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Failure of vaccination to prevent outbreaks of foot-and-mouth disease

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SUMMARY

Outbreaks of foot-and-mouth disease persist in dairy cattle herds in Saudi Arabia despite revaccination at intervals of 4–6 months. Vaccine trials provide data on antibody responses following vaccination. Using this information we developed a mathematical model of the decay of protective antibodies with which we estimated the fraction of susceptible animals at a given time after vaccination. The model describes the data well, suggesting over 95% take with an antibody half-life of 43 days. Farm records provided data on the time course of five outbreaks. We applied a 'SLIR' epidemiological model to these data, fitting a single parameter representing disease transmission rate. The analysis provides estimates of the basic reproduction number, R_0, which may exceed 70 in some cases. We conclude that the critical intervaccination interval which would provide herd immunity against FMDV is unrealistically short, especially for heterologous challenge. We suggest that it may not be possible to prevent foot-and-mouth disease outbreaks on these farms using currently available vaccines.

INTRODUCTION

Successful vaccination programmes prevent major epidemics of an infectious disease by generating 'herd immunity', which results when too few susceptibles remain in the population to sustain disease transmission [1, 2]. The establishment of herd immunity is made more difficult by strain variation in the infectious agent, varied host response to vaccination, and vaccines which provide only partial protection for a limited period of time [1, 3, 4]. These circumstances apply to a number of diseases of domestic animals, including foot-and-mouth disease.

Foot-and-mouth disease virus (FMDV) is an important and widespread pathogen of domestic livestock, responsible for lost productivity and restrictions on exports costing an estimated US$50 billion annually worldwide [5]. There is considerable debate regarding the optimal means of prevention and control, particularly in Europe where the EU has recently introduced a non-vaccination policy, preferring to rely on import controls and quarantine to prevent the introduction of the virus. Countries wishing to make animal exports to Europe are therefore under considerable pressure to maintain national herds free from FMDV. This has, however, often proved extremely difficult, as illustrated by recent epidemics in Zimbabwe and elsewhere [6].

In this paper we analyse data on vaccine trials and on FMDV outbreaks on dairy cattle farms in Saudi Arabia. The data are used to provide parameter estimates for a mathematical model of the impact of vaccination programmes at the population level [7, 8]. The model is based on standard epidemiological theory [1] but includes a more detailed representation of antibody responses to vaccination and the decay of these responses through time. The model is used to show why intensive vaccination programmes have

failed to prevent outbreaks of FMDV on these Saudia Arabian farms. The model suggests a general result that vaccines giving short-lived protection are unable to prevent epidemics of highly transmissible pathogens.

METHODS

Vaccination trial data

Data were available from two trials of commercial vaccines in Saudia Arabian cattle using standard methodologies [9, 10]. The trials involved 30 and 18 cattle over 6 months old and with a prior history of vaccination. In both trials all cattle were simultaneously vaccinated. For the first trial FMDV-specific total serum antibody titres were measured at 20, 50, 80 and 110 days post-vaccination. For the second trial antibody titres were measured at 22 days only. Maximum antibody titres are typically reached 7–10 days post-vaccination, although protective titres may be reached after only 2–3 days post-vaccination. Cattle are considered protected from foot-and-mouth disease when antibody titres exceed 100 (as measured by Liquid Phase Blocking ELISA), although this may vary with the severity of challenge [11, 12].

Outbreak data

Records were available for 18 FMDV outbreaks occurring on 12 dairy cattle farms in Saudi Arabia between 1988 and 1993. The farms typically contained 1500–4000 cattle, although calf rearing stations may be substantially larger. FMDV outbreaks affected between 2% and 53% of cattle on the farms despite vaccination of every animal with commercial vaccines at intervals of 4–6 months since 1986. The vaccines contain both FMDV serotypes circulating in Saudi Arabia. This regular vaccination of all cattle on the farm is an example of a 'pulse' vaccination programme [8]. Outbreaks have been reported as little as 18 days after vaccination. All cattle are revaccinated within a few days of the first reported case in an attempt to halt or slow the spread of infection. Animals are quarantined as soon as clinical signs are detected.

For five outbreaks on four farms data were available on the time course of the outbreak, the characteristics of the virus strain involved, and the control measures adopted (Table 1); this information allows a detailed analysis of these outbreaks. Three of

Table 1. *Characteristics of FMDV outbreaks on cattle farms in Saudi Arabia*

Farm	Date of outbreak	Number of cattle	Days since vaccination	Virus serotype	Virus homology	Days to revaccination	Number susceptible	Number affected	$\beta \times 1000$ (±S.E.)	R_0
Todhia	25.08.89	2804	71	O	1·0	0	606	431	3·01 (±0·030)	21·1
Todhia	07.03.94	2443	114	O	1·0	0	1340	749	2·15 (±0·007)	13·1
Medyan	19.02.91	1750	65	O	1·0	0–1	395	232	16·6 (±0·35)	72·8
Al-Kharj	26.09.92	1732	107	A	0·4	5	1554	663	2·57 (±0·017)	11·1
Bandria	27.10.93	2834	75	A	< 0·1	5	2834	140	0·30 (±0·002)	2·1

Number of cattle includes animals > 6 months old only and corresponds to H in Equations (2*a*) and (3). Virus homology corresponds to r in Equation (1). Number susceptible corresponds to $S(0)$ and is estimated using Equation (1) with the parameter values given in the legend to Figure 2. β represents the transmission rate and is estimated by fitting Equations (2*a*)–(2*d*) to the outbreak data shown in Figures 4 and 5. Standard errors (S.E.) of β do not allow for errors in the estimation of $S(0)$, expected to be up to +100% to −50%. R_0, the basic reproduction number, is calculated using Equation (3).

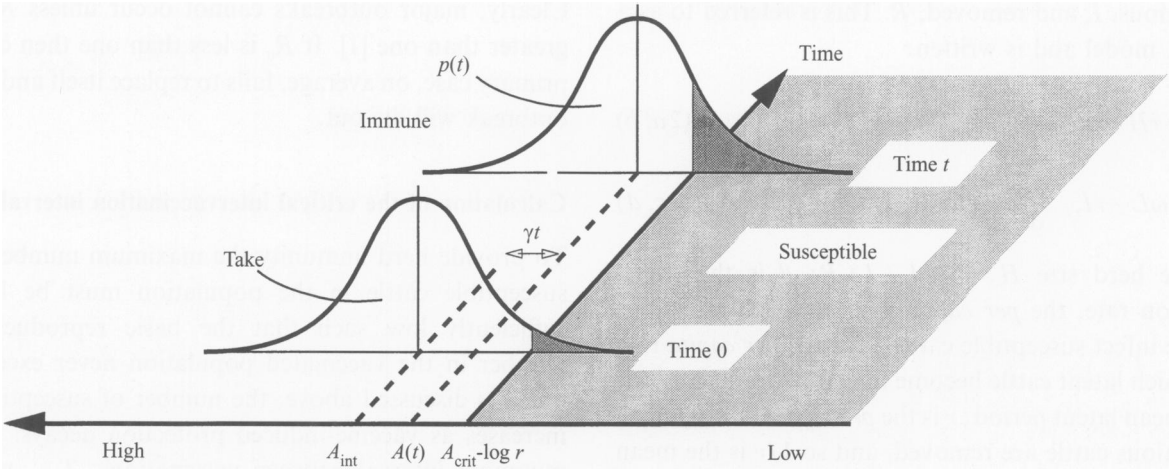

Fig. 1. A schematic overview of the model of antibody decay. Log antibody titres immediately after vaccination (time 0) are normally distributed around the mean A_{int} with variance σ^2. Those cattle with log antibody titres above the threshold $A_{crit} - \log r$ (where r is degree of homology) are protected (immune) and those with log antibody titres below the threshold are susceptible. Log antibody titre decays linearly through time at the rate γ so mean log antibody titre at time t is given by $A(t) = A_{int} - \gamma t$.

these outbreaks were type O virus (which were antigenically similar to the vaccine strains) and two were type A virus (and were also antigenically different from the vaccine strain). We confined attention to cattle over 6 months old, which had already received at least a primary and booster vaccination. This is because calves are normally kept apart from the main herd and are maternally protected (the mothers having been vaccinated) for 2–4 months. As a result, outbreaks among calves are delayed, typically by 20–25 days, and affect relatively few animals, typically 2–3%, and so have little or no impact on the initial course of an outbreak. We also tested for age-related patterns in the course of the outbreak among cattle over 6 months old using analysis of variance with cattle divided into five age classes, based on the number of lactations.

Model of decay of antibody titre

We describe the distribution of log (base 10) antibody titres by a normal probability density function, $N(A(t), \sigma^2)$, where $A(t)$ is the mean log antibody titre at time t after vaccination and the variance σ^2 is independent of A and t. We assume an exponential decay in antibody titre, and therefore, we can express the mean log antibody titre at time t as $A(t) = A_{int} - \gamma t$ where γ is a measure of the rate of decay of antibody titre and A_{int} is a measure of vaccine potency. We define a threshold log antibody titre, A_{crit}, below which cattle are susceptible to challenge with a homologous virus. It is possible that this threshold is itself variable [13] (for example, due to variation in challenge dose experienced by individual cattle) – if so, the variance in A_{crit}, may be treated as additive to σ^2 – but this is ignored here. For challenge with a heterologous virus the effective threshold becomes $A_{crit} - \log r$ where r is the ratio of serum antibody titre against heterologous virus to the titre against homologous virus, referred to as the relative homology.

From these arguments we suggest an expression for the proportion of cattle that have antibody titres above the threshold at time t after vaccination. We refer to this proportion as $p(t)$ which is given by:

$$p(t) = \tfrac{1}{2}\mathrm{erfc}\left(\frac{\gamma t - A_{int} + A_{crit} - \log r}{\sigma\sqrt{2}}\right), \quad (1)$$

where the term erfc refers to the complement of the error function [14]. A schematic representation of the model is shown in Figure 1.

Note that, while A_{int} represents the nominal log antibody titre at $t = 0$, in practice maximum antibodies are not obtained until $t = 10$ days, and the proportion initially protected by vaccination, referred to as vaccine take, is therefore given by $p(10)$.

Model of FMDV outbreaks

The dynamics of the early stages of outbreaks are described by the standard model for rates of change in the numbers of cattle which are susceptible to infection, S, latent (infected but not yet infectious), L,

infectious, I, and removed, R. This is referred to as a SLIR model and is written:

$$\frac{dS}{dt} = \tau H - \beta SI, \quad \frac{dL}{dt} = \beta SI - \omega L, \tag{2a, b}$$

$$\frac{dI}{dt} = \omega L - \nu I, \quad \frac{dR}{dt} = \nu I, \tag{2c, d}$$

where herd size $H = S+L+I+R$; β is the transmission rate, the *per capita* rate at which infectious cattle infect susceptible cattle; ω is the *per capita* rate at which latent cattle become infectious, and so $1/\omega$ is the mean latent period; ν is the *per capita* rate at which infectious cattle are removed, and so $1/\nu$ is the mean infectious period before cattle show clinical signs and are removed from the population. The model assumes that net transmission rates increase with herd size, giving the term βSI.

The parameter $\tau = -dp/dt$ describes the rate of recruitment of susceptibles at time t (appropriately scaled) due to the loss of vaccine-induced protection and is obtained from Equation (1), recalling that p is the proportion of cattle protected by vaccination and therefore declines through time. Another source of new susceptible cattle is the recruitment of young animals into the herd. For current purposes we assumed that recruitment balances losses due to mortality and that recruited animals have already been subject to a similar vaccination schedule. In these circumstances, recruitment will not change the distribution of antibody titres in the population and so does not affect the dynamics of the susceptible class. Another factor which may affect the number of susceptibles at the start of an outbreak is the prior history of FMDV infection, previously exposed cattle may retain some immunity to subsequent infection. In practice none of the five outbreaks occurred less than 4 years after a previous outbreak of the same virus serotype in the same herd. Because this interval is close to typical life-expectancy of cattle on these farms (approximately 5 years) we assumed no previous exposure to infection.

This model can be used to generate an estimate of the basic reproduction number, R_0, for foot-and-mouth disease in each of the farms at the time of each outbreak. R_0 is defined as the number of secondary cases which would be obtained directly from a single primary case in a fully susceptible population and is given here by the expression:

$$R_0 = \frac{\beta H}{\nu}. \tag{3}$$

Clearly, major outbreaks cannot occur unless R_0 is greater than one [1]. If R_0 is less than one then each primary case, on average, fails to replace itself and the outbreak will die out.

Calculation of the critical intervaccination interval

To provide herd immunity the maximum number of susceptible cattle in the population must be kept sufficiently low such that the basic reproduction number in the vaccinated population never exceeds one. As discussed above, the number of susceptibles increases as vaccine-induced protection decays. The minimum interval between vaccinations, T_{crit}, must satisfy the condition:

$$p(T_{crit}) \geqslant 1 - \frac{1}{R_0}, \tag{4}$$

where $p(t)$ is given by Equation (1) and R_0 is given by Equation (3).

Equation (4) assumes that antibody titres immediately after vaccination are independent of both the number of previous vaccinations and the time interval since the previous vaccination, as is consistent with available information [9] (recalling that all cattle have had at least a primary and a booster vaccination before entering the main herd).

Parameter estimation and model fitting

We estimated the rate decay of antibody titre, the parameter γ, as the slope of a least squares linear regression of log antibody titre, $A(t)$ against time, t. We used analysis of covariance to test for different slopes for individual cattle. The intercept of the regression provides an estimate of A_{int}; this estimate was scaled as an average including the results from the second vaccine trial, which did not provide an independent estimate of γ. We estimated the variance in log antibody titres, σ^2, directly from data taken at various times t from three different trials. Homogeneity of variances was tested using Bartlett's test and the goodness of fit of the normal distribution to the data was confirmed using the Kolgomorov–Smirnov test [15].

Other parameter estimates were taken from existing literature [16]. The latent period may vary from 2–14 days in individual cattle, but with a mean of 5 days, giving $\omega = 0{\cdot}2$ per day. The duration of infectiousness combines the period where cattle are infectious but show no clinical signs (1–2 days) and any delay before

cattle showing clinical signs are removed (0–1 days), with a mean approximately 2·5 days, giving $\nu = 0{\cdot}4$ per day.

We obtained estimates of the transmission rate, β for each outbreak by fitting the SLIR model to observed values of the number of cattle removed, R, through time. We fitted the model with a derivative-free nonlinear regression package, the BMDP AR routine, which uses a 5th order Runge–Kutta approximation to provide a numerical solution to the differential equations (2*a*)–(2*d*). We defined initial conditions (corresponding to time $t = 0$, the time of the first reported case) as follows: $S(0)$ was obtained from Equation (1) given the known time interval since vaccination (Table 1); $I(0)$ and $L(0)$ were calculated numerically, given the observed initial values of R. For each outbreak we fitted the model for the period up to 7 days after the herd was revaccinated to control the outbreak (Table 1); any impact of revaccination on transmission is expected to become apparent after 7–10 days.

From each outbreak we then calculated an estimate of the basic reproduction number, R_0, using Equation (3). Note that the only parameters considered to differ between outbreaks are the initial number of susceptibles, $S(0)$, (related to herd size and the interval since vaccination) and the transmission rate, β.

Using Equation (4) we explored the relationship between the critical intervaccination interval, T_{crit}, and R_0 for different virus relative homology, r. We also explored the relationship between T_{crit} and the half-life of vaccine-induced protection (which corresponds to the time t where $p(t) = 0{\cdot}5$ and is obtained by taking different values for the rate of decay of antibody titre, γ) for different values of A_{int}, which represent vaccines giving different initial levels of protection.

RESULTS

Decay of antibody titre

The log antibody titres, $A(t)$, obtained from 30 cattle at four different times after vaccination are shown in Figure 2. Analysis of covariance showed no significant difference in slopes for individual cattle ($F = 1{\cdot}7$; D.F. = 29, 60; $P > 0{\cdot}05$). The best fit regression line through the means has negative slope $\gamma = 0{\cdot}00743$ ($\pm 0{\cdot}000\,77$) with a coefficient of determination of 0·98 ($P < 0{\cdot}02$). This value of γ corresponds to antibody half-life of 43 days. The average estimate of A_{int} from

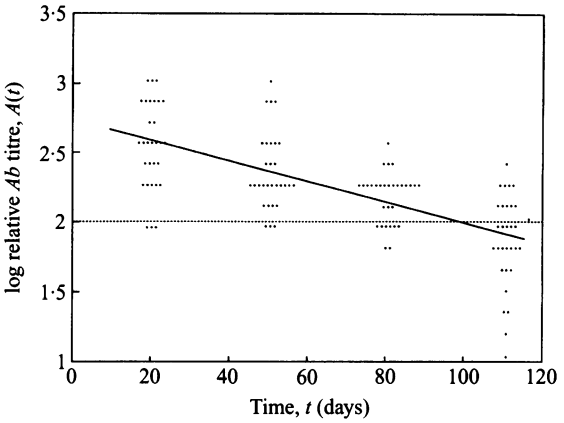

Fig. 2. The decay of antibody titre. Data from a trial of commercial FMDV vaccine in 30 cattle in Saudi Arabia. Individual log antibody titres were measured at 20, 50, 80 and 110 days (symbols). The best fit linear regression for the mean log antibody titre, $A(t)$ against time t is shown (solid line). This has the form $A(t) = 2{\cdot}73 - 0{\cdot}00743t$. The threshold log antibody titre giving protection against homologous virus, A_{crit}, is compared (horizontal line). Cattle with log antibody titres above this threshold are protected and those below this threshold are susceptible.

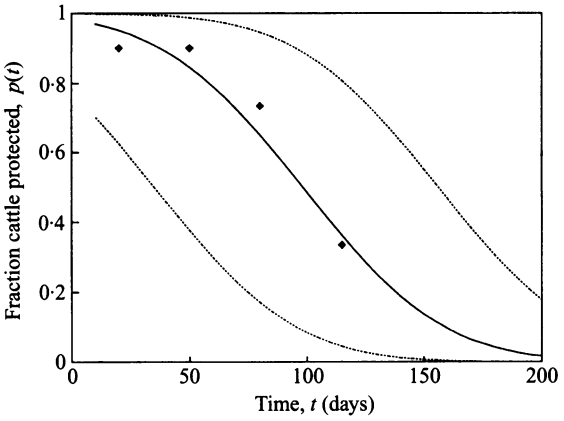

Fig. 3. The loss of vaccine-induced protection. Data as for Figure 2. The fraction of animals with log antibody titres above the protective threshold is shown at times 20, 50, 80 and 110 days. The expected fraction from Equation (1) with parameter values $A_{int} = 2{\cdot}73$, $\gamma = 0{\cdot}00743$, $\sigma = 0{\cdot}352$, $A_{crit} = 2{\cdot}0$ and $r = 1{\cdot}0$ are shown (solid line). The expected fractions for A_{int} corresponding to 70% and 99·9% take (fraction protected at 10 days) with other parameters identical are compared (broken lines).

the two trials is 2·73. The estimates of the variance of log antibody titres, σ^2, from 11 different times during three different trials were not significantly different ($\chi^2 = 15{\cdot}23$; D.F. = 10; $P > 0{\cdot}10$) and the weighted mean variance gave common $\sigma = 0{\cdot}352$. The distributions of $A(t)$ values shown in Figure 2 are well

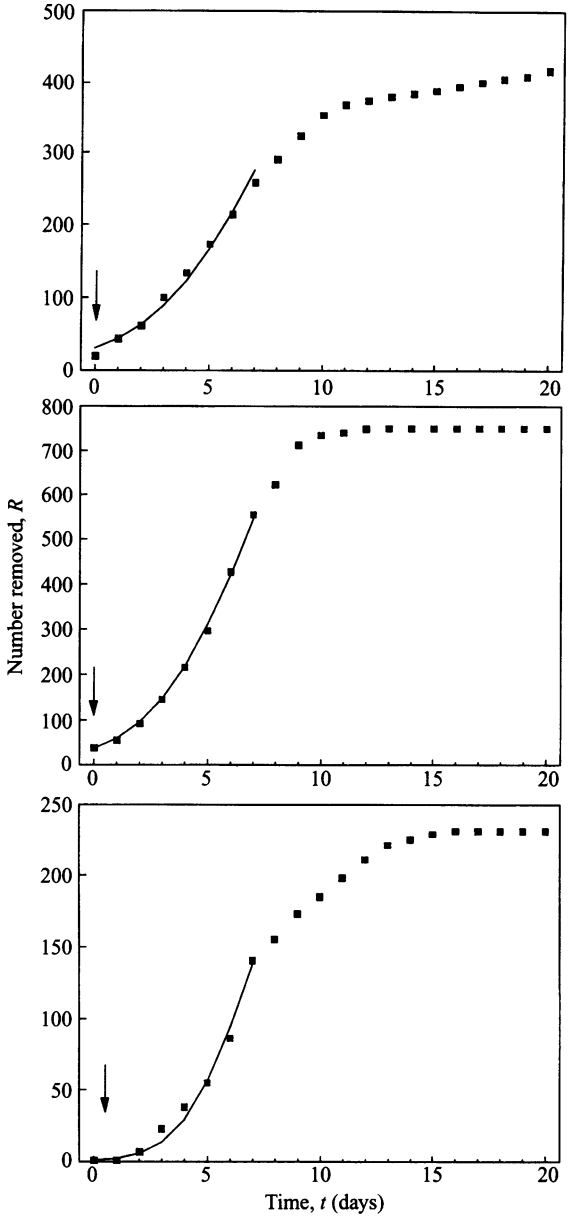

Fig. 4. FMDV outbreaks on cattle farms in Saudi Arabia: type O virus. Data are from three outbreaks on two different farms (see Table 1). Numbers of infected animals removed, R, are shown (symbols). The expected values from Equations (2a–d) with parameter values $\omega = 0{\cdot}2$ and $\nu = 0{\cdot}4$ and with β fitted are compared (solid line). The initial number of susceptibles, $S(0)$, is estimated using Equation (1) (see Table 1). The model is fitted up for up to 7 days following revaccination (indicated by arrows).

described by a normal distribution with mean $A(t)$ and variance σ^2, except for a slight discrepancy at $t = 110$ (Kolgomorov–Smirnov $D_{max} = 0{\cdot}164$; $n = 30$; $P = 0{\cdot}045$). These parameter values correspond to vaccine take, the fraction protected at $t = 10$ days, of 96·9%.

Using the same data as shown in Figure 2 the fraction of cattle with antibody titres above the protective threshold against time are shown in Figure 3. The expected fraction protected obtained from Equation (1) with the values of A_{int}, σ and γ given above are compared. Chi-squared tests show that the expected and observed values are not significantly different for any value of t ($\chi^2 \leqslant 1$, D.F. = 1, $P > 0{\cdot}10$). The half-life of vaccine-induced protection (corresponding to t when $p(t) = 0{\cdot}5$) is 98 days. Also illustrated in Figure 3 are the expected fractions protected against time for vaccines with take 70% and 99·9%, calculated using the appropriate values of A_{int} but assuming the same value of γ. This represents the full range of observed vaccine takes normally encountered [10].

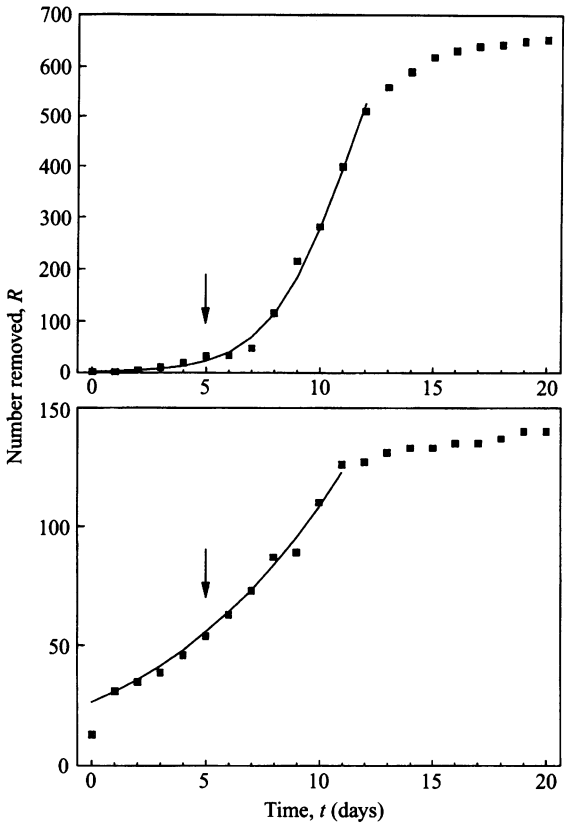

Fig. 5. FMDV outbreaks on cattle farms in Saudi Arabia: type A virus. Data are from two outbreaks on different farms (see Table 1). Other details are as for Figure 4 except that $S(0)$ is now estimated taking into account low virus homology.

FMDV outbreaks

The cumulative numbers of cattle infected and removed, R, over the first 20 days of three outbreaks of Type O FMDV and of two outbreaks of Type A

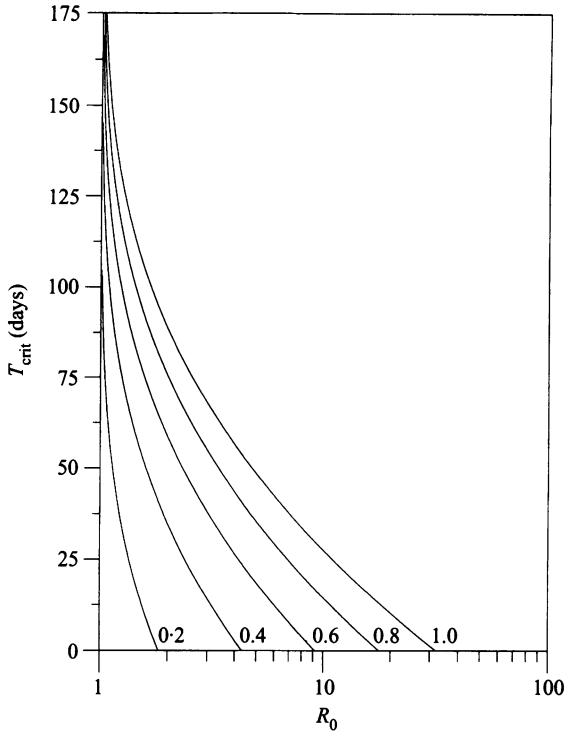

Fig. 6. The relationship between critical intervaccination interval, T_{crit}, and the basic reproduction number R_0 (log scale). Graph is plotted using Equation (4) with parameter values as for Figure 3. Different degrees of virus homology, r, are compared (values shown).

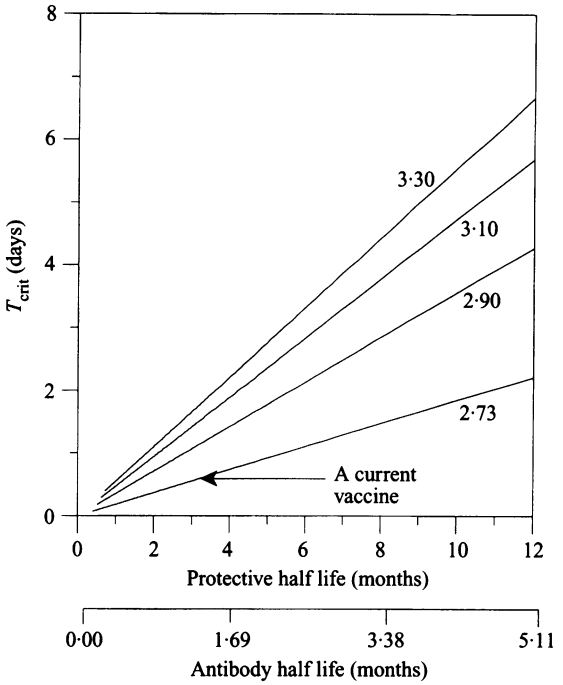

Fig. 7. The relationship between critical intervaccination interval, T_{crit}, and the duration of protection. Graph is plotted using Equation (4) with duration of protection expressed as the half-life (corresponding to 50% animals still protected) or, alternatively, the half-life of protective antibodies. Different initial antibody titres, A_{int} (corresponding to different vaccine take) are compared (values shown).

FMDV are shown in Figures 4 and 5 respectively. The times of revaccination are also indicated.

Analysis of variance showed no significant effects of age on the day of the outbreak (normalized by square-root transformation) of the first reported case in the age class ($F = 1{\cdot}97$; D.F. $= 4, 16$; $P > 0{\cdot}10$) or the (arcsine square-root transformed) fraction of cattle affected in the age class ($F = 1{\cdot}47$; D.F. $= 4, 12$; $P > 0{\cdot}20$) for the five outbreaks of interest. This implies that cattle over 6 months old can be considered as a single population in each case.

The estimated initial number of susceptibles, $S(0)$, for each outbreak, obtained using Equation (1) are given in Table 1. Fitting the model represented by Equations (2a)–(2d) provides estimates of β for each outbreak. With this one fitted parameter the model describes the data well (Figs 4 and 5) and, in most cases, also provides an indication of the impact of revaccination as an obvious change in trajectory 7–10 days later. The estimates of β vary considerably between outbreaks, by a factor of 50 or more (Table 1). This variability translates into high variability in the estimates of the basic reproduction number, R_0, with values ranging from 2 to more than 70 (Table 1).

Critical intervaccination interval

The relationship between the critical intervaccination interval, T_{crit}, and R_0 is shown in Figure 6. Using a vaccine with the characteristics described above, for homologous challenge ($r = 1{\cdot}0$) T_{crit} decreases rapidly as R_0 increases. T_{crit} is substantially lower for heterologous challenge ($r < 1{\cdot}0$).

The relationship between T_{crit} and the half-life of vaccine-induced protection is shown in Figure 7. From a given vaccine take (represented by A_{int}) T_{crit} increases almost linearly with half-life. T_{crit} is lower for vaccines with lower take (lower A_{int}).

DISCUSSION

The model represented by Equation (1) appears to be a good description of the decay of antibody titres (Fig. 2) and of the decay in the fraction of cattle protected following vaccination (Fig. 3). This description is based on three well defined and measurable quantities: the rate of decay of antibody; the shape of the population distribution of antibody titres; and the peak vaccine-induced antibody levels. In this study

the antibody decay function was consistent with an exponential form and the antibody titre distribution with a log-normal form. For a vaccine with 96·9% take (fraction of cattle protected 10 days after vaccination) 50% cattle are expected to be still protected 98 days after vaccination, a measure of the half-life of vaccine-induced protection. This half-life may be higher (or lower) for vaccines giving higher (or lower) take (Fig. 3). It is not known whether different vaccine batches produce different rates of decay of antibody titre, which would further affect the half-life of vaccine-induced protection.

The fraction of susceptibles in a herd at any time after vaccination represents those individuals where the vaccine failed to take, those individuals where vaccine-induced protection has been lost, and any susceptibles newly recruited into the herd. Susceptibility also reflects the homology of the challenge virus. For the outbreaks analysed here (Table 1) the susceptible fraction was estimated to range from 23% (challenge by antigenically similar virus 65 days after vaccination) to close to 100% (challenge with a virus antigenically very different from the vaccine strain 75 days after vaccination). For all five outbreaks the estimated number of susceptibles was, as required, greater than the lower limit represented by the number of animals actually infected during the outbreak (Table 1). The uncertainty associated with the estimate of the susceptible fraction is difficult to determine directly but is of the order of a factor 2 (see Fig. 3 and Table 1).

In contrast, the estimates of the disease transmission rate obtained from fitting Equations (2*a*)–(2*d*) to the outbreak data vary by a factor of 50 or more (Table 1). This is much greater than might be explained by errors in the estimation of the number of susceptibles. Other possible explanations include differences between virus serotypes (the lowest value is associated with Type A, the highest with Type O), or differences in environmental conditions and husbandry practices between farms which result in more or less favourable conditions for virus transmission (the two Type O outbreaks at the same farm give similar transmission rates). The variability in transmission rates translates into variability in the estimate of the basic reproduction number, R_0, (Table 1) which is additionally influenced by variability in herd size (see Equation 3). The basic reproduction number may exceed 70, which indicates very high virus transmissibility.

The SLIR model represented by Equations (2*a*)–(2*d*) provides a good description of the early stages of the five outbreaks (Figs. 4 and 5). The impact of revaccination can be seen by obvious changes in the trajectory of the outbreak 7–10 days later although transmission did not completely cease at this time. In the absence of revaccination or other control measures the model predicts that almost all susceptible cattle would become infected (unless R_0 is below 2) [1].

If major outbreaks are to be prevented in these herds then the basic reproduction number in the vaccinated herd must be reduced below one, which constitutes herd immunity. Although the available vaccines may give good take the duration of protection afforded is low compared with cattle life expectancy; this implies that revaccination must be given at frequent intervals if herd immunity is to be achieved. Current vaccination programmes (revaccinating every 4–6 months) should provide herd immunity against antigenically similar virus only if R_0 is below 2 (Fig. 6). The situation would be greatly improved if vaccines with greater duration of protection were available (Fig. 7). The problem is worse for antigenically different virus; for example, it is not possible, however frequently cattle are revaccinated, to prevent outbreaks of a virus with relative homology 0·6 if R_0 exceeds 10 (Fig. 6).

These results suggest that currently available vaccines are unlikely to be able to prevent FMDV outbreaks on these cattle farms, however frequently the animals are vaccinated. This is because of the high transmissibility of FMDV on the farms, the short duration of vaccine-induced protection and the presence of antigenically different viruses. Alternative preventative measures might include the change of husbandry practices to reduce virus transmission rates; for example, by maintaining cattle at lower densities or the more rapid removal of infectious animals. However, the results do suggest that vaccination can be effective in reducing transmission rates once an epidemic has begun, as has been discussed elsewhere [17].

The results also have implications for vaccines developed for other animal diseases such as kennel cough, feline leukaemia, feline influenza, equine influenza, equine rhinopneumonitis, orf and parainfluenza-3. Although take, at least against homologous challenge, may be high, these vaccines provide protection for limited periods and even very intense vaccination programmes are unlikely to result in herd immunity and so prevent outbreaks of disease. Trials of new candidate vaccines should be designed to assess the duration of protection, which will be a

major factor determining their potential for disease control at the population level.

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