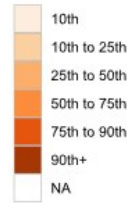


Figure S 5-F Maps with the degree of authorities at the county level based on percentile ranks for the beef cattle (top left), dairy cattle (top right), Swine (bottom left), and small ruminant (bottom right) networks

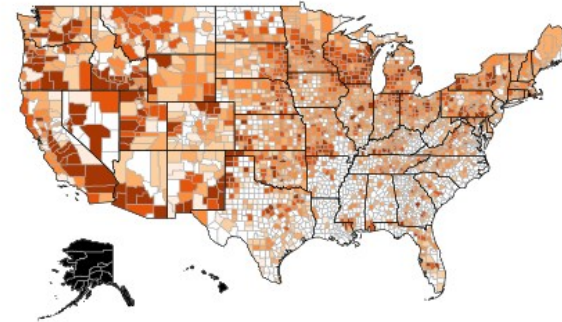
Beef cattle network hubs



Percentiles



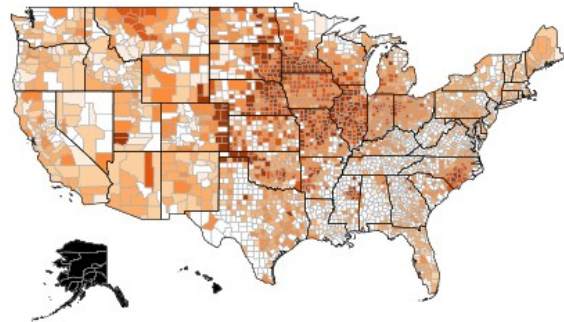
Dairy cattle network hubs



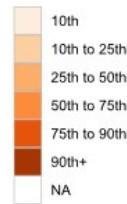
Percentiles



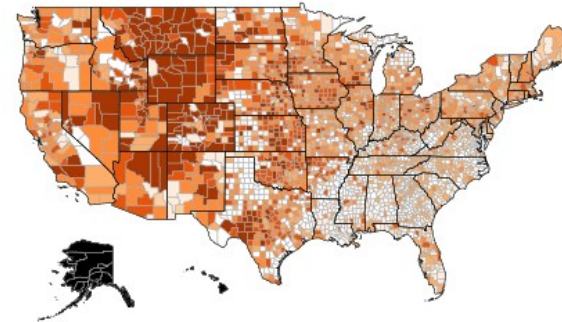
Swine network hubs



Percentiles



Small ruminant network hubs

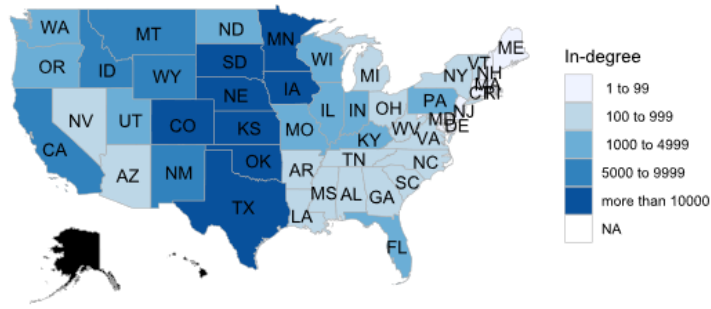


Percentiles

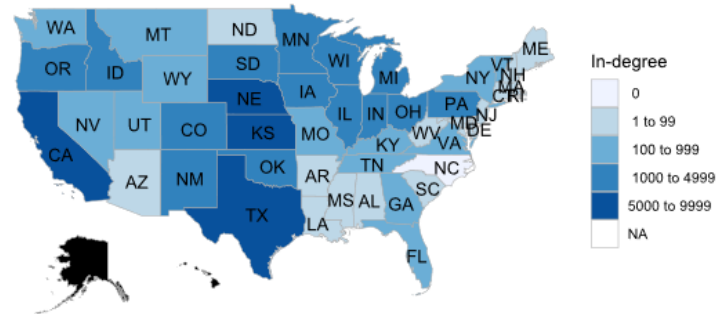


Figure S 5-G Maps with the degree of hubs at the county level based on percentile ranks for the beef cattle (top left), dairy cattle (top right), Swine (bottom left), and small ruminant (bottom right) networks.

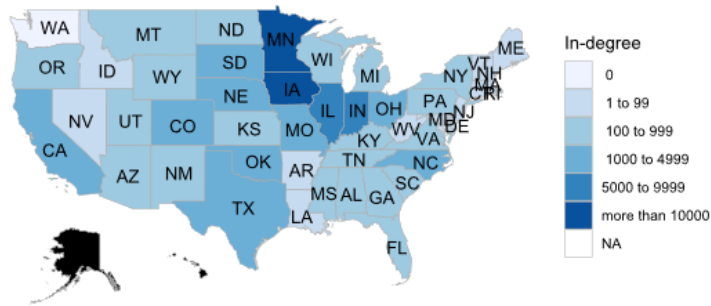
Beef cattle network in-degree



Dairy cattle network in-degree



Swine network in-degree



Small ruminant network in-degree

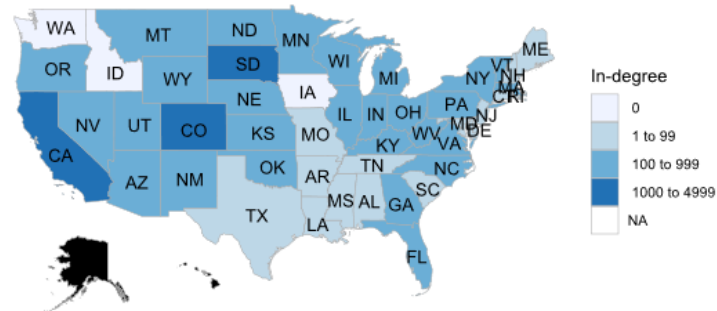
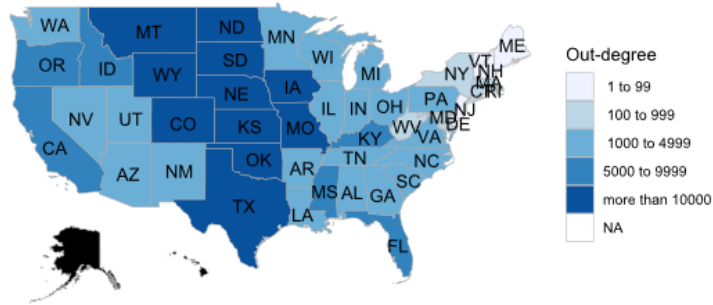
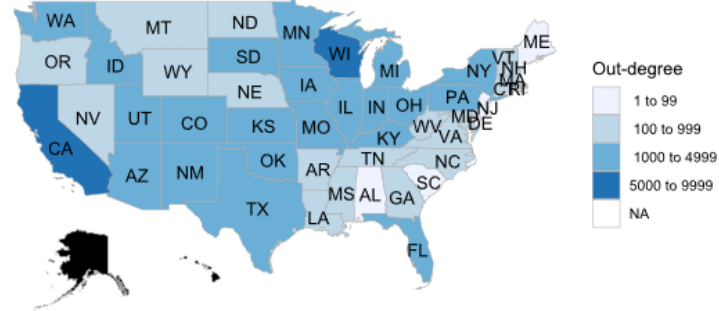


Figure S 5-H Node in-degree centrality at the state level for the beef cattle (top left), dairy cattle (top right), swine (bottom left), and small ruminant (bottom right) networks

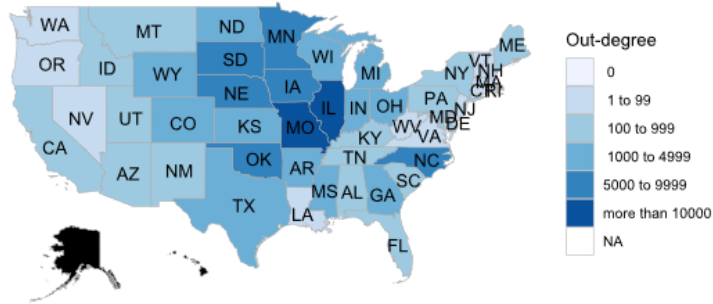
Beef cattle network out-degree



Dairy cattle network out-degree



Swine network out-degree



Small ruminant network out-degree

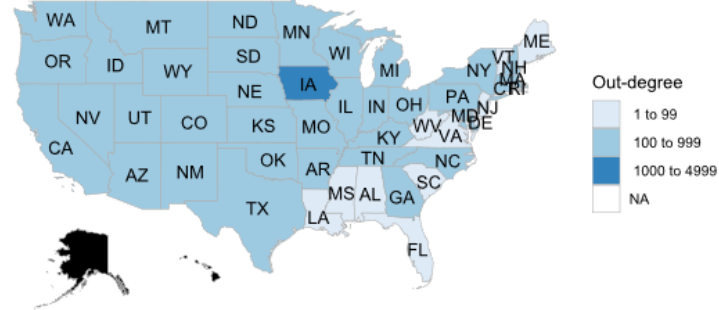


Figure S 5-I Node out-degree centrality at the state level for the beef cattle (top left), dairy cattle (top right), swine (bottom left), and small ruminant (bottom right) networks

Chapter 6 - Conclusions

The objectives of the research described in this document were to study the potential implications of hypothetical foot-and-mouth (FMD) disease outbreaks in U.S. beef feedlots, the evaluation of potential on-farm intervention strategies that can be implemented during those outbreaks, and the description of livestock movement patterns within the contiguous U.S. that might help to understand disease transmission at a national scale.

Due to the lack of FMD-related data applicable to immunologically naïve cattle population and specifically to U.S. beef feedlots, parameterization of mathematical models to study FMDv transmission is challenging. We firstly conducted an FMD expert survey to gather parameters applicable to field settings in U.S. beef feedlots. Our survey was the first study estimating parameters of the natural history and transmissibility of FMDv in U.S. beef feedlot cattle using expert opinion. Because the U.S. cattle is a immunologically naïve population, we assumed that an incursion of any FMD strain can cause a devastating impact, so we surveyed parameter values differentiating between virulence strain, dose of infection, and routes of infection instead of investigating parameters values related to a specific FMDv strain. The data synthesized in our survey can be used in mathematical models to evaluate the probability to detect FMD, simulate outbreak progression in beef feedlots, and assess the impact of control strategies on the outbreak progression. However, we highlight that the reported parameter values are strictly based on expert opinion and due to the variable natural history of FMD, the data reported in this study should be combined with experimental and outbreak-investigation data to produce more robust simulation models. In addition, reported parameter values such as decrease in feed consumption can help to investigate FMD detection during the pre-clinical stage of the disease which can be investigated by simulation modeling.

We then developed a mathematical model to evaluate FMD transmission within U.S. beef feedlots. In these premises, cattle are compartmentalized in multiple home-pens and they may have contact with cattle from other home-pens via multiple routes. Previous models have modeled FMD transmission with an assumption of homogeneous mixing, that means, once an infected animal is introduced into a farm, all animals in the farm will be infected. This assumption is clearly not applicable to large compartmentalized beef feedlots in the U.S. This is the first model for projecting FMDv transmission in contemporary U.S. beef cattle feedlots. Our findings suggest that feedlots that operated with more hospital pens have a projected longer duration of the outbreak. However, this clearly has economic implications because of the resources needed to build more facilities and have more personnel operating in different sectors of the feedlots. In addition, we did not model other indirect routes such as via feed trucks, or direct contact of cattle from different home pens in alleys during feedlot rounds which might accelerate the spread of infection. We also found that detection day based on observational surveillance of clinical cattle (assuming a 100% sensitivity) occurred within day 4 to 12. More sensitive methods for FMD detection such as a routine surveillance test should be explored in future models. Overall, our model is consistent with data available to date but can be improved with better data on FMDv survival in within-feedlot environments, FMDv infectious dose depending on the exposure route, potential for the virus airborne transmission in areas where the U.S. beef industry is concentrated, clinical presentation of FMD depending on the strain virulence, and sensitivity of the routine surveillance system based on visual observation by pen-riders.

The next step was to investigate on-farm intervention strategies to evaluate their efficacy during hypothetical FMD outbreaks. We tested a movement restriction strategy and two partial

depopulation strategies. The simulations based on our parameterization and assumptions suggested that the interventions were not highly effective in interrupting FMDv transmission in the feedlots modeled. Movement restrictions were found to decrease prolong the projected duration of the outbreak which might be helpful to provide more time to develop and implement other strategies such as vaccination in the feedlot. We did not model vaccination, but it certainly is a next step that can be implemented in our model. Finally, while application of depopulation strategies has found to be useful in other countries, the economic costs due to implementation, compensation, and animal losses (not investigated in our models) need to be considered in the U.S. due to the large concentration of cattle in feedlots to take an informed decision before implementing depopulation strategies. Moreover, the impact on the public level and animal welfare level should be considered when developing preparedness plans for disease control.

We finally investigated and described patterns of interstate movements for FMD susceptible species such as bovine (beef and dairy cattle), swine, small ruminants. Our analyses are the first to describe movements for livestock other than cattle at a national scale level. Outputs of the beef cattle network were consistent with the beef production type in which calves move from areas with large cow-calf operations to areas with high feeding capacity. Metrics estimated for the dairy cattle and swine networks confirmed that both industries are more geographically clustered compared to the beef cattle network. In all networks (except for the small ruminant network), up to 6 large trade-communities were found, and these were geographically well-defined. Community detection methods are important to inform policy because disease surveillance and disease response plans can be developed to target these areas. However, we emphasize that outputs in these analyses are based on methods and limitations described , and only represent inter-state livestock movements within the time-frame (1 year) in

which collected data. On the other hand, our outputs can be useful to generate hypotheses and to parameterize and conduct network modeling to evaluate disease transmission at a national scale level.