A simulation model of intraherd transmission of foot and mouth disease with reference to disease spread before and after clinical diagnosis

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Abstract. Intraherd transmission of foot and mouth disease virus (FMDV) was examined using a simulation model for a hypothetical 1,000-cow dairy, assuming clinical diagnosis was made when at least 1% (10 cows) or 5% (50 cows) had clinical signs of FMD, 1 index case cow, and transition state distributions for the latent, subclinically infectious, and clinically infectious periods of FMD calculated from published data. Estimates assumed for the number of animal-to-animal contacts (k) adequate for transmission ranged from 0.6 to 9.0 per hour (13.7–216.0 per day). A total of 40,000 iterations (5,000 for each scenario, assessing 4 adequate contact rates and 2 detection criteria) were run. The model predicted that FMD would not be diagnosed in the herd until 10.0–13.5 days after the index case cow had become infected, at which time between 65% and 97% of the cows (646–967 cows) to nearly 100% (978–996 cows) would already have become infected with the virus, if the number of cows showing clinical signs of FMD at the time of diagnosis were 10 or 50, respectively. At the time of diagnosis, the simulated number of infectious cattle varied substantially from 82–472 to 476–537 cows, depending on adequate contact rate and whether the diagnosis was made when 10 or 50 animals were showing clinical signs, respectively. The simulated number of infectious cows increased rapidly during the first few days after diagnosis. In the scenario where at least 10 cows showing clinical signs was necessary before a clinical diagnosis was made, each day after diagnosis, the number of infectious animals increased by nearly 100 to more than 200 cases per day up to day 5, assuming 0.57–9.0 animal-to-animal contacts per hour, respectively. Results obtained when it was assumed that at least 50 clinical cases were present at the time of diagnosis showed smaller relative increases because nearly one-half of the herd was projected to be infected at the time of diagnosis. From these results, it is clear that once an individual in a herd becomes infected with FMDV, herd infectivity is not static, rather it accelerates as would be expected as long as there are sufficient susceptible animals to sustain the increasing transmission rate, after which time the rate at which new infections occurs will diminish. Results indicate that biosecurity strategies aimed at minimizing both intraherd and inter- herd contact will be critical in minimizing the spread of FMD before the initial diagnosis is made. In addition, simulations suggest that very early clinical diagnosis of FMD and effective isolation or depopulation and disposal will be critical in limiting the number of infectious animals capable of transmitting the virus to other herds and thus in timely control of an epidemic. Early diagnosis will rely on early virus detection from animals in the preclinical phase of infection, rather than waiting for clinical signs to manifest in sufficient numbers to be noticed and to warrant investigation.

Foot and mouth disease (FMD) is one of the most economically important livestock diseases in the world. In recent years, large-scale epidemics have been observed in Taiwan in 1997,[11] the UK in 2001,[3] and Argentina in 2001, resulting in the slaughter of more than 4 million animals in the UK[10] and distribution of 178 million doses of vaccine in Argentina.[26]

One of the problems faced in developing diagnostic surveillance and control strategies for FMD is a lack of understanding of intraherd transmission of the virus. It is not well understood, for example, how rapidly or slowly virus might be transmitted among dairy cattle raised under current intensive management conditions or how many animals might already be infected or infectious at the time FMD would be diagnosed in a herd. Prerequisite to necessary risk assessment is an understanding for how herd infectiousness changes from the time the first animal is infected to animal disposal, as indicated by changing prevalence of in- fectious animals. Such information will clarify risks of FMD virus (FMDV) spread from herd to herd, as might be related to delays in diagnosis or in slaughter and disposal, and will help in design of individual herd biosecurity aimed at preventing introduction of FMDV into the herd.

Simulation modeling has been used to predict the spread and control of FMDV if it were endemic[8] or introduced into a noninfected country.[16,21,23–25] In ad- dition, simulation models have been used to evaluate and aid decision makers in identifying optimal disease

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eradication strategies. However, the predictive power of these models is limited by the quality of information used to determine parameter values as well as their basic adherence to biologic and epidemiologic principles. One of these principles is that the speed at which the virus is transmitted from animal to animal is dynamic in that initially after introduction into a herd, transmission takes place relatively slowly and then, as more animals become infectious, the speed accelerates until the supply of susceptible animals becomes sufficiently diminished that the speed decelerates.

If a model fails to take this dynamic property into consideration, the model simplifies the behavior of virus transmission and tacitly assumes that once a herd is infected (even by only 1 animal), it becomes infectious at some level after the predicted incubation period passes. In reality, however, disease dynamics may vary for an infectious disease in a herd over time. For instance, diagnosability and infectivity of the herd will vary if only a limited number of animals are subclinically or clinically infectious, as in the early stage of herd-level infection versus later when a substantial portion of the herd becomes infectious. These dynamics are a function of the incubation period of the disease and the rate at which an animal could move from the latent state to the subclinically infectious state and then to the clinically infectious state, which is the state required for clinical diagnosis. Herd dynamics also affect disease transmission, mainly through contact rates, where contagious disease would be expected to move more quickly through a herd in which animals have considerable physical contact with each other compared with those where there is little animal-to-animal contact. Consequently, it is important that disease transition state information and potential for intraherd contact be considered in characterizing dynamics of intraherd transmission.

This study predicted and evaluated intraherd transmission of FMDV in a hypothetical 1,000-cow dairy herd, assuming a range of animal-to-animal contact rates and alternative clinically infected prevalence cutpoints for diagnostic and for disposal delays of an FMD-infected herd.

Materials and methods

The model. A model was created in a spreadsheet software program[a] to simulate the spread of FMDV in a hypothetical 1,000-cow dairy herd in California. The model was stochastic, in that it included uncertainty information for various parameters. The model consisted of 5 FMD states: susceptible, latently infected, subclinically or clinically infectious, and immune.

The model was based on the Reed–Frost (RF) equation[1] and programmed as described previously:[7]

$$C_{t+1} = S_t(1 - q^{C_t}),$$

where C_t = number of infectious cases, t = time, S = number of susceptible animals, q = the probability of avoiding an adequate contact, p = the probability of making an adequate contact, or $1 - q$, and $p = k/(N - 1)$), where k = the number of adequate contacts (sufficient to cause disease transmission) any given individual makes in time period t, and N = the herd size.

Because of the nature of FMD, it was necessary to modify the basic RF equation to account for the initial noninfectious, latent period (l) and the fact that the duration of infectiousness is more than a single period (day in this model). To accomplish this, the RF equation was modified as

$$C_{t+1} = S_t(1 - q^{CI_t})$$

where CI_t = cumulative number of infectious animals at time t, and

$$CI_t = \sum_{d=0}^{D-1} C_{t-l-d},$$

where D = the mean duration of infectiousness and l = the mean duration of latency.

For example, if $l = 3$ days and $D = 7$ days, the total number of infectious (CI) animals on day 10 ($t = 10$) is the sum of those infected (C) between days 1 and 7, whereas those infected between days 8 and 10 will not begin their infectious period until days 11–13. Thus, the modified RF equation can be used to calculate the incidence of latently infected cases based on the number of susceptible animals times the probability of not avoiding adequate contact with the prevailing prevalence of infectious individuals.

Parameter estimates. Because of the highly contagious nature of FMD, the number of adequate contacts (k) was assumed to occur during a 1-hr time period. Although k is typically not measured directly, it may be estimated indirectly if an outcome, e.g., prevalence at a given time, is predefined. A range of contact rates was estimated using 2 approaches. In the first approach, we assumed from expert opinion[4] that 50% of an intensively managed, 1,000-cow dairy herd would probably be infected with FMDV, referred to here as the cumulative infection density, or CID_{50}, by 9 days after the index animal became infected. The number of adequate contacts necessary to achieve a CID_{50} of 9 days was identified as the value of k that generated a CID_{50} of 9, using a spreadsheet add-in.[b] For sensitivity analysis, k values that generated CID_{50} for 8 and 10 days also were selected.

The second approach taken was to subjectively estimate k value for a typical, intensively managed,

Table 1. Mean and statistical distribution (parameters) of duration of time spent in FMD-infected states for cattle.*

	Duration (day)	
State	Mean	Statistical distribution (parameters)
Latent	3.7	normal (3.7, 0.8)
Subclinically infectious	2.6	normal (2.6, 1.05)
Clinically infectious	18.4	Weibull (1.42, 20.23)

* Source: Burrows (1968), Sellers and Daggupaty (1990), and Bates et al. (2003).

Figure 1. Mean number of cows that would be clinically infectious for FMD virus, by days after diagnosis and variable number of adequate hourly contacts (k), in a hypothetical 1,000-cow dairy, assuming that a clinical diagnosis is based on at least 10 cows demonstrating clinical signs.

1,000-cow dairy herd and was based on extensive observation and experience in dairy cattle management and behavior by one of the authors. Estimation assumed 100–120 cows per corral and animal-to-animal contact that was sufficiently close to be reasonably certain that FMDV would be transmitted from an infectious animal to a susceptible animal, such as by nose-to-nose or nose-to-vulva physical contact. Estimation considered contacts made among cows with behavioral signs of estrus, as well as between bulls and cows throughout the estrous cycle, and contacts made during the twice-daily gathering and crowding of lactating cows before milking. Estimation also considered observations of physical contact across fences and across water troughs shared by corrals and of physical contact made with adjacent cows while eating or locked up in stanchions.

Durations of latent, preclinically infectious, and clinically infectious periods were estimated from published data on FMDV infection resulting from natural exposure[6,27] (Table 1) and were set as random variables that take on a new value for each model iteration. Infected cows were assumed to be immune for 20 days after they were no longer infectious.

Two scenarios for diagnostic delay were considered, one for which FMD was diagnosed when 1% (10 cows) had FMD lesions and the other when 5% (50 cows) had lesions. Use of these estimates is based on published reports[2] and personal experience in herd diagnosis of vesicular stomatitis in dairy herds[18,29] and on reports indicating age of lesions and clinical prevalence of cattle in UK herds that had lesions compatible with FMD at the time FMD was diagnosed.[10,17]

Model simulation. The model was constructed using a commercially available spreadsheet and a simulation add-in for Monte Carlo sampling.[c] Results were obtained for a 30-day period, beginning with when the index case animal became infected. A total of 40,000 iterations (5,000 for each scenario, assessing 4 contact rates and 2 detection criteria) were run. Results represent the simulated number of preclinically infectious, clinically infectious, and infected animals on the day
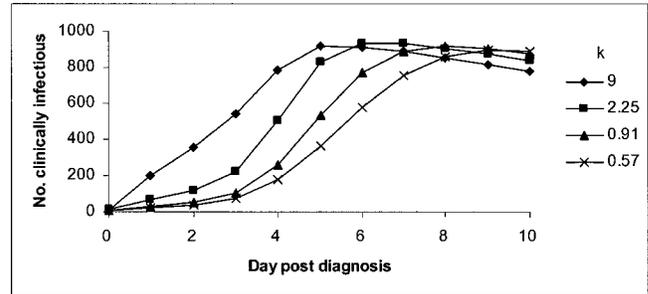
of initial herd-level diagnosis through 10 days after the simulated day of diagnosis.

Results

In the first approach to estimate k using estimates when CID_{50} was 8, 9, and 10 days, k was estimated to be 2.25/hour (54.1/day), 0.91/hour (21.8/day), and 0.57/hour (13.7/day), respectively. Values of k estimated from observations of daily dairy cattle contacts were 9 per hour or 4 times the maximum rate of 2.25 estimated in the first approach.

In the scenario that presumed FMD would be diagnosed in a herd if at least 1% (10 cows) of the herd were showing clinical signs, the mean time FMD would be diagnosed was predicted to range from 10.0 to 10.7 days after the herd index case became infected, as the number of adequate contacts per hour (day) varied from 9.0 (216.0) to 0.57 (13.7), respectively. If instead 5% (50 cows) were necessary to be demonstrating signs of FMD before a clinical diagnosis would be made, a delay of 0.2–2.8 days, i.e., 10.2–13.5 days after the index case became infected, would be expected, as the number of hourly adequate contacts varied from 9.0 to 0.57, respectively.

Assuming that a clinical diagnosis of FMD could be made if 10 (1%) cows were demonstrating clinical signs, the following herd-infection results were obtained. On the day of diagnosis, the simulated mean number of clinically infectious cows ranged from 10 to 12 as k varied from 0.57 to 9.0, respectively (Fig. 1). The simulated mean number of clinically infectious cows increased substantially over the next 5–9 days, depending on the presumed number of contacts. For instance, the simulated number of clinically infectious cows reached a peak of approximately 900, 5–9 days after clinical diagnosis, as k varied from 9.0 to 0.57, respectively.

Although approximately 10 cows were predicted to be clinically infectious on the day FMD was diagnosed

Table 2. Mean number of cows that would be infectious for FMD virus, by days after diagnosis and a variable number of adequate hourly contacts (*k*), in a hypothetical 1,000-cow dairy, assuming that a clinical diagnosis is based on at least 10 cows demonstrating clinical signs.

	Days after diagnosis										
k	0	1	2	3	4	5	6	7	8	9	10
9.00	472	687	856	941	959	945	916	887	852	815	778
2.25	224	429	676	864	952	970	956	931	903	870	837
0.91	114	240	440	662	834	927	956	951	930	902	871
0.57	82	169	316	502	685	825	907	939	938	920	894

in the herd, an additional approximately 7–50 times more cows were subclinically infectious, i.e., 72–462, for *k* = 0.57 and 9.0, respectively (Table 2; Fig. 2a). The number of infectious cows continued to double for the next 1–2 days after diagnosis for the lower contact rates (0.57–2.25). The maximum simulated mean number of infectious cows at a given time ranged from 939 (7 days after diagnosis) to 970 (5 days after diagnosis), as *k* varied from 0.57 to 2.25, respectively.

Results obtained when it was assumed that a clinical diagnosis of FMD could be made if 50 (5%) cows were demonstrating clinical signs differed more as *k* varied than those reported when it was assumed the diagnosis could be made with only 10 (1%) clinical cases. The most striking difference was that the simulated number of infectious cows present on the day

of diagnosis increased from 82–472 (1%) (Table 2; Fig. 2a) to 476–537 (5%) (Fig. 2b), when the diagnosis criterion increased from 10 to 50 clinically infected cows and as *k* increased from 0.57 to 9.0, respectively.

At the time when FMD was diagnosed in the herd (≥10 [1%] clinical cases), between 65% (646 cows) and 99% (986 cows) of the herd would already be infected (Fig. 3). The model predicted that virtually the entire herd (≥98%) would be infected within 1–3 days after diagnosis, as *k* varied from 9.0 to 0.57, respectively.

Discussion

The model predicted that an FMD-infected 1,000-cow herd would be diagnosed 10–13.5 days after the first cow became infected, assuming contact rates ranging from 0.57 to 9.0 per hour. In a previous study,[12] the intraherd "evolution" of FMD was reported using a simulation model designed for 2 regions in France. In their model, they assumed that a herd would be incubating (or latent) for 1 week (2 simulation time periods), with a given probability of detection, which varied depending on whether the herd was the index or a secondary case, after the latent period. The infectivity, measured as a dissemination rate, of the herd was presumed constant throughout the infectious life of the herd. They predicted that the index herd would be diagnosed 2 weeks after the index infection, compared with 10–13.5 days our model sim-
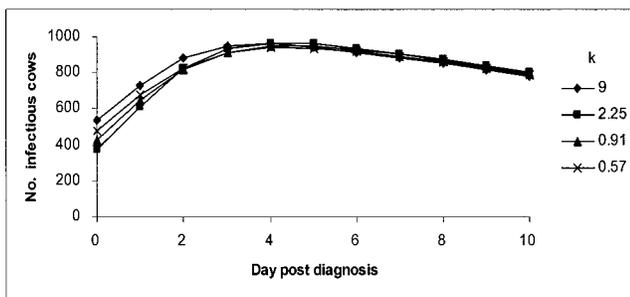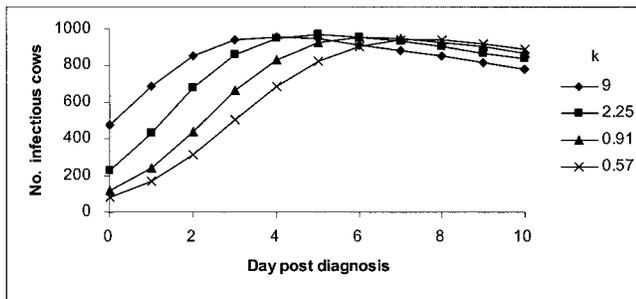

Figure 2. Mean total infectious prevalence of FMD, by days after diagnosis and variable number of adequate hourly contacts (*k*), in a hypothetical 1,000-cow dairy, assuming that a clinical diagnosis is based on at least **a,** 10 cows or **b,** 50 cows demonstrating clinical signs.
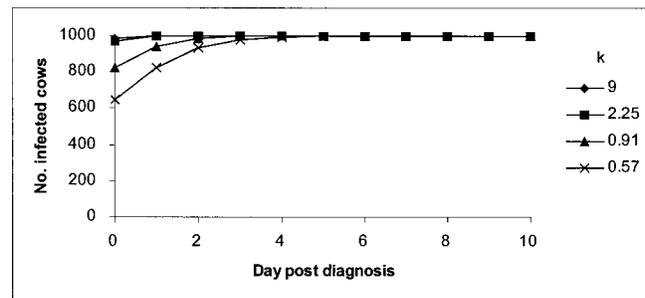

Figure 3. Mean prevalence of FMD, by days after diagnosis and variable number of adequate hourly contacts (*k*), in a hypothetical 1,000-cow dairy, assuming that a clinical diagnosis is based on at least 10 cows demonstrating clinical signs.

ulated. If 2 weeks were applied in the model examined here and if it is assumed that 10 clinically infected cows were necessary for a diagnosis of FMD, the entire herd would be infected by the time a diagnosis was made. This delay would increase the probability of interherd transmission of FMDV and likely increase the epidemic size from what has been predicted or observed in countries with less-intensive livestock production.

Although it may seem unlikely that as many as 50 clinical cases of FMD could be present before a diagnosis, it has its precedence, especially early in an epidemic. In the 2001 UK epidemic, there was a 20-day delay estimated between the primary infection, first diagnosis, and finding of the index case herd. Lesions in pigs from the likely source premises were estimated to be as old as 12 days, with 90% of the 527 pigs having lesions suggestive of FMD.[17] As many as 50% of the approximately 100 housed cattle in the index cattle herd (the 6th infected premises) were reported to have oral vesicular lesions on the day of diagnosis, believed to be 2–3 weeks postinfection. Furthermore, it was estimated that 69% of the FMD-infected dairy herds included cows with 2-day-old lesions, another approximately 15% with 3–4-day-old lesion, and about 5% with at least 5-day-old lesion.[17] In comparison, simulation results reported in this article predicted that 50% of the cows would show clinical signs 14–16 days after initial infection, as k varied from 2.25 to 0.57, respectively. Considering that the number of adequate contacts was likely no more than those used here, simulation results are consistent with those reported from the UK.

Several models[5,8,12–16,19,20–22,24,25] have been constructed to help evaluate the spread or control (or both) of FMD. None of them reported the consideration of intraherd transmission dynamics of the disease. However, one[25] of these models has reportedly used a supplemental model to simulate the airborne spread of the virus, modeling the intraherd virus transmission in FMD-infected swine herds (R. L. Sanson, personal communication). Based on the findings reported here, we believe that the intraherd disease dynamics must be estimated before a model can be used to accurately predict FMDV transmission between herds.

Although it may be mandated that slaughter of infected herds should occur on the same day as diagnosis, it was reported in the 1967–1968 UK epidemic that more than 25% were slaughtered 1 day and some as much as 3 days later.[9] In a previous study, it was reported that in the first 2 months of the 2001 UK FMD epidemic, time between reporting the disease and slaughter of the herd ranged between 1.1 and 2.9 days.[30] Even more dramatically, the mode delay for slaughtering FMDV-infected swine herds in Taiwan in 1997 was 11 days.[20] In contrast, studies from the 1981 FMD epidemic in Denmark, excluding the index herd, estimated the delay to have been only 15 hours.[28] It is clear from the results presented here how such delays could contribute to extended epidemics, whereby a large number of infectious animals could be available to transmit the virus to other herds.

The extensive intraherd transmission projected here for a typical, intensively managed dry-lot type of dairy herd has important implications for diagnostic medicine in developing herd and regional biosecurity programs, as well as for our ability to make a timely diagnosis of FMD. A challenge facing diagnostic medicine is the need to develop screening strategies for replacement livestock, as part of herd biosecurity aimed at minimizing introduction of FMDV into a herd. To minimize interherd transmission, regional, state, and national biosecurity also will require new diagnostic approaches that detect the virus much earlier than is possible using the current clinical signs signalment. The current surveillance strategy that relies on clinical signs of FMD will allow the infection to incubate and for many animals to transmit the virus to other herds after being culled or removed from the infected herd. In light of the potential for real-time diagnostic capability for FMDV detection, this traditional approach will need to be augmented by diagnostic surveillance that actively seeks out the virus, rather than waits for clinical signs to develop.

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b. Solver, Microsoft Corp., Redmond, WA.
c. @RISK, Palisades Corp., Newfield, NY.

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