

ORIGINAL ARTICLE

Factors Associated With Within-Herd Transmission of Serotype A Foot-and-Mouth Disease Virus in Cattle, During the 2001 Outbreak in Argentina: A Protective Effect of Vaccination

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Summary

Argentina suffered an extensive foot-and-mouth disease (FMD) epidemic between July 2000 and January 2002, 3 months after obtaining the official FMD-free without vaccination status conferred by the World Organization for Animal Health. This is one of the largest FMD epidemics controlled by implementation of a systematic mass vaccination campaign in an FMD-free country. In 2000, 124 herds were reported as FMD positive, 2394 herds in 2001 and one in January 2002; the total number of cattle herds in the country at that time was approximately 230 000. Estimates of FMD transmission are important to understand the dynamics of disease spread and for estimating the value for the parameterization of disease transmission models, with the ultimate goals of predicting its spread, assessing and designing control strategies, conducting economic analyses and supporting the decision-making process. In this study, the within-herd coefficient of transmission, β , was computed for herds affected in the 2001 FMD epidemic and categorized as low or high based on the median value of β . A logistic regression model was fitted to identify factors significantly associated with high values of β . Results suggested that the odds of having a high within-herd transmission were significantly associated with time from initial herd infection to disease detection, date of report, vaccination, and time from initial herd infection to herd vaccination. Results presented in this study demonstrate, in quantifiable terms, the protective impact of vaccination in reducing FMD transmission in infected herds. These results will be useful for the parameterization of epidemiological models aimed at quantifying the impact of vaccination and for the design and implementation of FMD emergency vaccination strategies in face of an epidemic.

Introduction

Foot-and-mouth disease (FMD), which is considered one of the most contagious animal diseases (World Organization for Animal Health (OIE), 2009), is endemic in

certain regions of Asia, Africa, the Middle East and South America. In South America, the disease was first introduced in the 1870s (Saraiva, 2004). Foot-and-mouth disease has an important economic impact because of the direct losses caused to animal production and the costs

associated with control of the disease and trade limitations (James and Rushton, 2002). Two of the world largest cattle meat producers, Brazil and Argentina, are located in South America. In the year 2000, there were approximately 230 000 cattle herds in Argentina (SENASA, unpublished observation).

Argentina was recognized as FMD-free-with vaccination in 1996 and FMD-free-without vaccination in May 2000 by the OIE. However, 124 herds were infected in August, 2000, with serotypes A (A/Arg/00) and O (O/Arg/00) FMD viruses. Brazil and Uruguay were also affected by this epidemic. Although the epidemic was considered controlled by the end of 2000 (Correa Melo et al., 2002) by using movement restriction and 'stamping out' strategies, early in 2001, a serotype A FMD virus, A/Arg/01, which was more virulent than A/Arg/00 (Konig et al., 2007; Garcia-Nunez et al., 2010), caused a new epidemic that affected 2519 herds throughout the country (Perez et al., 2004a). Movement restrictions were imposed, and two vaccine doses were applied to susceptible herds surrounding an outbreak through early April 2001, when compulsory mass vaccination of bovine herds twice a year was implemented nationwide except in Patagonia region, which remained FMD-free (Perez et al., 2004a). Differences of serotype A strains A/Arg/00 and A/Arg/01 antigenic sites from vaccine reference strain A24/Cruzeiro resulted in two consecutive vaccine reformulations to incorporate strains A/Arg/00 and A/Arg/01 to the vaccine (Mattion et al., 2004; Konig et al., 2007). Although infected herds were not intended to be vaccinated, certain infected herds with no evident clinical sign of disease were vaccinated at the emergency or at the systematic vaccination campaigns. The epidemic lasted through January 2002 (Perez et al., 2004a,b).

Field data collected from outbreaks occurred through 2001 in the FMD epidemic in Argentina provide important information to estimate parameters that are prerequisite for the formulation of disease spread epidemiological models, such as the within-herd transmission rate (β). Noteworthy, much of the information regarding parameterization of FMD virus transmission that is available in the peer-reviewed literature refers to serotype O strains, likely, because most of the epidemics recently reported in FMD-free countries were caused by serotype O FMD viruses and because serotype O is the most prevalent FMD virus serotype in the world (Orsel et al., 2007; Mardones et al., 2010). Subsequently, within-herd transmission of FMD virus has most frequently been assessed using experimental data (Orsel and Bouma, 2009; Orsel et al., 2009) and simulation models (Carpenter et al., 2004; Keeling, 2005), rather than field data.

In this study, the within-herd coefficient of transmission of serotype A FMD virus was computed using data

from a large FMD epidemic that affected Argentina in 2001; 2394 herd outbreaks were reported in Argentina in 2001, in what is considered one of the largest epidemics caused by serotype A FMD virus in an FMD-free country that has been controlled by implementation of a systematic mass vaccination campaign (Perez et al., 2004a). Furthermore, the association between the value of β and epidemiological factors, including vaccination status of the herd, was assessed. Results presented in this study will contribute to the parameterization of FMD spread models and to quantify the impact of vaccination campaigns in face of an FMD epidemic.

Materials and Methods

Data source

Official records from the 2394 FMD outbreaks reported in Argentina from February through December 2001 were obtained from the Argentine National Service for Animal Health and Agri-food Quality (SENASA). An FMD outbreak was defined as a herd in which FMD infection was officially recognized by a SENASA local veterinarian, based on the observation of FMD-like clinical signs and lesions (vesicular lesions in tongue, dental pad, interdigital, coronary and teat, lameness, salivation, pyrexia and mortality in young animals) in at least one animal in the herd, the results of the field investigation and/or serological sampling. Mortality was not considered because of the nil mortality rate, and only bovine herds were analysed because 97% of infected animals were cattle (Mattion et al., 2004).

Each record referred to a single outbreak and contained information about herd size, susceptible animals per age category: <1 year, 1–2 years or >2 years (non-diseased cattle in the herd at the beginning of the outbreak), initial and final (cumulative) number of cattle showing FMD-like clinical lesions, report date, serologic test results (available for some herds), estimated date of FMD virus introduction into the herd (based on age of the lesions), vaccination status (vaccinated or unvaccinated herd), date of vaccination, location of the herd recorded as decimal degrees coordinates based on a grid system used by SENASA and duration of the outbreak.

Computation of the within-herd transmission coefficient, β

Within-herd transmission of FMD virus was estimated using a modification of the mass action frequency-dependent principle (McCallum et al., 2001). The coefficient of transmission (β) was defined as the average number of individuals that are newly infected from an infectious individual per unit of time (De Jong, 1995); in lay terms,

β is a rate used to estimate how many susceptible individuals acquire the infection from an infectious individual in a susceptible population over a given period of time. For this study, we used the number of animals showing FMD-like lesions rather than the true number of infected animals; hence, if the proportion of FMD-infected animals that developed clinical signs remains, on average, the same throughout an outbreak, then estimates of β will remain unbiased. Because duration of the outbreaks was heterogeneous, the number of animals showing FMD-like lesions at the end of the outbreak was adjusted by the duration of the outbreak using $C_a = C/t$, where C is the number of new cases identified in the epidemic (the difference between the cumulative number of cases at the end of the epidemic and the number of cases at the beginning of the epidemic), C_a is the adjusted number of cases, and t is the duration of the outbreak in days; thus, C_a is an estimate of the expected number of cases caused by a single infected animal in 1 day. The value of β (per day) was consequently estimated as

$$\beta = \frac{NC_a}{SI}$$

where N is the number of animals in the herd, which was assumed to be constant through the duration of the outbreak, justified by the nil mortality rate observed in the epidemic and by the prohibition of animal movement imposed at the beginning of the epidemic, I is the number of animals infected at the time of outbreak detection, and S is the number of susceptible animals at the beginning of the outbreak, $S = N - I$.

Outbreaks ($n = 1001$, 41.8%) with incomplete or insufficient information or for which the *sine qua non*-condition for disease transmission $C > I$ could not be verified from the records were excluded from the analysis to control for potential information bias associated with inaccurate collection or recording of field data.

The frequency-dependent model assumes that the transmission of the disease is not dependent on animal density. This assumption was biologically sound to the authors because animals in free-range systems, which is the most common production system in Argentina, are free to move and contact animals with no imposed restriction. However, one may argue that animals in intensive production systems could have more contacts with more individuals in a day, compared to animals in extensive production systems; thus, a density-dependent model may be considered more appropriate than the frequency-dependent model used in this study. To assess whether results were different depending on whether density or frequency-dependent models were used to fit the data, in addition to the frequency-dependent formulation, the value of β was also computed using a density-

dependent approximation of the form $\beta = C_a/SI$, and results were compared with those obtained using the frequency-dependent model using a Spearman's rank correlation.

Statistical analysis

Zero-truncated probability distributions that best fitted the values of β in either and both vaccinated and unvaccinated herd outbreaks were identified using the @RISK® software (Palisade Corporation, New York/London v. 5.0).

Multivariate logistic regression

Herds with β values larger than the median value of β ($M\beta$) estimated for the epidemic were categorized as cases, whereas herds in which $\beta \leq M\beta$ were categorized as controls. Therefore, a case in this study was defined as an outbreak in which disease transmission was larger than the epidemic's background, which was defined as the median value of β . A multivariate logistic regression model was used to assess the association between herds with values of $\beta > M\beta$ and epidemiological factors hypothesized to influence the value of β . Scatter plots for all possible bivariate associations and correlation coefficient were computed to assess for preliminary potential relationship between the epidemiological factors and the values of β . Candidate epidemiological factors entered into the regression model were geographical location of the herd (to control for potential spatial dependence of the observations), duration of the outbreak in days, days to detection or d_{det} (defined as the difference, in days, between the date of SENASA detection, and the estimated date of FMD virus introduction into the herd), main age group of the herd and vaccination status (unvaccinated, vaccinated 0–4 post or 1–7, 8–14, 15–28 and >28 days before the estimated date of FMD virus introduction into the herd). Records with incomplete information of these variables were excluded from the analysis. Two-way interactions and quadratic terms were considered in all models and tested for significance ($P < 0.05$). Significant terms were retained in the model. Odds ratios and 95% confidence intervals were computed for variables included in the final model. Model fit was assessed using the Pearson chi-square goodness-of-fit statistic. Statistical analyses were performed using Minitab (Minitab Inc., State College, PA, USA).

Results

Summary statistics

A total of 1349 herds (56.4%) records were available for the analysis after removing records with insufficient or inaccurate information ($n = 1001$ with inaccurate

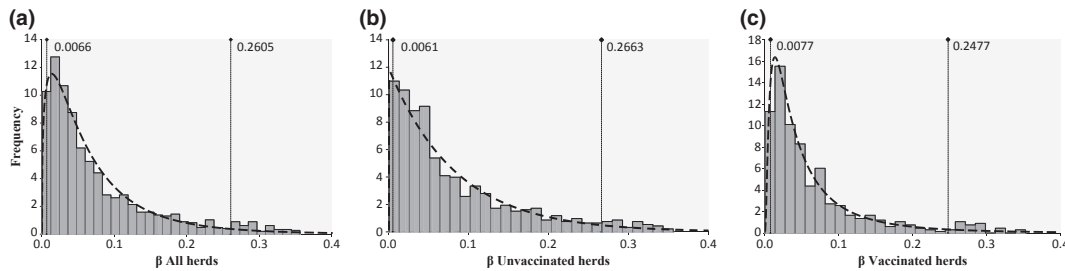


Fig. 1. Observed values (—) and fitted distributions (- -) for the coefficient of transmission β in all herds (unvaccinated + vaccinated) (a), unvaccinated herds (b) and vaccinated herds (c). Numbers at the top of the graphs represent the 90% probability interval of the distribution.

information and $n = 44$ records with missing outbreaks initial and/or end dates). The mean (median) values of β were estimated as 0.22 (0.06) for all herds, 0.26 (0.06) for unvaccinated herds and 0.17 (0.04) for vaccinated herds. The distribution that best fitted the β values for all herds was Pearson type six with parameters 1.3437, 5.2769 and 0.24513 and a most likely value of 0.077, whereas the distribution of β in vaccinated and unvaccinated herds was best fitted by a log-normal distribution with parameters 0.069158 and 0.09656, and a most likely value of 0.069, and by an exponential distribution with parameter 0.083 and most likely value of 0.083, respectively (Fig. 1). Visually, there was no evident trend of β during the epidemic time period (Fig. 2), whereas the bivariate association between time to detection and within-herd transmission was visually apparent (Fig. 3). Results obtained using the frequency-dependent model were moderately correlated (R -Spearman = 0.633, $P < 0.001$), with those obtained using the density-dependent model.

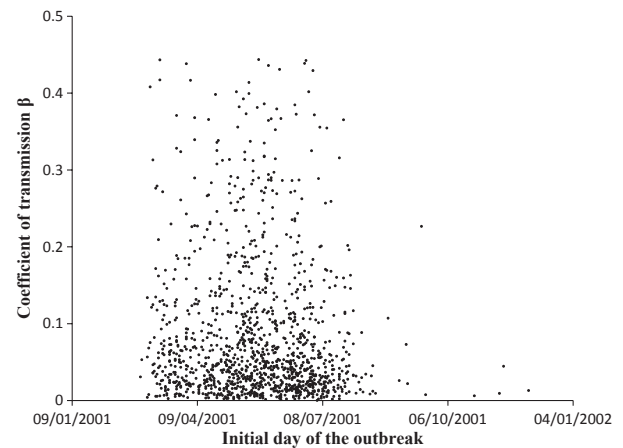


Fig. 2. Bivariate association between the coefficient of transmission, β , of foot-and-mouth disease and starting date of the outbreak during the 2001 Argentine epidemic.

Multivariate logistic regression

A total of 1221 outbreaks were used to fit the regression model, because 128 records in which vaccination date were missing were excluded from the analysis (Table 1).

Significant variables retained in the final multivariate logistic regression model were report date, d_{det} and vaccination status/days to vaccination (Table 1); interestingly, the odds for high disease transmission were lower for those herds in which infection took longer to detect (Fig. 3). The model fitted the data well (Pearson chi-square test, $P = 0.235$).

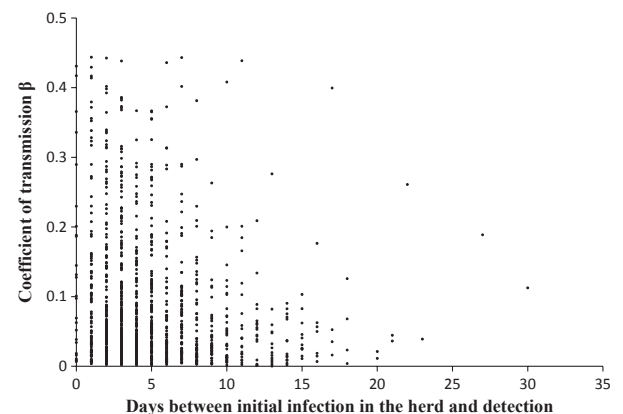


Fig. 3. Bivariate association between the days to detection and β . There is an evident inverse relationship of the values, as the number of days to detection increase, the within-herd transmission is lower.

Discussion

Within-herd transmission of the FMD epidemic reported in Argentina in 2001, which was computed using field data, was significantly associated with d_{det} , date reported, vaccination and time between vaccination and estimated date of virus introduction into the herd. Previous studies

regarding FMD transmission have been carried out under experimental conditions (Cox et al., 2007; Orsel and Bouma, 2009), in which the payload of the antigen in the

Table 1. Multivariate logistic regression association between selected epidemiological factors and foot-and-mouth disease within-herd transmission rates in Argentina, 2001

Variable	Category	<i>n</i>	Odds ratios	95% confidence intervals	<i>P</i> -value
Report date		1221	1.00	(0.99, 1.00)	0.004
Days to detection ^a		1221	0.94	(0.91, 0.97)	<0.001
Vaccination	Non vaccinated	823	*	*	Reference
	0–4 days after ^a	25	0.60	(0.26, 1.36)	0.218
	1–7 days before ^a	105	0.49	(0.32, 0.75)	0.001
	8–14 days before ^a	56	0.61	(0.35, 1.07)	0.085
	15–28 days before ^a	57	0.79	(0.45, 1.36)	0.391
	>28 days before ^a	156	0.69	(0.47, 1.01)	0.056

Pearson chi-square $P = 0.235$, log-likelihood = -823.690 , test that all slopes are zero $G = 45.219$, $P < 0.000$.

^aDays in relation to the estimated day of first infection in the herd.

vaccine, challenge dose, exposure, age and animal condition, strain used in the vaccine and challenge (normally homologous antigen used), and inoculation techniques is set under controlled conditions, but in which, arguably, epidemiological conditions observed in the field could hardly be replicated. In this study, we used observational data collected from one of the few large serotype A FMD epidemics controlled by vaccination reported in the international peer-reviewed literature.

In this study, the protective effect of the vaccine was evidenced by the association between vaccination and low rate of within-herd transmission. These results are in agreement with early studies, suggesting that emergency vaccination has a protective impact on disease transmission and that there is a decreased transmission rate within the herd even if the vaccine is applied soon before or even few days after initial infection in the herd (Cox and Barnett, 2009; Orsel and Bouma, 2009). Noteworthy, some authors suggest that there is an increased risk of animals becoming carriers as the time between vaccine and challenge decreases (Barnett and Carabin, 2002), which could not be assessed in this study because of the lack of data on persistently infected animals.

It is known that within- and between-herd disease spread is typically able to be controlled by systematic FMD vaccination with protective vaccines in endemic areas (Bergmann et al., 2004), but emergency vaccination effect in face of an epidemic on within-herd spread has not been previously evaluated in the field. Emergency vaccination has gained consideration as a control strategy during FMD outbreaks in disease-free areas, especially since the 2001 UK outbreak (Hutber et al., 2011). Experimental studies have shown that emergency vaccination can be an effective strategy to control FMD during an outbreak by reducing clinical disease, subclinical infection, excretion and transmission (Cox et al., 2007; Cox and Barnett, 2009; Orsel and Bouma, 2009; Hutber et al., 2011).

Results of this study showing that emergency vaccination in infected herds decreased within-herd transmission even when vaccination was applied soon after the start of the outbreak may have important applications when evaluating whether a ‘stamping out’ policy or emergency vaccination should be applied, especially because the international OIE ban length was shortened to 6 months when using emergency vaccination ‘to live’. Economic analyses of these two control strategies should be performed as well as considering aspects regarding animal welfare concerns, especially brought to attention after the UK 2001 outbreak. Use of emergency vaccination to control FMD epidemics is also likely to be increasingly used in the future because the performance of diagnostic methods capable of differentiating vaccinated from infected animals by detection of antibodies to non-structural proteins had improved and such methods are now officially accepted (Bergmann et al., 2003).

Estimated time between exposure to FMDV serotype O and earliest detection of infection (latent period) ranges from 3.1 to 4.8 days, and time between first positive samples and first clinical signs (subclinical period) ranges from 2 to 2.3 (Mardones et al., 2010). Therefore, it does take a certain period of time until every susceptible animal in the herd is exposed to the virus and, eventually, infected. In a scenario where animals are vaccinated at an early stage of herd infection, individual immunity raises in parallel to within-herd disease spread, so that if the rate of spread is lower than the rate of disease protection conferred by the vaccine, at certain point, at least some animals become immune and disease spread is restrained. During the latent period, there is no transmission to new individuals; additionally, disease transmission is lower in subclinical infected animals than in animals presenting clinical disease (Orsel et al., 2009).

Consistently with the results presented in this study, evidence on the effects of vaccination reducing within-herd transmission was observed in a field study in Laos

People's Democratic Republic in which morbidity, in villages vaccinated less than a month before the beginning of the outbreak, was lower than in villages with unvaccinated herds (Rast et al., 2010).

Argentine cattle have been systematically vaccinated up to 1 year before the beginning of the epidemic with A24/Cruzeiro strain, so it is expected that residual immunity was present in at least some animals older than 1 year.

Almost all vaccinated herds included for this study used a formulation with A/Arg/00. An early analysis of this epidemic reported that vaccines formulated with A/Arg/00 (trivalent O1/C-A24-A2000) induced 50–60% protection when challenged with the heterologous A/Arg/01 strain isolated in the epidemic (Mattion et al., 2004), which might explain, at least in part, the association between vaccination status and transmission rate detected in this study. Assessment of the protection conferred specifically by the homologous A/Arg/01 strain in within-herd transmission was not possible because data required for the analysis were available in only <10 herds vaccinated with A/Arg/01 and because herds vaccinated with the homologous strain (A/Arg/01) were not affected. For those reasons, it is very likely that the protective effect of vaccination may have been underestimated in this study.

Estimates of FMD transmission rates have been computed using experimental data, in which animals are typically more intensively evaluated for the detection of infection and clinical disease, compared to field conditions. In this study, FMD transmission rate was estimated using observational data on clinically diseased animals collected during the epidemic. Subclinically infected animals that went through the outbreak undetected were not accounted in the analysis. If, as expected, the proportion of infected animals that did not develop clinical signs was, on average, relatively constant throughout the duration of the outbreak, then the value of β estimated in this study would still be unbiased. However, values of β computed should be regarded as an estimate of the average within-herd transmission of the outbreak, as one would expect the value of β to decrease for each particular outbreak as the number of susceptible and infected animals decreases, and immunity increases, towards the end of the outbreak.

Long time-to-detection was also significantly associated with low risk of within-herd transmission. A possible explanation is that, for densely populated herds, which are typically managed through intensive production systems, disease might have spread faster and detection may have taken place earlier, compared to extensive production units, in which disease spread and disease detection are expected to be slower. This result is in agreement with early studies of this epidemic, which suggest that FMD may have been more easily detected in intensive production systems, especially at the beginning of the epi-

dem (Ward and Perez, 2004), where increased contact between animals occur, and higher transmission rates are found. Report date was also associated with disease transmission; initial outbreaks showing, in general, high values of β , likely, because the level of awareness among producers increased with time.

Values of β were independent of the geographical location of the herd, suggesting that the FMDV A/Arg/01 virulence was homogeneous throughout the country. Main age group of the herd was also independent from the value of β ; however, it is also possible that age-dependent associations could have been revealed if association with type of production would have been assessed, but such information was not available to the authors.

In conclusion, results presented in this study suggest, in quantitative terms, the effect of vaccination in the reduction of within-herd transmission of FMD virus, reinforcing the impact that emergency vaccination has in controlling FMD epidemics. Because of the transboundary nature of FMD spread, this result is particularly relevant for countries that withdrew FMD vaccination, but that are still exposed to FMD virus incursions from infected regions.

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