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Vaccination of cattle only is sufficient to stop FMDV transmission in mixed populations of sheep and cattle

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SUMMARY

We quantified the transmission of foot-and-mouth disease virus in mixed cattle-sheep populations and the effect of different vaccination strategies. The (partial) reproduction ratios (R) in groups of non-vaccinated and vaccinated cattle and/or sheep were estimated from (published) transmission experiments. A 4×4 next-generation matrix (NGM) was constructed using these estimates. The dominant eigenvalue of the NGM, the R for a mixed population, was determined for populations with different proportions of cattle and sheep and for three different vaccination strategies. The higher the proportion of cattle in a mixed cattle-sheep population, the higher the R for the mixed population. Therefore the impact of vaccination of the cattle is higher. After vaccination of all animals $R = 0{\cdot}1$ independent of population composition. In mixed cattle-sheep populations with at least 14% of cattle, vaccination of cattle only is sufficient to reduce R to < 1.

Key words: Cattle-sheep populations, foot-and-mouth disease virus, NGM, targeted vaccination, transmission.

INTRODUCTION

Foot-and-mouth disease (FMD) is a viral disease in cloven-hoofed animals caused by foot-and-mouth disease virus (FMDV). Transmission of FMDV is difficult to control. The magnitude of transmission of any infection is assessed using the reproduction ratio R [1, 2]. R is defined as the average number of new cases arising from a typical infected individual during its whole infectious period in a fully susceptible population. An infectious agent is able to cause major outbreaks only if R is > 1 [3]. For FMDV, R has been quantified using field data [4] and experimental data [5–12]. Using experimental data, R has been quantified for both vaccinated and non-vaccinated sheep-to-sheep transmission [7, 11] and for vaccinated and non-vaccinated cattle-to-cattle transmission [9, 10] (and in Bravo de Rueda *et al.*, unpublished observations). In addition, a partial R for non-vaccinated sheep to non-vaccinated cattle [13] has been quantified; however, this estimate alone is not sufficient to assess the magnitude of transmission of FMDV in a mixed population of cattle and sheep. In order to understand the transmission of FMDV in field conditions where different species co-exist, it is necessary to quantify R for heterogeneous populations (i.e. consisting of sheep and cattle).

Vaccination against FMDV has been recognized as an important tool for the control of FMDV. Vaccination against FMDV can prevent transmission of the virus both in field conditions [14–16] and experimentally [5, 7, 9–11, 17, 18]. In mainland Europe,

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FMDV was eradicated by prophylactic vaccination of cattle only [15]. In parts of South America, FMDV was successfully eradicated by vaccination of cattle only [16]. For example, in Uruguay, where cattle and sheep, mingle freely and where (before 2002) the proportion of sheep in the population was slightly higher than that of cattle, vaccination of cattle only was sufficient to eradicate FMDV [16, 19]. In the European Union, emergency vaccination of (all) susceptible species is an option during an FMDV outbreak (EU directive 2003/85). The Netherlands used emergency vaccination in the 2001 outbreak with vaccination of all FMDV-susceptible animals. However, it is unclear whether emergency vaccination of *all* susceptible species is necessary to control an epidemic or if targeting vaccination to certain species (e.g. only cattle) could be sufficient.

In the current study we developed a method to determine R for mixed populations consisting of cattle and sheep by using experimental transmission data and a technique known as the next-generation matrix (NGM) [20]. The method allows analysis of different vaccination strategies in different mixed populations consisting of cattle and sheep.

METHODS

Data source from experimental studies

Data available from direct contact transmission studies [7, 9–11, 13] (and in Bravo de Rueda *et al.* unpublished observations) were used. These data were collected from three cattle-to-cattle transmission studies (26 experimental groups), two sheep-to-sheep transmission studies (24 experimental groups) and one sheep-to-cattle transmission study (10 experimental groups). These transmission studies were selected because the raw data on the number of susceptible, infectious, and recovered animals were readily available, and because comparable methods were used in the experiments. The donors in all these studies were inoculated via the intranasal route using either FMDV O/NET/2001 or Asia-1 TUR/11/2000. Five of these six studies also contained data on transmission of FMDV after vaccination, using either FMDV O Manisa or FMDV Asia-1 Shamir as vaccine strains.

Quantification of (partial) R values by using experimental data

The SIR model [21] was used for the quantification of R cattle to cattle (R_{c-c}), sheep to sheep (R_{s-s}), and partial R sheep to cattle (partial R_{s-c}) for non-vaccinated animals and of R_{c-c}^{vac} and R_{s-s}^{vac} for vaccinated animals. The animals from the direct contact transmission studies [7, 9–11, 13] (and in Bravo de Rueda *et al.*, unpublished observations) were classified as susceptible, infectious, or recovered (S-I-R, respectively), at the start (S_0, I_0) and at the end (S_t, R_t) of the experiment. It was assumed that the animals were infectious if they tested positive by virus isolation (on secondary lamb kidney cells) or if they developed infection specific antibodies (detected by NS-ELISA). Contact animals were considered infected if they tested positive for FMDV or FMDV-specific antibodies during the experiment. Animals that were infectious during the experiment were considered as recovered at the end of the experiment (R_t). Data originating from experiments with the same donor species and same contact animal species were pooled for the calculation of the reproduction ratio R.

The recorded data as S_0, I_0, S_t and R_t and the frequencies at which they occurred (see Tables 1 and 2), were used to estimate the reproduction ratio R [22] for non-vaccinated and/or vaccinated groups by using the final size method [23, 24]. The R_{c-c}, R_{c-c}^{vac}, R_{s-s}, R_{s-s}^{vac} and partial R_{s-c}, and their 95% confidence intervals (CI) were calculated from the final sizes using the maximum likelihood estimation and exact confidence bounds [25] in Mathematica® (http://www.wolfram.com/mathematica/).

The null hypothesis that no difference existed between the estimates of R_{c-c} and R_{s-s}, R_{s-s} and partial R_{s-c}, and R_{c-c} and partial R_{s-c} was tested by using a two-sided test with a significance level of 0·05 [25].

Estimation of relative infectivities, susceptibilities and the unknown (partial) R values by using the separable mixing assumption

We built a 4×4 table using the (partial) R's between non-vaccinated/vaccinated cattle and non-vaccinated/vaccinated sheep. In this 4×4 table only five out of the possible 16 values were quantified using the experimental data. By assuming separable mixing, i.e. assuming that the (partial) R's are the product of a relative infectivity f_i [where i is either non-vaccinated cattle (nc), vaccinated cattle (vc), non-vaccinated sheep (ns), or vaccinated sheep (vs)] and a relative susceptibility g_i [where i is either non-vaccinated cattle (nc), vaccinated cattle (vc), non-vaccinated sheep (ns), or vaccinated sheep (vs)], we calculated the

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Table 1. *Final outcome from the transmission experiments with non-vaccinated animals*

Experiment	FMDV serotype	Animals	No. of animals/ group	S_0	I_0	S_t	R_t	Frequency	Reference
a	Asia-1	Calves	2	1	1	0	2	4	Bravo de Rueda *et al.*, unpublished
a	Asia-1	Calves	2	2	0	2	0	1	Bravo de Rueda *et al.*, unpublished
b	O	Calves	4	2	2	0	4	4	[10]
b	O	Calves	4	2	2	1	3	2	[10]
c	O	Cows	10	5	5	0	10	2	[9]
d	Asia-1	Lambs	4	2	2	0	4	2	[7]
d	Asia-1	Lambs	4	2	2	1	3	1	[7]
d	Asia-1	Lambs	4	2	2	2	2	3	[7]
e	O	Lambs	4	2	2	0	4	2	[11]
e	O	Lambs	4	2	2	1	3	1	[11]
e	O	Lambs	4	2	2	2	2	3	[11]
f	Asia-1	Lambs-calf	3	1	2	0	3	4	[13]
f	Asia-1	Lambs-calf	3	1	2	1	2	6	[13]

S_0 and S_t represent the number of susceptible animals at the start and at the end of the experiment; I_0 represents the number of infectious animals at the start of the experiment; and R_t represents the number of recovered animals at the end of the experiment. Frequency represents the number of experimental groups with the same outcome. Dashed lines separate the experimental groups of animals.

missing values in the table. Without loss of generality we chose non-vaccinated cattle to have a susceptibility of 1. Further, we assumed the relative susceptibility of vaccinated animals also to be 1, the same as the relative susceptibility of non-vaccinated animals. This assumption might seem counterintuitive, but local virus replication is often detected in vaccinated animals after challenge [26], indicating that vaccinated animals are still susceptible. In our calculations, the value is only necessary for filling the table. It does not influence the results on the diagonal, which are the only numbers that will be used (as will be explained below) in the calculation of the R values for the different strategies. Note that the reduction in transmission due to vaccination is

Table 2. *Final outcome from the transmission experiments with vaccinated animals*

Experiment	FMDV serotype	Animals	No. of animals/ group	S_0	I_0	S_t	R_t	Frequency	Reference
a	Asia-1	Calves	2	2	0	2	0	5	Bravo de Rueda *et al.*, unpublished
b	O	Calves	4	2	2	2	2	4	[10]
b	O	Calves	4	2	2	1	3	1	[10]
b	O	Calves	4	3	1	3	1	1	[10]
c	O	Cows	10	7	3	7	3	1	[9]
c	O	Cows	10	10	0	10	0	1	[9]
d	Asia-1	Lambs	4	2	2	2	2	4	[7]
d	Asia-1	Lambs	4	3	1	3	1	2	[7]
e	O	Lambs	4	2	2	2	2	2	[11]
e	O	Lambs	4	3	1	2	2	1	[11]
e	O	Lambs	4	3	1	3	1	2	[11]
e	O	Lambs	4	4	0	4	0	1	[11]

S_0 and S_t represent the number of susceptible animals at the start and at the end of the experiment; I_0 represents the number of infectious animals at the start of the experiment; and R_t represents the number of recovered animals at the end of the experiment. Frequency represents the number of experimental groups with the same outcome. Dashed lines separate the experimental groups of animals.

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Table 3. *(Partial) R values as estimated from infected non-vaccinated (NV) or vaccinated (V) animals to non-vaccinated (NV) or vaccinated (V) contact animals*

	From			
	NV cattle ($f_{nc} = 5{\cdot}3$)	NV sheep ($f_{ns} = 0{\cdot}87$)	V cattle ($f_{vc} = 0{\cdot}13$)	V sheep ($f_{vs} = 0{\cdot}075$)
To				
NV cattle ($g_{nc} = 1$)	**5·3**	**0·87**	0·13	0·075
NV sheep ($g_{ns} = 1{\cdot}3$)	6·9	**1·1**	0·17	0·10
V cattle ($g_{vc} = 1$)	5·3	0·87	**0·13**	0·075
V sheep ($g_{vs} = 1{\cdot}3$)	6·9	1·1	0·17	**0·10**

The values in bold were estimated from experimental data using the final size method. The other *R* values were based on the product of the relative infectivity (f_i) and relative susceptibility (g_j). We assumed that the relative susceptibility of both non-vaccinated and vaccinated cattle and sheep are equal. Without any loss of generality we took non-vaccinated cattle to have susceptibility equal to 1. Note: this table is not yet the NGM as the proportion of the different animal species and the proportion of vaccinated animals are still missing.

now assumed to be due to the lower infectivity of the vaccinated and then infected animals (Table 3).

Construction of a NGM

A NGM allows the analysis of the effect of different categories of individuals on the overall transmission, i.e. in a mixed population [27]. In our case, *R* for a mixed population of cattle and sheep depends on the proportion of each animal species in the population. In the matrix p_c is the proportion of cattle (i.e. the total number of cattle divided by the total number of cattle and sheep in a population) and $1 - p_c$ is the proportion of sheep in the same population. In the matrix the proportion of vaccinated animals per species are indicated by pv_c and pv_s, where pv_c and pv_s represent the proportion of vaccinated cattle and the proportion of vaccinated sheep, respectively. The relative infectivity f_i and relative susceptibility g_i from the above 4×4 table were added to the NGM. Thus, the elements of our matrix are functions of the relative infectivity (f_i), relative susceptibility (g_i), the proportion of cattle (p_c), and the proportion of vaccinated cattle and that of sheep (pv_c or pv_s).

Evaluation of the influence of different proportions of cattle (p_c) and sheep ($1 - p_c$)

We studied the influence of different proportions of cattle and sheep on the transmission of FMDV in our NGM. To illustrate this we used five different populations: (1) a population consisting of cattle only, (2) a population with a higher number of cattle than sheep, (3) a population with a relatively similar number of cattle and sheep, (4) a population with a higher number of sheep than cattle, and (5) a population consisting of sheep only. For defining the different mixed populations consisting of cattle and sheep we used proportions of known livestock populations from the FAOSTAT database [28]. In 2011 these p_c values were: 0·78 in The Netherlands (for population 2), 0·61 in Uruguay (for population 3), and 0·24 in New Zealand (for population 4). The proportions of the population of cattle (p_c per population) were included in the NGM. Finally, the dominant eigenvalue of the NGM, i.e. the reproduction ratio for the mixed populations, was determined for all five populations.

Evaluation of the effect of different vaccination strategies

We used the five above-mentioned populations to evaluate the effect of three different vaccination strategies for the control of FMD transmission. These strategies were: (1) vaccinating both species equally, thus $pv_c = pv_s$, (2) vaccinating all cattle with additional vaccination of sheep ($pv_c = 1$ and $pv_s \neq 0$) and, (3) vaccinating all sheep with additional vaccination of cattle ($pv_c \neq 0$ and $pv_s = 1$). The obtained results were plotted for each strategy. Because *R* depends on p_c, pv_c and pv_s, we calculated the proportion of animals that has to be vaccinated (or has to be present in a population) at which *R* reached the value of 1.

RESULTS

Quantification of (partial) *R* values by using experimental data

In groups where no vaccination was applied, R_{c-c} was estimated as 5·3 (95% CI 3·0–42) and R_{s-s} was

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estimated as 1·1 (95% CI 0·44–2·4). The partial R_{s-c} was estimated as 0·87 (95% CI 0·20–2·9) (bold values in Table 3). R_{c-c} was found to be significantly higher than R_{s-s} ($P = 0{\cdot}002$). Moreover, R_{c-c} was significantly higher than partial R_{s-c} ($P = 0{\cdot}005$). R_{s-s} was not significantly different from partial R_{s-c} ($P = 0{\cdot}56$) and therefore based on these results the susceptibility of cattle and sheep are considered similar.

In groups where vaccination was applied, the R^{vac}_{c-c} was estimated as 0·13 (95% CI 0·0032–0·83) and R^{vac}_{s-s} was estimated as 0·098 (95% CI 0·0026–0·65). The estimated relative infectivities (f_i), relative susceptibilities (g_i), and the (partial) R's are shown in Table 3.

Construction of the NGM

Equation (1) shows the 4 × 4 NGM in which the proportions of cattle and sheep and the proportion of vaccinated animals are included. In our matrix, because of the assumption of separable mixing, the dominant eigenvalue equals the sum of the elements on the diagonal (from top left to bottom right) which is called the trace of the matrix [27]. This dominant eigenvalue is the R for the mixed population described by the NGM [20, 27]. Thus

$$R(p_c, pv_c, pv_s) = p_c\big((1-pv_c)f_c g_c + pv_c f_{vc} g_{vc}\big) + (1-p_c)\big((1-pv_s)f_s g_s + pv_s f_{vs} g_{vs}\big).$$

For example, for a population consisting of non-vaccinated cattle only, the dominant eigenvalue of that matrix is $R(1,\ 0,\ 0) = f_c g_c = R_{c-c}$ and, for a population consisting of only vaccinated cattle, the dominant eigenvalue of that matrix is $R(1,\ 1,\ 0) = f_{vc} g_{vc} = R^{vac}_{c-c}$.

Equation 1: NGM with non-vaccinated and vaccinated animals. f_c and f_s correspond to the infectivity of cattle and of sheep, respectively. g_c and g_s correspond to the susceptibility of cattle and of sheep, respectively. The proportion of the population of cattle p_c and of sheep $1 - p_c$ depends on the characteristics of a mixed population. pv_c represents the proportion of vaccinated cattle and pv_s, the proportion of vaccinated sheep:

$$\begin{bmatrix} f_c g_c p_c(1-pv_c) & f_s g_c p_c(1-pv_c) & f_{vc} g_c p_c(1-pv_c) & f_{vs} g_c p_c(1-pv_c) \\ f_c g_s(1-p_c)(1-pv_s) & f_s g_s(1-p_c)(1-pv_s) & f_{vc} g_s(1-p_c)(1-pv_s) & f_{vs} g_s(1-p_c)(1-pv_s) \\ f_c g_{vc} p_c pv_c & f_s g_{vc} p_c pv_c & f_{vc} g_{vc} p_c pv_c & f_{vs} g_{vc} p_c pv_c \\ f_c g_{vs}(1-p_c) pv_s & f_c g_{vs}(1-p_c) pv_s & f_{vc} g_{vs}(1-p_c) pv_s & f_{vs} g_{vs}(1-p_c) pv_s \end{bmatrix}$$

Evaluation of the influence of different proportions of cattle (p_c) and sheep ($1 - p_c$)

In the different non-vaccinated mixed populations, for populations with 0%, 24%, 61%, 78% and 100% cattle, R was estimated to be 1·1, 2·1, 3·7, 4·4 and 5·3, respectively.

Evaluation of the effect of different vaccination strategies

Strategy 1: vaccination of both cattle and sheep

In Figure 1*a* we show the effect of vaccination when we vaccinate (the same proportion of) both cattle and sheep (so when $pv = pv_c = pv_s$) for populations consisting of cattle or sheep in different proportions. The R for a fully vaccinated mixed population with 0%, 24%, 61%, 78% and 100% cattle was 0·1, 0·11, 0·12, 0·12 and 0·13, respectively, i.e. always <1.

The percentage of the population that has to be vaccinated to achieve $R = 1$ is: 14%, 56%, 75%, 79% and 83% for populations with 0%, 24%, 61%, 78% and 100% cattle, respectively.

Strategy 2: vaccination of all cattle with additional vaccination of sheep

When in the populations no sheep, but only all cattle (thus 100% of the cattle) are vaccinated, R was 1·1, 0·90, 0·52, 0·35 and 0·13 for populations with 0%, 24%, 61%, 78% and 100% cattle, respectively (see Fig. 1*b*). The percentage of cattle in the population that has to be present to reach $R = 1$ (when all cattle are vaccinated) was 14%.

Strategy 3: vaccination of all sheep with additional vaccination of cattle

When in the populations no cattle, but only all sheep (thus 100% of the sheep) are vaccinated, R was 0·1, 1·4, 3·3, 4·1 and 5·3 for populations with 0%, 24%, 61%, 78% and 100% cattle, respectively (see Fig. 1*c*).

The additional percentage of the cattle population that has to be vaccinated to reach $R = 1$ was 0%, 29%, 72% and 78% and 83%, respectively, for populations with 0%, 24%, 61%, 78%, and 100% cattle, respectively.

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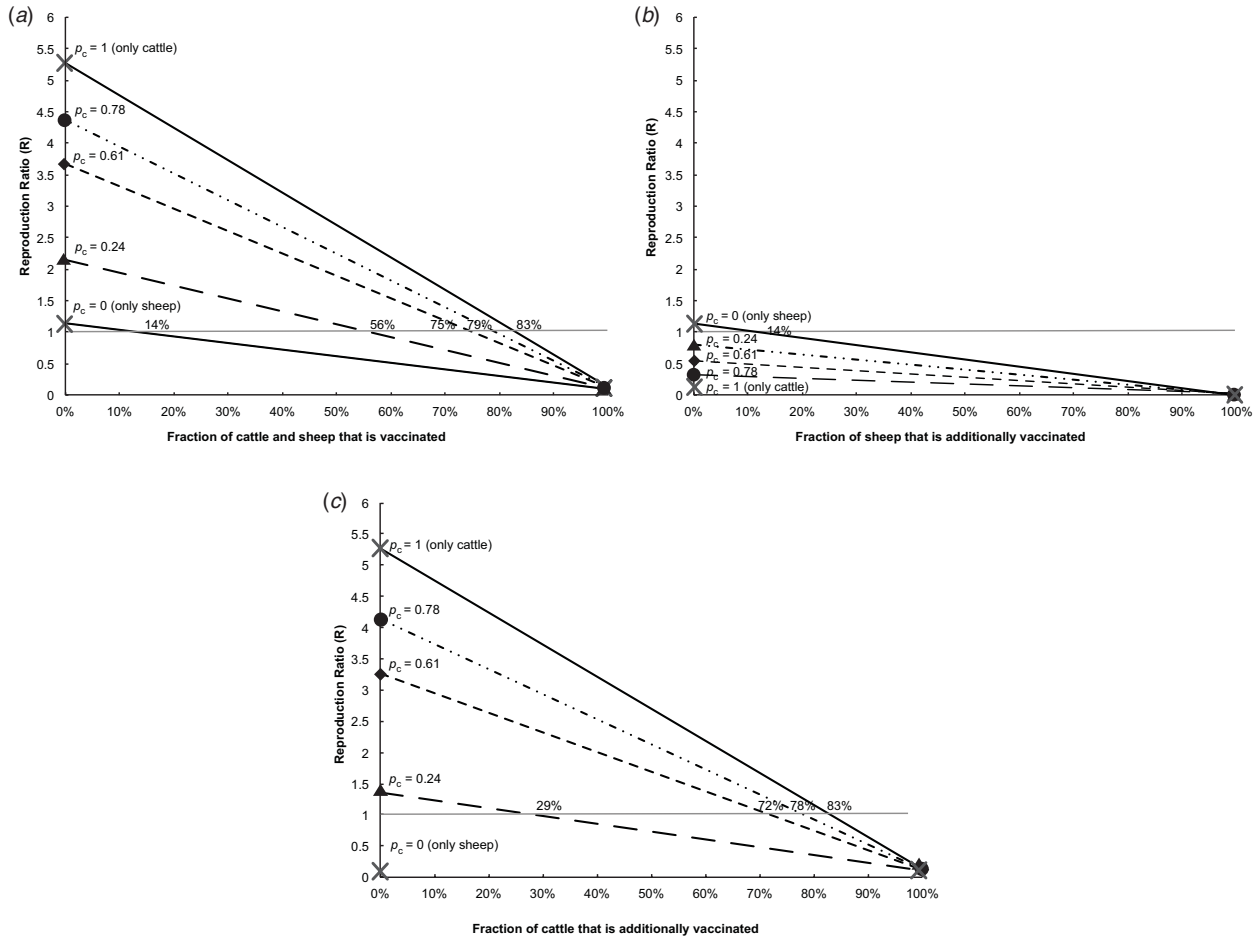

Fig. 1. The effect of different vaccination strategies on the reduction of R in mixed populations. (*a*) The effect of vaccination of both cattle and sheep (in equal proportions) on the reduction of R in different mixed populations with cattle and sheep. (*b*) The effect of vaccination of all cattle and additional vaccination of sheep on the reduction of R in different mixed populations with cattle and sheep. (*c*) The effect of vaccination of all sheep and additional vaccination of cattle on the reduction of R in different mixed populations with cattle and sheep. p_c represents the proportion of cattle of the mixed population. The threshold value of $R = 1$ is indicated by a grey line. The percentage of the population of (*a*) cattle and sheep, (*b*) sheep, or (*c*) cattle that needs to be (additionally) vaccinated to reach the threshold value of 1 is indicated.

DISCUSSION

In the current study we quantified the transmission of FMDV in mixed cattle-sheep populations and evaluated the effect of different vaccination strategies. The evaluation of different vaccination strategies was based on the transmission estimates from experimental transmission studies. The higher the proportion of cattle in a mixed cattle-sheep population, the higher the R for the mixed population is. Thus, the impact of vaccination of the cattle is higher. When the whole population is vaccinated, $R < 1$ regardless of the population composition. In mixed cattle-sheep populations with at least 14% of cattle, vaccination of cattle only is sufficient to reduce R to <1. The strategy of vaccinating cattle only for eradication purposes has been used in the past in continental Europe [15] and South America [16, 19] with success. Previous studies using mathematical modelling also predicted that for emergency vaccination, targeting cattle only is much more efficient than using other vaccination strategies [29]. Therefore, this strategy will be more cost-effective in countries with mixed populations of cattle and sheep where prophylactic vaccination is applied [30], as it would mean a reduction in the number of vaccine doses needed and in required manpower. Moreover, when using it as an emergency vaccination strategy, it would also mean a reduction in the time needed to immunize all the animals.

While our conclusions are valid for mixed cattle-sheep populations, different results might be expected for mixed populations where other FMDV-susceptible

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species are present. For instance, in The Netherlands, where routine annual vaccination of cattle only was used from 1953 to 1991, FMD outbreaks occurred between 1961 and 1967 in mixed cattle and pig farms. At that time, additional vaccination of pig herds was used effectively to control the outbreaks [31]. Additionally, in Asian countries, where the Asian buffalo (*Bubalus bubalis*) is a host of epidemiological importance [32], a vaccination strategy that includes (additional) vaccination of the Asian buffalo is probably advisable. Thus depending on the different species and percentages of these species in a population, different vaccination strategies might be needed. When quantitative data of transmission of FMDV for other animal species are known, this could be included in the NGM and then similar analyses can be performed for other heterogeneous populations.

In our analysis, we used data from transmission studies in which good quality vaccines, containing >6 PD_{50} per dose, were used. Experience in South America [33] shows that the strategy of vaccinating cattle only is only effective when good quality vaccines are used. The use of good quality vaccines is of course a prerequisite when using vaccination to control a disease. We used data from within-pen transmission studies in which cattle and/or sheep were mingling in one animal room, thus within-pen transmission occurred. However, in many situations, cattle and sheep within a population will have less intensive contact. Other studies show that transmission between pens is in general lower than within a pen [12, 34] and that between-herd transmission will be even lower [35]. Thus, the effect of targeting vaccination towards cattle will probably be even better under these circumstances than predicted in the current study. In the current study, we used a mathematical approach to calculate which vaccination strategies would be effective. In field situations, other aspects, e.g. vaccine quality, might influence the results. However, even if the quality of the vaccine batch is low, it is probably better to use it in cattle only than spread the available capacity over both species. Although we did use different serotypes in the current study, which produced similar results, there might be a different outcome for other virus strains. Moreover, our approach looks only at the scenario where eradication of FMDV is the goal, there may be an interest to consider scenarios where intermediate situations (FMDV still endemic) have also to be considered, but this has not been studied here.

We developed an NGM that can be used to evaluate the transmission of FMDV for mixed populations of cattle and sheep and we analysed the effect of a targeted vaccination strategy. We conclude that vaccination of cattle only in mixed populations consisting of sheep and cattle will in most cases be sufficient for controlling FMDV epidemics.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Anderson RM, May RM.** The invasion, persistence and spread of infectious diseases within animal and plant communities. *Philosophical Transactions of the Royal Society of London* 1986; **314**: 533–570.
2. **Heffernan JM, Smith RJ, Wahl LM.** Perspectives on the basic reproductive ratio. *Journal of the Royal Society of London: Interface* 2005; **2**: 281–293.
3. **Kermack WO, McKendrick AG.** A Contribution to the Mathematical Theory of Epidemics. *Proceedings of the Royal Society of London, Series A: Mathematical, Physical and Engineering Sciences* 1927; **115**: 700–721.
4. **Hagenaars TJ, *et al.*** Estimation of foot and mouth disease transmission parameters, using outbreak data and transmission experiments. *Revue Scientifique et Technique (International Office of Epizootics)* 2011; **30**: 467–77.
5. **Cox SJ, *et al.*** Emergency vaccination of sheep against foot-and-mouth disease: protection against disease and reduction in contact transmission. *Vaccine* 1999; **17**: 1858–1868.
6. **Eblé PL, *et al.*** Vaccination of pigs two weeks before infection significantly reduces transmission of foot-and-mouth disease virus. *Vaccine* 2004; **22**: 1372–1378.
7. **Eblé PL, Orsel K, Dekker A.** FMDV infection in vaccinated and non-vaccinated sheep: transmission to contact animals and diagnostic aspects. In: *Session of the Research Group of the Standing Technical Committee of EuFMD*. Jerez de la Frontera, Spain, 29–31 October 2012.
8. **Goris NE, *et al.*** Quantification of foot-and-mouth disease virus transmission rates using published data. *ALTEX* 2009; **26**: 52–54.
9. **Orsel K, *et al.*** The effect of vaccination on foot and mouth disease virus transmission among dairy cows. *Vaccine* 2007; **25**: 327–335.

10. **Orsel K, *et al.*** Vaccination against foot and mouth disease reduces virus transmission in groups of calves. *Vaccine* 2005; **23**: 4887–4894.
11. **Orsel K, *et al.*** Quantification of foot and mouth disease virus excretion and transmission within groups of lambs with and without vaccination. *Vaccine* 2007; **25**: 2673–2679.
12. **Van Roermund HJ, *et al.*** No between-pen transmission of foot-and-mouth disease virus in vaccinated pigs. *Vaccine* 2010; **28**: 4452–4461.
13. **Bravo de Rueda C, *et al.*** Estimation of the transmission of foot-and-mouth disease virus from infected sheep to cattle. *Veterinary Research* 2014; **45**: 58.
14. **Leforban Y.** How predictable were the outbreaks of foot and mouth disease in Europe in 2001 and is vaccination the answer? *Revue Scientifique et Technique* (*International Office of Epizootics*) 2002; **21**: 549–556, 539–547.
15. **Leforban Y.** Review of the status of foot and mouth disease and approach to control/eradication in Europe and Central Asia. *Revue Scientifique et Technique* (*International Office of Epizootics*) 2002; **21**: 477–492.
16. **Sutmoller P, *et al.*** Control and eradication of foot-and-mouth disease. *Virus Research* 2003; **91**: 101–144.
17. **Gibson CF, Donaldson AI.** Exposure of sheep to natural aerosols of foot-and-mouth disease virus. *Research in Veterinary Science* 1986; **41**: 45–49.
18. **Parida S, *et al.*** Emergency vaccination of sheep against foot-and-mouth disease: significance and detection of subsequent sub-clinical infection. *Vaccine* 2008; **26**: 3469–3479.
19. **Donaldson A.** The role of sheep in the epidemiology of foot-and-mouth disease and proposasls for control and eradication in animal populations with a high density of sheep. In: *Session of the Research Group of the Standing Technical Committee of EuFMD*. Borovets, Bulgaria, 5–8 September 2000.
20. **Diekmann O, Heesterbeek JA, Metz JA.** On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* 1990; **28**: 365–382.
21. **Becker NG.** *Analysis of Infectious Disease Data*. London: Chapman and Hall Ltd, 1989.
22. **Anderson RM, May RM.** *Infectious Diseases of Humans: Dynamics and Control*. Oxford: Oxford University Press, 1991.
23. **Velthuis AG, *et al.*** Design and analysis of small-scale transmission experiments with animals. *Epidemiology and Infection* 2007; **135**: 202–217.
24. **De Jong MCM, Kimman TG.** Experimental quantification of vaccine-induced reduction in virus transmission. *Vaccine* 1994; **8**: 761–766.
25. **Kroese AH, De Jong MC.** Design and analysis of transmission experiments. In: *Proceedings of the Annual Meeting of the Society for Veterinary Epidemiology and Preventive Medicine*. Noordwijkerhout, 2001, pp. 21–36.
26. **Cox SJ, *et al.*** Further evaluation of higher potency vaccines for early protection of cattle against FMDV direct contact challenge. *Vaccine* 2007; **25**: 7687–7695.
27. **Diekmann O, Heesterbeek JA, Roberts MG.** The construction of next-generation matrices for compartmental epidemic models. *Journal of the Royal Society of London: Interface* 2010; **7**: 873–885.
28. **Food and Agriculture Organization of the United Nations (FAO) database.** FAOSTAT (http://faostat.fao.org/site/569/default.aspx#ancor). Accessed 9 October 2013.
29. **Keeling MJ, *et al.*** Modelling vaccination strategies against foot-and-mouth disease. *Nature* 2003; **421**: 136–142.
30. **Yadin H, *et al.*** The NSP immune response of vaccinated animals after in-field exposure to FMDV. *Vaccine* 2007; **25**: 8298–8305.
31. **Van Bekkum J, Bool PH, Vermeulen CJ.** Experience with the vaccination of pigs for the control of foot-and-mouth disease in the Netherlands. *Tijdschrift voor Diergeneeskunde* 1967; **92**: 87–97.
32. **Maroudam V, *et al.*** Experimental transmission of foot-and-mouth disease among Indian buffalo (*Bubalus bubalis*) and from buffalo to cattle. *Journal of Comparative Pathology* 2008; **139**: 81–85.
33. **La Torre J.** Integrated procedures to assess FMD vaccine quality and herd immunity in Argentina. In: *Session of the Research Group of the Standing Technical Committee of EuFMD*. Vienna, Austria, 27 September–1 October 2010.
34. **Klinkenberg D, *et al.*** Within- and between-pen transmission of classical swine fever virus: a new method to estimate the basic reproduction ratio from transmission experiments. *Epidemiology and Infection* 2002; **128**: 293–299.
35. **Van Nes A, *et al.*** Implications derived from a mathematical model for eradication of pseudorabies virus. *Preventive Veterinary Medicine* 1998; **33**: 39–58.