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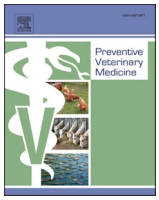

Untangling the stranglehold through mathematical modelling of *Streptococcus equi* subspecies *equi* transmission

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ABSTRACT

Strangles, a disease caused by infection with *Streptococccus equi* subspecies *equi* (*S. equi*), is endemic worldwide and one of the most frequently diagnosed infectious diseases of horses. Recent work has improved our knowledge of key parameters of transmission dynamics, but important knowledge gaps remain. Our aim was to apply mathematical modelling of *S. equi* transmission dynamics to prioritise future research areas, and add precision to estimates of transmission parameters thereby improving understanding of *S. equi* epidemiology and quantifying the control effort required. A compartmental deterministic model was constructed. Parameter values were estimated from current literature wherever possible. We assessed the sensitivity of estimates for the basic reproduction number on the population scale to varying assumptions for the unknown or uncertain parameters of: (mean) duration of carriership ($1/\gamma_C$), relative infectiousness of carriers (f), proportion of infections that result in carriership (p), and (mean) duration of immunity after natural infection ($1/\gamma_R$). Available incidence and (sero-) prevalence data were compared to model outputs to improve point estimates and ranges for these currently unknown or uncertain transmission-related parameters. The required vaccination coverage of an ideal vaccine to prevent major outbreaks under a range of control scenarios was estimated, and compared available data on existing vaccines. The relative infectiousness of carriers (as compared to acutely ill horses) and the duration of carriership were identified as key knowledge gaps. Deterministic compartmental simulations, combined with seroprevalence data, suggest that $0.05 < \widehat{f} < 0.5$ and that the duration of protective immunity after infection is likely 4–6 years. The presence of carriers alone may suffice to keep *S. equi* endemic in a population, implying that carriers cannot be ignored in control efforts. Weekly screening of herds for signs of strangles could be sufficient to ensure $R < 1$, provided all horses are screened for carriership post-infection. In some of worst-case scenarios, vaccination alone would not suffice to prevent major outbreaks from occurring. A stochastic agent-based model was also constructed and validated, and used to simulate a remount depot, to evaluate whether historical incidence data of recurrence of strangles within individuals could be explained without the assumption that one in four horses fail to mount a lasting immune response. These simulations demonstrated that the observed data could have occurred without that assumption.

1. Introduction

Strangles, a disease caused by *Streptococcus equi* spp *equi* (*S. equi*), is endemic nearly worldwide with substantial impact on the equine industry and on equine health and welfare (Boyle et al., 2018; Mitchell et al., 2021).

Progression towards quantifying the effort required for the control of *S. equi* has been made by our recent work to find an estimate for the range of the basic reproduction number (R_0) from data of outbreaks in naive populations, in the absence of interventions (Houben et al., 2022).

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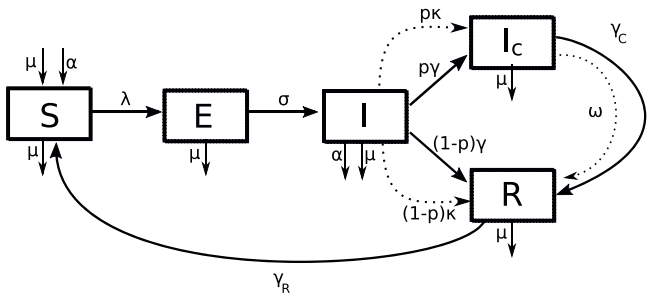

Fig. 1. Basic compartmental model of *S. equi* infection. Parameter descriptions and values are listed in Table 1. Interventions are indicated by dashed lines, solid lines represent the natural history of the disease. *S*: susceptible, *E*: exposed but not infectious, *I*: infectious (strangles), I_C: infectious (carrier), *R*: recovered from infection, convalescent immunity, μ: birth and death (natural causes) rate, α: the disease induced mortality rate, λ: force of infection, σ: rate of transition from *E* to *I*, *p*: probability of becoming a carrier after infection, γ: rate of recovering from acute disease, γ_C: daily rate of horses losing carriership status, γ_R: rate of loss of protective immunity, κ: daily rate of removing horses with clinical disease from the general population, ω: daily rate of removing carriers from the general population.

This can provide an estimate for the range of the contact rate (β) between infectious and susceptible horses for use in epidemiological models for strangles exploring intervention scenarios. After an outbreak, a proportion of convalescent animals fail to clear the pathogen from their guttural pouches or sinuses (Newton et al., 1997; Riihimäki et al., 2018; Tscheschlok et al., 2018; Boyle et al., 2018). These animals remain infectious, without themselves displaying clinical signs of disease, and are considered to be carriers. The *S. equi*-horse-system is complicated by this and related factors in non-naive populations. These aspects will influence infection dynamics and hence most likely also the effectiveness of interventions. Important knowledge gaps remain concerning some of these epidemiological parameters of *S. equi*, such as the duration of carriership, the duration of protective convalescent immunity, and the relative infectiousness of carriers. We can, however, make use of the estimates of R_0 and (derived from that) β in a model to determine how ranges of values for the unknown parameters influence control effort.

The duration of carriership has been described to last anywhere from several months to lifelong (Newton et al., 1999; Boyle et al., 2018; Gröndahl et al., 2015). However, limited data is available on the mean duration of carriership or the distribution of duration thereof, in particular in the absence of interventions. The longest recorded duration of carriership after clinical disease in one study was 56 months (Newton et al., 1999). Another study prospectively followed a group carrier horses after a recorded outbreak, but only up to 45 weeks (Pringle et al., 2019). Prospective long-term follow up data of carriers until self-cure is rare, as many horses undergo treatment upon diagnosis, which is why obtaining sufficient records on the duration of carriership without interventions is difficult.

The probability of becoming a carrier after infection has been reported in several descriptions of outbreaks of strangles, and appears to be 10–40% (Newton et al., 1997; Gröndahl et al., 2015; Riihimäki et al., 2018; de Brauwere and Kirton, 2019; Delph et al., 2019), although most reports are in the 10–20% range. In a 1999 study with prospective sampling of equine premises after outbreaks of strangles in the UK, at least one carrier was found in one in four outbreaks (Newton et al., 1999).

The duration of protective immunity after natural infection lacks precise reports of its mean duration or the distribution of its duration. It is likely that local immunity plays an important role independent of the serological response (Galan and Timoney, 1985; Jacobs et al., 2000), making extrapolation of duration of protective immunity from serological data an invalid approach. The current assumption for the duration of protection against reinfection is that it must have a bimodal distribution where approximately 25% of horses fail to develop protective immunity lasting more than a few months, and the remaining 75% are resistant to reinfection for a long duration, usually assumed to be ≈ 5 years (Waller et al., 2014; Boyle et al., 2018). This assumption is primarily based on the following text in Todd (1910), transcribing findings at an army horse remount depot where *…a four years' experience with horses over two years of age, in which 2195 had it once, 543 twice, and 121 three times, and 1641 remained unaffected.* Although Todd in his 1910

Table 1
Model parameters.

Parameter	Description	Deterministic model input	Stochastic model input	Source
$1/\mu$	Birth and death rate	1/5475 per day	Normal distribution 1/3650 ± 365 per day	None
β	Group housing contact parameter	0.199 per day	0.199 per day	(Houben et al., 2022) and Equation (7)
$1/\sigma_L$	Duration of latency (no clinical signs, not infectious)	7 days	Poisson(7)	(Boyle et al., 2018)
$1/\sigma_P$	Duration of pre-infectious period (clinical signs, not infectious)	3 days	Poisson(3)	(Boyle et al., 2018)
$1/\sigma$	$1/\sigma_L + 1/\sigma_P$	10 days	Poisson(10)	
$1/\gamma$	Duration of / recovery from from acute infection (and infectiousness)	14 days	Poisson(14)	(Boyle et al., 2018)
$1/\gamma_C$	Recovery from carriership	Varied	1825 days	(Newton et al., 1999; Pringle et al., 2019)
$1/\gamma_R$	Loss of protective immunity after infection	Varied	Normal distribution, mean and sd varied (see text)	(Boyle et al., 2018; Waller et al., 2014)
f	Relative infectiousness of carriers	$f \in (0, 1)$	0.25	None
p	Proportion of infections resulting in carriership	$p \in (0.1, 0.4)$	0.1	(Newton et al., 1997; Riihimäki et al., 2018; Delph et al., 2019)
α	Daily mortality rate as a result of disease	Total mortality as a result of disease 3 (0−10)%, set at $0.03*\gamma$	Death with probability of 0.03/14 each day spent in state *I*	Todd (1910): 0–3%; Sweeney et al. (2024): 8.1%; Piché (1984): 3.6%; Christmann and Pink (2017): 11%
$1/\omega$	Number of days until detection of carriership and treatment/ isolation (after resolution of acute disease)	$\omega \in (0, \infty)$ days	Not modelled	
$1/\kappa$	Number of days until detection of acute disease and removal from herd	$\kappa \in (0, \infty)$ days	Not modelled	

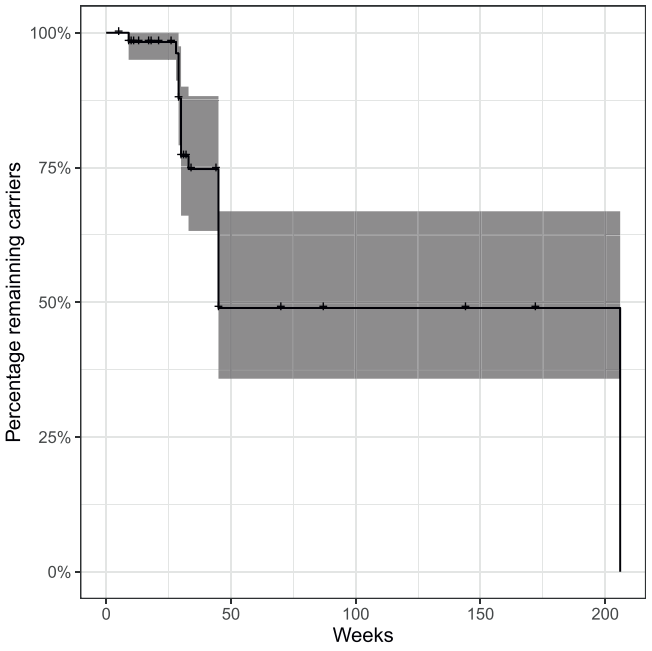

Fig. 2. Kaplan-Meier plot of duration of carriership, collated data (Newton et al., 1999; Pringle et al., 2019). Horses that were treated, died, or lost to follow up are censored (+).

paper does not make the inference that one in four horses do not mount lasting convalescent immunity, this interpretation was made explicitly later (Hamlen et al., 1994) and has since been cited in other work (Sheoran et al., 1997) and has been incorporated in both the first as well as the revised *S. equi* consensus statement (Sweeney et al., 2005; Boyle et al., 2018). In an infection-rechallenge experiment, when six ponies were re-challenged with a 10^{10} CFU intranasal dose 20 days after recovering from disease resulting from a 10^{8} CFU intranasal dose, all six ponies remained disease-free (Galan and Timoney, 1985), although it should be noted that 3/6 had received an immunisation course prior to the first intranasal challenge; the immunisation had failed to prevent clinical strangles in 10/10 of the ponies it had been administered to. A 1994 study described an infection experiment where 2/12 foals that had been previously among a herd of foals which experienced a strangles outbreak, were affected with clinical signs of strangles when re-exposed 6 months later (Hamlen et al., 1994). The proportion of poor responders in that experiment would be 1/6 or approximately 17%. The main drawback for extrapolation from the study by Hamlen *et al* is that its subjects were exclusively foals aged 5–7 weeks at the time of the initial outbreak, and they cannot be assumed to have had mature immune responses at that time and some may have benefited from protection by maternal antibodies, interfering with the development of acquired immunity. Furthermore, it is not entirely clear from that paper whether the previously exposed foals that demonstrated clinical signs of strangles in the second phase did or did not demonstrate clinical signs of strangles in the initial outbreak. In another study (Sheoran et al., 1997), local and serological protective antibody was demonstrated to last up to at least 28 weeks in convalescent horses after experimental infection by intranasal inoculation; within that time-span, these authors did not report observing a proportion of horses with markedly poor or rapidly declining immune responses. If such a marked bimodal distribution in the duration of convalescent immunity truly exists, then this affects the suitability of a simple SEIRS model, as possibly the *Recovered* compartment should be split into two, reflecting the long and short convalescent immunity. If a large proportion of animals returns to the *Susceptible* compartment soon after recovering from infection, epidemics might persist indefinitely.

Several options for immmunisation against *S. equi* currently exist. An extract vaccine (Hoffman et al., 1991), a live-attenuated vaccine (Borst et al., 2011) and a multi-component protein vaccine (Robinson et al., 2020) are commercially available, of which the latter demonstrated the highest clinical efficacy after experimental challenge of 94% after a course of three immunisation doses (Robinson et al., 2020).

The relative infectiousness of carriers compared to horses with typical strangles is a parameter for which no current estimate exists. Infectiousness depends on discharge of infectious material from airways or abscesses (Boyle et al., 2018), and therefore carriers, who produce much less discharge, may be less infectious than horses with strangles.

Compartmental deterministic models can provide insights into the likely range of unknown or uncertain parameters and be used to explore the effect of varying assumptions for a range of parameter values on model outcomes, and thus can highlight key areas of future (field) research. For example, Shi et al. (2023) recently published a mathematical stability analysis of a compartmental strangles model. As a case study, they applied it to reported disease incidence from an outbreak in an open herd with unknown, but probably variable levels of immunity against *S. equi* described by Christmann and Pink (2017).

Stochastic models can incorporate the effect of random events, to

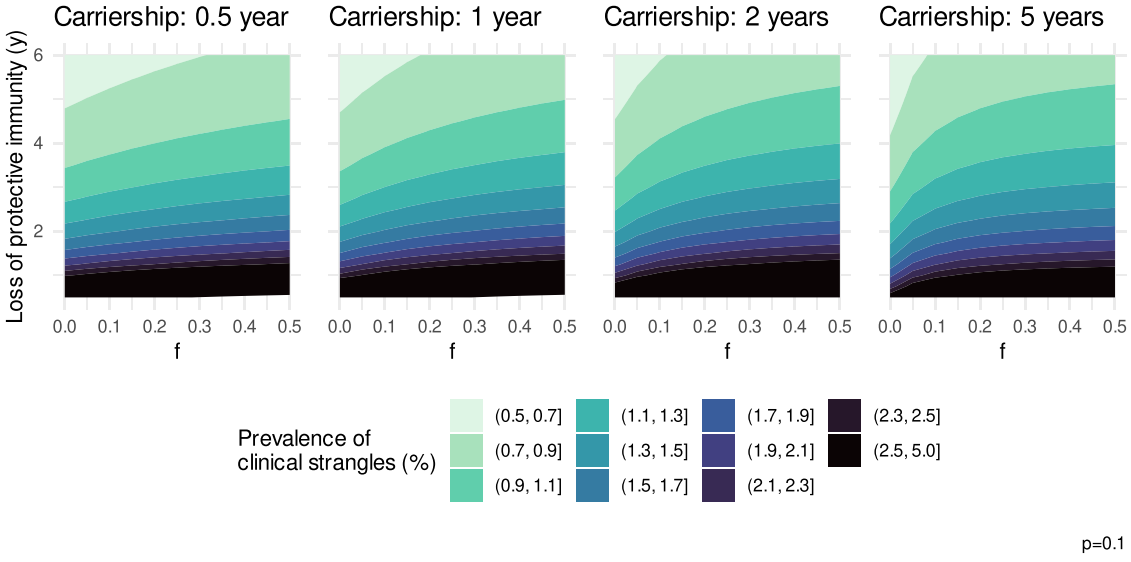

Fig. 3. Expected prevalence of strangles cases in a steady-state situation without control measures in the population.

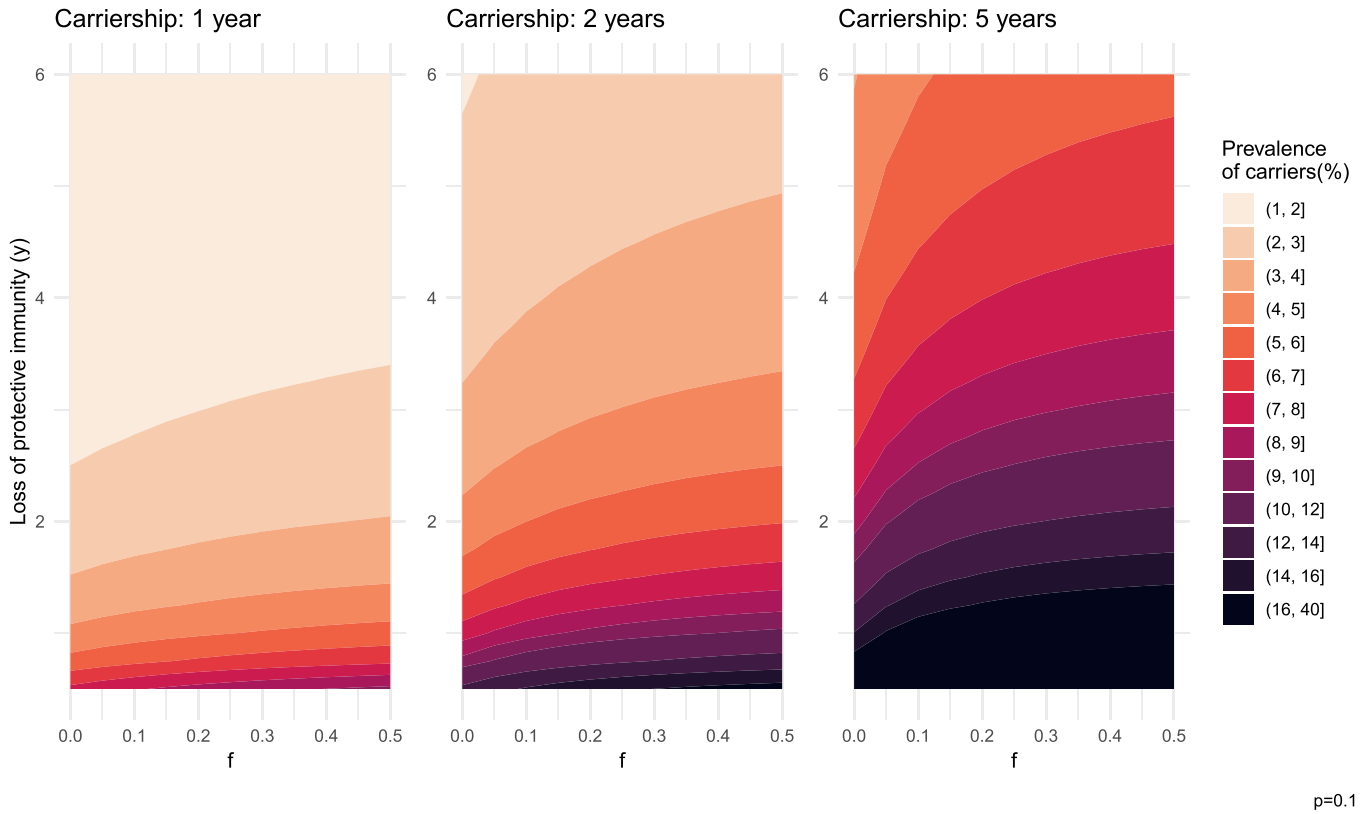

Fig. 4. Expected prevalence of apparently healthy horses shedding *S. equi* (carriers), in a steady-state situation without control measures in the population.

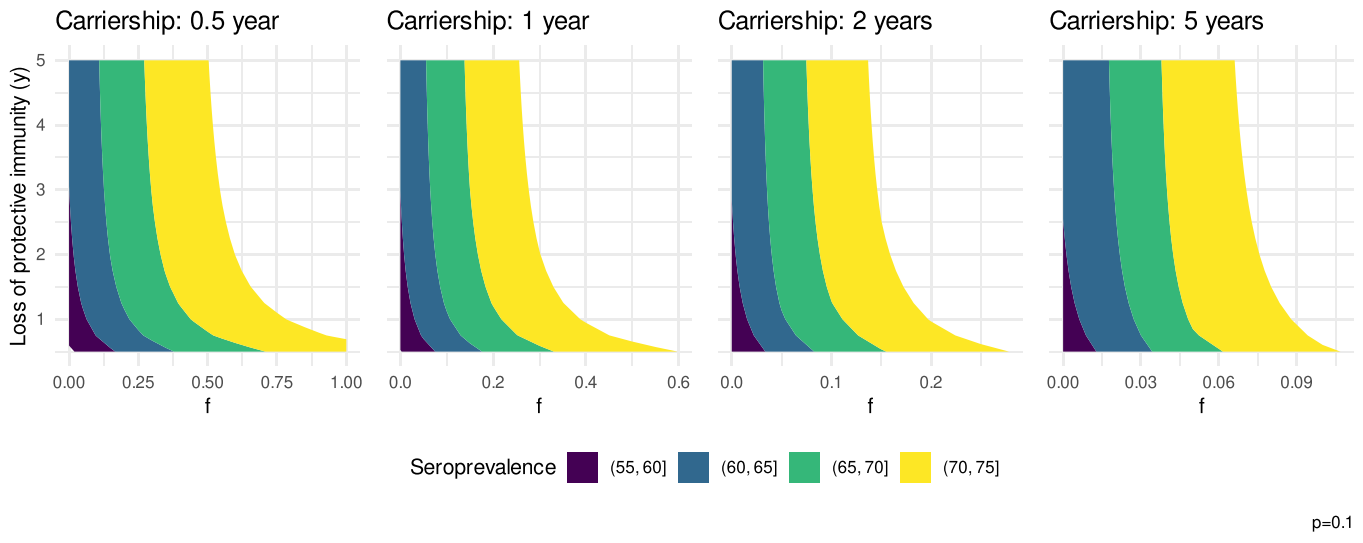

Fig. 5. Expected percentage of horses in the population with convalescent immunity, for a range of relative infectiousness of carriers (f) and γ_R. Note that the x-axis is not the same for different panels.

mimic the effect of chance in real world conditions, a feature which is inherently absent from deterministic models. Compartmental deterministic models are best suited to modelling dynamics in very large populations, as in smaller populations chance effects play a greater role. Agent-based (also termed individual-based) stochastic models are better suited to modelling smaller populations, can track each individual in the simulation and record how the events that occur during the simulation affect each individual in it. Over sufficient repetitions of runs of a stochastic model, a distribution of likely outcomes emerges.

Stochastic models (Glass et al., 2002; Machado et al., 2021; Baguelin et al., 2010) and even agent-based stochastic models (de la Rua-Domenech et al., 2000) have seen previous applications in the field of equine infectious disease research. The model applied by de la Rua-Domenech et al. unfortunately is not publicly available and is written in a proprietary programming language.

A parallel aim for this report was therefore to implement and validate a stochastic agent-based model of disease spread in equine populations in an open-source statistical computing language (R) with which many researchers have prior experience, improving accessibility and repeatability for further work.

Our main aims were to add precision to current estimates of key epidemiological parameters of *S. equi*, provide estimates for

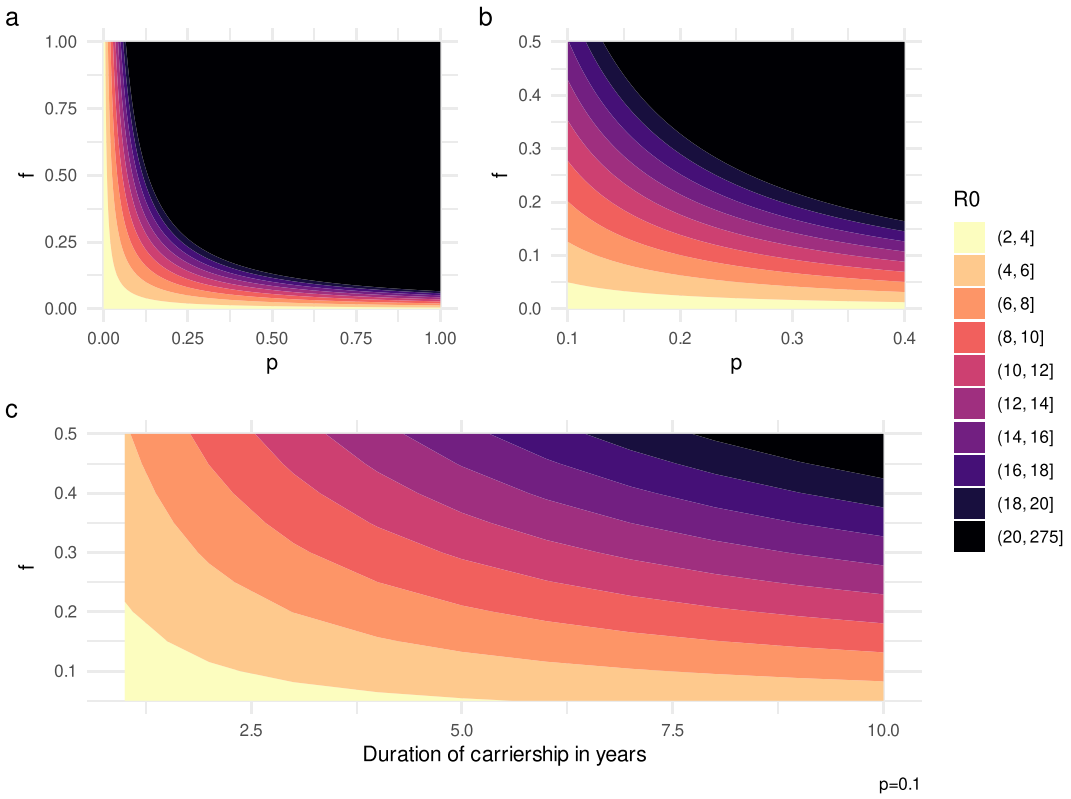

Fig. 6. (a) and (b); $R_0(p, f)$ at the population scale; (b) is a subsection of (a) where $p \in (0.1, 0.4)$ (Newton et al., 1997; Riihimäki et al., 2018; Jaramillo-Morales et al., 2022). For (a) and (b), $\gamma_C = 1/1825$ i.e. carriership duration of 5 years. (c): $R_0(\gamma_C, f)$ at the population scale; $p = 0.1$, $1/\gamma_C \in (1, 10)$.

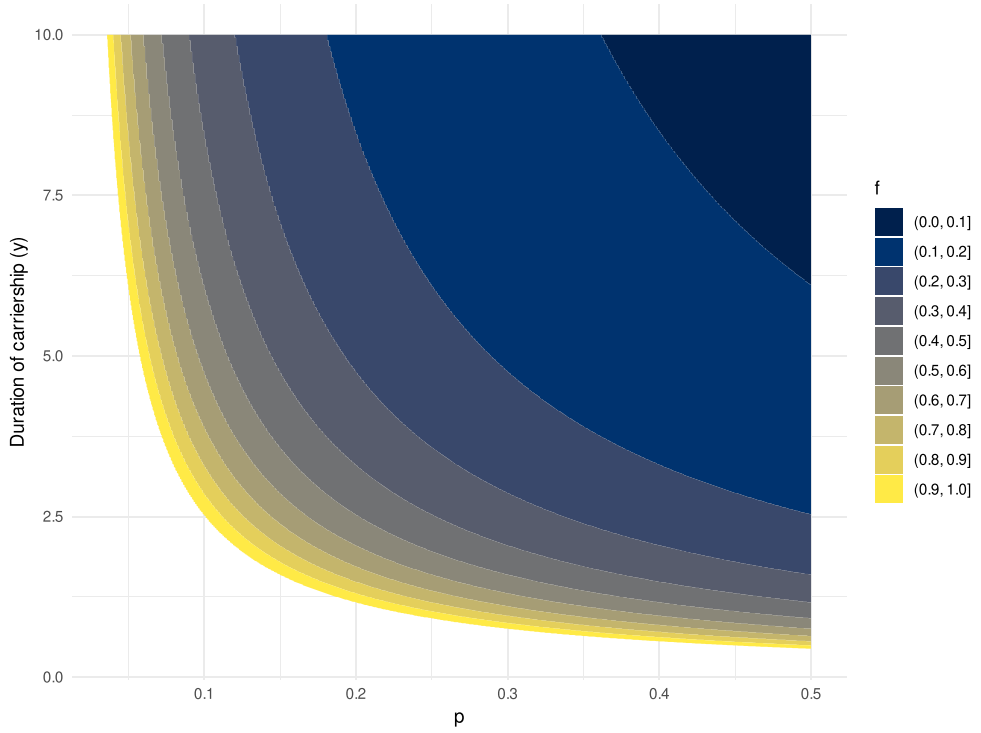

Fig. 7. A visualisation of the parameter values of p, γ_C, and f required to create a population-level $R_0 \geq 18$, which would give a herd immunity threshold $\geq 94\%$ (Robinson et al., 2020). The darker the shading, the less infectious carriers need to be to still arrive at $R_0 \geq 18$.

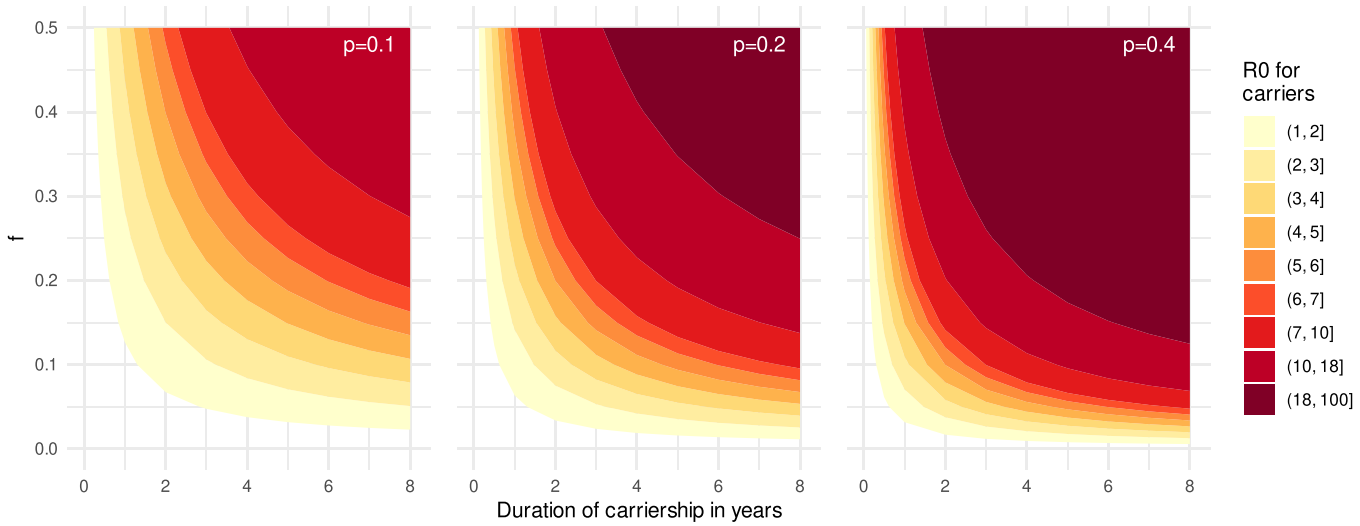

Fig. 8. *R* for carriers only (assuming all acute infections are identified and isolated instantly) for a range of duration of carriership, probability of becoming a carrier after infection (p) and relative infectiousness of carriers (f). In the non-shaded areas of the graph, $R < 1$.

epidemiological parameters which previously did not exist, and highlight key knowledge gaps in epidemiological parameters of *S. equi*.

2. Methods

A compartmental model for *S. equi* transmission was constructed (Figure 1). A review of available literature was carried out to find estimates for parameters required to inform the model, and for any prior descriptions of models for *S. equi* transmission dynamics. In addition, an agent-based stochastic model was constructed. All models were built in R version 4.1.2 (R Core Team, 2021). Differential equations were solved numerically using the deSolve (Soetaert et al., 2010) package.

2.1. Model parameterisation

Assumptions about parameter values and their sources are collated in Table 1.

Recovery after carriership, loss of protective immunity and other parameters that occur over time are, in mathematical modelling, considered as rates per unit of time, therefore $1/\gamma$, for example, gives the (mean) number of days it takes for a horse to recover from acute disease and infectiousness.

2.2. Compartmental deterministic model of S. equi

The model depicted in Figure 1 is described by differential equations (1) - (5) where S is susceptible, E is exposed but not infectious, I is infectious (strangles), I_C is infectious (carrier), R is recovered from infection, convalescent immunity, μ is the birth and death (natural causes) rate, α is the disease induced mortality rate, λ is the force of infection, σ is the rate of transition from E to I, p is the probability of becoming a carrier after infection, γ is the rate of recovering from acute disease, γ_c is the daily rate of horses losing carriership status, γ_R is rate of loss of convalescent protective immunity, N is the total number of horses. The following interventions are also incorporated into the model: κ which is the daily rate of removing horses with clinical disease from the general population and ω which is the daily rate of removing carriers from the general population.

$$\frac{dS}{dt} = \mu N + \alpha I - \frac{\beta SI}{N} - \frac{f\beta SI_C}{N} + \gamma_R R - \mu S \tag{1}$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} + \frac{f\beta SI_C}{N} - \sigma E - \mu E \tag{2}$$

$$\frac{dI}{dt} = \sigma E - \gamma I - \kappa I - \mu I - \alpha I \tag{3}$$

$$\frac{dR}{dt} = (1-p)\gamma I + \gamma_C I_C + \omega I_C + (1-p)\kappa I - \gamma_R R - \mu R \tag{4}$$

$$\frac{dI_c}{dt} = p\gamma I + p\kappa I - \gamma_C I_C - \omega I_C - \mu I_C \tag{5}$$

In this model, horses with new infections that are identified through screening for clinical signs (and presumably quarantined) are instantly transferred to their next compartment (R or I_C), skipping whatever remaining time they would have been ill and infectious but not contributing to new infections. This does result in infectious and ill horses no longer having the opportunity to die as a result of the disease during what would have been their remaining time in compartment I, which leads to a decrease in α. We considered the alternative option of adding a compartment Q with a fixed (obligatory) quarantine period with an α similar to the I compartment. However, this would have the effect of artificially inflating mortality due to disease. Given the low overall mortality due to disease, we opted to apply the first approach and let κ be a rate. ω, the rate at which convalescent horses are checked for carriership by (e.g. by guttural pouch sampling) is also a rate, which resembles reality as treatment of carriers is swift compared to γ_C.

Based on Equations (1) - (5), R_0 without interventions can be described as a function of p:

$$R_0(p) = \frac{\sigma}{\sigma+\mu} * \frac{\beta}{\gamma+\mu+\alpha} + p * \frac{\gamma}{\gamma+\mu+\alpha} * \frac{f\beta}{\gamma_c+\mu} \tag{6}$$

If the time-span is short enough to assume $p = 0$ (because no horse has had sufficient time passed since infection to be able to be considered a carrier), which was the case for $\widehat{R}_0 = 2.7$ (Houben et al., 2022) in new outbreaks, the second term on the right hand side of Equation (6) vanishes, and the contact parameter β can be directly calculated as:

$$\beta = R_0(0) * \frac{\sigma}{\sigma+\mu} * (\gamma+\mu+\alpha) \tag{7}$$

The force of infection is described by:

$$\lambda = \frac{\beta I}{N} + \frac{f\beta I_C}{N} \tag{8}$$

2.2.1. Dynamics at the population scale

Having calculated a contact parameter β using Equation (7),

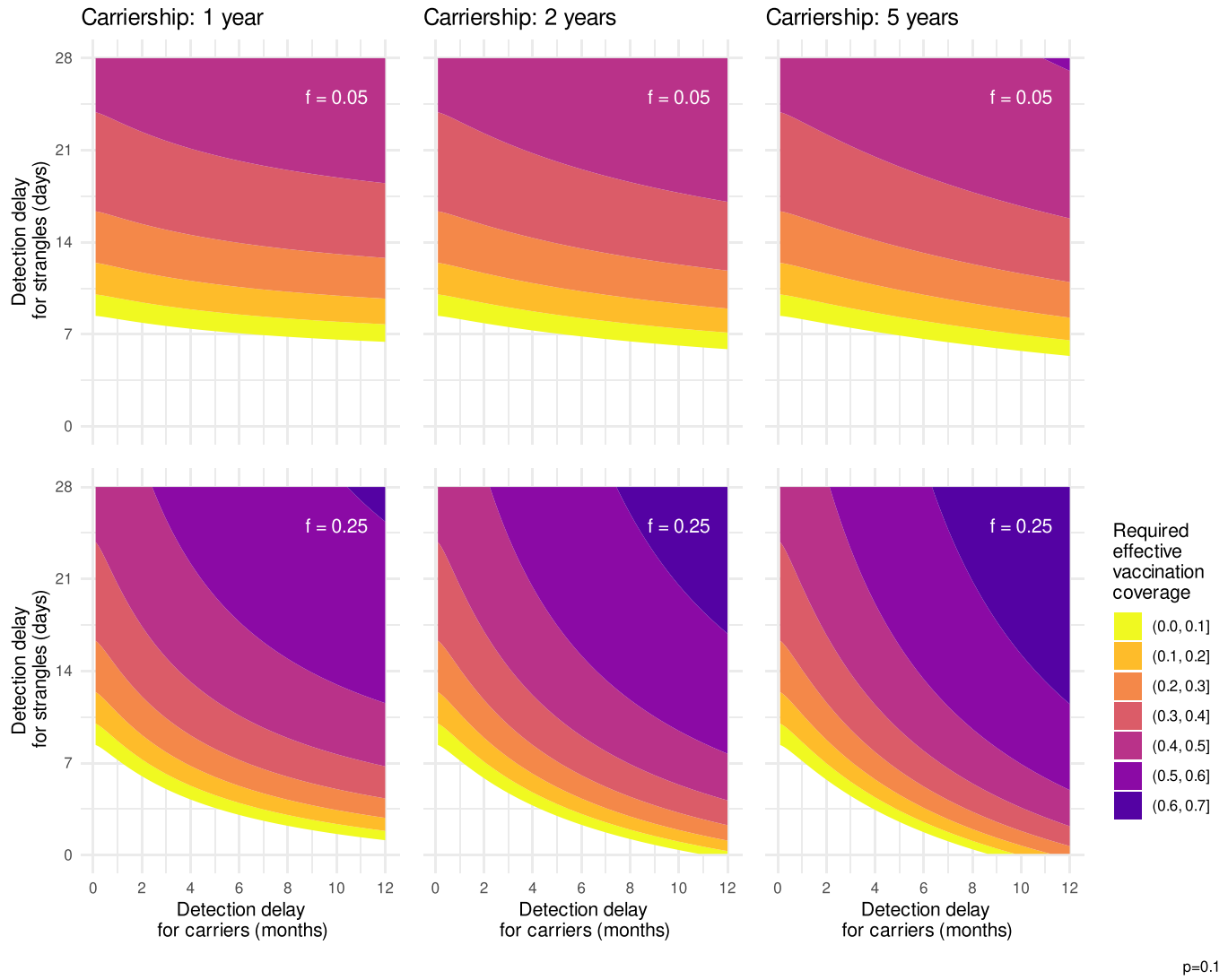

Fig. 9. Depiction of combinations of the delay in detection of acute cases ($1/\kappa$), delay in detection of convalescent carriers($1/\omega$), and vaccination coverage, required to achieve $R < 1$. The acute disease detection delay is given in days, the carrier detection delay is given in months. The non-shaded areas of the graph indicate combinations of parameter values for κ and ω that lead to an $R < 1$, indicating that the combination of acute disease and carrier detection is sufficient for $R < 1$. For combinations of parameter values in the shaded area of the graph, the shading colour indicates the level of vaccination required to prevent major outbreaks under those circumstances.

Equation (6) can be used to calculate R_0 for time-spans exceeding those of a single outbreak. The relative influence of unknown or uncertain parameters (f, p, γ_C, γ_R) on the final estimate of R_0 was evaluated. The compartmental model was run for 10,000 days (until a steady state was reached), at which point $(R + I_C)/N^*100$ at steady state was taken to be the expected seroprevalence, $(I_C)/N^*100$ the expected prevalence of carriers, and I/N^*100 the prevalence of animals with clinical signs of strangles. Results were compared to real-world observational data (Minai and Araghi-Sooreh, 2020; Todd, 1910).

Finally, the interventions presented in Figure 1 were used to construct the following equation for the reproduction number R in a population where control measures are active:

$$R = \frac{\sigma}{\sigma+\mu} * \frac{\beta}{\gamma+\mu+\alpha+\kappa} + p * \frac{\gamma}{\gamma+\alpha+\mu+\omega} * \frac{f\beta}{\gamma_c+\mu+\omega} \quad (9)$$

$R = 1$ was then computed for a range of assumptions for ω, κ, p and f. For this paper, vaccinations are not explicitly modelled but vaccination is evaluated in the context of the herd immunity threshold of $1 - \frac{1}{R}$. This implies the assumption of a perfect vaccine, with 100% efficacy for the prevention of both clinical disease and infectiousness. Although data is available on clinical efficacy of *S. equi* vaccines (Jacobs et al., 2000; Robinson et al., 2020), no quantitative data on the effect of vaccination on infectiousness or R is currently available. We therefore use the herd immunity threshold as a means to assess what vaccine efficacy would be required to achieve the effect of vaccination that is being modelled. Any interaction between vaccination, ω and κ was not evaluated.

2.3. Stochastic agent-based model

The stochastic agent-based model algorithm is described in the text box. In the agent-based stochastic model, values for μ, σ, γ_C and γ_R for different individuals are independent and identically distributed and drawn randomly from a Poisson distribution with a rate of $\lambda = Value$. γ_R is randomly and independently distributed with a Normal distribution; γ_R is also independent of the individual's prior infections or prior values for γ_R. Two implementations were trialled: For a model applying the Sellke construction (Diekmann et al., 2013) a horse acquires an infection if $\lambda > Q$ where Q is a an individual's threshold for becoming infected; Q is randomly drawn from an exponential distribution with a mean rate of 1 (Diekmann et al., 2013) and λ is recalculated for each time-step via

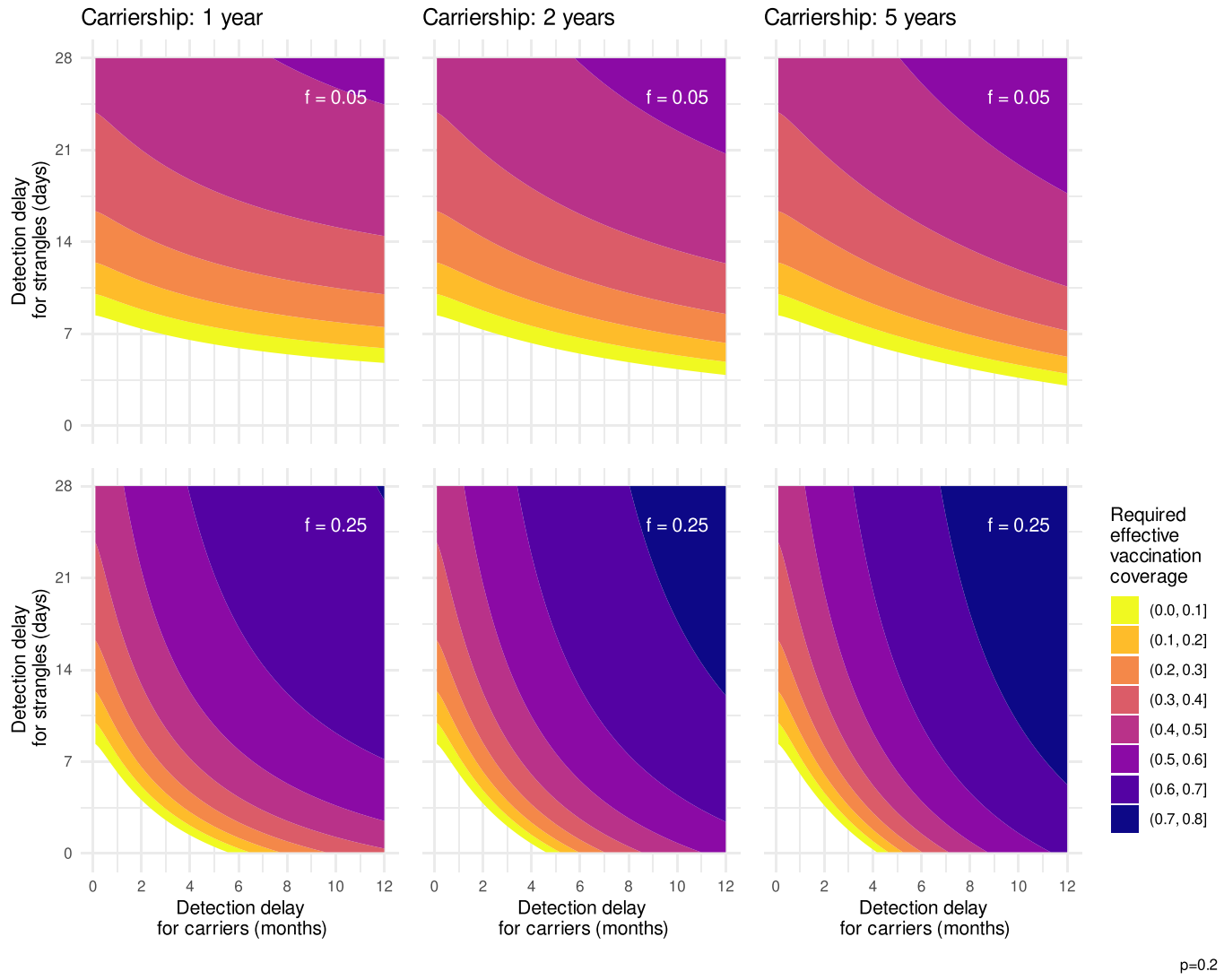

Fig. 10. As figure 9, but with $p = 0.2$.

Equation (8). For the second model, for all daily contacts between an infectious and susceptible individual (occurring at probability $\frac{SI}{N}$) a Bernoulli trial (Lequime et al., 2020) of $\beta > Q$; $Q \in (0, 1)$ (where Q is randomly drawn from a uniform distribution) determines whether the contact is successful. Discrete-time simulation with time steps of one day were applied for both implementations.

2.3.1. *Validation of the stochastic agent-based models*

The compartmental deterministic and individual-based stochastic models were run with parameter assumptions from Table 1 and compared to longitudinal incidence data from reports of naturally occurring outbreaks (Newton et al., 2000; Tscheschlok et al., 2018). The proportion of simulations resulting in an outbreak and the mean size of major outbreaks were compared to expected values, based on R_0 (Diekmann et al., 2013).

2.3.2. *Remount depot dynamics*

Since the interpretation that 1 in 4 horses do not mount lasting convalescent immunity, which was taken from Todd's data *a posteriori,* has not been substantiated since, the possibility of an alternative interpretation of the data was investigated. The necessity for the assumption of a bimodal distribution of the duration of convalescent immunity was assessed by reproducing the proportions observed in the remount depot described in Todd (1910). We wished to determine this to validate our choice for a single *Recovered* compartment in the compartmental deterministic model, instead of two *R* compartments each representing one of the fractions. A stable population of horses was assumed; no new horses were added throughout the simulation, and also there were no exits from the population; it is unclear whether horses entered and/or exited the population that is described by Todd (1910). It is also unclear from the report whether any outbreaks occurred in the four year observation period, but since only about a third of the population escaped infection ($1641/(2195 + 543 + 121 + 1641) = 0.36$) it is likely transmission of *S. equi* was ongoing during the observation period. As the immune status of the horses entering the remount in question is unknown, the proportion of horses that escaped infection throughout the four year period was ignored, as that quantity is dependent on the prior immune status of individuals in the herd at the start of the observation period. Instead, the recorded outcome, for each run of the simulation, was the proportion, out of all horses that presented signs at least once, that presented signs once, twice, or three times. These distributions were assessed for similarity to the distribution reported by Todd (1910) of 2195/2859 (77%), 543/2859 (19%), and 121/2859 (4%) respectively. An outbreak was seeded on the first day of the simulation in a fully susceptible population of 1000 adult horses without interventions and then run for four years. Parameters ($1/\sigma_L$, $1/\sigma_P$, γ, γ_C) were identically and independently distributed as described in Table 1

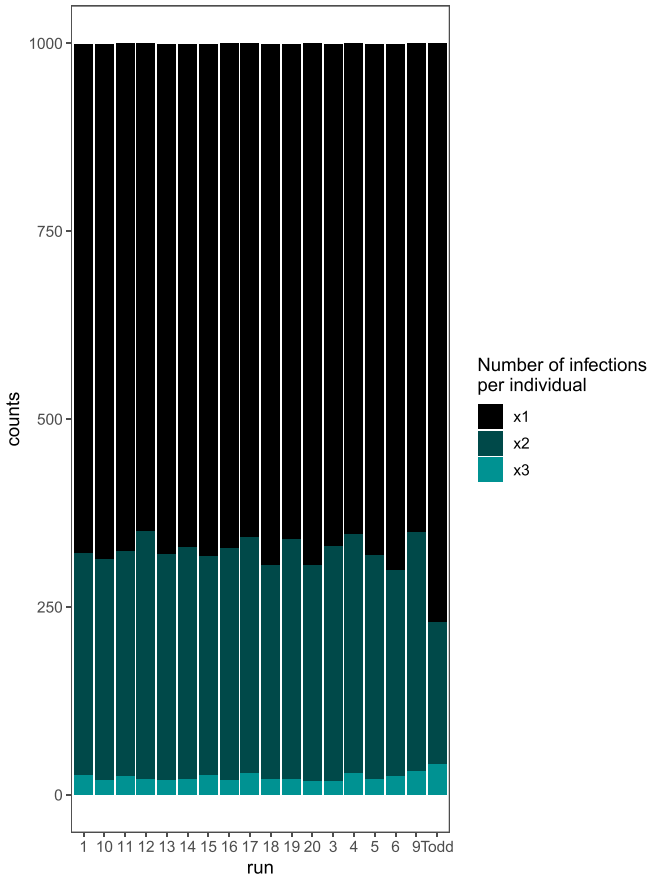

Fig. 11. Single four-year run outcomes of a remount depot simulation of 1000 adult horses, with $p = 0.1$, $f = 0.25$, $1/\gamma_R = 4 \pm 2$ years, $1/\gamma_{R_C} = 5$ years. Outcomes of the proportion of horses infected once, twice or three or more times are identified by colour and compared to the outcome reported by Todd (1910), which is provided in the column labelled Todd on the right.

and the text section Model parametrisation. A value for γ_R was assigned randomly for each infection; in other words, the assigned duration of protective immunity in a horse after a repeat infection was independent of the duration of protective immunity after a previous infection. This means that there was no assumption of consistent poor responders in the population.

3. Results

A Kaplan-Meier plot (Figure 2) of collated data from two reports of carriership duration (Newton et al., 1999; Pringle et al., 2019) shows that 50% of horses remain carriers between 1 and 4 years. As can be seen in the Kaplan-Meier plot, a large proportion of horses are censored; most censoring is because the horse is treated before it can self cure. We predominantly use the range of one to five years for the mean duration of carriership as model inputs.

3.1. Dynamics at the population scale

3.1.1. Expected range for mean duration of convalescent immunity, carriership, and f

The deterministic compartmental models were run until a steady state was reached, for a range of values of f, γ_C and γ_R, and with the value of p fixed at 0.1. The resulting prevalence of horses showing clinical signs of strangles (compartment I, at steady state) is presented in Figure 3. Neither γ_C nor f matters much here and the main driver of the outcome is the duration of convalescent immunity - in a large enough herd, the prevalence of infectious animals is so high that an animal can be expected to become re-infected soon after protective immunity has waned. Assuming a prevalence of clinical disease of 0.88% (Todd, 1910), the duration of protective immunity post-infection is estimated to be 4–6 years, depending on both f and γ_C, where the precise value for f is only of influence in the range of $0 < f < 0.5$.

In Figure 4 the expected prevalence of carriers, again in a steady state, is presented. These percentages are only expected to occur in populations where no control effort for *S. equi* is in place. Unfortunately, no suitable real-world data to compare these outcomes to was available; retrieved reports on carrier prevalence do not meet the assumption of no intervention or are not random cross-sectional surveys (Jaramillo-Morales et al., 2022; Durham and Kemp-Symonds, 2020; Libardoni et al., 2016).

The expected seroprevalence, as a proxy for convalescent immunity, in populations without control of *S. equi* is presented in Figure 5. As in the previous paragraphs, runs of the deterministic compartmental model until steady state were repeated for a range of values for f, γ_C and γ_R, and with $p = 0.1$.

Assuming that mean carrier duration is 0.5–5 years, and that convalescent immunity lasts ≥2 years and is measurable serologically (which for bacterial diseases is not always true), $\widehat{f} \in (0.05, 0.5)$. This estimate is based on the highest reported seroprevalence in (likely) non-vaccinated horses, which is 74% (Minai and Araghi-Sooreh, 2020). The results of repeating this analysis with $p = 0.2$ are presented in the Appendix (Figure A2). Another noteworthy conclusion from Figure 5 is that at least 55% of horses would expected to have convalescent immunity in this scenario of no control effort, regardless of f, γ_C and γ_R.

3.1.2. The basic reproduction number at the population scale

The dependency of population-level R_0 on p and f is visualised in Figure 6a and b. Figure 6b indicates that variation between the current best guess of $p \in (0.1, 0.4)$ is in the flat section of the graph and does not have much effect on R_0 unless f is high. This holds true for alternative assumptions of $1/\gamma_C \in (0.5, 10)$ years (Figure A1 in the Appendix). As the R_0 of 2.7 (Houben et al., 2022) for horses with acute disease (ignoring carriers altogether) was used to inform the parameters of this model, all estimates of R_0 incorporating infectious animals with acute disease as well as carriers are > 2.7.

A closer look with a smaller range for $f \in (0.05, 0.5)$; p fixed at 0.1; and $1/\gamma_C \in (1, 10)$ is shown in Figure 6c.

3.1.3. Could S. equi be eliminated by vaccination alone?

Figure 7 demonstrates the parameter values for f, γ_C and p that are required to arrive at a population-level $R_0 > 18$, the point at which the herd immunity threshold is $> 94\%$, which is higher than currently available vaccines can possibly achieve (Robinson et al., 2020). So if $R_0 > 18$, control and/or elimination of *S. equi* by vaccination alone is impossible and additional control measures will always be required besides vaccination. The non-shaded areas of the graph indicate a situation where $f > 1$ (i.e. carriers are *more* infectious than acutely ill animals) which is highly implausible; we can therefore safely assume that for those combinations of p, f and $1/\gamma_C$, R_0 will never be > 18.

3.1.4. Can carriers alone sustain endemicity c.q. can S. equi be eliminated without addressing carriers?

Figure 8 shows R for a range of values for f, γ_C and p, if acutely ill horses are assumed to have no role in epidemiology (due to, for example, immediate identification and isolation of acute cases) and $1/\gamma = 1$. In the non-shaded areas of the graph, $R_0 < 1$ which means that under those parameter assumptions, carriers alone would not suffice to keep *S. equi* endemic.

Figure 8 demonstrates that for this question, p is important. With $\widehat{p} = 0.4$, $R < 1$ for carriers only for very short (and implausible (Newton et al., 1997; Riihimäki et al., 2018) assumptions of $1/\gamma_C$ is R from carriers alone < 1. With $p = 0.1$ however, the non-shaded area of the graph

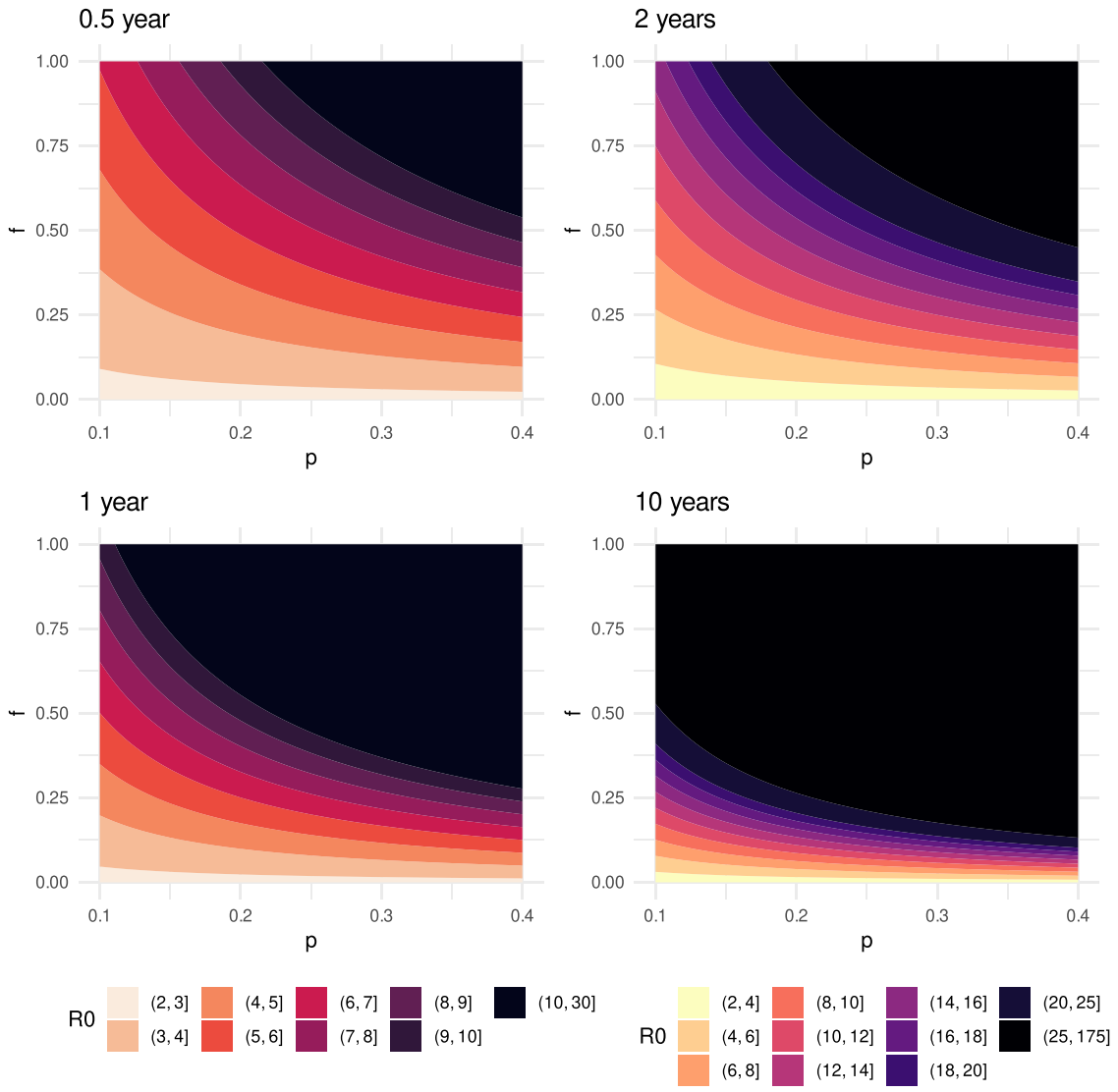

Fig. A1. A.12.

covers values of $1/\gamma_C$ and f that may apply for natural infections of *S. equi*.

3.1.5. Incorporating test-and-isolate and vaccination strategies

Results are presented in Figures 9 and 10. These graphs highlight that if all animals are screened for carriership prior to re-introduction to the herd (i.e. $\omega = 1$), an interval for screening for acute disease of ≈ 8 days should suffice to prevent the occurrence of major outbreaks. It becomes apparent that the assumption for γ_C matters less for the overall outcomes than those for f and p.

3.2. Stochastic model

3.2.1. Model validation

Steps taken to validate the stochastic model are presented in the Appendix.

3.2.2. Stochastic model of remount depot dynamics

The mean proportion of horses infected once, twice, or three or more times in 10 repeated runs of 1000 adult horses for a duration of 4 years are presented for $1/\gamma_{R_C}$ of 1 or 5 years, $1/\gamma_R$ of 1–6 years, and standard deviation for $1/\gamma_R$ of 1 or 2 years, is presented in a supplementary item (Figure A7). Figure 11 demonstrates that assuming $p = 0.1$, $f = 0.25$, $1/\gamma_C = 1825$ days, $1/\gamma_R = 1460 \pm 7$ days results in a distribution of horses infected once, twice, or three times over the course of four years which are similar the proportion given by Todd (1910). Variation in assumptions for $p \in (0.1, 0.4)$ and $f \in (0.1, 0.5)$ had minimal effect on the overall outcome (Appendix Figure A7).

4. Discussion

Expected range for mean duration of convalescent immunity, carriership, and f

For the duration of convalescent immunity, the range of 4–6 years drawn from the simulations in Figure 3 are similar to existing assumptions on the duration of convalescent immunity (Waller et al., 2014).

It should be noted here that estimates (for f and $1/\gamma_R$) are based on assumptions that in the populations where the highest seroprevalence was recorded, horses were able to mix unhindered and no effort was made to control *S. equi*, which may be incorrect. In addition, carrier horses were assumed to consistently have detectable antibody titers, which also may be incorrect (Gröndahl et al., 2015; Durham and Kemp-Symonds, 2020). More data on seroprevalence in stable herds were *S. equi* is uncontrolled could increase the precision of $\widehat{f}$ achieved by modelling.

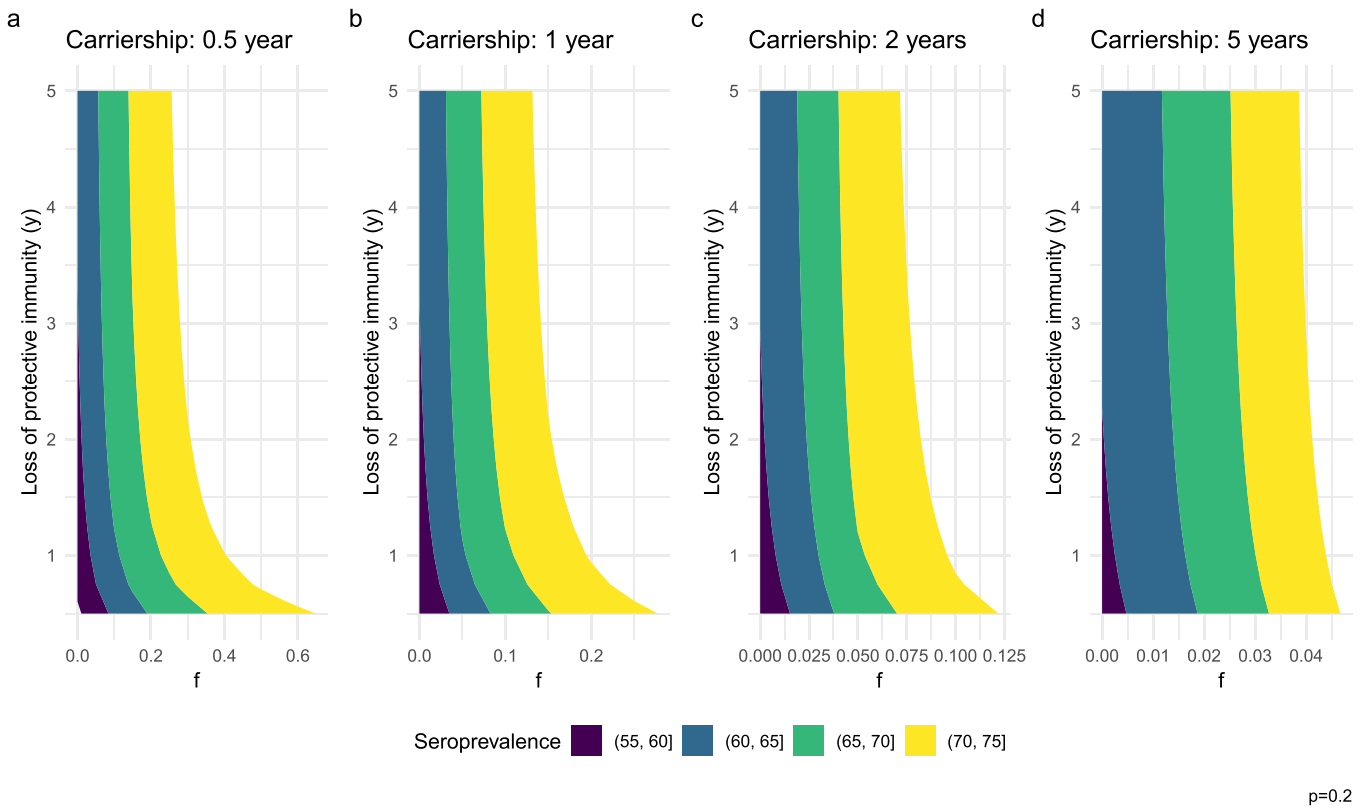

Fig. A2. A.13.

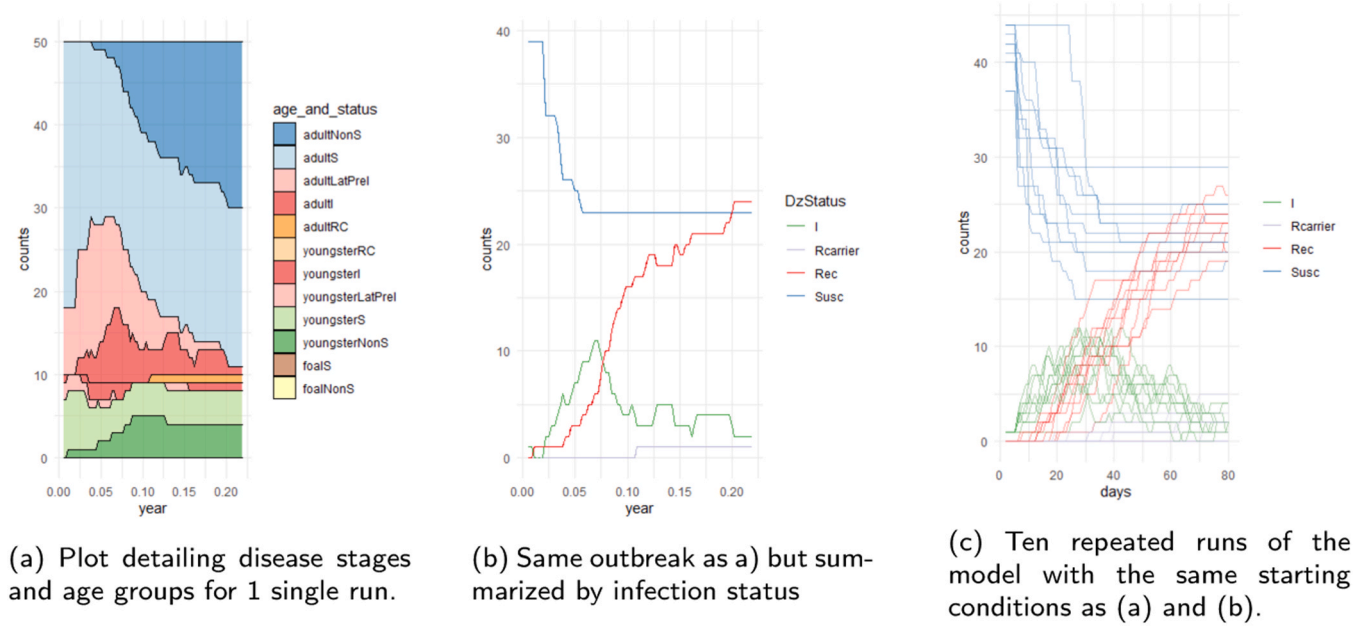

Fig. A3. Runs of the individual-based stochastic model with 10 young horses and 40 adults.

Our estimate of $\beta = 0.199$ was derived from an estimate for R_0 from previous work (Houben et al., 2022) which was a weighted mean of individual R_0 estimates from outbreaks in naive herds. It differs substantially from the estimate by Shi et al. of $\beta = 4.091 \times 10^{-3}$. However, in the simulation from Shi et al. it was assumed that all horses present at the breeding farm or newly arrived during the months of the outbreak were fully susceptible, which may not be a correct assumption, as their actual immune status and strangles history were not reported in the original outbreak report. If a substantial proportion of the horses is assumed to be susceptible but is in fact not, the resulting estimate of β may be an underestimation. The model used in the present manuscript was more simple than the model applied by Shi et al. as our aims were principally to estimate ranges for key epidemiological parameters rather than to fit our model to specific circumstances.

Our estimated range for $f \in (0.1, 0.5)$ is substantially higher than the 4.86×10^{-4} of Shi et al.. One reason why the estimate by Shi et al. may

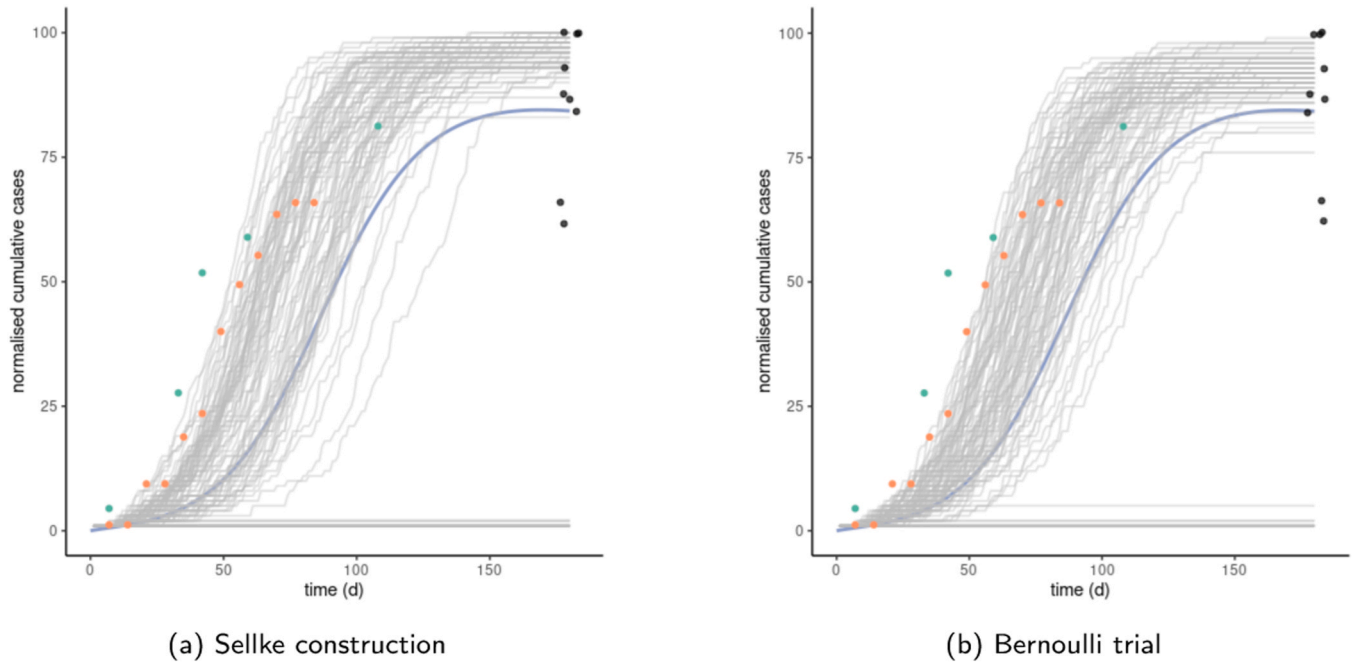

Fig. A4. Deterministic compartmental model prediction (blue line), repeated runs of the stochastic model in a herd of 100 group housed adults (grey lines) and two naturally occurring outbreaks in green (Tscheschlok et al., 2018) and orange (Newton et al., 2000) dots (with number of animals normalised to 100), showing the cumulative number of cases for the exponential part of the outbreak, for both the model applying the Sellke construction (a) and the model applying a Bernoulli trial to determine successful contacts (b).

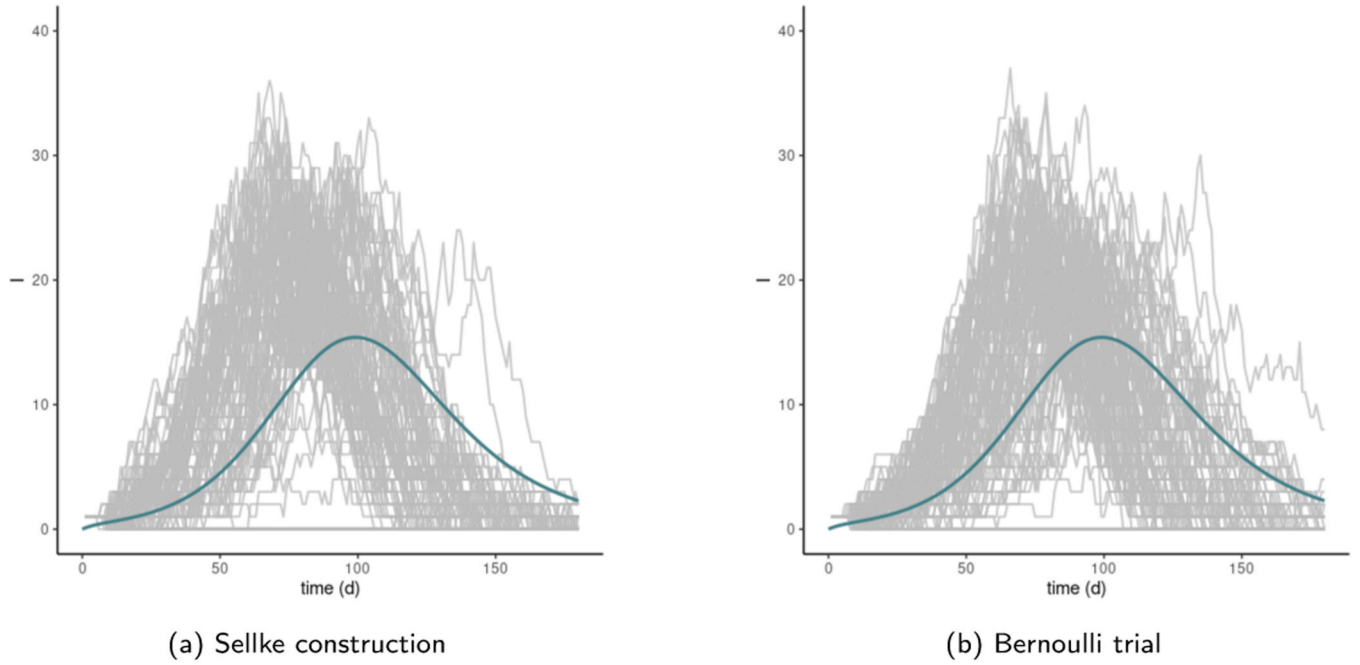

Fig. A5. Deterministic compartmental model prediction (green line), repeated runs of the stochastic model in a herd of 100 group housed adults (grey lines), for both the model applying the Sellke construction (a) and the model applying a Bernoulli trial to determine successful contacts (b).

be incorrect is their assumption that the total of four horses which during the course of the several-months long outbreak were diagnosed with some form of guttural pouch pathology, were in fact strangles carriers at the start of the outbreak, even though the authors of the outbreak report described that these were sequelae of strangles episodes during the outbreak.

Figure 4 can be compared to reports of *S. equi* positives on cross-sectional surveys, in herds where it is likely no control effort for *S. equi* is in place, such as Jaramillo-Morales et al. (2022) and Libardoni et al. (2016) which reported 13.5% and 2.3% respectively. There are important caveats to extrapolating from these studies however. Libardoni et al. reports PCR results of nasal swabs of 1010 apparently healthy equines from 341 farms in Rio Grande, Brazil and Jaramillo-Morales et al. reports culture results of endoscopically-guided guttural pouch swabs from 137 horses from 15 farms. Results from both studies were likely affected by clustering of samples within farms, as for *S. equi*, it is

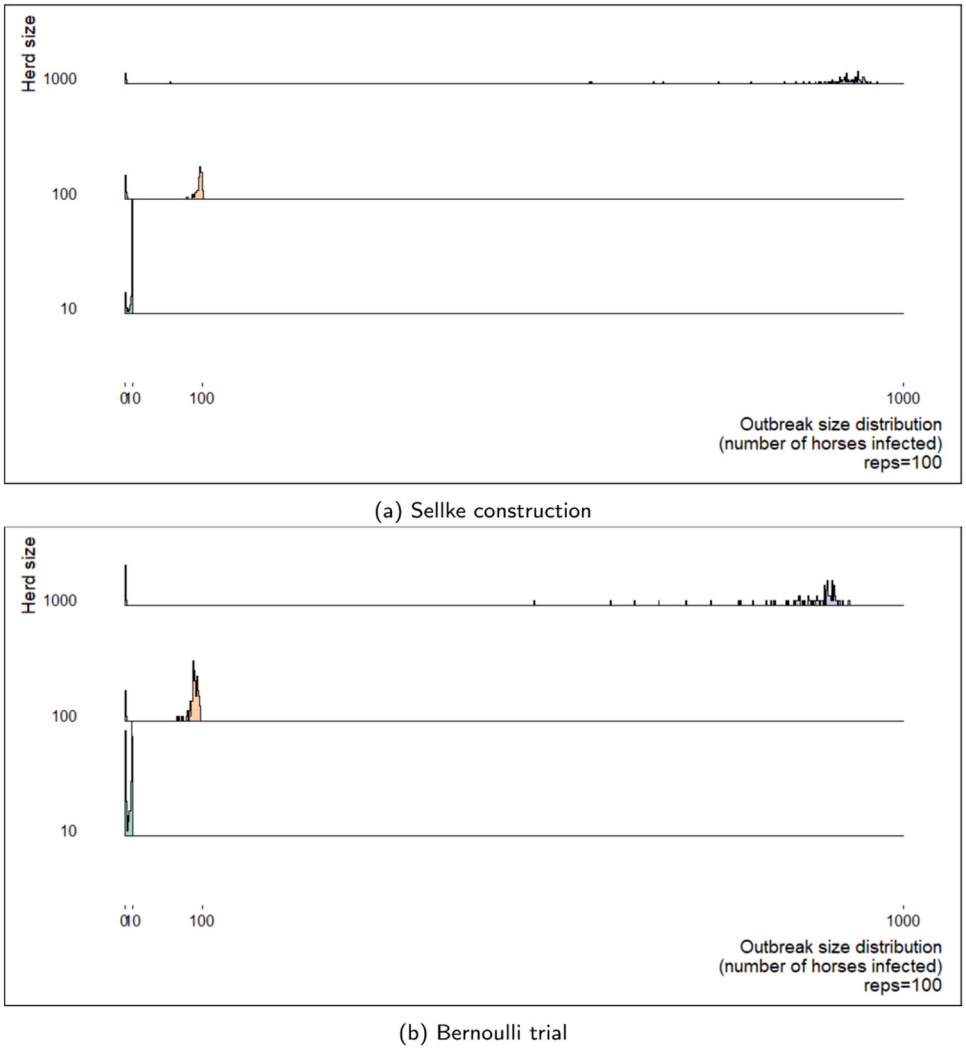

Fig. A6. Plots demonstrating the binomial distribution of outbreak size of (a) the Sellke construction and (b) the Bernoulli trial method.

Table A1
Performance of the stochastic models; 100 runs in herds of 1000 horses for 150 days.

Method	Bernoulli	Sellke	Expected
Proportion of major outbreaks	0.87	0.90	0.915[a] or 0.63[b]
Mean size of major outbreaks	863	916	915
Runtime (s)	7971	8657	N/a

[a] For Reed-Frost model or
[b] general stochastic epidemic (Diekmann et al., 2013)

likely that the presence of one positive animal on the farm influences the likelihood of other horses on the farm testing positive. Jaramillo-Morales et al. tested 9 animals per farm, and Libardoni et al. tested 3 animals per farm, on average, indicating that the prior study is more prone to distortion of results by clustering than the latter. Secondly, the method of diagnosis of shedding influences sensitivity of testing (Pringle et al., 2019). Neither report applied the gold standard of guttural pouch lavage and PCR of the acquired sample, therefore both were affected by decreased sensitivity (compared to the reference standard), and their results were likely underestimations. Considering the issues affecting these two studies, it is difficult to draw meaningful conclusions on the likely values of $1/\gamma_R$ or f based on these two reports. The carrier prevalence of 13.5% from Jaramillo-Morales et al. does not really fit with any of other estimates derived from the models - a prevalence this high would only be possible with a much shorter duration of convalescent immunity. The report of 2.3% Libardoni et al. would fit with our other assumptions if $1/\gamma_R \approx 2$ years, but this prevalence was established using an insensitive detection method and is likely an underestimation. We must therefore conclude that there currently is insufficient real-world data that can be used to compare to the model outcome parameters.

The basic reproduction number at the population scale

The expected range for R_0 at the population scale remains wide. When assuming $p = 0.1$, $1/\gamma_C \in (1, 10)$ years and $f \in (0.05, 0.25)$, $4.3 < \widehat{R}_0 < 13.2$). It is clear, therefore, that further precision for these estimates is needed to be able to come to a truly usable estimate for the effort required to control (or eradicate) strangles.

Could S. equi be eradicated by vaccination alone?

If $p = 0.1$, the mean duration of carriership would need to be < 2.5 years for eradication of *S. equi* to be possible by vaccination alone, assuming 100% of animals is vaccinated with a vaccine with an efficacy of 94% (Robinson et al., 2020). If p is actually closer to 0.2, then the mean carrier duration would need to be half that. Of course, it is unlikely that it will ever be possible to achieve a vaccination coverage of 100%, nor is it likely that carriers would remain unaddressed in any eradication effort.

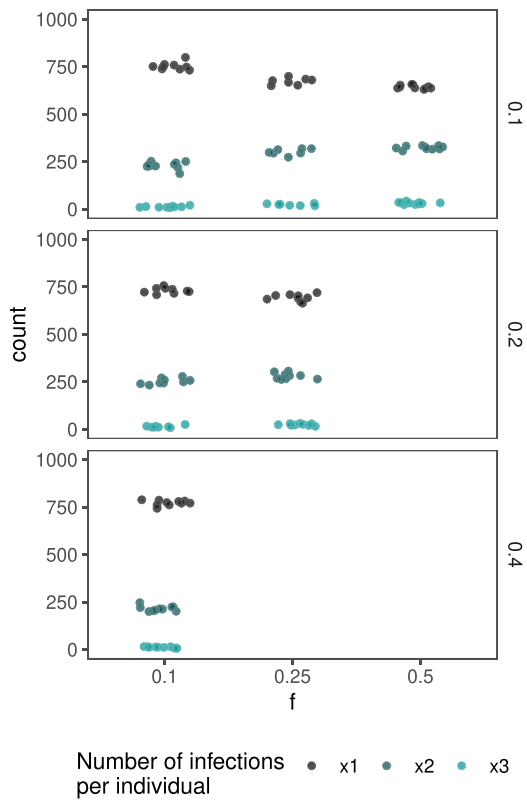

Fig. A7. Number of horses infected once, twice, or three times when simulating a remount depot of 1000 horses over a period of 4 years, effect of f (columns) and p (rows) on outcome. Each dot represents the final tally of one run. γ_R is fixed at 4 ± 2 years and γ_{R_c} at 5 years.

Can carriers alone sustain endemicity?

Carriers are assumed to play an important role in endemicity of strangles (Newton et al., 1997; Mitchell et al., 2021), but their importance in *S. equi* epidemiology has so far not been quantified. From Figure 8, and with information gained from Figure 5 that $0.05 < f < 0.5$, mean carrier duration would need to be ≈ 3 years or less for $R_0 < 1$. With p=0.2, it is ≈ 14 months. With higher $\widehat{f}$, the tolerance for carriers decreases, but f may be as low as 0.05. In the absence of good data or estimates on the mean duration of carriership, it is not possible to conclude with certainty whether carriers on their own suffice to keep $R_0 > 1$ and to keep *S. equi* endemic. Control efforts which ignore the carrier state may therefore be unsuccessful.

Incorporating test-and-isolate and vaccination strategies

The range of combinations of ω and κ which result in $R < 1$ can be considered favourable. For large, extensively managed herds, a weekly check for clinical signs of strangles (including fever) would suffice to prevent outbreaks occurring, as long as all affected horses are screened and treated for carriership after clinical disease, prior to re-introduction into the herd. If for example, checks for strangles are performed daily, there exists a tolerance for a prolonged presence of carriers in the herd at least for the lower ranges of f. This might explain why, for example, the *S. equi* screening process described by de Brauwere and Kirton (2019) was highly successful at preventing strangles outbreaks, despite relying on serological screening for carriers before allowing horses into the herd, which has been demonstrated to be an imperfect predictor of carriership (Durham and Kemp-Symonds, 2020). This study did not investigate the effect of vaccination on transmission dynamics and only provided an insight into the vaccine coverage that would be required for a perfect (protection against disease and protection against infectiousness) vaccine. Future work could explicitly explore the effects of vaccines when realistic estimates their effectiveness during field use are available.

For the scenarios with higher p and f, it becomes apparent that currently available vaccines might not suffice to prevent major outbreaks under those circumstances. Vaccine efficacy (both in terms of reduction of clinical signs and infectiousness) would need to be up to 80% which may be difficult to achieve with currently available vaccines, based on data from experimental challenge studies that used a high infectious dose. Future data from the use of vaccination to prevent outbreaks of natural infection are required in order to determine the actual impact of vaccination strategies.

When interpreting the results from Figures 9 and Figures 10, it is important to note here that an absence of major outbreaks does not mean absence of transmission; if $R < 1$ minor outbreaks (short outbreak chains) are still possible, but the number of infected individuals will not be in the same order of magnitude as the number of individuals at risk at the start of the outbreak. However, in future work evaluating cost-benefit of prevention strategies, the monetary and reputations costs of even a minor outbreak should be taken into consideration as well.

Our results here are similar to those of Shi et al. (2023) who concluded that screening was the most effective measure.

Remount depot dynamics

The results from the agent-based stochastic simulation in Figure 11 suggest that the current assumption that there must be a bimodal distribution for the duration of convalescent protective immunity may be incorrect and that future modelling studies do not need to incorporate this assumption. When assuming a duration of convalescent protective immunity of 4 years with a standard deviation of 2 years, only 6.7% of

Stochastic model pseudocode

Read disease parameters

Create horses

- assign latency and infectious period (random draw from poisson distribution)
- assign duration of carriership (random draw from poisson distribution)

Start day simulations (repeat until required number of days is reached)

- disease status evolution (latent to infectious, infectious to recovered, etc)
- infect new horses (see text for description) and write to record
- collate daily totals, write daily record

infections leads to immunity of < 365 days and 3.9% of infections leads to protective immunity of < 180 days. The results presented in Figure 11 suggests the assumption that 25% of horses fail to mount a protective immune response after natural infection does not need to be true to explain the results cited by Todd (1910) over a four-year period. In our model to replicate Todd's data, we did not account for the possibility that during the observation period, other infectious diseases besides *S. equi* were circulating and may have contributed to some clinical respiratory disease. We cannot know whether or not this was the case, but it is worth pointing out that the interpretation of the data that says 25% of horses do not mount convalescent immunity also does not account for the circulation of other infectious agents causes respiratory disease. Furthermore, the presence of persistently infected carriers within these populations may have re-stimulated the immune responses of recovered horses, such that they may have appeared to have maintained protective immunity for longer. Although these remount depot incidence data may be old, they are reliable and were also acquired under circumstances where control of the disease appears to have been near absent, making them good reference data for this simulation.

This finding should be considered good news; if it were true that a large proportion of the population fails to mount an immune response of substantial duration after natural disease, then there may be concerns as to whether a significant proportion of vaccinated horses are likewise poor responders. Results from vaccine efficacy trials (Jacobs et al., 2000; Robinson et al., 2020) did not indicate such an effect, which is consistent with the findings from this simulation. The findings from our stochastic agent-based model provide clarity for future work in mathematical modelling of *S. equi* on the input parameter of convalescent immunity.

4.1. Main limitations

The mean duration of infectiousness chosen as a starting parameter was 14 days in all analyses in this paper, while acknowledging that an assumption of infectiousness of two weeks may seem short when infectiousness can last up to six weeks (Boyle et al., 2018). However, the period of two weeks was chosen to reflect the observation that infectiousness probably is highest over a shorter period, when the production of infectious discharge is greatest. In this paper, β was calculated directly from $\widehat{R}$ and $1/\gamma$; therefore, a longer assumption for γ would have led to a lower $\widehat{\beta}$, with little to no change on most of the other findings in this paper. The only deterministic model-based outcomes that would have been obviously affected are those in Figure 9 and Figure 10, where the intersection with the y-axis would change corresponding to the change in $\widehat{\gamma_R}$. To incorporate the assumption of decreasing infectiousness over a longer time, a two-phase approach for $\widehat{\beta}$ could have been chosen: higher in the first weeks, lower in later weeks. However, this approach was considered unnecessarily detailed for the current purposes of the model. It can be considered for future implementations.

Some questions were omitted from analyses in the current study. For one, the potential influence of the presence of carriers in the herd on the duration of convalescent immunity in herdmates was not investigated.

5. Conclusion

Through compartmental deterministic modelling, this study made an estimate of the duration for convalescent immunity of 4–6 years, and that carriers may be up to 20 times less infectious than horses with strangles. Through stochastic modelling, we have demonstrated that it is not necessary to assume that 1/4 convalescent horses fail to mount an effective immune response after infection. Further, this study has highlighted the importance of a more precise estimate for the duration of convalescent immunity, of relative infectiousness of carriers, and, to a lesser extent, the probability of becoming a carrier after infection and the duration of carriership. We have provided predictions as to which combinations of intensity of screening and/or vaccination will result in the prevention of major outbreaks, showing that weekly screenings might suffice in otherwise ideal circumstances. In our worst-case scenarios, we demonstrated that vaccination alone may not be able to prevent the occurrence of major outbreaks.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Waller reports a relationship with Intervacc AB that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Additional deterministic model output figures

Figures A1 - A2.

A.1. Stochastic model validation

Example simulation outputs are shown in Figure A3

Predictions from the deterministic compartmental and repeated runs of stochastic models are displayed in Figure A5, and compared to to two naturally occurring outbreaks (Newton et al., 2000; Tscheschlok et al., 2018) in Figure A4. Table A1 lists model metrics of performance. Figure A6 demonstrates the expected bimodal distribution of outbreak final sizes is present in both versions of the stochastic model Fig. A5, Fig. A6.

Because of the threshold properties of the prototype stochastic model, on which the current stochastic model is based, a two-point distribution of outbreak final sizes in individual simulation runs is expected, with either outbreaks where only a handful of individuals get infected, and larger outbreaks where the number of individuals that become infected over the course of the epidemic is in the order of magnitude of the population size at the start. The probability and eventual size of a major outbreak can be predicted based on R_0 (Diekmann et al., 2013). For sufficiently large populations, the probability of only a minor outbreak occurring can be calculated as the smallest solution to $\theta = e^{-R_0(1-\theta)}$ and the final size of major outbreaks as the positive solution to $x = 1 - e^{-R_0 x}$ (Diekmann et al., 2013). The results for both implementations of the model are provided in Table A1

A.2. Results from remount depot simulations

Figure A7.

References

Baguelin, M., Newton, J.R., Demiris, N., Daly, J., Mumford, J.A., Wood, J.L.N., 2010. Control of equine influenza: scenario testing using a realistic metapopulation model of spread. J. R. Soc. Interface 7, 67–79. https://doi.org/10.1098/rsif.2009.0030. ⟨http://rsif.royalsocietypublishing.org/content/7/42/67⟩.

Borst, L.B., Patterson, S.K., Lanka, S., Barger, A.M., Fredrickson, R.L., Maddox, C.W., 2011. Evaluation of a commercially available modified-live streptococcus equi subsp equi vaccine in ponies. Am. J. Vet. Res. 72, 1130–1138. https://doi.org/10.2460/ajvr.72.8.1130 (publisher: American Veterinary Medical Association).

Boyle, A., Timoney, J., Newton, J., Hines, M., Waller, A., Buchanan, B., 2018. Streptococcus equi infections in horses: Guidelines for treatment, control, and prevention of strangles–revised consensus statement. J. Vet. Intern Med 32, 633–647. https://doi.org/10.1111/jvim.15043. ⟨https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5867011/⟩.

de Brauwere, N., Kirton, R., 2019.Prevention of the carrier state; strangles screening and outbreak management in the UKas largest horse sanctuary, In: Dorothy Havemeyer Foundation Workshop Getting to grips with strangles and other streptococcal diseases., n/a.

Christmann, U., Pink, C., 2017. Lessons learned from a strangles outbreak on a large standardbred farm. Equine Vet. Educ. 29, 138–143. https://doi.org/10.1111/eve.12451.

Delph, K.M., Beard, L.A., Trimble, A.C., Sutter, M.E., Timoney, J.F., Morrow, J.K., 2019. Strangles, convalescent streptococcus equi subspecies equi m antibody titers, and presence of complications. J. Vet. Intern. Med. 33, 275–279. https://doi.org/10.1111/jvim.15388. ⟨https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6335513/⟩.

Diekmann, O., Heesterbeek, H., Britton, T., 2013.Mathematical Tools for Understanding Infectious Disease Dynamics: Ch 13.⟨https://www.jstor.org/stable/j.cttq9530⟩.

Durham, A.E., Kemp-Symonds, J., 2020.Failure of serological testing for antigens a and c of streptococcus equi subspecies equi to identify guttural pouch carriers.Equine Veterinary Journal n/a. 10.1111/evj.13276.

Galan, J.E., Timoney, J.F., 1985. Mucosal nasopharyngeal immune responses of horses to protein antigens of streptococcus equi. Infect. Immun. 47, 623–628. ⟨https://www.ncbi.nlm.nih.gov/pmc/articles/PMC261338/⟩.

Glass, K., Wood, J.L.N., Mumford, J.A., Jesset, D., Grenfell, B.T., 2002. Modelling equine influenza 1: a stochastic model of within-yard epidemics. Epidemiol. Infect. 128, 491–502. https://doi.org/10.1017/S0950268802006829.

Gröndahl, G., Båverud, V., Ljung, H., Melys, V., Aspán, A., Riihimäki, M., 2015. Longitudinal observations of silent carriers of streptococcus equi in a swedish yard. Equine Vet. J. 47, 22. https://doi.org/10.1111/evj.12486_50.

Hamlen, H.J., Timoney, J.F., Bell, R.J., 1994. Epidemiologic and immunologic characteristics of streptococcus equi infection in foals. J. Am. Vet. Med. Assoc. 204, 768–775.

Hoffman, A.M., Staempfli, H.R., Prescott, J.F., Viel, L., 1991. Field evaluation of a commercial m-protein vaccine against streptococcus equi infection in foals. Am. J. Vet. Res. 52.

Houben, R.M.A.C., van Maanen, C., Kemp-Symonds, J., Waller, A.S., Sloet van Oldruitenborgh-Oosterbaan, M.M., Heesterbeek, J.a.P., 2022.Estimation of the basic reproduction number for streptococcus equi spp equi outbreaks by meta-analysis of strangles outbreak reports.Equine Veterinary Journal 10.1111/evj.13865.

Jacobs, A.a.C., Goovaerts, D., Nuijten, P.J.M., Theelen, R.P.H., Hartford, O.M., Foster, T. J., 2000. Investigations towards an efficacious and safe strangles vaccine: submucosal vaccination with a live attenuated streptococcus equi. Vet. Rec. 147, 563–567. https://doi.org/10.1136/vr.147.20.563. ⟨https://veterinaryrecord.bmj.com/content/147/20/563⟩.

Jaramillo-Morales, C., Gomez, D.E., Renaud, D., Arroyo, L.G., 2022. Streptococcus equi culture prevalence, associated risk factors and antimicrobial susceptibility in a horse population from colombia. J. Equine Vet. Sci. 111, 103890 https://doi.org/10.1016/j.jevs.2022.103890. ⟨https://www.sciencedirect.com/science/article/pii/S0737080622000284⟩.

Lequime, S., Bastide, P., Dellicour, S., Lemey, P., Baele, G., 2020. nosoi: A stochastic agent-based transmission chain simulation framework in r. Methods Ecol. Evol. 11, 1002–1007. https://doi.org/10.1111/2041-210X.13422.

Libardoni, F., Machado, G., Gressler, L.T., Kowalski, A.P., Diehl, G.N., dosSantos, L.C., Corbellini, L.G., de Vargas, A.C., 2016. Prevalence of streptococcus equi subsp. equi in horses and associated risk factors in the state of rio grande do sul, brazil. Res. Vet. Sci. 104. https://doi.org/10.1016/j.rvsc.2015.11.009. ⟨http://www.sciencedirect.com/science/article/pii/S0034528815300965⟩.

Machado, G., Corbellini, L.G., Frias-De-Diego, A., Dieh, G.N., DosSantos, D.V., Jara, M., de Freitas Costa, E., 2021. Impact of changes of horse movement regulations on the risks of equine infectious anemia: A risk assessment approach. Prev. Vet. Med. 190, 105319 https://doi.org/10.1016/j.prevetmed.2021.105319.

Minai, E., Araghi-Sooreh, A., 2020. Assessment of streptococcus equi infection in apparently healthy working horses of urmia region by indirect ELISA method. Vet. Clin. Pathol. Q. Sci. J. 14, 219–227. https://doi.org/10.30495/jvcp.2020.1880960.1246. ⟨https://jvcp.tabriz.iau.ir/article_677915.html⟩.

Mitchell, C., Steward, K.F., Charbonneau, A.R.L., Walsh, S., Wilson, H., Timoney, J.F., Wernery, U., Joseph, M., Craig, D., van Maanen, K., Hoogkamer-van Gennep, A., Leon, A., Witkowski, L., Rzewuska, M., Stefańska, I., Żychska, M., van Loon, G., Cursons, R., Patty, O., Acke, E., Gilkerson, J.R., El-Hage, C., Allen, J., Bannai, H., Kinoshita, Y., Niwa, H., Becú, T., Pringle, J., Guss, B., Böse, R., Abbott, Y., Katz, L., Leggett, B., Buckley, T.C., Blum, S.E., CruzLópez, F., FernándezRos, A., MarottiCampi, M.C., Preziuso, S., Robinson, C., Newton, J.R., Schofield, E., Brooke, B., Boursnell, M., de Brauwere, N., Kirton, R., Barton, C.K., Abudahab, K., Taylor, B., Yeats, C.A., Goater, R., Aanensen, D.M., Harris, S.R., Parkhill, J., Holden, M.T.G., Waller, A.S., 2021. Globetrotting strangles: the unbridled national and international transmission of streptococcus equi between horses. Microb. Genom. 7, mgen000528 https://doi.org/10.1099/mgen.0.000528. ⟨https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8190609/⟩.

Newton, J.R., Wood, J.L.N., Dunn, K.A., De Brauwere, M.N., Chanter, N., 1997. Naturally occurring persistent and asymptomatic infection of the guttural pouches of horses with streptococcus equi. Vet. Rec. 140, 84–90. https://doi.org/10.1136/vr.140.4.84. ⟨http://veterinaryrecord.bmj.com.proxy.library.uu.nl/content/140/4/84⟩.

Newton, J.R., Wood, L.N., DeBrauwere, N., Chanter, N., Verheyen, K., Mumford, J.A., 1999.Detection and treatment of asymptomatic carriers of streptococcus equi following strangles outbreaks in the UK, In: Proceedings from the Equine Infectious Diseases Conference V!!!, 82-87.

Newton, J.R., Verheyen, K., Talbot, N.C., Timoney, J.F., Wood, J.L.N., Lakhani, K.H., Chanter, N., 2000. Control of strangles outbreaks by isolation of guttural pouch carriers identified using pcr and culture of streptococcus equi. Equine Vet. J. 32, 515–526. https://doi.org/10.2746/042516400777584721.

Piché, C.A., 1984. Clinical observations on an outbreak of strangles. Can. Vet. J. 25, 7–11. ⟨https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1790498/⟩.

Pringle, J., Venner, M., Tscheschlok, L., Bächi, L., Riihimäki, M., 2019. Long term silent carriers of streptococcus equi ssp. equi following strangles; carrier detection related to sampling site of collection and culture versus qpcr. Vet. J. 246, 66–70. https://doi.org/10.1016/j.tvjl.2019.02.003. ⟨http://www.sciencedirect.com/science/article/pii/S1090023318301783⟩.

R Core Team, 2021.R: A language and environment for statistical computing.⟨https://www.R-project.org/⟩.

Riihimäki, M., Aspán, A., Ljung, H., Pringle, J., 2018. Long term dynamics of a streptococcus equi ssp equi outbreak, assessed by qpcr and culture and seM sequencing in silent carriers of strangles. Vet. Microbiol. 223, 107–112. https://doi.org/10.1016/j.vetmic.2018.07.016. ⟨http://www.sciencedirect.com/science/article/pii/S0378113518303456⟩.

Robinson, C., Waller, A.S., Frykberg, L., Flock, M., Zachrisson, O., Guss, B., Flock, J.I., 2020. Intramuscular vaccination with strangvac is safe and induces protection against equine strangles caused by streptococcus equi. Vaccine 38, 4861–4868. https://doi.org/10.1016/j.vaccine.2020.05.046 institution: Department of Bacteriology, Animal Health Trust, Lanwades Park, Kentford, Newmarket, CB8 7UU, UK.

de la Rua-Domenech, R., Reid, S.W.J., González-Zariquiey, A.E., Wood, J.L.N., Gettinby, G., 2000. Modelling the spread of a viral infection in equine populations managed in thoroughbred racehorse training yards. Prev. Vet. Med. 47, 61–77. https://doi.org/10.1016/S0167-5877(00)00161-6. ⟨http://www.sciencedirect.com/science/article/pii/S0167587700001616⟩.

Sheoran, A.S., Sponseller, B.T., Holmes, M.A., Timoney, J.F., 1997. Serum and mucosal antibody isotype responses to m-like protein (SeM) of streptococcus equi in convalescent and vaccinated horses. Vet. Immunol. Immunopathol. 59, 239–251. https://doi.org/10.1016/S0165-2427(97)00074-3. ⟨http://www.sciencedirect.com/science/article/pii/S0165242797000743⟩.

Shi, L., Hu, J., Jin, Z., Shi, L., Hu, J., Jin, Z., 2023. Dynamics analysis of strangles with asymptomatic infected horses and long-term subclinical carriers. Math. Biosci. Eng. 20, 18386–18412. https://doi.org/10.3934/mbe.2023817.

Soetaert, K., Petzoldt, T., Setzer, R., 2010. Solving differential equations in r: Package deSolve. J. Stat. Softw. 33, 1–25. https://doi.org/10.18637/jss.v033.i09.

Sweeney, C.R., Timoney, J.F., Newton, J.R., Hines, M.T., 2005. Streptococcus equi infections in horses: guidelines for treatment, control, and prevention of strangles. J. Vet. Intern. Med. 19, 123–134.

Sweeney, C.R., Benson, C.E., Whitlock, R.H., Meirs, D.A., Barningham, S.O., Whitehead, S.C., Cohen, D., 2024. Description of an epizootic and persistence of streptococcus equi infections in horses. J. Am. Vet. Med. Assoc. 194, 1281–1286.

Todd, A.G., 1910. Strangles. J. Comp. Path Ther. 23, 212–229.

Tscheschlok, L., Venner, M., Steward, K., Böse, R., Riihimäki, M., Pringle, J., 2018. Decreased clinical severity of strangles in weanlings associated with restricted seroconversion to optimized streptococcus equi ssp equi assays. J. Vet. Intern. Med. 32, 459–464. https://doi.org/10.1111/jvim.15037.

Waller, A.S., Sellon, D.C., Sweeney, C.R., Timoney, P.J., Newton, J.R., Hines, M.T., 2014. Chapter 28 - streptococcal infections.⟨https://www.sciencedirect.com/science/article/pii/B9781455708918000282⟩, 10.1016/B978-1-4557-0891-8.00028-2.