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or no replacement of ewes, and different frequencies of examination / testing. The outcome of each control strategy was evaluated by reduction in infection or elimination (defined as 99% confident that no sheep were infected with C. pseudotuberculosis) and the number of ewes remaining in the breeding flock.

Lancing abscesses reduced the prevalence of infection when the initial prevalence of infection was less than 0.60, but elimination was unlikely. A vaccine efficacy of 0.79 led to elimination of disease from the flock, provided that the endemic prevalence of infection was below 0.60. A combination of vaccination and clinical examination reduced the prevalence of infection at a faster rate (five rounds of clinical examination were assumed) than using clinical examination or vaccination alone. Serological testing led to elimination of infection after five tests, but was highly dependent upon the diagnostic test sensitivity and specificity and management options used: a test sensitivity of 0.90 always resulted in elimination: a test specificity greater than 0.90 prevented removal of many false positive ewes and consequently prevented a large reduction in lamb production.

The choice of control strategy should be based on the need to eliminate infection from a flock and balanced against the costs of control; here the costs were replacing breeding ewes and reduced lamb productivity. Elimination was most likely with a serological test with sensitivity and specificity above 0.90 (this is not yet available), but vaccination combined with clinical examination reduced infection rapidly with little impact on lamb productivity. Further research is required to develop a diagnostic test with at least 0.90 specificity and sensitivity in field conditions before any methods can be recommended with confidence.

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The control of *Corynebacterium pseudotuberculosis* infection in sheep flocks: a mathematical model of the impact of vaccination, serological testing, clinical examination and lancing of abscesses.

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Abstract

A mathematical model framework of *Corynebacterium pseudotuberculosis* infection was used to evaluate strategies for control and elimination of caseous lymphadenitis (CLA) in sheep. Control strategies tested were vaccination, serological testing and removal of seropositives, clinical examination and removal of sheep with abscesses lancing abscesses, and, where appropriate, combinations of these. The vaccine efficacy and rate of waning immunity were estimated from published experimental studies. Control options with varying efficacy (not all currently possible) were evaluated with combinations of: three infection rates, six demographic assumptions, three at endemic equilibrium, three when infection was recently introduced and including either replacement or no replacement of ewes, and different frequencies of examination / testing. The outcome of each control strategy was evaluated by reduction in infection or elimination (defined as 99% confident that no sheep were infected with *C. pseudotuberculosis*) and the number of ewes remaining in the breeding flock.

Lancing abscesses reduced the prevalence of infection when the initial prevalence of infection was less than 0.60, but elimination was unlikely. A vaccine efficacy of 0.79 led to elimination of disease from the flock, provided that the endemic prevalence of infection was below 0.60. A combination of vaccination and clinical examination reduced the prevalence of infection at a faster rate (five rounds of clinical examination were assumed) than using clinical examination or vaccination alone. Serological testing led to elimination of infection after five tests, but was highly dependent upon the diagnostic test sensitivity and specificity and management options used: a test sensitivity of 0.90 always resulted in elimination: a test specificity greater than 0.90 prevented removal of many false positive ewes and consequently prevented a large reduction in lamb production.

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1 Introduction

Caseous lymphadenitis (CLA) is caused by infection with *Corynebacterium pseudotuberculosis.* In countries where CLA is endemic it is one of the main causes of condemnation of ewes at the abattoir (Stoops et al., 1984). *C. pseudotuberculosis* invades damaged and intact skin (Nairn and Robertson, 1974). Bacteria are then engulfed by macrophages and taken to a draining lymph node local to the site of infection (Burrell, 1978), within which an abscess may form. If the lymph node is superficial (e.g. prescapular, submandibular or parotid) the abscess is a visible, overt swelling below the skin: if the lymph node is not superficial (e.g. retropharyngeal, mediastinal or ileac), a

hidden or covert abscess forms. *C. pseudotuberculosis* also migrate within macrophages, and from these, abscesses can form in lung or kidney parenchyma (Pepin et al., 1991).

CLA was introduced into sheep in the United Kingdom in 1991, through the importation of infected Boer goats (Lloyd et al., 1990). Infection is still spreading through the national flock and new cases of CLA have been identified through passive surveillance and research since 1991 (Binns et al., 2002; Baird et al., 2004). It is still unclear whether CLA will cause large economic loss to the sheep industry in the UK. However, the disease is taken seriously by the industry and attempts are being made to prevent transmission between flocks. For example, serological testing (Dercksen et al., 2000), is being used to identify low risk groups of sheep (www.sac.ac.uk/cla) and enable segregation of rams at sale.

The current control methods used in the UK by some farmers include culling of clinically diseased sheep, lancing of superficial abscesses, serological testing and removal of seropositive sheep and use of a specially licensed vaccine. In the Netherlands, Schreuder et al. (1994) reported elimination of CLA from two sheep flocks. This was done using a double antibody sandwich ELISA (ter Laak et al., 1992) for *C. pseudotuberculosis*. When the flock was tested for the first time approximately 30% of sheep were seropositive. These sheep were removed and a second test was done; 2% of sheep were seropositive at the second test. Seropositivity and, by assumption, infection was then eliminated from these flocks by removal of these 2% of sheep. In Australia, prior to vaccination, the within flock prevalence of *C. pseudotuberculosis* infection was approximately 53% (Batey et al., 1986). In the 1990s a vaccine (Glanvac-3^{TM} Commonwealth Serum Laboratories Ltd., Victoria, Australia) was licensed for use in sheep. Since introduction of the vaccine the prevalence of abscesses *post mortem* has reduced to 2% in flocks where the vaccination guidelines were followed (Paton et al., 2003). Vaccination is not licensed in the UK but research is being carried out develop a suitable vaccine (Fontaine et al., 2006).

Eradication is the removal of a pathogen globally such that no further intervention is required; this has only been achieved with smallpox (Dowdle and Hopkins, 1993), although rinderpest may be the first animal exemplar. In contrast, elimination of infection from a population results in control measures not being required directly, but increased biosecurity and/or immunization must be implemented to reduce the risk of re-introduction of infection and subsequent transmission from populations in which the pathogen remains (Dowdle and Hopkins, 1993). Control of a pathogen reduces its incidence and prevalence, but control is continually required to maintain the reduction. The reduction achieved is generally dependent on the amount of effort applied, and the effectiveness of the technology available.

Demonstration of elimination from a flock is not straight forward, as all diagnosis and surveillance have less than perfect sensitivity. For most practical purposes, demonstration of elimination "beyond reasonable doubt" is useful, i.e. elimination of infection is defined with a specified degree of confidence. For example, in a maedi-visna control programme run by the Scottish Agricultural College, a flock is classified 'disease-free' if all sampled sheep test negative where the proportion sampled will detect a 2% prevalence with a 95% degree of confidence (www.sac.ac.uk). For the current paper, we define elimination of *C. pseudotuberculosis* as the probability that no infected sheep are present with 99% confidence.

Control of disease and infection requires resources. One of the control strategies we consider is removal of infected sheep. This is a considerable cost, in that replacement sheep (which might risk re-introduction of infection) must be acquired if the flock is not to decrease substantially in size or there will be a reduced output, typically a reduced number of lambs produced. These costs must be weighed against the likely outcome of any intervention. When the costs of control are high, for example if many ewes are removed from the flock, control may only be feasible if elimination is likely. Other control measures, such as a change of in management practices to reduce transmission, or vaccination, might be tolerated even if elimination is unlikely, if the costs are low and prevalence of disease reduces. This paper explores the impact of several control strategies

against *C. pseudotuberculosis* on both the prevalence of infection and the likelihood of elimination.

A transmission model for *C. pseudotuberculosis* infection was developed and parameterised (O'Reilly et al., 2008) using data from four infected flocks from Northern Ireland (Malone et al., 2006). The model was an extension of a standard susceptible-exposed-infected-recovered model, designed to capture within-host development of disease. Abscess location, and hence disease, was divided into overt and covert sites with the host abscessed at one or other or both sites (Figure 1). Overt abscesses included those located in the parotid, submandibular, prefemoral, popliteal and mammary lymph nodes (LN). Respiratory abscesses included those located in the lungs and mediastinal and bronchial LNs. Infection was assumed to be transmitted via one of three routes: overt to overt (with transmission coefficient β), respiratory to respiratory (π) or respiratory to overt (κ). Model results indicated that overt (to overt or respiratory) transmission was the predominant route (O'Reilly et al., 2008). Respiratory abscesses were assumed to remain infectious for life. If a sheep developed respiratory infection, then it cycled between only respiratory abscesses and both respiratory and overt abscesses. The outputs of the model indicated that the rates of transmission varied between flocks, resulting in a variable prevalence of abscessed sheep at endemic equilibrium.

In this paper we expand this model (O'Reilly et al., 2008) to explore different control strategies under alternative management strategies in a flock of 500 ewes. We also explore the effect of several transmission parameters. Use of mathematical models to explore the effects of control in several epidemiological situations has been illustrated in several studies (O'Callaghan et al., 1999; Smith et al., 2007; Lu et al., 2008). Importantly, these studies outline which demographic and epidemiological circumstances are necessary for control of infection to be effective.

2 Materials and Methods

2.1 Parameter values used in the model

In O'Reilly et al. (2008), an immune sheep was assumed to be protected from re-infection for life. This assumption was adequate for the data available, where sheep were exposed to infection for a comparatively short duration (<3 years). Here, we consider infection dynamics in a population over many generations, and so the duration of immunity may impact on model predictions. To date, there are no experimental studies that have examined the duration of immunity to natural infection with *C. pseudotuberculosis*. Many studies have been published on the effects of vaccination (Table 2), and so it was assumed that the rate of loss of immunity induced by natural infection was equal to immunity induced by vaccination, i.e. sheep in the immune class (*I*) moved to the susceptible class (*S*) at a constant rate, ω. Thus, the duration of protection (waning immunity) was assumed to follow a negative exponential distribution with loss parameter ω, and initial proportion protected, v_0.

The parameters used in the model were estimated from published vaccine studies (Table 2) as follows. Each study (s) consists of a control group and a vaccinated group, and so the efficacy (Y_s) at each recorded interval t_s was defined by,

$$\log(Y_s) = \log(v_0) - \omega t_s$$

The parameter estimation was implemented in WinBUGS (Lunn et al., 2000). Diffuse priors were set for the parameters v_0 and ω. The model was run for 10,000 iterations of which the first 1,000 were discarded. Two chains with different initial conditions were used to check for model convergence. The best-fitting parameter values were v_0=0.79 (95% credible intervals (c.i.) = 0.67 - 0.89) and ω=1/771 days (95% c.i. = 1/428 – 1/3849 days) respectively.

In O'Reilly et al. (2008) the estimated rate of overt to overt transmission varied between flocks, and so in the current study three different values for transmission coefficients

were considered. The value of the transmission coefficients, overt (β), respiratory (π) and respiratory to overt (κ)) that were estimated in O'Reilly et al. (2008) were adjusted to fit the prevalence levels reported in cross-sectional studies (Stoops et al., 1984; Batey, 1986; Arsenault et al., 2003) that corresponded to low, medium and high values of transmission resulting in prevalences of 0.20, 0.40 and 0.60 respectively. The ratio of the values for the transmission coefficients β: κ: π was kept constant at 10:1:1. The basic reproduction number (R_0) (Anderson and May, 1991) was used to summarise these three situations, and was calculated numerically.

2.2 Population size and contact structure

In O'Reilly et al. (2008) the population was modelled as proportions and all compartments summed to unity (hence the population size did not change). Here we use a deterministic model where the population size changed over time, with groups of breeding ewes, breeding rams, and lambs that reflect typical sheep farming practice in the UK. It also allows calculation of the number of sheep infected by control strategy implemented. All simulations were carried out in MatLab (release 2008a).

The 500 ewes were divided into annual age-cohorts, denoted by the subscript i, represented in the deterministic equations below. Each cohort had a separate set of differential equations, but the cohorts mixed homogeneously, and were equally susceptible to infection. Each year, all ewes in the tenth cohort were removed from the flock, i.e. 10yrs was the maximum life span. At the end of the breeding season, the sheep present in age cohort i were updated to cohort $i+1$ and, with the exception of some control strategies, lambs added to the first age cohort (i.e. replacements). A 20% annual replacement rate, typical for most sheep flocks (Anon., 2005), was implemented by removal of 9% of ewes from all age groups: 100 ewes were introduced each year to the youngest cohort ($i=1$) to maintain a flock size of 500. Replacement ewes were considered in three different infection states: all susceptible, up to ten infected, or replacement ewes from the flock with infection corresponding to the prevalence in this age group (this was dependent on the strategy explored).

The deterministic equations for cohort i for the basic model framework (Figure 1) are listed below and the parameters are defined in Table 1;

$$\frac{dS_i}{dt} = I_i\omega - S_i\lambda r$$

$$\frac{dF_i}{dt} = S_i\lambda r + O_i\varphi(1-p)(1-q) + F_i(\tau_R + \mu)$$

$$\frac{dC_i}{dt} = S_i\lambda(1-r) + O_i\varphi(1-p)q - C_i(\tau_O + \mu)$$

$$\frac{dR_i}{dt} = F_i\tau_R + B_i\varphi - R_i(\tau_B + \mu)$$

$$\frac{dO_i}{dt} = C_i\tau_O - O_i(\varphi + \mu)$$

$$\frac{dB_i}{dt} = R_i\tau_B - B_i(\varphi + \mu)$$

$$\frac{dI_i}{dt} = O_i p\varphi - I_i(\omega + \mu)$$

The rate of infection, λ, is defined by,

$$\lambda = \sum_{i=1}^{10}(\beta(O_i + B_i) + (\pi + \kappa)(R_i + B_i))/N_i$$

where N_i is the population size in cohort i.

The ram:ewe ratio was 1:40 (Anon., 2005). The ram group was modelled with no age structure and had a negative exponential distribution for an average life expectancy of 5 years. Rams had direct contact with the ewe group for 35 days per year, during the mating period in August-September. There was no direct contact between the lamb and ram groups. The control strategies presented were also implemented in the ram group, but we report only results from the breeding ewes.

The lamb group was populated 168 days after the rams were in contact with the ewes, corresponding to the average gestation period of sheep. The average number of lambs per ewe was 1.6 (Anon., 2005) resulting in 800 lambs per 500 ewes per year, that is 4000 lambs over 5 years. The life of a lamb was assumed to be 167 days. Lambs born to ewes susceptible to *C. pseudotuberculosis* were born susceptible to infection. Lambs born to ewes either infected or immune had maternal antibodies that protected against infection:

data from Robertson (1980) on the seropositivity of lambs was used to model the loss of maternal antibodies (O'Reilly, 2006). A proportion (*m)* (corresponding to the proportion of infected and immune ewes) of lambs was added to the maternally immune class for the first eight weeks with no loss of immunity. Lambs were assumed to enter the susceptible class at a rate ω_L (Figure 1).

The model was run for 50 years to reach demographic equilibrium before the introduction of infection. The effectiveness of control was examined in two epidemiological situations: epidemic and endemic. An epidemic describes spread of infection in a finite population where the rate of infection changes over time such that the prevalence changes. Endemic infection occurs when the rate of infection and the prevalence do not change over time, resulting in persistence of infection (Keeling and Rohani, 2008). For the epidemic situation, the model was run until 0.10 of the population was infected and control initiated. For the endemic situation, the model was run for 150 years when equilibrium was reached.

2.3 Control strategies examined using the model framework

The six control strategies are considered for control of *C. pseudotuberculosis*, labelled A-F. Strategies A-C assume an epidemic where 0.10 of ewes are infected when control begins. Strategies D-F assume an endemic rate of infection where the prevalence is either 0.20, 0.40 or 0.60, depending on the value of R_0. Ewes were either tested once every five years (in strategies A, C, D and F) or five times during one year (in strategies B and E). Where ewes were replaced once every year (prior to mating; strategies A and D), lamb production was maintained. Culling for other reasons continued and ewes culled for other reasons were not included in the estimates for impact on productivity. The effect on lamb production was monitored by assessing the number of ewes present at lambing and control versus no control.

After each round of serological testing or clinical examination the probability of elimination was assessed. In a deterministic model the prevalence will never completely reach zero, and so binomial sampling was used to assess the probability that no infected

sheep were present in the flock. For an estimated prevalence $\tilde{p}$, and the number (n) of ewes in the flock, the probability that there were no infected sheep $\Pr(x=0)$ was calculated, $\Pr(x=0)=\binom{n}{x}\tilde{p}^{n}(1-\tilde{p})^{n-x}$. If $\Pr(x=0)$ was greater than 0.99, infection was considered to be eliminated from the flock.

2.3.1 Vaccination

In simulations all sheep were vaccinated annually, a proportion (v_0) were protected (thus entering the immune class) and the remainder ($1-v_0$) remained susceptible to infection (Figure 1). Ewes and rams were vaccinated before mixing, and lambs were vaccinated at weaning (133 days).

2.3.2 Serological diagnosis of sheep and removal from the flock

Accurate estimates of serological sensitivity (η_S) and specificity (θ_S) are not currently available for the diagnostic tests used in the UK. The double antibody sandwich ELISA developed by ter Laak et al. (1992) and modified by Dercksen (2000) was tested in sheep flocks with a known disease status and the sensitivity and specificity were reported as 0.79 and 0.99. When used in four naturally infected flocks the average sensitivity and specificity were 0.88 and 0.55 respectively, with considerable variation between flocks (Malone et al., 2006). The test characteristics reported by Malone et al. (2006) and the test sensitivity and specificity required for elimination were evaluated using this model. The number of ewes removed and the effect on lamb production to achieve this were estimated.

The diagnostic test sensitivity and specificity were varied from 0.5 to 0.99, assuming different rates of transmission of *C. pseudotuberculosis* in the flock, and also at endemic equilibrium or when infection reached 0.10. No uncertainty of η_s and θ_s were included. We assumed that only sheep with abscesses were diseased. The number of test positive sheep (T^+) that were abscessed (D^+) was calculated as:

$$D^+ \mid T^+ = \eta_s (C + F + R + O + B) .$$

The number of sheep that were not abscessed (D^-) but were test positive was calculated as:

$$D^- \mid T^+ = (1 - \theta_s)(S + I) .$$

2.3.3 Clinical examination

It was assumed that sheep with overt (*O* or *B*) abscesses were detected during clinical examination, with a sensitivity η_c. The sensitivity of clinical examination in simulations was varied between 0.5 and 0.99. The specificity (given that the flock was known infected and that the site of abscesses would be local lymph nodes and that any abscesses where *C. pseudotuberculosis* was not definite could be tested using culture) was set at 1.00. Consequently, the number of sheep removed at each round of clinical examinations (C^+) was,

$$C^+ = \eta_c (O + B)$$

Clinical examination was assessed under the same six strategies as serological testing, and the prevalence and probability of elimination estimated.

2.3.4 Lancing abscesses

Lancing abscesses increased the rate of overt recovery (φ), for example by changing the value of φ from 1/21 days to 1/5 days. Lancing overt abscesses during gestation was considered impractical, and so the value of φ was returned to 1/21 days during this period. Research into the environmental survival of *C. pseudotuberculosis* suggests that lancing abscesses might increase the infectiousness of overt abscesses because the exuded material remains infectious for up to 8 months if not removed (Baird and Fontaine, 2007). To this end, the overt transmission coefficient was increased by 50% and any change in prevalence recorded.

2.3.5 Combinations of interventions

Vaccination was combined with lancing abscesses and clinical examination. Serological testing and vaccination were not combined because vaccination results in sheep frequently testing seropositive when not abscessed (Paton et al., 1991).

3 Results

3.1 Model simulations without controlling infection

An example of a model simulation is illustrated in Figure 2, left subplot. The number of ewes in the population increases by 100 at the start of each year, representing the influx of replacement ewes. An increase in the number of ewes with overt abscesses is observed shortly after, and a corresponding reduction in the number susceptible. The seasonal demographics are expected to induce a seasonal (minor) epidemic. Figure 2 (right) illustrates the relationship between R_0 and the prevalence of infection at equilibrium. When R_0 is low, small changes in the transmission coefficients result in a large change in the proportion infected (solid line in Figure 2, right). The 2.5^{th} and 97.5^{th} credible intervals of ω were used to obtain levels of confidence for the relationship between R_0 and the proportion infected at equilibrium (dashed lines in Figure 2). The prevalence varied by no more than 0.10 when values of ω were varied within this range. R_0 was 1.35, 2.10 and 4.13 when the prevalence of abscesses was 0.20, 0.40 and 0.60 respectively, as shown by the circles in Figure 2, right, and these values of R_0 were used for the rest of the analysis (Table 3). It should be noted that the relationship between R_0 and the proportion infected is affected by the uncertainty of ω, particularly at high values. For example, when the prevalence is 0.20 the corresponding value of R_0 varies between 1.28 and 1.47 and when the prevalence is 0.60 the value of R_0 varies between 3.56-7.20 when using the lower and upper credible intervals of ω.

3.2 Vaccination

The vaccine efficacies required for the probability of elimination to be greater than 0.99 were 0.32, 0.58 and 0.86 when R_0 was 1.35, 2.10 and 4.13 respectively. Use of the

vaccine always resulted in a reduction in the prevalence of abscesses, but did not affect the distribution of these abscesses.

3.3 Serological diagnosis of sheep and removal from the flock

Table 4 summarises the probability of elimination, the number of ewes removed or associated lamb losses for each control strategy where the sensitivity and specificity was varied. Elimination of infection was possible in all management options, but only when assuming a certain sensitivity or above. Elimination was more likely when controlling for infection during the epidemic phase than during the endemic phase of infection. In all strategies a lower sensitivity was required to eliminate infection during the epidemic phase of infection. For example, the sensitivity required for elimination of infection was 0.86 for strategy C and 0.90 for strategy F and over 100 fewer lambs were produced in strategy F, when the only difference in strategy was control of infection during the endemic phase for strategy F. The test specificity affected the number of ewes removed, as expected, the number of false positives increased as the specificity reduced. Typically, a diagnostic specificity greater than or equal to 0.90 prevented more than 250 ewes being removed during over the five year control programme. In addition to reducing the size of the ewe flock, in strategies C and F where ewes were not replaced, the control programme resulted in a drop in the number of lambs produced per year of 305 and 442 respectively.

Two examples of removal of ewes using serological testing are illustrated in Figure 3; the left subplot illustrates strategy E where ewes were tested five times during one year, and the right subplot illustrates strategy D where ewes were tested and removed once a year for five years. In both cases the first round of testing removed the majority of infected ewes, and the remaining tests were required to reduce the prevalence to a point where elimination was likely. The number of ewes remaining at the end of the control programme depended upon whether ewes were replaced at the end of each year, both strategy A and D included replacement of ewes; 395 ewes remained at the end of five tests in strategy D, fewer remained in the other scenarios, ranging from 190 to 294 (Table

5). In all strategies the value of the test sensitivity had a greater effect on the probability of elimination than the test specificity.

Using the sensitivity and specificity reported by Malone et al. (2006) for the sandwich ELISA, the probability that there were no infected sheep was greater than 0.95, and in strategies A, B and C the probability of elimination was greater than 0.99. However, over 400 ewes were removed under each of the six control scenarios, because of the low value of the test specificity.

In the first year of testing for scenario C (assuming $\eta_S = \theta_S = 0.90$), 87 ewes were removed and 139 fewer lambs produced. As strategy F assumed a higher prevalence of infection (endemic as opposed to epidemic), 184 ewes were removed in the first year, resulting in 294 fewer lambs produced.

3.3.1 Re-introduction of infection through replacements

When at least one infected ewe was present in the new introductions, infection in the whole flock was never below one infected sheep, although the prevalence reduced. Consequently elimination was not possible when infection was reintroduced once a year.

3.3.2 Effect of varying the basic reproduction number (R_0)

A change in R_0 through varying the transmission coefficients altered the rate of infection. Consequently each time the population was tested, and infected ewes remained, the increase in prevalence changed according to R_0. When R_0=1.35, elimination of disease occurred when the diagnostic test had a lower sensitivity and specificity than when R_0=2.10. For example in strategy D where R_0=1.35 a sensitivity of 0.82 was required for elimination, as opposed to when R_0=2.10 a sensitivity of 0.86 was required. When R_0=4.13 the sensitivity required for elimination was 0.89. A similar trend was observed in all control strategies.

3.4 Clinical examination

When clinical examination was tested under each control strategy, elimination of disease was unlikely (Table 5). The prevalence of infection was reduced from pre-control levels (either 0.10 for the epidemic strategy or 0.40 for the endemic scenario) to 0.05 or below within five rounds of examination. Fewer infected ewes were removed and the prevalence of infection was lower after control when clinical examination was implemented during the epidemic phase of infection (Table 5).

3.5 Lancing abscesses

In all cases elimination was not possible if lancing abscesses was the only control method applied. The effect of lancing overt abscesses on the reduction in prevalence depended on the pre-control value of R_0. For example, when R_0=1.35 reducing the average duration of overt abscesses ($1/\varphi$) brought the proportion of sheep infected to below 0.01 (Figure 4A). When R_0 was 2.10 or 4.13 (Figures 4B and 4C) the post-control prevalence reduced but did not reach <0.01. When R_0=2.10 the proportion of sheep with overt abscesses decreased, however as $1/\varphi$ was reduced in value the proportion of sheep with respiratory abscesses increased until $1/\varphi$=8 days and then began to decrease. In simulations where R_0=4.13 as $1/\varphi$ was reduced the proportion of ewes with abscesses in both sites reduced while the proportion of ewes with respiratory abscesses increased.

3.6 Combining control measures

Combining vaccination and lancing abscesses reduced the proportion infected in the flock, and consequently increased the probability of eliminating disease. Assuming that R_0=4.13, when vaccination was combined with lancing abscesses the proportion infected was reduced to <0.001, and the proportion of ewes with respiratory abscesses decreased with decreasing $1/\varphi$. This was an improvement on each separate control method, because neither resulted in a reduction in the proportion of sheep infected to <0.001.

Combining clinical examination with vaccination for the first five years only (tested in strategy A, C, D and F) reduced the prevalence of infection in comparison to each control option used individually (Table 5). In addition, fewer ewes were removed, and

consequently lamb production was less affected. However, the prevalence was not reduced to that required for elimination. Running the control programme for longer would lead to elimination, and within fewer years than using clinical examination alone.

4 Discussion

A reduction in prevalence and incidence of *C. pseudotuberculosis* infection can be achieved using all the strategies investigated in this paper. The outcomes of all strategies are variable; infection can be controlled or eliminated, and the effect on ewe numbers and lamb productivity varies with each control strategy and assumed rate of infection.

There are a number of unknowns, to which the outcomes are sensitive, that also highlight that decisions currently taken to control or eliminate *C. pseudotuberculosis* are not fully informed and further information are required before any control can be recommended confidently. Important unknowns include whether sheep with respiratory infection with *C. pseudotuberculosis* always, sometimes or never develop superficial abscesses. Sheep with only respiratory abscesses can transmit infection to susceptible sheep (Ellis et al., 1987), but there is no direct evidence for the link between respiratory and overt abscess formation. In the model framework developed on four flocks which had been infected with CLA for up to three years (O'Reilly et al., 2008), all sheep with respiratory abscesses developed overt abscesses every 33 days because this was the best fit for the data. In reality, there is a possibility that some sheep with respiratory abscesses do not develop overt abscesses, and therefore would not be detected by clinical examination. Consequently, the results might overestimate the success of clinical examination as a control option.

A second unknown is whether it is possible to lance abscesses without contaminating the environment and so increasing the likelihood of transmission. Transmission via the environment is not explicitly included in the current model. Its inclusion would require considerably more information on the effect of extrinsic factors, such as weather

(seasonality) and pasture rotation. Consequently, it might be that the current model does not capture the consequence of lancing with any accuracy.

A third unknown is waning immunity following natural infection. This is biologically more plausible than the life-long immunity assumed in O'Reilly et al. (2008), but unstudied. It was modelled by assuming a transition from complete immunity to full susceptibility. Other researchers have illustrated the importance of considering partial immunity within a general framework, where immune individuals develop partial susceptibility to reinfection (Gomes et al., 2004). There is currently little information on immunity to *C. pseudotuberculosis* infection, and so data used to estimate ω were based on vaccination studies rather than natural infection. Additionally, we have not included superinfection (where abscessed individuals may acquire further infection from external sources), which may affect model predictions. Experimental studies that examine immunity from natural infection are required to improve estimates of ω.

The final unknown is whether the prevalence of infected sheep reported by Malone et al. (2006) and Baird et al. (2004) are adequate for estimation of the prevalence at equilibrium, although they provide the best estimate of the prevalence of infection in recently exposed populations in the UK. To account for this uncertainty, each control strategy was investigated with a prevalence of infection ranging between 0.20 and 0.60.

With all these provisos the results from the modelling still provide some useful insights and guidance for future research. The outputs of the model indicate that implementation of a control programme should begin as soon as *C. pseudotuberculosis* is confirmed to reduce the losses from controlling infection. The control options described in this paper could be used in conjunction with reducing transmission to improve the effectiveness of control, as shown by the using different values of R_0 in the simulations. For example, when R_0 was assumed to be 4.13 the required vaccine efficacy was above the estimated value of efficacy for currently available vaccines. Reducing the opportunity for transmission in flocks with a high prevalence would increase the probability of elimination compared with vaccinating alone. Although vaccination reduced the

prevalence of *C. pseudotuberculosis* and in most cases eliminated infection, the reduction in prevalence was slow, even with a high vaccine efficacy, reflecting field observations (Paton, 1997). Combining vaccination with clinical examination results in a rapid reduction in prevalence, but elimination was unlikely. However, control of infection was achieved quickly and where control was implemented during the epidemic phase, without the loss of many ewes. Consequently, vaccination might be a suitable option if control of infection is an acceptable outcome.

For elimination, serological testing with a test sensitivity and specificity above 0.90 was the most suitable option. In large flocks such as breeding ewes, where infection is at a low prevalence, test specificity is important in order to maintain flock size and lamb production. A test with these characteristics is currently unavailable, and remains a challenge for diagnostic developers.

Lancing abscesses reduced the flock prevalence of infection to less than 0.01 when R_0 was small. However, lancing abscesses when R_0=4.13 resulted in increase in the proportion of sheep with respiratory abscesses. This occurred because the proportion of sheep with overt abscesses is reduced because of the reduction in the average duration of overt infection. Consequently development of additional respiratory infection occurs at a faster rate, which in-turn increases the rate of transmission of respiratory abscesses. As we assumed that respiratory infection does not resolve, the prevalence of respiratory infection increases. Increasing the proportion of sheep with respiratory disease is undesirable; sheep with respiratory abscesses are more difficult to detect and abscesses have been associated with chronic emaciation, death and loss of productivity (Stoops et al., 1984). We are confident enough in our results to recommend that lancing of abscesses should not be used as a control for CLA, although it might remain a valuable intervention for individual sheep when the prevalence of infection is low.

This paper has concentrated on the effects on breeding ewes because CLA is predominantly a disease of adult sheep rather than lambs. A deterministic framework was used because the number of ewes in the flock was large, and the underlying dynamics

were of interest. Because the model was not stochastic, specific predictions on small groups, such as breeding rams, are not reported in this paper. In these smaller groups, stochastic processes, such as fade-out of infection or a sudden change in prevalence, are likely to dominate the infection process, and will not be predicted by a deterministic model (Turner et al., 2006).

The simulations presented in this paper illustrate the importance of selecting the most suitable control strategy according to the prevalence of infection and the potential outcome of a control programme. For example, by combining control measures, such as vaccination and clinical examination, a reduction in prevalence was achieved but elimination was unlikely. If elimination is the preferred outcome, and thus controlling reintroduction of infection becomes a priority, serological testing is preferable. However serological testing comes at a cost of removing unaffected sheep. It is therefore important that the choice of control measures selected is based upon the initial prevalence and the preferred outcome of control.

5 Conclusion

Use of mathematical modelling allowed exploration of a variety of control strategies for *C. pseudotuberculosis* using a number of strategies that would be of considerable expense if tested in field conditions. The results from this analysis highlight the importance of understanding the disease process before application of control strategies. There is insufficient information on the cycling of *C. pseudotuberculosis* within infected hosts, immunity to *C. pseudotuberculosis* and the duration of survival of infectious bacteria in the environment. All three of these factors influence the probability of success of any control programme. Elimination of *C. pseudotuberculosis* from a flock with the assumptions in this paper is not likely with the current diagnostic tests. Control with an effective vaccine would be possible and lead to minimum production costs, assuming that vaccination reduced the prevalence of abscesses. The results can be used to guide future research programmes and so improve recommendations for control.

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Captions for Tables and Figures

Table 1. Parameters for transmission model of *C. pseudotuberculosis*

Table 2. Estimates of vaccine efficacy where the interval between vaccination and challenge was varied

Table 3. Expected proportion infected in each class from simulations using different values of the transmission coefficients for the transmission model.

Table 4. Predicted outcome of serologic CLA diagnosis in a ewe flock tested in six different strategies, where a prevalence of 0.40 was assumed.

Table 5. Results of simulations where serological testing, clinical examination and vaccination were used to control infection, where a prevalence of 0.40 was assumed.

Figure 1. Description of the *C. pseudotuberculosis* transmission model. The compartments are shown in boxes and the rates of movement from one compartment to the next are illustrated by the arrows. The dashed black arrow illustrates the effect of vaccination.

Figure 2. Left: Simulation illustrating the change in numbers of ewes in each infection group over the course of two years. Arrows indicate when a cohort of ewes were added to the population, resulting in an increase in population size. Right: Simulations illustrating the relationship between the value of R_0 and the proportion infected at equilibrium. Both the best-fitting value of the rate of waning immunity ω=1/771 days) and 95% credible intervals (dashed line) are illustrated, along with the values of R_0 and corresponding prevalence of infection used when examining different control scenarios.

Figure 3. Illustration of serological testing using scenario E (left) and scenario D (right). The diagnostic sensitivity and specificity were 0.90 in both scenarios. Downward arrows indicate where ewes were added to the flock and upward arrows indicate where ewes were removed.

Figure 4. Effect on the prevalence of infection when the duration of overt infection was reduced. Simulations are shown assuming different values of R_0; A; R_0=1.35, B; R_0=2.10, C; R_0=4.13.

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Tables and Figures

Table 1. Parameters for transmission model of *C. pseudotuberculosis*

Symbol	Parameter	Estimate, assuming a different prevalence			Reference
Transmission coefficients		0.20	0.40	0.60	
β	Overt to overt transmission	0.0018	0.0023	0.0051	1
κ	Respiratory to overt transmission	<0.0001	<0.0001	<0.0001	1
π	Respiratory to respiratory transmission	<0.0001	<0.0001	<0.0001	1
Abscess development					
τ_R	Rate to respiratory infectiousness	1/41 days			1
τ_O	Rate to overt infectiousness	1/49 days			2, 3
τ_B	Rate to additional overt abscess infectiousness	1/12 days			1
φ	Rate of loss of overt infectiousness	1/21 days			3
Proportions					
p	Proportion with overt abscesses where one abscess was present	0.3922			1, 4
q	Proportion with secondary abscesses that are not respiratory	0.4292			1
Flock demography					
μ	Death rate (ewes)	1/(10x365) days			
Vaccination and immunity					
ω	Rate of loss from complete protection from infection	1/771 days			This paper
ω_L	Rate of loss immunity from maternal antibodies	1/56 days			6
v	Proportion of vacinees that were immediately fully protected	0.79			This paper
m	Proportion of lambs that were immune to infection	Variable according to the proportion infected in ewe group			

[1] O'Reilly et al., 2008
[2] Pepin et al., 1988
[3] Ashfaq & Campbell 1980
[4] Burrell, 1978
[5] Eggleton et al., 1991a, Eggleton et al., 1991b, Sutherland et al., 1992
[6] Robertson 1981

Table 2. Estimates of vaccine efficacy where the interval between vaccination and challenge was varied

Group	Interval between vaccination and challenge (days)	Number in study	Number abscessed	Proportion abscessed	Efficacy
Sutherland 1992					
1	90	81	27	0.33	0.66
2	365	10	4	0.40	0.6
control	90	42	42	1.00	
Eggleton (1991a)					
1 (moncomponent)	16	38	4	0.11	0.8
2 (5 in 1)	16	38	3	0.08	0.85
3 (5 in 1 + selenium)	16	24	2	0.08	0.84
control	16	33	17	0.52	
Eggleton (1991b)					
1	30	20	5	0.25	0.7
control	30	18	1	0.83	
2	180	19	10	0.53	0.31
3	180	15	4	0.27	0.65
4	180	17	1	0.06	0.92
5	180	20	1	0.05	0.94
6	180	20	5	0.25	0.68
control	180	13	10	0.77	
7	365	18	10	0.56	0.27
Eggleton (1991c)					
1 (high toxoid)	168	14	3	0.21	0.76
2 (high toxoid-toxon-cells)	168	15	4	0.27	0.69
3 (low toxin-toxoid)	168	18	4	0.22	0.75
4 (low toxin-toxin-cells)	168	20	5	0.25	0.72
control	168	17	15	0.88	
Piontkowski (1998)					
1	224	18	8	0.44	0.56
control	224	10	10	1.00	

Table 3. Expected proportion infected in each class from simulations using different values of the transmission coefficients for the transmission model.

Simulation outputs	*Value of basic reproduction number*		
	1.35	*2.10*	*4.13*
Endemic prevalence of infection	0.20	0.40	0.60
Proportion with:			
• *Overt abscesses*	0.02	0.04	0.20
• *Respiratory abscesses*	0.07	0.13	0.06
• *Both abscesses*	0.11	0.22	0.34
Proportion of all ewes with overt disease	0.13	0.26	0.40
Proportion of infected ewes with overt disease	0.65	0.65	0.67

Table 4. Predicted outcome of serologic CLA diagnosis in a ewe flock tested in six different strategies, where a prevalence of 0.40 was assumed.

Control scenario	*Test sensitivity required for elimination of infection*	*Number of ewes removed*	*Ewe replacements / lamb losses*
A – epidemic disease, ewes replaced, tested once every year for five years	0.85 or above	Always greater 250 if Sp was less than 0.99	Up to 50 ewes were replaced each year when elimination was possible, no lamb losses
B – epidemic disease, ewes not replaced, tested five times in one year	0.85 or above. Use of 0.80 was possible when Sp was 0.99	Always greater than 250 if Sp was less than 0.9	No lamb losses
C – epidemic disease, ewes not replaced, tested once every year for five years	0.86 or above. Use of 0.85 was possible when Sp was 0.7 or above	Always greater than 250 if Sp was less than 0.9	More ewes were removed when the Sp was low, resulting in fewer lambs. For example when Sp = 0.90, 305 fewer lambs were produced during five years.
D – endemic disease, ewes replaced, tested once every year for five years	0.89 or above. Use of 0.88 was possible when Sp was 0.9 or above	Always greater than 250 if Sp was less than 0.99	Approximately 50 ewes were replaced every year, no lamb losses
E – endemic disease, ewes not replaced, tested five times in one year	0.87 or above. Use of 0.86 was possible when Sp was 0.80 or above	Always greater than 250 if Sp was less than 0.99	No lamb losses, up to 50 per cent of ewes were replaced by end of five tests
F – endemic disease, ewes not replaced, tested once every year for five years	0.90 or above. Use of 0.89 was possible when Sp was 0.8 or above	Always greater than 250 if Sp was less than 0.9	More ewes were removed when the Sp was low, resulting in fewer lambs. For example when Sp = 0.90, 442 fewer lambs were produced during five years.

Table 5. Results of simulations where serological testing, clinical examination and vaccination were used to control infection, where a prevalence of 0.40 was assumed.

Control scenario	*Control method*	*Number of ewes removed during control programme*	*Number of lambs not produced due to control programme*	*Prevalence of infection in ewe group at end of programme*	*Probability of elimination*
A – epidemic disease, ewes replaced, tested once every year for five years	Serological testing [1]	284	170	0	1
	Clinical exam only [2]	103	165	0.01	0.03
	Clinical exam and vaccination [3]	81	130	0.00	0.42
B – epidemic disease, ewes not replaced, tested five times in one year	Serological testing	221	354	0.00	1
	Clinical exam only	88	141	0.01	0.09
	Clinical exam and vaccination	-	-	-	-
C – epidemic disease, ewes not replaced, tested once every year for five years	Serological testing	190	304	0.00	1
	Clinical exam only	101	162	0.01	0.04
	Clinical exam and vaccination	81	130	0.00	0.45
D – endemic disease, ewes replaced, tested once every year for five years	Serological testing	395	632	0.00	1
	Clinical exam only	333	533	0.02	0
	Clinical exam and vaccination	274	438	0.01	0.06
E – endemic disease, ewes not replaced, tested five times in one year	Serological testing	294	470	0.00	1
	Clinical exam only	295	472	0.02	0
	Clinical exam and vaccination	-	-	-	-
F – endemic disease, ewes not replaced, tested once every year for five years	Serological testing	294	470	0.00	1
	Clinical exam only	315	504	0.05	0
	Clinical exam and vaccination	270	432	0.01	0.08

[1] diagnostics assumed $\eta_s = 0.90, \theta_s = 0.90$

[2] diagnostics assumed $\eta_c = 0.90$

[3] efficacy assumed $v_0 = 0.79$

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Figure1

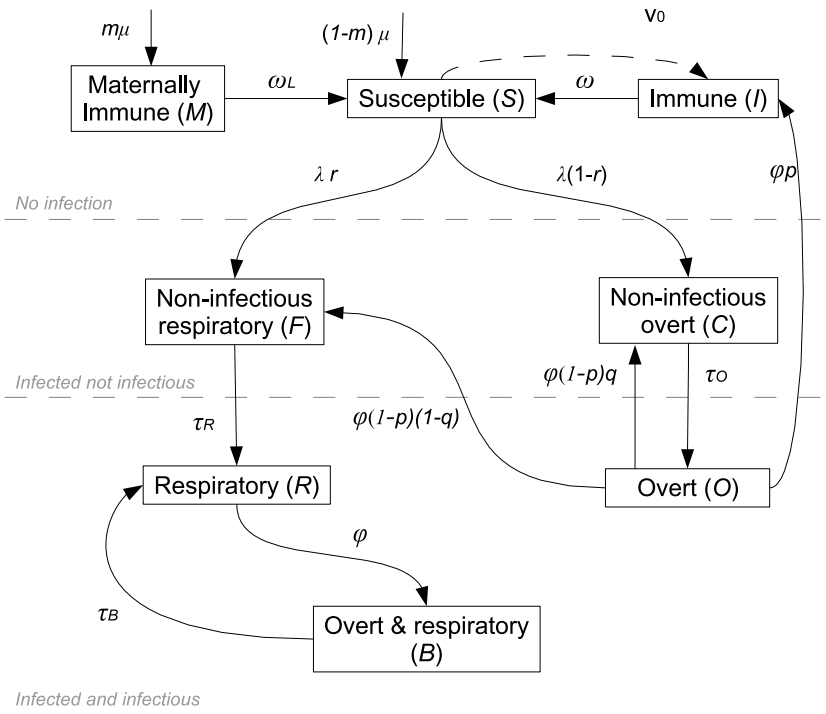

mμ
(1-m) μ
v0
Maternally Immune (M)
ωL
Susceptible (S)
ω
Immune (I)
λ r
λ(1-r)
φp
No infection
Non-infectious respiratory (F)
Non-infectious overt (C)
Infected not infectious
φ(1-p)q
τO
τR
φ(1-p)(1-q)
Respiratory (R)
Overt (O)
φ
τB
Overt & respiratory (B)
Infected and infectious

Figure2

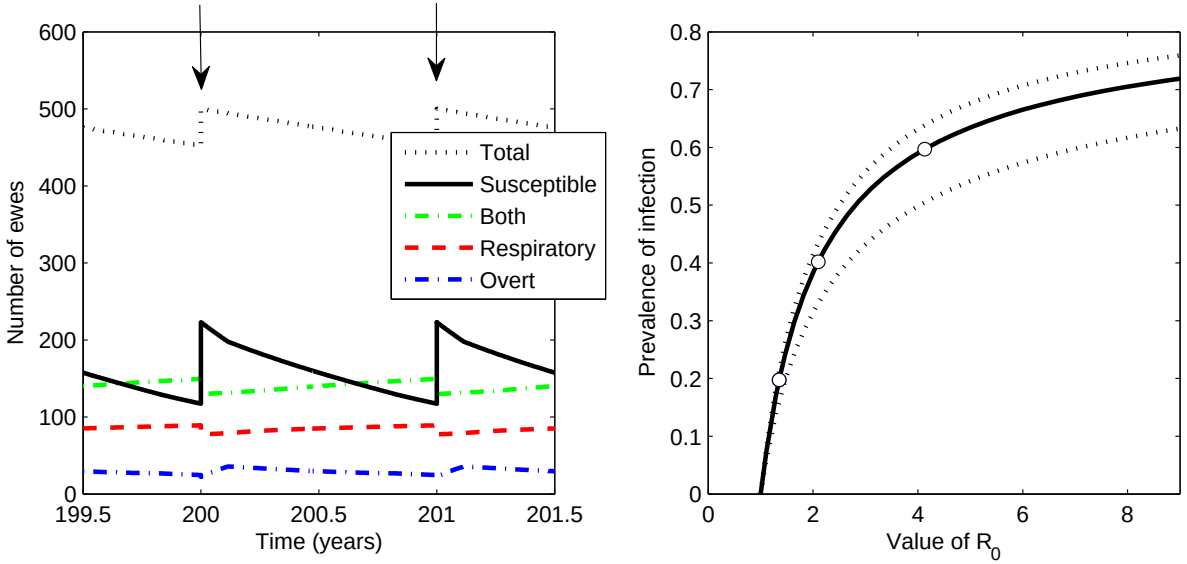

600
500
400
300
200
100
0
199.5
200
200.5
201
201.5
Time (years)
Number of ewes
Total
Susceptible
Both
Respiratory
Overt
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
Value of R0
Prevalence of infection

Figure3

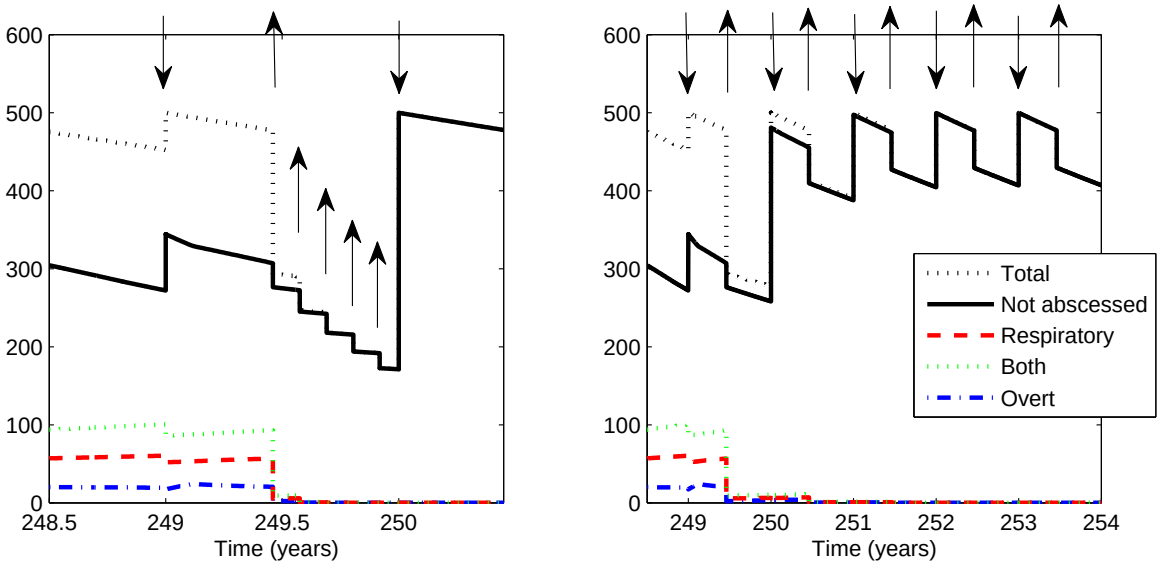
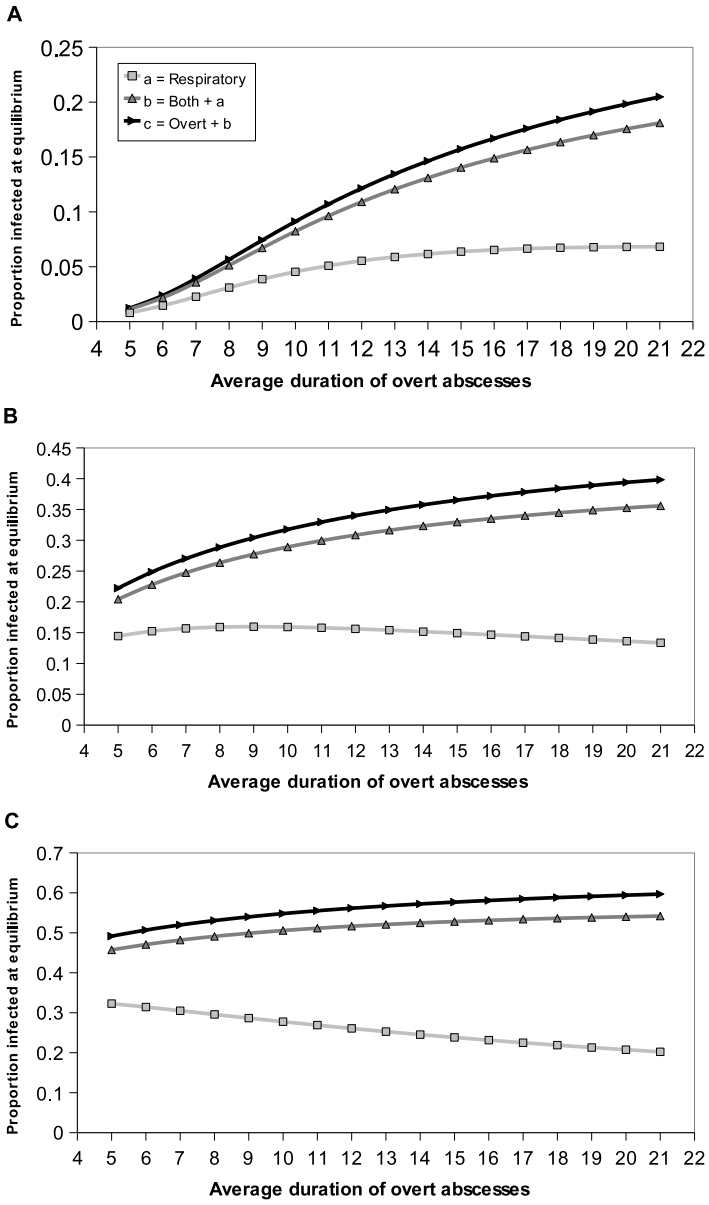

600
500
400
300
200
100
0
248.5
249
249.5
250
Time (years)
249
250
251
252
253
254
Time (years)
Total
Not abscessed
Respiratory
Both
Overt

Figure4


A
Proportion infected at equilibrium
0.25
0.2
0.15
0.1
0.05
0
a = Respiratory
b = Both + a
c = Overt + b
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Average duration of overt abscesses
B
Proportion infected at equilibrium
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Average duration of overt abscesses
C
Proportion infected at equilibrium
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Average duration of overt abscesses