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Modelling equine influenza 1: a stochastic model of within-yard epidemics

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SUMMARY

This paper demonstrates that a simple stochastic model can capture the features of an epidemic of equine influenza in unvaccinated horses. When the model is modified to consider vaccinated horses, we find that vaccination dramatically reduces the incidence and size of epidemics. Although occasional larger outbreaks can still occur, these are exceptional. We then look at the effects of vaccination on a yard of horses, and in particular at the relationship between pre-challenge antibody level and quantity of virus shed when challenged with the virus. While on average, a high antibody level implies that less virus will be shed during the infectious period, we identify a high degree of heterogeneity in the response of horses with similar pre-challenge antibody levels. We develop a modified model that incorporates some heterogeneity in levels of infectivity, and compare this with the simpler model.

INTRODUCTION

Equine influenza virus causes a serious clinical disease of equidae with a nearly worldwide distribution. The disease is common in most countries apart from Australia, New Zealand, Iceland and Japan, which enforce strict quarantine on incoming animals [1].

Clinical signs in fully susceptible horses infected with equine influenza virus include a high temperature and depression, a harsh cough and a serous and subsequently muco-purulent nasal discharge. These signs usually become evident between 1 and 2 days post infection and can last several days. If they are rested, recovery in most animals is uneventful and occurs within 2 weeks of the infection (see [1, 2]).

Equine influenza is highly contagious, and serious epidemics have been reported. These epidemics occur particularly in unvaccinated populations, but also sometimes in fully vaccinated populations. In most outbreaks, mortality tends to be extremely low, although morbidity is high.

Equine influenza viruses belong to the family orthomyxoviridae. All viruses isolated from horses to date have been type A and there are two recognized subtypes referred to as A/equine 1 (H7N7) and A/equine 2 (H3N8). Although all reported outbreaks since 1980 have been subtype 2 [3], there has been some serological evidence of subtype 1 circulating in Eastern Europe [4]. The prototype for A/equine 2 was isolated from a major pandemic, which started in Miami in 1963 (see [5, 6]) and then spread over North America throughout 1963 [7] and through Europe during 1965 [2].

Antigenic drift and shift

Equine influenza viruses are similar to other mammalian influenza viruses in that they undergo continuous genetic and antigenic drift, which improves the ability of the viruses to transmit in semi-immune

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populations and reduces vaccine efficacy [3, 8]. Both sub-types of virus are thought to be able to persist in equine populations, and do not require wildlife or other reservoirs. Detailed experimental and epidemiological studies have demonstrated that antigenic drift in the A/equine 2 strain has, progressively, had a substantial impact on vaccine efficacy [8].

As in man, completely new strains of virus do appear sporadically, derived from recombination or adaptation of avian or other influenza viruses to the new mammalian host. This sudden appearance of a new strain of the virus is termed antigenic shift. The A/equine 2 virus was thought to have thus appeared in 1963. In March 1989, an equine influenza epidemic occurred in China, with morbidity of 81% and mortality of up to 20% in some herds [9]. Although the virus was identified as being of the same surface antigenic types (H3N8) as the Miami virus, it was found to be antigenically distinct from other equine viruses and molecular analysis suggested that it was of avian origin [9]. This avian derived virus does not appear to have persisted in the horse population since 1990 [3].

Vaccination

An ideal vaccine will prevent both clinical disease and transmission of infection over long periods of time after vaccination. An important feature of current equine influenza vaccines is that the protection they afford diminishes with time, and horses must be repeatedly vaccinated to maintain the required level of protection [1, 10]. Horses with levels of immunity that have declined so that they are insufficient to protect against infection, will frequently still be protected against severe clinical disease. If such horses do become infected, they will experience a reduced infectious period and shed less virus than a naive animal [10, 11]. These effects occur against a background of antigenic drift of virus away from vaccine strains. Experimental studies have demonstrated that drift has a greater impact on failure to prevent transmission than on clinical protection [8]. Thus, commercially available equine influenza vaccines have achieved greater success in preventing clinical signs of disease than in preventing transmission. Despite being moderated, many vaccines have failed even to prevent clinical signs during outbreaks [8, 12, 13]. A substantial proportion of horses are sub-clinically affected during outbreaks in vaccinated populations, this being as much as 50% in one outbreak [2].

As an alternative to challenging vaccinated horses with the influenza virus, vaccines can be tested by measuring the levels of antibody to the virus that they induce in vaccinated horses. A clear relationship has been demonstrated between the level of antibody measured by single radial haemolysis (SRH), and the degree of protection against experimental [11, 14, 15] and field [16, J. A. Mumford and D. M. Jesset, data on file] infection. There have been a number of studies that have attempted to identify the level of antibody (as measured by SRH) that corresponds to protection from infection (see [11, 14, 15, 17]) with results ranging from 65 mm^2 [17] to 154 mm^2 [11], depending on the challenge route and dose used. Unfortunately, not all horses react in the same way to the vaccines, with some 'poor responders' showing low levels of antibody after vaccination [1]. In general, a yard of horses that have been identically vaccinated will manifest a range of antibody levels when measured by SRH.

This is the first in a series of papers in which we aim to capture the spatio temporal dynamics of epidemics of equine influenza. The following questions need to be addressed.

1. What effect does vaccination have on the immunity of horses to infection, and what implications does this have for a yard of horses?
2. What are the characteristics of a vaccine that will imply that it has a high probability of preventing large-scale outbreaks of EI?
3. How does a horse's immunity change with time from the last vaccination, and how is this affected by antigenic drift?
4. How does the size and physical structure of the yard (that is, the number and distribution of barns or stables) influence the risk of an epidemic?
5. What effect does the age structure of a yard (that is, the number of horses of different ages) have on the probability of epidemics?

We explore these issues using mathematical models of epidemic spread and its control by vaccination.

Mathematical models have a long history in the study of epidemics, particularly in human health [18–20], but also more recently in diseases of domesticated animals and wildlife [21]. Deterministic models [19] can be used to describe epidemics in a large population, but in small systems, such as a yard of horses, stochastic models [22, 23] should be used to take account of the effects of demographic stochasticity. A number of models have been constructed for describing influenza in humans (for example [24]),

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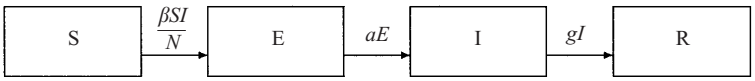

Fig. 1. The transitions between categories in the model of equine influenza in a homogenous population, where $1/a$ is the latent period for the disease, $1/g$ is the infectious period, and β is the transmission parameter.

many of which take into account the effects of co-circulating strains [25]. All cases of equine influenza recorded since 1980 have been of the same subtype, and while there is evidence both of antigenic shift [9] and of antigenic drift [8], this is not as extreme as that seen in human influenza viruses. In this paper, we refine the basic SEIR model for microparasitic infection [19], assuming that the horse population is being infected by a single strain of equine influenza. Although different strains of virus have been isolated from single outbreaks on occasion, these are most unusual.

In this paper, we focus on questions 1 and 2, above, and briefly consider 4. We begin by developing and testing a basic framework for within-yard transmission.

We demonstrate that a simple (stochastic) SEIR model can capture the features of an epidemic of equine influenza, and then consider the case where the yard of horses has been vaccinated using a partially effective vaccine. A simple homogeneous vaccination model is constructed, assuming that all horses react in the same way to the vaccine.

Rather than consisting of identical individuals, a vaccinated population generally contains horses with different levels of antibody to the influenza virus and circulating antibody levels induced by conventional vaccines correlate with protection [17]. The heterogeneities present in a data set of experimentally infected ponies are examined, and a model of equine influenza that incorporates some of this heterogeneity is derived. Finally, we compare simulations of the homogeneous and heterogeneous models of a vaccinated population, and discuss the implications for vaccination programmes and future modelling of equine influenza.

METHODS

Model of equine influenza

A stochastic SEIR model [26] is used to simulate a single epidemic of equine influenza [EI] in a yard of horses. We assume that there is only one strain of influenza circulating at any time and thus a fixed population of size N is divided into four categories: those susceptible to the disease, those exposed to the disease, those infected, and those recovered from infection. As the period considered is the length of a single epidemic, the horses in the recovered class are assumed to be completely immune. Figure 1 describes the transitions between categories in the model, where $1/a$ is the latent period for the disease, $1/g$ is the infectious period, and β is the transmission parameter. Following de Jong et al. [27], we assume a true mass-action transmission term. This model allows us to investigate the variability in epidemics for fixed parameters, but does not model variation attributable to uncertainty in these parameters.

Table 1 gives the transition rates and probabilities for the model. Following [26], the next event to occur is selected according to these probabilities, and the time to the event is an exponentially distributed random variable with mean $1/P$. The deterministic analogue of these equations is given in the Appendix.

The basic reproduction ratio [19], R_0, is a key parameter that represents the expected number of secondary cases caused by a single infective in a wholly susceptible population. The equation for R_0 for this model can be calculated to be

$$R_0 = \frac{\beta}{g}.$$

In this model, if $R_0 = 1$, the probability of a single primary case causing any secondary cases in a fully susceptible population is approximately $\frac{1}{2}$, and if $R_0 < 1$, we would expect the disease to die out more often than not.

Data set for unvaccinated horses

The above model is fitted to data from an epidemic that occurred at a racetrack in New York State in 1963 [6]. The epidemic of A/equine 2 that passed through the United States in this year is believed to be the first contact that these horses had had with this subtype of the virus, and thus it is reasonable to model the outbreak as beginning with one infected horse in a group of susceptibles.

Figure 2(a) reproduces the observed epidemic curve given in [6]. The graph shows the number of new clinical cases diagnosed on each day. Assuming that

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Table 1. *Transition rates and probabilities for the homogeneous model represented in Figure 1*

	Transition rate	Transition probability
$S \to E$	$\frac{\beta SI}{\mathrm{N}}$	$\frac{\beta SI}{NP}$
$E \to I$	aE	$\frac{aE}{P}$
$I \to R$	gI	$\frac{gI}{P}$
Sum	$P = \frac{\beta SI}{N} + aE + gI$	1

the gap between onset of infectivity and onset of symptoms is constant, this graph should be identical to that giving the number of new infectives per day (subject to a horizontal shift of 1 or 2 days), and thus can be compared to output from our model in order to fit the parameters in the model.

Once the parameters have been estimated, the model is validated on an independent data set from another racetrack in New York in the same year [6]. The data set gives the 'scratches' or number of horses out of a group of 600 that failed to race per day over a 37-day period.

Estimating parameters for an unvaccinated population

In order to use the stochastic SEIR model to simulate epidemics of EI, the values of the parameters a, g and β must be estimated. Both a and g can be readily estimated from experimental data measuring the quantity of virus shed after exposure to the virus, as $1/a$ is the average latent period between contact with infection and the onset of infectivity and $1/g$ is the average infectious period [19].

Estimating the parameter β is more difficult, as it does not represent an easily measured biological feature of EI, but rather is a combination of the infectivity of the disease and the contact rate between horses. Standard estimates of β based on serology (such as in [28]) cannot be used since EI is not endemic at the yard level. Instead, we estimate β by comparing observed and expected epidemic curves.

A complication arises in reconciling the size of the recorded epidemic with the epidemic size predicted by the model. The data set records 275 cases among 450 horses. In order to reproduce this level of morbidity

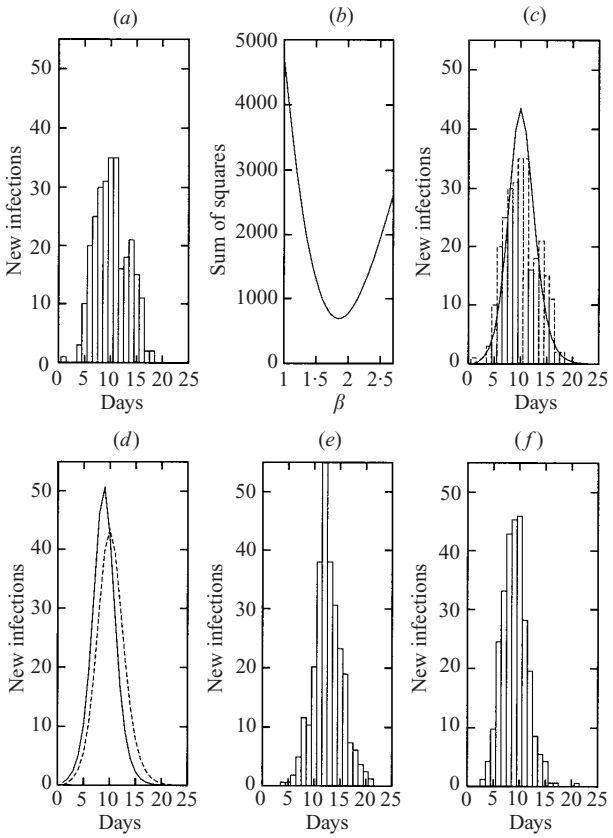

Fig. 2. (a) The number of new cases per day in an outbreak of EI at a racetrack in New York in 1963, reproduced from [6]. (b) Sum of squares of the difference between the epidemic curve in an (a) and the average epidemic curve from the model for a range of β values. (c) The average epidemic curve from the model with estimated value $\beta = 1.85$ super-imposed over the data. (d) The curve produced by the deterministic equations, with the stochastic average shown as a dashed line for comparison. (e), (f) Example realizations from the model with $\beta = 1.85$.

for realistic values of a and g, the model would require the value of β to be in the order of 0·3. However, for low values of β such as this, realizations of the model are highly stochastic and many outbreaks last for over 100 days. For values of β large enough to produce a genuine epidemic, similar to that seen in the data, the model predicts that outbreaks of influenza that take off will result in between 85% and 100% morbidity. We reconcile this discrepancy by assuming that not all cases of influenza are reported, and scale down the output of our model (with a population of 450) to give an epidemic size of 275 cases. This under-reporting assumption is not unrealistic – as commented in [6]:

'… there was considerable reluctance by some officials to recognise or make known the fact that the horses quartered

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at their tracks were experiencing an outbreak of the disease. These factors tended to minimize the severity of the recorded epidemic.'

Since the model is stochastic, the size and shape of realizations vary, and we use average curves to fit β. Even for relatively high transmission rates there is a non-zero probability that the index case will not lead to an epidemic [22]. We identify these realizations as those where fewer than five horses became infected. We performed 100000 realizations for given values of the parameters, and then averaged and scaled the output of realizations where more than five horses become infected to give a smooth epidemic curve with the correct epidemic size. We then compared our data set to the average curves for a range of values of β, taking our estimate of β to be the value for which the sum of squares of the difference between the observed data and the simulated epidemic was minimal. Other objective functions (for example log least squares) give similar results to those reported here.

Homogeneous model of EI in a vaccinated population

After a yard of horses has been vaccinated, the effective reproductive rate, R_0^* is given by $R_0^* = R_0(S/N)$, where S is the number of susceptible horses in the population [19, 27]. Given a vaccine that entirely prevents infection, $N(1-(1/R_0))$ of the population would need to be immunized to reduce R_0^* to 1.

Vaccinating all the horses within a yard is not an unreasonable aim. Of course, if the vaccine was ideal, this would be sufficient to prevent any of the horses in the yard from becoming infected. It is more likely, however, that the vaccine will not prevent infection in all vaccinated animals, but will reduce the average infectivity and infectious period of the vaccinated horses that do become infected.

One method for determining the effects of partially effective vaccines such as these is to calculate the efficacy of the vaccine and then compute from this the critical vaccine coverage required to reduce R_0^* to 1. A good example of this approach in estimating the probability of eradicating HIV in San Francisco is given in [29].

An alternative approach is to calculate values of the parameters in the SEIR model such that they are consistent with a population where all horses have been vaccinated, but are susceptible to infection at a reduced level. Epidemic sizes can then be estimated from simulations of the model with these modified parameter values, a_V, g_V and β_V. We will refer to the model as the *homogeneous* vaccination model, as it assumes that all horses react in the same way to the vaccine.

Estimating parameters for the homogeneous vaccination model

We estimate the parameters in the homogeneous vaccination model using a data set (J. A. Mumford and D. M. Jesset, 'Three experimental studies of efficacy of conventional equine influenza vaccines', data on file) compiled for 88 ponies (28 controls and 60 vaccinates) giving the pre-challenge antibody level (measured by SRH) and virus titres measured on each of 7 days for every pony. We would expect the transmission parameter, β to depend on the similarity of challenge and vaccine strains. To better model the situation in the field, where challenge virus is never identical to vaccine strain, we included trials where vaccine and challenge strains differed. Further work will consider more explicitly the effect of strain variation.

As titre is measured on a logarithmic scale, the total measured titre of virus excreted by a given pony is calculated as follows:

$$\text{Total titre} = \log_{10}(10^{t_1}+10^{t_2}+10^{t_3}+10^{t_4}+10^{t_5}+10^{t_6}+10^{t_7}-6),$$

where $t_1, \ldots, t_7$ are the titres of virus detected on each day. We assume that this sum of measured titre is proportional to the total quantity of virus shed by the horses over the period of 7 days. We subtract 6 from the sum of terms within the logarithm to ensure that a pony for which no virus was detected is calculated to have a total of zero, and so that a pony with only one day of detected virus will have a total equal to the titre on that day. Similarly, in calculating average total titre over a group of M ponies we have

$$\text{Average titre} = \log_{10}\left(\frac{10^{T_1}+10^{T_2}+\cdots+10^{T_M}-M+1}{M}\right)$$

where T_i is the total titre of pony i.

The values of the parameters a_V and g_V can be estimated directly from the data. We assume that the reproduction ratio, $R_0 = \beta/g$ is proportional to the average titre excreted by the horses, and estimate β_V by comparing the average titre excreted by the

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vaccinated horses with the average excreted by the controls (whose transmission parameter, β, is known). That is,

$$\beta_V = g_V \frac{\beta}{g} \frac{\text{(average titre of vaccinates)}}{\text{(average titre of controls)}}.$$

RESULTS

Fitting the unvaccinated model

The latent and infectious periods of equine influenza are easily derived from experimental data. Following [30] the parameters are set at $1/a = 1{\cdot}25$ days and $1/g = 5{\cdot}5$ days. These figures agree with those calculated for naive unvaccinated control ponies in [11].

The parameter β is calculated using data in [6]. In Figure 2(b) we show the curve giving the sum of squares of the difference between the observed time series and the average epidemic curve of the model, for β in the range 1·0 to 2·5. The curve suggests that the optimal β is 1·85. Using the asymptotic properties of the likelihood ratio, the 95% confidence boundary for the sum of squares is calculated to be 751 which implies a confidence interval for β of $1{\cdot}74 \leqslant \beta \leqslant 1{\cdot}98$. In Figure 2(c) the epidemic curve corresponding to $\beta = 1{\cdot}85$ is superimposed on the data. This epidemic curve, which is the averaged and scaled output of a stochastic model, gives a better fit to the data for these parameter values than the deterministic analogue (see Fig. 2(d) for a comparison), which gives a more pronounced epidemic peak. For comparison, the transmission parameter of the deterministic model is estimated to be 1·6 by least squares. The stochastic model is, however, more appropriate for describing epidemics in small communities, such as those discussed here.

Figures 2(e) and (f) give example (scaled) realizations for the stochastic model with $\beta = 1{\cdot}85$, $g = 0{\cdot}1818$ and $a = 0{\cdot}8$. As our method of estimating β is somewhat simplistic, we tested the bias and precision of the estimator by performing a similar estimation of β for epidemic realizations of the model with β set to its estimated value of 1·85. We repeated this for each realization where the disease took off over 5000 simulations, and then calculated the mean and standard deviation of the re-estimated values of β. The mean of these estimations was 1·91 and the standard deviation 0·34 suggesting that the estimator tends to slightly overestimate β. For comparison, we re-estimated β from the data by minimizing the sum of square of the difference between the data and the simulations after they had been log transformed. We again estimated β to be 1·85. However tests showed this estimator to be more highly biased with an identical test to the one above having mean 1·99 and standard deviation 0·34.

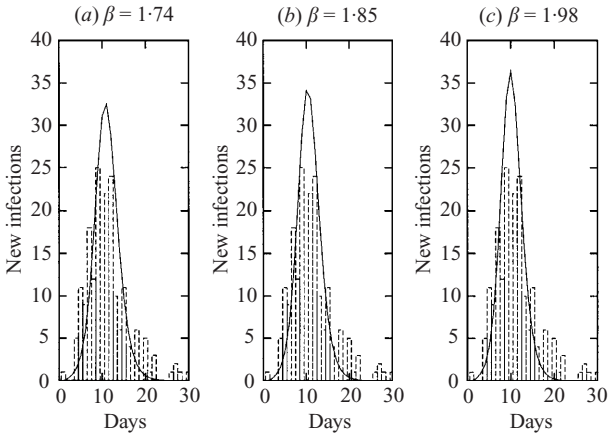

Fig. 3. Figure shows 'scratches' at a racetrack in New York in 1963 (see [6]) and the epidemic curve obtained for the racetrack using the estimate value, $\beta = 1.85$. The curves corresponding to either side of the 95% confidence interval are also shown.

The estimated value of β implies that $R_0 = 10{\cdot}18$; that is, an infected horse in a susceptible population should, on average, infect 10·18 other horses. Translating the confidence interval for β gives a 95% confidence interval for R_0 of $9{\cdot}57 \leqslant R_0 \leqslant 10{\cdot}89$.

Validation of the model

The model is validated using a second (independent) data set from the same New York epidemic. The data set gives the 'scratches' (horses that did not race) at a race-course for weekdays and Saturdays. The model is simulated with the parameters estimated above, and $N = 600$, and is then scaled to give an epidemic size (on non Sundays) of 180. Figure 3(b) gives the epidemic curve superimposed on the data for this racetrack, showing a good overall fit to the data. For comparison, Figure 3(a) and (c) gives the curves corresponding to the values of β at either side of the confidence interval (that is, $\beta = 1{\cdot}74$ and $\beta = 1{\cdot}98$).

Fitting the homogeneous model of vaccinated horses

No horses with pre-challenge antibody level above 180 mm^2 (measured by SRH) excreted any virus when

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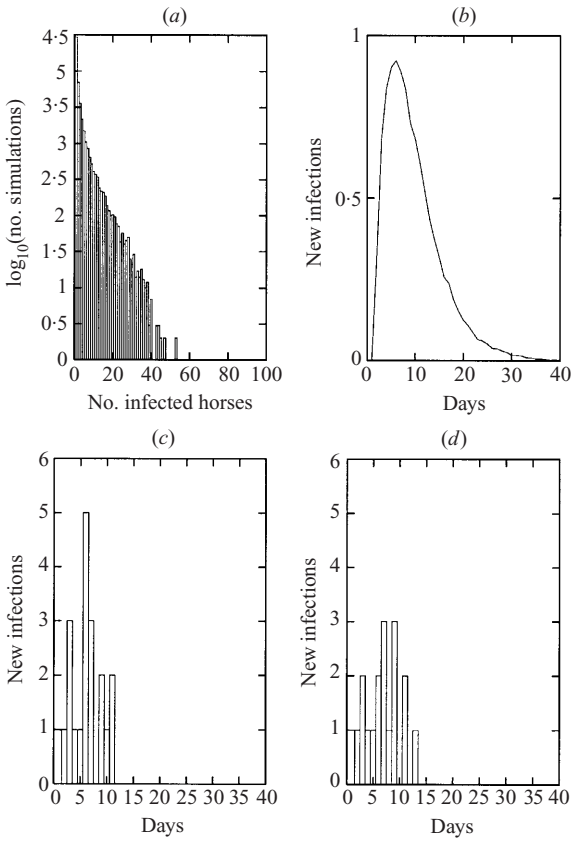

Fig. 4. Results of 50000 realizations of the homogenous model of vaccinated horses for a population size of 100, and parameter values $1/gv = 1.5$ days and $\beta v = 0.47$. Figure (a) gives the distribution of epidemic sizes using a logarithmic scale. (b) gives the averaged epidemic curve over the epidemics that infected more than five individuals, and (c) and (d) are example realizations from the trials.

challenged (J. A. Mumford and D. M. Jesset, data on file), so for comparison with the heterogeneous model discussed later, we have omitted these animals in estimating parameters for our homogeneous model of partially vaccinated horses. We set $a_V = a$ and estimate $1/g_V = 1{\cdot}5$ and $\beta_V = 0{\cdot}47$, giving an R_0 of 0·72. This represents a big reduction from the unvaccinated horses.

Experimental simulations of the homogeneous vaccination model

Figure 4(a) shows the distribution of epidemic sizes after 50000 realizations of the SEIR model with the above parameter values, setting the population size to be 100. Figure 4(b) shows the epidemic curve averaged over those realizations where more than five horses became infected, and Figure 4(c) and (d) gives example realizations from the simulations. As we would expect for a model with R_0 less than 1, the simulations show much more stochasticity, with a relatively low probability of a large epidemic occurring.

Comparison of different yard sizes

Repeating the above simulations with identical parameter values, but setting N to each of the values 20, 50 and 200, we find that for this low value of R_0, yard size has little effect on the epidemic size.

Analysis of homogeneity assumption

The previous model assumes that all horses react identically to vaccination. We test the validity of this assumption using experimental infection data (J. A. Mumford and D. M. Jesset, data on file). Figure 5 gives a bar chart showing the total titre excreted against pre-challenge antibody level for all vaccinated ponies in this data set. Gaps in the chart correspond to ponies that excreted no measurable virus on any of the 7 days.

The average total titre excreted by the control ponies of 4·52 which is significantly more than that excreted by the vaccinates. The total titre excreted by an infected pony does, on average, decrease with increasing pre-challenge antibody level. However, it is important to note the high level of heterogeneity in the total titre excreted by ponies of similar pre-challenge antibody level. It is clear from Figure 5 that ponies with high pre-challenge antibody can still excrete a high titre of virus, although they are less likely to do so.

The most distinctive change that occurs with increasing pre-challenge antibody is an increase in the number of ponies that excreted little or no virus. For each antibody level of 0, 20, … , 200, the 20 ponies with pre-challenge antibody closest to this are found, and we calculate the percentage of these with a low total titre (in this case, titre $< 1{\cdot}2$). A plot of this is given in Figure 6, confirming that the percentage increases as the pre-challenge antibody level increases.

If we exclude the ponies with titre less than 1·2 from the calculation, the total titre of ponies with pre-challenge antibody level between 1 mm² and 80 mm² is not significantly different from the total titre of ponies with prechallenge between 80 mm² and 180 mm² ($P = 0{\cdot}68$, t test).

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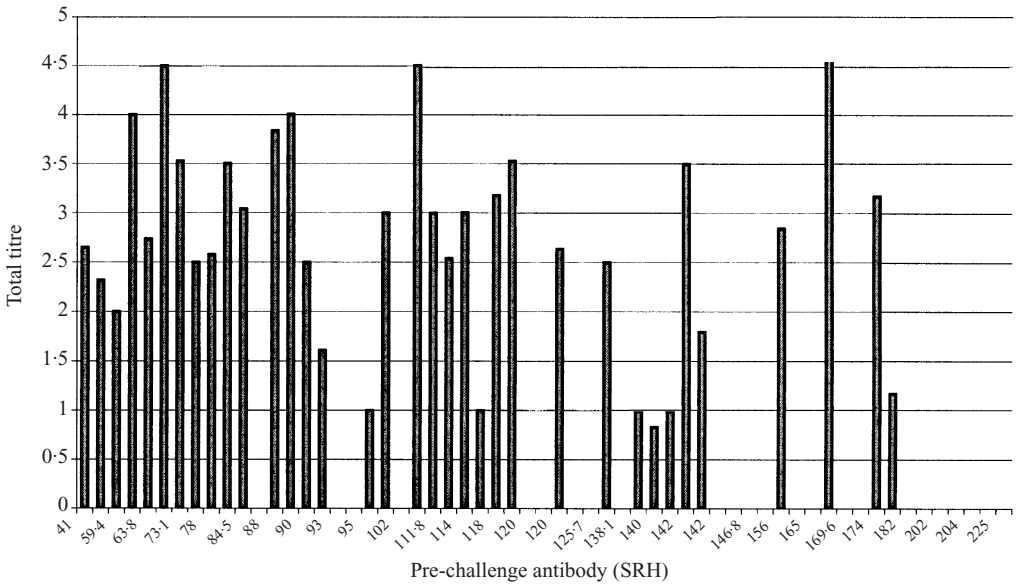

Fig. 5. Vaccinated ponies are ordered along the x-axis according to pre-challenge antibody as measured by SRH. On the y-axis the total titre excreted by each of these animals is plotted (thus gaps in the bar chart indicate ponies that excreted no virus).

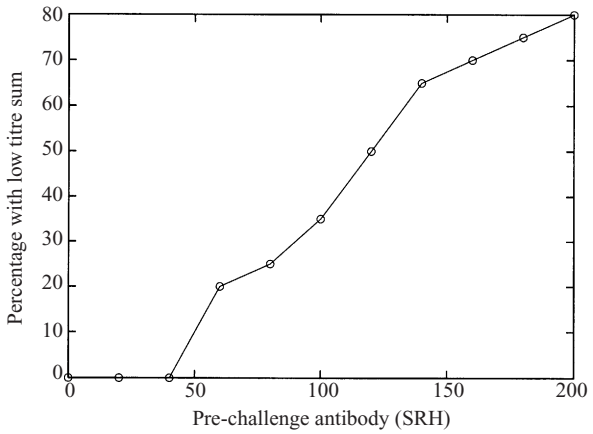

Fig. 6. For each antibody level, the 20 ponies with pre-challenge antibody closest to this value are considered. The plot shows the percentage of these ponies with an total sum of titre less than 1.2.

A heterogeneous model of vaccinated horses

To incorporate the heterogeneities found in the above analysis, the horse population is divided into three groups:

(1) S_1: horses with low pre-challenge antibody level (for example: 1–80 mm² as measured by SRH);
(2) S_2: horses with medium pre-challenge antibody level (for example: 80–180 mm², as measured by SRH);
(3) R: horses with high pre-challenge antibody level that are considered to be immune,

where we assume that all antibody results from vaccination, and do not take into account past infection. Figure 7 shows the transitions between categories in this new model with new parameters β'_V, g'_V and f. We assume that the latent period, $1/a$ is unchanged.

The initial state of the model is determined by the distribution of horses in the three states S_1, S_2 and R. Horses in set S_2 that are exposed to infection, undergo infection as horses in group S_1 with probability f, and pass straight to group R with probability $(1-f)$, where $0 < f < 1$. This latter case corresponds to the 'low titre' ponies in Figure 5 discussed above. The probability f is estimated from the data for horses with pre-challenge antibody of 80–180 mm², and β'_V and $1/g'_V$ are estimated as for the homogeneous model.

Fitting and simulating the heterogeneous model

The values of the parameters are estimated to be

$$\beta'_V = 0{\cdot}5 \quad f = 0{\cdot}5 \quad \frac{1}{g'_V} = 3{\cdot}1 \text{ days}$$

maintaining the latent period, $1/a$, at 1·25 days. The initial distribution of horses in each of the categories S_1, S_2 and R is determined from data concerning serological responses to a new vaccine [16]. These horses have had regular vaccinations, and for a

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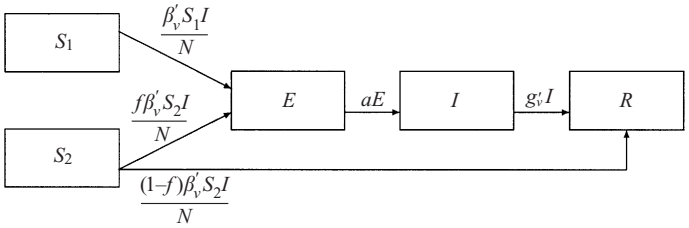

Fig. 7. Transitions between classes in the heterogeneous model of vaccinated horses.

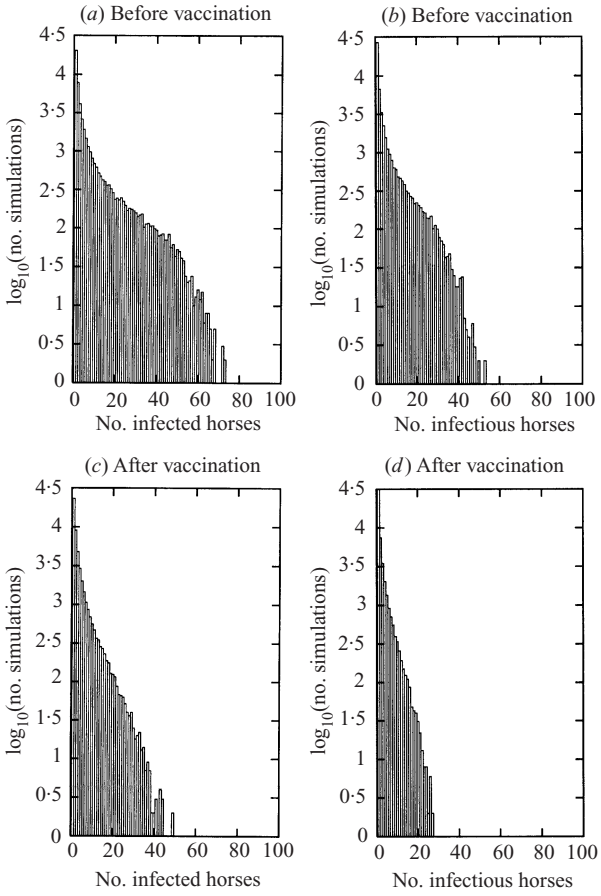

Fig. 8. The distribution of epidemic sizes after 50000 realizations of the new model, with initial conditions representing the distribution of 100 horses before and after vaccination. Figures (a) and (c) give the distribution of the number of horses *infected*, while Figs. (b) and (d) give the distribution of the number of *infectious* horses.

population size of 100, the distribution before a booster dose is given as $S_1 = 19$, $S_2 = 77$, $R = 4$ and the distribution after this booster is $S_1 = 1$, $S_2 = 75$, $R = 24$. Figure 8 shows the distribution of epidemic sizes before and after the vaccination, determined from 50000 realizations of the model with the above parameter values and the two different initial conditions. In calculating the distribution of epidemic sizes, there is some ambiguity over whether horses that pass directly from group S_2 to R (having been infected without becoming infectious) should be considered as part of the epidemic. Compared with horses in S_1, these 'low titre' horses are much less likely to be noted as among the cases in a yard, unless blood samples are taken, as they are less likely to show symptoms [16, 2]. Figure 8 shows the distribution of epidemic sizes before and after vaccination counting infected and then infectious horses. In both cases, the distribution of epidemics before vaccination has a longer tail than that after vaccination, with the probability that an epidemic will infect more than 10 horses (of the 100) dropping from 0·18 to 0·08 after vaccination. The probability that more than 10 horses will become infectious drops from 0·12 before vaccination to 0·03 after vaccination.

DISCUSSION

Modelling epidemic in unvaccinated horses

This paper demonstrates that an epidemic of equine influenza can be described by a simple stochastic model. While the parameters a and g in the model can be calculated directly from experimental data, it was necessary to estimate β by fitting the model to an epidemic. In comparing the average epidemic curve for $\beta = 1{\cdot}85$ and the data, the biggest discrepancy lies at the peak of the epidemic curve. This may be caused by spatial heterogeneities at the racetrack (for example, reduced transmission between, rather than within, barns or stables) which tend to reduce the epidemic peak and increase the epidemic duration. Future work will investigate the effects of spatial heterogeneity on the transmission of EI.

Our calculations resulted in an estimate of R_0 of 10·18 (95% CI 9·57–10·89). This is the first time that R_0 has been estimated from real data for equine influenza and is consistent with clinical observations

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that this infection is highly contagious in unvaccinated populations.

Effects of vaccination

Our results underline that vaccination has dramatically reduced the probability and size of epidemics of equine influenza. It should be noted that, although occasional larger epidemics are predicted by both models of vaccinated horses, in over 80% of realizations, fewer than 5% of the horse population became infectious. As discussed in [31, 32], disproportionate attention is often paid to large epidemics while small outbreaks may go undetected. This bias should be taken into account when vaccine efficacy is computed from field data.

Variability in titre of vaccinated horses

The degree of variability in titre excreted by horses of similar pre-challenge antibody level is surprising. This variability in response to challenge may have resulted from variabilities in the experimental procedure, from measurement errors, or may be a genuine feature of influenza in horses.

Variability in the experimental challenge could be due to variations caused by the vaccination procedure, or variations in the quantity of virus inhaled during challenge. In the experiments under consideration, ponies were placed in a small box, two ponies at a time, over a period of 80 min and subjected to an aerosol challenge [33]. The potential variability in virus inhaled has not been quantified. The suggestion that the variation is caused by vaccination can be largely eliminated by considering the control ponies. The total titres of unvaccinated horses range from 1·85–5·2, with S.D. 1·1 (as compared to S.D. 1·6 and a range of 0–4·5 for the vaccinates). Although vaccination has increased the number of ponies that do not excrete any measurable virus, the variation in those that do excrete virus (S.D. 1·05) is not markedly different from the controls.

There is a very real possibility that measurement error could be contributing to the variability seen in the titre calculations for each horse. The calculations are made by taking a nasal swab from each horse every day over a 7 day period, and then calculating the virus titre from two eggs per dilution, from neat to 10^{-3} per swab. Little is known about the dynamics of virus excretion – for example, whether it occurs continuously or in pulses – and thus it is hard to determine how representative an individual swab is of the quantity of virus the horse has excreted that day. Further measurement errors may then occur in the process of calculating titre, especially for swabs with a low virus titre. An experiment that involved taking two (or more) swabs from the same horse (at a small time interval) would allow us to quantify the effects of the above two factors.

Although the uncertainties discussed above are likely to lead to some errors in the data, it seems very unlikely that these effects could contribute to produce the vast range of titre sums calculated for this data set – from no virus excreted, to a sum of 4·5 $\log EID50$ excreted over 3 days. Thus it appears that at least some of the variation in the data is a product of heterogeneities in the behaviour of horses infected with EI, either due to the virus itself, or to genetic variability in horses.

The heterogeneous model

We incorporate some variability in the levels of infectivity of vaccinated horses exposed to EI into the model by dividing the susceptible vaccinates into two classes, S_1 and S_2, according to antibody level. While retaining the assumption that the process of exposure to equine influenza is homogeneous (all susceptible horses in groups S_1 and S_2 have the same probability of infection), we introduce heterogeneity by assuming that a proportion of horses in S_2 (the so-called 'low titre' ponies in Fig. 5) will pass directly to the recovered class without becoming infectious. This is a simplification of a real process by which such horses do excrete some virus. However, if the logarithmic scale of titre measurement is taken into account, the low titre ponies in Figure 5 excreted at most 0·3% of the average total titre of the ponies in group S_1, and 0·05% of the average of the control ponies, implying that an R_0 for these ponies would be less than 0·005.

It should also be noted that ponies in Figure 5 with a measured total titre of zero may have excreted some virus. Of the 42 ponies in group S_2, 17 had a measured total titre of zero, but of these 17, 11 seroconverted. Only 14 ponies in group S_2 did not seroconvert, and 8 of these were measured to have excreted virus. It is quite conceivable that the ponies measured to have excreted no virus did in fact excrete virus, but that virus excretion did not coincide with a daily measurement, or was at too low a level to be detected. Thus it is acceptable to group horses that excreted no detected virus with those that excreted virus at a very low level.

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Comparison of homogeneous and heterogeneous vaccination models

The heterogeneous model of vaccinated horses allows us to isolate the horses that excrete virus at a very low level from other infectious horses. Clearly, this model captures only one of the many forms of heterogeneity present in the dynamics of EI, but by comparing it with the basic homogeneous model, we can determine the impact that this form of heterogeneity has on the dynamics. Simulations suggest that the two models give similar results. Indeed, under a transformation

$$R_{new} = R+(1-f)S_2$$
$$S_{new} = S_1+fS_2$$

we can translate the heterogeneous model into the form of the homogeneous model, with susceptibles S_{new} and recovered animals R_{new}. However, in this form, we cannot identify the number of horses that have experienced low level infection, and can only calculate the size of the epidemic in terms of infectious horses.

Translating the form for the reproductive ratio from the homogeneous model we can deduce that the average number of infectious secondary cases caused by a single infected is given by

$$\bar{R}_0 = \frac{\beta'_V}{g'_V}\frac{(S_1+fS_2)}{N}.$$

To ensure $\bar{R}_0 \leqslant 1$, the distribution of horses must satisfy $S_1+fS_2 \leqslant 0{\cdot}65 \times N$.

While both vaccination models give comparable results, initial conditions are more easily calculated for the heterogeneous model, as these are classified from antibody levels. In addition, the heterogeneous model provides more information on levels of infection and infectivity in an epidemic.

CONCLUSION

This paper successfully derives a simple model for the dynamics of equine influenza. Future work will consider the spatio-temporal dynamics of infection and how the explicit strain dynamics of equine influenza interacts with vaccination history [34].

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APPENDIX

Deterministic equations

The deterministic analogue of the SEIR model is given by the following equations:

$$\dot{S} = -\frac{\beta SI}{N}$$
$$\dot{E} = \frac{\beta SI}{N} - aE$$
$$\dot{I} = aE - gI$$
$$\dot{R} = gI.$$

The deterministic analogue of the heterogeneous model for vaccinated horses is given by:

$$\dot{S}_1 = -\frac{\beta' S_1 I}{N}$$
$$\dot{S}_2 = -\frac{\beta' S_2 I}{N}$$
$$\dot{E} = \frac{\beta'(S_1+fS_2)I}{N} - aE$$
$$\dot{I} = aE - g'I$$
$$\dot{R} = g'I + \frac{(1-f)\beta' S_2 I}{N}.$$

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