

Optimising vaccination strategies in equine influenza

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Abstract

A stochastic model of equine influenza (EI) is constructed to assess the risk of an outbreak in a Thoroughbred population at a typical flat race training yard. The model is parameterised using data from equine challenge experiments conducted by the Animal Health Trust (relating to the latent and infectious period of animals) and also published data on previous epidemics (to estimate the transmission rate for equine influenza). Using 89 ponies, an empirical relationship between pre-challenge antibody and the probability of becoming infectious is established using logistic regression. Changes in antibody level over time are quantified using published and unpublished studies comprising 618 ponies and horses. A plausible Thoroughbred population is examined over the course of a year and the model is used to assess the risk of an outbreak of EI in the yard under the current minimum vaccination policy in the UK. The model is adapted to consider an alternative vaccination programme where the frequency of vaccination in older horses (2-year-olds and upwards) is increased. Model results show that this practical alternative would offer a significant increase in protection. Spread of infection between yards is also considered to ascertain the risk of secondary outbreaks.

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1. Introduction

Equine influenza (EI) is a highly contagious infectious disease of equidae, which in fully susceptible animals causes a high temperature, harsh cough, and mucopurulent or serous nasal discharges. Secondary bacterial infections cause significant problems [1] and broncho-pneumonia occurs in a proportion of cases. In partially immune animals, the signs of disease are moderated and may just consist of a mild cough or mucopurulent nasal discharge [2].

Vaccination against equine influenza has been practised since the 1960s but although vaccines have improved considerably since then, there are continued problems with failure of efficacy under field conditions. Most products available internationally consist of whole killed virus, or sub-unit vaccines. The datasheets for most licensed equine influenza vaccines in Europe recommend that an annual booster dose of vaccine be given after an initial course of three doses.

In this paper we construct and parameterise a stochastic model of equine influenza to assess the risk of an outbreak in a flat race training yard under this recommended dosing

schedule (which also represents the minimum vaccination policy under the Jockey Club rules in the UK). This model represents the next step forward from previous work which was based on simulating the management life cycle of a Thoroughbred population [3]. A stochastic model is essential when dealing with relatively small populations as chance events (such as failure of the infection to transmit) become important [4]. The model assumes that all horses in a yard are in one of four states: susceptible to infection (*S*), exposed to infection but not yet infectious (*E*), infectious (*I*) and resistant (*R*). Such ‘compartmental’ population models have been used successfully to study many infectious diseases including malaria [5] and measles [6]. The response of horses to administered vaccines and the relationship between the vaccine and infectious virus strains are critical factors in determining vaccine efficacy in the field [7]. In this paper, we only consider the situation where the strains are homologous.

The SEIR model is parameterised from several data sets. The latent and infectious periods are ascertained from a group of ponies which were vaccinated against, and subsequently challenged with, equine influenza.

The transmission rate has previously been estimated for unvaccinated animals [8] and we assume that in vaccinated animals it is less than or equal to this rate. A key component

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of the model is an empirical relationship between pre-challenge antibody and probability of becoming infectious (given exposure) which was derived from quantitative evaluation of data from equine challenge experiments performed at the Animal Health Trust. By using this relationship in conjunction with the model it is possible to simulate epidemic development in a yard provided that antibody levels of all the horses in the yard are known (other complicating factors such as horse age, gender and vaccine history need not be considered).

A realistic yard population structure, which takes account of population dynamics over the course of a year in a flat race training yard (e.g. sale of older horses and purchase of yearlings), is incorporated into the model which is then used to assess the risk of an outbreak of equine influenza in the yard under the current minimum policy in accordance with Jockey Club rules. A key preliminary finding of the models was that small epidemics are far more likely than large epidemics [8] and these small outbreaks could be responsible for maintaining equine influenza in the population at large. Consequently, our definition of risk includes small outbreaks and throughout the paper we ask: *If equine influenza were introduced to the yard (from an external contact), what are the probabilities of epidemics affecting 3 and 10% of the yard population?*

The model is then adapted to consider an alternative vaccination strategy (where the frequency of vaccination of older horses is increased) and the probabilities of both small and large epidemics are again estimated, providing a quantitative comparison between the current minimum policy and a plausible alternative. Finally, a two-yard model is implemented to address the question of risk of transmission between yards. This can occur locally at shared training areas such as gallops and nationally at race meetings. This two-yard model is the beginning of a more complex model which will look at large spatial scales, up to the national level.

2. Methods

2.1. Transmission parameters

The stochastic SEIR model uses the three-key epidemiological parameters for equine influenza: latent period ($1/a$), infectious period ($1/g$) and transmission rate (β). The first two rates (a and g) have been estimated from clinical observation of 27 homologously vaccinated ponies that were subsequently challenged with influenza and went on to show symptoms (Table 1). These data clearly show the benefits of vaccination against equine influenza when compared with a control group (Fig. 1). Vaccination reduces the probability of becoming infectious (given contact with infection) from a probability of 1.0 to a probability of 0.47 on average. It also increases the latent period from 1.75 to 2.5 days (both mean values) and reduces the infectious period from 4.8 to 2.5 days (again, both mean values). All these dif-

Table 1
Model parameters

Name	Symbol	Value
Latent period	$1/a$	2.52 days
Infectious period	$1/g$	2.48 days
Transmission rate (unvaccinated)	β_u	1.85 per day
Transmission rate (vaccinated)	β	$0 \leq \beta \leq \beta_u$ per day

ferences are statistically significant at the 95% confidence level.

The transmission rate is notoriously difficult to estimate, as it is a combination of infectivity and contact rates between horses, but was successfully done for equine influenza in unvaccinated animals [8]. This was achieved by fitting an SEIR model to epidemic data and varying the transmission rate until the discrepancy between the model and the data was at a minimum (using the sum of the squares of the

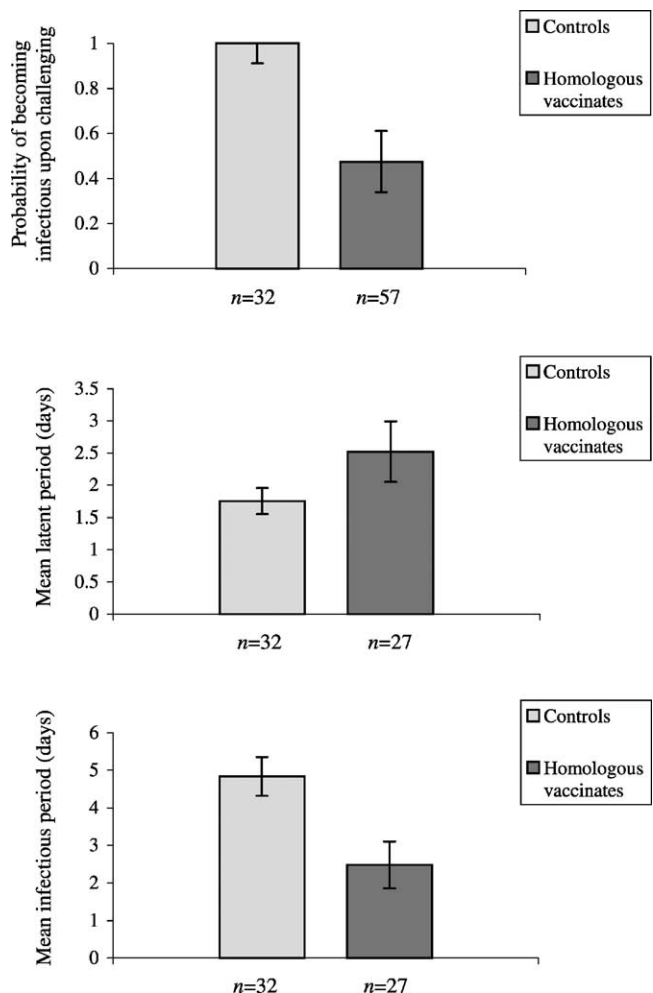


Fig. 1. Differences in: (a) probability of infection given exposure; (b) latent period; and (c) infectious period between groups of unvaccinated and homologously vaccinated ponies. Mean values are shown along with 95% confidence intervals and n represents the sample size.

Table 2
Transitions and their probabilities for the one-yard version of the model

Description	Transition	Probability of transition in time δt
A horse becomes exposed to the virus	$S \rightarrow E$	$(\beta SI/N)\delta t$
A horse becomes infectious	$E \rightarrow I$	$aE\delta t$
A horse recovers	$I \rightarrow R$	$gI\delta t$

N is the total number of horses in the yard at any time (i.e. $N = S + E + I + R$).

difference between the observed data and the simulated epidemic). The model was then validated using an independent data set.

It is not clear generally how imperfect vaccination impacts on transmission rates, and importantly, this aspect has never been studied in equine influenza. Notable exceptions outside the field of equine influenza occur for Aujeszky's disease virus in pigs [9] and human immunodeficiency virus in man [10]. In this paper we consider all values for the transmission rate up to and including that for unvaccinated animals (Table 1). In the presentation of some results (see Section 2.2) we consider a plausible intermediate value of the transmission rate because otherwise complex three-dimensional plots are necessary to show how the risk of an epidemic depends on time, vaccination strategy and transmission rate.

The stochastic model uses the rates (a , g and β) to calculate the probabilities of both when and which events occur in the standard Monte Carlo fashion [11]. A summary of the transitions and their probabilities is given in Table 2.

2.2. Demographic parameters

A notional but realistic British Thoroughbred flat race training yard population structure is used. Typically there are around 100 horses in the yard. The age structure of the yard is noted as younger and older horses have different vaccine dosing schedules. In the racing industry all horses have their official birthday on 1 January and so throughout the year no horse changes age class. The yard contains four age classes: yearlings, 2-, 3- and 4-year-olds.

Some older horses (2-, 3- and 4-year-olds) are lost from the yard throughout the second half of the year (July–December), for example through injury or sale to a stud farm. Following de la Rua-Domenech et al. [3], the probability of departure is assumed to follow a normal distribution during these months. Yearlings enter the yard in the latter part of the year. The probability of an admission is assumed to follow a lognormal distribution (spanning the months September–December) with the peak in late October to coincide with the peak in yearling sales. The skewness of this distribution represents the rapid build-up of sales in October, which after October falls off slowly through the winter [3]. The mean number of horses from

Table 3
Initial number of horses and average number of imports and exports over the year

Age	Initial number	Mean imports per year	Mean exports per year
Yearling	0	52	n/a
2-year-olds	52	n/a	8
3-year-olds	44	n/a	40
4-year-olds	4	n/a	4

each age class to leave and enter the yard over the entire year is prescribed in the model as are the initial number of horses in each class (Table 3). These numbers are typical for flat race training yards [12]. The mean number of horses to leave and enter on a given day is simply the product of the prescribed mean and the value of the normalised distribution (normal or lognormal) on that day. This daily mean is then used in a realisation of a Poisson process to determine the actual numbers of horses from each age class departing and entering the yard on a given day.

Because the population dynamics in the yard are stochastic (e.g. it is most likely that a yearling will enter in late October but it could be as late as December) 100 replicate model simulations were used to build up a typical scenario of population dynamics in flat race training yards, capturing the average behaviour and also the variability. A typical replicate (Fig. 2) shows a characteristic dip in the population size around September as older horses generally leave the yard before the new yearlings arrive. This replicate also shows how the age structure of the population changes over the course of a year.

2.3. Vaccine derived antibody levels

A yearling coming into the yard will either be immunologically naïve to influenza or would have been vaccinated previously (infection is not common on stud farms). This affects their dosing schedule, as previously vaccinated yearlings often have to wait for a designated time until it is appropriate for further doses to be administered. Here, we assume that in previous and current years 25% of incoming yearlings are naïve and 75% have previously been vaccinated, which is in accordance with field observations [2]. Consequently, each age class is subdivided into 'naïve' and 'previously vaccinated' categories.

Published observational data from a study in racing yards involving 468 horses [2] and data from a subsequent and similar unpublished study involving 150 horses were used to estimate the mean antibody level of a horse vaccinated under the current minimum policy at any point during the year. These same data showed that the variance in the antibody levels between horses was approximately constant over time ($s = 30.0$) and further, that the distribution of any antibody levels at any time fitted normal distribution (validated by the Kolmogorov–Smirnov test) and these assumptions were

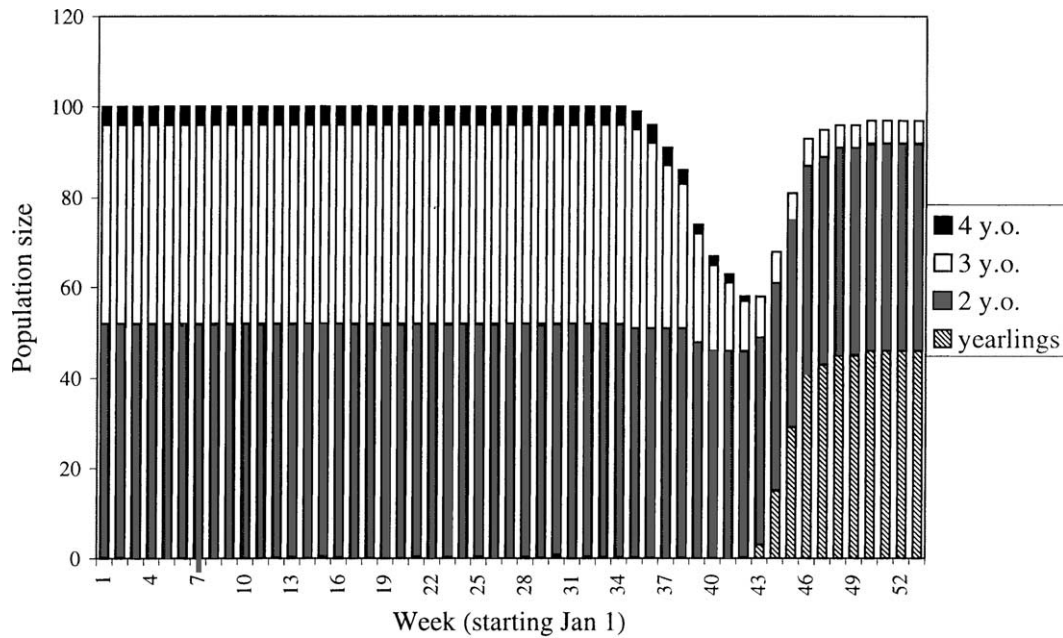


Fig. 2. An example, from the model, of the population dynamics within a yard over the course of a year with age structure denoted by: (i) yearlings: diagonal stripes; (ii) 2-year-olds: solid grey; (iii) 3-year-olds: solid white; and (iv) 4-year-olds: solid black.

used in the model when simulating the antibody levels of a population of horses. The mean antibody levels under the current minimum policy are given in Fig. 3.

An alternative strategy in which 2-, 3- and 4-year-old horses are vaccinated every 6 months (as opposed to annually) was also investigated and the mean antibody levels for this scenario are given in Fig. 4. We estimated these based on the assumption that the peak values and rates of decline following vaccination are robust to changes in the inter-dose interval.

2.4. Relationship between infectivity and antibody levels

We have evaluated data from our experiments (involving 32 unvaccinated and 57 homologously vaccinated ponies) and have shown an empirical relationship between pre-challenge antibody level (conferred by vaccination) and the probability of becoming infectious upon challenging with a homologous virus strain (Fig. 5). Pre-challenge antibody is measured by single radial haemolysis (SRH)

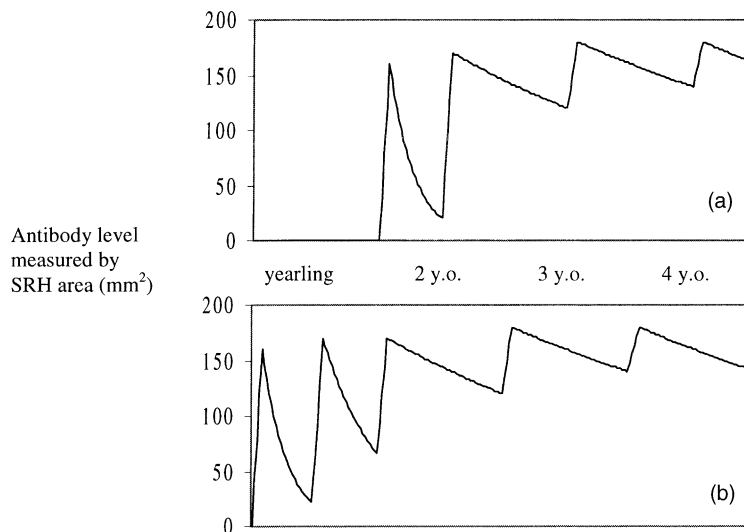


Fig. 3. Mean antibody levels over a 4-year period (yearling to 4-year-old) measured by single radial haemolysis (SRH) area (mm²) for (a) horses entering the yard naïve to vaccination; and (b) horses vaccinated prior to entering the yard under the current minimum policy. Mean values and distributions (not shown) were calculated from a sample size of 618 animals.

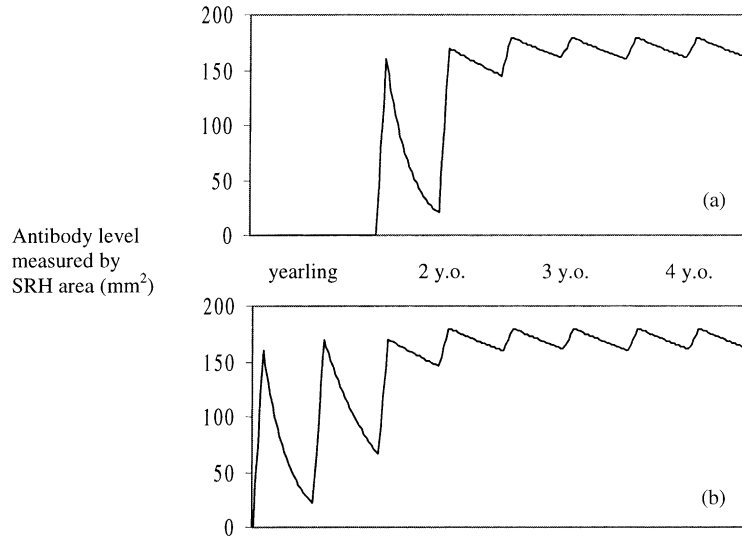


Fig. 4. Mean antibody levels over a 4-year period (yearling to 4-year-old) measured by single radial haemolysis (SRH) area (mm^2) for (a) horses entering the yard naïve to vaccination; and (b) horses vaccinated prior to entering the yard under a strategy where all horses are vaccinated every 6 months. Mean values and distributions (not shown) were calculated from a sample size of 618 animals and interpolated under the assumption that peak responses and decay rates are robust to changes in the inter-dose interval.

area (mm^2) [13] and virus excreted is measured in units of $\log_{10}(\text{EID}_{50})$, \log_{10} 50% egg infectious doses per millilitre [14]. All unvaccinated horses excreted virus whereas 53% of the vaccinated horses excreted no detectable virus (these appear as gaps in the bar chart, Fig. 5). The probability of excreting virus was high if the pre-challenge antibody level was low and vice versa. Non-linear regression of these data suggested the best fit to this relationship was sigmoidal (Fig. 6).

Thus, for every horse in the yard, in any given week there is an antibody level conferred by vaccination. For each an-

tibody level there is an associated probability of becoming infectious upon challenge. As antibody levels change over time, for each week we use these probabilities (together with the binomial function) for each horse to determine whether the horse should be put into the susceptible class (*S*) or the resistant class (*R*). The latter class assumes the horse has no part in the epidemic process and corresponds to a horse that excretes no virus. This method is equivalent to sampling many representative yards in a given week rather than following specific yards and horses over the course of a year. One hundred binomial trials were performed in replicates to

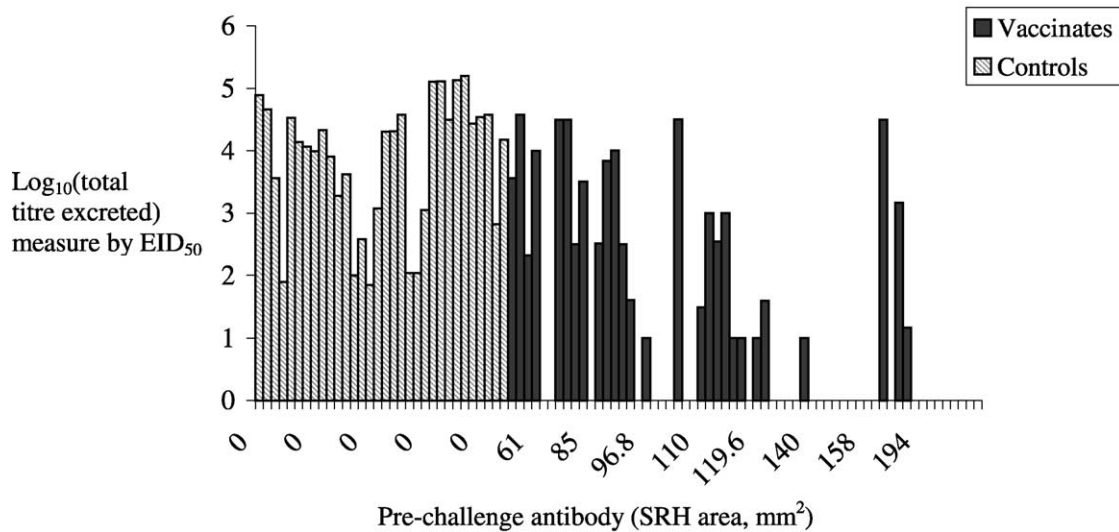


Fig. 5. Total titre excreted by vaccinated ($n = 57$) and unvaccinated ($n = 32$) ponies ($\log_{10}(\text{EID}_{50})$ (ml)) as a function of their pre-challenge antibody level (SRH, mm^2). Gaps in the bar chart correspond with vaccinated ponies that did not excrete detectable virus.

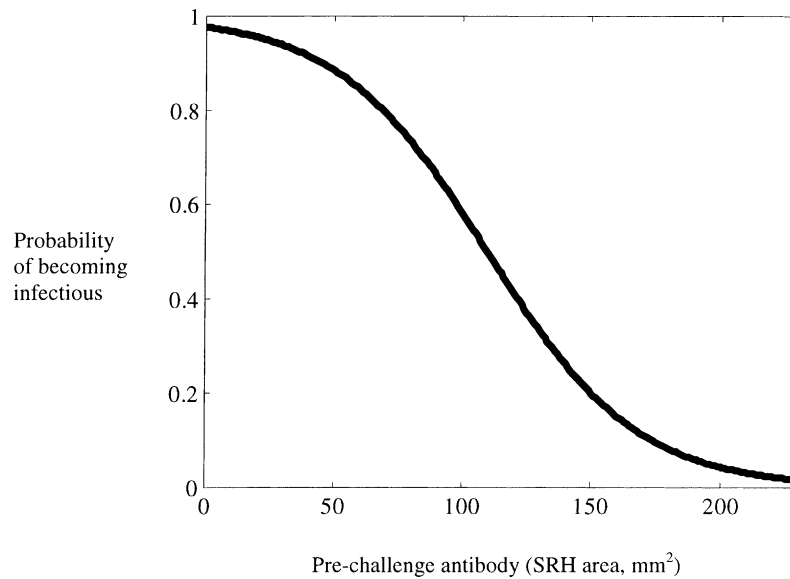


Fig. 6. Non-linear regression of homologous challenge data giving the probability of becoming infectious as a function of antibody level (SRH, mm^2). For sample size, see Fig. 5.

Table 4
Transitions and their probabilities for the two-yard version of the model

Description	Transition	Probability of transition in time δt
A horse in yard A becomes exposed to the virus	$S_A \rightarrow E_A$	$((1-\mu)\beta S_A I_A/N_A + \mu\beta S_A(I_A + I_B)/(N_A + N_B))\delta t$
A horse in yard B becomes exposed to the virus	$S_B \rightarrow E_B$	$((1-\mu)\beta S_B I_B/N_B + \mu\beta S_B(I_A + I_B)/(N_A + N_B))\delta t$
A horse in yard A becomes infectious	$E_A \rightarrow I_A$	$aE_A\delta t$
A horse in yard B becomes infectious	$E_B \rightarrow I_B$	$aE_B\delta t$
A horse in yard A recovers	$I_A \rightarrow R_A$	$gI_A\delta t$
A horse in yard B recovers	$I_B \rightarrow R_B$	$gI_B\delta t$

Subscripts A and B denote horses belonging to yards A and B, respectively. The parameter μ is the proportion of time spent at shared training facilities (here, we assume $\mu = 10\text{h}$ per week).

ensure that an accurate distribution of horses in the S and R classes, according to probability theory, was obtained.

Once all the horses were assigned to either the S or R classes, one of the susceptible horses was given an infectious status (I) to initiate the epidemic. The model then ran until the infection had died out of the population and the size of the epidemic was recorded. Again, 100 replicates of the model were used to give a reliable central estimate of risk. Given that the model sampled 100 different populations (to capture the variability of the population dynamics), 100 different binomial trials (to incorporate the chance of different outcomes for initial conditions) and 100 different epidemics for each initial condition (because of the inherent chance effects in the stochastic process of the spread of infection) then a total of 1 million epidemics were simulated for a given week of the year. After all simulations were completed, the probabilities of an epidemic affecting at least 3% and at least 10% of the population were calculated for that week.

The model was then adapted to couple together two similar yards one of which contained one infected horse initially. The coupling is due to mixing at a shared training facility

(such as training gallops). The proportion of time spent at the shared training facility (μ) was assumed to be 10 h per week (based on horses spending Sunday at rest and, on average, around 1 h and 40 min at exercise daily). The model assumes that the transmission rates within a yard and between yards are the same. A summary of the transitions and their probabilities is given in Table 4. This version of the model was used to assess the risk of transmission between yards using the same method as the ‘one-yard’ case, described earlier.

3. Results

The following results address the question: *If equine influenza were to enter the yard (from an external contact) in a given week of the year, how likely is it that there will be a small epidemic or a large epidemic?* Probabilities of an outbreak affecting 3 and 10% of the yard population under the current minimum policy are presented as three-dimensional surface plots (Figs. 7 and 8, respectively). The x -axes represent the transmission rate for equine influenza in vaccinated

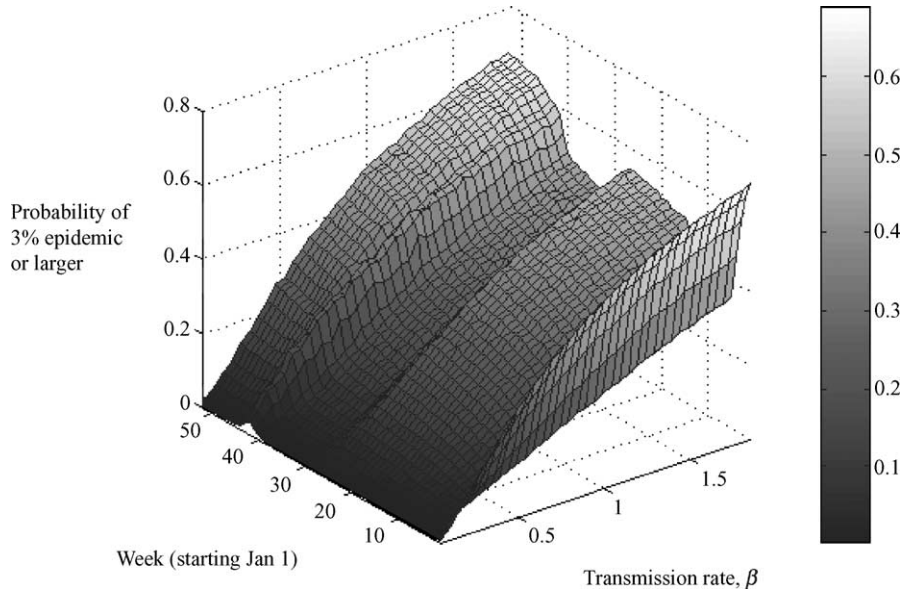


Fig. 7. Surface plot showing the probability of an epidemic affecting at least 3% of the yard population under the current minimum vaccination policy as a function of the transmission rate, β , and the week of the year (week 1 represents the week beginning 1 January).

animals and the y-axis represent the week of the year under consideration. The z-axis represent the probabilities mentioned earlier.

Currently, there is uncertainty as to the value of the transmission rate, β . However, in vaccinated animals it is assumed to be less than (or equal to) the transmission rate in unvaccinated animals, which was found to be $\beta_u = 1.85$ [8], which corresponds to $R_0 = 10.18$. Once a good bound on the transmission rate is obtained for vaccinated horses

it will be possible to more accurately quantify the risk of within-yard outbreaks. For a particular value of β , we see that the probability of an epidemic varies throughout the year. Periods of high risk correspond with periods when the antibody status of horses in the yard is generally low. Also, as the transmission rate increases, the probability of an epidemic increases asymptotically towards one. Although these are intuitive results, we have begun to move away from qualitative predictions to quantitative ones. Further, the rate at

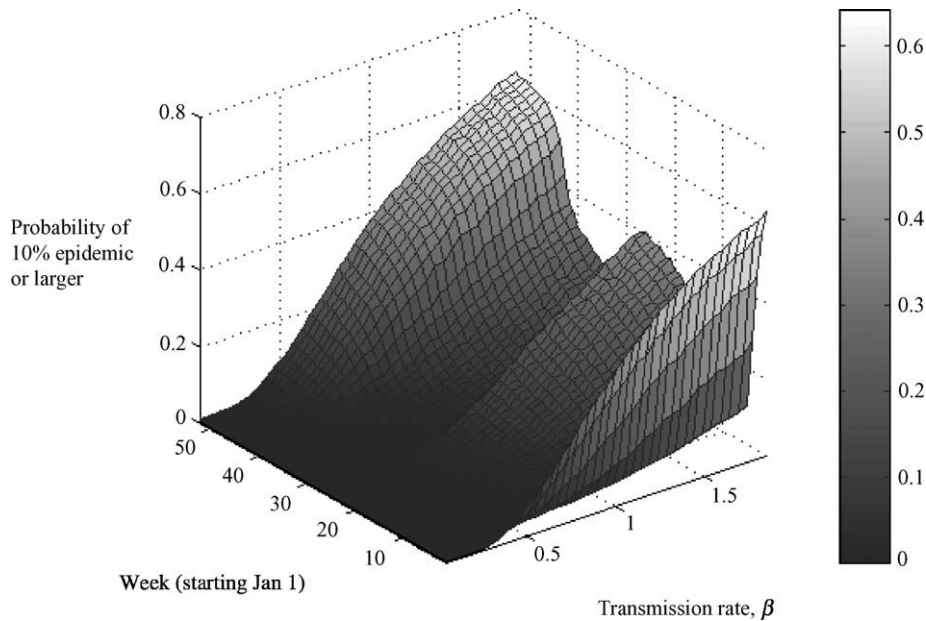


Fig. 8. Surface plot showing the probability of an epidemic affecting at least 10% of the yard population under the current minimum vaccination policy as a function of the transmission rate, β , and the week of the year (week 1 represents the week beginning 1 January).

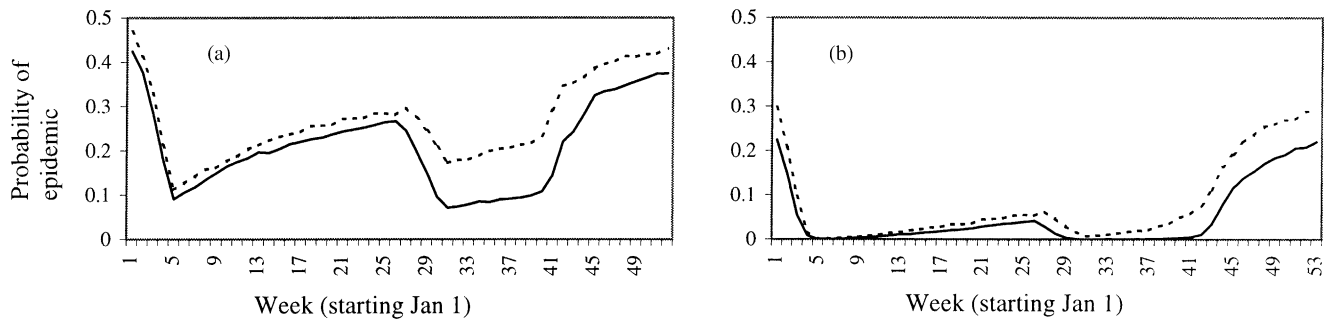


Fig. 9. Comparison of the probability of: (a) a 3% outbreak or larger; and (b) a 10% outbreak or larger under the current minimum vaccination policy (dashed line) and the alternative six monthly vaccination strategy (solid line). The transmission rate is $\beta = 1.0$.

which the probability of an epidemic approaches 1.0 as β increases will be a useful guide in assessing risk against the backdrop of virus evolution in further studies. For clarity and comparison, subsequent results focus on a plausible intermediate value of $\beta = 1.0$.

The alternative strategy put forward here involves all horses being vaccinated every 6 months after their initial course of three doses. The probabilities of both small and large epidemics are reduced under this vaccination strategy (Fig. 9). Importantly, the risk of an epidemic is always smaller under the alternative six monthly strategy compared with the current minimum policy. Moreover, the reduction in risk is highly significant at certain times of the year and these times frequently correspond to peaks in racing activity (when the risk of 'recruitment' of infection is relatively high). Further, the biggest reduction in risk occurs around September and October which is typically when new yearlings arrive. Again, this corresponds to a period of high risk of 'recruitment' of infection from incoming yearlings.

Results concerning the probability of an epidemic in a yard neighbouring one which has just 'recruited' the infection show that the risk of secondary transmission (i.e. between yards) is small but not insignificant (Fig. 10).

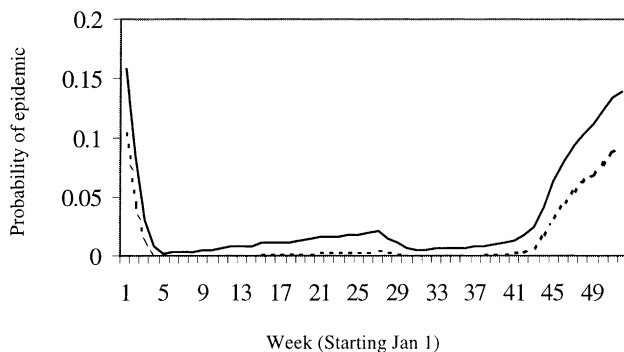


Fig. 10. Probability of an epidemic affecting: (i) at least 3% (solid line) and (ii) at least 10% (dashed line) of a neighbouring yard population with shared training facilities with a yard that has just 'recruited' the infection from an external contact. Mixing time, μ at the shared facility is assumed to be 10h per week and the transmission rate is $\beta = 1.0$.

At certain times of the year the probability of infection spreading between yards reaches values around 0.15.

4. Discussion

We have constructed and parameterised a model that can predict the likelihood of an outbreak of equine influenza in a training yard of Thoroughbred racehorses. A stochastic formulation of the model is used to capture the inherent variability in epidemic development. The latent period and infectious period for equine influenza in a vaccinated population are established from clinical observations (Table 1, Fig. 1). The transmission rate is more difficult to estimate. However, it is known for an unvaccinated population [8] and this provides an upper bound to the transmission rate. Current on-going research is utilising data from the 1989 epidemic in the UK which will increase the accuracy of this key parameter, giving scope for the model to be a truly quantitative tool in helping to control equine influenza.

Parameterising the empirical relationship between antibody level and the probability of becoming infectious (which has been recognised qualitatively for some time [7]) is a significant and novel aspect of the model. Its power lies in the fact that only the antibody levels of the horses need be known (further information such as horse age, gender and vaccine history is not required). Antibody levels and their dynamics are fairly easy to derive from scientific studies of vaccination (e.g. [2,7,15–17]) and allow an unlimited choice of vaccination scenarios to be considered. However, here we assume that ponies and Thoroughbreds are interchangeable (i.e. data from ponies is applied to Thoroughbreds), but believe this to be satisfactory [18]. By including statistical variance of antibody levels, the model captures the effects of poor responders to vaccination, which is an important observation in the field and also from experimental challenges [14]. Future work will aim to extend this approach of considering the antibody levels of hosts in a population to the general area of imperfect vaccines, perhaps including human influenza (though this would require excellent data relating antibody levels to susceptibility).

The model predicts that the alternative strategy (which involves increasing the frequency of vaccination in older horses to 6 months instead of 1 year) significantly lowers the risk of small and large outbreaks. Although this is an intuitive result, by parameterising a model for the spread of equine influenza in training yards we have begun to quantify the benefits of vaccination strategies which could help in policy decision making in equine influenza. Further, this type of model allows us to investigate the association between any aspect of equine influenza (e.g. infectious period) and the risk of an epidemic at the population. The alternative strategy investigated here is plausible both in terms of logistical operation and also in adhering to ethical practice. It may be possible to refine this strategy so that peaks in the level of protection coincide with periods of high risk (e.g. the high racing season). This is an important consideration which will form the basis for future work. Currently, we assume that the risk of 'recruiting' the infection into the yard is constant over time. In reality, the risk will depend on racing seasons and sales. Obtaining relative risks is fairly straightforward (e.g. by comparing the number of race meetings in certain weeks). However, establishing an absolute risk remains a more difficult challenge.

The preliminary spatial model, which considers two yards coupled by a shared training facility, shows that secondary transmission is a real concern. Currently the transmission rate at the shared training facility (such as gallops) is assumed equal to that within a yard. In reality, the transmission rate on the gallops is likely to be lower. However, because of the uncertainty of the value of the transmission rate generally, here they were assumed to be equal and, thus, the model provides a worst-case scenario. Future work will build on this two-yard model to consider spatial spread up to the national level. It is hoped that model validation will be achieved by examining spatial data for the 1989 epidemic in the UK.

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