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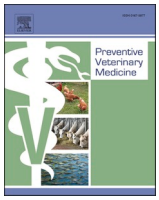

Simulating partial vaccine protection: BCG in badgers

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ABSTRACT

In wildlife disease management there are few diseases for which vaccination is a viable option. The human vaccine BCG has been used for the control of bovine tuberculosis in badgers since 2010 and is expected to increase. Understanding the long-term effects of repeated vaccination campaigns on disease prevalence is vital, but modelling thus far has generally assumed that a vaccine provides perfect protection to a proportion of the population, and that animals exposed to a repeated vaccination have a second independent chance of becoming protected. We held a workshop with experts in the field to obtain consensus over the main pathways for partial protection in the badger, and then simulated these using an established model. The available data supported the possibility that some individuals receive no benefit from the BCG vaccine, others may result in a delayed disease progression and in the remaining animals, vaccine protected the individual from any onward transmission. Simulating these pathways using different levels of overall efficacy demonstrated that partial protection leads to a reduced effect of vaccination, but in all of the identified scenarios it was still possible to eradicate disease in an isolated population with no disease introduction. We also identify those potential vaccination failures that require further investigation to determine which of our proposed pathways is the more likely.

1. Introduction

There are very few wildlife diseases for which vaccination is a viable option (Blancou et al., 2009). However, with both wildlife and human diseases, modellers assume that vaccination is generally perfect, even if only temporary (Anderson and May, 1982; Yang and Silveira, 1998). Relatively little attention has been paid to imperfect vaccines and the consequences of such partial protection, despite vaccination being rarely, if ever, perfect (Gandon et al., 2003; Read et al., 2015). One such model looked at imperfect vaccination against paratuberculosis (*Mycobacterium avium* subsp. *paratuberculosis*) in cattle and concluded that partially protective vaccines may have complex or detrimental effects at the herd level (Lu et al., 2013). A closely related bacterium *Mycobacterium bovis* is circulating in a wildlife reservoir, the European badger (*Meles meles*) (Godfray et al., 2018), and is responsible for bovine tuberculosis (bTB), causing serious economic damage. Use of the human vaccine Bacille Calmette-Guérin (BCG) is proposed for cattle (Godfray et al., 2018), and has been implemented in badgers since 2010. Intramuscular vaccination with BCG reduces disease severity in experimentally infected captive badgers (Corner et al., 2008; Chambers et al.,

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2011; Lesellier et al., 2011; Balseiro et al., 2020) and has shown to provide a level of herd immunity for unvaccinated cubs (Carter et al., 2012).

The protection granted by BCG can be tested experimentally but not against typical chronic bTB (requiring months/years of incubation). In captive badgers, typical bTB lesions develop within 12 weeks in all animals challenged endobronchially with a single dose of *M. bovis*, likely to be unrepresentative of the infection pressure encountered naturally (i.e. lower dose, possibly repeated exposure). Under such experimental conditions, BCG reduced the extent of disease in infected badgers (Lesellier et al., 2011) and their risks of excretion, with *M. bovis* confirmed by culture in tracheal mucus, urine and faeces, in a smaller proportion of vaccinated badgers than controls – a 66% reduction (Chambers et al., 2011). In two field trials under natural infection pressure, BCG appeared to reduce the risk of badgers becoming infected. In a first trial, the probability of badgers turning positive to *ex vivo* bTB tests was reduced in vaccinated groups by 76% when using dual diagnostic tests and by 54% when using triple diagnostic tests (Chambers et al., 2011). A herd immunity effect was also observed: when more than a third of the social group were vaccinated, the risk to unvaccinated cubs was reduced by 79% (Carter et al., 2012). In a second trial, the probability of infection was not only shown in live badgers (vaccine efficacy was estimated at 36% at the start of the trial and 84% by the end) (Gormley et al., 2017), but also when evaluated *post mortem*: the proportion of badgers with *M. bovis* in tissues confirmed by culture was reduced by 65% (Gormley et al., 2017). In this later trial, the efficacy of BCG vaccination to prevent infection in new naïve badgers was estimated at 59% (95% CI = 6.5–82%), but infectiousness from already infected badgers was not considered to be reduced (Aznar et al., 2018). This latter study confirmed a degree of herd protection in non-vaccinated badgers but could find no difference in the pathology of vaccinated badgers that became infected, although many of these may have been infected prior to vaccination (Gormley et al., 2021). Overall, it emerges from these studies in captive and wild badger groups that BCG can protect against bTB infection, and also against the development of disease and excretion, but only partially, and that bTB must be studied at evolving stages, not just as present/absent.

In England, the Government now proposes to implement large scale vaccination for the long-term control of bTB in badgers in place of culling. This will require tools to allow accurate predictions of this intervention effect on long-term disease dynamics, in both badgers and cattle. Mathematical and simulation models in general, and for bTB in badgers, have to date, incorporated assumptions that vaccination provides complete protection from disease (technically, simulated vaccinated individuals may become infected as long as there is no infectiousness or increased mortality), and further, that repeated vaccination gives an independent probability of becoming protected (Barlow, 1996; Wilkinson et al., 2004; Hardstaff et al., 2013; Abdou et al., 2016). To adapt these models in the light of emerging evidence, the authors recently held a workshop to discuss the potential effects of BCG vaccination in badgers, based on the latest available information from ongoing trials and R&D work. The specific aim of this work was to examine the effect of badger vaccination on temporal bTB infection prevalence in badgers, comparing partial protection to full protection. Additionally, the authors considered it particularly informative to establish the probability that the incomplete protection provided by BCG vaccination could eradicate endemic bovine TB in the native badger population.

2. Methods

2.1. Exploration of possible transmission routes

By using a standard Susceptible-Exposed-Infectious (SEI) model (with no recovered state) we defined a full list of possible pathways by which BCG vaccination of badgers could interrupt disease progression and pared this down to the plausible ones (Fig. 1). Thus, unvaccinated 'susceptible' animals in state 'S' become infected at rate βSI and move to the exposed 'E' state. From here they progress at a fixed rate to being infectious 'I'. This model also includes the standard vaccinated state, V_1, where individuals are assumed to be protected from disease (animals may actually become infected but do not show any disease progression nor any transmission or increased mortality and would remain test negative). State V_2 represents vaccinated healthy animals which *can* become infected (E_{v2}) with the probability reduced by factor '2a', and possibly progress to being infectious (I_{v2}) with probability reduced by '2b' compared to non-vaccinated animals. Animals in an alternate infectious state (e.g. I_{v2}) may infect other susceptible animals with an adjusted probability ($\beta_2 SI_{v2}$).

If exposed (E: infected) or infectious (I) animals are vaccinated, they could potentially move to alternate states. Post-exposure vaccination with BCG has produced no marked benefit against *M. tuberculosis* in guinea pigs (Henao-Tamayo et al., 2009) or mice (Vilaplana et al., 2011), although other vaccines are being considered for potential post-exposure vaccination in humans (Andersen and Scriba, 2019). On discussion, there was no evidence found in the available badger studies where test positive animals could have been vaccinated, to support any post-exposure or therapeutic effects, so we concluded such pathways could be ignored.

The workshop considered the full SEI model (Fig. 1) and discussed the various vaccination studies performed on captive badgers (Corner et al., 2008, 2010; Lesellier et al., 2009, 2011, 2019, 2020; Chambers et al., 2011, 2017; Murphy et al., 2014; Balseiro et al., 2020; Birch et al., 2021) and field studies in England (Carter et al., 2012), Ireland (Gormley et al., 2017), plus unpublished studies by the authors. Evidence for each of the pathways were then discussed and plausible parameter values mutually agreed. The consensus output was then used to re-code an established individual based badger/bTB model (Wilkinson et al., 2004; Smith et al., 2012, 2016; Smith and Budgey, 2021) and to compare the workshop output with the original model (full protection) for an annual vaccination strategy. Current badger vaccination strategies use an annual application to ensure that all captured cubs born each year are vaccinated. This means the duration of protection is not a critical parameter, assuming that vaccine coverage is adequate, and revaccination does not change the protection status compared with

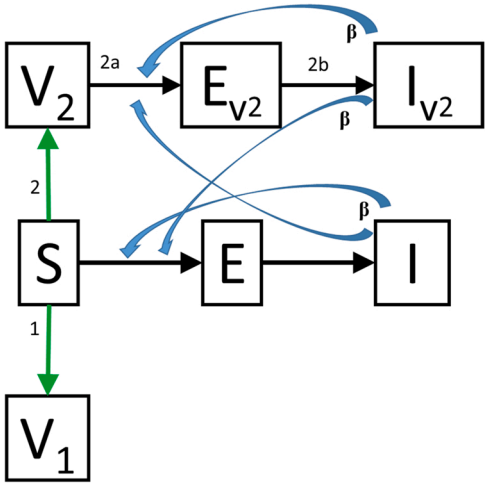

Fig. 1. The final consensus agreed list of pathways for the effects of BCG vaccination on bTB progression in badgers. The black lines indicate natural progression of disease, and the green lines the potential transfer of state following vaccination. The β infection links apply equally to the S-E transition and the V_2-E_{v2} transition. The pathways 2a and 2b represent a proportionate reduction to the equivalent pathways. Additional pathways may occur if vaccination affects already infected animals (states E and I) but there was no evidence to support such pathways.

single vaccination.

The original model included two infectious states: a single-site excretor (animals culture positive at one body location: sputum, faeces, urine or bite wounds) and a multi-site excretor (animals culture positive at more than one body location), where the latter is assumed to be twice as infectious. This dual state infectious category was maintained and assumed not to vary due to vaccination.

Pathway 1 represents full protection from disease. It is accepted that an animal *may* become infected by *M. bovis* (exposed), but would remain unlikely to become test positive, and in any case would not become infectious. This is the standard assumption for vaccination in most models. As field studies found that the probability of becoming test positive after vaccination was reduced by 76% (Carter et al., 2012), the consensus agreement was that between 70% and 90% of vaccinated susceptible badgers would enter state V_1, thus either 10% or 30% of badgers could enter V_2 state.

Pathway 2 represents partial protection. An animal may become infected (βSI multiplied by 2a) and progress to being infectious (natural rate multiplied by 2b). We consider that the probability of becoming infected is multiplied by a factor, and for an exploration of this effect the participants agree to investigate a factor of 0.5 and 1, where the latter means the animal has no protection at all and is just as likely to become infected as an unvaccinated animal. Once 'exposed' and infected (E_{v2}) it is possible that an animal may progress to become infectious. Here, due to limited evidence, we explore multipliers of 1.0 and 0.0. An infected animal would either progress to being infectious at the same rate as non-vaccinated animals or would never progress to this state. We assumed here that failure of the vaccine to protect at this point would make an animal just as likely to transmit disease, so the β_2 value employed is identical to that for unvaccinated animals. The reduced disease observed in vaccinated badgers across several studies (Chambers et al., 2011; Lesellier et al., 2011; Gormley et al., 2017) may imply that bacterial excretion is in fact reduced, thus reducing β_2 and increasing vaccine efficacy at the population level. However, we did not feel able to quantify this, and the effect would be contained within the previous multiplication factors to reach the infectious stage.

We assumed that vaccine protection was for the lifetime of the badger. In the field, assuming an annual vaccination effort, an animal would likely be re-vaccinated one or two years after the initial capture (depending on trapping efficacy), but this is assumed not to change the vaccinated state the animal is already in. Thus, they cannot transfer from V_1 to V_2 or vice versa. A more complex model could examine differential levels of protection with age, and with re-vaccination, but there are currently no data to justify this.

2.2. Model parameters

A stochastic individual-based simulation model (Smith et al., 2016) was used to estimate the bTB prevalence of the identified badger vaccine pathways and the results presented as the mean of 100 simulations. The model is written in Python and a full description given in Supplementary File 1 according to the ODD protocol (Grimm et al., 2006).

A trap-and-vaccinate strategy was simulated in a badger population with a density representative of south-west England, which comprised 217 contiguous social groups on 255 contiguous farms. For the purposes of the model, it was assumed that vaccination of the entire population was attempted, but success was dependent on the proportion of farms participating in the control programme (assumed to be 70%) and the efficacy of trapping animals that were thereby accessible: also assumed to be 70% in line with the Randomised Badger Culling Trial results (Smith and Cheeseman, 2007). An annual vaccination campaign was simulated each year in June. The mechanistic processes of badger demographics, movement and epidemiology were simulated. These figures could similarly apply to oral vaccination if bait uptake was assumed to be 70%.

A no vaccination strategy was simulated, that stabilised after 100 model years at a mean badger social group size of approximately eight animals, and a mean disease prevalence of 0.15. The transmission coefficient (β) was adjusted to ensure bTB prevalence in the unvaccinated population was consistent with a prevalence of 15%, as seen in an unperturbed population (Delahay et al., 2013). All vaccination scenarios started from this point and simulated five, ten and fifty years of vaccination followed by a further period of no vaccination, ending at 175 model years.

The default model vaccine pathway (Smith et al., 2016) gave each trapped badger a 0.7 probability of full protection after which they did not become infected, otherwise no protection was given. Animals could be revaccinated in subsequent years and the probability of protection each time was independent; if an animal failed to achieve protection on one occasion, it could receive full protection at subsequent capture and the protective effect of the vaccine was for life.

For the additional scenarios, the probability of full, partial or no protection from the vaccine was set independently for each animal. Animals could be vaccinated multiple times, but subsequent vaccinations had no additional effect. This is a simplistic assumption and the effects of repeated vaccination were not simulated here as we had no robust data to base this on. The protective effect of the vaccine was for life, but vaccination had no effect when given to infected animals.

In these additional scenarios, badgers could become one of: (i) fully protected by the vaccine, i.e. did not become diseased: state V_1; (ii) partially protected, when the probability of becoming infected or infectious was modified from that of an unvaccinated animal: state V_2; or (iii) not protected, when the probability of becoming infected or infectious was not modified from an unvaccinated animal: they remain in state S. Vaccinated animals receiving partial or no protection that became infected or infectious, transmitted infection with the same probability as unvaccinated animals and experienced the same additional mortality as unvaccinated animals. The full set of probabilities applied in each scenario is given in Table 1. Because of the risk that 70% protection may be unrealistic, a further set of simulations with protection set to 60% were also run (Table 1), but not presented in the graphs.

3. Results

In the no vaccination scenario, the mean bTB prevalence in the badger population remained stable at around 0.15 throughout the simulation.

Simulating a five-year vaccination campaign, the mean prevalence decreased and immediately began to increase slowly when vaccination was discontinued (Fig. 2). Several potential partial protection scenarios (2, 4, 5, and 6) resulted in a reduced effect of vaccination (i.e. prevalence was higher than the default vaccination scenario). This reduced efficacy was consistent throughout the simulation. If the partial protection was applied to 90% of vaccinated animals (scenarios 7–9), or when partially protected animals could not become infectious (scenario 3), then the effect of vaccination was very similar or even slightly better than the default vaccination scenario (scenario 1: Fig. 2). If we assumed protection was 0.6 rather than 0.7, then all lines were slightly higher but the overall relationships did not change (lines not shown on Fig. 2).

Simulating an annual vaccination policy for ten years, resulted in the overall prevalence further reducing during the control period, and produced a more distinct difference between the scenarios (Fig. 3). The least effective vaccination scenarios (2, 4, 5, 6,10, 13 and 14) were those where the probability of full protection was low (0.7 or 0.6), and either some vaccinated animals were fully infectious (scenarios 2, 4, 6, 10, 14); or where a proportion of animals received no protection and thus these could become infectious (scenarios 5, 13, 14).

If full protection applied to 90% of vaccinated animals but the others could become infectious, then the resulting prevalence was similar to the default scenario of full protection for 70% of badgers (Fig. 3). In the remaining scenarios, where at least 70% of vaccinated badgers became fully protected and partial protection did not permit these animals to be

Table 1
Probability of full vs partial protection is denoted by colour. 0.7/0.3 blue; 0.7/0.1 green; 0.9/0.1 orange. Protection given to partially protected animals is denoted by dashing: full protection from infectiousness (solid); half protection from exposure (long dash); no additional protection (short dash). Default scenario where badgers can become fully protected when re-vaccinated: dotted purple; no vaccination: solid grey.

	Proportion of vaccinated animals receiving:			Additional probability factor of becoming:	
Scenario	Full protection	No protection	Partial protection	Infected	Infectious
0. No vaccination	-	-	-	-	-
1. Default (old model) (dotted)	0.7	-	0	-	-
2. short dash	0.7	0	0.3	1.0	1.0
3. solid	0.7	0	0.3	1.0	0
4. long dash	0.7	0	0.3	0.5	1.0
5. solid	0.7	0.2	0.1	1.0	0
6. long dash	0.7	0.2	0.1	0.5	1.0
7. short dash	0.9	0	0.1	1.0	1.0
8. solid	0.9	0	0.1	1.0	0
9. long dash	0.9	0	0.1	0.5	1.0
10.	0.6	0	0.4	1.0	1.0
11.	0.6	0	0.4	1.0	0
12.	0.6	0	0.4	0.5	1.0
13.	0.6	0.3	0.1	1.0	0
14.	0.6	0.3	0.1	0.5	1.0

infectious (scenarios 3 and 8), or where partially protected animals could become infectious but the probability of being fully protected was 90% (scenario 9), then the badger prevalence remained lower than the default scenario throughout.

During the vaccination period, there was a clear difference in the rate of decline of the prevalence between scenarios. After simulating the end of vaccination, the difference between the scenarios increased slowly, but even in the worst case the mean prevalence did not reach twice that of the default scenario even after 50 years (Figs. 2 and 3). Nonetheless, this suggests that disease eradication would be hard to achieve even after ten years of annual application of a vaccine that induces only partial protection. In a small number of cases, however, annual vaccination for five or ten years did lead to disease eradication sometime later with the best performing scenario (3) having a chance of disease eradication with a 10-year strategy of 17–37% after a 25-year to 75-year horizon (Table 2). In contrast, if the annual vaccination strategy was continued for 50 years, then mean disease prevalence declined to almost zero in all scenarios (Fig. 4) with an 7–59% probability of diseases eradication by year 25, a 64–99% probability of disease eradication at the end of the strategy; increasing to 90–100% twenty-five years later. Continuous annual vaccination could achieve about a 50% chance of disease eradication by year 25 in five of the 14 simulated scenarios.

4. Discussion

This represents the first attempt to simulate bTB in badgers using vaccine performance characteristics which do not assume full protection from infection and/or disease. There are only limited data on which to base the assumptions used here and some potential outcomes have not been simulated yet; for example, it is plausible that repeated natural exposure to *M. bovis* will eventually overcome vaccine protection. The degree of vaccine protection is likely to depend on multiple factors, such as individual age, vaccination history, sex, and co-morbidities. Although evidence from human trials suggests BCG vaccination of neonates may induce long-lived immunity (Dockrell and Smith, 2017), neonatal cattle vaccinated with BCG were protected against bTB at 12, but not 24 months (Thom et al., 2012). The duration of immunity for BCG in badgers is unknown. On the basis of available data from cattle experiments (Parlane et al., 2014), it is likely that repeated vaccination of badgers would increase the level of protection that an individual gains, but for this initial investigation such temporal individual-based effects have not been accounted for.

We simulated a plausible distribution of different outcomes following BCG vaccination, based on expert opinion and the data available currently. We acknowledge that there are several assumptions both in the model itself, and within our interpretation of BCG vaccination outcomes. Further, we do not suggest any one specific simulated scenario is more likely to be a correct interpretation of real-life, but rather that we have likely encompassed the realistic outcomes within the distribution of scenarios simulated. An important result of this work is that of these plausible pathways many (scenarios 3, 4, 5, 7, 8, 9 and 11) give a similar probability of success as a simulation of a fully protective BCG vaccine (scenario 1).

The simulations demonstrate that in all scenarios presented here, disease eradication is possible and with 50 years of annual vaccination appears very likely. However, it is important to note that external

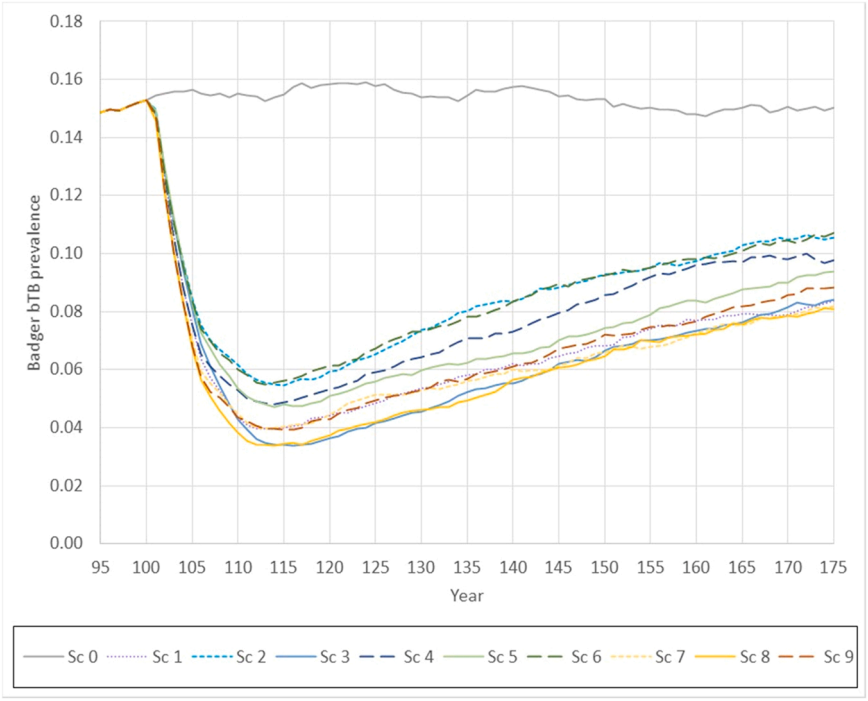

Fig. 2. Average disease prevalence across 100 replicates under each of main simulated vaccine effect pathways with five years of annual vaccination. The pathway scenarios are given in Table 1: 0 is no vaccination, 1 is the original model, 2–4 has full protection at 07, 5 and 6 also include a 0.2 probability of no protection at all, and 7–9 has full protection at 0.9.

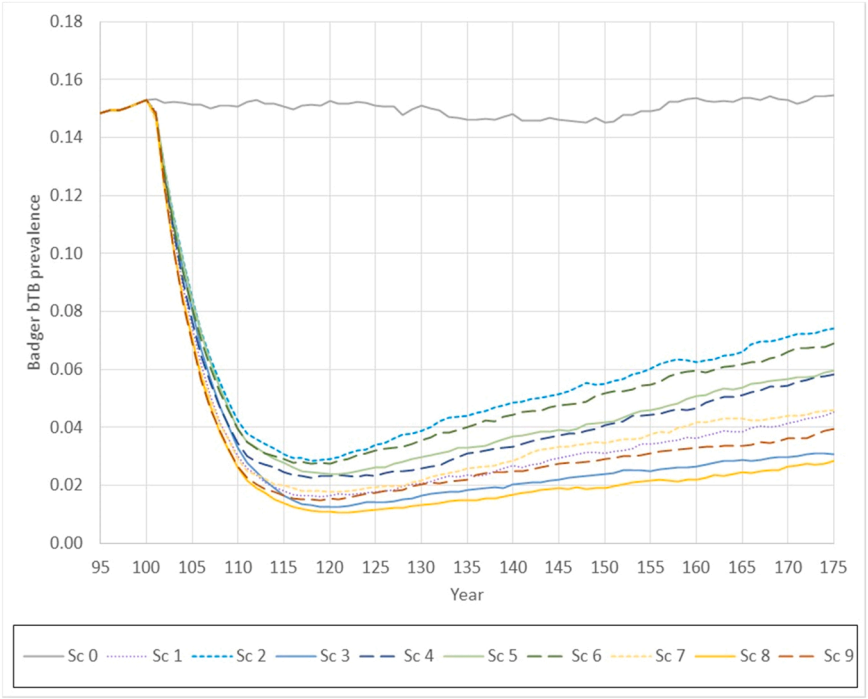

Fig. 3. Average disease prevalence across 100 replicates under each of main simulated vaccine effect pathways with ten years of annual vaccination. The pathway scenarios are given in Table 1: 0 is no vaccination, 1 is the original model, 2–4 has full protection at 07, 5 and 6 also include a 0.2 probability of no protection at all, and 7–9 has full protection at 0.9.

infection pressure was not included within these simulations. Infected badgers could not immigrate into the vaccination area and infected cattle were not simulated. This would also imply that rigorous badger sett surveying is required, so that pockets of infection are not missed. Nonetheless, the data presented are an important finding as they demonstrate that eradication of endemic bTB in badgers is theoretically possible.

Additionally, this work demonstrates that if a proportion of vaccinated badgers present the same infection risk as non-vaccinated badgers (scenarios 2, 4 and 6) then vaccination may be much less effective.

Table 2
Probability of disease eradication (percentage of simulations resulting in disease eradication) at 25, 50 and 75 years after the start of vaccination in year 100, assuming no immigration. This shows that even when vaccination only lasted five or ten years there is a small possibility of disease eradication in future years, and that in all scenarios vaccination for 50 years gave a high probability of diseases eradication.

Year	125	125	125	150	150	150	175	175	175
Vaccination Duration	5	10	50	5	10	50	5	10	50
0	0	0	0	0	0	0	0	0	0
1	0	5	43	1	11	99	4	13	100
2	1	0	7	1	0	83	1	1	92
3	0	17	53	4	34	100	4	37	100
4	0	2	20	0	7	97	0	11	100
5	0	3	16	2	8	94	2	11	99
6	0	3	9	1	4	95	1	7	98
7	1	2	39	1	11	98	2	16	99
8	0	10	59	2	20	100	2	23	100
9	1	5	50	3	20	99	4	24	100
10	0	0	1	0	3	64	0	4	90
11	2	20	45	4	32	99	6	35	100
12	0	0	15	0	2	95	0	5	99
13	0	1	5	1	2	86	1	3	96
14	0	0	3	0	1	79	1	2	96

Therefore, it is important to establish these parameters through empirical observations. Another area of importance is defining what proportion of vaccinated badgers receive no benefit from the vaccine, since in those scenarios (scenarios 5, 6, 13 and 14), overall efficacy was also lower.

Here we demonstrate that badger vaccination could be an option for bTB management. Recent data indicate that vaccination post-cull is likely to be particularly effective (Smith and Budgey, 2021). It is important to qualify however, that badger vaccination in a bTB eradication strategy must be part of a larger suite of controls. It would become increasingly important to prevent cattle-to-badger infection as vaccination progresses to avoid re-infection. Indeed cattle-to-badger infection has been shown to be more frequent than badger-to-cattle infection in both the Low Risk Area of England (Rossi et al., 2022) and in Northern Ireland (Akhmetova et al., 2021), although the reverse has been reported in endemic areas of England (Crispell et al., 2019). In terms of monitoring the effectiveness of badger vaccination, the prevalence of bTB in badgers is the easiest metric to measure in the field, through either live capture and sampling (combined with subsequent laboratory diagnostic tests) or Road Traffic Accident (RTA) post-mortem surveys. These data can then be used as an estimate of the force of infection upon farmed cattle, and subsequently inform changes in bTb management and control policy.

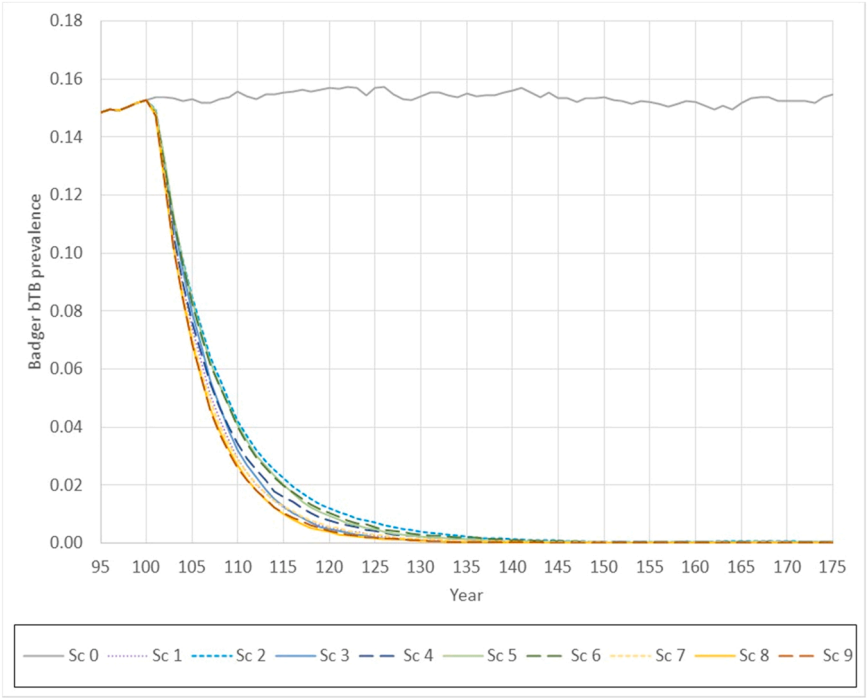

Fig. 4. Average disease prevalence across 100 replicates under each of nine simulated vaccine effect pathways with fifty years of annual vaccination. The pathway scenarios are given in Table 1: 0 is no vaccination, 1 is the original model, 2–4 has full protection at 07, 5 and 6 also include a 0.2 probability of no protection at all, and 7–9 has full protection at 0.9.

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Conflict of interest

The authors all declare there are no conflicts of interest associated with this submission.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2022.105635.

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