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Evaluating the effectiveness of badger vaccination combined with cattle test-and-removal in managing Bovine Tuberculosis: Insights from a two-host and multi-route transmission model

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ABSTRACT

Bovine tuberculosis (bTB) has a complex infection ecology and is difficult to control in many countries, including Ireland. For many years, the Irish national bTB eradication programme relied on cattle-based control measures, including test-and-removal with related movement restrictions. In the early 2000s, badger culling was added as a part of the control measure in the national programme. As badgers are protected animals under Wildlife Acts, making culling undesirable, this practice is now progressively being replaced by badger vaccination. However, it is unclear whether badger vaccination, in combination with the cattle test-and-removal and movement restriction, is sufficient to eradicate bTB, or whether additional measures will be needed. Assessing the impact of badger vaccination on reducing bTB in cattle is complex due to the involvement of multiple hosts and transmission routes. Key contributors include transmission to and from wildlife (e.g., European badger, *Meles meles*), the persistence of *Mycobacterium bovis* in the environment, and – due to imperfect diagnostic tests - the movement of infected cattle and residual infection in the herd. Understanding of relative contribution of these infectious sources is a key knowledge gap. This study aims to assess the impact of badger vaccination, in addition to cattle test-and-removal and movement restriction, on bTB eradication at a regional level and to assess whether additional interventions are needed. Additionally, we investigate the contribution of several transmission mechanisms such as, local cattle, residual infection, badgers and introduced cattle on the transmission of bTB at the level of both the individual and the herd. To achieve this, we developed a metapopulation model that includes each of the above-mentioned transmission mechanisms for the Kilkenny badger vaccination trial area. The model incorporates within-herd transmission for cattle and within-territory transmission for badgers, and also transmission between herds, both via cattle trade movements and via overlapping badger territories. Our results show that cattle-to-cattle transmission contributes most to new cattle infections at the individual animal (cattle) level, while breakdowns at the herd level usually involve multiple routes. Badger vaccination, when combined with cattle test-and-removal programme, may not be sufficient to achieve eradication in this region. We highlight the need for additional interventions that target cattle, badger, and movement to form a comprehensive intervention strategy, including cattle vaccination, improve farm biosecurity, badger vaccination and risk-based trading.

1. Introduction

Bovine tuberculosis (bTB), which is caused mainly by *Mycobacterium bovis*, is endemic in Ireland. It can infect various mammals, including cattle, humans, and wildlife species including deer, badgers (*Meles meles*), and wild boars (*Sus scrofa*) (Broughan et al., 2013). Humans are at risk of contracting bTB through the consumption of contaminated milk, a risk that can be reduced through pasteurization, while other animals mostly acquire infections from contaminated environments including droplets, aerosols, and pasture. Transmission between species,

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such as cattle and badgers, occurs as they share habitats, which complicates the control of bTB. Bovine tuberculosis has a detrimental economic impact on the cattle industry due to loss of productivity and international trade restrictions, which is the primary motivation for bTB eradication.

In many countries, bTB eradication has primarily relied on a cattle test-and-removal programme, which includes both testing and removal of animals as well as movement restriction for infected herds. The main screening test of herds is conducted using a tuberculin-based skin test, such as the single intradermal comparative cervical tuberculin (SICCT) test, and animals that test positive are slaughtered. Herds in which positive animals are detected lose their official TB-free status. Under EU legislation, these herds are subjected to ongoing full-herd testing and movement restrictions until two consecutive negative full-herd tests are achieved, administered at approximately 60-day intervals (Brooks-Pollock et al., 2014; DAFM, 2018). This period of herd restriction, also known as a herd episode, is triggered by a so-called 'bTB breakdown'. This marks the start of a period of herd restriction, during which cattle movements are restricted. Several countries, including Australia, the Netherlands and several northern European countries, have successfully eradicated bTB (More et al., 2015; Orrico et al., 2022). In Ireland, progress towards eradication progressed rapidly during the first decade of the eradication programme, with cattle incidence decreasing from 17 % in 1954 to 0.5 % in 1965 (More and Good, 2006). In recent years, however, progress towards eradication has stalled, in part due to the presence of infected wildlife such as badgers.

The role of badgers in the epidemiology of bTB infection in cattle was clarified based on several large-scale badger culling trials conducted in Ireland (Olea-Popelka et al., 2003; Griffin, More, et al., 2005; Griffin, Williams, et al., 2005; More and Good, 2006; Ryan et al., 2023), and badger culling was subsequently added as an additional control measure in the national eradication programme (Ryan et al., 2023). However, alternatives to culling are required, given that badgers are protected animals under national legislation (Wildlife Act, 1976; Wildlife (Amendment) Act, 2000). The efficacy of vaccinating badgers with Bacille Calmette-Guérin (BCG) vaccines has been assessed by experimental and field trials, resulting in vaccination efficacies ranging from 36 % to 84 % (Corner et al., 2008; Aznar et al., 2011, 2018; Gormley et al., 2017; Martin et al., 2020; Chang et al., 2023). Routine BCG vaccination of badgers was introduced as policy in 2018 as part of the national eradication programme and it is now being progressively rolled out across the country. In 2019, the Irish government committed to extend badger vaccination nationwide to phase out badger culling (Ryan et al., 2023).

Recently, a follow-up assessment on the impact of badger vaccination on local cattle-badger transmission dynamics in the Kilkenny badger vaccination trial area was conducted (Chang et al., 2023). This study found that although badger vaccination can reduce the average between-herd reproduction number (R_0) to below 1, about 30 % of herds can still transmit bTB to more than one other farm (that is, between-herd $R_0 > 1$). Consequently, the effectiveness of badger vaccination on bTB transmission at a regional level remains uncertain. The question remains as to whether badger vaccination, in combination with the cattle test-and-removal programme, can eradicate bTB, or whether additional measures will be needed.

Assessing the impact of badger vaccination on reducing cattle bTB incidence requires consideration of both the multiple hosts and transmission routes involved. At a local level, *M. bovis* can be shed into the environment, where it may survive for an extended period, depending on the substrates and environmental conditions (Rodríguez-Hernández et al., 2016; Allen et al., 2021). Therefore, reinfection can occur even after the removal of infected cattle, due to the presence of *M. bovis* in the environment. Additionally, badgers usually reside on farms and move between farms (Mullen et al., 2013; Campbell et al., 2019), sharing contaminated environments with cattle. Badgers can become infected from one herd and subsequently spread bTB to neighbouring herds, leading to contiguous spread in a local area (Rossi et al., 2021; Chang et al., 2023). This local transmission can be influenced by the spatial heterogeneity of between-species contacts (Crispell et al., 2019; Rossi et al., 2021; Chang et al., 2023). Furthermore, infected cattle might remain undetected in a herd (so-called residual infection), with the potential for ongoing shedding of *M. bovis*, due to the imperfect sensitivity of the diagnostic test (Conlan et al., 2012; Lahuerta-Marin et al., 2018; Nunez-Garcia et al., 2018). In addition, the trade of infected but undetected cattle can introduce infections to previously uninfected herds and areas (Gilbert et al., 2005; Gopal et al., 2006; Conlan et al., 2012; Palisson et al., 2016). A quantitative understanding of two-host transmission with multiple transmission routes remains a key knowledge gap (Green et al., 2008).

Mathematical models play a crucial role in improving our understanding of complex infectious disease systems as they allow the contribution of different transmission mechanisms, routes, and hosts to be assessed. In the case of bTB, within-herd models have been developed to estimate key parameters such as the infectious period, latent period, and transmission rate parameters for cattle (Kao et al., 1997; Griffin et al., 2000; Alvarez et al., 2014). Some models have extended their scope to assess the relative importance of different transmission routes, incorporating both within-herd transmission and between-herd transmission via cattle movements (Green et al., 2008; Brooks-Pollock et al., 2014). However, to date these models have often simplified the role of badgers in bTB transmission, treating them as background environmental infectious pressure. Concurrently, there were badger-specific models that have focused on assessing interventions related to badgers, such as badger vaccination and culling (Smith et al., 2001, 2022; Wilkinson et al., 2004; Abdou et al., 2016; Aznar et al., 2018; Smith and Delahay, 2018), without consideration of the role of cattle. Although some studies have explored bTB transmission between cattle and badgers, they typically used simple models that investigate two-host transmission, ignoring the within-herd and between-herd structure, as well as spatial heterogeneity (Smith, 2001; Cox et al., 2005; Brooks-Pollock and Wood, 2015). To comprehensively assess the effect of interventions targeting different transmission routes, a spatial transmission model that considers transmission dynamics between two species and incorporates local transmission and movement-mediated transmission is essential.

This study aims to assess the impact of badger vaccination, combined with the cattle test-and-removal programme, on bTB eradication at a regional level and to assess whether additional interventions are needed. To achieve this, we expand our existing (local) bTB transmission model (Chang et al., 2023) to a multi-host and multi-routes model that includes movement-mediated transmission using actual cattle movement data. This model allows us to investigate the relative contribution of local cattle, residual infection, badgers and introduced cattle on the transmission of bTB at the level of both the individual and the herd. In addition to assessing the impact of badger vaccination, we explore other interventions that can strengthen the eradication programme. These additional interventions include badger selective culling, cattle vaccination, improving farm biosecurity, risk-based trading and pre-movement trading. It is important to note that these additional interventions are explored conceptually, and their detailed assessment will require further empirical trials.

2. Materials and methods

To achieve these goals, we developed a stochastic, spatially explicit metapopulation model. The model was developed by extending the existing R package SimInf framework (Widgren et al., 2016, 2019). Section 2.1 described the model, including local transmission, regional transmission, attribution of infection sources, and interventions. Data descriptions are provided in Section 2.2. Parameters for the model and sensitivity analysis are presented in Sections 2.3 and 2.4.

2.1. Model formulation

2.1.1. Local transmission

In this study, a local area is defined as a herd of cattle along with its associated badger territories and directly neighbouring herds. Badger territories were modelled as the joined Thiessen polygons of a main sett and some sub-setts (Byrne et al., 2019, 2022). Within each local area, our local transmission model incorporates both within-herd/within-territory transmission and interspecies transmission (between badgers and cattle). This local transmission model is adapted from a previous study (Chang et al., 2023). There are two types of subpopulations, cattle herds and badger social groups. Each subpopulation has its own spatial unit, which corresponds to a specific area, such as a farm area or a badger territory area depicted in Fig. 1 by the blue circle and the green rectangle respectively. A farm can consist of several fragments of land that can be spatially dispersed, and we assume that cattle spend time on each fragment proportional to its area. Since these two species co-habit in a region, the study area can be visualized as an overlay of two layers, a farm location map and a badger territory map, where a farm can overlap with several territories and a territory can overlap with several farms.

The model utilizes a stochastic Susceptible (S) – Infectious (I) compartmental model with two environmental layers (E_c and E_b for cattle and badger respectively) to simulate the dynamics of transmission within a spatial unit. All the transmission events are modelled as occurring indirectly via the environment (see details in S1 Compartments and transition). We do not distinguish direct and indirect transmission, as droplet and aerosol transmission, commonly recognised as direct transmission for bTB, also involve an environmental stage due to the survival of *M. bovis* in the air. Therefore, we modelled all these transmission routes as a single environmental transmission route, with a calibrated exponential decay function of *M. bovis* in the environment (Chang et al., 2023). Infected animals are considered to shed infectious material immediately after infection (that is, we assumed that there is no latent period, but a sensitivity analysis was conducted in Supplement 3). Infectious material decays in the environment, modelled as a deterministic process with a constant decay rate. Susceptible cattle or badgers can become infected following exposure to *M. bovis* shed by animals of their own species. Susceptible animals can also be exposed to *M. bovis* shed by animals of the other species whenever spatial units of cattle herds and badger territories overlap. The amount of exposure from the other species is determined by the ratio of the overlapping area to each spatial unit area, as defined in the between-species connection matrix. To maintain a stable population size, the natural death rate and the birth rate of each species are assumed to be equal, and all new-born animals are assumed to be susceptible to infection.

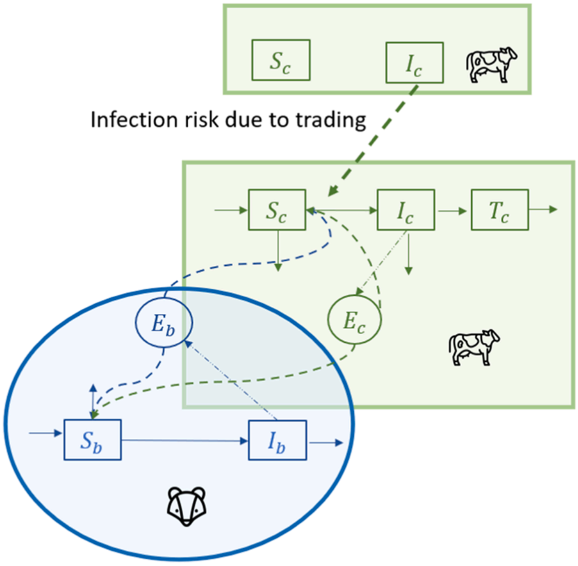

Fig. 1. A schematic representation of the bTB transmission model, illustrating transmission dynamics within a local area and between-herd transmission via movement. Badger territory and farm are the two spatial units in the local transmission (blue circle and green rectangle). E_b and E_c represent the environmental contamination in each badger territory and farm. S and I represent Susceptible and Infectious compartment). T_c represent test-positive cattle. The transitions between animal compartments are represented by the solid lines and environmental transmissions are represented by the dashed lines. All the transition process are described in detail in Supplement1.

In contrast to the previous model (Chang et al., 2023), this model incorporates the cattle test-and-removal and movement restriction measures that form part of the national bTB eradication programme in Ireland. In the model, all herds are scheduled for periodic screening tests using SICCT. These tests are scheduled on a random date and are conducted annually with a fixed interval of 365 days. For each screening test, the number of positive test results in a farm are assumed to follow a binomial distribution, where each test is considered as an independent trial. The probability of successfully detecting a positive animal equals the sensitivity of screening tests. A positive test result occurring in at least one animal in a herd signifies a herd bTB breakdown, triggering the immediate removal of all test-positive cattle in the model. Removed animals are replaced with newborn cattle to maintain a constant herd size. These newborn animals are assumed to be susceptible. In addition, movement restrictions are implemented during the period following the detection of test-positive cattle. During this restricted period, herds experiencing a breakdown are banned from trading activities. The trading restriction is only lifted (that is, the period of herd restriction ends) when two consecutive full-herd negative SICCT tests are achieved. For the implementation of risk-based trading, a risk classifier has been added as a compartment that records the number of days that each herd has remained test negative.

In reality, the random sample testing of herds, contiguous testing and private tests also exists, in addition to the annual screening tests and re-tests. Furthermore, in recent years the gamma interferon blood test was used to re-test inconclusive cattle (Ryan et al., 2023). These testing practices were not specifically modelled in the model; rather we assumed a test sensitivity of 0.8 (See Table 1), which is at the higher end of published estimates, to account for their impact. The impact of applying higher sensitivity tests can be seen in the Supplement 3.

In the model, infected badgers experience mortality at a rate that is equal to the sum of the bTB-induced death rate and natural background mortality rate. This ensures a stable badger population in the study area. Additionally, due to stochasticity and the small population size within each territory, a territory can become empty and subsequently be colonized by susceptible badgers.

2.1.2. Regional transmission

Intra-area transmission (that is, transmission between subpopulations in the same area) can occur due to shared environments between the two species or due to cattle movements. The spatial overlap between species leads to between-species transmission (Chang et al., 2023), but also establishes indirect connections, creating a chain-like network that links all herds and badger territories. This mechanism accounts for both between-herd (via cattle-badger-cattle) and between-territory (via badger-cattle-badger) transmission. Furthermore, infected but undetected cattle can be introduced to previously uninfected local areas through trading, potentially leading to long-distance bTB spread. Within this model, we assume that there is no between-herd transmission through contact between cattle across farm boundaries, or through farm equipment, fodder or manure moved between farms. As recent studies showed that badger inter-group interactions were rare, comprising only 1 % of all interactions (Byrne et al., 2024), we have assumed no direct between-territory transmission.

We incorporate movement-mediated transmission into the model

Table 1
Constant parameters.

Parameter (unit per day))	Description	Values	Source
Parameter estimation based on infection data			
$\beta_{c,c}$	Transmission rate parameter cattle to cattle	1e−5	(Chang et al., 2023)
$\beta_{b,c}$	Transmission rate parameter badger to cattle	4e−6	(Chang et al., 2023)
$\beta_{b,ub}$	Transmission rate parameter badger to unvaccinated badger	9e−5	(Chang et al., 2023)
$\beta_{c,ub}$	Transmission rate parameter cattle to unvaccinated badger	5e−4	(Chang et al., 2023)
$\beta_{b,vb}$	Transmission rate parameter badger to vaccinated badger	5.1e−4	(Chang et al., 2023)
$\beta_{c,vb}$	Transmission rate parameter cattle to vaccinated badger	4.4e−4	(Chang et al., 2023)
μ	*M. bovis* decay rate parameter	0.004	(Chang et al., 2023)
φ	shedding rate parameter $\frac{\mu^2}{(1-e^{-\mu}+\mu)}$	0.002	Based on μ
Parameters derived from literature			
γ_b	Infectious badger death rate	2.74e−3	(Little et al., 1982; Cheeseman et al., 1985).
α_c	Cattle background death rate	9.13e−4	(Poola et al., 2005; Maher et al., 2008)
α_b	Badger natural death rate	7.52e−4	(Anderson and Trewhella, 1985; Rogers et al., 1997)
SE	Sensitivity of the skin test	0.8 (unitless)	(De la Rua-Domenech et al., 2006; Clegg et al., 2011; Lahuerta-Marin et al., 2018; Nunez-Garcia et al., 2018)

based on observed cattle movement patterns. In the model, we assume that infected cattle were infected at the selling farm and ignore the possibility of transmission at the market during trading. The timing of cattle movements, including the exact date for each trade, is determined through a stochastic process implemented using Gillespie's algorithm, the same as other model transitions. When a trade occurs, we select trading partners and their trading intensities (the number of cattle in each movement) based on the trading frequency derived from trade movement data. To determine the number of infectious cattle involved in a trade, we sample from a binomial distribution. The sample size is the total number of traded cattle, and the probability that infectious cattle are selected is determined by the proportion of infectious cattle relative to the total cattle population in the selling herd. Once infectious cattle are selected, the model increments the number of infectious cattle in the buying herd and the number of susceptible cattle in the selling herd. Concurrently, it incrementally decreases the number of infectious animals in the selling herd and the number of susceptible animals in the buying herd. This modelling approach captures the risk of infection through cattle movement while ensuring that the total population of both the selling and buying herds remains constant after trading.

2.1.3. *Attribution of infection sources*

Within this model, we aim to distinguish the relative importance of different infection sources, at both the individual and herd levels.

At the individual (cattle) level, three infection sources were possible, including:

1) Local cattle: infection attributable to E_c exposure. For example, this source relates to infected cattle, present but as yet undetected in the herd, which can continue to shed *M. bovis* in the local environment (E_c layer). Additionally, infected cattle that were previously present but subsequently removed also contribute to this source, as *M. bovis* excreted by them can still be present.
2) Badgers: infection attributable to local E_b exposure where badger territories are connected to a herd. For example, this source relates to infectious badgers (contemporaneous and/or historical), each contributing to the *M. bovis* in the local environment (E_b layer).
3) Introduced cattle: infection from introduced cattle via cattle movement.

At the herd level, the source of infection for each bTB restriction was determined after considering the animals that were detected at the first positive test (the so-called breakdown test). Four sources of infection were possible, including:

1) Residual infection (that is, infected but undetected cattle): a herd breakdown is associated with the presence - at the end of the previous bTB restriction - of infected but undetected cattle. Residual infection can lead to further transmission following a bTB breakdown, however, in each such case the (initial) infection source was classified as residual infection alone (rather than from multiple infection sources). In other words, residual infection as identified as the infection source whenever (1) was present, regardless of the additional presence of (2), (3) and/or (4).
2) Reinfection from E_c (environment previously contaminated by cattle): a herd breakdown in which cattle infection can be solely attributed to infection following local E_c exposure. This source relates to environmental contamination of *M. bovis* from infected cattle that were present during the previous herd restriction but removed before this restriction had ended.
3) New infection from badgers: a herd bTB breakdown in which cattle infection can be solely attributed to infection following local E_b exposure. This source relates to infected badgers, including badgers currently and/or historically present.
4) Introduced cattle: a herd breakdown in which infection was introduced via cattle movement. Introduced infected cattle shed *M. bovis* to the environment E_c, potentially causing new infections that cannot be distinguished from those caused by (2). Here, introduced cattle was considered the source of infection if either (4) alone, or (4) plus (2), were present.

At times, multiple sources of infection were identified. A classification of 'multiple sources' was made if either [(2) and (3)], [(2) and (4)], [(3) and (4)] or [(2), (3), and (4)] was present.

In summary, therefore, herd-level infection sources were determined as follows:

- Residual infection if (1) present, regardless of the additional presence of (2), (3), and/or (4)
- Reinfection from E_c if (2) alone
- New infection from badgers if (3) alone
- Introduced cattle if (4) alone, or [(4) and (2)]
- Multiple sources if [(2) and (3)], [(3) and (4)] or [(2), (3), and (4)].

2.1.4. *Interventions*

This is a conceptual study and does not directly relate to interventions as are currently in use in Ireland. Rather, a number of different interventions were considered here, including many that are already incorporated within the national bTB eradication programme in Ireland.

In this study, cattle test-and-removal and movement restrictions was considered the default scenario. A number of interventions were then added to the default scenario, either individually or in combination, targeting transmission routes relating to cattle movement, badgers and cattle farms.

We first investigate four interventions targeting movement-mediated transmission:

1) Default (D): Infected herds are movement-restricted until testing negative at two consecutive full-herd tests conducted 60-day apart.
2) Risk-based trading (RBT): Herds can only trade with herds having an equivalent or lower risk classifier than their own. Cattle purchases from outside the study area are redirected to herds within the study area that have an equivalent or lower risk classifier.
3) Pre-movement testing (PMT): Cattle are tested prior to movement unless both the individual and the herd of origin were bTB tested in the preceding six months.
4) Movement ban (MB): All trade movements are banned in this study area.

To implement risk-based trading, we developed a rewiring algorithm that assesses the herd status before cattle movement and rewires trades involving high risk. When a trade occurs, we compare the risk classifier of the selling herd to that of the buying herd. If the selling herd has a higher risk level, we randomly select a new selling herd from the study area with a lower risk classifier.

Secondly, we investigate interventions targeting badgers:

1) Default (D): No badger interventions.
2) Badger vaccination with 50% coverage (BV50): 50% of badgers are vaccinated with BCG vaccine, modelled by adjusting the transmission rate parameters as $(50\% * \beta_{b,vb} + 50\% * \beta_{b,ub})$ and $(50\% * \beta_{c,vb} + 50\% * \beta_{c,ub})$.
3) Badger vaccination with 100 % coverage (BV): All badgers are assumed to be vaccinated to assess the maximum potential of badger vaccination, modelled by using $\beta_{b,vb}$ and $\beta_{b,vb}$ as the transmission rate parameters (Note: this scenario may not be feasible in reality but is used for exploratory purposes.)
4) Selective culling (SC): Infectious badgers are assumed to be removed on average every year. This scenario is exploratory, because achieving annual testing of infectious badgers depends on capture frequency and test sensitivity. These removed infectious badgers are replaced by the susceptible badgers as we assume that selective culling does not reduce the badger population size.

Thirdly, we investigate interventions on cattle farms.

1) Default (D): Cattle are tested annually, and all positive cattle are removed and replaced by susceptible cattle. Herds with positive tests are banned from trading activities until two consecutive negative full-herd tests are achieved.
2) Cattle vaccination (CV): The efficacy of cattle vaccination has been investigated in the field and in experimental settings, with estimates ranging from 0 to 89 % (Conlan et al., 2015; Bayissa et al., 2021; Retamal et al., 2022; Fromsa et al., 2024). We assume that cattle vaccine can have similar impact on reducing the transmission rate parameter as the badger vaccination (40 % reduction on the transmission rate parameter). (Note: this scenario is used for exploratory purposes, given that cattle vaccination is not currently available).
3) Improved farm biosecurity (IFB): This intervention assumes a reduction in badger-to-cattle transmission of 50 %. The intervention is conceptual in nature and does not consider any specific measure(s) for improved farm biosecurity.

2.1.5. *Herd level regional R*

We calculate the herd level regional basic reproduction ratio (R_0) under each intervention scenario using the simulated herd prevalence after reaching equilibrium ($R_{intervention} = \frac{1}{1-Herd\ Prevalence}$). $R_{intervention}$ represents the average number of herds that an infected herd can infect under a certain intervention strategy, assuming all herds are susceptible and considering the network structure between herds in this study area. If the simulated herd prevalence decreases to 0, it indicates that bTB can be eradicated by the specific intervention strategy ($R_{intervention} < 1$). However, if herd prevalence decreases but reaches a new endemic stage, the intervention strategy cannot eradicate bTB ($R_{intervention} > 1$).

2.2. *Data*

2.2.1. *Cattle holding, location, and infection data*

We used data from a previous badger vaccination trial area conducted in Kilkenny County between 2009 and 2012 (Aznar et al., 2018). This trial provided simultaneous information on both cattle and badgers at the same time and place. Cattle holding data, incidence data and locations during the period of 2009 to 2012 were extracted from the Animal Health Computer System (AHCS) database and the Land Parcel Identification System (LPIS) database, which are maintained by the Irish Government's Department of Agriculture, Food and Marine (DAFM). Herd size was used as a proxy for the spatial unit area in the simulation model. The median herd size in this study area is 97. To avoid extremely high relative badger density values resulting from dividing badger densities by very small herd sizes, a herd size of 30 cattle was assumed for herds where actual herd size was less than 30, which accounts for 15 % of herds. The initial value for infectious cattle in the simulation was determined based on the number of cattle that tested positive in 2009.

2.2.2. *Cattle movement data*

Cattle movement data during the study period were extracted from DAFM's Animal Identification and Movement (AIM) database. The trading event that occurs via a mart (that is, a cattle trading market) were simplified in the model as a trade between farms. Cattle movements were analysed as discrete herd-to-herd pairs and classified as either an outward movement, representing movements out of a herd, or inward movement, representing movements into a herd. Throughout the four-year duration, 1335 herds within the study area registered a total of 65,336 inward movements involving 218,659 cattle, with 80 % of these originating from outside the study area. In addition, 56,707 outward movements were recorded, with 75 % of these movements directed towards herds outside the study area. To account for herds located outside the study area, we included an external herd in the model. This external herd represents all the herds located beyond the study area boundaries and was assigned with a fixed prevalence equal to the national prevalence in cattle. The movement data were used to construct a between-herd connection matrix, capturing trading rates and trading intensity among the herds.

2.2.3. *Badger data*

The badger data used in this study were the same data as used in Chang et al. (2023). The badger infection dataset was obtained from Aznar (2018), where badger blood samples were tested using the Enfer multiple antigen ELISA system for detection of *M. bovis* antibodies. The location of 255 badger territories were obtained from Byrne et al. (2019), Byrne et al. (2022) and Milne et al. (2022). The number of infectious and susceptible badgers within each social group were used as the initial values in the simulation. In addition, overlays of badger territories and farm locations were used to construct a between-species connection matrix. This matrix records the proportion of shared area between each farm and each badger territory relative to the total area of that farm or badger territory.

2.3. Parameters

There are two types of parameters in the model: constant parameters and spatially varying parameters.

Constant parameters remain uniform for all the subpopulations; these include transmission rate, decay rate and death rate parameters. We determined these constant parameters by adopting estimations from a previous local transmission model and from existing literature (see justification of their values and reference in Supplement 2). For example, the decay rate parameter of *M. bovis* is estimated to be 0.004 per day, indicating a high level of persistence in the environment.

The spatially varying parameter defines parameters specific to each subpopulation. It is generated by combining parameters and matrices into a structured dataset. Primarily, local data contain essential information such as the area of a subpopulation, the between-species connection matrix and the between-herd connection matrix. We use herd sizes to represent the spatial unit's area. Herd size for each farm is calculated as the average number of cattle in a herd based on test data collected over a year, extracted from AHCS. To represent the area of a badger territory, we calculated a weighted sum of herd sizes from farms that overlap with the respective badger territory. Both the between-species connection matrix and the between-herd connection matrix define connections between subpopulations. These connections are directional, so both matrices consist of "from" and "to" entries to specify the subpopulation's ID. In the between-species connection matrix, the final entry, referred to as "ratio", defines the proportion of overlap between "from" and "to" subpopulation. This proportion is calculated by dividing the overlap area by the area of the "from" subpopulation. The between-herd connection matrix has two additional entries: "trading rate", "trading count". These entries define the daily number of trades from the "from" herd and destinated for the "to" herd, as well as the number of cattle in each trade.

Given that 80 % of trading activities involved herds outside of the study area, we created an extra herd to represent the external herds outside of the study area. The cattle prevalence in this external herd is assumed to be 0.2 % to match the national cattle prevalence 0.2 % (Male Here et al., 2022).

2.4. Sensitivity analysis

We conducted a sensitivity analysis on the constant parameters. The transmission rate parameters (βs) and the decay rate parameter (μ) were simultaneously estimated using infection data, which is challenging due to identifiability issues. To solve this, we introduced and validated a quantification method using historical infection data in the estimation (Chang and de Jong, 2023). Applying this method to bTB transmission resulted in a high persistence of *M. bovis* with $\mu = 0.004$ per day (Chang et al., 2023). In comparison, another modelling study by Brooks-Pollock et al. (2014) estimated a lower persistence of *M. bovis* in the environment with fivefold higher μ (0.02 per day). Both estimations align with a literature review indicating that *M. bovis* can survive in the stored slurry up to 6 months in winter and on pasture 2 months in summer (Allen et al., 2021). To examine the impact of the assumption about *M. bovis* persistence on the model outcome, we re-estimated all the transmission rate parameters when $\mu = 0.02$ per day, resulting in higher βs compared to the default (high persistence) parameter set. We used $\mu = 0.02$ and its corresponding re-estimated βs as a low persistence parameter set in the sensitivity analysis. Table 2

In addition, we conducted sensitivity analysis for infectious period and latent period of badger and the sensitivity of skin test using a one-at-a-time approach, with the range of these parameters shown in Table 3. Furthermore, a global sensitivity analysis was conducted by drawing 1000 parameter sets from entire parameter range, and results were shown in Supplement 3.

Table 2
Transmission rate and decay rate parameters for sensitivity analysis under low persistence assumption.

Parameter (per day)	Low persistence assumption	Source
$\beta_{c,c}$	3.56e−5	(Chang et al., 2023)
$\beta_{b,c}$	2.5e−5	(Chang et al., 2023)
$\beta_{b,ub}$	5.3e−4	(Chang et al., 2023)
$\beta_{c,ub}$	1.7e−3	(Chang et al., 2023)
$\beta_{b,vb}$	3.2e−4	(Chang et al., 2023)
$\beta_{c,vb}$	1.6e−3	(Chang et al., 2023)
μ	0.02	Brooks-Pollock et al. (2014)
φ	0.01	Scaled based on μ (Chang and de Jong, 2023)

Table 3
Parameters range for sensitivity analysis.

Parameter	Range
γ_b	(1/730, 1/182.5) per day
SE	(0.5, 0.95)
Latent period of badger	(0, 90) days

3. Results

3.1. The impact of different interventions

We compared the observed infection data from the trial with simulation results under the default scenario (cattle test-and-removal and movement restrictions), using parameter sets based on high and low persistence assumptions. As our model does not simulate the dynamic process of vaccination, it may not fully capture the on-going transmission dynamics observed during the trial. The post-trial culling of badgers further limited our comparison to only four data points. Simulation results generally align with the observed trial data for cattle incidence and badger prevalence (see Supplement S4). Under the default scenario, herd incidence rates are simulated to be 14 % under the assumption of high *M. bovis* persistence (line 1 in Fig. 2 A) and 6 % under the assumption of low *M. bovis* persistence (line 1 in Fig. 2B).

3.1.1. Single route intervention

Based on this model and assumptions about additional interventions, none of the additional interventions, when considered in isolation but combined with the default scenario, appear to eradicate bTB. For example, adding badger vaccination to the default scenario, whether at 50 % or 100 % coverage, leads to a modest absolute reduction in herd incidence (1 to 2 %, as indicated in lines 5 and 6 in Fig. 2). In comparison, selective badger culling reduces badger-to-cattle transmission by decreasing the infectious period of badgers, resulting an absolute reduction of 3 % to 5 % in herd incidence (Line 7 in Fig. 2).

Based on our results, risk-based trading, pre-movement testing and even movement ban, together with the default cattle-based control programme, cannot eliminate bTB (lines 2, 3 and 4 in Fig. 2). This is because badgers, residual infection, and the survival of *M. bovis* in the environment each facilitate the persistence of bTB in a region. However, movement-targeted interventions are more significant when *M. bovis* persistence is low compared to when it is high (compare lines 2, 3 and 4 in Fig. 2B to Fig. 2 A). Cattle vaccination and improved farm biosecurity, which seeks to protect cattle from becoming infected, appears to be relatively effective, reducing herd incidence by half to one-third (lines 8 and 9 in Fig. 2).

3.1.2. Multi-routes interventions

We also assessed combinations of interventions that target multiple routes. In total, 120 scenarios were simulated, involving 5 measures

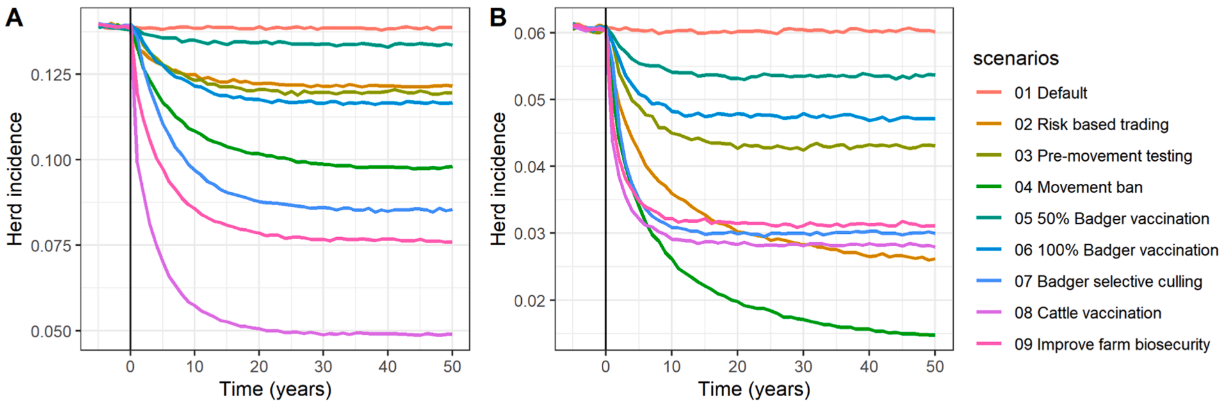

Fig. 2. The effect of interventions (for lines 02–09, in addition to the default scenario) on herd-level annual incidence under the assumption of high and low M. bovis persistence A) high persistence (M. bovis decay rate parameter as 0.004 per day). B) low persistence assumption (M. bovis decay rate parameter 0.02 per day). Lines 02–09 shows the combined effect of each additional intervention combined with default scenario. Black vertical line at time 0 year is the starting point when additional interventions are applied.

targeting the badger route, 3 measures targeting the cattle route, and 4 measures targeting the movement route under two parameter sets) (Fig. 3). The default scenario was included with each combination of interventions.

In general, stringent intervention combinations that combine multiple transmission routes can bring $R_0<1$. Under the assumption of low *M. bovis* environmental persistence, movement-targeted interventions, along with cattle vaccination or badger vaccination with selective culling, show promise in bringing $R_0<1$ (Fig. 3B). Under the assumption of high *M. bovis* environmental persistence, however, additional interventions targeting all three routes are needed (Fig. 3 A). In both scenarios, implementing movement-related controls seem important in order to achieve $R_0<1$.

3.2. Relative contribution of infection sources to cattle infections and herd breakdowns

We use the model to quantify the roles of different sources of infection within the study area to cattle infections (Fig. 4 A) and herd breakdowns (Fig. 4B) under the default scenario. Results from two distinctive parameter sets, representing low persistence and high persistence of *M. bovis* in the environment, were plotted separately in Fig. 4.

At individual animal (cattle) level, our simulations predict that other cattle are the main source of infection for new cattle infections, accounting for 63.4 % (61.8 % - 64.7 %) of infections under the high persistence assumption and 47.3 % (45.1 % - 49.5 %) under the low persistence assumption. Badger-to-cattle transmission accounts for another 30–41 % of the new cattle infections. In contrast, movement-mediated transmission plays a minor role, accounting for 6 % of new

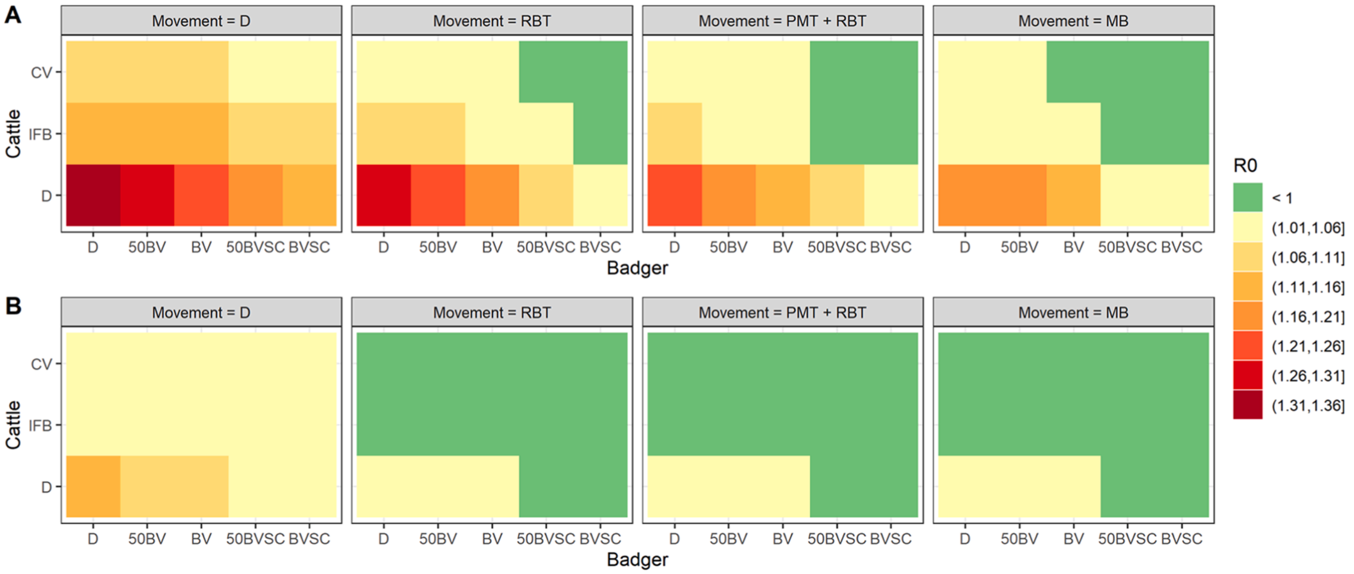

Fig. 3. Basic reproduction ratio for each intervention strategy (in addition to the default scenario) under A) high and B) low M. bovis persistence assumption. Colours in tile represent R values with green representing R<1 and yellow/ red represent R > 1. The X-axis shows five badger route interventions (D: default with no intervention in badger; 50BV: 50 % badger vaccination; BV: 100 % badger vaccination; 50BVSC: 50 % badger vaccination with selective culling; BVSC: 100 % badger vaccination with selective culling). The Y-axis shows 3 cattle interventions (D: default with test and removal in cattle; IFB: improve farm biosecurity combined with default test and removal in cattle; CV cattle vaccination combined with test and removal in cattle). The four panels show the 4 interventions target movement (D: default with movement restriction for breakdown herds; RBT: risk-based trading combined with default movement restriction for breakdown herds; PMT +RBT: pre-movement trading with risk-based trading combined with default movement restriction for breakdown herds; MB: movement ban combined with default movement restriction for breakdown herds).

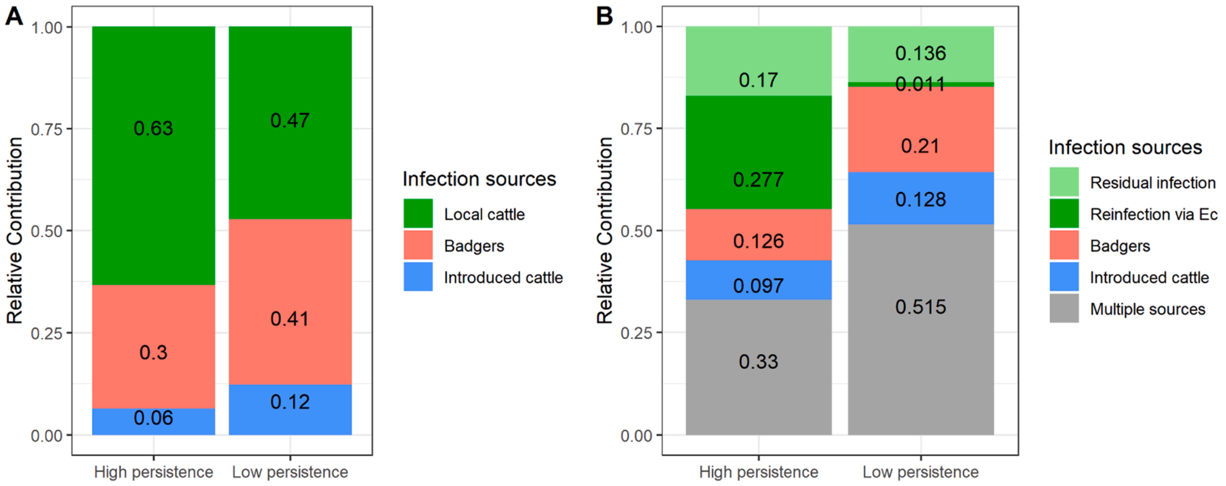

Fig. 4. Predicted relative contribution of infection sources to cattle infections (A) herd breakdowns and (B) under the assumption of high and low M. bovis persistence. Colours in bars represent the proportions attributed to each infection source. Note: as shown in Fig. 2, the total number of cattle infections and herd breakdowns differ between the high and low persistence assumptions, which should be considered carefully when comparing the relative contribution between low persistence and high persistence assumptions.

cattle infections under high persistence assumption and 12 % under low persistence assumption.

At herd-level, under the assumption of high persistence within the environment, cattle-related sources of infection are important, including residual infection (with 17 %) and reinfection due to environment contaminated by cattle (27.7 %). Further, a notable number of bTB breakdowns could be attributed to introduced cattle (12.6 %), followed by a slightly lower proportion due to badgers (9.7 %). Under the assumption of low persistence, there is some reduction in the contribution of residual infection to bTB restrictions (13.6 %), a negligible contribution from environment contaminated by cattle (1.1 %), and a concomitant increase in the importance of other infection sources, including badgers (21 %) and introduced cattle (12.8 %). In a large proportion of breakdowns, multiple infection sources were identified, accounting for 33 % of all bTB restrictions under the high persistence assumption and 51.5 % under the low persistence assumption. This reflects a complex interplay among different infection sources and transmission routes, as would be expected in a highly endemic situation.

4. Discussion

4.1. Goal of study

Bovine tuberculosis has a complicated infection ecology and has proved difficult to control in many countries, including Ireland, where wildlife contributes to *M. bovis* transmission. The use of default cattle-based control measures (test-and-removal and movement restriction) alone has proved insufficient to eradicate bTB in Ireland. Badger vaccination has recently been introduced as part of the national eradication programme coincident with a phasing out of widespread badger culling. However, it remains unclear whether badger vaccination – in combination with the cattle test-and-removal programme – will be sufficient to achieve eradication, or if additional interventions are required to enforce the national programme. An assessment of the impact of badger vaccination on bTB transmission is complex due to the involvement of multiple hosts and routes. In addition to wildlife involvement, it is now recognised that residual infection (the presence of infected but undetected cattle) and the movement of infected (but undetected) cattle, each due to imperfect diagnostic testing, as well as the persistence of *M. bovis* in the environment, each contribute to bTB transmission either within and/or between farms (Brooks-Pollock et al., 2014). To this point, the relative contribution of these infection sources has been poorly understood and is likely to vary in different spatial contexts. This study has sought to address this challenge through the development of a multi-host and multi-route transmission model. The model assessed the impact of badger vaccination on bTB transmission, and explored the efficacy of various interventions that target other transmission routes, whilst considering local influencing factors such as relative badger density and cattle movement patterns. In addition, the model has been used to quantify the relative contribution of different sources to new infection in cattle and to herd breakdowns.

4.2. Summary of results and comparison with other studies

Our modelling demonstrates that badger vaccination, in combination with the cattle test-and-removal programme, can reduce bTB in cattle but is unlikely to achieve bTB eradication. In this assessment, transmission rate parameters and vaccination efficacy were estimated from a local cattle-badger transmission model, using infection data from the same trial (Chang et al., 2023). This earlier study estimated the efficacy of vaccination as a 43 % reduction in badger-to-badger transmission and a 12 % reduction in cattle-to-badger transmission, which can bring the average between-herd R_0 to 0.85 (Chang et al., 2023). However, the impact of badger vaccination on a regional level could be questioned due to the spatial heterogeneity- with 30 % of herds having between-herd $R_0 > 1$ (Chang et al., 2023). This current study results suggest that bTB is likely to persist in this area, despite badger vaccination and the cattle test-and-removal programme. Under the badger vaccination scenario, the herd-level regional R_0 was above 1 (based on the calculation described in 3.2.2). This is not the average between-herd R_0 of all herds (that is, 0.85) but rather the regional R_0 which depends on the network structure between high-risk herds and low-risk herds in a region. If high-risk herds are clustered with other high-risk herds, bTB can persist in these high-risk areas and spread to low-risk areas through cattle movement or connected badger territories, thus sustaining endemic bTB within a region (that is, regional $R_0 > 1$). This could explain why models that did not account for spatial heterogeneity often yield more optimistic results for badger vaccination (Wilkinson et al., 2004; Smith et al., 2022). For example, previous studies based on the same trial have suggested that 40 % coverage badger vaccination could eradicate bTB in badgers (Aznar et al., 2018).

According to our model, cattle contribute significantly to new cattle infections (45–65 %; that is, at individual animal [cattle] level) in this study area. This aligns with a previous modelling study that found cattle to be the primary source of cattle infections (Donnelly and Nouvellet, 2013). Furthermore, whole genome sequencing (WGS) studies suggested that within-species transmission (such as cattle-to-cattle) is more frequent than between-species transmission (such as badger-to-cattle) (Van Tonder et al., 2021; Akhmetova et al., 2023). However, the direction and relative importance of between-species transmission (particularly cattle-to-badger and badger-to-cattle) varied across different study areas, based on the results of WGS studies, reflecting the important influence of spatial contexts. Based on an assumption of 80 % for the sensitivity of the SICCT, we predicted that residual infection is the cause of 13.6–17 % of herd breakdowns. This aligns with previous estimates of 16 % (Green et al., 2008). Further, cattle movement accounts for 9.7–12.8 % of herd breakdowns (but potentially higher as multiple sources are not included here), consistent with previous studies indicating that movement plays a lesser role than local transmission (Green et al., 2008; Clegg et al., 2015; Palisson et al., 2016). That said, movement can seed infection to non-infected herds and areas, distant from the selling herd.

The relative contribution of different infection sources can vary because of several factors including the infection history of a herd, badger density, local movement patterns and assumptions on parameters (Supplement 3). In newly infected areas, badgers and introduced cattle are more likely to introduce infections into a herd than in high-risk areas. In addition, the estimated contribution of badgers ranges from 27 % in low badger density area to 59 % in high badger density area within Kilkenny (Supplement 5). Interventions aimed at different transmission routes, such as badger vaccination or cattle vaccination, can also influence the relative contribution of infection sources.

In our model, between-herd transmission is assumed to occur indirectly via the cattle-badger-cattle transmission route or through cattle movement. Similarly, between-territory transmission was assumed to occur indirectly via badger-cattle-badger. In reality, there may be additional between-herd transmission mechanisms, such as sharing equipment between farms or contact between cattle in neighbouring herds across fences. Badger movement may serve as an additional mechanism for transmission between badger social groups, although their impact may be small as inter-group interactions were rare, comprising 1 % of all interactions (Byrne et al., 2024). This implies that in real life bTB may spread more quickly between badger social group and be harder to control via badger vaccination than the model suggested. The challenge of incorporating these mechanisms in the model lies in parameterisation and distinguishing these mechanisms. Data on the sharing of equipment, cattle contact near fencing between herds, and badger movement between territories are required to understand these between-herd and between-territory transmission mechanisms. As a result, our model assumes between-herd transmission to occur solely through between-species transmission (via cattle-badger-cattle), which could lead to an overestimation of the badger contribution on herd breakdowns. As the transmission parameters were estimated with the same model assumption (Chang et al., 2023), the total between-herd transmission is not overestimated. Rather, the attribution of breakdowns due to contiguous spread via sharing equipment and cattle contact between neighbouring herds are now attributed to badgers. Hence, one could interpret the contribution of badgers as a source of infection for herd breakdowns as a combination of badgers and other source that cause contiguous spread. Nevertheless, even with an assumption favouring between-species transmission, our model consistently indicates that badger vaccination, in combination with the cattle test-and-removal programme, is unlikely to eradicate bTB. This emphasizes the importance of a multifaceted approach to control bTB.

While this model provides valuable insights into the efficacy of badger vaccination, it is essential to acknowledge its limitations. Vaccination is modelled as a non-dynamic process using weighted transmission rate parameter dependent on vaccination coverage. This restricts the exploration of vaccination frequency required to achieve a certain vaccination coverage. To address this, a model with a dynamic vaccination process and detailed data on vaccination coverage at the sett level would be needed.

In the model, parameters for badger culling, cattle vaccination, and improved farm biosecurity were based on assumptions. Therefore, the simulated impacts of these interventions are more aspirational and conceptual, in contrast to the assessment of the impact of badger vaccination which is based on empirical evidence. For example, this model assumed that badger selective culling does not influence the badger population. However, the actual impact of badger culling on badger population and badger movement – which could vary across different regions - requires further investigation (Griffin, Williams, et al., 2005; Carter et al., 2007). A comprehensive assessment of badger culling would require an individual-based badger model that incorporates badger movement and social perturbation, which should be validated by empirical data (Smith et al., 2016). The assumption that improved farm biosecurity can halve badger-to-cattle transmission lacks empirical support, as no trials have yet been conducted to investigate the impact of biosecurity (O'Hagan et al., 2016; Bouchez-Zacria et al., 2024). Similarly, cattle vaccination is modelled to reduce cattle susceptibility by 50 %, which is a conceptual exploration, as vaccines are not yet commercially available. Implementation of cattle vaccine would require a vaccine-compatible diagnostic test to distinguish vaccinated from infected animals (DIVA). It is crucial for future trials to assess cattle vaccination with DIVA (Conlan et al., 2015).

4.3. Uncertainty and sensitivity analysis

The uncertainties in model parameters stem from parameter estimations derived from both infection data and the literature. The simultaneous estimation of transmission rate and decay rate parameters from infection data presents a challenge of identifiability. To illustrate, the infection probability can be attributed to a higher load of exposure with low transmission rate parameters or a lower load of exposure with high transmission rate parameters. Our previous study on the estimation method improved the quantification of environmental transmission, but also might have practical limitations when observations were not frequent enough, especially for endemic diseases (Chang and de Jong, 2023). Hence, we conducted this study with two very different persistence assumptions, with a half-life for *M. bovis* decay in the environment of either 177 days (as we estimated) or 35 days. Although the relative contribution of the different infection sources is influenced by this five-fold difference in decay rate, the model nonetheless gives a robust conclusion on the impact of badger vaccination on bTB control. Other parameters that are estimated from literature also have uncertainties, including the infectious period of badgers, the sensitivity of skin test, and the latent period (Supplement 2). Changes in these parameters can influence the relative contribution of infection from badgers, residual infection and cattle movements, but a global sensitivity analysis has shown the robustness of our conclusion regarding the efficacy of badger vaccination (Supplement 3).

We also acknowledge that our knowledge of badger population size and distribution is imperfect. However, the badger population used as the input in the simulation was the same as the value used during parameter estimation. If the badger population was underestimated, infection rate parameters would have been overestimated, compensating for the impact of underestimation of badger population on simulated bTB transmission dynamics. The badger population was modelled to be stable, resulting in a bTB pseudo-endemic stage. In reality, badger populations can be more stochastic and are influenced by intervention policies, which in turn, affect bTB transmission dynamics. For instance, more than 500 badgers were culled in this study area after the vaccination trial, possibly explaining the observed decrease in cattle incidence after the trial. Conducting long-term badger surveillance to monitor badger population dynamics and bTB prevalence among badgers can further improve our understanding of bTB dynamics.

5. Conclusion and recommendation

In conclusion, this study unravels the relative contributions of local cattle, residual infection, badgers and movement as infection sources, both at the level of the animal (cattle) and the herd. It highlights the multifactorial nature of bTB transmission and their dependence on the spatial context. Badgers and cattle each play a crucial role in this two-host transmission model. Our findings suggest that badger vaccination, in combination to the cattle test-and-removal programme, may not be sufficient to eradicate bTB in this study area. Achieving bTB eradication may require a comprehensive intervention strategy that simultaneously targets multiple transmission routes, including badgers, cattle and cattle movement. An improved understanding of badger ecology and bTB epidemiology in other regions in Ireland will enhance our understanding and facilitate the extrapolation of the results from this study.

CRediT authorship contribution statement

You Chang: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Stefan Widgren:** Writing – review & editing, Supervision, Software, Methodology, Conceptualization. **Mart C.M. de Jong:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Jamie A. Tratalos:** Writing – review & editing, Validation, Data curation. **Simon J. More:** Writing – review & editing, Validation, Conceptualization. **Nienke Hartemink:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known conflict of financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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