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Within-farm transmission dynamics of foot and mouth disease as revealed by the 2001 epidemic in Great Britain

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ABSTRACT

This paper uses statistical and mathematical models to examine the potential impact of within-farm transmission dynamics on the spread of the 2001 foot and mouth disease (FMD) outbreak in Great Britain. We partly parameterize a simple within farm transmission model using data from experimental studies of FMD pathogenesis, embed this model within an existing between-farm transmission model, and then estimate unknown parameters (such as the species-specific within-farm reproduction number) from the 2001 epidemic case data using Markov Chain Monte-Carlo (MCMC) methods. If the probability of detecting an infected premises depends on farm size and species mix then the within-farm species specific basic reproduction ratios for baseline models are estimated to be 21 (16, 25) and 14 (10, 19) for cattle and sheep, respectively. Alternatively, if detection is independent of farm size, then the corresponding estimates are 49 (41, 61) and 10 (1.4, 21). Both model variants predict that the average fraction of total farm infectiousness accumulated prior to detection of infection on an IP is about 30–50% in cattle or mixed farms. The corresponding estimate for sheep farms depended more on the detection model, being 65–80% if detection was linked to the farms' characteristics, but only 25% if not. We highlighted evidence which reinforces the role of within-farm dynamics in contributing to the long tail of the 2001 epidemic.

Introduction

The economic cost of the UK's epidemic of foot-and-mouth disease (FMD) in 2001 was directly reflected in export bans, control measures and compensation; and also indirectly by reduced revenue from tourist and other activities in the affected areas (Anderson, 2002). The epidemic was also one of the first where the real-time analyses of mathematical epidemiologists played an important role in making predictions, identifying risk factors, assessing the likely impact of control measures and ultimately informing policy decisions (Ferguson et al., 2001a,b; Keeling, 2001). The work done at the time has been much reviewed since (Haydon et al., 2004; Kao, 2002, 2003; Keeling, 2005; Kitching et al., 2006, 2007; Woolhouse, 2004), with various refinements and retrospective analyses continuing to be published (Keeling et al., 2003) and more recently (Chis Ster and Ferguson, 2007; Schley et al., 2009a,b; Tildesley et al., 2009).

The availability of relatively high quality epidemiological data from the 2001 epidemic coupled with detailed data on the demography of the UK livestock population mean that the 2001 epidemic provides a good testing-ground for novel statistical methods to analyse the spread of acute infections where spatial location plays an important role. Some of these studies (Chis Ster et al., 2009; Jewell et al., 2009) estimated the number of unobserved infections; the number of infected farms culled as part of the control process before their infection had been detected. Modelling approaches have addressed the impact of differently implemented control policies, such as culling of contiguous premises (CP culling) and vaccination using spatially explicit microsimulation models (Keeling et al., 2003; Kao, 2003; Tildesley et al., 2007; Parham et al., 2008; Tildesley et al., 2009).

A range of heterogeneities affecting the transmission dynamics of FMD have been explored in recent statistical models, including: assortative contacts between farms of different types (Chis Ster and Ferguson, 2007), different susceptibility and infectivity for different species and size-dependent infectiousness of farms (large farms being more infectious than small ones – Ferguson et al., 2001b). Nevertheless, one of the key criticisms of much of the modelling work to date is that transmission dynamics within farms have been oversimplified (Haydon et al., 2004; Kitching et al., 2005); most existing models treat the farm (rather than the animal) as the fundamental epidemiological unit. In addition, the epidemiological characteristics of farms have often been assumed to be simple: e.g. a fixed latent period after infection, then constant

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infectiousness until culling (Ferguson et al., 2001a,b; Keeling, 2001; Chis Ster and Ferguson, 2007). The counter-argument is that the farm is the appropriate scale for most models, since control is applied at the farm-level and there is not much data with which to parameterize more detailed models incorporating within-farm dynamics.

As FMD infects more animals on an infected premise, then the infectiousness of that farm to other farms will change. How infectiousness varies through time and how that temporal evolution depends on the number and type of the animals on the farm will be important in predicting the effectiveness of different control measures. For example, the timescale over which the infectiousness profile of a farm peaks relative to the average infection-to-cull delay for an IP determines what proportion of onward transmission one would expect to block by culling IPs alone. Our past work examined the impact of such temporal changes in a simpler parametric framework (Chis Ster et al., 2009). The infectiousness profile was modelled in a separable manner: a time-varying component identical for all farms scaled by a nonlinear term which was a function of herd size/species at a farm (in the subsequent text, the term herd refers to the total number of animals of the same species at a farm and is most relevant to mixed farms). This sort of average infectiousness profile has been estimated to peak at around 3–4 days post infection, though the effect of infection control measures imposed on diagnosed farms was implicitly included in this estimate (Chis Ster et al., 2009). A goal of modelling within-farm dynamics should therefore be to use a simple mechanistic model of transmission on a farm to derive that farm's infectiousness over time, together with the probability of detection of infection on the farm; both quantities will be dependent on numbers and types of animals present on the farm.

One of the reasons models of within-farm dynamics have been little explored is the lack of data on farm-level transmission to directly validate them. There are patchy data from serology, lesion dating and estimated proportions of affected animals from the 2001 epidemic in the UK, nevertheless this is not of sufficient quantity or quality to extract robust conclusions. Previous attempts at modelling FMD at the within-farm level (Carpenter et al., 2004; Thornley and France, 2009) have been essentially exploratory scenario analysis due to the absence of data to estimate relevant parameters.

Realistic transmission experiments are difficult owing to the need and cost for high levels of bio-security. Even with results from farm-scale experiments to help characterize the within farm epidemic, there would remain two crucial farm level uncertainties which bear heavily on how within-farm dynamics influence the between-farm epidemic. The first is the level of seeding: on average, how many animals of each species are initially infected when a farm becomes infected and subsequently infectious? In trying to estimate the within-farm species-specific basic reproduction ratio, some prior estimate of seeding (i.e. initial conditions for the within-farm epidemic) is needed. Secondly, to link within-farm and between-farm dynamics, we require some understanding of the relationship between the extent of infection on a farm and the probability that infection will be detected by the farmer and reported to veterinary authorities. For instance, is the probability of detection a function of the absolute number of animals of a specific species with clinical signs (irrespective of farm size), or of the proportion of animals with signs?

In this paper we develop a range of mathematical models of between and within-farm transmission and fit them to the 2001 FMD epidemic data using modern statistical techniques. This coherently relates the epidemic dynamics on three different epidemiological scales: the individual animal (within-host dynamics), the individual farm (within-farm dynamics), and the population of farms (between-farm dynamics). The data from animal infection experiments (Alexandersen et al., 2002, 2003c) involving the UK 2001 strain of FMD virus (FMDV), are used to parameterize the infectious profile of individual animals as a function of time since infection. In addition, our work is consistent with a recent experimental study which examined the relationship between clinical signs and infectiousness in cattle (Charleston et al., 2011). A within-farm transmission model allows us to generate the infectious profile of each farm from that of the individual animals on the farm. The aim of the paper then is to assess how much can be learn about the within-farm epidemiology of FMD from the 2001 between-farm epidemic data.

Finally, we use data from the between-farm epidemic in Cumbria in 2001 to try and make inferences about the unknown aspects of within-farm dynamics (seeding, detection), and assess the implications of within-farm dynamics for the epidemic as a whole.

The Bayesian inferential framework we use here is broadly similar to that used in our previous work (Chis Ster et al., 2009). We apply this to data from the UK 2001 FMD epidemic in Cumbria recorded after the national movement ban (NMB) and ignore the small number of pig farms affected (3% of all UK farms and less than 1% of all UK IPs, Chis Ster and Ferguson, 2007).

The 2001 epidemic in Cumbria (comprising 39% of all IPs) was of particular epidemiological interest partly because Cumbria was the most intensely affected area in the UK 2001 epidemic and partly due to the role of (farms') land fragmentation in enhancing transmission. The analysis carried out at the time of the epidemic suggested that higher levels of terrestrial fragmentation in Cumbria may have exacerbated the epidemic there, possibly as a result of greater movement of people and vehicles between parcels (Ferguson et al., 2001a,b). Our focus on Cumbria is also pragmatic in order to reduce the computing requirements for undertaking inference bearing in mind the relative complexity of a model that includes both within-farm and between farm transmission dynamics.

Methods

Here we describe the models we use to fit the 2001 Cumbria epidemic data. These build on past work (Ferguson, 2001; Keeling, 2001) and more recently (Chis Ster and Ferguson, 2007; Chis Ster et al., 2009; Diggle, 2006), and fall into three categories: between farm models (BFM), within-farm models (WFM), and hybrid farm model (HFM). For the BFM the study unit is the farm, as in our previous work. The other two classes of models each include the two main additional features intended to capture details of disease progression on a farm: a farm infectiousness profile that results from disease dynamics within the farm, and a probability of detection depending on farm size and species related to interventions and control policies. The WFM treats both of these as explicitly depending on the number of infected animals on a farm, whereas the HFM models the within-farm epidemic infectiousness mechanistically, but assume the probability of detection identically for all farms. We condition our analyses on the state of the epidemic on 23rd February as in earlier work (Chis Ster and Ferguson, 2007; Chis Ster et al., 2009; Diggle, 2006).

Description of the data

Our data consist of 6782 non-empty farms in Cumbria, excluding pig-only farms. There were 890 (13%) designated IPs (881 with infection date recorded to be after 23rd February); 2738 (40%) culled as part of control policy and the remaining 3154 (47%) escaped infection. Details on Cumbria representativeness for the whole UK epidemic are given in the Supplementary Information (SI).

The within farm model (WFM)

This subsection details the key developments made in the current study over our previous work, i.e. the mathematical model of disease transmission dynamics within a farm. As data are available on daily basis, we use a discrete time model (the continuous time version of the model is given in the SI). Unknown parameters are estimated by embedding this model within the between-farm model published previously (Chis Ster et al., 2009), or made the subject of sensitivity analysis.

Let $S(t)$ represent the number of susceptible animals on a single-species farm at time t (days since the infection at farm has started), and $n(t, j)$ be the number of infected animals on a farm at time t who were infected time j before t. The relative infectiousness of an animal of infection age j follows an infectiousness profile, denoted by $\phi(j)$. Therefore, the total infectious load of a farm at time t, $P(t)$ is given by:

$$P(t) = \sum_{j=0}^{t} \varphi(j) n(t, j) \tag{1}$$

We assume animals seeding infection of a farm on day $t = 0$ have infectious age 0, so:

$n(0,0) = I_0$ and $n(0, j) = 0, j > 0$.

The infection process is modelled thus:

$$\begin{aligned} &S(0) = N - I_0 \\ &S(t) = S(t-1) \times \max(1 - \beta P(t)/N, 0), \quad t > 0 \\ &n(t,\ j) = n(t-1, j-1), \quad t > 0 \ \text{ and } \ j > 0 \\ &n(t, 0) = S(t) - S(t-1), \quad t > 0 \end{aligned} \tag{2}$$

Here, β is the within-farm transmission coefficient.

If the infectious profile $\phi(\,)$ is normalized to unity then the within-farm reproduction number is simply given by $R_0 = \beta$.

A number of experiments are valuable for parameterising this model because they supply data on animals' viral shedding through time-since-infection. In particular, they provide these data for 'naturally' infected animals; animals infected by inoculation have significantly accelerated disease progression (Alexandersen et al., 2003a). Cattle were infected with the same strain of FMD virus (FMDV) that caused the 2001 UK epidemic (FMDV O UKG 2001) by being placed in contact with animals which had been inoculated with this virus. It was found that in animals infected by contact, temperature, viraemia, virus in the breath, and virus in nasal and oral swabs all reached their peak levels simultaneously around 5 days after infection. Similarly, there are reports that the levels of virus in nasal and rectal swabs from sheep infected by contact with the UK 2001 strain of FMDV peak 4–5 days after infection (Alexandersen et al., 2003c). These assumptions are in agreement with recent experimentally derived estimates of the latent, incubation and infectious periods of 4.6 (3.1, 7.2), 4.1 (2.9, 5.9) and 1.7 (0.3, 4.8) days, respectively (Charleston et al., 2011).

Accordingly, we take the infectious profiles for individual animals to be a one-parameter functional form which rises from zero to a peak before decaying exponentially, i.e. mathematically described below.

$$\phi(j) = \theta^2 j \exp(-\theta j) \tag{3}$$

We consider and discuss two parameter scenarios: the peak time scale chosen as $\theta^{-1} = 4$ days for cattle and $\theta^{-1} = 5$ days for sheep and another situation in which they are chosen to be slightly shorter, i.e. $\theta^{-1} = 3$ days for cattle and $\theta^{-1} = 4$ days for sheep (this is referred to in as timescale 1 or 2 and denoted by TS1 and TS2 respectively). The resulting profiles for scenario TS1 are shown in Fig. 1a. We discuss the effect of these two scenarios on the resulting within farm dynamics in the subsequent sections.

The description of within-farm epidemics for mixed farms is a simple extension of Eq. (2) for the single species farm infectivity profile. The total infectious weight of a mixed farm is:

$$F(t) = R_I P_c(t) + P_s(t) \tag{4}$$

where R_I measures the infectiousness of cattle relative to sheep. If we allow for assortative mixing between species on a farm (parameterized by β), the infectiousness of a farm, F, becomes species-specific:

$$\begin{bmatrix} F_c(t) \\ F_s(t) \end{bmatrix} = \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix} \begin{bmatrix} P_c(t) \\ P_s(t) \end{bmatrix} \tag{5}$$

Assortative mixing allows the two species to differentially infect each other on a farm. Homogeneous (random) mixing corresponds to $\rho = 1$. The data provided limited information on the value of ρ within-farms, as reflected by very poor MCMC convergence when we attempted to estimate this parameter (to be contrasted with previous work which was able to estimate assortativity of mixing in between farm transmission, Chis Ster and Ferguson, 2007). We therefore performed a sensitivity analyses for three different values of, i.e. $\rho = 0.3$, $\rho = 0.6$ and $\rho = 1$. We focus on the results for $\beta = 1$ but discuss how greater assortativity of mixing affect the within farm species-specific estimates.

Two key aspects of within-farm dynamics are the process of seeding of infection on a farm and how infection is detected on a farm; both directly affect estimates of within-farm R_0 values. We considered two model variants for seeding: one where a certain *proportion* of the animals on a farm are initially infected; and one where a certain *number* of the animals on a farm are initially infected.

Since the within-farm model includes time-since-infection, there is also a question of how long these initial seed animals have been infected when they first contact other animals on the farm. The most natural choice is that seed animals are infected exactly when the farm is estimated to have been infected, corresponding to infection by contact rather than import (given we model transmission which occurred after the national movement ban of 23rd February). However, we carried out a sensitivity analysis to this assumption, by examining the effect on farm and overall dynamics of assuming seed animals were infected 1–2 days before the within-farm dynamics starts.

The unknown infection times, and the possibility of hidden infections amongst proactively culled farms, necessitate modelling the time between infection and detection on a farm. We define the cumulative infectiousness by day t post infection for each species (with $x = c, s$ standing for cattle and sheep respectively) as:

$$Y_x(t) = \sum_{j=0}^{t} P_x(j) \tag{6}$$

This can be interpreted as a rough proxy for the species-specific contribution to the total history of disease symptoms on a farm, under the assumption that infectiousness is correlated with the development of signs. The hazard that a farm is detected on day t since its infection is assumed to increase sub-linearly with $Y_x(t)$, and scales with the proportion rather than the absolute number of infected animals on a farm; i.e. it increases nearly linearly for a small proportion of infected animals and saturates when the infection prevalence is large. We define a *detection threshold* parameter, α_x, to quantify when saturation of the detection hazard occurs. The hazard for surviving detection on day t is given for mixed farms (and single species farm accordingly) by

$$h(t) = 1 - \exp\left(-\left(\frac{Y_c(t)}{\alpha_c N_c} + \frac{Y_s(t)}{\alpha_s N_s}\right)\right) \tag{7}$$

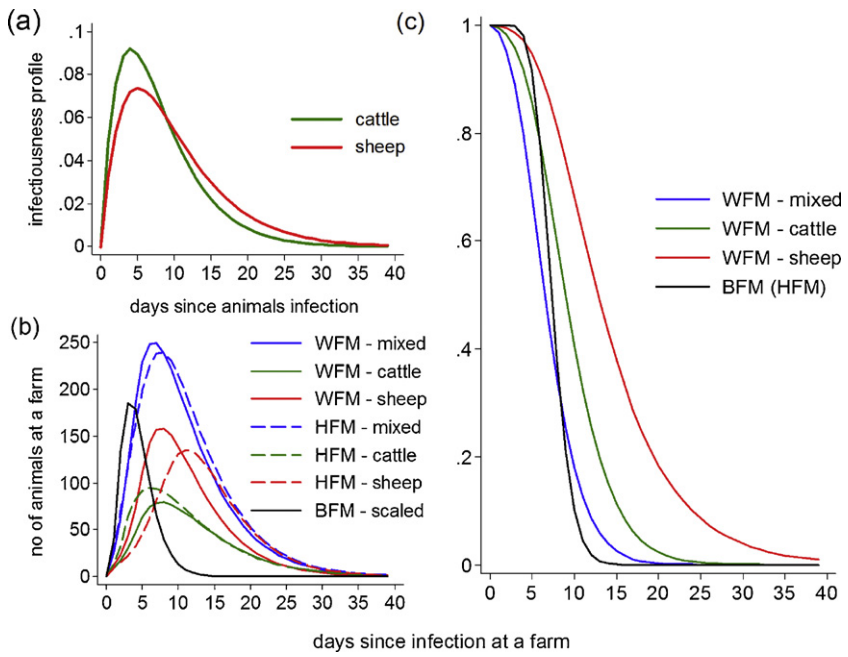

Fig. 1. (a) Individual animal infectiousness profile by species; TS1 profile shown. (b) Average farm-level infectious profiles across IPs by species on farm. (c) The average probability of surviving detection as a function of time since farm infection as predicted by WFM, HFM and BFM model variants. The estimates used are presented in Table 1 (TS1 and 0 days as initial seed animals' offsets).

Here we denote the number of animals of a given species x by N_x. We also explored models where the time of detection depended on the absolute number of infected animals on a farm (independent of a farm's size), but these models fitted the 2001 epidemic data substantially less well than models assuming detection depended on per-capita prevalence (results not shown). Details on the discrete-time version of these models are given in SI.

If $\exp(-H(j))$ denotes the probability of surviving detection function until day j (H is the cumulative hazard from Eq. (7)) for a farm of type x and K is the maximum duration of a farm epidemic ($K=40$ days is an appropriate approximation), we now define the average proportion of infectiousness accumulated by a farm prior to its detection adapted from Fraser et al. (2004). That is

$$q_x = \frac{\sum_{j=0}^{K} P_x(j)\exp(-H_x(j))}{Y_x(K)} \tag{8}$$

for a single species farm x (with the appropriate generalisation using Eq. (4) for a mixed farm). We average this quantity (8) across all designated farm cases of same type, i.e.

$$Q_x = \frac{\sum_{no\,farms} q_x}{no\,farms} \tag{9}$$

and this defines the average fraction of infectiousness accumulated by a farm of that type before being reported. In the absence of any control measures, this would correspond to the proportion of onward infection to other farms caused by an index farm prior to detection of infection on that index farm.

Farm susceptibility is included as analysis of the 2001 outbreak data has revealed that not only were cattle farms more susceptible than sheep farms, but also that mixed farms could be more susceptible than single species farms (Ferguson et al., 2001a,b). We allow farm susceptibility to saturate with respect to farm size. Parameters D_c, D_s control the farm susceptibility saturation level. Susceptibility in mixed farms is set to be greater than that of single species farms, and this is captured by an additional multiplicative parameter denoted by R_{Sus}. The susceptibility of a farm of type x, S_x, is then defined as:

$$\begin{aligned} S_x &= \frac{N_x}{N_x + D_x}, x = c, s \\ S_{mix} &= R_{sus}\left(\frac{N_c}{N_c + D_c} + \frac{N_s}{N_s + D_s}\right) \end{aligned} \tag{10}$$

Note that this functional form assumes sub-linear scaling of the susceptibility of a farm with the number of animals on the farm, consistent with the results of our previous work (Chis Ster et al., 2009).

The other components of the force of infection for this model variant are similar to those used in past work. All models treat the spatial component of the force of infection similarly to that study (Chis Ster et al., 2009), i.e. using a power law kernel function $k(d)$ of distance between farms d. This reflects the fact that contacts between farms are confined locally, and depend on the distance between farms, denoted by d_{ij}. The hazard at time t imposed on the susceptible farm i by the infectious farm j infected τ_j days ago depends on the infectiousness of farm j as given by the within-farm model, thus:

$$\lambda_{ij}(t) = k(d_{ij})\beta_0 S^i_{farm\,type}(R_I P_{c,j,\tau_j}(t) + P_{s,j,\tau_j}(t)) \tag{11}$$

The hybrid farm model (HFM)

This model variant uses the within-farm model described above to describe the time evolution of infectiousness on a farm, but uses a simple (discretised) gamma distribution to describe the time delay from infection to report on a farm, independent of farm size and type:

$$\Gamma(t; \text{shape}, \text{scale}) = t^{\text{shape}-1}\frac{\exp(-t/\text{scale})}{\text{scale}^{\text{shape}}\Gamma(\text{shape})}$$

We estimate the parameters of this distribution.

The between farm model (BFM)

The unit of this model is the farm and the model structure follows that used in our previous work carried on these data, with farms classified as one of the three states: reported as case and consequently culled, infected but not reported (hidden infections) and survived infection. The mathematical formulation is briefly reviewed in the SI and presented in detail in our past work (Chis Ster et al., 2009).

Model fitting and model comparison

Reversible jump MCMC methods have been previously applied in similar situations when the dimension of the parameter space is a parameter itself (Gibson and Renshaw, 1998; O'Neill and Roberts, 1999; O'Neill, 2002). Details on the parameters' updating and infection times imputation are given in the SI.

Model choice/comparison for the type of models considered here is challenging because of missing data, the dimensionality of which is estimated. The WFM and HFM model variants predict different, variable numbers of hidden infections (each of which counts as a model parameter) and methods for model choice in this context are beyond the scope of this paper. While not attempting formal model selection, we present some indications of model fit to illustrate that inclusion of within-farm dynamics results in a comparable fit to the data. In particular, we calculate the Deviance Information Criterion (DIC) statistic as developed in Celeux et al. (2006), Gelman et al. (2000). More detail is given in the SI. We also present results on how well different models reproduce the observed epidemic time-series. For all 3 model variants (pure BFM, WFM and HFM), we estimated the daily incidence by farm type using the daily cumulative force of infection in the same manner as in Chis Ster et al. (2009), i.e. one-step ahead prediction of incidence at time $t+1$ conditioned on observed cases up to time t, averaging across a set of equilibrated MCMC parameter chains.

Results

BFM parameter estimates

The estimates resulting from fitting the BFM model to the 2001 FMD epidemic restricted to Cumbria and conditioned on 23rd February are comparable to those obtained by fitting to the whole UK data (Chis Ster et al., 2009). Sheep-only farms are the least susceptible, large mixed farms (i.e. those whose size-dependent susceptibility has saturated) are estimated to be 3.17 (2.7, 3.7) times more susceptible than large single species farms, and the presence of cattle increases a farm's susceptibility with herd size more sharply than sheep (SI). Cattle are more infectious than sheep (Table 1) and farm infectiousness profile displays a similar peak around 3.3 (2.8, 3.7) days – regardless its species components and size (Fig. 1b). The mean delay from infection to report is estimated at 8.5 (8.4, 8.6) days, a value close to that estimated when fitting the model to the whole UK data. The baseline infectiousness parameter (4976 (3045, 6663)) has a similar scale to the corresponding UK estimate (Chis Ster et al., 2009). Although less convincing than for the fit to the whole UK dataset, we also found some degree of support for an increase in overall transmission before the epidemic peak and in the tail (Table 1), i.e. the estimate of the relevant parameter was 0.95 (0.83, 1.16) – with about 30% probability that its value is greater than 1. The spatial kernel decays more rapidly with distance than that estimated for the whole country, perhaps unsurprisingly since we restricted our analysis to Cumbria.

WFM parameter estimates

We refer to species-specific reproduction numbers (R_0), seeding and detection threshold as within-farm parameters, and the baseline, susceptibility, herd infectivity ratio and spatial kernel parameters as between-farm parameters. Between-farm parameters are robustly estimated, with values fairly similar to those obtained fitting the BFM. Table 1 presents model results for the within-farm model variants which assume an initial proportion of animals on a farm are infected, while Supplementary Information (SI) presents comparable estimates for model variants assuming a fixed number of animals are initially infected.

The farm-level property that influences between-farm transmission the most is farm infectiousness through time. High R_0 values and low initial proportions of animals infected can generate similar farm-level infectious profiles as lower R_0 values and higher initial proportions infected, meaning, estimates of R_0 and seeding parameters are negatively correlated (see Fig. 8 in SI). Without any constraints on the seeding parameters, the model estimated unfeasibly low levels of seeding of infection (whether proportions or numbers of animals) and very large R_0 values. We therefore imposed the biologically realistic constraint that initial seeding of infection on a farm had to involve at least one animal for each species on that farm, and, when assuming fixed numbers of animals were initially infected (see SI), we assume that initial numbers infected in each species are proportional to the relative (farm-level) susceptibilities of the two species. When assuming a fixed proportion of animals on each farm are initially infected, we examined imposing lower bounds on the proportion infected of 2%, 5% and 10% independently for cattle and sheep (again subject to the additional constraint that at least 1 whole animal needed to be infected), giving 9 model variants.

The R_0 values then estimated are strongly determined by assumptions about seeding of infection on farms (see SI). Estimates of the proportion of sheep initially infected are rather close to their imposed lower bounds, though estimates of the initial proportion of cattle infected are less strongly influenced by the choice of lower bounds (see SI). As other parameters values for these model variants do not differ substantially, in the main text we present the results for 5% seeding lower bounds for both cattle and sheep. The initial proportion in cattle is estimated to about 11%, and that in sheep hits its lower bound of 5%.

The infectiousness profiles averaged across farms of different types are displayed in Fig. 1b. The detection threshold parameter estimates are relatively independent of the constraints imposed above. According to (7), mixed farms are detected most quickly and the values we obtained (i.e. 11.6 (9, 13) and 28 (19, 34)) for cattle and sheep respectively mean that they are followed by cattle-only farms, with sheep-only farms taking longest to be detected. This is epidemiologically plausible as infected cattle are the first to display clinical signs; mixed farms hold a considerable number of cattle (Fig. 2 in SI). The predicted detection survival curves for these parameters, averaged across Cumbrian IPs are shown in Fig. 1c.

We assess the sensitivity of estimates to the timescale for infectiousness to peak in an individual animal, and how long animals that seed infection in a farm have been infected for at the time of their introduction to the farm. As expected, assuming both faster within-animal shedding profiles (variant TS2) and that the initially infected animals on a farm were infected before the time of infection of the farm as a whole leads to faster peaking of the farm infectiousness profile (Fig. 2). However, the effect is not large, and survivorship profiles are even less affected. However, when animal-level infectiousness peaks earlier the estimated values for R_0 are generally smaller (Table 1 and SI). The effect of different minimum bounds imposed for initial seeding proportions on species R_0 are given in Table 2.

Table 1
Parameter estimates (mean and 95% credible intervals) for model variants estimating initial proportions of animals infected with 5% as lower limits for each species. TS1 and TS2 represent the two scenarios explored (see main text) for the timescales of development of infectiousness in individual animals. 'Offset' represents how long (in days) animals seeding infection on a farm had been infected before they were introduced to the farm. Q (not an independent parameter) is the average fraction of infectiousness accumulated by an IP prior to detection (by farm type).

		Within farm model				Hybrid farm model				Between-farm model
		TS1		TS2		TS1		TS2		
		$C=0$ $S=0$	$C=1$ $S=1$	$C=0$ $S=0$	$C=1$ $S=1$	$C=0$ $S=0$	$C=1$ $S=1$	$C=0$ $S=0$	$C=1$ $S=1$	
	Log likelihood	−7826 (−7964, −7724)	−7861 (−7988, −7755)	−7886 (−8007, −7781)	−7896 (−8010, −7798)	−7255 (−7324, −7185)	−7240 (−7347,−7163)	−7259 (−7328, −7189)	−7240 (−7312, −7169)	−7186 (−7271, −7107)
	DIC	17,057	17,180	17,176	17,196	15,123	15,220	15,166	15,164	15,254
	No of hidden infections	100 (81, 121)	104 (87, 126)	109 (91, 130)	105 (88, 126)	67 (53, 81)	66 (53, 81)	69 (54)	67 (54, 82)	72 (7.8) (57, 88)
Within farm parameters	R_0R_0 cattle	21 (16, 25)	19 (15, 23)	15 (13, 18)	12 (10, 15)	49 (41, 61)	43 (31, 68)	36 (30, 42)	33 (25, 37)	
	R_0 sheep	14 (10, 19)	13 (10, 16)	9 (7, 12)	8 (6.6, 10)	10 (1.4, 21)	10 (1.15, 23)	7.3 (1.1, 14)	4.7 (1.16, 11.5)	
	Initial prop cattle (%)	7 (6.2, 8.1)	7.8 (6.8, 8.4)	7 (6.7, 7.5)	7 (6.8, 7.6)	7.3 (6.5, 9.2)	7.8 (6.3, 9.1)	8.3 (7.6, 10.2)	7.8 (6.3, 9.1)	
	Initial prop sheep (%)	5.4 (5.1, 6.3)	5.2 (5.1, 6.4)	6.3 (6.1, 6.7)	6.9 (6.6, 7.2)	5.5 (5, 7)	5.4 (5.0, 6.9)	5.4 (5.0, 6.9)	5.4 (5, 6.6)	
	α_C – cattle detection threshold	11 (9, 13)	11 (9, 13)	14 (5, 18)	11 (9, 13)					
	α_S – sheep detection threshold	27 (19, 34)	28 (19, 27)	33 (23, 42)	28 (19, 27)					
	Prop Q – cattle	41%	40%	53%	47%	42%	44%	53%	53%	
	Prop Q – sheep	67%	68%	78%	76%	25%	24%	25%	29%	
	Prop Q – mixed	33%	33%	45%	41%	43%	44%	53%	54%	
	β_0Baseline β_0	7 (2, 13)	20.1 (2, 41)	3.7 (2.8, 6.8)	14 (5, 18)	5 (1.5, 11)	2.8 (1.4, 8.9)	8.1 (2.1, 12)	1.52 (1.3, 4.1)	4976.7 (996) (3045, 6663)
	RS – farm level susc. ratio	3.1 (2.6, 3.8)	2.97 (2.5, 3.6)	3.15 (2.8, 3.7)	3.12 (2.6, 3.7)	3.4 (2.8, 4.1)	3.2 (2.7, 3.8)	3.4 (2.8, 3.8)	3.3 (2.9, 3.5)	3.17 (0.3) (2.7, 3.7)
Between farms parameters	RI – farm level inf. ratio	74 (24, 138)	52 (22, 90)	65 (30, 150)	41 (27, 108)	75 (32, 150)	88 (51, 170)	52 (34, 140)	29 (11, 67)	6.7 (2.6) (3.1, 13.8)
	DC – cattle susceptibility saturation scale	120 (85, 162)	122 (86, 164)	124 (102, 150)	133 (109, 173)	111 (79, 161)	117 (77, 158)	110 (80, 126)	130 (95, 168)	100.7 (13.8) (76, 128)
	DS – sheep susceptibility saturation scale	1023 (714, 1455)	1063 (625, 1576)	1081 (543, 1594)	1164 (762, 1386)	1232 (876, 1654)	1280 (790, 1821)	1131 (820, 1526)	1632 (1104, 1938)	1068.6 (167) (561, 1375)
	a – Kernel offset	2097 (1568, 2505)	2016 (1396, 2737)	2009 (1427, 2834)	2583 (1556, 2907)	2325 (1679, 2940)	2214 (1460, 2876)	1898 (1434, 2433)	2170 (1687, 2632)	1915 (266) (1415, 2447)
	γ – Kernel power	3.2 (2.9, 3.4)	3.1 (2.8, 3.4)	3.3 (3.2, 3.5)	3.3 (2.8, 3.4)	3.3 (2.9, 3.5)	3.2 (2.8, 3.5)	3.1 (2.8, 3.6)	3.2 (2.9, 3.3)	3.1 (2.8, 3.3)
	Day post infection infectiousness peaks									3.3 (0.2) (2.8, 3.7)
	Infectiousness profile power									3.1 (0.8) (1.8, 4.8)
	Infection to report distribution mean					8.4 (8.2, 8.6)	8.5 (8.4, 8.6)	8.4 (8.3, 8.6)	8.5 (8.4, 8.6)	8.5 (0.07) (8.4, 8.6)
Time	Infection to report distribution variance					3.6 (3.3, 4.1)	3.7 (3.3, 4.1)	3.6 (3.3, 4.1)	3.7 (3.3, 4.1)	3.7 (0.2) (3.3, 4.1)
	1st May increase in transmission									0.95 (0.83, 1.11)

Table 2
R_0 estimates (mean and 95% credible intervals) for model variants estimating initial proportion of cattle and sheep infected on a farm, as a function of the minimum % bounds on the initial proportion of cattle (column headings) and sheep (row headings) assumed to be infected.

					Initial proportion of cattle infected					
					2% R0 cattle	5%	10%	2% R0 sheep	5%	10%
Initial proportion of sheep infected	WFM	TS1	$C=0$, $S=0$	2%	77 (67, 82)	38 (26, 63)	44 (40, 49)	25 (16, 31)	20 (15, 25)	20 (16, 28)
				5%	29 (23, 32)	21 (16, 25)	18 (15, 22)	15 (11, 21)	14 (11, 19)	13 (9, 20)
				10%	20 (16, 25)	19 (16, 24)	15 (13, 20)	11 (7, 16)	11 (8, 16)	11 (7, 16)
			$C=1$, $S=1$	2%	38 (28, 46)	29 (22, 36)	23 (16, 35)	18 (15, 29)	17 (13, 24)	18 (14, 25)
				5%	23 (18, 27)	19 (15, 23)	17 (12, 21)	15 (11, 21)	14 (10, 16)	14 (10, 20)
				10%	20 (14, 25)	15 (12, 19)	13 (10, 16)	11 (7, 16)	10 (7, 14)	10 (6, 13)
		TS2	$C=0$, $S=0$	2%	55 (50, 60)	19 (16, 27)	14 (11, 19)	14 (10, 19)	11 (8, 14)	12 (9, 16)
				5%	21 (18, 23)	15 (13, 18)	11 (9, 13)	8 (6, 10)	9 (7, 12)	8 (6, 10)
				10%	16 (14, 19)	14 (11, 16)	10 (8, 11)	8 (5, 10)	8 (6.7, 9)	6 (3, 8)
			$C=1$, $S=1$	2%	44 (39, 49)	17 (14, 22)	13 (10, 19)	13 (9,17)	11 (8, 16)	11 (9, 15)
				5%	18 (16, 20)	12 (10, 15)	9 (8, 11)	8 (6, 9)	8 (6, 10)	7 (5, 10)
				10%	14 (12, 16)	11 (9, 13)	8 (7, 9)	5 (3, 8)	6 (4, 8)	6 (4, 9)
	HFM	TS1	$C=0$, $S=0$	2%	55 (43, 67)	58 (42, 72)	51 (44, 60)	17 (1, 30)	15 (1, 30)	12 (1.2, 25)
				5%	51 (42, 62)	49 (42, 61)	46 (39, 55)	7 (1.1, 23)	7.6 (1.4, 19)	8 (1.4, 21)
				10%	41 (29, 51)	44 (34, 58)	44 (31, 55)	8 (1.1, 18)	5 (1., 15)	6 (1.3, 17)
			$C=1$, $S=1$	2%	42 (32, 52)	63 (53, 73)	86 (35, 135)	18 (8, 28)	11 (1.2, 23)	15 (1.5, 43)
				5%	65 (41, 103)	43 (31, 68)	40 (32, 81)	12 (0.24, 39)	10 (1.2, 23)	6.5 (1.1, 16)
				10%	32 (22, 42)	32 (22, 43)	34 (26, 43)	6 (1, 16)	9 (1.22, 27)	8 (1.3, 26)
		TS2	$C=0$, $S=0$	2%	45 (37, 51)	45(33, 57)	33 (28, 40)	12 (1, 24)	9 (1.2, 20)	11 (1.4, 21)
				5%	36 (29, 43)	36 (30, 42)	31 (28, 34)	3.7 (0.1, 13)	5 (1.1, 14)	3.7 (1.1, 14)
				10%	31 (23, 39)	33 (22, 41)	29 (20, 31)	3.8 (0.1, 8.1)	4.7 (1.1, 20)	4 (1, 13)
			$C=1$, $S=1$	2%	32 (23, 41)	44 (34, 57)	36 (26, 46)	8.5 (1, 16)	7 (1.2, 21)	12 (3, 29)
				5%	26 (19, 34)	33 (25, 36)	26 (23, 27)	7.5 (1, 17)	5 (1.3, 11)	4.7 (1.1, 13)
				10%	23 (16, 31)	26 (19, 21)	24 (17, 30)	5 (1.1, 12)	4.8 (1.2, 13)	4 (1.1, 12)

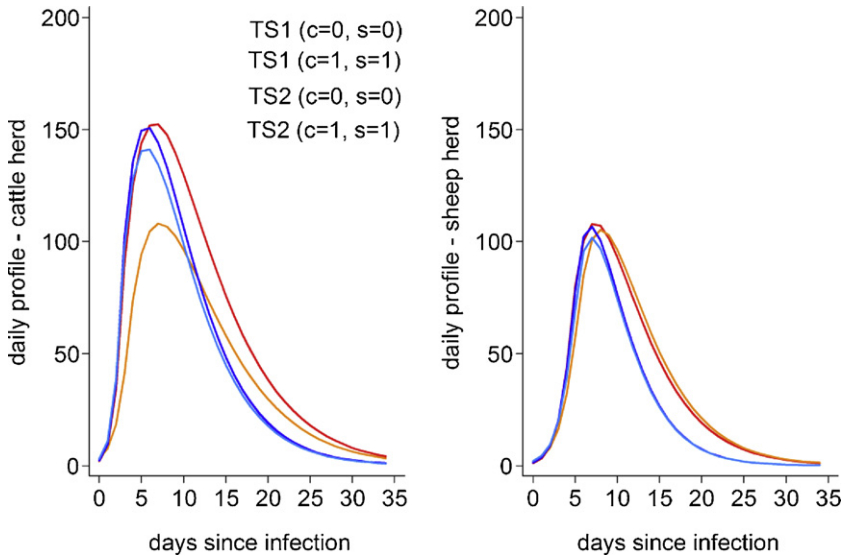

Fig. 2. The effect of animal species specific timescale (TS1 and TS2) and initial seed animals' offsets ($c = 0$ and $s = 0$ stand for 0 days for cattle and sheep, respectively) on the herd dynamics for each species. The herd size is 300 animals. The values for basic reproduction ratios (species specific R_0s) and species initial proportions are displayed in Table 1.

For model variants presented in Table 1 we investigated the extent to which species-specific within herd dynamics were affected by the departure from homogeneous mixing, i.e. changes resulting from $\rho < 1$. The negative correlation between R_0 estimates and initial seeding proportions complicated the interpretation of these results. The estimate of the initial proportion infected estimate for sheep hits the imposed lower limit of 5% however, and there is some indication that more assortative mixing is compensated for by increased transmission within species, with R_0 larger for lower ρ (Table 3).

As mentioned above, the parameter with the most noteworthy scale change compared with the pure BFM model results is the baseline transmission β_0 parameter (Table 1). Here values are reduced to below 10 from about 5000. However, this is solely due to the introduction of infectious profiles based on the numbers of animals on a farm, which take large absolute values on average.

HFM parameter estimates

We estimate that the probability of escaping detection for the HFM drops sharply after about 7 days and becomes negligible after 12–13 days for farms classified as reported (Fig. 1c). Histograms of the estimated detection-to-cull delays for proactively culled farms in the HFM model are fairly compact and similar in form to the corresponding histograms for the BFM. By comparison, the histograms of estimated infection-to-cull delays under the WFM have much longer tails (Fig. 3), and the corresponding mean detection-survivorship curves (Fig. 1b) are longer, and show marked differences between species. These differences in detection also influence the estimated number of hidden infections. The numbers of hidden infections estimated by WFM and HFM are compared by species in SI Figs. 4 and 5. The WFM consistently estimate higher numbers of hidden infections, mostly on sheep farms. Here, the difference between hidden infections in the HFM and WFM shows up among farms culled under the 3 km local policy (more than 80% of all farms culled under that policy were sheep-only farms). All the models predicted most hidden infections occurred before the peak of the epidemic, however the HFM predicted half as many early culled farms to be infected (∼35%) than the WFM (∼70%) (SI Table 2). Proportions of culled farms estimated to be infected during the tail of the epidemic were similar in both the HFM and WFM (∼4%), however the proportions during the peak were higher in the WFM than the HFM (2.6% vs. 1.6%). Table 4.

The predicted number of reported case by farm type given in Tables 5 and 6 in SI also highlight the effect of the probability of detection of sheep farms only cases; the WFM model tends to overestimate the number of IPs in sheep-only farms relative to the HFM model. Similarly, the detection model strongly influences the estimates of the fraction of infectiousness accumulated by a farm prior to detection (Eq. (9)) across farms of different types. The most noticeable difference is displayed in sheep farms: WFM predicts a proportion almost three fold higher than HFM, i.e. 68% vs. 25% (Table 4).

The R_0 estimates for cattle (Table 1 and SI Table 3) estimated by the HFM are higher than for the WFM. This is because the higher hazards of detection make for a tighter distribution of infectious periods, forcing within farm epidemics to peak more quickly in compensation. All models match the empirical times from infection to report well, including the more dispersed pattern for sheep (SI – Figs. 6 and 7).

Table 3
The effect of different degrees of mixing (ρ) between species on within-farm R_0 and initial proportion infected parameter estimates for the WFM baseline model variant (parameters in Table 1 for TS1 and offsets $C = 0$, $S = 0$).

ρ	Cattle		Sheep	
	R_0	Initial proportion	R_0	Initial proportion
0.3	26	8.4%	18	5%
0.6	33	7.8%	15	5%
1	20	11%	14	5%

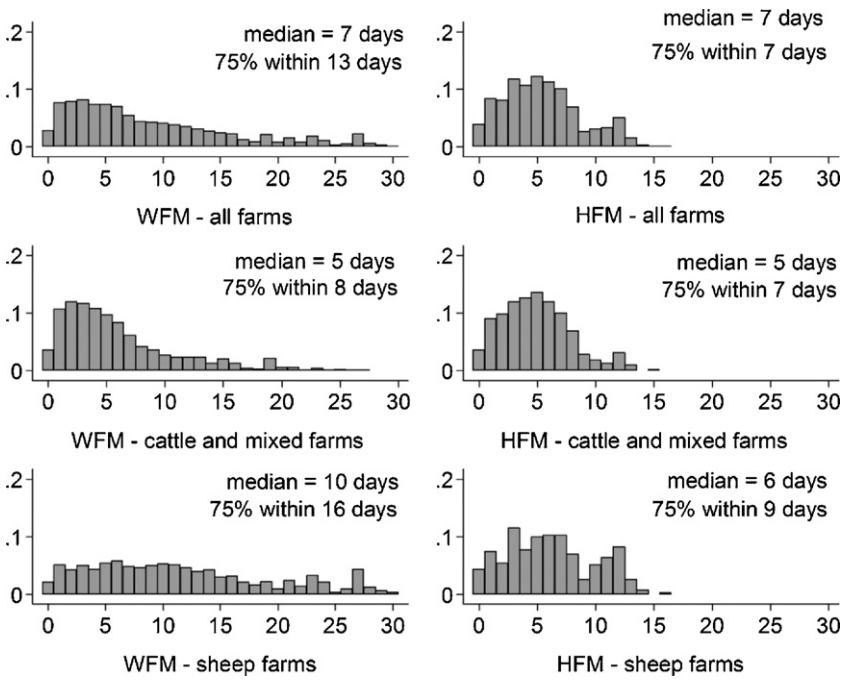

Fig. 3. Time since infection to cull as predicted by WFM and HFM. The parameter estimates correspond to those in Table 1 for TS1 and 0 days as initial seed animals' offsets by farms type.

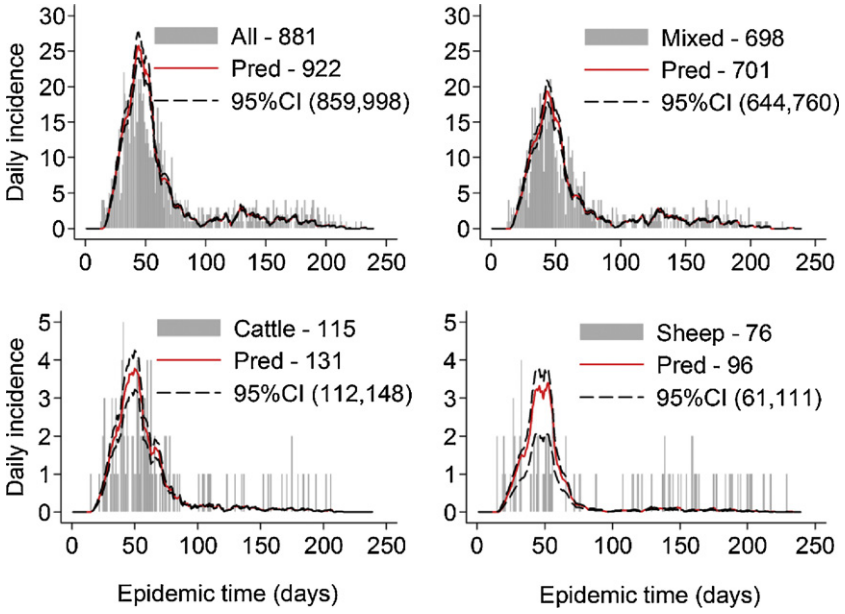

Fig. 4. Case incidence time series by farm type as predicted by WFM model variant using the estimates presented in Table 1 (when initial proportion of infected animals estimated).

Table 4
The average fraction of total farm infectiousness accumulated prior to detection (Q) on an IP by farm type.

Q – by farm type	WFM				HFM			
	TS1		TS2		TS1		TS2	
	$C=0$ $S=0$	$C=1$ $S=1$	$C=0$ $S=0$	$C=1$ $S=1$	$C=0$ $S=0$	$C=1$ $S=1$	$C=0$ $S=0$	$C=1$ $S=1$
Cattle	41%	40%	53%	47%	42%	44%	53%	53%
Sheep	67%	68%	78%	76%	25%	24%	25%	29%
Mixed	33%	33%	45%	41%	43%	44%	53%	54%

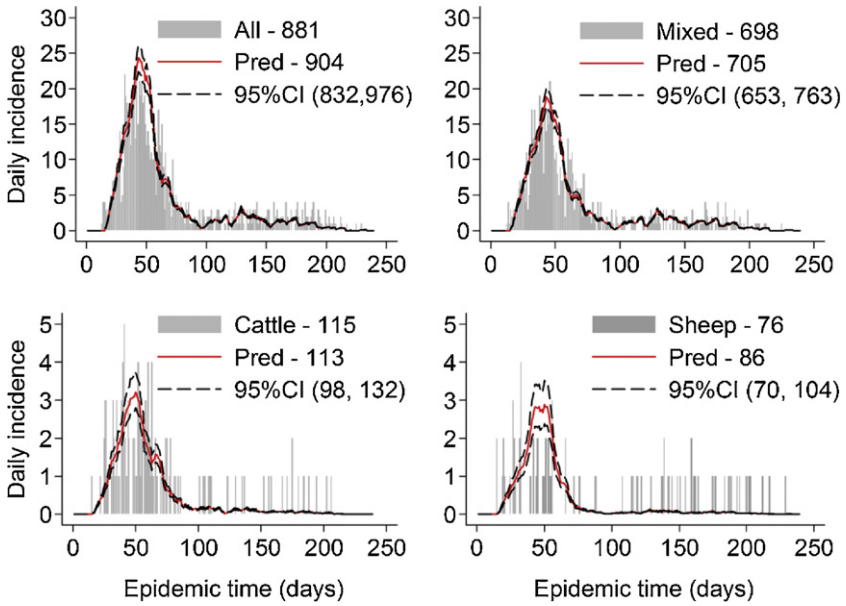

Fig. 5. Case incidence time series by farm type as predicted by WFM model variant using the estimates presented in Table 1 (when initial proportion of infected animals estimated).

Model fit

DIC values were lower for the HFM than the WFM. In a classical situation (i.e. with complete data) this difference would indicate the HFM fits better than the WFM. However, as mentioned in the SI, there is not an established formal interpretation of this statistic when models differ in the inferred dimensionality of missing data (here, larger number of inferred unobserved infections for the WFM), and a lack of theory generally for the use of the DIC for complex non-linear models. We are therefore urge caution in applying too much weight to the imputed values of this statistic.

Using one step ahead prediction of incidence at time $t+1$ conditioned on observed cases up to time t, the incidence time-series for cattle-only and mixed farms are fairly well reproduced by both sets of models incorporating within-farm dynamics. Although not a particularly discriminatory comparison, sheep-only farms are more accurately tracked by the HFM (Table 1 and Fig. 1). The BFM variant (with worse DIC than the HFM) produces similar results to the HFM, suggesting the main influence on models' ability to fit incidence time series is how detection of infection is modelled (see Discussion).

The difference in these results between the WFM and HFM highlights the importance of how detection of infection is modelled, and provides post hoc justification for approaches ignoring the possibility of differences in detection by farm size or composition. Beside this, the HFM supports larger differences between species in within-farm R_0 values than the WFM, with estimates of R_0 for sheep being considerably lower in the HFM model variant.

Discussion

This paper continues a series of retrospective statistical analyses aimed at understanding the epidemiology of the 2001 UK FMD outbreak. The present analysis incorporates known features of the pathogenesis of FMD, and is aimed at exploring to what extent the farm-level data collected in the 2001 outbreak allows inference regarding within-farm transmission dynamics. In bringing together information from these different scales, we have been able to explore the relevance of within-farm dynamics to our understanding of the epidemic as a whole. In the absence of full-scale field experiments, or more detailed data from outbreaks on farm-level epidemics, inferences from outbreak data on between farm-spread provide the only window onto parameters determining the within-farm spread of FMD. Formal model selection was not appropriate due to missing data, but DIC statistics and one-step-ahead predictions suggest that, while differing in their accounts of the epidemic, the models are comparable in their ability to capture the dynamics of the epidemic.

The added layer of complexity in tracking the course of epidemics on each farm adds substantially to the computational cost of inferential models. We therefore restricted our analysis to Cumbria, the area of Britain which suffered the most intense transmission (Wilesmith et al., 2003). A further advantage of studying Cumbria is that this area saw substantial numbers of infections of sheep and mixed farms, allowing species differences to be resolved better than would have been possible if another area (e.g. Devon) had been chosen. Clearly restricting the analysis to a single area limits our ability to generalise the results, though we might expect within-farm transmission dynamics to be more determined by husbandry practices than physical location.

In addition to tracking the number and stage of infection of infected and susceptible animals on a farm, within farm models need to represent the seeding process (i.e. the initial conditions on each farm after infection) and the detection process. Seeding is perhaps the least quantitatively understood aspect of FMD epidemiology, and proved to be one of the most challenging aspects of our analysis. Similar epidemic curves can arise with higher levels of seeding and lower values of R_0, or vice versa. This leads to a natural negative correlation between estimates of these quantities, and we found a tendency towards inferring very low levels of infection seeding and very high within-farm R_0 values. To cope with this, we constrained the level of seeding, and then investigated the effects of different choices of lower bounds the estimates of both seeding and R_0, as discussed in "Results" section.

The estimated values of within-farm R_0 and seeding of infection implies there were relatively few rounds of infection on most IPs in 2001 prior to infection being detected and the farm being culled (or at least subject to controls). While these estimates are not biologically unreasonable, the fact that most animals would be expected to be infected within 2 generations of infection (at least on

cattle farms) offers retrospective support to using models of FMD transmission which represent farms as the relevant epidemiological unit, albeit using time-varying infectiousness profiles rather than constant infectiousness through time (Chis Ster et al., 2009).

Some of the more interesting results from our analysis arise from exploring different models of the delay from infection to report of infection on IPs. To disentangle the effects of allowing the infectious profile of a farm to be determined by within-farm dynamics from those due to the new model of detection, we introduced the HFM model variant. This includes the mechanistic within-farm account of infectiousness, but models the delay from infection to report as determined by a fixed probability distribution which is independent of farm properties, in the same manner as the pure BFM.

As described above, the WFM predicts notably longer times to detection for sheep farms than the BFM or HFM. This may reconcile the apparent inconsistency between the fact that veterinarians' estimates of infection to report did not vary by farm-type, and the expectation that R_0 be higher among cattle, which, in addition, have more obvious clinical signs (Alexandersen et al., 2003a,b,c). We indeed estimate higher within-farm R_0 values for cattle, but the longer delays to detection for sheep farms suggest that the empirical estimates of infection times made by veterinarians during the epidemic (used as priors in our inference) may have been under-estimated for sheep farms (where lesion dating and sampling a substantial proportion of animals on a farm may have been more difficult). The longer time to detection explains why the average cumulative amount of infectiousness occurring on sheep farms prior to their detection predicted by WFM (~67%) is three fold greater than that predicted by the HFM model variant (~25%) (Table 4).

As in our previous work (Chis Ster et al., 2009), the reversible jump MCMC approach used here allows us to infer the number of unobserved ("hidden") infections, *i.e.* the number of infected farms which were culled as part of the control effort without their infection having been tested or assessed. Models including within-farm dynamics seem to consistently estimate higher (but still relatively small) numbers of hidden infections compared with the results of the pure BFM (SI). Moreover, the WFM estimates higher numbers of hidden infections than the HFM (mainly among sheep farms), showing that this difference is driven by the differing modelled detection mechanism, and the longer tails it produces in reporting delays. It should be born in mind that these small numbers of unobserved infections do not directly influence the predicted efficacy of CP culling as a control measure, since the major impact of CP culling was relatively local (i.e. within 10–15 km) depletion of susceptible farms before they become infected.

In our earlier work, models which included an ad hoc increase in transmissibility from early May 2001 (attributed to slackening in bio-security) fitted significantly better than those assuming constant infectiousness over time. Conversely, the results in this paper suggest that when within-farm dynamics are accounted for, the long tail seems to emerge more naturally from the different distributions and timing of farm infectiousness as the epidemic progressed – though this conclusions needs validation with true simulation studies.

We did find support for the hypothesis that the susceptibility of mixed farms was higher than would be expected by simply adding the susceptibility due to the individual species (Eq. (8)). Together with the typically larger number of animals on mixed farms, and the higher relative infectiousness of cattle, this confirms the central role of mixed farms in propagating the epidemic in 2001.

We explored sensitivity of results to different levels of mixing between species on a farm similarly to our past work (Chis Ster, 2007), where the simpler framework used there allowed formal estimation of a parameter controlling the mixing of herds of different farm types. While no clear picture emerged once within farm dynamics were included, more assortative mixing tended to be consistent with more intense species-specific transmission on a farm (Table 3).

The shape of a typical farm's infectious profile is crucial in determining what proportion of its infectious potential (i.e. the area under the curve of cumulative infectiousness with time since infection) is prevented by a control measure that affects the farm a certain time after its infection. Observing Fig. 2, we note that for the BFM detection typically occurred after the peak of farm infectiousness. Taking into account within farm dynamics, the WFM predicts that detection typically occurred after peak infectiousness for sheep farms, but that for cattle or mixed farms detection and peak infectiousness roughly coincide. The implication is that – particularly for farms with cattle present – reducing detection and cull delays is expected to have a large impact on transmission.

One interesting finding in our past work (Chis Ster et al., 2009) was a large estimated drop in a farm's infectiousness after it was reported. This result remains true for both WFM and HFM model variants applied to Cumbria. The magnitude of the drop is high, but imprecise – a factor of around 50, with an improvement in DICs of around 10 compared with models with no drop (SI Table 3 for WFM results). As with the BFM (Fig. 2 in Chis Ster et al., 2009), the effect in the WFM (and HFM, results not shown) is to flatten the average farm-level infectious profile, though it is not clear whether this is attributable to lower R_0 values or lower levels of seeding: the WFM model variant estimates lower initial proportions in cattle whereas the HFM model variant estimates lower R_0 values.

Our estimates of the magnitude of drop in farm infectiousness after report emphasizes the importance of encouraging rapid reporting, finding infected farms as quickly as possible and questions the significance of rapid IP culling so long as infection is detected rapidly and biosecurity restrictions imposed on each IP. However, the significance of such a change in policy recommendations plus the indirect way in which the impact of reporting on infectiousness has been estimated means additional direct evidence of biosecurity effectiveness would be desirable. The importance of limiting transmission from farms with substantial numbers of symptomatic animals (whether through effective restrictions or rapid culling) remains unarguable; indeed, the long tail of the epidemic in Cumbria may have been at least partly driven by secondary infections caused by the relatively few farms with long reporting delays which were identified once the epidemic started to decline. There were 9 farms (5 sheep-only, 4 mixed) reported after 1st May which for which the reporting date was more than 15 days later than the infection date estimated by veterinarians (Fig. 11 in SI).

Lastly, we feel that the current approach is at the edge of what can be achieved in terms of extracting information from this dataset in a rigorous fashion, and note that extra, standardized information about the extent of infection on farms upon culling (e.g. random-sample virus isolation and serology) would be extremely useful in allowing more robust conclusions about the within-farm dynamics of FMD.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2012.07.002.

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