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1 **Epidemiological modelling of chlamydial abortion in sheep flocks**

2

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15

15 **Abstract**

16 *Chlamydophila (C.) abortus*, responsible for chlamydial abortion (commonly  
17 known as Enzootic Abortion of Ewes [EAE]), causes major financial losses to the  
18 sheep industry worldwide. There remain many uncertainties surrounding the  
19 epidemiology of EAE. The aim of this study was to construct an epidemiological  
20 model to simulate EAE based on current knowledge of the disease, and in doing so,  
21 identify knowledge gaps that need to be addressed through further research. Key  
22 parameters that impact upon the development of the disease, such as the rate of  
23 contact between naïve ewes and infected material, are defined. Sensitivity analysis  
24 was undertaken for parameter values that are unknown to explore their impact upon  
25 the pattern of disease. The simulated results show the importance of the transmission  
26 rate (i.e. contact) and the number of infected replacements introduced at the start of an  
27 outbreak. Depending upon the rate of transmission, the year in which the peak  
28 number of affected ewes occurs and the number of years over which a high number of  
29 animals are affected varies. This suggests that a better understanding of the underlying  
30 processes that drive transmission of *C. abortus* is needed. Furthermore, if infected  
31 ewes could be identified prior to parturition, when they shed the organism in large  
32 numbers, the impact of EAE on sheep flocks could be greatly reduced.

33

34 **Keywords:** *Chlamydophila abortus*; EAE; epidemiological model; disease  
35 transmission, sheep

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## 38 1. Introduction

39           Enzootic Abortion of Ewes (EAE), caused by the Gram-negative obligate  
40 intracellular bacterium *Chlamydophila (C.) abortus*, is an important production  
41 disease of sheep flocks in many countries (Buendía et al., 2001; Longbottom and  
42 Coulter, 2003; Aitken and Longbottom, 2007). The bacterium has an affinity with  
43 mucosal membranes and, following invasion of the placenta, causes disease, which  
44 takes the form of abortion, stillbirths, the birth of weakly premature lambs and  
45 seemingly normal lambs (Longbottom and Coulter, 2003). Abortions typically occur  
46 during the last 2-3 weeks of gestation. The cost of the disease to British farming has  
47 been estimated to be in the region of £6 - £20 million per annum (Bennett, 2003;  
48 Wood, 1992). Infection is also zoonotic, with particularly serious consequences for  
49 pregnant women (Helm et al., 1989; Longbottom and Coulter, 2003). The  
50 implementation of effective control measures is highly desirable on economic, human  
51 health and animal welfare grounds.

52           As the disease is commonly transmitted between flocks by infected stock,  
53 control at the individual farm level can have benefits both for that and other flocks.  
54 Farmers will implement control measures where the cost of action is lower than the  
55 benefits. Knowledge of the costs and benefits is required in order to select these  
56 measures. Such knowledge is also useful to policy makers who may wish to promote  
57 or support the uptake of disease control strategies. A simple estimate of the costs and  
58 benefits of alternative control strategies has been made previously using a fixed set of  
59 assumptions (Milne and Dalton, 1988/89). More detailed estimates have not been  
60 made, in part due to a lack of data, which is a common problem associated with  
61 animal diseases. Where data are incomplete, epidemiological models can provide new

62 insights into a disease (Graat and Frankena, 2001; Pfeiffer, 2004; Thrusfield, 2005)  
63 and into disease control choices, as has been shown for Bovine Viral Diarrhoea (Stott  
64 et al., 2003). In the case of EAE, no data are available from field studies on the  
65 number of ewes that become infected in different years. Typically, it is the ewes  
66 aborting in year 2 (the abortion ‘storm’) that are recorded, whereas the ewes with less  
67 severe or no clinical signs may go unrecognised and not recorded. Furthermore, there  
68 are few data on the disease incidence in other years of an outbreak. A range of values  
69 for uncertain parameters can be tested in models and by comparing simulated results  
70 with observed data, factors impacting on disease patterns can be explored (de Jong,  
71 1995). Though not predictive, exploratory models built in this way can thus assist  
72 decision-makers.

73 As there remain many uncertainties surrounding the epidemiology of EAE, the  
74 aim of this study was to construct an epidemiological model to simulate EAE based  
75 on current knowledge of the disease. This will identify knowledge gaps that need to  
76 be addressed through further research. Key parameters that impact on our current  
77 understanding of disease processes are defined and, where data are not available, a  
78 range of possible values are explored. Simulated outcomes of an EAE outbreak in a  
79 flock are compared with reported field data. Finally, differences between the  
80 simulated values and those reported from the field are discussed with reference to  
81 future research needs, to enable the effective selection of control measures for EAE.

82

## 83 **2. Methods**

### 84 *2.1 Theoretical background to construction of the model*

85 Mathematical models of disease are simplified representations of a real

86 situation (Thrusfield, 2005). While it is important to capture key processes, increasing  
87 the level of detail modelled does not necessarily improve the quality of the simulation  
88 (Humphry et al., 2005). Thus, it is recommended that simple models are constructed  
89 in the first instance with complexity added later, if necessary (Graat and Frankena,  
90 2001). One approach that is widely used for infectious diseases is that of a SIR model  
91 as described by Graat and Frankena (2001). In this type of model, animals move  
92 between different disease states such as ‘susceptible’, ‘infectious’ and ‘recovered’  
93 (hence the terms ‘SIR’ and ‘state transition’). The transition probabilities between  
94 states can be fixed or variable depending upon certain factors, such as the number of  
95 infectious animals. It may also be necessary to include stochastic or ‘random’ events  
96 that can affect the spread of a disease within a population, for example, direct contact  
97 events between individual animals, as these may explain some of the observed  
98 variation in the development of a disease within a flock or herd (Graat and Frankena,  
99 2001; Thrusfield, 2005).

100

## 101 2.2 *EAE model construction*

102 Three underlying features of EAE determined the general framework of the  
103 model described here. Firstly, a set of distinct disease states are identifiable, these  
104 being uninfected, latently infected, infected/diseased and immune. A state transition  
105 form was therefore appropriate and adopted for the model. Secondly, since the pattern  
106 of disease takes several years to develop (Aitken and Longbottom, 2007) the model  
107 needed to be multi-annual and a time period of 10 years was set as sufficient for the  
108 simulations required. Thirdly, and as a consequence of building a multi-annual model,  
109 it was considered necessary that the model should encompass some aspects of normal

110 flock dynamics. These random and planned events, such as replacement of animals,  
111 are likely to affect the development of EAE in a flock. An Excel© (Microsoft  
112 Corporation) spreadsheet was used as the modelling environment allowing  
113 transparency of the mathematical relationships simulated.

114 The model tracks individual ewes, defined by parity and disease state, and can  
115 accommodate flocks of any size between 1 and 500 ewes. The initial distribution of  
116 parities within the flock was representative of a real flock and thereafter was  
117 determined by the annual number of replacements and losses. Each ewe encounters a  
118 series of events that occur chronologically over a year, which starts with the  
119 introduction of replacement animals in the autumn. In total eight annual events were  
120 simulated. In chronological order these were mating, mortality pre-lambing, clinical  
121 disease  $t_1$ , infection with EAE  $t_1$ , clinical disease  $t_2$ , infection with EAE  $t_2$ , mortality  
122 post lambing and replacement. The model encompasses two time periods ( $t_1$  and  $t_2$ ) in  
123 which clinical disease could develop or infection acquired. This was necessary to  
124 simulate cases where ewes become infected and develop clinical disease within a  
125 single pregnancy (Blewett et al., 1982). Using the random number generator facility  
126 within Excel©, a Monte Carlo simulation was used to determine individual ewes that  
127 died or were replaced for reasons other than parity and all ewes that reached 5 parities  
128 were replaced.

129 The terms 'clinical disease' and 'clinically affected' are used in this paper to  
130 identify ewes in which *C. abortus* has invaded the placenta, resulting in either  
131 abortion, stillbirths, or the birth of weakly premature or seemingly normal lambs.  
132 With regard to the introduction of infection, it was assumed that the flock was EAE  
133 naïve in Year 1 and that the source of infection was latently infected replacement

134 ewes. This is a common source of EAE infection to naïve flocks (Philips and  
135 Clarkson, 2002; Aitken and Longbottom, 2007). The proportion of replacements that  
136 may be infected when introduced to a flock is an unknown quantity that could affect  
137 the development of disease within a flock. Within the model this parameter was  
138 therefore constructed as a user defined variable so that alternative values could be  
139 tested.

140 Disease transmission occurs via the oral-nasal route (Jones and Anderson,  
141 1988). Affected ewes shed large numbers of *C. abortus* with placental material and  
142 uterine fluids at parturition (Aitken and Longbottom, 2007). Although EAE  
143 transmission rates are not known, it is likely that as for other infectious diseases the  
144 number of new cases (effective disease contacts) in any one time period will be  
145 related to a range of factors. These include the number of infectious and susceptible  
146 animals and the level of contact between them in the previous time period. Such a  
147 relationship is captured by the Reed-Frost function (Abbey, 1952) that was used in the  
148 model:  $C_{t+1} = S_t (1 - q^{C_t})$ , where:  $t$  = the time period;  $C_{t+1}$  = the number of infectious  
149 cases in time period  $t + 1$ ;  $S_t$  = the number of susceptible animals in time period  $t$ ; and  
150  $q$  = the probability of an individual not making effective contact. The disease status  
151 (infectious,  $C_{t+1}$ ; susceptible,  $S_t$ ) of individual ewes is identified within the model.  
152 The probability of an individual not making effective contact ( $q$ ) in time period 't' is  
153 unknown and must be defined. Therefore, this variable was user definable in order to  
154 explore a range of possible contact levels. Having calculated the number of new  
155 cases, a Monte Carlo simulation was used to identify the individual ewes that would  
156 acquire infection.

157           The disease, after primary infection of a naïve ewe with *C. abortus*, can  
158 develop along one of two pathways, moving through either 3 or 4 disease states  
159 (Figure 1). For the purposes of this model, ewes will progress along pathway A if  
160 infection is acquired while non-pregnant or during pregnancy but after 110 days  
161 gestation. Infection in such ewes becomes latent and manifests as disease in the  
162 subsequent pregnancy. This is based on the observation that infection after 110 days  
163 gestation will not lead to disease in that pregnancy, however such animals may  
164 develop clinical disease in the subsequent pregnancy (Longbottom and Coulter, 2003;  
165 Aitken and Longbottom, 2007). Protective immunity develops after clinical disease  
166 and such ewes will not exhibit further clinical signs even though immunity is not  
167 necessarily sterile (Papp and Shewen, 1996; Papp et al., 1998).

168           Ewes will progress along pathway B when infection is acquired during  
169 pregnancy, but before 110 days of gestation. In flocks where mating is spread over  
170 more than one oestrus cycle ewes will be at different stages of gestation at any one  
171 time period. Since disease typically occurs in the last 2-3 weeks of gestation, naïve  
172 ewes that are mated later are at risk of acquiring infection from earlier mated diseased  
173 ewes (Blewett et al., 1982). For this reason two time points when disease could  
174 manifest or be acquired were included in the model. Thus, ewes developing clinical  
175 disease at  $t_1$  can transmit infection to naïve ewes, which will develop clinical disease  
176 at  $t_2$ .

177           The day of mating is therefore important in the development of disease within  
178 a flock. For each ewe a Monte Carlo simulation calculates the day on which  
179 successful mating occurs but the average gestation length of infected ewes is not  
180 known, only that it may be shortened by up to 2-3 weeks. To allow an investigation of

181 the effect of variability in the timing of parturition and the shedding of infectious  
182 organisms, the average number of days that this occurs pre-term was thus constructed  
183 as a user defined variable.

184

### 185 2.3 Model simulation

186 A flock of 100 lowground ewes was selected for the simulation. The  
187 replacement rate in this flock was 24% with 4% mortality each year. A range of  
188 possible values for the three user defined variables (the number of infected  
189 replacements that are introduced, the average number of days pre-term when *C.*  
190 *abortus* is present in the environment and the probability of an individual not making  
191 effective contact) were selected in order to run the model (Table 1).

192 For each of these cases the model was run 1000 times and the average number  
193 of ewes in each disease state calculated. The simulated averages can be compared  
194 with the limited field observations and three epidemiological aspects are specifically  
195 examined: (1) the impact of variable levels of contact between ewes, which would  
196 depend upon the management system such as whether or not ewes are housed; (2) the  
197 effect of variation in the average number of days pre-term when ewes are infectious;  
198 and (3) how the number of infected replacements introduced affects the development  
199 of disease in a flock.

200

## 201 3. Results

202 Five scenarios (A-E in Table 1) were investigated to explore the effect of  
203 variability relating to unknown epidemiological parameters for transmission of EAE.

204 The first scenario (A) investigated a range of probabilities of avoiding effective

205 contact ( $q$ ) with *C. abortus*, when four infected replacements were introduced in year  
206 1 and infected ewes shed the agent on average 14 days pre-term (Figure 2a). It can be  
207 seen that as the probability of avoiding effective contact falls, the percentage of  
208 clinically affected animals rises. Where  $q=0.94$ , the proportion of clinically affected  
209 ewes peaks at 29% in year 2. Thereafter the proportion of affected ewes drops until  
210 year 5, after which time the number rises, forming a plateau at 15-20%. Where  $q$  is  
211 greater than 0.94, the peak occurs in year 3 and a similar pattern of disease to  $q=0.94$   
212 then follows, although the number of affected animals is lower. Additionally, in this  
213 scenario there is a high proportion of clinically affected ewes in both years 2 and 3, in  
214 all cases.

215 The impact of extending the average gestation length of affected ewes by 7  
216 days compared to scenario A, but keeping all other assumptions constant, can be seen  
217 in scenario B (Figure 2b). The consequential pattern of disease is the same as for  
218 scenario A with the exception that the peak number of clinically affected ewes occurs  
219 in year 3 for all cases. Scenarios C and D consider the impact of introducing low and  
220 high numbers of infected replacements in year 1 respectively and all other  
221 assumptions are as per scenario A. Where only 1 replacement is infected (Figure 2c)  
222 the peak number of infected ewes is lower than in scenario A and occurs later, in  
223 years 3 to 5. When a high number ( $n=12$ ) of infected replacements are introduced, the  
224 peak occurs in year 2 and is higher than for scenario A (Figure 2d). Scenario E shows  
225 the effect of increasing the probability of ewes gaining infection compared to those  
226 tested in scenario A. With these higher values a clear single peak in clinically affected  
227 ewes occurs in year 2 and in all cases the maximum number of affected ewes is  
228 greater than 40%. Where the probability of avoiding effective contact is 0.8,

229 changing the time at which ewes shed *C. abortus* from 14 to 7 days pre-term has little  
230 impact.

231

#### 232 4. Discussion

233 Sheep latently infected with *C. abortus* cannot be identified by serological  
234 tests or clinical criteria making it difficult to prevent introduction of the disease to  
235 naïve flocks (Jones et al., 1995). For this reason, reliable data on the pattern of disease  
236 development after introduction in the field is limited and information on infected  
237 animals is usually only gathered after high levels of abortion occur in a flock. The  
238 pattern of EAE that is typically recorded is low numbers of abortions in Year 1, with  
239 an abortion ‘storm’ involving 20-30% of ewes the following year. Thereafter, year 3  
240 onwards, the abortion rate is reported to be around 5-10% and primarily affects  
241 younger replacement ewes (Aitken and Longbottom, 2007).

242 The model described in this paper investigates the impact of a range of  
243 uncertain parameters on the pattern of disease (assuming no control interventions)  
244 following the introduction of *C. abortus* to a naïve flock. The simulated results  
245 demonstrate that these parameter values do indeed impact upon the development of  
246 the disease within a flock (Figure 2). However, the simulated results do not coincide  
247 exactly with reported field observations in one or more of the following ways: the  
248 year in which the maximum percentage of clinically affected ewes typically occurs;  
249 the number of years in which high levels of ewes are clinically affected; and the  
250 percentage of clinically affected ewes in the peak year and thereafter.

251 The pattern of disease development simulated by the model changes with the  
252 probability that ewes will avoid effective contact ( $q$ ) as shown in Figures 2. These

253 results suggest that the transmission rate, which will be affected by the infectious  
254 dose, incubation period and rate of contact, is an important factor in the development  
255 of the disease within a flock. Flock management practices, such as housing or  
256 implementation of control measures including isolation of aborting ewes and removal  
257 of infected material, will affect the rate of contact and this may be one reason for  
258 variation in reported patterns of disease in the field. In the model it has been assumed  
259 that *C. abortus* is introduced by infected replacements in year 1 only. In practice,  
260 infected replacements could be introduced with a greater frequency, for example  
261 where home-bred lambs that acquire infection from their dam are retained (Wilsmore  
262 et al., 1984), or where transmission could occur by other routes. These other routes  
263 include venereal transmission, but this is not thought to be an effective route in  
264 practice (Appleyard et al., 1985), and infection acquired from persistently infected  
265 ewes that shed *C. abortus* (Papp and Shewen, 1996; Papp et al., 1998), though the  
266 importance of such animals is unclear. This may relate to the required infectious dose,  
267 which is currently under investigation.

268         Whilst the average number of days pre-term when ewes shed *C. abortus* is  
269 unknown, a comparison of the model results for 14 and 7 days pre-term suggest that  
270 this is not an important factor in the pattern of disease development although some  
271 variation is observed (Figure 2a,b,e). The model indicates that the disease pattern is  
272 influenced by the number of infected replacements (1, 4 and 12) introduced in year 1.  
273 The highest number tested in the model represents around a 50% prevalence in the  
274 replacements introduced, in which the peak of clinically affected ewes occurs in year  
275 2 at 34% (Figure 2d). In contrast, where only one infected replacement is introduced  
276 (approximately 4% prevalence) the peak occurs later and where the contact rate is also

277 low ( $q=0.97$ ) does not occur until year 5 (Figure 2c). Thus, different numbers of  
278 infected replacements introduced in year 1, which is likely to occur in the field, may  
279 explain some of reported variation in EAE outbreaks (Longbottom and Coulter,  
280 2003).

281 The pattern of disease simulated in scenario E most closely resembles reported  
282 outbreaks from the field (Figure 2e). In this scenario, higher effective contact rates  
283 ( $1-q$ ) were assumed ranging from 0.5 to 0.1. The percentage of animals affected (50%  
284 at the peak) includes aborting ewes, which are typically reported from the field, and  
285 ewes with less severe signs of *C. abortus* infection. Chalmers et al. (1997) record that  
286 78% of lambs born to experimentally-infected ewes were born dead, either aborted or  
287 stillborn, whilst 22% were born alive. Extrapolating from this, if 30% of sheep  
288 typically abort then a further 8.5% of a flock might be clinically affected. Thus, the  
289 peak in clinically affected ewes observed in scenario E that might appear high may be  
290 a true reflection of the disease. Given the number of uncertainties and their  
291 importance to the development of the disease, reliable epidemiological data are  
292 essential to fully validate the model. Such data will depend upon the accurate  
293 diagnosis of infection, symptomatic and latent. Moreover, if an accurate test for *C.*  
294 *abortus* was available it would be possible to remove or isolate infected ewes prior to  
295 the development of clinical signs, thus preventing the spread of disease to uninfected  
296 animals. Livingstone et al. (2005) have described the application of a recently  
297 developed serological assay based on the polymorphic outer membrane protein,  
298 POMP90, that was shown to detect high antibody levels to *C. abortus* in infected  
299 ewes prior to abortion that might be of future value in this context.

300

## 301 **5. Conclusions**

302 The results from the simulation model support the hypothesis that the  
303 transmission rate for EAE is high and that the number of infected replacements  
304 introduced at the start of an epidemic is low (see Figure 2e). There are, however, a  
305 number of uncertainties such as the transmission rate and infectious dose, which are  
306 currently under investigation, partly instigated by this work. Alternatively, if more  
307 and higher quality field data was available it would be possible using a model such as  
308 this to test a range of hypotheses with greater rigour. A survey of sheep farmers in the  
309 UK has been undertaken by the authors to gather further data from the field and the  
310 results will be used to further develop this model. Anecdotally there are also a number  
311 of reports of reduced fertility associated with EAE and the model could be used to  
312 explore this effect if data becomes available. After the model has been validated it  
313 will be possible to incorporate the impact of control measures into the model so that  
314 their costs and benefits can then be estimated. In this way better decision support can  
315 be provided to farmers and policy makers.

316

### 317 **Conflict of Interest Statement**

318 None of the authors (CEM, GJG, GE, DL) has a financial or personal relationship  
319 with other people or organisations that could inappropriately influence or bias the  
320 paper entitled “Epidemiological modelling of chlamydial abortion in sheep flocks”.

321

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325

326

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389 **Figure captions**

390

391 Figure 1. EAE disease state pathways.

392

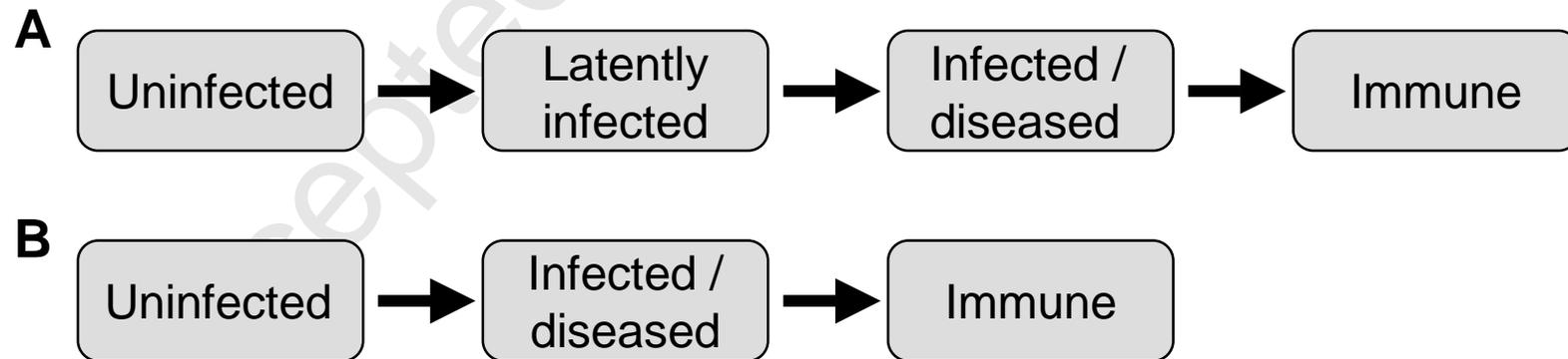
393 Figure 2. EAE model simulation scenarios. The percentage of ewes clinically  
394 affected by EAE was determined following simulation of five scenarios: scenario A  
395 (a), B (b), C (c), D (d) and E (e) (see Table 1). These scenarios investigated a range of  
396 probabilities of avoiding effective contact with *C. abortus* that either varies from 0.97  
397 to 0.94 (a-d) or from 0.9 to 0.5 (e); where 4 (a, b and e), 1 (c) or 12 (d) infected  
398 replacements are introduced; and where *C. abortus* is shed by infected ewes an  
399 average of 14 (a, c-e) or 7 (b and e) days pre-term. Graph lines 1-5 represent cases 1-5  
400 of each scenario depicted in Table 1.

- 1 Table 1. Possible values of uncertain assumptions used in simulations for a flock of  
 2 100 lowground ewes.

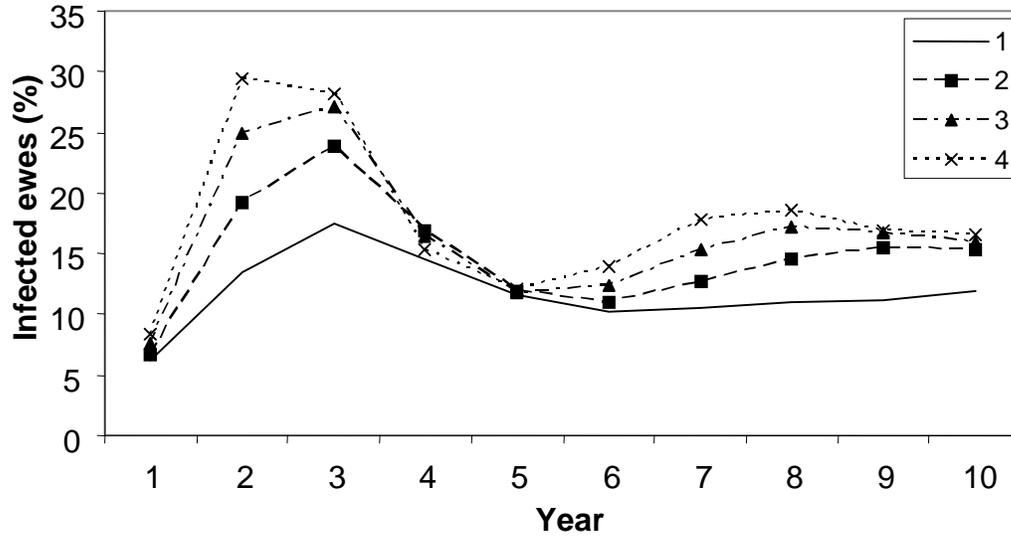
Scenario	Case	Number of infected replacements introduced in year 1	Probability of an individual not making effective contact (used in Reed-Frost equation)	Average number of days pre-term of parturition
A	1	4	0.97	14
	2	4	0.96	14
	3	4	0.95	14
	4	4	0.94	14
B	1	4	0.97	7
	2	4	0.96	7
	3	4	0.95	7
	4	4	0.94	7
C	1	1	0.97	14
	2	1	0.96	14
	3	1	0.95	14
	4	1	0.94	14
D	1	12	0.97	14
	2	12	0.96	14
	3	12	0.95	14
	4	12	0.94	14
E	1	4	0.9	14
	2	4	0.8	14
	3	4	0.7	14
	4	4	0.5	14
	5	4	0.8	7

3

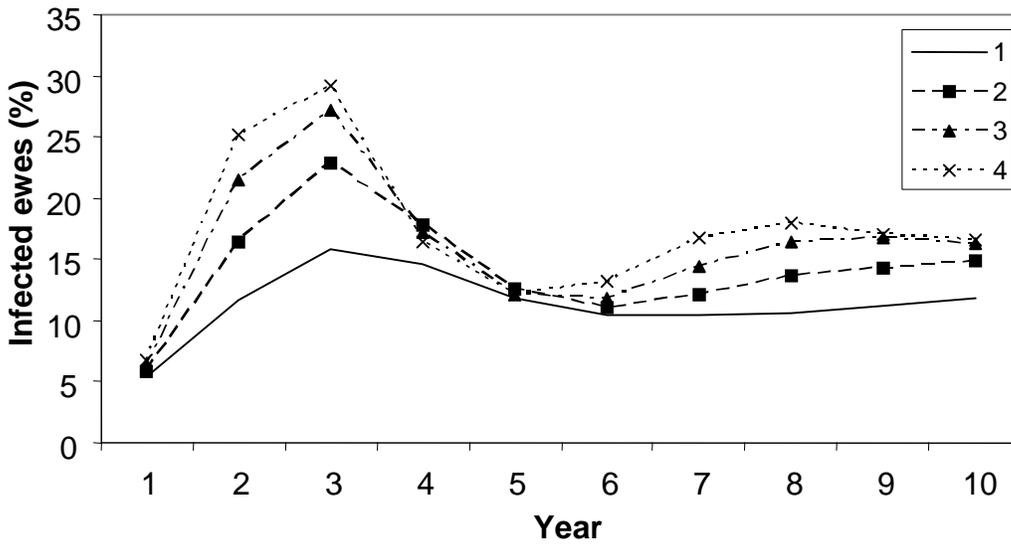
Figure 1



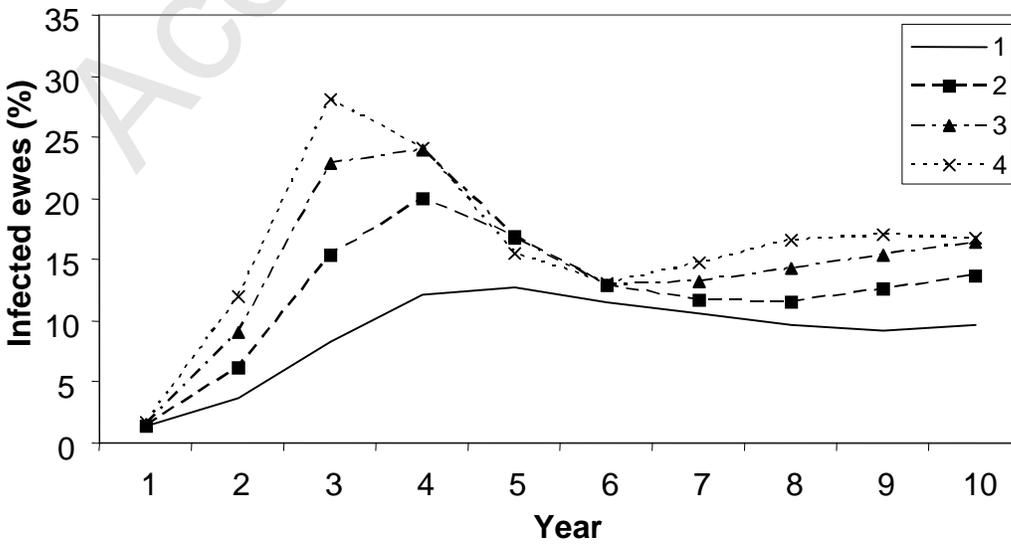
a



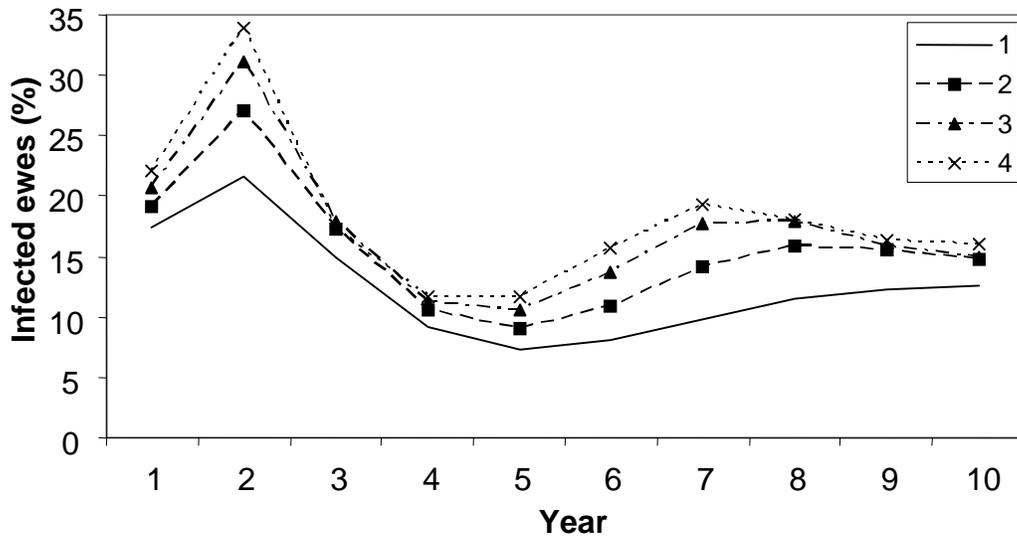
b



c



d



e

