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Modelling the impact of vaccination on tuberculosis in badgers

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SUMMARY

Tuberculosis (TB) in livestock, caused by *Mycobacterium bovis*, persists in many countries. In the UK and Ireland, efforts to control TB through culling of badgers (*Meles meles*), the principal wildlife host, have failed and there is significant interest in vaccination of badgers as an alternative or complementary strategy. Using a simulation model, we show that where TB is self-contained within the badger population and there are no external sources of infection, limited-duration vaccination at a high level of efficacy can reduce or even eradicate TB from the badger population. However, where sources of external infection persist, benefits in TB reduction in badgers can only be achieved by ongoing, annual vaccination. Vaccination is likely to be most effective as part of an integrated disease management strategy incorporating a number of different approaches across the entire host community.

Key words: Mycobacteria, Spatial modelling, tuberculosis (TB), vaccine policy development, zoonoses.

INTRODUCTION

Wildlife hosts for disease are a major contributory factor to the persistence of disease in livestock throughout the world. Where wildlife act as reservoirs for infections or contribute to a multispecies reservoir community, successful eradication of disease requires effective control of infection in the wildlife population. The optimal method for such control is dependent on the characteristics of both host and the disease. The most commonly deployed method of disease control in wildlife populations is to reduce the population to a level below which the disease cannot persist (the threshold population), as exemplified by the reduction of the white-tailed deer (*Odocoileus viginianus*) population in Minnesota to a density which reduced tuberculosis (TB) circulation within the population [1]. However, depopulation causes perturbation, which can change movement patterns in populations, altering patterns of social interactions [2–5] and potentially enhancing opportunities for disease transmission at the individual level.

TB, caused by the bacteria *Mycobacterium bovis*, is a persistent and worsening problem in livestock populations in many parts of the world, including the majority of European countries where comprehensive test-and-cull policies have been in place for over 50 years. One of the major reasons for the failure to eliminate TB from the European cattle population is thought to be the existence of a substantial wildlife

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host community, based around badgers (*Meles meles*), wild boar (*Sus scrofa*) and red deer (*Cervus elaphus*), with different individual species assuming a greater importance in different parts of the continent [6]. In Britain and Ireland, badgers act as the principal wildlife host species for TB. Badgers infected with *M. bovis* have also been found in continental Europe (France and Spain) [6, 7], although their role in the persistence of TB in continental Europe is currently thought to be as spillover rather than reservoir hosts.

Results of a large-scale field trial in Britain have shown that for badger culling to be effective in reducing TB, either in badgers or in cattle, it must be done at high levels of efficiency (in excess of 70% population reduction) and over large areas of land (141–150 km^2) [8]. The UK government is currently coordinating trials in two pilot areas to determine whether these levels of culling are achievable [9]. One alternative or complementary approach to wildlife culling is vaccination. Vaccination has been used successfully to control various wildlife diseases [10], and an *M. bovis* strain bacille Calmette-Guérin (BCG) vaccine has now been developed and licensed for use in the UK [10]. Vaccination has the potential to contribute to the control of TB in badgers in the UK because it does not cause perturbation of the badger population and may act synergistically with culling in helping to reduce levels of disease. The development of TB vaccines is ongoing, and data on the effects of these vaccines on the development of infection at the individual level are starting to emerge [11–13]. The BCG vaccine is currently being deployed on wild badger populations in parts of Britain [14], although this Badger Vaccine Deployment Project (BVDP) is not being carried out specifically with the aim of evaluating the benefits of vaccination in reducing TB in badgers at the population level.

In this paper, we use a spatial stochastic simulation model to evaluate the likely effectiveness of vaccination at the population level in reducing TB infection in badgers across a range of population densities, and hence contribute to an understanding of the requirements for a successful vaccination campaign to reduce or eradicate TB in badgers. Modelling approaches have been used extensively in the past to examine TB dynamics and control in wildlife species including badgers [15–20] and possums [21–23]. Because of the multispecies nature of the TB host community, in which some TB spread is likely to occur in the different livestock and wildlife components [24], we also account for some background infection from these external sources. Specifically, we address three components that can influence the success of a vaccination strategy: (1) the proportion of the population treated by the vaccine, which incorporates both uptake and effectiveness (protection) at the individual level; (2) the duration of any vaccination campaign; and (3) the potential influence of external sources of infection.

METHODS

The model

We used the spatial simulation model of TB in badger populations described by Hardstaff *et al.* [20]. Within the model, space is represented by a grid of square cells (12 × 12), with each cell representing a badger territory. Within each territory, the numbers of individuals in each age (cub, yearling, adult), sex (male, female) and disease state (susceptible, latent, infectious) category can be tracked through time. The model is stochastic, with progression of disease between susceptible, latent and infectious states based on probabilities derived from the literature [20]. Latency may be defined differently for different host–disease systems. For TB in badgers, latency is a state of containment of the infection where there is an absence of excretion. A badger with latent TB is therefore in an infected-but-not-infectious state [25–27]. Badgers pass from a latent to infectious state in the course of progression of the infection. Hardstaff *et al.* [20] included the possibility of infectious badgers reverting to a latent state. However, the evidence for this is not conclusive, and it was omitted from the model for the current study. For each potential transition between disease states, a random number between 0 and 1 was generated and the transition occurred if that number was less than or equal to the specific probability. Transmission of infection could occur within territories (intra-group transmission) or between neighbouring territories (inter-group transmission), where a neighbour was a contiguous territory either directly to the north, east, south or west of the focus territory. Data from the simulations were obtained from the central 10 × 10 territories only, in order to avoid biases due to edge effects. Time in the simulation progressed in discrete iterations corresponding to the four seasons in a year that were of equal length and therefore of equal weighting. A second layer to the simulation represented the habitat quality of each territory in the form of a carrying capacity, with the link between

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this and badger group size being established through density-dependent cub mortality [20]. The balance between fecundity and cub mortality was calibrated in an initial series of runs under a range of habitat qualities (equilibrium group sizes of 2–20, representing the full range of group sizes recorded in Europe), to establish the parameter values that maintained the required equilibrium group sizes. Assumptions within the model were as follows: only adult females can breed; breeding is unaffected by disease status; dispersal is by adults and to contiguous territories only; all cubs are born susceptible to disease; there is no vertical or pseudo-vertical disease transmission; and there is homogenous mixing within social groups.

Susceptible individuals could be vaccinated and develop immunity to infection, according to a probability that reflected the proportion of the population reached and protected by the vaccine. The badger BCG vaccine has undergone tests in the laboratory and is currently being deployed in the field in both Ireland and the UK. Laboratory vaccination tests and initial results from a field trial have shown a decrease in the severity of infection following vaccination, evidenced by vaccinated badgers having lower lesion scores, more restricted distribution of lesions and lower bacilliary load [11, 28, 29]. Vaccinated badgers are also less likely to be culture positive [30], less likely to seroconvert [30], and be less infectious due to reduced excretion of bacilli [13]. Due to the variation in the badger immune reaction and variable sensitivity and specificity of the diagnostic tests, the true efficacy of the vaccine at the individual level for badgers is difficult to evaluate. Overall vaccine effectiveness at the population level is also affected by the proportion of animals that can be reached by the vaccine. Based on the current mode of deployment through trapping and inoculation, this is determined by the trapping rate of badgers, which has been estimated as 35–85% [31] and 33–68% [32]. Results from the oral bait badger vaccination study [33] and the BVDP [34] are not yet available. Because of this uncertainty surrounding the parameters of vaccination, we took a relatively simple approach to modelling vaccination. We used a single probability that incorporated the probability of an individual being reached by the vaccine (uptake efficacy) together with the probability of the vaccine inducing complete (lifelong) protection (protection efficacy). We used two values for this combined probability in our simulations: 50% and 80%. For a vaccination strategy with an overall target of 80% effectiveness at the population level (80% of the population being protected by the vaccine), each individual would be subjected to a 80% combined probability of being reached by, or taking up, the vaccine (uptake efficacy) and being protected by the vaccine (protection efficacy). Vaccine efficacy referred to hereafter represents this combined probability of uptake and protection.

Modelling the different scenarios

Baseline scenarios: long-term, ongoing vaccination

We used the model to establish a baseline for the maximum potential benefits of vaccination based on long-term, ongoing vaccination programmes implemented annually, and then compared these against the relative effectiveness of vaccination programmes of fixed duration (1, 4, 10 years). Initially, we ran the model across a range of equilibrium group sizes from 4 to 12 individuals per group in increments of two, representing the range of group sizes found in Europe. The equilibrium group size was identical across the grid at the start of each simulation. Each simulation was run for an initial 50 years (200 seasons) to allow the populations to stabilize according to the pre-determined equilibrium group size. Then we introduced infection in different ways as described below and allowed 25 years for the disease dynamics to stabilize. Vaccination was introduced at this point and implemented annually for the next 60 years. Each model configuration was run 50 times to produce an adequate sample size. We recorded the following data every 'summer' season: group size; number of empty/filled territories (grid cells); number of intra-group infections; number of inter-group infections; number of external infections; and number of infectious groups.

For baseline scenario 1 (no external infection, ongoing annual vaccination), TB was introduced in the form of a single infected badger in a single group, selected at random. This simulated a population with badger-derived infection, for example from a dispersing infected badger moving into a TB-naive population. After the period of stabilization of infection, we introduced vaccination every year at 50% or 80% efficacy. The 80% figure represents a 'best case' scenario (e.g. as may be produced by a combination of 90% uptake efficacy combined with 90% protection efficacy), and 50% represents a more

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realistic situation in the field (e.g. as may be produced by a combination of 70% uptake efficacy combined with 70% protection efficacy). For baseline scenario 2 (external infection, ongoing annual vaccination), simulations were run as described for scenario 1, but external infection was included as an external trickle infection with a probability of 0·01 on an annual basis. This level of external infection was chosen as it has a significant impact on disease persistence, especially at low group sizes [20].

Experimental scenarios: fixed-duration vaccination

For experimental scenario 1 (no external infection, fixed-duration annual vaccination), simulations were run as described for baseline scenario 1, but vaccination was carried out once each year for periods of 1, 4 and 10 years at 50% or 80% efficacy. For experimental scenario 2 (external infection, fixed-duration annual vaccination), simulations were run as described for baseline scenario 2, but vaccination was carried out once each year for periods of 1, 4 and 10 years at 50% or 80% efficacy.

Analyses

To compare the overall reduction in prevalence of annually deployed vaccine, exponential curves and associated 95% confidence intervals were fitted to the data to determine which lines were significantly different from one another. This was undertaken using R 2.12.2 [35].

Sensitivity analysis

Sensitivity analysis was carried out to determine which parameters had the greatest influence on disease prevalence and group size. The sensitivity analysis took into account the different scenarios used within the study, covering different efficacies of vaccination across three equilibrium group sizes 4, 8 and 12. The results were analysed using boosted regression trees within the 'R' statistical and programming environment [35], using the gbm package [36]. The results are shown in full in the online Supplementary Material.

RESULTS

Baseline scenarios

In the absence of external infection (baseline scenario 1), the application of annually repeated vaccination over the full time-span of the model led to a decrease in prevalence for all group sizes (Fig. 1*a*, *c*). Disease was reduced or eliminated more quickly in smaller group sizes and with higher vaccine efficacies. For example, at equilibrium group size $n=6$, 80% vaccine efficacy resulted in the elimination of disease within 56 years, compared to 85 years at 50% vaccine efficacy. In the presence of external infection (baseline scenario 2), both 50% and 80% vaccine efficacy reduced prevalence over time (Fig. 1*b*, *d*), although the presence of external infection reduced the rate of disease reduction. For example, external infection increased the time taken to reduce prevalence to 1% at equilibrium group size $n=6$ with a vaccine efficacy of 80% from 14 years to 19 years. In the presence of external infection (baseline scenario 2), disease was never eliminated, and it was never reduced below 1% for the larger group sizes. Reductions in prevalence were significantly lower for a 50% vaccine efficacy in the presence of external infection (Fig. 1*b*) compared to the lower group sizes ($k\leqslant 8$) for 50% vaccine efficacy without external infection (Fig. 1*a*) and 80% vaccine efficacy with and without external infection (Fig. 1*c*, *d*) and (Fig. 1*a*), respectively.

Experimental scenarios

In the absence of external infection (experimental scenario 1), fixed-term annual vaccination prevented the persistence of disease at the lowest equilibrium group size considered ($n=4$), and disease was still relatively unstable for an equilibrium group size $n=6$ (see online Supplementary Material). The greatest reduction in prevalence was achieved for small group sizes and higher vaccine efficacies (Table 1). Vaccination over periods of 1, 4 or 10 years, for equilibrium group sizes of 10 and 12 initially reduced prevalence. However, following the cessation of vaccination, even in the absence of external infection, prevalence subsequently recovered for equilibrium group sizes $n=10$ and 12, remained stable for equilibrium group size $n=8$, but did not recover for equilibrium group sizes $n=4$ and 6. The tipping point for disease recovery occurred between equilibrium group sizes $n=8$ and 10 (Figs 2*a*, *c*, 3*a*, *c*).

In the presence of external infection (experimental scenario 2), at equilibrium group size $n=4$, the likelihood of disease persistence increased, although disease still died out in the majority of simulations. At higher equilibrium group sizes of $n\geqslant 6$, the dynamics of infections were more stable. At these equilibrium

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Table 1. *The percentage reduction in prevalence achieved under different scenarios with different vaccination efficacies*

Badger equilibrium group size	Vaccination conditions											
	Scenario 1						Scenario 2					
	50% efficacy			80% efficacy			50% efficacy			80% efficacy		
	1 yr	4 yr	10 yr	1 yr	4 yr	10 yr	1 yr	4 yr	10 yr	1 yr	4 yr	10 yr
4	100·0	100·0	100·0	100·0	100·0	100·0	25·0	52·4	79·0	28·2	61·4	84·8
6	95·5	89·7	99·1	93·6	96·0	98·4	14·6	45·0	70·7	26·7	54·9	82·1
8	45·5	35·3	63·8	24·2	48·3	75·8	14·2	34·0	61·3	21·6	49·2	75·4
10	9·7	31·8	53·6	17·1	41·4	69·7	9·9	30·3	54·1	17·5	41·6	69·8
12	7·2	26·4	46·6	13·6	36·7	63·1	7·9	25·9	48·1	14·0	35·4	62·9

Scenario 1, no external infection and fixed-duration annual vaccination.
Scenario 2, external infection and fixed-duration annual vaccination.

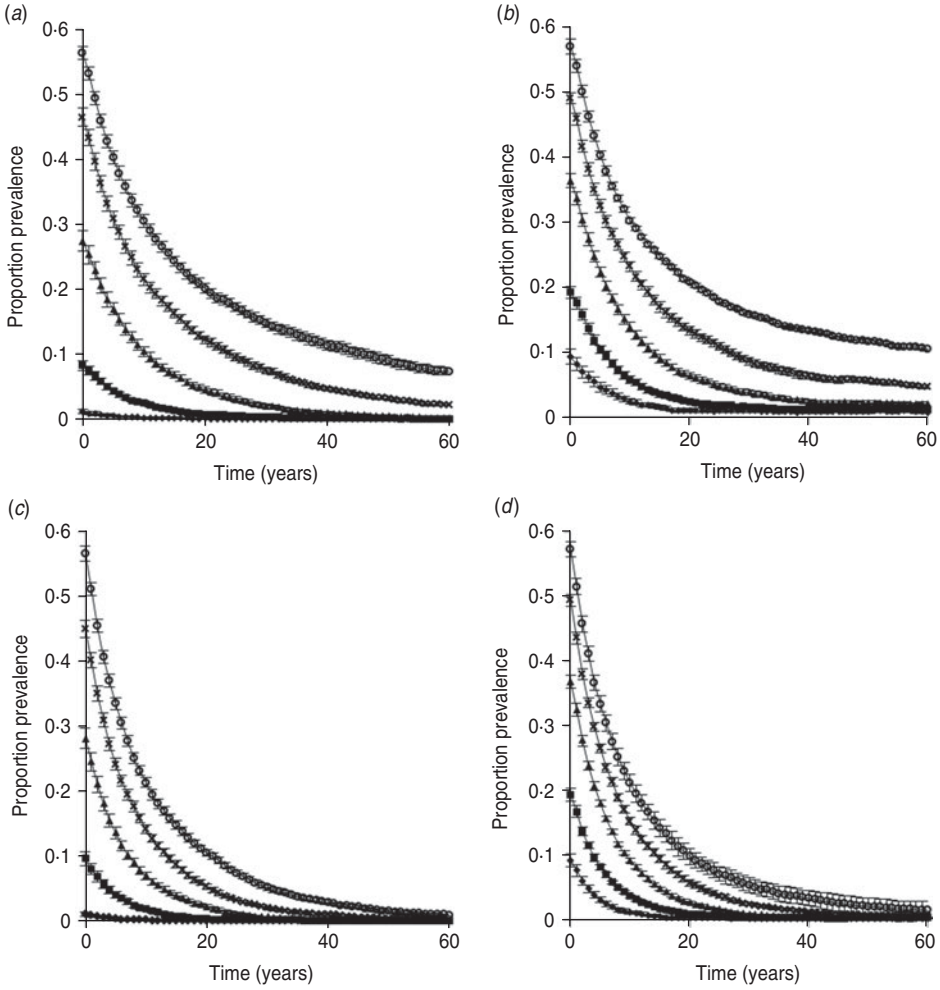

Fig. 1. Relationship of prevalence with time for equilibrium group sizes of 4–12 subject to ongoing, annually repeated vaccination. (*a*) Vaccine efficacy 50%, no external infection; (*b*) vaccine efficacy 50%, external infection; (*c*) vaccine efficacy 80%, no external infection; (*d*) vaccine efficacy 80%, external infection. Equilibrium group sizes: $n=4$ (diamonds); $n=6$ (squares); $n=8$ (triangles); $n=10$ (crosses); $n=12$ (open circles).

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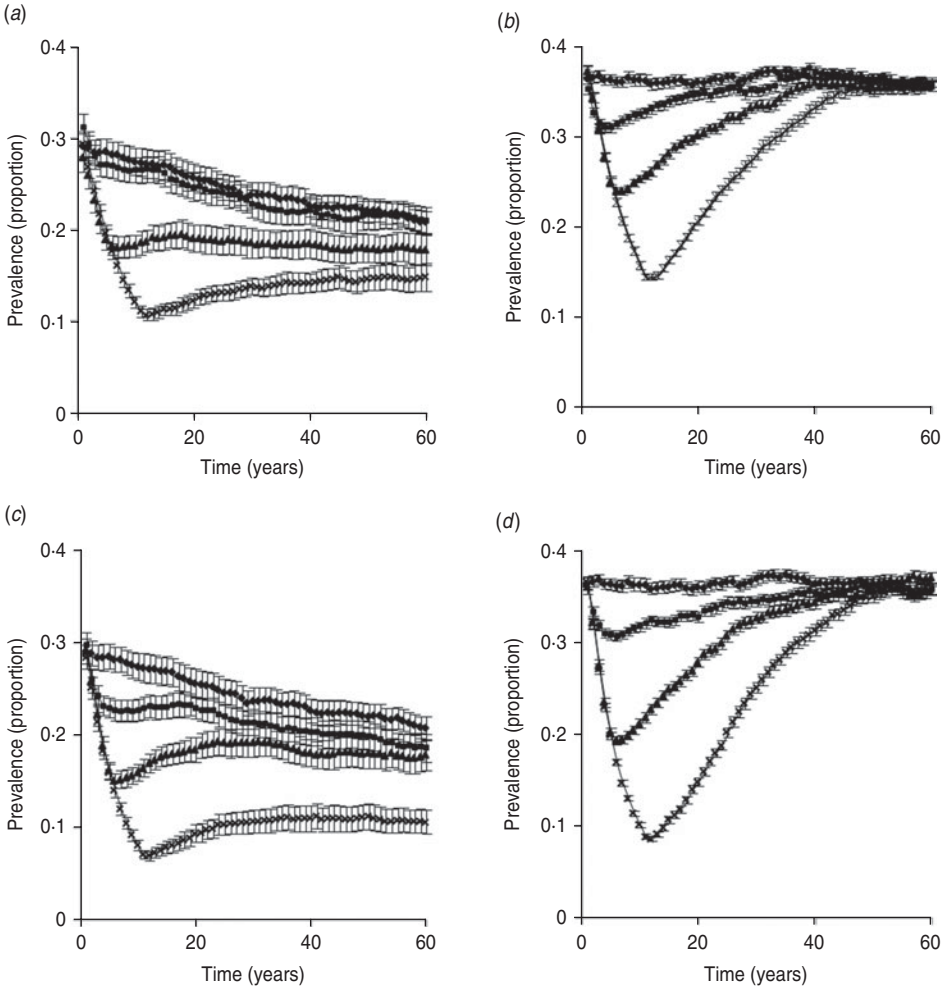

Fig. 2. Relationship of prevalence with time for equilibrium group size $n = 8$ for different fixed-term duration vaccination campaigns. (*a*) Vaccine efficacy 50%, no external infection; (*b*) vaccine efficacy 50%, external infection; (*c*) vaccine efficacy 80%, no external infection; (*d*) vaccine efficacy 80%, external infection. No vaccination (diamonds); 1-year vaccination (squares); 4-year vaccination (triangles); 10-year vaccination (crosses).

group sizes, the existence of external infection resulted in higher equilibrium prevalence in the absence of any vaccination campaign and reduced considerably the ability of vaccines to reduce or eliminate disease (Fig. 2*b*, *d*, Table 1). Following cessation of vaccination, the presence of external infection increased the rate of recovery of the disease, with prevalence returning to pre-vaccination levels under all conditions of vaccination (Figs 2*b*, *d*, 3*b*, *d*).

DISCUSSION

A high level of vaccine efficacy (80%, incorporating both uptake and complete, lifelong protection), reduces TB prevalence in badgers to lower levels more rapidly than a lower level of vaccine efficacy (50%), and is more effective at reducing disease in larger groups. Vaccination with low efficacy carried out over a limited time period has some benefits in reducing disease for lower equilibrium group sizes of $n \leqslant 8$. However, at higher equilibrium group sizes ($n = 10$ and 12), prevalence recovers quickly following the cessation of vaccination. Recovery of disease is aided considerably by the presence of external infection. The impact of external infection on disease prevalence and recovery following vaccination is especially significant for the lower group sizes. For these equilibrium group sizes ($n \leqslant 6$), the presence of external infection negates any benefits of fixed-term vaccination, with disease recovering rapidly following the cessation of vaccination. Where sources of external infection persist, benefits in TB reduction in badgers can only be achieved by ongoing, annual vaccination.

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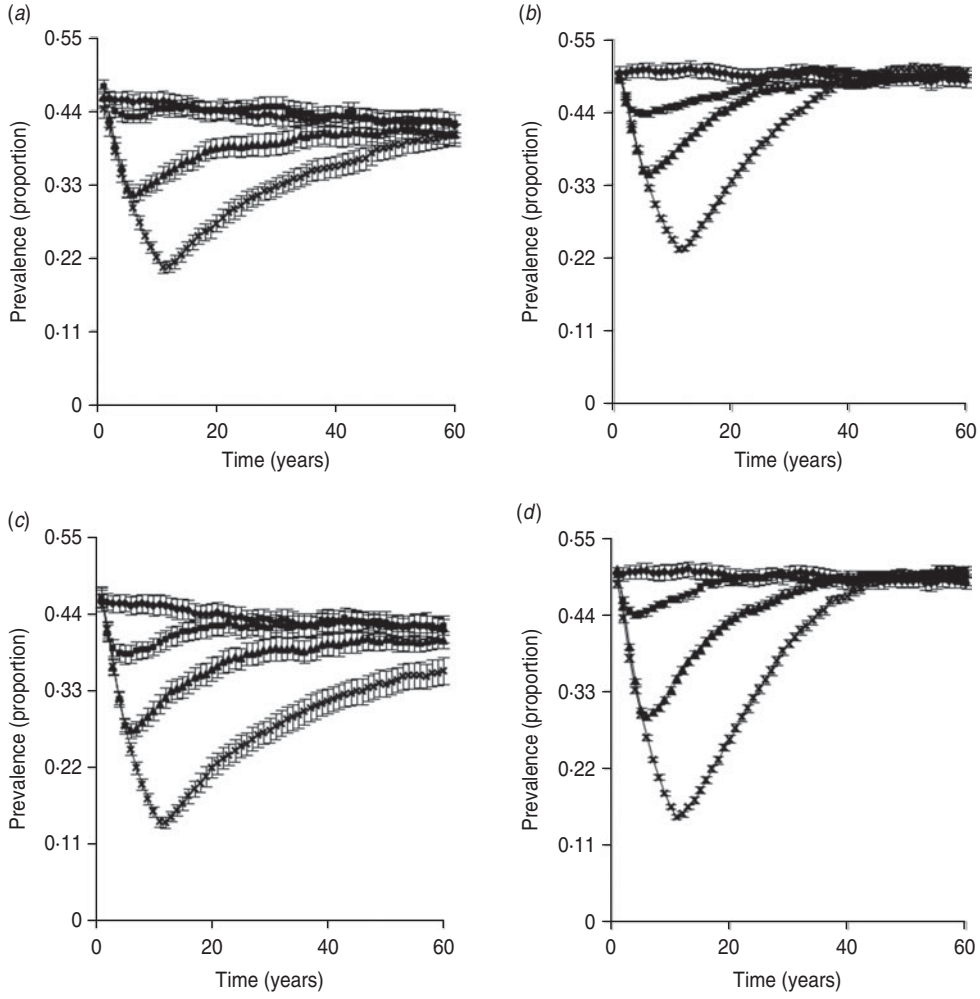

Fig. 3. Relationship of prevalence with time for equilibrium group size $n = 10$ for different fixed-term duration vaccination campaigns. (*a*) Vaccine efficacy 50%, no external infection; (*b*) vaccine efficacy 50%, external infection; (*c*) vaccine efficacy 80%, no external infection; (*d*) vaccine efficacy 80%, external infection. No vaccination (diamonds); 1-year vaccination (squares); 4-year vaccination (triangles); 10-year vaccination (crosses).

The sensitivity analysis showed that for all but the smallest group sizes, prevalence is affected most significantly across all group sizes by intra-group infections and the rate of transfer of individuals between latent and infectious states. The effect of vaccination on these parameters will be to reduce the overall number of individuals entering the infectious state, which will therefore reduce intra-group infections. Thus, vaccination acts directly on the key parameters in TB dynamics in badgers. Where vaccination can be maintained annually on an ongoing basis, these targeted impacts mean it can be extremely effective in reducing and eliminating TB, although this may still take some time for populations with larger group sizes. However, when vaccination is carried out for only a limited period, especially in larger group sizes, its constraining effects on these three key parameters are removed, and the disease can recover rapidly as a result. External sources of infection, which help to seed further disease into the badger population, will exacerbate both these effects, reducing the effectiveness of vaccination in the first place and enhancing the recovery of disease following cessation of vaccination.

Our model assumed that once badgers are vaccinated, they are fully protected and cannot become infected. Recent laboratory-based studies of badger vaccination have demonstrated that vaccinated badgers can still become infected, although they exhibit less severe infection and are therefore less likely to shed bacteria [12, 28, 29]. However, the results from these studies were a result of experimental challenge, and it is uncertain to what extent these results are transferable to wild, free-living badgers. Other wild

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species that act as host for *M. bovis*, when vaccinated with BCG and subjected to experimental challenge, have shown similar partial protection. These species include possums (*Trichosurus vulpecula*) [37], ferrets (*Mustela furo*) [38] and white-tailed deer (*Odocoileus viginianus*) [39]. The way we have incorporated vaccination into our model therefore provides a best-case scenario, and if the protective effect is only partial, then the effectiveness of vaccination in reducing TB in wild badgers will be less than predicted by our model. This is especially likely to be the case for free-living badgers, where other stressors will affect pathogenesis and uptake of vaccine, for example prior exposure to other environmental bacteria, which may prevent the vaccination from evoking the full immune response necessary to develop specific immunity to *M. bovis* [40].

In field trials on possums in New Zealand, using a combination of intranasal aerosol and conjunctival instillation, a vaccine efficacy of 69% has been achieved [41], and in a separate trial, using oral vaccination, an efficacy of 87–100% (mean of 95% for females and 96% for males) at the individual level was recorded [42]. Thus, once BCG uptake occurs, it is possible to achieve high levels of efficacy. For TB control in possums through vaccination, models have suggested that between 40% and 52% of the population must be protected at any one time [21, 22]. To achieve this, and based on 100% vaccine efficacy at the individual level, annual vaccination rates of 25–40% are required [21]. A reduction in efficacy below 100% will lead to a higher requirement in terms of the proportion of the population needing to be reached. Thus, although vaccination could eradicate TB in possums, even at relatively modest uptake rates, Barlow [21] considered it the least effective alternative when comparing it with culling and fertility control. In a more recent modelling study, Ramsey & Efford [23] estimated that vaccination with an uptake rate of 95% and an efficacy rate of 90% could control a TB outbreak in possums in a 1 km^2 outbreak area in 8 years, if a 5·5 km control buffer was in place around the original outbreak area. These authors also found that vaccination was the least cost-effective option for TB control in possums compared to culling alone or an integrated strategy involving culling, fertility control and/or vaccination. An additional important factor in relation to possums in New Zealand is that vaccination does nothing to reduce population densities and may even lead to population increases [21].

If BCG shows significantly higher efficacy at the individual level in wild badger populations than in captive ones, the limiting factor in determining the effectiveness of BCG vaccination in reducing TB in badgers will be the uptake rate of the vaccine. In the UK, as part of a BVDP [14], badgers are being trapped and vaccinated for 6 years. The results of our model suggest that, providing a high level of efficacy can be achieved, this duration of vaccination may lower TB prevalence in the short term. However, our results also suggest that, if group sizes in the area of the BVDP are large, TB levels may recover again following cessation of vaccination. Moreover, the reliance of the BVDP on trapping will act to reduce the net efficacy, because trapping efficiency for badgers (and hence the vaccine uptake rate when trapping is the sole method used) varies between 35% and 85% [43]. It is highly unlikely that an uptake rate as high as that in possums (95%, based on aerial baiting [44]) is achievable on a consistent basis for wild badger populations, especially if vaccine delivery requires trapping. Even with a net vaccine efficacy of 80%, the higher efficacy used in the model, low or even moderate trapping efficiency of badgers may reduce the overall net efficacy in the BVDP further, towards or below 50%, the lower efficacy that we modelled. If BCG efficacy in wild badger populations proves to be as high as has been observed in possums (95%), and an efficient oral bait delivery system for a badger vaccine can be developed so that $\geqslant$85% of the population can be reached, a net vaccine efficacy of around 80% may be achievable. However, given the current laboratory-based evidence for badgers and the reliance on trapping for uptake, a net efficacy (combining uptake and protection) of 50% may be a more conservative guide. Our use of overall vaccination efficacies of 50% and 80% lies within the range of likely values for a trap-and-vaccinate approach based on evidence from previous field studies, and will be relevant to the interpretation of the data from the field trials in the UK and Ireland, as well as for future development of vaccination strategies.

There are many potential sources of *M. bovis* for infecting badgers, both environmental and animal. *M. bovis* has been isolated from soil from around badger setts and latrines [45], and may survive for varying lengths of time and under a range of conditions in water and on a variety of feed [46–48]. The vaccination of badgers will aid the reduction of *M. bovis* excretion decreasing environmental contamination

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from the population itself (self-perpetuated disease). Other infected wild species may present a hazard to badgers from their excretion of *M. bovis*. In the UK, infection has been discovered in deer and other species [49, 50] which are considered to be spillover hosts. Since the badger may be a source of infection into these communities, a reduction in disease levels in the badger population may result in less frequent infection within the other species populations and break the disease cycle. However, in countries where other wild species are presented as reservoirs of infection, for example wild boar and red deer [51], these species may act as sources of infection for the badger population, and the disease-specific benefits of vaccinating badgers would be much reduced. Vaccination of livestock rather than wildlife may be an alternative or complementary future control option and the efficacy of this is currently being tested [52–55]. However, under current regulations, vaccination of cattle will not be possible in the EU, unless tests (DIVA tests) that can distinguish between immune reactions that originate from a natural infection rather than those acquired through vaccination, become more practical and widely available [56, 57].

This work has highlighted the inherent difficulties in the use of vaccination to reduce diseases such as TB in wildlife and hence the risks to cattle. For vaccination to be effective, high levels of the population need to be reached and protected by the vaccine. Our model has shown that vaccination alone could be an effective disease control strategy for TB in higher-density badger populations only if vaccine efficacies (combining uptake and effectiveness at the individual level) of around 80% are reached and vaccine is deployed annually for long periods. In lower-density badger populations, vaccination at a lower efficacy can be effective in reducing the disease, but its effectiveness is reduced by the presence of external sources of infection, and this phenomenon is more pronounced at lower population densities. Vaccination of badgers may aid the reduction of infection in the host community generally, for example reducing spillover of infection to sympatric species, but effective long-term TB reduction across an entire wildlife host community is unlikely to be achievable by vaccination alone, even where badgers are the sole TB reservoir. Instead, it will require a complementary suite of control measures, potentially combining vaccination with other methods such as culling and fertility control an integrated strategy, and concurrently targeting the reduction of TB in both the badgers and other members of the host-community.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268813000642.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Carstensen M, Brien DJO, Schmitt SM.** Public acceptance as a determinant of management strategies for bovine tuberculosis in free-ranging U.S. wildlife. *Veterinary Microbiology* 2011; **151**: 200–204.
2. **Tuyttens FAM, *et al.*** Spatial perturbation caused by a badger (*Meles meles*) culling operation: implications for the function of territoriality and the control of bovine tuberculosis (*Mycobacterium bovis*). *Journal of Animal Ecology* 2000; **69**: 815–828.
3. **Carter SP, *et al.*** Culling-induced social perturbation in Eurasian badgers *Meles meles* and the management of TB in cattle: an analysis of a critical problem in applied ecology. *Proceedings of the Royal Society of London, Series B* 2007; **274**: 2769–2777.
4. **Sunde P, *et al.*** Behavioural responses of GPS-collared female red deer *Cervus elaphus* to driven hunts. *Wildlife Biology* 2009; **15**: 454–460.
5. **Scillitani L, Monaco A, Toso S.** Do intensive drive hunts affect wild boar (*Sus scrofa*) spatial behaviour in Italy? Some evidence and management implications. *European Journal of Wildlife Research* 2010; **56**: 307–318.
6. **European Food Safety Authority.** The community summary report on trends and sources of zoonoses and zoonotic agents in the European Union in 2007. *EFSA Journal* 2009 (http://www.efsa.europa.eu/de/scdocs/doc/223r.pdf).
7. **Martin-Atance P, *et al.*** Bovine tuberculosis in a free ranging red fox (*Vulpes vulpes*) from Donana National Park (Spain). *Journal of Wildlife Diseases* 2006; **41**: 435–436.
8. **Jenkins HE, Woodroffe R, Donnelly CA.** The duration of the effects of repeated widespread badger culling on cattle tuberculosis following the cessation of culling. *PLoS ONE* 2010; **5**: e9090.
9. **Anon.** Pilot badger culls to go ahead in England. *Veterinary Record* 2011; **169**: 668.

10. **Robinson PA, *et al.*** BCG vaccination against tuberculosis in European badgers (*Meles meles*): a review. *Comparative Immunology, Microbiology and Infectious Diseases* 2012; **35**: 277–287.
11. **Lesellier S, *et al.*** Immunological responses following experimental endobronchial infection of badgers (*Meles meles*) with different doses of *Mycobacterium bovis*. *Veterinary Immunology and Immunopathology*, 2009; **127**: 174–180.
12. **Corner LAL, *et al.*** Oral vaccination of badgers (*Meles meles*) with BCG and protective immunity against endobronchial challenge with *Mycobacterium bovis*. *Vaccine* 2010; **28**: 6265–6272.
13. **Lesellier S, *et al.*** Protection of Eurasian badgers (*Meles meles*) from tuberculosis after intra-muscular vaccination with different doses of BCG. *Vaccine* 2011; **29**: 3782–3790.
14. **Fera. Badger Vaccine Deployment Project** (www.defra.gov.uk/fera/bvdp). Accessed June 2011.
15. **White PCL, Harris S.** Bovine tuberculosis in badger (*Meles meles*) populations in south-west England: the use of a spatial stochastic simulation model to understand the dynamics of the disease. *Philosophical Transactions of the Royal Society of London, Series B* 1995; **349**: 391–413.
16. **White PCL, Harris S.** Bovine tuberculosis in badger (*Meles meles*) populations in south-west England: an assessment of past, present and possible future control strategies using simulation modelling. *Philosophical Transactions of the Royal Society of London, Series B* 1995; **349**: 415–432.
17. **Smith GC, *et al.*** A model of bovine tuberculosis in the badger *Meles meles*: an evaluation of control strategies. *Journal of Animal Ecology* 2001; **38**: 509–519.
18. **Wilkinson D, *et al.*** A model of bovine tuberculosis in the badger *Meles meles*: an evaluation of different vaccination strategies. *Journal of Applied Ecology* 2004; **41**: 492–501.
19. **White PCL, Lewis AJG, Harris S.** Fertility control as a means of controlling bovine tuberculosis in badger (*Meles meles*) populations in southwest England: predictions from a spatial stochastic simulation model. *Proceedings of the Royal Society of London, Series B* 1997; **264**: 1737–1747.
20. **Hardstaff JL, *et al.*** Impact of external sources of infection on the dynamics of bovine tuberculosis in modelled badger populations. *BMC Veterinary Research* 2012, **8**: 92.
21. **Barlow ND.** Control of endemic bovine TB in New Zealand possum populations: results from a simple model. *Journal of Applied Ecology* 1991; **28**: 794–809.
22. **Roberts MG.** The dynamics of bovine tuberculosis in possum populations, and its eradication or control by culling or vaccination. *Journal of Animal Ecology* 1996; **65**: 451–464.
23. **Ramsey DSL, Efford MG.** Management of bovine tuberculosis in brushtail possums in New Zealand: predictions from a spatially explicit, individual-based model. *Journal of Applied Ecology* 2010; **47**: 911–919.
24. **White PCL, *et al.*** Control of bovine tuberculosis in British livestock: there is no 'silver bullet'. *Trends in Microbiology* 2008; **16**: 420–427.
25. **Gallagher J, *et al.*** Role of infected , non-diseased badgers in the pathogenesis of tuberculosis in the badger. *Veterinary Record* 1998; **142**: 710–714.
26. **Gavier-Widen D, *et al.*** Pathology of natural *Mycobacterium bovis* infection in European badgers (*Meles meles*) and its relationship with bacterial excretion. *Veterinary Record* 2001; **148**: 299–304.
27. **Corner LAL, *et al.*** *Mycobacterium bovis* infection in the Eurasian badger (*Meles meles*): the disease, pathogenesis, epidemiology and control. *Journal of Comparative Pathology* 2011; **144**: 1–24.
28. **Lesellier S, Palmer S, Dalley DJ.** The safety and immunogenicity of Bacillus Calmette-Guerin (BCG) vaccine in European badgers (*Meles meles*). *Veterinary Immunology and Immunopathology* 2006; **112**: 24–37.
29. **Corner LAL, *et al.*** Vaccination of European badgers (*Meles meles*) with BCG by the subcutaneous and mucoasal routes induces protective immunity against endobronchial challenge with *Mycobacterium bovis*. *Tuberculosis* 2008; **88**: 601–609.
30. **Chambers MA, *et al.*** Bacillus Calmette-Guerin vaccination reduces the severity and progression of tuberculosis in badgers. *Proceedings of the Royal Society of London, Series B* 2011; **278**: 1913–1920.
31. **Smith GC, Cheeseman CL.** Efficacy of trapping during the initial proactive culls in the randomised badger culling trial. *Veterinary Record* 2007; **160**: 723–726.
32. **Byrne AW, *et al.*** Population estimation and trappability of the European badger (*Meles meles*): implications for tuberculosis management. *PLoS ONE* 2012; **7**: e50807.
33. **Aznar I, *et al.*** Trial design to estimate the effect of vaccination on tuberculosis incidence in badgers. *Veterinary Microbiology* 2011; **151**: 104–111.
34. **Wilson GJ, Carter SP, Delahay RJ.** Advances and prospects for management of TB transmission between badgers and cattle. *Veterinary Microbiology* 2011; **151**: 43–50.
35. **R Development Core Team.** R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (http://www.R-project.org). 2010.
36. **Ridgeway G.** Generalized Boosted Models: a guide to the GBM package. (www.cran.r-project.org), 2007. Accessed 16 February 2011.
37. **Cross ML, *et al.*** Lipid-formulated BCG as an oral-bait vaccine for tuberculosis: vaccine stability, efficacy, and palatability to brushtail possums (*Trichosurus vulpecula*) in New Zealand. *Journal of Wildlife Diseases* 2009; **45**: 754–765.
38. **Qureshi T, *et al.*** Partial protection against oral challenge with *Mycobacterium bovis* in ferrets (*Mustela furo*) following oral vaccination with BCG. *International Journal of Tuberculous Lung Disease* 1999; **3**: 1025–1033.
39. **Nol P, *et al.*** Efficacy or oral and parental routes of *Mycobacterium bovis* bacilli calmette-Guerin

vaccination against experimental bovine tuberculosis in white-tailed deer (*Odocoileus virginianus*) a feasibility study. *Journal of Wildlife Diseases* 2008; **44**: 247–259.

40. **Brandt L, *et al.*** Failure of the *Mycobacterium bovis* BCG vaccine: some species of environmental mycobacteria block multiplication of BCG and induction of protective immunity to tuberculosis. *Infection and Immunity* 2000; **70**: 672–678.
41. **Corner LA, *et al.*** The efficacy of bacille Calmette-Guerin vaccine in wild brushtail possums (*Trichosurus vulpecula*). *Res Vet Sci* 2002; **73**: 145–152.
42. **Tompkins DM, *et al.*** Oral vaccination reduces the incidence of tuberculosis in free-living brushtail possums. *Proceedings of the Royal Society of London, Series B* 2009; **276**: 2987–2995.
43. **Smith GC, Cheesman CL.** Efficacy of trapping during the initial proactive culls in the randomised badger culling trial. *Veterinary Record* 2007; **160**: 723–726.
44. **Warburton B, Thomson C.** Comparison of three methods for maintaining possums at low density. Wellington: Department of Conservation, 2002, 20 pp.
45. **Sweeney FP, *et al.*** Immunomagnetic recovery of *Mycobacterium bovis* from naturally infected environmental sample. *Applied and Environmental Microbiology* 2006; **43**: 364–369.
46. **Young JS, Gormley E, Wellington EMH.** Molecular Detection of *Mycobacterium bovis* and *Mycobacterium bovis* BCG (Pasteur) in Soil. *Applied and Environmental Mircrobiology* 2005; **71**: 1946–1952.
47. **Palmer MV, Whipple DL.** Survival of *Mycobacterium bovis* on feedstuffs commonly used as supplemental feed for white-tailed deer (*Odocoileus virginianus*). *Journal of Wildlife Diseases* 2006; **42**: 853–858.
48. **Michel AL, *et al.*** Bovine tuberculosis in African buffaloes: observations regarding *Mycobacterium bovis* shedding into water and exposure to environmental mycobacteria. *BMC Veterinary Research* 2007; **3**: 23–30.
49. **Mathews F, *et al.*** Bovine tuberculosis (*Mycobacterium bovis*) in British farmland wildlife: the importance to agriculture. *Proceedings of the Royal Society of London, Series B* 2006; **273**: 357–365.
50. **Delahay RJ, *et al.*** Bovine tuberculosis infection in wild mammals in the South-West region of England: A survey of prevalence and a semi-quantitative assessment of the relative risks to cattle. *Veterinary Journal* 2007; **173**: 287–301.
51. **Gortazar C, *et al.*** Progress in the control of bovine tuberculosis in Spanish wildlife. *Veterinary Microbiology* 2011; **151**: 170–178.
52. **Buddle BM, *et al.*** Effect of oral vaccination of cattle with lipid-formulated BCG on immune responses and protection against bovine tuberculosis. *Vaccine* 2005; **23**: 3581–3589.
53. **Lopez-Valencia G, *et al.*** Field evaluation of the protective efficacy of *Mycobacterium bovis* BCG vaccine against bovine tuberculosis. *Research in Veterinary Science* 2010; **88**: 44–49.
54. **Buddle BM, *et al.*** Low oral BCG doses fail to protect cattle against an experimental challenge with *Mycobacterium bovis*. *Tuberculosis* 2011; **91**: 400–405.
55. **Hope JC, *et al.*** Identification of surrogates and correlates of protection in protective immunity against *Mycobacterium bovis* infection induced in neonatal calves by vaccination with *M. bovis* BCG Pasteur and *M. bovis* BCG Danish. *Clinical and Vaccine Immunology* 2011; **18**: 373–379.
56. **Buddle BM.** Vaccination of cattle against *Mycobacterium bovis*. *Tuberculosis* 2001; **81**: 125–132.
57. **Sopp P, *et al.*** development of a simple, sensitive, rapid test which discriminates BCG-vaccinated from *Mycobacterium bovis*-infected cattle. *Vaccine* 2008; **26**: 5470–5476.