Demonstrating frequency-dependent transmission of sarcoptic mange in red foxes

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Summary
Understanding the relationship between disease transmission and host density is essential for predicting disease spread and control. Using long-term data on sarcoptic mange in a red fox Vulpes vulpes population, we tested long-held assumptions of density- and frequency-dependent direct disease transmission. We also assessed the role of indirect transmission. Contrary to assumptions typical of epidemiological models, mange dynamics are better explained by frequency-dependent disease transmission than by density-dependent transmission in this canid. We found no support for indirect transmission. We present the first estimates of $R_0$ and age-specific transmission coefficients for mange in foxes. These parameters are important for managing this poorly understood but highly contagious and economically damaging disease.

Keywords: Age-specific infection, basic reproductive number, frequency-dependent transmission, indirect transmission, SEI model.
Introduction

Rates of disease transmission are typically assumed to increase with host density for most directly transmitted infections but to be unrelated to density for sexually and indirectly transmitted diseases [1]. Increasingly, studies are challenging this assumption, suggesting that behaviours mediating contact rates do not always show simple relationships with host density [2]. Many diseases are also transmitted indirectly through contact with contaminated substances known as fomites, a pathway only recently incorporated into wildlife disease models [3, 4]. Insight into pathogen spread is informative for controlling disease: non-linear dynamics can result in ineffective culling [5]; disease-induced extinction risk increases when transmission is density-independent [6]; and indirect transmission can promote disease persistence [3]. Given the threat of emerging infectious diseases, the possibility of domestic-wildlife cross-infection and the cost of disease control [7, 8], understanding transmission mechanisms is clearly important.

Sarcoptic mange, caused by the highly contagious mite Sarcoptes scabiei, affects over 100 domestic and wild mammalian species [9]. Mange is a potential emerging disease [7], posing a risk for endangered species and domestic-wildlife infection [8]. The economic costs of controlling mange are substantial [10]. Despite its importance, fundamental aspects of mange epidemiology, including genetic resistance and transmission dynamics in wild populations, are poorly understood [9]. Further, mange occurs in a range of species exhibiting different levels of sociality [11-14].

Mange epizootics have caused significant declines in red fox Vulpes vulpes populations worldwide [11, 15, 16]. Previous mange models have only considered direct, density-dependent transmission [12, 17] but off-host mite survival [9] and low inter-group contact in foxes [18] suggest that indirect transmission is likely. Moreover, the social nature of foxes suggests that the traditional assumptions of density- and frequency-dependent disease transmission might be complicated [19]. We developed a model of mange spread and fitted it to a long-term dataset. This model allowed us to: (i) estimate epidemiological parameters; (ii) explore whether transmission is frequency- or density-dependent; and (iii) assess the potential role of indirect transmission.

Methods

An urban fox population in Bristol, UK, experienced a mange epizootic [20], followed by an enzootic phase [11], during a four-decade long study (1977 to present). Pre-epizootic spring population density (adults and juveniles) was exceptionally high (58.3 individuals km\(^{-2}\)) and
post-epizootic density was reduced by >95% [20]. Monthly mange prevalence was
determined for juveniles (<1 year old) and adults (>1 year old), given observed age-related
patterns (see electronic supplementary material (ESM) for full details).

Using an age-structured Susceptible-Exposed-Infected (SEI) model, we tested two
forms of direct transmission: density- and frequency-dependent transmission (MD and MF,
respectively, Figure 1) (see ESM for full model details). Two epidemiological parameters, the
transmission coefficient, \( \beta \), and infectious period, \( \gamma \), were estimated by fitting the models to
data. To account for potential age-specific variation in prevalence between juveniles \( j \) and
adults \( a \), the SEI model included age-specific transmission, denoted by the coefficients \( \beta_{jj} \)
and \( \beta_{aa} \). The exposed class was included to incorporate the time taken between foxes
becoming exposed to the mites and becoming infectious, typically 30 days (Table 1). Mean
time to disease-induced mortality \( \alpha \) is estimated to be 100 days (Table 1) which, with a life-
expectancy without the disease of 2 years, translates to a 7-fold increase in mortality rate due
to mange. Recovered individuals were assumed to return directly to the susceptible class
because re-infection of individuals was observed (S. Harris unpublished data). Host
demography was modelled assuming a fixed background per capita mortality rate (Table 1)
and an annual birth pulse. The total population density \( N \) was reset annually to an observed
post-breeding density \( N_k \), to simulate the birth pulse, with susceptible juveniles \( S_{bj} \)
introduced into the population each year, \( t \) (i.e. \( S_{bj} = N_k(t) - N \)).

In models MD and MF, indirect transmission was combined with direct transmission
(Figure 1), given that indirect pathways are unlikely to be the sole transmission mechanism.
An additional compartment \( F \) followed mite density on fomites and the transmission
coefficient, \( \beta_f \), described infection through the contact of susceptible individuals with free-
living mites on infected substrates. Due to paucity of data, the rate that mites are released into
the environment, \( \omega \), was a fitted parameter, assumed to depend on the reproductive rate of the
mites and individual parasite loads.

Parameter estimates were determined using maximum likelihood (see ESM for full
methods) in R 3.1.0 (www.r-project.org). Where possible, initial parameter values were
estimated from the literature [11, 20, 21] (Table 1). To determine the performance of the
disease transmission models, predicted dynamics were compared with a null model with
time-invariant disease prevalence. Evidence for inter-annual variation in post-breeding
density, density- versus frequency-dependent transmission, and the role of indirect
transmission were assessed by performing model selection using Akaike’s Information
Criterion (AIC) [22]. The basic reproductive number, \( R_0 \), determining the probability of
disease invasion, was calculated for the best AIC model using a ‘next generation matrix’ [23] (see ESM).

Results

Age-related patterns in the monthly prevalence of mange (Figure S2) suggest some seasonality, particularly in juveniles. Prevalence data were overdispersed with respect to the binomial distribution (variance inflation factor, $\hat{\nu} = 2.79$) and, therefore, all model likelihoods were calculated using the beta-binomial distribution [22]. SEI models consistently outperformed the null model (Table S1). AIC values for the null and all eight time-varying disease models are presented in the ESM (Table S1). The most parsimonious models ($M_F$ and $M_{FI}$) indicated strong support for frequency-dependent mange transmission in the Bristol fox population. The frequency-dependent model incorporating indirect transmission ($M_{FI}$) performed well but model comparison showed that the extra parameters did not justify the increased complexity relative to model $M_F$ (Figure 2a,b) [22]. $M_F$ captured observed prevalence patterns in both juveniles (Figure 2a) and adults (Figure 2b); the discrepancy between empirical and observed juvenile prevalence from May to July is probably due to the window of offspring birth being rather wider in reality than in our model. Density-dependent models did not perform well (Figure 2c,d), overestimating juvenile prevalence from April to June.

The 95% confidence intervals (CIs) of $R_0$ are all above one, consistent with mange persistence in the population (Table 2). The best estimate of $\beta_{jj}'$ was ten times higher than $\beta_{aa}'$, with no overlap between CIs (Table 2), suggesting a key role of juveniles for mange transmission. The wide CIs and the discrepancy between the best model estimate of $\gamma$ (Table 2, corresponding to 30 days) and the estimate from the literature [21], may reflect trade-offs between $\gamma$ and unknown parameters.

Discussion

This study presents the first published model of mange transmission dynamics in foxes. The estimate of $R_0$ is consistent with mange invading the Bristol fox population and is similar in magnitude to that estimated for mange in chamois Rupicapra rupicapra [$R_0=4.8-5.1$; 12]. In other fox populations, the relationship between mange and density is unclear [11, 15, 24]. However, contrary to expectation, frequency-dependent transmission of mange appears most probable in the Bristol fox population, implying that the per capita rate of infectious contact remains constant despite increases in densities of infected individuals. This
is consistent with fox behaviour, since opportunities for infectious contact may be limited due
to low inter- and intra-group encounters [18, 25]. Density-dependent models particularly
overestimated juvenile disease prevalence post-birth, when movement is limited. The
minimal effect of density on mange is supported by the observation that mange persists at
low fox densities [20], because frequency-dependent diseases can be sustained at lower host
densities than density-dependent diseases [26]. The contrast between our results and those of
assessments of mange transmission in chamois, a species which does not show complex
group structuring, and for which density-dependent transmission of mange was well-
supported [12], emphasises the role of sociality in mediating disease dynamics within a
population [1, 2, 5, 19]. Further work is needed to examine how transmission mechanisms
vary across different species affected by the same disease.

We found no support for indirect transmission. This could reflect the limited role of
this pathway between social groups in the study area: although inter-group den sharing
promoted mange transmission in a Russian fox population [16], this behaviour may be less
frequent in the Bristol population. Poor support for indirect transmission also suggests poor
support for the importance of alternative hosts. In single host – single pathogen models,
alternative hosts may appear to play a role equivalent to indirect transmission, especially
where the vectors are host generalists (as in the case of mange mites). However, in Bristol,
there was only evidence of mange transmission from foxes to dogs during the initial epizootic
phase, and no evidence of transmission from dogs to foxes (S. Harris unpublished data).
Thus, consistent with our findings on indirect transmission, the role of alternative hosts is
likely to be negligible. These findings should recognize, however, that population-level SEI
models do not discriminate between inter- and intra-group encounter rates and, thus, could
overestimate the importance of direct transmission between individuals of the focal species.
Simulations of individual-level behaviour may provide further insight into the relative
importance of transmission mechanisms.

The predicted age-specific prevalence may reflect the restricted post-birth movement
of juveniles [27] and the subsequent pulse of infection driven by the naïve source of
susceptible juveniles. The high predicted age-specific transmission rate suggests either that
juveniles are more prone to infection given contact (owing to less effective immune systems
and increased nutritional stress from independent foraging) and/or that they encounter
infected individuals more often than adults (owing to life-stage specific movement patterns);
however, combining data on all individuals younger than one may mask underlying
mechanisms. Mange is probably maintained by older individuals since adults have a longer
time to become infected compared to the short disease duration in younger individuals. Such insight into age-specific transmission is important for disease control. This study provides the first estimates of stage-dependent transmission rates and $R_0$ for mange in foxes and suggests that the dominant transmission mechanism is frequency-dependent. These results indicate the importance of sociality in mange transmission and highlight the need to test long-standing assumptions of disease transmission.

Acknowledgements

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References


Table 1. Definition of fitted and fixed parameters used in SEI models.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Fixed or fitted parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{jj}, \beta_{aa}$</td>
<td>Age-specific density-dependent transmission (day$^{-1}$)</td>
<td>a</td>
</tr>
<tr>
<td>$\beta'<em>{jj}, \beta'</em>{aa}$</td>
<td>Age-specific frequency-dependent transmission (individual$^{-1}$ day$^{-1}$)</td>
<td>a</td>
</tr>
<tr>
<td>$\beta_f$</td>
<td>Indirect transmission (day$^{-1}$ per unit of fomite) (age-invariant)</td>
<td>a</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Infectious period = 1/ $\gamma$ (day$^{-1}$)</td>
<td>a</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Latent period = 1/ $\sigma$ (day$^{-1}$)</td>
<td>30 days</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Disease-induced mortality rate = 1/ $\alpha$ (day$^{-1}$)</td>
<td>100 days</td>
</tr>
<tr>
<td>$\mu_j$</td>
<td>Juvenile <em>per capita</em> mortality probability (year$^{-1}$)</td>
<td>0.3$^b$</td>
</tr>
<tr>
<td>$\mu_a$</td>
<td>Adult <em>per capita</em> mortality probability (year$^{-1}$)</td>
<td>0.5$^b$</td>
</tr>
<tr>
<td>$\omega$</td>
<td><em>Per capita</em> reproductive rate of mite on infected individuals (day$^{-1}$)</td>
<td>a</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>Rate of loss of the pathogen in environment = 1/ $\epsilon$ (day$^{-1}$)</td>
<td>10 days</td>
</tr>
<tr>
<td>$S_{0j}$</td>
<td>Initial density of susceptible juveniles (km$^{-2}$)</td>
<td>21</td>
</tr>
<tr>
<td>$S_{0a}$</td>
<td>Initial density of susceptible adults (km$^{-2}$)</td>
<td>36</td>
</tr>
<tr>
<td>$I_{0j}$</td>
<td>Initial density of infected juveniles (km$^{-2}$)</td>
<td>0.01</td>
</tr>
<tr>
<td>$I_{0a}$</td>
<td>Initial density of infected adults (km$^{-2}$)</td>
<td>0.01</td>
</tr>
<tr>
<td>$F_0$</td>
<td>Initial density of fomites (normalised)</td>
<td>1</td>
</tr>
</tbody>
</table>

$^a$ Fitted parameter

$^b$ Annual probabilities were converted to daily rates by $-\ln(\mu)/360$
Table 2. Estimated parameter values for the best-fitting model (95% CIs in parentheses estimated by bootstrapping 10,000 replicates, see ESM). See Table 1 for epidemiological parameter descriptions.

<table>
<thead>
<tr>
<th>Model</th>
<th>$\beta'_{ji}$</th>
<th>$\beta'_{aa}$</th>
<th>$\gamma$</th>
<th>$\Phi^a$</th>
<th>$R_0$</th>
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<td>$M_F$</td>
<td>0.340</td>
<td>0.030</td>
<td>0.039</td>
<td>0.247</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td>(0.164–0.705)</td>
<td>(0.006–0.06)</td>
<td>(0.029–0.15)</td>
<td>(0.156–1.54–)</td>
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<tr>
<td></td>
<td>0.030</td>
<td>0.030</td>
<td>0.039</td>
<td>0.247</td>
<td>2.67</td>
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<td>(0.156–1.54)</td>
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</table>

$^a$Dispersion parameter, $\phi$, indicating that data are overdispersed.
Figure legends

Figure 1. SEI compartment model diagram illustrating age-specific density-dependent direct transmission with host demography (M_D). Indirect transmission and fomite dynamics are indicated in grey (M_DI). Transmission terms in brackets are replaced with \((\beta_{aa}S_aI_a + \beta_{ja}S_jI_j)N\) and \((\beta_{ij}S_iI_i + \beta_{ai}S_aI_h)N\) for frequency-dependent models (M_F and M FI) (Table 1 provides parameter definitions).

Figure 2. The predicted probability of infection (open circles) for (a and b) the frequency-dependent model (M_F), and for (c and d) the density-dependent model (M_D), for juveniles (left panels) and adults (right panel), against the observed prevalence data (closed circles). Dotted lines indicate the predicted probability of infection for models including indirect transmission (M_FI and M_DI, respectively). 95% CIs were calculated from likelihood profiles.
\[ \gamma I_a \]

- **S_a**: \( \mu_a S_a \) → \( \mu_a E_a \) → \( (\alpha + \mu_a)I_a \)

- **E_a**: \( \beta_{aa} S_a I_a + \beta_{ja} S_a I_j \) + \( \beta_j S_a F \) → \( \alpha + \mu_a \)

- **I_a**: \( \gamma I_a \)

- **S_j**: \( \mu_j S_j \) → \( \mu_j E_j \) → \( (\alpha + \mu_j)I_j \)

- **E_j**: \( \beta_{jj} S_j I_j + \beta_{aj} S_j I_a \) + \( \beta_i S_i F \) → \( \alpha + \mu_j \)

- **I_j**: \( \gamma I_j \)

- **F**: \( \varepsilon F \)

- **Infection and mortality**

- **Fomite dynamics**

- **Births and maturation**
ESM 1.1: Data

In the UK, the Bristol fox population experienced a sarcoptic mange epizootic from 1994 to 1996; prevalence peaked in the autumn of 1995 when it was estimated that close to 100% of the population was infected [1]. At the start of the epizooty, the total (adults i.e. animals >1 year old and juveniles, i.e. animals < 1 year old) fox population density was 58.3 individuals km$^{-2}$; this declined by >95% by the end of 1996 [1]. Population recovery was slow and mange has remained at enzootic levels since 1996 [2]; by 2014, prevalence levels were very low (S. Harris unpublished data). Annual post-breeding population densities [3, 4], were estimated from capture-mark-recapture data [e.g. 1]. Four years with missing estimates (1996, 1997, 2000, 2001) were determined by linear interpolation.

Prevalence and mortality data used in this analysis were based on data collected from a 14km$^2$ area of suburban Bristol through the recapture of radio-collared or marked individuals, and recovery of fox carcasses, from 1994 to 2010 (n=1662 records; S. Harris unpublished data) [sampling protocols are described in 2, 5]. Mange diagnosis was classified according to the disease manifestation [for a review of clinical symptoms see 6]; class I and class II infections were defined as no evidence of, and presence of, hyperkeratotic mange, respectively [see 5]. Due to the small monthly sample sizes, class I and class II data were combined to obtain the number of infected individuals per month. Monthly prevalence was then calculated as the proportion of infected juveniles and adults respectively. Prevalence data were not sufficiently detailed to add a pre-emergent age class. To determine uncertainty in the prevalence data, 95% confidence intervals were calculated from likelihood profiles.

Mean monthly sample sizes for adults (2.61, SD ± 0.79, n = 502) and juveniles (5.53, SD ± 1.30, n =1061) were consistent during the year (Figure S1), with the exception of a peak in juvenile capture and mortality records in the summer months, which reflects the newly mobile juveniles (Figure S1A). Juveniles were sampled (Figure S1A), on average, twice as frequently as adults (Error! Reference source not found. Figure S1B), reflecting the age distribution of the population. Mean sample sizes of infected individuals for monthly prevalence data were low for both age classes (adults 0.63, SD ± 0.28, n = 120; juveniles 0.99, SD ± 0.33, n = 191; Figure S2). Age-related patterns in the monthly prevalence of mange (Figure S2) suggest some seasonality, particularly in juveniles. Confidence intervals are wide, however, indicating substantial uncertainty in the data.
Although *S. scabiei* is conventionally classified as a macroparasite, because it displays several microparasite attributes (the small mites reproduce directly and rapidly on the host and are able to transfer directly between host individuals), a microparasite modelling approach was applied in this study to estimate the epidemiological parameters, $\beta$ and $\gamma$, and compare pathways of mange transmission in foxes. An SEI model was used in which densities ($N$) of individuals in a given population are categorised into classes according to their disease status as susceptible ($S$), exposed ($E$), and infected ($I$) (i.e. $N = S+E+I$) (Figure 1). Two forms of direct transmission were modelled. Density-dependent transmission was the first direct mechanism modelled ($M_{DI}$). Here, the transmission rate is proportional to the densities of both susceptible and infected groups within the population ($\beta SI$), resulting in prevalence increasing linearly with the density of these two groups. The second mode of direct transmission, frequency-dependent ($M_{F}$), assumes that the infection rate is dependent on the proportion of infective individuals in the population ($\beta' SI/N$); thus, opportunities for contact between an infectious and susceptible individual are assumed to be independent of population size [7].

Given that indirect pathways are unlikely to be the sole transmission mechanism of mange, Models $M_{DI}$ and $M_{F}$ include both indirect transmission and direct transmission, with an additional compartment ($F$) following the densities of mites in the environment [8] (Figure 1). For analytical tractability, it was assumed that $\beta_f$ was not age-specific. Under average ambient conditions, all life stages of the mite can survive an average of 10 days off the host, but this can increase to several weeks if conditions are optimal [6]. The parameter $\omega$, the rate that mites are released into the environment, had to be fitted because, although it is known that female mites produce 3-4 eggs per day, with an average life expectancy of 5 weeks [9], parasite loads and the rate at which mites are released from the host remain undetermined.

Foxes breed annually and, for modelling purposes, it was assumed that all juveniles are born on April 1st (Harris & Smith 1987). Thus, for convenience, the total population density was reset annually to a post-breeding density ($N_b$), occurring in March because this process was modelled at the end of the month. In this way, a pulse of new susceptible individuals ($S_b$) was introduced into the population each year ($S_b = N_b(t) - N$). The post-breeding density $N_b(t)$ was defined as the total (combined juvenile and adult) population density estimate for year $t$, based on an independent set of density data (S. Harris unpublished data).

To account for potential age-specific variation in prevalence, for both density-and frequency-dependent transmission, a “Who Acquires Infection From Whom” (WAIFM) transmission matrix
[10] was used to denote transmission from one class to another, e.g. for frequency-dependent transmission:

\[
\beta' = \begin{bmatrix}
\beta'_{jj} & \beta'_{aj} \\
\beta'_{ja} & \beta'_{aa}
\end{bmatrix},
\]

(S1)

where \(j\) and \(a\) represent juveniles and adults respectively and \(\beta'\) is the frequency-dependent transmission coefficient. To reduce uncertainty in parameter estimates and to maintain analytical tractability, and because the addition of more complex contact rates was not supported by the data, it was assumed that juvenile-adult transmission, \(\beta'_{ja}\), was equal to juvenile-juvenile transmission, \(\beta'_{jj}\), and that adult-juvenile transmission, \(\beta'_{aj}\), equaled adult-adult transmission, \(\beta'_{aa}\). Each year, at the time of the birth pulse, juveniles in a given disease state matured into adults of the corresponding disease class. The following ordinary differential equations (ODEs) describe disease dynamics between birth pulses according to the frequency-dependent SEI model (MF):

\[
\frac{dS_j}{dt} = -\mu_j S_j - \left(\beta'_{jj} I_j + \beta'_{aj} I_a\right) \frac{S_j}{N} + \gamma I_j \\
\frac{dE_j}{dt} = -\mu_j E_j - \sigma E_j - \left(\beta'_{jj} I_j + \beta'_{aj} I_a\right) \frac{S_j}{N} \\
\frac{dI_j}{dt} = -(\alpha + \mu_j) I_j + \sigma E_j - \gamma I_j \\
\frac{dS_a}{dt} = -\mu_a S_a - \left(\beta'_{aa} I_a + \beta'_{ja} I_j\right) \frac{S_a}{N} + \gamma I_a \\
\frac{dE_a}{dt} = -\mu_a E_a - \sigma E_a - \left(\beta'_{aa} I_a + \beta'_{ja} I_j\right) \frac{S_a}{N} \\
\frac{dI_a}{dt} = -(\alpha + \mu_a) I_a + \sigma E_a - \gamma I_a,
\]

(S2)

**ESM 1.3: Parameter fitting and model selection**

The SEI model parameters were fitted to the prevalence data using maximum likelihood. This analysis is based on the assumption that the transmission rate, \(\beta\), of mange in a population, \(N\), of \(S\) susceptible individuals produces \(I\) infected individuals per day, given that \(E\) individuals were exposed to the mite and became infectious. The probability an individual in the population is infected, \(p\), is given by \(I/N\). Predictions of the model can be compared to empirical observations on the prevalence of infected individuals by considering the process of field data collection as a series of binomial trials. Let the months in the total time series be denoted by \([m = 1, 2, 3, \ldots, D]\). Within a given month, each individual sampled can be considered as a trial, with the total number of
individuals sampled in each age class denoted \( n_x \). Assuming that the probability of becoming infected, \( p_x \), is uniform among individuals sampled of age \( x \), the number of infected individuals within an age class, \( y_x \), will follow a binomial distribution. Thus, the likelihood at time \( m \) that proportion \( p_x \) of either juveniles or adults in the population are infected, given that a random sample of \( n_x \) individuals includes \( y_x \) infectives, is:

\[
L(p_x | n_x, y_x) = \binom{n_x}{y_x} p_x^{y_x} (1 - p_x)^{n_x - y_x}. \tag{S3}
\]

Observed variation in the rate of infection can arise as a result of sampling error, including undiagnosed or misdiagnosed cases, or due to the effects of unmeasured factors such as individual variation in parasite load or susceptibility. If these sources of variation are unaccounted for and result in overdispersed data, then unnecessarily complex models can be selected when using information theoretic approaches because model precision will be overestimated [11, 12]. To measure the degree of dispersion in the data, the variance inflation factor, \( \hat{\nu} \), was estimated by dividing the variation in the observed data (saturated model, where the number of parameters equals the number of observations) by the variation in the most complex binomial model [11]. If overdispersion is present (\( \hat{\nu} \geq 2 \)), a compound distribution can be fitted to the data instead [11]. For binomial data, an appropriate compound distribution is the beta-binomial distribution. This model assumes that variation in \( p_x \) across samples within a given time period is described by the beta distribution:

\[
f(p_x; \bar{p}_x, \phi) = \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)} p_x^a (1 - p_x)^b, \tag{S4}\]

where the parameter \( \phi \) quantifies the variation in \( p_x \), \( \bar{p}_x \) is the mean probability of success, \( \Gamma(x) \) is the complete gamma function, \( a = \bar{p}_x / \phi \), and \( b = (1 - \bar{p}_x) / \phi \). Substituting equation (S4) into equation (S3) gives the compound beta-binomial distribution. If \( \theta \) is the set of model parameters required to calculate \( \bar{p}_x \) and the dispersion coefficient \( \phi \), then the likelihood of \( \theta \) at time \( m \) can be calculated as:

\[
L(\theta | n_x, y_x) = \frac{\Gamma(n_x+1)\Gamma(a+b)\Gamma(y_x+a)\Gamma(n_x-y_x+b)}{\Gamma(y_x+1)\Gamma(n_x-y_x+1)\Gamma(a)\Gamma(b)\Gamma(n_x+a+b)}. \tag{S5}\]

Equation (S4) approximates the binomial distribution as the dispersion parameter, \( \phi \), approaches zero. The total log-likelihood of the model, defined by \( \theta \) and given all the data, is then the log of equation (S5) summed over age classes \( j \) and \( a \) over the total time period, \( D \):

\[
LL(\theta | \text{data}) = \sum_{m=1}^{D} \left\{ \sum_{j=1}^{n_j} \left( \ln L[\theta | n_{jm}, y_{jm}] \right) + \sum_{a=1}^{n_a} \left( \ln L[\theta | n_{am}, y_{am}] \right) \right\}. \tag{S6}\]
To determine the ability of the disease transmission model to fit the data, it is useful to compare predicted dynamics with a null model in which disease prevalence is constant in time. A beta-binomial null model ($M_{H}$) was fitted which simply assumed that the probability a sampled individual in each age class was diseased was, on average, time-invariant ($p_x = \bar{p}_x$). The ability of SEI models to capture patterns in the prevalence data was determined by comparing the likelihoods of the null model, $M_{H}$, and those models that included disease parameters ($M_D$, $M_F$, $M_{DI}$, $M_{FI}$).

In general, it is necessary to use a discrete approximation because epidemiological ODE models cannot be solved analytically due to their non-linear properties. Thus, to obtain prevalence patterns, $p_x(m)$, predicted by each SEI model, the associated system of equations (eqn S2) was solved using the fourth-order Runge-Kutta method [13]. The set of model parameter values fitted to the monthly age-specific prevalence data for direct transmission were $\theta = \{\beta_{ij}, \beta_{ai}, \gamma, \phi\}$ and $\theta = \{\beta'_{ij}, \beta'_{ai}, \gamma, \phi\}$ for density- and frequency-dependent transmission respectively; for models that include indirect transmission, the models were defined by $\theta = \{\beta_{ij}, \beta_{ai}, \beta_f, \omega, \gamma, \phi\}$ and $\theta = \{\beta'_{ij}, \beta'_{ai}, \beta_f, \omega, \gamma, \phi\}$. Parameter estimates were determined by maximising the total model log-likelihood (eqn S6) using the “optim” function in R 3.1.0 (www.r-project.org). To distinguish between the competing models, Akaike’s Information Criterion (AIC) was used; to avoid instances where the best AIC model does not have the lowest AIC value due to uncertainty from sampling error, all models with $\Delta\text{AIC} \leq 6$ units were considered to have some level of support [11, 14]. A bootstrap approach was used to calculate 95% confidence intervals for each parameter of the best fitting model selected by AIC. Specifically, 1000 model replicates were fitted by re-sampling the prevalence data between years, but from the same month. All analyses were conducted in R 3.1.0 (www.r-project.org).

**ESM 1.4: Basic Reproductive Number**

### 1.4.1. Theoretical background

The basic reproductive number, $R_0$, is defined as the expected number of secondary cases attributed to a typical infectious individuals in an entirely susceptible population [15]. Thus, in cases where $R_0 < 1$, a pathogen will not successfully invade when a typical infectious individual causes less than one infection in an entirely susceptible population. Such populations exhibit a stable disease-free equilibrium. When $R_0 > 1$, a pathogen will successfully invade causing instability in the disease-free equilibrium. In this regard, $R_0$ is a threshold parameter, reflecting whether a pathogen will successfully invade a population, describing the stability of a system’s disease-free equilibrium.
The above definition is acceptable in homogeneous populations and calculations of $R_0$ are well established for such models [15]. However, in heterogeneous populations, where infected individuals can be classified into discrete classes (e.g. by age or behaviour), defining a typical infectious individual is less straightforward, and estimating $R_0$ more complex [15-17]. Theoretically, in such cases, separate $R_0$ values for each class can be calculated; however, this does not provide a single value for estimating the likelihood of disease invasion in the entire population [10]. Further, averaging the individual $R_0$ values for each class to obtain a composite $R_0$ value leads to erroneous estimates, since it does not account for the proportion of infected individuals in each class. This can lead to $R_0$ being underestimated for heterogeneous populations [10]. Thus, it is necessary to account for the rate at which infection is transmitted between these heterogeneous classes by weighting $R_0$ according to the expected level of infection in each class in an entirely susceptible population [15].

In homogeneous compartment models, there are two dynamical phases of infection, whereas in heterogeneous models there are three phases. For a detailed description of these phases see [10]. The second phase in heterogeneous models is analogous to the stable stage distribution (SSD) of demographic models [18] and it is during this phase that an infection will successfully invade or die out. As with the SSD in demographic models [19], $R_0$ provides insight into the eventual growth rate of infection, while the growth of a disease in the early phase is independent of $R_0$. In some instances, conditions favouring disease spread will change, and so $R_0$ may no longer be a suitable measure of disease transmission [17]. Nevertheless, $R_0$ continues to be a meaningful measure of disease spread since, in many disease systems, peak prevalence of infected hosts and the final size of an epidemic are increasing functions of $R_0$ [17].

In heterogeneous cases, $R_0$ is frequently determined using a ‘next generation matrix’ (NGM) [15-17, 20]. Here, the demographic equivalent of ‘being born’ into a ‘generation’ refers to ‘becoming infected’ [20]. $R_0$ is determined during the second dynamical phase, because this stage is independent of the initial conditions and presents a natural weighting of the number of infections caused by an initial infected individual, in each class [10].

In heterogeneous models, in order to find the next generation matrix, $K$, it is necessary to consider infectious individuals of $m$ distinct classes of which $r$ are infected. $x = x_1, \ldots, x_m$ is the density of individuals in compartment $i$ and $x_0$ is the disease-free equilibrium. Since the relative change in susceptibles is small during the initial phase of invasion, their numbers can be fixed at the disease free equilibrium [20]. To calculate $K$, two matrices need to be determined from the model; $F$, which describes the rate at which new infections arise (gains) and $V$, that describes the rate at which individuals enter or leave the infectious class due to infection, recovery or death (losses) [15].
Although there may be several ways to define $F$ and $V$, there is usually only one that is biologically meaningful \[21\]. The rate of change of $x_i$ is given by:

$$\frac{dx_i}{dt} = F_i(x) - V_i(x).$$ (S7)

Here, $F_i(x)$ is the rate of new infections in compartment $i$ and $V_i(x) = V_i^+(x) - V_i^-(x)$, where $V_i^+$ describes the rate at which individuals enter compartment $i$, whilst $V_i^-$ describes the rate at which individuals leave the $i$th compartment.

In order to form the NGM, the following assumptions should be met \[15, 21\].

1. If a compartment contains no individuals, there can be no movement of individuals out of the compartment, through death, infection or other means.
2. No movement between compartments can be negative.
3. If the population is disease-free, there can be no movement into the infectious population (e.g. through density-independent immigration of infectious individuals).
4. There can be no movement of infections into classes that are defined as non-infectious.
5. The disease-free equilibrium is locally asymptotically stable in the absence of new infections.

Assuming that these conditions are met, the NGM $K$ can then be formed from the partial derivatives of the matrices $F_i$ and $V_i$, such that:

$$F = \left[ \frac{\partial F_i}{\partial x_s}(x_0) \right]$$ and $$V = \left[ \frac{\partial V_i}{\partial x_s}(x_0) \right],$$ (S8, S9)

where $i, s = 1, ..., r$. The $(s,k)$ entry of $V^{-1}$, describes the average length of time an infected individual introduced to compartment $k$ spends in compartment $s$, and the $(i,s)$ entry of $F$ is the rate at which an infectious individual in compartment $s$ produces new infections in compartment $i$. The product of these matrices, $FV^{-1}$, is the NGM $K$. Thus, the $(i,k)$ entry of $FV^{-1}$ provides the expected rate of new infections in compartment $i$ produced by an infectious individual introduced to compartment $k$. When the matrix element $FV_{i,k} = 0$, no new cases produced in infected state $k$ can be in infected state $i$ immediately following infection.

1.4.2. Calculating $R_0$

In the model described above (eqn S2), each age class has individuals in susceptible, exposed and infected disease compartments, such that the vector $x = (S_j, E_j, I_j, S_a, E_a, I_a)$ and the disease free equilibrium $x_0 = (S_j, 0, 0, S_a, 0, 0)$, with $S_j = S_{0j}$ and $S_a = S_{0a}$ defined as the initial densities. To define the NGM for this model, it is necessary to examine how new infections arise and how individuals move
between disease states. Since there are four infected states \((E_j, E_a, I_j, I_a)\), the resulting system will be four-dimensional. To define the rate of new infections, evaluated at the disease-free equilibrium, the matrix \(F\) was constructed for the above model as:

\[
F = \begin{bmatrix}
0 & 0 & \frac{S_{0j}}{N} & \frac{S_{0j}}{N} \\
0 & 0 & \frac{S_{0a}}{N} & \frac{S_{0a}}{N} \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}.
\]  

(S10)

To define how individuals can move between compartments, the matrix \(V\) is:

\[
V = \begin{bmatrix}
(\sigma + \mu_j) & 0 & 0 & 0 \\
0 & (\sigma + \mu_a) & 0 & 0 \\
-\sigma & 0 & (\alpha + \mu_j + \gamma) & 0 \\
0 & -\sigma & 0 & (\alpha + \mu_a + \gamma)
\end{bmatrix}.
\]  

(S11)

Since \(V\) is a non-singular M-matrix [17], it can be inverted to obtain \(V^{-1}\):

\[
V^{-1} = \begin{bmatrix}
\frac{1}{(\sigma + \mu_j)} & 0 & 0 & 0 \\
0 & \frac{1}{(\sigma + \mu_a)} & 0 & 0 \\
\frac{\sigma}{(\sigma + \mu_j)(\alpha + \mu_j + \gamma)} & 0 & \frac{1}{(\alpha + \mu_j + \gamma)} & 0 \\
0 & \frac{\sigma}{(\sigma + \mu_a)(\alpha + \mu_a + \gamma)} & 0 & \frac{1}{(\alpha + \mu_a + \gamma)}
\end{bmatrix}.
\]  

(S12)

These matrices are then multiplied to obtain:

\[-FV^{-1}\]

\[
= \begin{bmatrix}
0 & 0 & \frac{S_{0j}}{N} & \frac{S_{0j}}{N} \\
0 & 0 & \frac{S_{0a}}{N} & \frac{S_{0a}}{N} \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix} \begin{bmatrix}
\frac{1}{(\sigma + \mu_j)} & 0 & 0 & 0 \\
0 & \frac{1}{(\sigma + \mu_a)} & 0 & 0 \\
\frac{\sigma}{(\sigma + \mu_j)(\alpha + \mu_j + \gamma)} & 0 & \frac{1}{(\alpha + \mu_j + \gamma)} & 0 \\
0 & \frac{\sigma}{(\sigma + \mu_a)(\alpha + \mu_a + \gamma)} & 0 & \frac{1}{(\alpha + \mu_a + \gamma)}
\end{bmatrix}.
\]
$$= \begin{bmatrix} \sigma \beta'_{jj} & S_{0j} & \sigma \beta'_{aj} & S_{0j} & \beta'_{jj} & S_{0j} & \beta'_{aj} & S_{0j} \\ \frac{(\sigma + \mu_j)(\alpha + \mu_j + \gamma)}{N} & \frac{(\sigma + \mu_a)(\alpha + \mu_a + \gamma)}{N} & \frac{\alpha + \mu_j + \gamma}{N} & \frac{\alpha + \mu_a + \gamma}{N} & 0 & 0 & 0 \\ \sigma \beta'_{ja} & S_{0a} & \sigma \beta'_{aa} & S_{0a} & \beta'_{ja} & S_{0a} & \beta'_{aa} & S_{0a} \\ \frac{(\sigma + \mu_j)(\alpha + \mu_j + \gamma)}{N} & \frac{(\sigma + \mu_a)(\alpha + \mu_a + \gamma)}{N} & \frac{\alpha + \mu_j + \gamma}{N} & \frac{\alpha + \mu_a + \gamma}{N} & 0 & 0 & 0 \end{bmatrix} \quad \text{(S13)}$$

However, of the four infected states, only two are ‘states-at-infection’, i.e. the state in which an individual becomes infected or has their ‘epidemiological birth’ [22]. In this model, $E$ is the only state-at-infection, as an individual can only be in the state $I$ after the latent period, not immediately after infection. NGM calculation relies only on the states-at-infection [22], which in this example are identified as the two non-zero rows of $F$. Following established methods [22], $FV^{-1}$ is pre- and post-multiplied by an auxiliary matrix, $E$, whose column elements relate to the non-zero rows of $F$:

$$E = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \quad \text{(S14)}$$

Hence, the next-generation matrix is:

$$K = -E'FV^{-1}E = \begin{bmatrix} \frac{(\sigma + \mu_j)(\alpha + \mu_j + \gamma)}{N} & \frac{(\sigma + \mu_a)(\alpha + \mu_a + \gamma)}{N} & \frac{\alpha + \mu_j + \gamma}{N} & \frac{\alpha + \mu_a + \gamma}{N} \\ \frac{\sigma \beta'_{jj}}{N} & \frac{\sigma \beta'_{aj}}{N} & 0 & 0 \\ \frac{\sigma \beta'_{ja}}{N} & \frac{\sigma \beta'_{aa}}{N} & 0 & 0 \\ \frac{(\sigma + \mu_j)(\alpha + \mu_j + \gamma)}{N} & \frac{(\sigma + \mu_a)(\alpha + \mu_a + \gamma)}{N} & \frac{\alpha + \mu_j + \gamma}{N} & \frac{\alpha + \mu_a + \gamma}{N} \end{bmatrix} \quad \text{(S15)}$$

Here, the epidemiological meaning of the elements is clear, where $\sigma/(\sigma + \mu)$ is the mean length of the latent period (i.e. probability of transitioning from infectious class $E$ to $I$) and $1/(\alpha + \mu + \gamma)$ is the mean length of the infectious period (i.e. the probability of transitions out of the $I$ infectious state).

The NGM is non-negative, such that the dominant eigenvalue is non-negative and, as shown previously [17], is a threshold parameter for the stability of the disease-free equilibrium. Associated with this eigenvalue is a non-negative eigenvector, $w$, that effectively describes the distribution of infected individuals that produce the greatest number, $R_0$, of secondary infections per generation [21]. Thus $R_0$ and $w$ together describe a ‘typical’ infectious individual, where $R_0$ is the spectral radius, $\rho$, or the dominant eigenvalue of the next-generation matrix:

$$R_0 = \rho(K). \quad \text{(S16)}$$

For models including indirect transmission, the overall $R_0$ is equal to $R_0 + R_0^{\text{indirect}}$, where $R_0^{\text{indirect}}$ is calculated as [23]:

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\[ R_0^{\text{indirect}} = \frac{\omega \beta f(S_{0j} + S_{0a})}{m(\mu + \alpha + \gamma)}. \] (S17)

\( R_0 \) was calculated for the most parsimonious model selected by AIC, using the parameter value estimates obtained from maximum likelihood. To determine the 95\% confidence intervals for \( R_0 \), parameters values were resampled from a truncated multivariate normal distribution, using the mean and 95\% confidence intervals from the model fitting process. CIs were then calculated for \( R_0 \), from the 10,000 bootstrap replicates that were run using ‘rtmvnorm’ from the ‘tmvtnorm’ package in R 3.1.0 (www.r-project.org).
Table S1. Model selection results for null and SEI models. The number of parameters (K), log-likelihoods (LL), and AIC values for each model are presented. Parameters are defined in the Methods, and Table 1.

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameters</th>
<th>K</th>
<th>Log-likelihood</th>
<th>AIC</th>
<th>ΔAIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MH Null model</td>
<td>$\bar{f}, \bar{p}, \varphi$</td>
<td>3</td>
<td>-325.92</td>
<td>657.83</td>
<td>25.83</td>
</tr>
<tr>
<td>MD Density-dependent</td>
<td>$\beta_{ij}, \beta_{ai}, \gamma, \varphi$</td>
<td>4</td>
<td>-320.48</td>
<td>648.97</td>
<td>16.96</td>
</tr>
<tr>
<td>MF Frequency-dependent</td>
<td>$\beta'<em>{ij}, \beta'</em>{ai}, \gamma, \varphi$</td>
<td>4</td>
<td>-312.00</td>
<td>632.00</td>
<td>0</td>
</tr>
<tr>
<td>MDI Density-dependent + Indirect</td>
<td>$\beta_{ij}, \beta_{ai}, \gamma, \varphi, \beta_l, \omega$</td>
<td>6</td>
<td>-320.46</td>
<td>652.92</td>
<td>20.92</td>
</tr>
<tr>
<td>MFI Frequency-dependent + Indirect</td>
<td>$\beta'<em>{ij}, \beta'</em>{ai}, \gamma, \varphi, \beta_l, \omega$</td>
<td>6</td>
<td>-311.67</td>
<td>635.34</td>
<td>3.34</td>
</tr>
</tbody>
</table>
Figure S1. Monthly number of individuals of total sampled foxes (no fill) and infected foxes (blue) from 1994 – 2010. (A) Juveniles; (B) adults. Boxes show the sample median, minimum and maximum. Error bars indicate the lower and upper quartiles and outliers are indicated by open circles.
Figure S2. Mean monthly prevalence of mange infection for juveniles (dashed line, open circles) and adults (solid line, closed circles) from 1994 – 2010, with 95% confidence intervals.
Figure S3. The predicted population density (a) and prevalence (b) for the frequency-dependent SEI model (M_F). Solid lines indicate predicted density for juveniles and adults of susceptible and exposed individuals (S_j, S_a, E_j, E_a) and predicted density and prevalence of infected juveniles and adults (I_j and I_a), against the observed population density and age-specific prevalence data (dashed lines).
Supplementary References


6. Arlian L.G. 1989 Biology, host relations, and epidemiology of *Sarcoptes scabiei*. *Annu Rev Entomol* 34, 139-161


