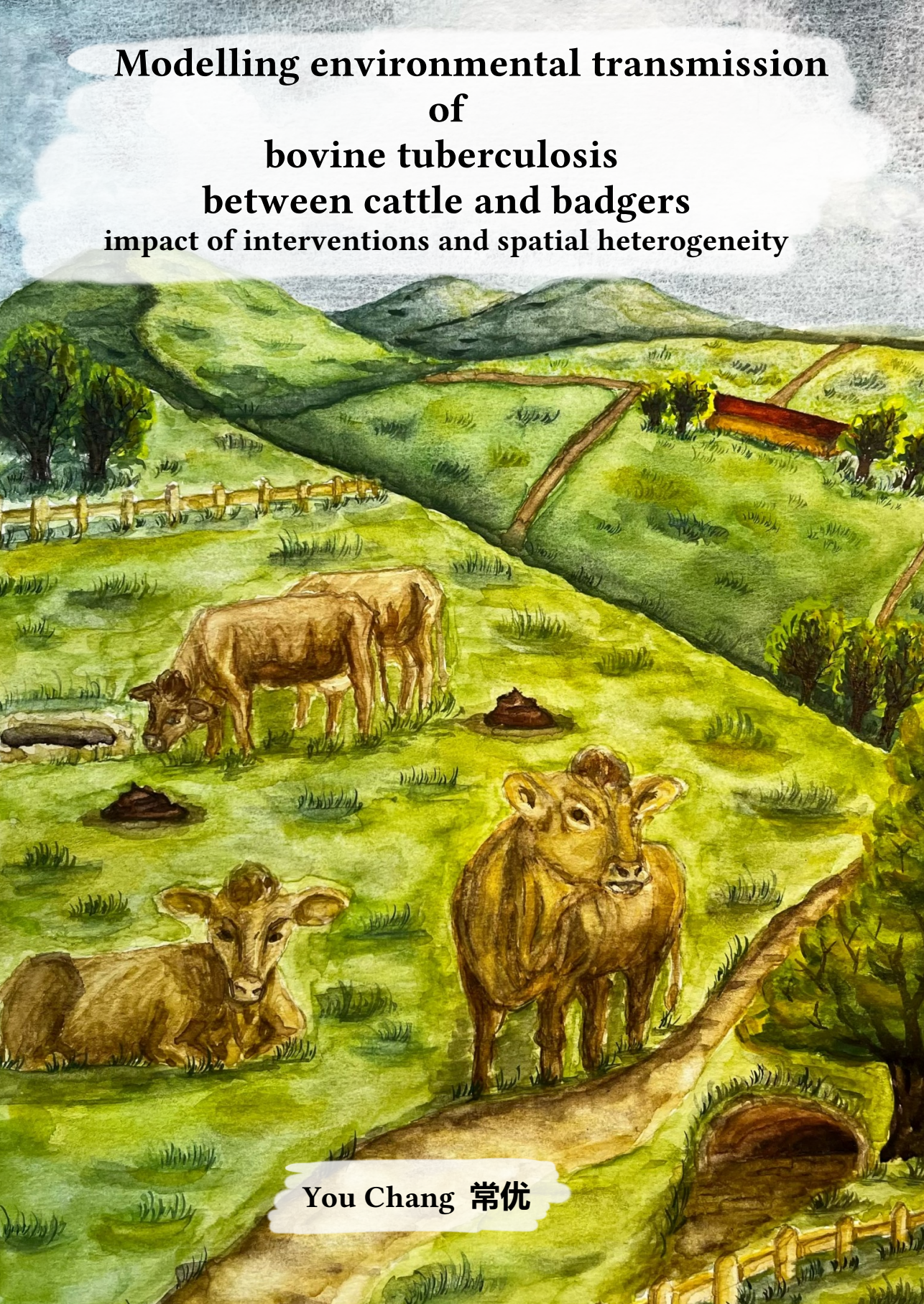
# Modelling environmental transmission of bovine tuberculosis between cattle and badgers

## impact of interventions and spatial heterogeneity



You Chang 常优

# Propositions

1. Eradicating bovine tuberculosis requires a multifaceted strategy rather than pointing fingers at cattle or badgers.
   (this thesis)

2. Heterogeneity makes the transmission dynamic system more stable and harder to control.
   (this thesis)

3. Epidemiological research's impact on public health policy is limited in societies lacking transparency and freedom of speech.

4. Modelling' role in improving our understanding of complex systems is underappreciated compared to its role in prediction.

5. AI is not promoting human intelligence.

6. Despite all downsides, the one-child policy has an advantage of empowering daughters.

Propositions belonging to the thesis, entitled

Modelling environmental transmission of bovine tuberculosis between cattle and badgers; impact of interventions and spatial heterogeneity

You Chang

Wageningen, 24 June 2024

# Modelling environmental transmission of bovine tuberculosis between cattle and badgers; impact of interventions and spatial heterogeneity

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# Modelling environmental transmission of bovine tuberculosis between cattle and badgers; impact of interventions and spatial heterogeneity

**You CHANG**

**Thesis**

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# 1

# General introduction

1

# 1.1 Background

## 1.1.1 Globally situation

Bovine tuberculosis (bTB) is an important zoonotic disease affecting cattle and wildlife worldwide. *Mycobacterium bovis*, a member of the *Mycobacterium tuberculosis* complex, is the main causative agent [1]. This intracellular bacterium is closely related to the agent for human TB [2], posing a threat to both animal and human health. The World Organization for Animal Health (WOAH) classified bTB as a notifiable disease, thereby requiring the reporting of its occurrence. Between 2017 and 2018, 82 out of 188 countries reported the presence of bTB in cattle [3]. The widespread of bTB extends across all continents (figure 1.1), with the highest prevalence in Africa and parts of Asia [4, 5]. Despite extensive eradication programs in developed countries, bTB remains a challenge in countries like the UK, Ireland, the U.S. and New Zealand. This study focuses on the Republic of Ireland (ROI).

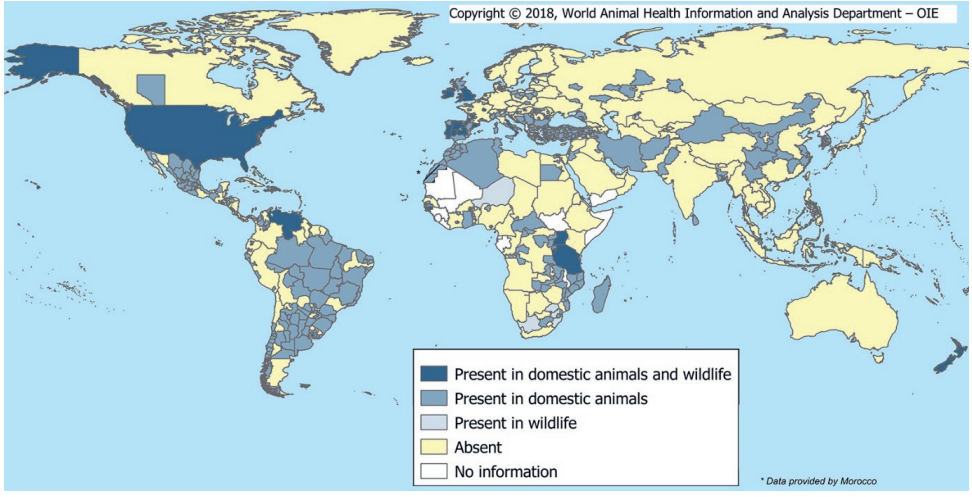


Figure 1.1: Global distribution of bovine tuberculosis in 2017-2018 [3].

## 1.1.2 Clinical signs and pathology

bTB has variable clinical signs indicative of a general state of illness, including weight-loss, fluctuating fever and pneumonia [6]. The disease is characterized as a chronic granulomatous caseous-necrotizing inflammation process, that mainly affects lungs and lymph nodes [7]. The entry point of *M. bovis* influences the location

of lesions; inhalation typically causes lesions in nasopharynx, lower respiratory tract and associated lymph nodes, while ingestion might cause lesions in mesenteric lymph nodes [8, 9]. The progression of bTB, from initial exposure to clinical signs, varies from a few months to several years. Lesions may stay localized or generalise to other organs [7]. Infected animals usually carry infection till they die [10]. In countries where bTB surveillance programs are implemented, most infected cattle are identified at the initial stage and advanced forms are rarely observed [8, 11, 12].

### 1.1.3 Host species for *M. bovis*

Cattle are the main host for *M. bovis*, but many mammals including wildlife species and humans can also become infected. Host species are usually classified as maintenance hosts, spill-over hosts or dead-end hosts [13, 14]. Maintenance hosts allow the persistence of infection through intra-species transmission alone, such as European badger (*Meles meles*) in the UK and ROI, brushtail possum (*Trichosurus vulpecula*) in New Zealand, white-tailed deer (*Odocoileus virginianus*) in North America, bison (*Bison bison*), African buffalo (*Syncerus caffer*), greater kudu (*Tragelaphus strepsiceros*) [15, 16]. Spillover hosts can transmit infections to other species but cannot maintain the infection alone without maintenance hosts, such as wild boars (*Sus scrofa*), ferrets (*Mustela putorius furo*), goats (*Capra aegagrus hircus*) [15]. Species like lions (*Panthera leo*), leopards (*P. pardus*), cheetahs (*Acinonyx jubatus*) and humans usually do not contribute to ongoing infection, which are identified as dead-end hosts [10]. However, the classification of host status can be ambiguous and controversial, as it depends not only on the characteristics of the individual as a host, but also on host density. Host density can change across different areas, over time or under different disease control measures [17].

### 1.1.4 Transmission of bTB

Similar to other respiratory infections, the transmission process of bTB involves three stages: shedding of *M. bovis* from an infectious host, its survival and relocation in different environments, and its establishment in susceptible individuals [18]. The main routes for shedding include pathogen-laden aerosols and droplets, but also, to a lesser extent, urine and faeces, sputum and wound discharge [19]. The behaviour of *M. bovis* between shedding and acquisition has not been studied

much, except for its ability to survive in a wide range of environments, both under experimental and natural conditions [20]. Inhalation is considered as the main route for acquiring *M. bovis*, because of the low minimum infectious dose via the respiratory route compared to the oral route [21] and the higher prevalence of lesions in respiratory tract compared to lesions elsewhere. This has led to a common belief that transmission via direct contact is the dominant route, which is based on the assumption that inhalation of *M. bovis* occurs only via direct contact. However, this assumption might be incorrect and simplifies the process between shedding and acquisition.

In farm environments, pathogens can re-aerosolize from contaminated soil or animal faeces. This process of re-aerosolization has been studied in the context of airborne transmission of antimicrobial resistance (AMR) in farm settings [22, 23], offering a plausible mechanism for *M. bovis* re-aerosolization. While aerosol transmission via close contact and faecal-to-oral transmission are well-recognised, other transmission mechanisms like faecal-to-aerosol and aerosol-ground-aerosols might also be important for bTB transmission. Instead of using a binary classification of direct and indirect transmission, the main difference between all these transmission mechanisms lies in the duration of *M. bovis* in the environment. In this thesis, we define "environmental transmission" to include all the transmission mechanisms involving the environment, both through direct contact (immediate acquisition of pathogens, when *M. bovis* staying in the environment for a short period of time) or indirect route (delayed acquisition of pathogens, when *M. bovis* might have survived in the environment for an extended period).

Multiple factors can contribute to bTB persistence. Due to environmental persistence of *M. bovis*, re-infection in a herd can still occur despite cattle test-and-removal control in place. In addition, infected badgers usually reside near farm [24], sharing the contaminated environments with cattle. Badgers can act as vectors that become infected from one herd and subsequently transmit to neighbouring herds, leading to continuous spread [25]. Furthermore, because of the imperfect diagnostic test, some infected cattle might remain undetected and contribute to on-going transmission within the herd [26, 27]. If these infected but undetected cattle are moved to other herds during the trading, it can introduce infections to previously uninfected

areas.

### 1.1.5 Zoonotic impact

As a zoonotic disease, bTB can be transmitted to humans via the consumption of unpasteurized milk. This mainly poses a risk in developing countries, where milk is often not pasteurized [28]. It is estimated to be responsible for 10-15% of human TB globally [29]. In 2016, there were approximately 147,000 new cases of zoonotic TB reported in people and 12,500 deaths globally [30]. However, the exact impact of *M. bovis* on human TB might be underestimated in endemic areas [29, 31], due to a lack of routine surveillance data for bovine TB in humans in low-income countries and high tuberculosis burden countries. In addition, these countries have limited resources to distinguish *M. bovis* and *M. tuberculosis*, resulting in assuming all cases are due to *M. tuberculosis* [31, 32].

### 1.1.6 Economic impact

In addition to its zoonotic threat, bTB has a large economic impact on the cattle industry. Substantial costs are incurred directly from reduced productivity of infected cattle, and more importantly from the extensive surveillance. These measures include culling of infected animals, movement restriction, and pre-export testing to enable international trading under current international agreements [33, 34]. The global economic burden was estimated to be 3 billion annually [5, 35]. In the Republic of Ireland, the direct cost of bTB in 2021 was estimated to be €105 million, with €67 million paid by the government, €35 million by farmers and €3million by the EU [36]. The economic impact is one of the main motivations for bTB eradication.

### 1.1.7 Eradication of bTB

The eradication scheme of bTB in many countries mainly relies on test and removal of infected cattle. Many European countries, where wildlife was not involved in bTB transmission, achieved eradication and hold the status of being “officially tuberculosis free” (OTF), including the Netherlands, Sweden, and Denmark [34, 36, 37]. A country can be granted as OTF status when the percentage of bTB-infected herds does not exceed 0.1% for at least six consecutive years [38].

In ROI, a cattle-based control program started in 1954, in line with the European Union Directive 65/432/EEC [37]. This program requires regular herd testing using a single intradermal comparative tuberculin test (SICTT) with positive animals being slaughtered. Herds that fail the skin test (i.e. that have one or more animals test positive in the skin test) are placed under movement restrictions until they pass two follow-up tests, which are administered at approximately 60-day intervals according to EU legislation. Additional measures, including post-mortem cattle surveillance at the slaughterhouse, contiguous testing, and random sample testing, have also been implemented [39]. The first decade of the eradication program saw great progress with cattle incidence decreasing from 17% in 1954 to 0.5% in 1965 [40]. However, the incidence remained stable over the next few decades, which is partially attributed to transmission from badgers.

Since the identification of the first bTB infected badgers in 1975 [41], lots of research has been done to investigate the role of badgers in bTB transmission and the effectiveness of badger culling [40, 42–44]. In 2000, badger culling was implemented as a supplementary measure to achieve bTB eradication in cattle. Between 2002 and 2016, around 6,000 badgers were culled per year [45], which was associated with a further reduction in bTB incidence in cattle. However, given the protected status of badgers in Ireland under Wildlife Acts [46, 47], an alternative to culling had to be found. Therefore, vaccinating badgers with Bacille Calmette-Guérin (BCG) vaccines was assessed by experimental and field trials [1, 48–52].

Between 2009 to 2012, a field trial in Kilkenny investigated the effect of badger vaccination on bTB incidence within natural badger populations. Based on the badger infection data, BCG vaccination is estimated to reduce badger susceptibility by 59% [52]. The study estimated that the disease can be eliminated with a 40% vaccination coverage in combination with current control strategies in cattle based on national herd prevalence and badger prevalence [1]. In 2018, routine badger vaccination using injecting BCG was established as part of the Irish bTB eradication programme. Large-scale vaccination of badgers has been rolled out under the new strategy, with over 20,000 km2 covered by the vaccination programme and 6,586 badgers captured in vaccination areas in 2021 [36].

## 1.2 Problem statement and knowledge gaps

Although previous studies from the Kilkenny trial have provided an important understanding of the potential of badger vaccination, the effectiveness of this intervention in eradicating bovine tuberculosis (bTB) remains uncertain. There remain some significant gaps in our understanding. Firstly, the efficacy of badger vaccination was estimated in a single-host (badger) transmission system, which ignored the impact of local cattle infections on bTB transmission. Moreover, the quantitative role of environmental transmission remains unclear, presenting challenges to assessing interventions. Lastly, the extrapolation of the trial results to a national level assumed a homogenous effect of vaccination across the country, ignoring the spatial heterogeneity in local infection levels, badger and cattle densities, etc. These gaps are the motivation for this thesis, which aims to investigate how local factors influence the effectiveness of badger vaccination in eradicating bTB.

### 1.2.1 Objective of the thesis

The objective of this thesis is to assess the effectiveness of badger vaccination in combination with the current cattle-based control measures, in achieving bTB eradication in ROI. This thesis aims to improve the scientific understanding of the transmission between badgers and cattle, considering spatial context and different transmission routes, and provide evidence-based recommendations to policymakers on bTB eradication programme. To achieve these aims, the thesis is divided into three sub-objectives:

1. Develop a method to quantify environmental transmission using infection data.
2. Quantify the transmission between cattle and badgers via environment considering the spatial context, and assess the impact of badger vaccination on local transmission.
3. Develop decision support tools for assessing interventions at a regional level, and assessing the impact of (combinations of) badger vaccination and other additional measures.

1

### 1.2.2 Outline of the thesis

The thesis is organized into five chapters, beginning with this introductory chapter (Chapter 1). Subsequently, three research chapters (Chapters 2-4) are dedicated to addressing individual sub-objectives. The thesis concludes with a comprehensive general discussion (Chapter 5).

Chapter 2: A novel method to quantify environmental transmission

Quantifying environmental transmission without environmental data is challenging [53]. The commonly-used trajectory-fitting method might not be able to simultaneously estimate back decay rate and transmission rate parameters, especially for endemic diseases like bTB. To solve this issue, Chapter 2 develops a novel statistical method to estimate transmission rate and decay rate parameters simultaneously using only infection data. We simulate a simple SIS model with environmental transmission and use the simulated data to validate this estimation method. We also compare this novel method with the trajectory fitting method to explain why our method outperforms existing methods by using more information from infection data.

Chapter 3: bTB environmental transmission between cattle and badger and R Maps

A quantitative understanding of cattle and badgers in bTB transmission is elusive, especially given the spatial variation in local factors. In addition, the quantitative importance of the environment has barely been assessed [54], despite its potential importance. To address these issues, Chapter 3 uses the method developed in Chapter 2 to quantify the environmental transmission of bTB in a cattle-badger system. Both cattle and badger infection data from the badger vaccination trial in County Kilkenny are used to estimate transmission rate and decay rate parameters in vaccinated and unvaccinated areas. With the parameter estimates, basic reproduction ratio ($R_0$) maps are generated to identify high-risk areas and understand the badger vaccination impact in local areas.

Chapter 4: Is badger vaccination sufficient to eradicate bTB?

After assessing the impact of badger vaccination at local levels, Chapter 4 aims to assess its impact at a regional level in eradicating bTB, when combined with

existing cattle-based controls. To achieve this, Chapter 4 develops a multi-host and multi-route transmission model, using parameter estimates from Chapter 3. Through simulations, we aim to assess badger vaccination impact on cattle herd incidence and predict the relative contribution of different routes. In addition, this model can serve as a decision support tool that can explore the impact of various interventions targeting different single or multiple routes.

Chapter 5 General discussion

Chapter 5 analyses the main findings of this thesis in a broader context to answer how spatial heterogeneity might influence the intervention assessment when intervention target on one host, using badger vaccination in bTB as an example. The challenges in eradicating bTB were discussed and suggestions on future research is suggested.

# 2

# A novel method to quantify environmental transmission

You Chang, Mart C.M. de Jong

This chapter is published as You Chang and Mart C.M. de Jong. "A novel method to jointly estimate transmission rate and decay rate parameters in environmental transmission models." Epidemics 42 (2023): 100672.

**Abstract**

In environmental transmission, pathogens transfer from one individual to another via the environment. It is a common transmission mechanism in a wide range of host-pathogen systems. Incorporating environmental transmission in dynamic transmission models is crucial for gauging the effect of interventions, as extrapolating model results to new situations is only valid when the mechanisms are modelled correctly. The challenge in environmental transmission models lies in not jointly identifiable parameters for pathogen shedding, decay, and transmission dynamics. To solve this unidentifiability issue, we present a stochastic environmental transmission model with a novel scaling method for shedding rate parameter and a novel estimation method that distinguishes transmission rate and decay rate parameters. The core of our scaling and estimation method is calculating exposure and relating exposure to infection risks. By scaling shedding rate parameter, we standardize exposure to pathogens contributed by one infectious individual present during one time interval to one. The standardized exposure leads to a standard definition of transmission rate parameter applicable to scenarios with different decay rate parameters. Hence, we unify direct transmission (large decay rate) and environmental transmission in a continuous manner. More importantly, our exposure-based estimation method can correctly estimate back the transmission rate and the decay rate parameters, while the commonly used trajectory-based method failed. The reason is that exposure-based method gives the correct weight to infection data from previous observation periods. The correct estimation from exposure-based method will lead to more reliable predictions of intervention impact. Using the effect of disinfection as an example, we show how incorrectly estimated parameters may lead to incorrect conclusions about the effectiveness of interventions. This illustrates the importance of correct estimation of transmission rate and decay rate parameters for extrapolating environmental transmission models and predicting intervention effects.

## 2.1 Introduction



In many infectious diseases, pathogens are shed into the environment on surfaces, in water, in air, etc. Pathogens persist there, and subsequently infect individuals that are exposed to the contaminated environment. This is called environmental transmission. A wide range of human and animal infections are transmitted via the environment [55–58]. For example, cholera, rotavirus, norovirus, *Campylobacter jejuni*, enterotoxigenic *Escherichia coli*, bovine tuberculosis, foot and mouth disease and Hepatitis E virus can transmit via contaminated environment such as water, food, surfaces, urine, faeces etc. [20, 59–62]. Respiratory infections, such as influenza, rhinovirus and SARS-CoV2 can be transmitted when an infectious person exhales virus particles to aerosols, droplets, which can be taken up by other individuals (either directly from the air or via fomites) [63–65]. The existence of various environmental transmission routes makes it important for us to understand better environmental transmission dynamics.

Mathematical models can be constructed to understand the underlying transmission dynamics and then be used to predict the effects of intervention strategies [66, 67]. In addition, models can also be extrapolated to scenarios where future transmission conditions are different due to environmental changes. We need accurate predictions if we want to be prepared for new situations and take measures to mitigate the possible effects. Several quantification approaches have been used for this purpose, such as the well-established risk factors analysis and dynamic models [68].

Relative risk analysis finds associations between interventions and the risk of infection assuming the same exposure in a reference population and an intervention population. Relative risks can provide some insight into the efficacy of interventions [69–71]. However, the magnitude of the impact cannot be extrapolated to other situations or populations where the exposure is different, as the relationship between exposure and infection probability is not linear [72–76]. Therefore, dynamics modelling is often preferred over risk factor analysis when predicting future risks [68].

However, there are challenges in dynamic modelling for environmental transmis-

sion. Environmental contamination is usually unobserved or observed under lab circumstances, which may differ from the normal circumstances of pathogen transmission. In the absence of correct and detailed environmental contamination data, the shedding rate, decay rate, and transmission rate parameters are structurally not jointly identifiable [53, 77]. For example, a certain rate of infection can be the result of a lower transmission rate parameter per pathogen with more pathogens in the environment or of a higher transmission rate parameter per pathogen with fewer pathogens. Measuring environmental data or the rates of shedding or decay processes via experiments have been suggested to help this unidentifiability issue [53, 77, 78]. However, environmental data measurements and experiments can be expensive, unethical when involving pathogen challenging, and the natural inoculation is usually different from experimental inoculation.

Another challenge is the lack of a suitable estimation method for quantifying environmental transmission. A widely used estimation method is based on fitting observed infection data to the trajectories simulated by ordinary differential equation (ODE) models [77–80], which we call trajectory-based estimation. The underlying mathematical models of this estimation are easy to build, and one can add complexity in transmission mechanisms with different routes [58]. However, a recent simulation study [81] shows that models with different mechanisms can have similar fits, making it impossible to distinguish the model with the correct transmission mechanisms from other models.

In contrast, another quantification method estimates transmission rate parameters based on linking exposure to infection probability. This exposure-based method has been used both in quantifying direct transmission [82–84] and indirect transmission [61, 85–87]. Bootsma et al. [88] has attempted to apply this exposure-based method for environmental transmitted infection in hospitals but had difficulties in reconstructing the history of the exposure to infectious individuals. Here we postulate that adapting this exposure-based estimation method to environmental transmission would be challenging, but promising.

Therefore, the main objective of our paper is to solve the not jointly identifiable issue when quantifying environmental transmission. We start out by building a stochastic environmental transmission model with a novel scaling method. Then,

we present our novel estimation method for environmental transmission by adapting the exposure-based estimation. In order to evaluate exposure-based estimation method and compare with the trajectory-based estimation, we analysed simulated infection data using our stochastic environmental model. We illustrate our newly developed model with a case study on the prediction of the impact of disinfection on environmental transmission. This shows the importance of correctly estimating parameters for drawing correct conclusions on the effect of interventions, and more generally, for extrapolation transmission model results.

## 2.2 Models and Results

In this section, we will first explain the environmental transmission model framework (Section 2.2.1) and present a novel scaling method for shedding rate by standardizing exposure (Section 2.2.2). The model will then be applied to simulate a time series of infection data (Section 2.2.3). Then, the simulated data will be analysed by two different statistical methods (exposure-based and trajectory-based) to assess whether they can estimate back decay rate and transmission rate parameters (Section 2.2.4). Furthermore, the robustness of the exposure-based estimation method will be tested by sensitivity analysis (Section 2.2.5). In the end, we will explore the application of the environmental transmission model by predicting the impact of disinfection (Section 2.2.6).

### 2.2.1 Environmental transmission model

We adopted a stochastic SIS stochastic compartmental model with an extra environment compartment (figure 2.1). Infections are assumed to occur through the environmental compartment only.

We model in continuous time t with discrete individuals. Thus, ($S_t$, $I_t$) are discrete numbers of susceptible and infectious individuals. ($S_t$, $I_t$) make discrete jump to ($S_t + 1$, $I_t - 1$) for recovery at rate $\beta \frac{E(t)}{N} S_t$ and to ($S_t - 1$, $I_t + 1$) for infection at rate $\alpha I_t$. In the interval between these events, the ($S_t$, $I_t$) population state does not change. In contrast, $E(t)$ is a continuous variable for environmental contamination in continuous time. To distinguish continuous from discrete variables, we use the subscript notation for time t for discrete variables ($S_t$ and $I_t$, both in continuous time), and the parentheses notation for the continuous variable $E(t)$.

In each interval between any two sequential state transitions $t \in (t1, t2)$, the number of infectious individuals ($I_t$) during the interval is determined as $I_{t1}$ and is constant. Remember that the interval ends when $I_t$ changes to $I_{t2}$. During the interval, the infectious individuals $I_{t1}$ shed pathogens in the environment at constant rate $\varphi I_{t1}$ and in the environment pathogens decay with a changing rate $\mu E(t)$. These two processes during each interval between state transitions $(t1, t2)$ are modelled deterministically because of the large number of pathogens in the environment:

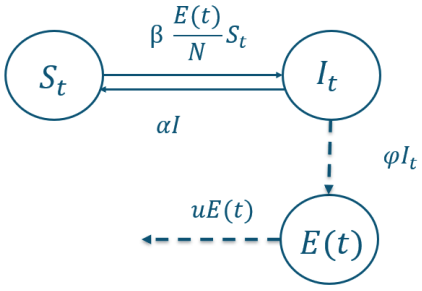


Figure 2.1: **A schematic representation of the stochastic SIS model with transmission through the environment.** $S_t$, $I_t$ represent susceptible, infectious compartments and $E(t)$ represents the environmental compartment. The solid lines represent the flow of individuals (stochastic discrete jumps) to another state. The transmission from $S_t$ to $I_t$ occurs at rate $\beta\frac{E(t)}{N}S_t$ and the transition from $I_t$ to $S_t$ occurs at rate $\alpha I_t$. The dotted lines represent the flow of pathogens in the environment, modelled as deterministic processes, $\varphi I_t$ represents the shedding rate at which infectious individuals shed pathogens into environment and $\mu E(t)$ represents the decay rate at which pathogens decay in the environment.

$$\frac{dE(t)}{dt} = \varphi I_{t1} - \mu E(t) \tag{2.1}$$

Where $\mu$ is pathogens' decay rate parameter, i.e. the rate at which viable pathogens become inactivated or removed from the environment, and $\varphi$ is the shedding rate parameter, i.e. the rate at which pathogens are added to the environment by each infectious individual during the interval. When starting from a clean environment with one infectious individual present, the environmental contamination increases with time and reaches a plateau when the shedding rate in the population equals the decay rate of environmental pathogens ($E(equilibrium) = \frac{\varphi}{\mu}$). If the infectious individual is recovered or removed, environmental contamination decreases exponentially with time: $E(t) = e^{-\mu(t-t_{equilibrium})}E(equilibrium)$ (figure 2.2).

The state transitions (solid lines in figure 2.1) are modelled by a continuous-time discrete-state Markov process via Gillespie's Direct Method [89]. The detailed algorithm of simulation is given in Section 2.2.3.

We calculate the basic reproduction number $R$ for this environmental model. The ordinary differential equation of the model in figure 2.1 can be written as:

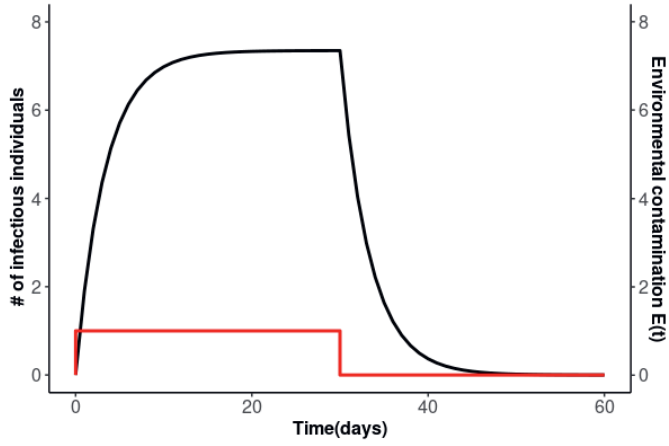


Figure 2.2: An example showing the discrete jumps in $I_t$ and continuous changes in $E(t)$. The red line represents $I_t$ jumping first from 0 to 1 and then later from 1 to 0 and the black line represents the $E(t)$ resulting from that. Environmental contamination builds up till equilibrium and decays after removal of the infectious individual.

$$\frac{dS}{dt} = -\beta \frac{E\,S}{N} + \alpha I \tag{2.2}$$

$$\frac{dI}{dt} = \beta \frac{E\,S}{N} - \alpha I \tag{2.3}$$

$$\frac{dE}{dt} = \varphi I - \mu E \tag{2.4}$$

We obtain the Next Generation Matrix from the transmission matrix (T) and transition matrix ($\Sigma$) using I and E as the two states in that order [90]:

$$T = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix}, \quad \Sigma = \begin{bmatrix} -\alpha & 0 \\ \varphi & -\mu \end{bmatrix} \tag{2.5}$$

The reproduction ratio is thus the largest eigenvalue of $-T\Sigma^{-1}$, hence $R = \frac{\beta\varphi}{\alpha\mu}$.

We can also calculate the $R$ of the stochastic model (figure 2.1) from biological interpretation by determining: 1) how long an infectious individual stay infec-

tious (expected value of t); 2) how long environmental contamination stays in the environment (exponential decay with $\mu$); 3) how many pathogens are shed into environment by an infectious individual per time unit ($\varphi$); 4) how many individuals are expected to be infected per unit of environmental contamination per time unit ($\beta$). From that it follows that:

$$R = \int_0^\infty \int_0^\infty \varphi\beta e^{-\mu x} \alpha t e^{-\alpha t} dx dt = \frac{\beta\varphi}{\alpha\mu} \tag{2.6}$$

### 2.2.2 Scaling the shedding rate parameter

The shedding rate parameter $\varphi$ and the transmission rate parameter $\beta$ are not structurally jointly identifiable from infection data [53]. Therefore, the shedding rate is usually scaled to unity or another fixed value [91–93].

However, choosing a fixed value for the shedding rate parameter $\varphi$ makes it difficult to interpret the transmission rate parameter $\beta$ among different decay rate parameter $\mu$. For example, the environmental contamination and the exposure to environmental contamination during an interval become lower and lower with increasing values of the decay rate parameter $\mu$. The transmission rate parameters $\beta$ is estimated by fitting the exposure to a dose-response curve based on an observed infection probability ($P = 1 - e^{(-\beta * exposure)}$). Consequently, when decay rate is large and the exposure is low, the estimates of the transmission rate parameters $\beta$ have to increase proportionally when a certain infection probability is observed. This relationship between $\beta$ and $\mu$ can be seen in the basic reproduction rate ($R = \frac{\beta}{\alpha\mu}$ when $\varphi = 1$). When $\mu$ is close to infinity, $\beta$ is also close to infinity which is hard to interpret because the ratio between $\beta$ and $\mu$ is not infinite. In reality, transmission with a large decay rate parameter $\mu$ is seen as direct transmission, with the basic reproduction ratio as $R = \frac{\beta}{\alpha}$. The interpretation of $\beta$ is incomparable among transmission with different $\mu$, which creates a sharp distinction between direct and environmental transmission.

Therefore, we propose a scaling method that generates a consistent interpretation of $\beta$. This is inspired by our work on experimental transmission where often the probability of infection is observed [61, 86, 87]. In an imagined transmission ex-

periment, susceptible individuals are put in a clean environment with infectious individuals. Susceptible individuals get exposed to pathogens shed by infectious individuals. The infection status of susceptible individuals is observed in an interval (e.g., a day in the following text), from which the probability of infection can be calculated. This probability is a certain value, despite whether susceptible individuals get exposed directly during close contact or indirectly via environment. In fact, this probability is dependent on the total exposure during a day and the transmission rate parameter ($P = 1 - e^{(-\beta * exposure)}$). During the first day of the experiment, the exposure is a fixed value among different transmission mechanism assumptions because of no historic environmental contamination. The total exposure to one infectious individual during a day starting with no historic contamination is represented as 1 in direct transmission, while as $\int_0^1 E(t)\,dt$ when assuming an environmental transmission. Therefore, we standardize the exposure to environmental contamination shed by one infectious individual during a day to one unit, which generates a consistent interpretation of transmission rate parameter among different transmission mechanism assumptions.

We firstly solve equation 2.1 to derive the environmental contamination for every time point $(t1 + \tau)$ within an interval $(t1,\ t2)$, where $t1$, $t2$ represent any two sequential time points at which transition events occur:

$$E(t1 + \tau | I_{t1}, E(t1)) = \frac{(1 - e^{-\tau\mu})}{\mu} \varphi I_{t1} + e^{-\tau\mu} E(t1) \tag{2.7}$$

$I_{t1}$ and $E(t1)$ are the number of infectious individuals and environmental contamination, respectively, at the start of the interval, the time point $t1$ (i.e., at the moment at which the latest transition occurred). The total exposure to the environmental contamination during $(t1, t1 + \tau)$ is then the integral of equation 2.7 as:

$$\int_{t1}^{t1+\tau} E(t | I_{t1}, E(t1))dt = \frac{(-1 + e^{-\mu\tau} + \mu\tau)}{\mu^2} \varphi I_{t1} + \frac{1 - e^{-\mu\tau}}{\mu} E(t1) \tag{2.8}$$

The exposure consists of two parts; the exposure to the environmental contamination shed by $I_{t1}$ during $(t1, t1 + \tau)$, and the exposure to the environmental contamination at time $t1$ resulting from the historical infectious number before

$t1$. Our goal is to standardize the first part of the exposure in an observation time interval of unit length to an amount equal to the number of infectious individuals $I_{t1}$, which means ($\tau = 1$) and $\frac{(-1+e^{-\mu}+\mu)}{\mu^2}\varphi I_{t1} = I_{t1}$. The shedding rate is then derived as $\varphi(\mu) = \frac{\mu^2}{-1+e^{-\mu}+\mu}$.

We plot $E(t)$ and the integral of $E(t)$ over time to illustrate the difference between scaling methods ($\varphi = 1$ and $\varphi(\mu) = \frac{\mu^2}{-1+e^{-\mu}+\mu}$). In an example scenario, one infectious individual is present for 1 day and removed after that. When the shedding rate is fixed at a constant (e.g. $\varphi = 1$ in the figure 2.3A & C), higher values of $\mu$ would lead to a lower $E(t)$ (figure 2.3A) and thus lower exposure to $E(t)$ (figure 2.3C). Eventually for $\mu \to \infty$, $E(t)$ is close to 0, plotted here by taking $\mu = 100$ per day (Green line in figure 2.3). With an observed infection probability during the first day, the transmission rate parameter increases with increasing $\mu$ because the exposure on the first day decreases with $\mu$ (figure 2.3C). However, when $\varphi(\mu) = \frac{\mu^2}{-1+e^{-\mu}+\mu}$, all the curves have the same exposure during the first day, i.e. equal to 1, for all the $\mu$ including $\mu \to \infty$ (red dot in figure 2.3D). When $\mu \to \infty$ (Green line in figure 2.3B), the exposure for each day is equal to 1 when $I_t$=1 and 0 when $I_t$=0, which is as expected for a direct transmission. The standardized exposure leads to a consistent interpretation of the transmission rate parameter.

The difference between more direct ($\mu$ = 100) and more environmental transmission ($\mu$ = 0.01) can be seen when we compare the infection probability on the second day (figure 2.3B). In more direct transmission, the infection probability on the second day would be zero as the exposure is zero (area under the green line in figure 2.3B on the second day). In contrast, the infection probability on the second day for environmental transmission would be non-zero, as the exposure is still present (area under the blue line in figure 2.3B on the second day). This straightforward interpretation is the advantage of our standardization that allows a consistent interpretation of transmission rate parameter among different $\mu$.

This scaling method has the advantage of unifying the direct and environmental transmission. When $\varphi(\mu) = \frac{\mu^2}{-1+e^{-\mu}+\mu}$, $R = \frac{\beta\mu}{\alpha(-1+e^{-\mu}+\mu)}$. The term $\frac{\mu}{(-1+e^{-\mu}+\mu)}$ can be interpreted as the total exposure to pathogens from the first day to infinity contributed by one infectious individual present one day $(1 + \frac{1-e^{-\mu}}{\mu} + \left(\frac{1-e^{-\mu}}{\mu}\right)^2 \ldots +$

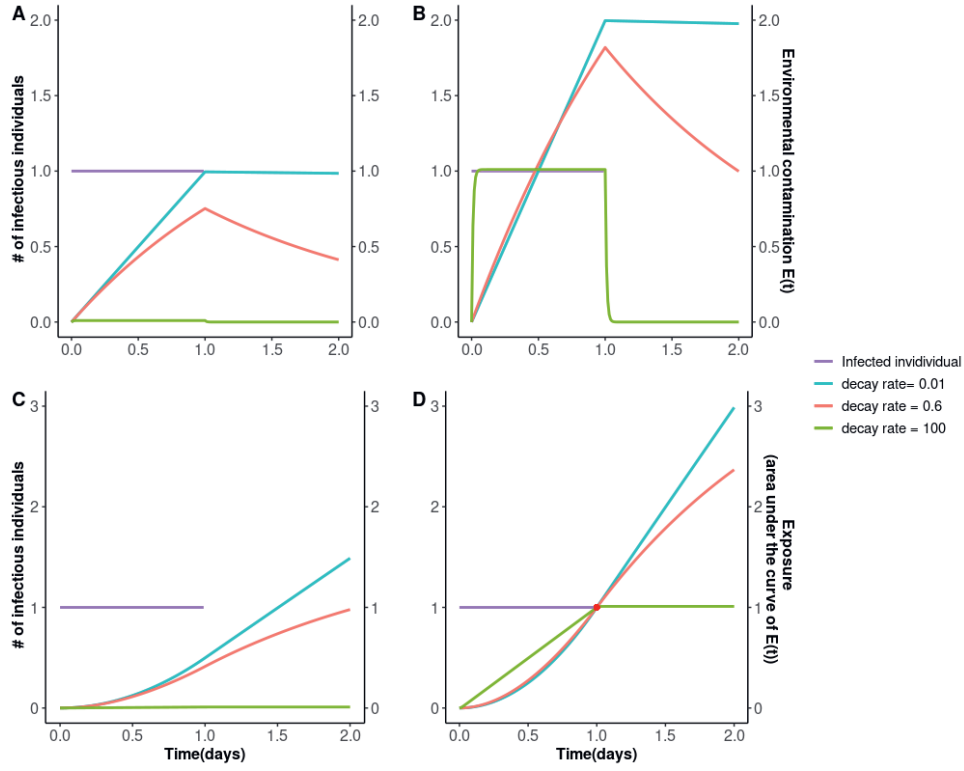


Figure 2.3: The environmental contamination (at moment t) and the accumulated exposure (from 0 to t) to the environmental contamination, with two scaling methods for shedding rate. (A) & (B) show the changes of environmental contamination (at moment t) over time and (C) & (D) show the changes of accumulated exposure (from 0 to t) to environmental contamination over time. (A) & (C) represent the shedding rate $\varphi = 1$ and (B) & (D) represent the shedding rate $\varphi(\mu) = \frac{\mu^2}{-1+e^{-\mu}+\mu}$. The purple line shows that the infectious individual was present on the first day and removed on the second day. The blue, red and green lines show how the $E(t)$ changes over time, where the area under $E(t)$ represents the exposure. The red dot in the (D) shows that the exposure is unified to 1 among different decay rate parameter.

$\left(\frac{1-e^{-\mu}}{\mu}\right)^n + \ldots) = \frac{\mu}{(-1+e^{-\mu}+\mu)}$, where $\frac{1-e^{-\mu}}{\mu}$ is the fraction of exposure in the next day. The contribution of the first day's exposure when the infectious present is usually seen as the contribution of the direct transmission and the rest of exposure is usually seen as the indirect transmission via environment. Therefore, the reproduction ratio consists of two parts: the direct transmission $(\frac{\beta}{\alpha} * 1)$ when both susceptible and infectious individuals present at the same time, and the environmental transmission after infectious individuals being removed or recovered $(\frac{\beta}{\alpha}\frac{1-e^{-\mu}}{(-1+e^{-\mu}+\mu)})$. When $\mu \to \infty$,

$(\frac{1-e^{-\mu}}{(-1+e^{-\mu}+\mu)}) \to 0$, hence the transmission is only contributed by direct transmission.

### 2.2.3 Stochastic simulation of environmental transmission model

As the exposure to environmental contamination has been derived in Section 2.2.2, we can now explain how to use such an environmental transmission model to simulate transmission. The two state transitions (infection or recovery) are modelled by a continuous-time discrete-state Markov process via Gillespie's Direct Method [89]. During an interval between two transition events $(t1, t2)$, $S_t$, $I_t$ are constant equal to $S_{t1}$ and $I_{t1}$, but the infection rate is not constant, due to the deterministic change in $E(t)$ given by equation 2.1. Therefore, we adjusted Gillespie's algorithm to consider the continuous changes in hazard rate with the corresponding rates summarized in table 2.1.

Table 2.1: The processes in the interval $(t1, t1+\tau)$. Here the hazard rate for the interval is given, and the relation to the probability as explained in the text.

| Process | Definition | The hazard rate for the event happening in interval $(t1, t1+\tau)$ |
|---|---|---|
| Infection | $(S_t, I_t) \to (S_t - 1, I_t + 1)$ | $\int_{t1}^{t1+\tau} \beta \frac{S_{t1} E(t)}{N}\, dt = \beta \frac{S_{t1}}{N} \int_{t1}^{t1+\tau} E(t) dt$ |
| Recovery | $(S_t, I_t) \to (S_t + 1, I_t - 1)$ | $\int_{t1}^{t1+\tau} \alpha I_{t1}\, dt = \alpha I_{t1} \tau$ |

The adjusted Gillespie's algorithm is as follow:

1. Simulate the time that the next event occurs.

   (a) The probability of an event in an interval $(t1, t1+\tau)$. The probability that one or more infection or recovery events occur during an interval follows a Poisson process, and the probability of no event occurring during $\tau$ is the zero term of the Poisson distribution with the expected number of events occurring during an interval $\tau$ as the parameter. Since, $E(t)$, in the instantaneous rate of getting infected (hazard rate $\beta \frac{S_{t1} E(t)}{N}$), is not a constant in the interval, the expected number of infections during $(t1, t1+\tau)$ depends on the area under the curve of $E(t)$, namely $\int_{t1}^{t1+\tau} E(t) dt$. Note, that when taking the integral over the environment

one needs always to take into account the starting value $E(t)$ at the starting time $t1$.

$$P(no\ event \in \tau) = e^{-\int_{t1}^{t1+\tau}(\beta \frac{S_{t1}}{N} E(t) - \alpha I_{t1})dt} \tag{2.9}$$

The hazard rate for a recovery is constant and thus its integral $\int_{t1}^{t1+\tau} \alpha I_{t1} dt$ is just the rate times $\tau$ i.e., $\alpha I_{t1} \tau$.

The probability that one or more events happens during an interval $\tau$ is $1 - P(no\ event \in \tau)$.

(b) Obtain a realisation of the random time interval between events through the inverse transform sampling technique. Random numbers are drawn from a uniform distribution $U(0,1)$ and the corresponding realisation of the random time interval $\tau$ between events can be numerically determined by solving $\tau$ for each realisation of the random number p from distribution $U(0,1)$:

$$1 - e^{-\beta \frac{S_{t1}}{N} \int_{t1}^{t1+\tau} E(t)dt - \alpha I_{t1} \tau} = p \tag{2.10}$$

2. Simulate which event occurs. The quotient of either the infection rate or the recovery rate over the interval $\tau$ over the sum of all rates in the interval determines which event happens at the time point determined by step 1. Given the value of $\tau$ as drawn by step 1, one of the events can be drawn from the probability of the events, for example, the probability of an infection event given the interval $\tau$ is:

$$\frac{\beta \frac{S_{t1}}{N} \int_{t1}^{t1+\tau} E(t)dt}{\beta \frac{S_{t1}}{N} \int_{t1}^{t1+\tau} E(t)dt + \alpha I_{t1}\ \tau} \tag{2.11}$$

3. Sampling procedure. The simulated data are continuous in time while infection data are observed in discrete time intervals in reality. Here, we discretize the continuous-time to discrete-time because the observation of the infection data is on a discrete-time interval (e.g., on daily basis in this study). The

number of infectious and susceptible individuals are observed at the beginning of each day. The number of new cases in each day is integrated over the discrete-time interval.



The input parameters used in the baseline simulation scenario are listed below (table 2.2).

Table 2.2: Input values for the environmental transmission simulation

| Variables | Definition | Value |
|---|---|---|
| $\beta$ | Environmental transmission rate parameter | 0.0015 $day^{-1}$ |
| $\alpha$ | Recovery rate parameter | 0.02 $day^{-1}$ |
| $\mu$ | Decay rate parameter | 0.05 $day^{-1}$ |
| $\varphi$ | Shedding rate parameter | $\frac{\mu^2}{-1+e^{-\mu}+\mu}$ =2.02 $day^{-1}$ |

Stochastic environmental transmission was simulated in 10 farms with 100 animals for each farm, starting with a clean environment and 10 infectious animals in each farm or from a pseudo-endemic state with 67 infectious animals in each farm with the equilibrium environmental infectious pressure ($\frac{\mu}{-1+e^{-\mu}+\mu} * 67 = 2720$ units for $\mu = 0.05$ per day).The simulation results for transmission in the baseline scenario (using parameters in table 2.2) including a transient phase and a pseudo-endemic phase were shown figure 2.4.

### 2.2.4 Comparing estimation methods

The simulated infection data were used to assess two different estimation methods, exposure-based and trajectory-based, in back-estimating the underlying parameters $\mu$ and $\beta$. The recovery rate parameter can be estimated when individual level data on infection status is available; therefore, the parameter can be assumed to be known in the comparison below. The shedding rate parameter is also not estimated because it is a function of decay rate parameter. The analysis was done separately for the transient phase (figure 2.4A) and the pseudo-endemic phase (figure 2.4B).

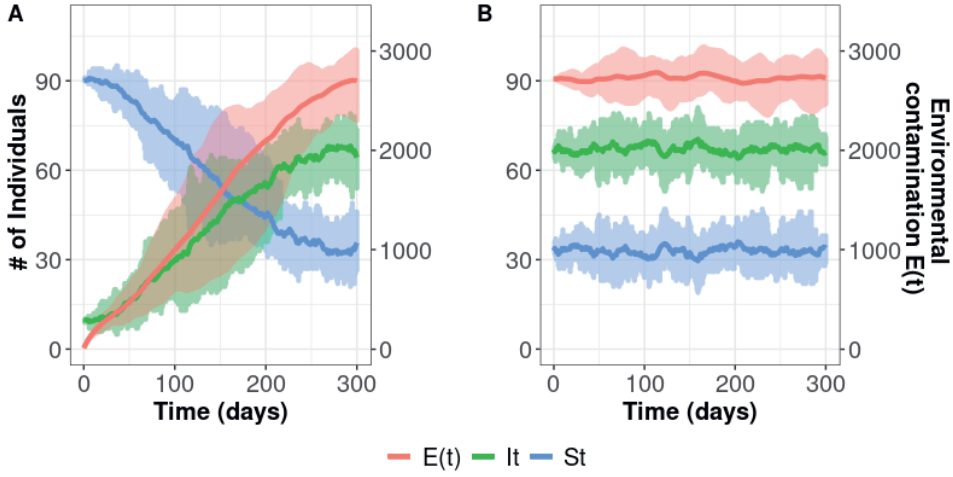


Figure 2.4: The simulation results for the transmission in a transient phase (A) and in a pseudo-endemic phase (B). The red lines represent the number of infectious individuals $I_t$, blue lines the number of susceptible individuals $S_t$ and green lines the environmental contamination $E(t)$. Coloured areas show the envelop from 10 simulation repeats and solid lines show the average of simulations.

### Exposure-based estimation method

We fitted the stochastic transmission model to exposure data using maximum likelihood estimation. The exposure was calculated from observed infection data and the past number of infectious individuals was considered in the calculation. In particular, the number of new cases over each observation time interval $(i, i+1)$, follows a binomial distribution with probability $1 - e^{\frac{-\beta(\int_i^{i+1} E(t|I_i,\ E(i))dt)}{N}}$ and binomial total $S_i$, the number of susceptible individuals at $i$ time where $i, i+1$ are the discrete integer time intervals. The likelihood as a function of $\beta$ and $\mu$ is given by

$$\mathcal{L}(\theta) = \prod_i (1 - e^{\frac{-\beta(\int_i^{i+1} E(t|I_i,\ E(i))dt)}{N}})^{cases_i} (e^{\frac{-\beta(\int_i^{i+1} E(t|I_i,\ E(i))dt)}{N}})^{(S_i - cases_i)} \tag{2.12}$$

where $cases_i$ is the observed number of new cases (obtained by summation in the simulation) in the interval $(i, i+1)$. The challenge in this likelihood function is that is $\mu$ is inside $\int_i^{i+1} E(t|I_i,\ E(i))dt$ which needs to be constructed by iterating equation 2.7 and equation 2.8.

To profile the likelihood of $\mu$, a set of $\mu$ is used to construct the time-series exposure

dataset for each day ($\int_i^{i+1} E(t|I_i,\ E(i))dt$). Then for each exposure dataset, $\log(L(\beta))$ is maximized. The optimization can be achieved by defining a generalized linear model with cloglog link since the expected number of cases in each day follows: $\mathcal{E}(cases_i) = S_i(1-e^{\frac{-\beta(\int_i^{i+1} E(t|I_i,E(i))dt)}{N}})$. Transforming the formula with the cloglog link, we derive:

$$\log\left(-\log\left(1-\mathcal{E}(\frac{cases_i}{S_i})\right)\right) = \log(\beta) + \log\left(\frac{\int_i^{i+1} E(t|I_i,E(i))dt}{N}\right) \tag{2.13}$$

where $\log(\beta)$ is the intercept and $\log\left(\frac{\int_i^{i+1} E(t|I_i,E(i))dt}{N}\right)$ is an offset, which is an explanatory variable with the coefficient equal to 1 and which depends on the historical infection data and decay rate parameter $\mu$. The estimated $\beta$ can be calculated as $\widehat{\beta} = e^{C0}$, where $C_0$ is the estimated intercept from equation 2.13. The AIC value for each $\mu$ constructed exposure dataset is calculated by $-2 * \log(L(\beta)) + 4$ and plotted against the $\mu$ (figure 2.5 A&D). In addition, we maximized the $\log(L(\mu))$ for a set of $\beta$ and thus obtained the profile likelihood for $\beta$ (figure 2.5 B&E). To obtain a profile likelihood of R, a grid of $\beta$ and $\mu$ were generated and the AIC of each pair of $\beta$ and $\mu$ is calculated. Then for each R, the minimum AIC value is plotted against $R$ (figure 2.5 C&F). The likelihood surface is visualized by a 2D contour plot (figure 2.7).

**Trajectory-based estimation method**

Trajectory-based method, also called trajectory matching or curve fitting, is used frequently to estimate parameters for dynamic systems. This method conducts the inference with a deterministic model assuming that the dynamic process is deterministic, and the observation error is the only cause of variation between trajectory modelled and the observed data. The ODE model with environmental transmission can be simulated using equations 2.2 to 2.4

To fit the deterministic trajectory to infection data, one needs to include stochasticity into the model by adding a random error to the trajectory values. The maximum likelihood method returns the log-likelihood of the data, given some combination

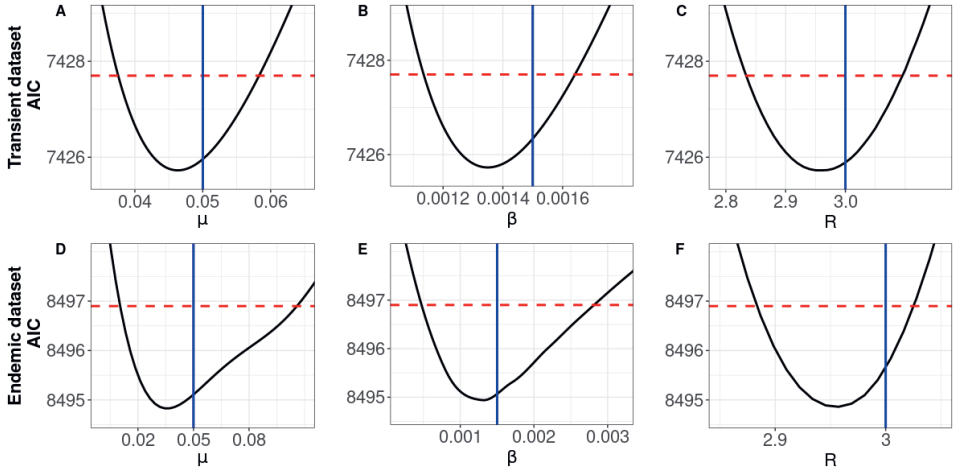


Figure 2.5: Profile likelihood for parameters by exposure-based estimation.

of parameters and then via optimizing algorithms it gives parameter pairs with the maximum likelihood. The observation errors can also be assumed to follow other distributions than Gaussian, such as Binomial, or Poisson. We used the POMP package using maximum likelihood estimation assuming Gaussian distribution [94] because it is the most commonly assumed distribution and most distributions generate a similar fit to data [77][95]. A Nelder-Mead search was used to optimize parameters. The likelihood function can be written as:

$$\mathcal{L}(\theta) = \prod_i \frac{1}{\sqrt{2\pi\sigma^2}} e^{\left(-\frac{(I_i - Y_i)^2}{2\sigma^2}\right)} \tag{2.14}$$

Where $I_i$ is the observed number of infectious at each time interval and $Y_i$ is the solution of ODE models and $\sigma$ is the variance for measurement. To profile over a parameter, we fix the value of that parameter at each of several values, then maximize the likelihood over the remaining parameter (figure 2.6). The likelihood surface is visualized by a 2D contour plot.

**Estimation results**

Using the exposure-based estimation method, we obtained accurate estimates for the transmission rate parameter ($\beta$), decay rate parameter ($\mu$) and the basic

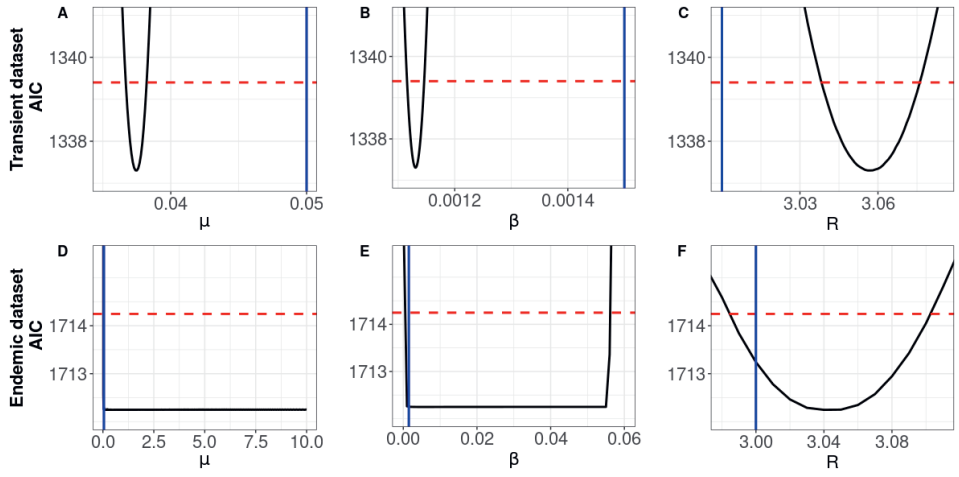


Figure 2.6: Profile likelihood for parameters by trajectory-based estimation. The first row (A, B, C) analysed transient phase and the second row (D, E, F) analysed the pseudo-endemic phase. In the different columns the profile likelihood of $\beta, \mu$ and $R$ are shown respectively. The blue solid lines represent the input parameter values and the intercepts of red dashed lines and black lines represent confidence bounds of the estimation by showing minimum AIC value plus 2.

reproduction ratio (R). The input values (blue lines in figure 2.5) fall inside the confidence bounds, which is where the red dashed lines (minimum AIC + 2) cross the profile likelihood, for both transient and pseudo-endemic phases. This can also be seen in the likelihood contour plot, where input parameters are well inside the contour plots (figure 2.7A&B). The pseudo-endemic phase yielded wider confidence bounds for both $\beta$ and $\mu$, compared to the transient phase.

The first row (A, B, C) analysed transient phase and the second row (D, E, F) analysed the pseudo-endemic phase. In the different columns the profile likelihood of $\beta, \mu$ and $R$ are shown respectively. The blue solid lines represent the input parameter values and the intercepts of red dashed lines and black lines represent confidence bounds of the estimation by showing minimum AIC value plus 2.

In comparison, the trajectory-based method performed worse in back-estimation of the parameters. While $\beta$ and $\mu$ estimated by trajectory-based method are still close to the input values in the transient phase dataset, the input values are actually outside the confidence bounds (figure 2.6 A, B, C). The confidence bounds and the likelihood contour (figure 2.7C) are both very narrow from the transient

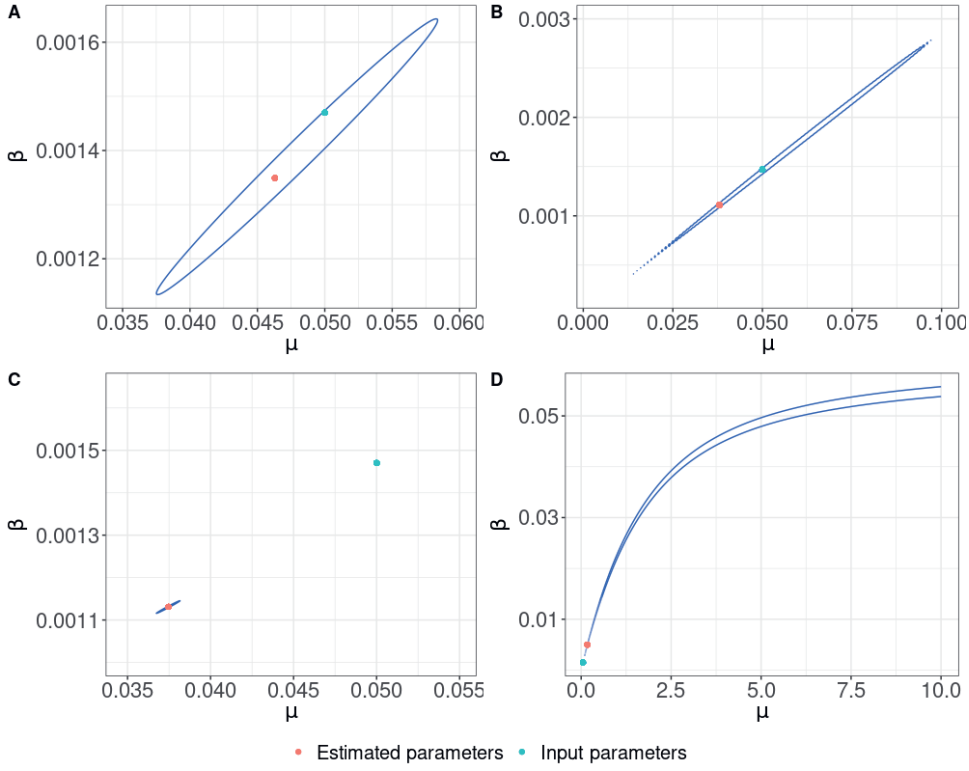


Figure 2.7: The 2D contour plots where the blue line ellipses show confidence bounds (minimum AIC value plus 2). (A) shows the contour plot for the exposure-based method with the transient phase and (B) with the pseudo-endemic phase. (C) and (D) show the contour plot for the trajectory-based method with the transient phase and the pseudo-endemic phase. The red dots show the estimated values for $\beta$ and $\mu$ and the blue dots represent the input values for $\beta$ and $\mu$.

phase dataset. For the pseudo-endemic phase dataset, both $\widehat{\mu}$ and $\widehat{\beta}$ have wide confidence bounds (figure 2.6 D, E) with an open contour plot (figure 2.7D) and hence parameters cannot be estimated back. Even though the reproduction ratio can be estimated, wrong estimates for $\widehat{\mu}$ and $\widehat{\beta}$ can form misleading information on the relative importance of direct and environmental transmission in a system.

### The comparison of two statistical methods

As we found that the exposure-based estimation performed better than the trajectory-based estimation (figures 2.5 and 2.6), we investigated the reason by calculating the autocorrelation for the residuals from the two statistical models (figure 2.8). To estimate the transmission parameters back, statistical models need to use the

autocorrelation information in infection data, because the transmission process is about the correlation in time between infectious individuals in the past and infections occurring later on. Therefore, residuals for a correctly fitting model should have no autocorrelation, because the statistical model should capture all the autocorrelation. We found that the residuals from the exposure-based method have no significant autocorrelation; this is the case for the transient as well as the pseudo-endemic phase (red bars in figure 2.8). However, the residuals from the trajectory-based method show high autocorrelation, which indicates that a large part of the autocorrelation information in the infection data is not captured by the trajectory-based method.

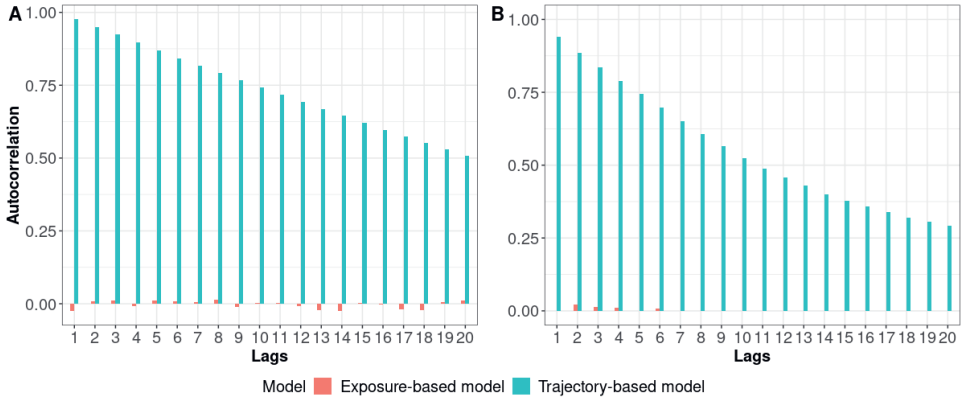


Figure 2.8: The autocorrelation of residuals. Red bars represent the autocorrelation of residuals from the exposure-based statistical model and blue bars from the trajectory-based statistical model. (A) shows the autocorrelation in the transient phase and (B) in the pseudo-endemic phase.

The exposure-based estimation method links the probability of infection to exposure using a dose-response equation, where the exposure is calculated from the observed historical number of infectious individuals. In this way, each observed datapoint can change the prediction of exposure-based estimation model in the future. The more recent observed data matter more for what happens in the next observation time step in the exposure-based method, leading to a higher autocorrelation in the infection data at smaller time lags. Therefore, the exposure-based method does use the autocorrelation information in the infection data and leaves no autocorrelation in residuals. In comparison, in the trajectory-based method, the trajectories are determined by varying the set of parameters and the possible initial infection data

and then the best fit trajectory is selected by comparing these different trajectories with observed data. Selecting best fit trajectory is only influenced by observed data in a way that it accounts for the uncertainty in observing each datapoint by using the correlations with all past and all future observations. The trajectory-based estimation method, therefore, cannot fully use the autocorrelation information in the data and thus autocorrelation remains present in the residuals.

### 2.2.5 Sensitivity analysis on transmission quantification

Sensitivity analysis was performed to test whether exposure-based estimation can estimate back $\beta$, $\mu$ and $R$ under scenarios with different input parameters in data simulation. There are three independent input parameters ($\alpha$, $\mu$ and $\beta$) during simulation. The recovery rate parameter ($\alpha$) is assumed to be known and not involved in parameter estimation nor sensitivity analysis. The decay rate parameter ($\mu$) is a relative value to the observation time unit. When the observation interval is too big compared to the value of the decay rate parameter, the pathogen dynamics occur fast and infection dynamics behave similarly to direct transmission [55]. Although the fast decay rate parameters could hamper the practical joint identifiability of $\beta$ and $\mu$ (see sensitivity analysis of $\mu$ in figure 2.9), this practical identifiability can be improved by increasing the observation intervals.

Therefore, here we present whether changing input transmission rate parameter $\beta$ would influence the estimation of $\beta$, $\mu$ and R. For each $\beta$, the other two input parameters $\alpha$, $\mu$ were fixed at the values shown in table 2.2. A dataset including the transient phase and the pseudo-endemic phase were simulated with 10 repeats for each dataset. The input values (red lines) fell within confidence bounds of estimation (figure 2.9). This means that the estimation of $\beta$, $\mu$ and $R$ is not sensitive to the choice of input $\beta$ in both transient phase and pseudo-endemic phase datasets. The exposure-based estimation method is robust for environmental transmission.

The sensitivity analysis for the trajectory-based method showed that estimates were not correct and different input parameters did not improve parameter estimations (see Supplement 2.4.2).

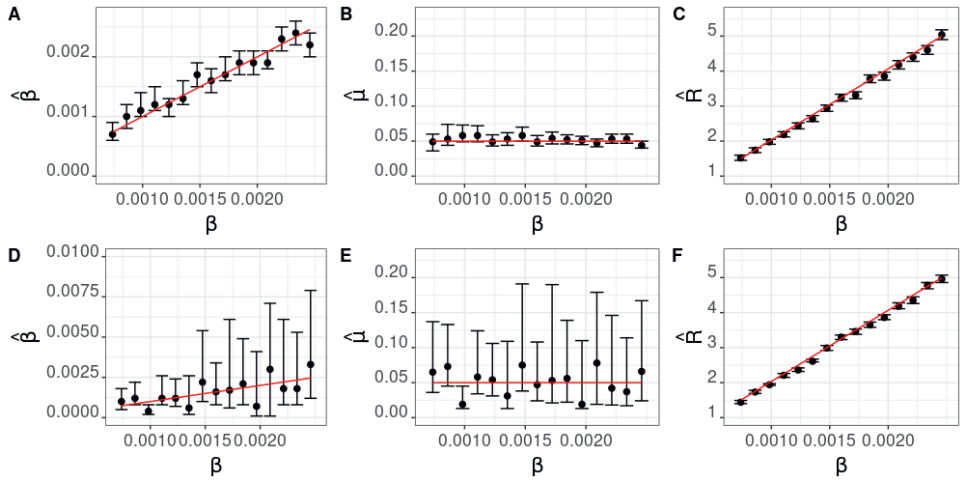


Figure 2.9: The sensitivity analysis on the impact of different input $\beta$ on parameters estimation ($\widehat{\beta}$,$\widehat{\mu}$ and $\widehat{R}$) by the exposure-based method. The first row (A, B, C) analysed transmissions from a transient phase while the second row (D, E, F) analysed transmission from a pseudo-endemic phase. (A, D) show parameter estimation for $\beta$, (B, E) for $\mu$ and (C, F) for $R$ among different datasets. The red solid lines represent the true parameter values. The dots represent the estimated parameters with the error bar.

### 2.2.6 Application: impact of disinfection and estimation of minimum disinfection frequency

An important aim of correctly estimating parameters is to correctly predict the effect of interventions by extrapolating models. We will now show an application of our approach, by quantifying the impact of an often-used control measure: routine disinfection. This intervention is one of the most important and standard preventive measures for all infectious diseases, but especially for diseases for which few other interventions are available e.g., norovirus in humans, African Swine fever in pigs, and antimicrobial resistant microorganisms in animals and hospitals. We derive the impact of routine disinfection on the reduction of $R_0$, using the environmental modelling approach presented in this paper. This analysis is done to illustrate that correctly estimated parameters are crucial for drawing correct conclusions on whether interventions targeted at the environment are sufficient to control an infectious disease.

When introducing routine disinfection with a frequency once every x days, the

original equilibrium breaks, and the number of infectious individuals decreases as the environmental contamination is reduced. The transmission dynamics gradually reach a new equilibrium where the total number of infectious individuals in x days is again the same as the number of recovered individuals. The environmental contamination $E(t)$ changes periodically from 0 after disinfection to a certain level until the next disinfection. The total exposure to the environmental contamination during this x days can be derived from equation 2.8 as $\frac{-1+e^{-\mu x}+\mu x}{-1+e^{-\mu}+\mu} I_t$. In the equilibrium stage, the total number of infections in an interval between two disinfection is therefore $\beta\frac{-1+e^{-\mu x}+\mu x}{-1+e^{-\mu}+\mu} I^*\frac{S^*}{N}$, where $I^*, S^*$ represent the number of infectious and susceptible individuals at the equilibrium. The total number of recovered individuals during the interval x is $\alpha I^* x$, which equals the number of new cases, leading to: $\beta\frac{-1+e^{-\mu x}+\mu x}{-1+e^{-\mu}+\mu} I^*\frac{S^*}{N} = \alpha I^* x$. Hence, we derive the effective reproduction ratio for after disinfection:

$$R_{disinfection} = \frac{N}{S^*} = \frac{-1+e^{-\mu x}+\mu x}{(-1+e^{-\mu}+\mu)x}\ \frac{\beta}{\alpha} \tag{2.15}$$

where $R_{disinfection}$ represents the effective reproduction ratio under a regime of disinfection. With estimates of decay rate and transmission rate parameters, one can predict the minimum regular disinfection frequency (Supplement 2.4.3).

We use an example to show how important the correct estimation of decay rate and transmission rate parameters is regarding predicting interventions. The example infection has a basic reproduction ratio $R = 3$ with the decay rate 0.1 per day (the lowest pink line in figure 2.10). In this infection, the disinfection impact is very effective, as a disinfection routine every 8 days would be sufficient to control this infection by bringing the $R$ below 1. However, with the wrong estimation of decay rate and transmission rate parameters given the correct estimation of $R$, the interpretation of disinfection impact can be very incorrect and misleading. For example, if the decay rate is estimated as 3 per day (the highest line in figure 2.10), the disinfection routine every 8 days would not be sufficient because it only has a marginal reduction on $R$ ($R_{disinfection} = 2.7$). Even with a daily disinfection routine, the $R_{disinfection}$ is still above 1, which leads to the wrong conclusion that disinfection is not effective and is not able to control this infection. Therefore, only with the

right estimation of decay rate parameter and transmission rate parameter can we predict interventions correctly.

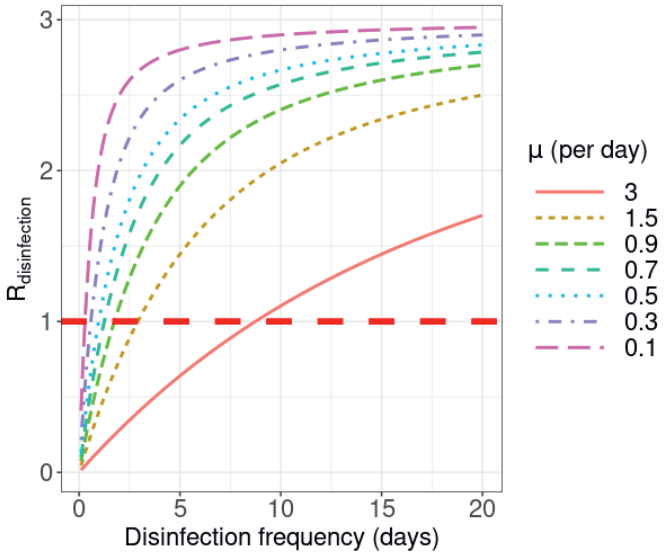


Figure 2.10: The effective reproduction ratio after disinfection ($R_{disinfection}$) under different disinfection frequencies. The different colour lines showed transmissions with different decay rate, but all the transmissions have the same basic reproduction ratio ($R = 3$). The intercept of $R_{disinfection}$ with the red dashed line ($R = 1$) represents the minimum required disinfection frequency to bring $R$ below 1.

## 2.3 Discussion

A better understanding of environmental transmission is of vital importance for assessing and predicting the impact of intervention measures. Although risk factor analysis has been widely used to assess the impact of interventions [69–71], it has limitations in predicting future risks or risks under different scenarios. Hence, dynamic models have often been preferred [68]. However, dynamic models for environmental transmission have difficulties in jointly identify underlying parameters. Therefore, this paper aims to improve the estimation for environmental transmission models by introducing a novel scaling method and using calculated exposure for a better understanding of environmental transmission and prediction of environmental interventions.

Our novel scaling method uses a continuous decay rate parameter to distinguish

more direct from more environmental transmission. A continuous decay rate aligns with the reality that direct and environmental transmission lie along a continuum. Direct transmission can be seen as a special case of environmental transmission where pathogens have an extremely high decay rate in the environment [77, 96–99]. For example, droplets transmission, often seen as direct transmission, can be modelled as environmental transmission with pathogens decaying in a few minutes [100] In addition to the unification of direct and environmental transmission models, transmission model with this scaling method still provides the relative contribution of the environment and the direct contact to the transmission.

In comparison, other studies usually assume two transmission routes when the environment is involved [77, 80]. One route accounts for the transmission when susceptible and infectious individuals are present at the same time, and another route accounts for environmental transmission routes (or so-called indirect routes) [77, 80, 82]. However, with only infection data, the estimations might not represent the true mechanisms and reproduction ratio $R$ [81]. This can be understood intuitively by an example: an animal getting infected directly by licking another infectious animal cannot be distinguished from licking excreta that have been shed very recently by infectious animals [101]. Therefore, our method of unifying the undistinguishable two routes provides a good alternative to understanding the transmission mechanism.

We show that our exposure-based estimation can jointly estimate transmission rate and decay rate parameters. In comparison, the commonly used trajectory-based estimation method failed to correctly identify the parameter values, as the true parameters often fell outside the confidence bounds. This confirms the findings of [81] which also showed that this trajectory-based model cannot estimate back the transmission parameters and $R$. However, our study is the first to solve this issue by using a novel exposure-based estimation method in environmental transmission. In addition, our sensitivity analysis also showed the robustness of the exposure-based estimation and the limitation that observations need to be frequent enough relative to the decay rate parameter (Supplement 2.4.1)

The exposure-based method performs better because it makes use of autocorrelation by giving the correct weight to data from previous observation periods. One may

argue that our infection data are simulated with autocorrelation which is not a compulsory choice. The choice to model the transmission process in this way is based on the notion that the transmission process in real life is all about the correlation in time and space, due to the nature of the spread of infections and infectious particles in time and space. The number of new cases is assumed to depend on the actual number of infectious individuals in the previous time points through environments, which has been used in many stochastic simulation models [91, 102, 103].

This model assumes the independent action of each pathogen which means each pathogen has the same probability of infecting other individuals. The underlying dose-response function is the exponential function, as can be seen for example from the likelihood (equation 2.3), while other dose-response functions such as linear, exact-Poisson, approximate beta-Poisson, and log-normal functions can be assumed but were not studied in this paper [78]. The transmission rate, decay rate and shedding rate parameters are assumed as constant in this model, while this is unlikely to hold for many environmentally transmitted pathogens [104]. Future research is needed for example for the parameterization of the nonconstant decay rate.

Furthermore, we show how transmission models with correct parameter estimation can be extrapolated to predict interventions correctly. To illustrate this, we derived the formula to predict the maximum disinfection impact on reducing the reproduction ratio. This prediction can provide important suggestions on infection control. For example, for pathogens with a high decay parameter in the environment, the disinfection alone may not be able to bring the $R_{disinfection}$ below 1 regardless of high disinfection frequency. Thus, other interventions that target removing the infectious individuals from the environment such as quarantine or culling infectious animals are needed. On the other hand, for pathogens with a low decay parameter in the environment, the interventions such as test and removal, quarantine may not be able to bring $R$ below one 1 and disinfection and environmental interventions that remove pathogens in the environment are of crucial. Only with the correct estimation of transmission rate and decay rate parameters, can we predict interventions correctly and select effective control measures.

## 2.4 Supplement

### 2.4.1 The impact of decay rate on infection dynamics

When the decay rate is relatively large compared with the observation time unit, the pathogens' dynamics is so fast that they are similar to the direct transmission and can be difficult to be distinguish from the direct transmission and estimate the environmental impact. As shown in figure 2.11, when the decay rate is large, infection dynamics look very similar and can hardly be distinguished from each other.

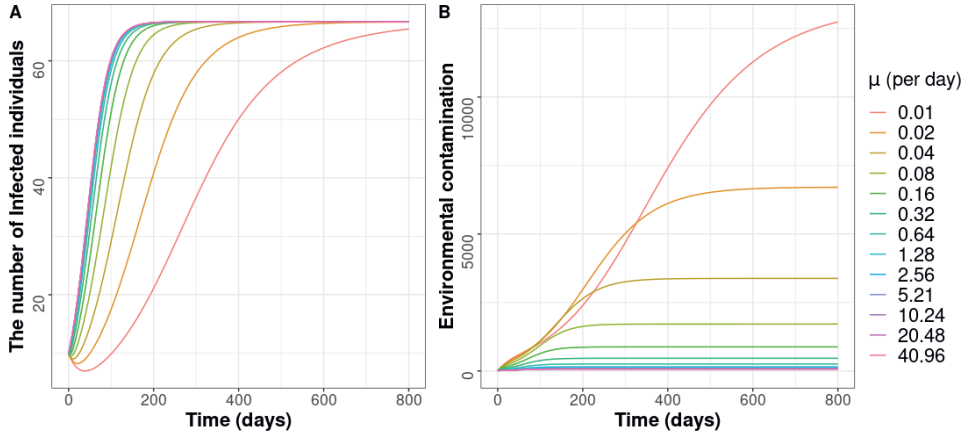


Figure 2.11: Infection dynamics and environmental contamination modelled via a deterministic differential ordinary equation model comparing dynamics for different decay rate parameters with fixed $R$ ($R = 3$).

### 2.4.2 Sensitivity analysis of decay rate parameter on parameter estimation

We also explore the decay rate parameter's impact on parameter estimation. $R$ and $\alpha$ were fixed at the value shown in table 2.2, while $\mu$ was set at multiple values ranging from 0 to 1 per time unit and $\beta$ was changing accordingly to allow a fixed $R$. The similar procedure of simulation and parameter estimation were performed as described in section 2.3. In datasets including transient dynamics, the exposure-based estimation can identify $\beta$ and $\mu$ especially when $\mu$ is smaller than 0.1 per time unit (per day in our simulation). When pathogens decay fast or the observation time step is large, the decay rate parameter ($\mu$) per observation time

unit increases, which increases the difficulty in identifying these two parameters, although the reproduction ratio can still be estimated accurately. Hence, increasing the frequency of observation, can improve the practical identifiability issue for $\mu$ and $\beta$.

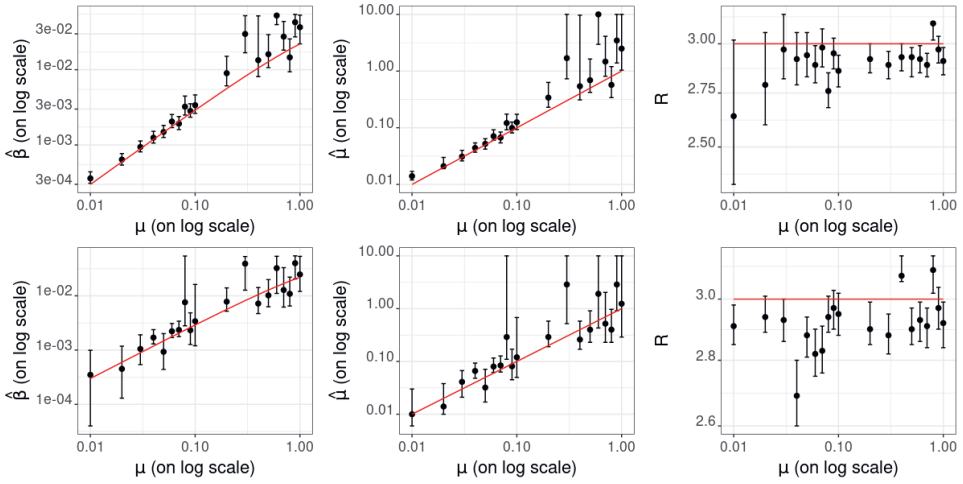


Figure 2.12: The sensitivity analysis on the impact of $\mu$ on parameters estimation ($\widehat{\beta}$,$\widehat{\mu}$ and $\widehat{R}$) by exposure-based method.

The first row analysed transmissions from a transient phase while the second row analysed transmission from a pseudo-endemic phase. The first column shows parameter estimation for $\beta$, the second column for $\mu$ and the third column for $R$ among different datasets. The red solid lines represent the true parameter values. The dots represent the estimated parameters with the error bar.

### 2.4.3 Sensitivity analysis of transmission rate parameters on parameter estimation by trajectory-based estimation

Although trajectory-based estimation does not perform well. We also did the sensitivity analysis to show whether different input $\beta$ would improve the estimation. The performance of trajectory-based estimation is robust and similar as discussed in section 2.3. $\beta$ and $\mu$ cannot be estimated accurately as the true parameters mostly fall outside of the confidence bounds (figure 2.13).

The first row (A, B, C) analysed transmission with a transient phase while the

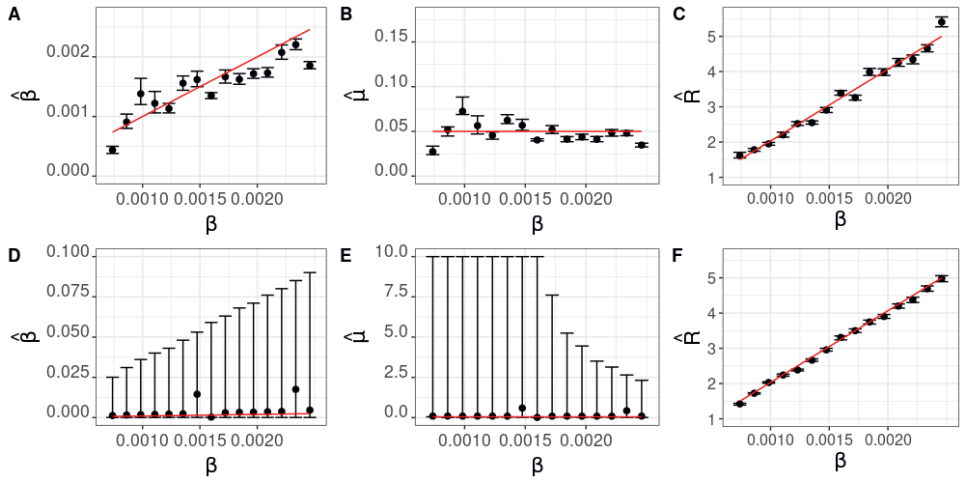


Figure 2.13: The sensitivity analysis on the impact of $\beta$ on parameters estimation ($\widehat{\beta}$,$\widehat{\mu}$ and $\widehat{R}$) by trajectory-based method.

second row (D, E, F) analysed transmission from the pseudo-endemic phase (A, D) show parameter estimations for $\beta$, (B, E) for $\mu$ and (C, F) for $R$ among 10 different datasets. The red solid lines represent the true parameter values (for the pseudo-endemic phase these are the same as in the transient case only the scale in the graph differs). The dots represent the estimated parameters with the error bar.

### 2.4.4 The minimum regular disinfection frequency

The required minimum frequency of the disinfection, which can be derived by letting $R_{disinfection}$ smaller than 1, depends on the pathogens persistence, i.e. decay rate parameter, and the transmission rate parameter. By letting equation 2.15 smaller than 1, we derived:

$$x < \frac{\alpha}{\beta\mu}(-1+e^{-\mu}+\mu) + \frac{1}{\mu}(LambertW(-e^{-\frac{\alpha}{\beta}(-1+e^{-\mu}+\mu)-1})+\frac{1}{\mu} \tag{2.16}$$

### 2.4.5 Code availability

The code for generating data in this study is available at http://git.wur.nl/chang025/environmental-transmission-model_epidemics

## 2.5 Acknowledgment

We thank Nienke Hartemink for her very helpful discussion and suggestions, which led to considerable improvements of the manuscript.

# 3



# bTB Environmental transmission between cattle and badger, and R Mapping

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**Abstract**

Bovine tuberculosis (bTB), caused by *Mycobacterium bovis*, is one of the most challenging and persistent One Health issues in many countries worldwide. In several countries, bTB control is complicated due to the presence of wildlife reservoirs of infection, i.e. European badger (*Meles meles*) in Ireland and the UK, which can transmit infection to cattle. However, a quantitative understanding of the role of cattle and badgers in bTB transmission is elusive, especially where there is spatial variation in relative density between badger and cattle. Moreover, as these two species have infrequent direct contacts, environmental transmission is likely to play a role, but the quantitative importance of the environment has not been assessed. Therefore, the objective of this study is to better understand bTB transmission between cattle and badgers via the environment in a spatially explicit context and to identify high-risk areas.

We developed an environmental transmission model that incorporates both within-herd/territory transmission and between-species transmission, with the latter facilitated by badger territories overlapping with herd areas. Model parameters such as transmission rate parameters and the decay rate parameter of *M. bovis* were estimated by maximum likelihood estimation, using the infection data from badger and cattle collected during a four-year badger vaccination trial. Our estimation showed that the environment can play an important role in the transmission of bTB, with a half-life of *M. bovis* in environment around 177 days. Based on the estimated transmission rate parameters, we calculate the basic reproduction ratio ($R$) within a herd, which reveals how relative badger density dictates the transmission. In addition, we simulated transmission in each small local area to generate a first between-herd $R$ map under scenarios with and without badger vaccination.

## 3.1 Introduction

Bovine tuberculosis (bTB) is one of the most complicated, persistent and expensive One Health issues globally. While its primary impact is on bovines, it can infect many other mammals, including human and wildlife animals [105]. bTB is very persistent in livestock globally, due to the involvement of several wildlife species in bTB transmission. Notable examples include badgers in UK and Ireland, brushtail possums in New Zealand, wild boars in Spain [106], red deer in Austria [107] and African buffalo in South Africa [108]. Although pasteurization of milk can reduce human infection, *Mycobacterium bovis* is estimated to cause ~ 10% of total human TB cases in developing countries [109, 110]. The impact of bTB extends beyond public health with substantial economic consequences, costing approximately USD 3 billion globally [111]. In the Republic of Ireland (bTB) alone, more than 15,000 cattle have been removed annually over the last decade. In 2020, the total programme expenditure cost was €97 million, and is rising year-on-year [112].



The Irish national bTB eradication programme is underpinned by a test and removal strategy, leading to the slaughter of all cattle that are positive to the single intradermal comparative tuberculin test (SICTT), performed at least annually in each Irish herd [45]. This strategy has been successful in eradicating bTB in some countries such as Australia and some northern European countries [34]. In Ireland, however, progress has stalled in the national eradication programme [40, 113], at least in part due to the presence of other reservoirs of infection, including badgers (*Meles meles*; [44]). Badger vaccination has proved effective at reducing badger susceptibility, both in pen and field studies [44, 50, 52], and a badger vaccination program is now being progressively incorporated in national programme [114, 115].

A number of different approaches have been used in recent studies to investigate the role of badger in bTB transmission and persistence. In ROI, badger culling trials resulted in a significant decrease in cattle incidence in areas of badger culling compared to reference areas [44, 116, 117]. In Britain, the Randomised Badger Cull Trial (RBCT) found evidence for decreased risk of bTB breakdown in proactive cull areas, however post-hoc analysis suggested that a transitory increased risk to neighbouring areas could occur [118]. Using a case-control design, badger relative abundance in the vicinity of cattle herds was identified as an important

risk factor for bTB herd breakdown risk in Britain [119] and Ireland [120]. In addition, studies of road-killed badgers found strong evidence that badgers and cattle are colonized by the same *M. bovis* strain in the same area [121, 122]. Most recently, genomic epidemiology has been used to understand transmission direction between species, generally suggesting that within-species transmission is more common than between-species transmission in study areas [123–126]. The relative importance of cattle and badgers appears to be context-specific [25, 124, 126, 127]. Although these studies provide important insight that badger bTB is associated with cattle bTB, a quantitative understanding of how relative badger density impacts the bTB transmission in this cattle and badger episystem is still lacking.

The main transmission routes of bTB are believed to be droplets, aerosols and faecal to oral transmission [20]. These three transmission mechanisms are intrinsically similar involving an environmental vehicle such as droplets, aerosols, faeces and urine etc. *M. bovis*-laden droplets and aerosols may also settle onto pastures and contribute to subsequent environment to oral transmission. The distinction between these transmission routes lies in the duration between the shedding moment and the time point of inhaling or ingesting *M. bovis*. Buddle et al. [128] have proposed a role for environmental transmission as an explanation for the variable efficacy observed in an overview of vaccine trials for the control of tuberculosis in cattle, wildlife and humans. *Mycobacterium tuberculosis* complex (MTBC) has been demonstrated to be present at the wildlife-environment-livestock interface in Spain [129] and Italy [130] and more specifically *M. bovis* has been detected in badger faeces in the UK [131] and experimentally infected cattle [132]. In recent global positioning system (GPS) studies, badgers barely have direct contact with cattle, suggesting that environmental transmission may indeed play an important role in bTB transmission [133, 134]. However, to this point the quantitative importance of bTB transmission via environment has barely been considered [54]. Therefore, this study aims to gain a better understanding of the quantitative role of badgers and cattle in bTB transmission via environmental transmission and quantify the impact of relative badger density on bTB transmission in a spatial context. With this information, we can identify high-risk areas for transmission where bTB might sustain locally and assess whether badger vaccination along with the test-and-removal strategy is sufficient to control transmission in different areas.

## 3.2 Materials and methods

In this study, we aim to understand the local transmission of bTB in a cattle and badger system. To this end, we develop an environmental transmission model that incorporates both within-herd/territory transmission and between-species transmission.

In Section 3.2.1, we present the structure of an environmental transmission model for the cattle and badger system. The model parameterisation, which is partially drawn from existing literature, is described in Section 3.2.2, and the estimation of transmission and decay rate parameters from time-series infection data is presented in Section 3.2.3. The infection data used in the estimation are explained in Section 3.2.4. With the estimated parameters, we use the next generation matrix (NGM) method to calculate the basic reproduction ratio for the within-herd transmission and investigate the impact of the relative badger density on the within-herd $R$. Furthermore, we use simulation to generate between-herd $R$ maps (Section 3.2.5).



### 3.2.1 Model description

We developed a stochastic compartmental model with environmental transmission for a cattle and badger system. In this system, a herd of cattle and a social group of badgers refer to the animals of interest, whereas a farm and a badger territory each refer to a spatial unit. A farm is a spatial location for a herd, with all cattle in the herd registered to the same herd identifier. In Ireland, a farm can consist of several fragments of land, which can be spatially dispersed, and we assume that cattle spend time on each fragment proportionally to its area. A badger territory is an area where a social group of badgers primarily resides, which usually contains a main sett and several outlier setts. The model incorporates a geographic overlay of these two spatial units, where the between-species transmission and the spatial spread are assumed to occur.

#### A completely shared area with one farm and one badger sett territory

To explain this environmental transmission model, we first look at a conceptual spatial structure in a small local area where one farm and one badger territory are completely overlapping (figure 3.1). In this local area, individual badgers from one social group and individual cattle from one herd share the same environment (light

blue circle in figure 3.1). Cattle, unvaccinated badgers, and vaccinated badgers are the three types of animals in the model, abbreviated as c, ub and vb in subscripts. Vaccinated and unvaccinated badgers can exist in the same area because of the ongoing vaccination programme, and they are assumed to differ in terms of susceptibility, but not infectivity [52]. All individual animals are classified into 3 compartments: susceptible (S), latent (O), and infectious (I). Susceptible individuals can get infected by the same species or the other species at a certain transmission rate, after being exposed to the *M. bovis*. When infection become established, animals can become infectious, although the length of the latent period is controversial. Infectious animals can shed *M. bovis* into the environment of their spatial units. We assume that *M. bovis* in the environment (denoted as $E_c, E_b$) are distributed evenly in the farm and the badger territory, which is the same area in this example (light blue circle in figure 3.1). Since the vaccination is assumed not to reduce badgers' infectivity [52], the amount of *M. bovis* shed by infectious badgers is represented by compartment $E_b$, regardless of whether the infectious badgers are vaccinated or unvaccinated.

The transmission rate from cattle to cattle is $\beta_{c,c} S_c \frac{E_c}{N_c}$. The $\beta_{c,c}$ represents the cattle transmission rate parameter per contact with one unit of $E_c$ per day. Here, we use cattle number $N_c$ to represent the area size, hence for each susceptible bovine, the probability that the contact with $E_c$ is made is equal to $\frac{E_c}{N_c}$. The same rules apply to all the other transmission rates. For example, the transmission rate from badger to cattle is $\beta_{b,c} S_c \frac{E_b}{N_c}$ in which the probability that the contact with $E_b$ is made for each susceptible badger is $\frac{E_b}{N_c}$ . We use one denominator in both cattle and badgers to have a unified representation of the area in this two-host system. In transmission rate parameter $\beta_{b,ub}$ and $\beta_{b,vb}$, we do not distinguish whether the infection source badger is vaccinated or unvaccinated (the first b of the subscript), because the vaccination is assumed not to reduce the infectivity and environmental contamination from the vaccinated or unvaccinated badgers is not distinguished in $E_b$.

Infected animals (O compartment) can develop further into infectious state (I compartment) at a rate of $\lambda_c I_c$ and $\lambda_b I_b$. Infectious animals are removed at a rate of $\alpha_c I_c$ and $\alpha_b I_b$, caused by cattle test-and-removal and by bTB-induced badger death

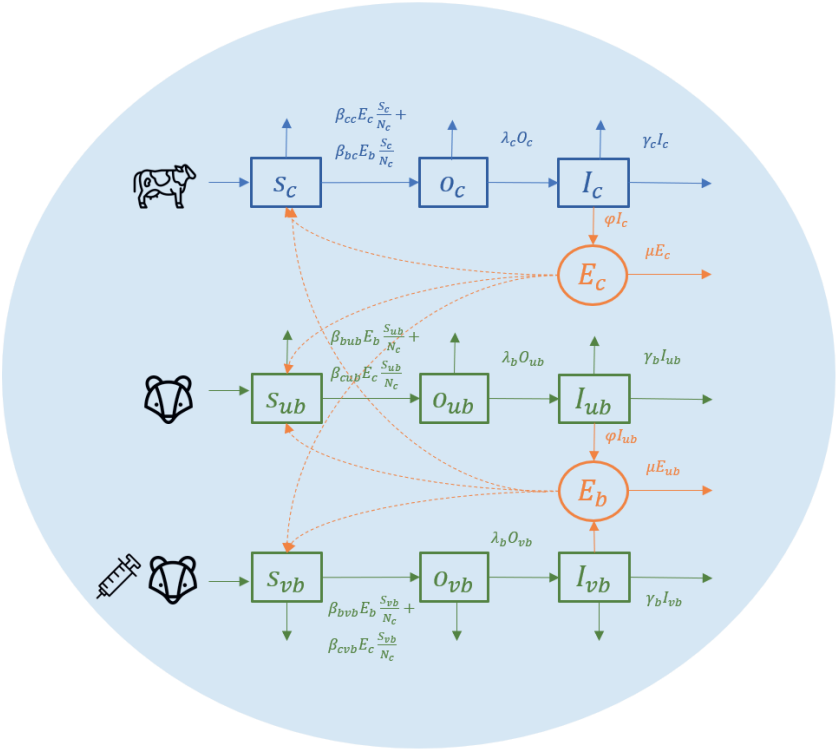


Figure 3.1: A conceptual diagram of within-herd/territory transmission in a completely shared area with one farm and one badger sett territory

respectively. We assume the background death rate parameters are equal to the birth rate of animals ($\alpha_c$, $\alpha_b$) and all newborn animals are susceptible.

Infectious animals can shed *M. bovis* into the environment where *M. bovis* subsequently decays. The shedding and decay of *M. bovis* is modelled deterministically:

$$\frac{dE_{c(i)}}{dt} = \varphi I_{c(i)} - \mu E_{c(i)} \tag{3.1}$$

$$\frac{dE_{b(j)}}{dt} = \varphi I_{ub(j)} + \varphi I_{vb(j)} - \mu E_{b(j)} \tag{3.2}$$

where $i$, $j$ denotes the index for farm and badger territories respectively. We assume

that the decay of *M. bovis* has the same decay rate parameter $\mu$ despite the different infection source and strains ($\mu E_c$ for cattle and $\mu E_b$ for badgers). The shedding rate parameter $\varphi$ is scaled as a function of the decay rate parameter ($\frac{\mu^2}{-1+e^{-\mu}+\mu}$) (Chapter 2). The reason for this scaling is that the shedding rate parameter $\varphi$ and the transmission rate parameter $\beta$ are structurally not jointly identifiable from infection data [53]. Therefore, we choose to fix the shedding rate parameters and estimate the different transmission rate parameters from infection data (more details in equation 3.5 and 3.6). With the standardisation ($\varphi = \frac{\mu^2}{-1+e^{-\mu}+\mu}$), the transmission rate parameters represent the transmission rate from one typical infectious individual to a susceptible individual during one interval starting in a clean environment (Chapter 2).



**Many farms and many badger territories that partially overlap**

We then consider the spatial structure of badger territories and farms in the full model. Badger territories can overlap with several farms, hence badgers act as vectors that facilitate between-herd transmission. Similarly, herds can overlap with several badger territories and facilitate the transmission between different badger social groups (figure 3.2). To account for the spatial structure in the model, the exposure from the other species is weighted by the ratio of (the total area of overlap between farms and badger territories) and (the total area of farms or badger territories). The denominator in the transmission rate for badgers is also adjusted with the weighted cattle number as a representation of the badger territory area. The ordinary differential equation version of the transmission is presented in equation 3.3 and 3.4.

$$\frac{dO_{c(i)}}{dt} = \beta_{c,c} S_{c(i)} \frac{E_{c(i)}}{N_{c(i)}} + \beta_{b,c} S_{c(i)} \frac{\sum_{j=1,..k} E_{b(j)} \frac{A_{(ij)}}{AT_{(j)}}}{N_{c(i)}} - \lambda_c O_{c(i)} \tag{3.3}$$

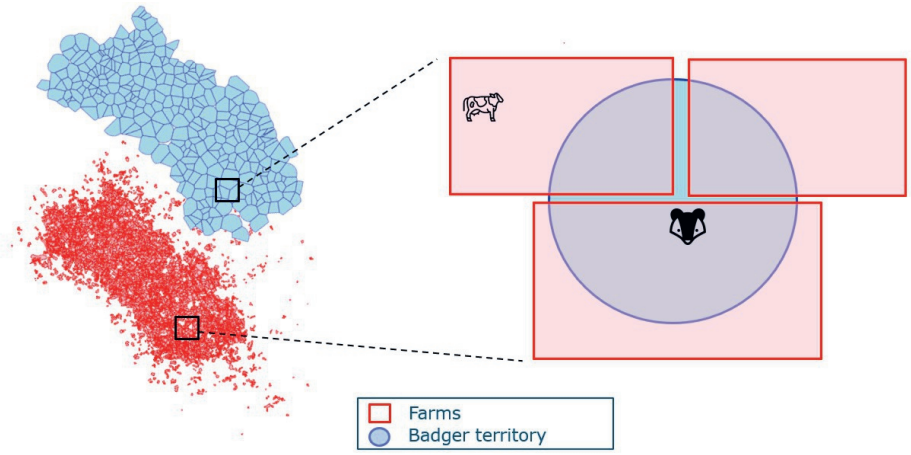


Figure 3.2: An example of the spatial structure of farms and badger territories. The blue map represents badger territories, and the red irregular shapes delineate farm boundaries.

$$\frac{dO_{b(j)}}{dt} = VC\left(\beta_{b,vb} S_{vb(j)} \frac{E_{b(j)}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,vb} S_{vb(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}\right) + (1-VC)\left(\beta_{b,ub} S_{vb(j)} \frac{E_{b(j)}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,ub} S_{vb(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}\right) - \lambda_b O_{b(j)} \tag{3.4}$$

Farms and badger territories are the two spatial units in the model where $i, j$ denotes the index for farm and badger territories respectively. $A_{(ij)}$ denotes the total area of overlap between farm $i$ and territory $j$. $\frac{A_{(ij)}}{AF_{(i)}}$ represents the proportion of farm $i$ that overlaps with territory $j$. Similarly, $\frac{A_{(ij)}}{AT_{(j)}}$ is the proportion of territory $j$ that overlaps with farm $i$.

Cattle on farm $i$ can get infected by *M. bovis* on the farm excreted by cattle ($E_{c(i)}$) at rate $\beta_{c,c} S_{c(i)} \frac{E_{c(i)}}{N_{c(i)}}$ or excreted by badgers whose territories overlap with the farm $i$ at rate $\beta_{b,c} S_{c(i)} \frac{\sum_{j=1..k} E_{b(j)} \frac{A_{(ij)}}{AT_i}}{N_{c(i)}}$. Multiple badger territories ($j = 1..k$) can overlap with farm $i$, so the contribution from these territories ($j = 1..k$) are summed. For each territory j, only the part of the territory that is located inside farm $i$ can pose a

threat on infecting cattle, hence each $E_{b(j)}$ is adjusted to $E_{b(j)}\frac{A_{(ij)}}{AT_i}$.

Similarly, badgers can get infected by badgers in their own territory $j$ or by cattle in farms that overlap with $j$. As mentioned in Section 3.2.1, we use a unified representation of the area, namely the number of cattle in that area. Therefore, the area of badger territory is represented by the weighted number of cattle as $\sum_{i=1..m} N_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}$, as territory j overlaps with different farms ($i = 1..m$). A proportion of the badgers are vaccinated, denoted as $VC$ (vaccination coverage). Vaccinated badgers are assumed to have reduced susceptibility but the same infectivity as the unvaccinated badgers. Therefore, transmission from infectious badgers to vaccinated badgers is modelled as $(VC)\beta_{b,vb}S_{vb(j)}\frac{E_{b(j)}}{\sum_{i=1..m} N_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}}$ and transmission from infectious badgers to unvaccinated badgers as $(1-VC)\beta_{b,ub}S_{ub(j)}\frac{E_{b(j)}}{\sum_{i=1..m} N_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}}$. For cattle-to-badger transmission, only part of farm $i$ is located inside the badger territory j, so $E_{c(j)}$ is adjusted with $E_{c(j)}\frac{A_{(ij)}}{AF_i}$. Therefore, the cattle-to-badger transmission rate is denoted as $(VC)\beta_{c,vb}S_{vb(j)}\frac{\sum_{i=1,..m} E_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}}{\sum_{i=1..m} N_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}}$ for vaccinated badgers and $(1-VC)\beta_{c,ub}S_{ub(j)}\frac{\sum_{i=1,..m} E_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}}{\sum_{i=1..m} N_{c(i)}\frac{A_{(ij)}}{AF_{(i)}}}$ for unvaccinated badgers.

### 3.2.2 Model parameterisation

There are 14 parameters in this model. Six model parameters were estimated from the literature (table 3.1). The details on explanation and references for those parameters can be found in Supplement 3.5.1. In addition, transmission rate and the decay rate parameters of *M. bovis* in the environment are estimated by fitting time-series infection data into a dose-response function (Section 3.2.3).

Table 3.1: Model parameters

| Parameter | Description | Value |
|---|---|---|
| $\beta_{c,c}$ | Transmission rate parameter from cattle to cattle | estimated |
| $\beta_{b,c}$ | Transmission rate parameter from badges to cattle | estimated |
| $\beta_{b,ub}\frac{N_b}{N_c}$ | Transmission rate parameter from badger to unvaccinated badger | estimated |
| $\beta_{c,ub}\frac{N_b}{N_c}$ | Transmission rate parameter from cattle to unvaccinated badger | estimated |
| $\beta_{b,vb}\frac{N_b}{N_c}$ | Transmission rate parameter from badger to vaccinated badger | estimated |
| $\beta_{c,vb}\frac{N_b}{N_c}$ | Transmission rate parameter from cattle to vaccinated badger | estimated |
| $\varphi$ | The shedding rate parameter of *M. bovis* | standardised |
| $\mu$ | *M. bovis* decay rate parameter | estimated |
| $1/\gamma_c$ | Infectious period for cattle | 101 days |
| $1/\gamma_b$ | Infectious period for badgers | 365 days |
| $1/\lambda_c$ | Latent period for cattle | 1.8 days |
| $1/\lambda_b$ | Latent period for badgers | 90 days |
| $\alpha_c$ | The cattle background death rate | 9.13e-4 $day^{-1}$ |
| $\alpha_b$ | The badger natural death rate | 7.52e-4 $day^{-1}$ |

### 3.2.3 Statistical analysis

We estimate transmission rate and decay rate parameters by fitting time series infection data into the model. The core of this method is to relate the exposure to hazards and the hazards to the infection probability (Chapter 2). We first reconstruct the exposure in this two-host environmental transmission model and then fit the

cattle and badger infection data and exposure to the statistical model to estimate transmission rate and decay rate parameters.

**Reconstruction of exposure**

From equation 3.1, we derive the environmental contamination ($E(t)$) as a function of time and the number of infectious individuals (equation 3.5). The exposure to the environmental contamination during one time interval is the integral of $E(t)$ as $\int_0^1 E(t|I_t, E_0)$ shown in equation 3.6.

$$E(t|I_t, E_0) = \frac{\left(1 - e^{-t\mu}\right)\mu}{-1 + e^{-\mu} + \mu} I_t + e^{-t\mu} E_0 \tag{3.5}$$

$$\int_0^1 E(t|I_t, E_0) \; = I_t \; + \frac{1 - e^{-\mu}}{\mu} E_0 \tag{3.6}$$

Here, $E_0$ denotes the environmental contamination of at the start of an interval and $I_t$ denotes the number of infectious individuals (cattle or badgers) during this interval. These equations were used to construct $E_c$ and $E_b$ and exposure by integrating on each farm and territory.

**Likelihood function**

The number of new cases over each observation time interval $(\tau, \tau + \Delta)$ follows a binomial distribution with a binomial total susceptible individuals number at each time interval. The probability used in the binomial distribution is the probability of getting infected. From equation 3.3-3.4, the probability of getting infected can be derived for cattle and badgers respectively as:

$$P_c = 1 - e^{-(\beta_{c,c} \frac{\int_\tau^{\tau+\Delta} E_{c(i)}(t|I_{c(i)\tau}, E_{c(i)}(\tau))dt}{N_{c(i)}} + \beta_{b,c} \frac{\sum_{j=1..k}(\int_\tau^{\tau+\Delta}(\frac{E_{b(j)}(t|I_{b(j)\tau}, E_{b(j)}(\tau)) * A_{(ij)}}{AT_{(j)}})dt)}{N_{c(i)}}} \tag{3.7}$$

$$P_{ub} = 1 - e^{-(\beta_{b,ub} \frac{\int_\tau^{\tau+\Delta} E_{b(j)}(t|I_{b(j)\tau}, E_{b(j)}(\tau))dt}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AT_{(i)}}} + \beta_{c,ub} \frac{\sum_{i=1..m}(\int_\tau^{\tau+\Delta}(E_{c(i)}(t|I_{c(i)\tau}, E_{c(i)}(\tau)) \frac{A_{(ij)}}{AT_{(i)}})dt)}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AT_{(i)}}})} \tag{3.8}$$

$$P_{vb} = 1 - e^{-(\beta_{b,vb} \frac{\int_{\tau}^{\tau+\Delta} E_{b(j)}(t|I_{b(j)\tau}, E_{b(j)}(\tau))dt}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,vb} \frac{\sum_{i=1..m} (\int_{\tau}^{\tau+\Delta} (E_{c(i)}(t|I_{c(i)\tau}, E_{c(i)}(\tau)) \frac{A_{(ij)}}{AF_{(i)}})dt)}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}})} \tag{3.9}$$

Where $I_{c(i)\tau}$ , $I_{ub(j)\tau}$ and $I_{vb(j)\tau}$ represent the $I_c$ at farm I, $I_{ub}$ and $I_{vb}$ at territory j at the beginning of $(\tau, \tau + \Delta)$. $I_{c(i)\tau}$, $I_{ub(j)\tau}$ and $I_{vb(j)\tau}$ are integers and change discretely in jumps of 1. $E_{c(i)}(\tau)$ and $E_{b(j)}(\tau)$ represent $E_{c(i)}$ and $E_{b(j)}$ at time $\tau$. $E_{c(i)}(\tau)$ and $E_{b(j)}(\tau)$ changes continuously.

The likelihood as a function of transmission rate parameters and decay rate parameters is given by:

$$L(\theta) = \prod_{x} (P)^{cases_x} (1 - P)^{(S_x - cases_x)} \tag{3.10}$$

Where $P$ represents either $P_c$, $P_{ub}$ or $P_{vb}$ from equation 3.7- 3.9.

### 3.2.4 Data

The infection data and geographic data for cattle and badgers are extracted to quantify parameters as described in Section 3.2.3. The new cases in each observation interval are used to calculate the probability of infection in each interval in equation 3.7- 3.9 and the prevalence at the beginning of each observation time interval in each spatial unit is used to reconstruct the exposure as described in Section 3.2.3.

#### Badger data

The badger vaccination trial ran from 2009 to 2013 in the Kilkenny area [49]. A 750 square kilometre study area was divided into 3 zones (A, B, C) from north to south. Badgers were captured using cages or restraints. Badger setts were identified and their locations recorded. Blood samples were collected at each capture and tested using ELISA [136]. Captured badgers were assigned to the sett closest to where they were trapped, with most capturing taking place directly outside sett entrances. All the captured badgers in zone A and 50% of the captured badgers in zone B

received a placebo. Half of the captured badgers in zone B and all the captured badgers in zone C received oral BCG vaccine (Danish strain 1331, at dose 108 cfu).

Details of the badger infection dataset from the vaccination trial and the location of badger territories were described elsewhere [52, 137]. In total, there were 1759 trapping records. Each record contains the information from the trapping of a single badger: badger ID, sett ID, infection status, date of examination, vaccine status, date of vaccination, vaccine code etc. From all the trapping records, we extracted 440 pairs of trapping records, from badgers that were captured more than once. Each pair of capture records consists of two examination results, namely the serology status at the beginning and the end of the interval, with the infectious status being negative at the beginning. Each pair of capture record has an outcome of 0 or 1 infection, which can be used to calculate the probability of infection during an interval, namely $P_{ub}$ and $P_{vb}$ in equation 3.7- 3.9.

In addition, the number of infectious badgers at each territory $j$ at the time x ($I_{b(j)x}$) is needed on the right side of equation 3.7- 3.9. We calculated $I_{b(j)x}$ by multiplying the badger bTB prevalence by the number of badgers per territory. The number of badgers per territory was calculated using minimum number alive. Badger prevalence were calculated from 1759 trapping results. The spatial and temporal resolution in the model is at territory and day levels while the data are limited compared to the resolution in this model. Therefore, we fitted badger bTB prevalence at the territory level at different time points with several generalized additive models (GAMs), and then used the best fitting GAM to predict the badger bTB prevalence for each day in each territory (see details about the GAMs in Supplement 3.5.3 In addition, a sensitivity analysis was conducted to assess the impact of uncertainty in badger prevalence on the parameter estimation (see Supplements 3.5.4).

**Cattle data**

Cattle data were extracted from the Animal health computer system (AHCS) dataset and Land parcel Identification System (LPIS) of the Irish Government's Department of Agriculture, Food and Marine (DAFM). The AHCS dataset comprises bTB test records on more than 98% of herds, including Single Intradermal Comparative Tuberculin test (SICTT), Interferon gamma array, Enzyme-Linked Immunosorbent Assay (ELISA) test and slaughterhouse inspection results. Herds are tested

by the SICTT test at least once a year. The sensitivity of tests was assumed to be 100% in this study. Positive cattle are removed within 2-4 weeks of testing by staff from DAFM. In AHCS dataset, each record consists of the number of cattle tested, the date of the test, the type of the test, the number of positive cattle, the number of inconclusive cattle etc. When there are inconclusive tests in the herd, field veterinarians re-test the cattle or the herd within 3 months. From 2009 to 2013, there were 6787 test records from 1335 herds in this badger vaccination trial area. In all these events, 696 records from 390 herds were positive. In each data line, the new cases in a herd during an interval is the $P_c$ in equation 3.7. The number of infected animals at the start of the interval time x ($I_{c(i)_\tau}$) is used to construct the exposure (right side of the equation 3.7).



The LPIS dataset delineates the land parcels making up each farm. Many Irish farms consist of several land fragments [138–140]. For historic and topological reasons, the extent of fragmentation varies within Ireland. In the region of this study, approximately 20% of farms are single-fragment farms. The remaining 80% of farms have an average of 5 fragments with a mean distance between same-farm fragments of 3.3 km. The movement within a herd but amongst different fragments was not recorded. Therefore, we assume that the time cattle spend on each fragment is proportional to the area of the fragment.

### 3.2.5 Basic reproduction ratio R

#### Within-herd R

The Next Generation Matrix (NGM) is a commonly used method to derive the basic reproduction ratio for a compartmental model [90]. With the estimated transmission and decay rate parameters, we can calculate the basic reproduction ratio for this cattle badger system in a theoretical local area as: $NGM = \begin{bmatrix} R_{c,c} & R_{b,c} \\ R_{c,b}\frac{N_b}{N_c} & R_{b,b}\frac{N_b}{N_c} \end{bmatrix}$, where

$$R_{c,c} = \frac{\beta_{c,c}\mu}{(-1+e^{-\mu}+\mu)} \frac{\lambda_c}{(\alpha_c+\lambda_c)} \frac{1}{\alpha_c+\gamma_c}$$

$$R_{b,c} = \frac{\beta_{c,c}\mu}{(-1+e^{-\mu}+\mu)} \frac{\lambda_c}{(\alpha_c+\lambda_c)} \frac{1}{\alpha_b+\gamma_b}$$

$$R_{c,b} = VC * \left( \frac{\beta_{c,vb}\mu}{(-1+e^{-\mu}+\mu)} \frac{\lambda_b}{(\alpha_b+\lambda_b)} \frac{1}{\alpha_c+\gamma_c} \right) + \frac{(1-VC)\beta_{c,ub}\mu}{(-1+e^{-\mu}+\mu)} \frac{\lambda_b}{(\alpha_b+\lambda_b)} \frac{1}{\alpha_c+\gamma_c}$$

$$R_{b,b} = \frac{VC * \beta_{b,vb}\mu}{(-1+e^{-\mu}+\mu)} \frac{\lambda_b}{(\alpha_b+\lambda_b)} \frac{1}{\alpha_b+\gamma_b} + \frac{(1-VC)\beta_{b,ub}\mu}{(-1+e^{-\mu}+\mu)} \frac{\lambda_b}{(\alpha_b+\lambda_b)} \frac{1}{\alpha_b+\gamma_b} .$$

$\frac{N_b}{N_c}$ represents the relative badger density compared to cattle in a local area. We used this term rather than the term relative abundance, because in our model $N_c$ is a proxy of the area under consideration, with the implicit assumption that cattle density is spatially uniform. Thus, the relative badger density cannot be reduced by simply increasing the number of cattle, as such an increase would mean an enlargement of the land area. $VC$ represents the vaccination coverage and (1- $VC$) represents the proportion of unvaccinated badgers. We use $VC$ = 0% and 100% to calculate the partial reproduction ratio under unvaccinated and fully vaccinated areas. The largest eigenvalue of this matrix is the basic reproduction ratio within this local area is derived as:

$$R = \frac{1}{2}\left( R_{c,c} + R_{b,b}\frac{N_b}{N_c} \right) + \frac{1}{2}\sqrt{(R_{c,c} + R_{b,b}\frac{N_b}{N_c})^2 - 4(R_{c,c} * R_{b,b}\frac{N_b}{N_c} - R_{c,b}R_{b,c}\frac{N_b}{N_c})}$$

R represents the average number of new infections per case within this isolated local area such as a farm with a badger territory lying completely inside the farm.

However, in reality, badgers' territories connect multiple local areas. Badgers act as vectors in the sense that they get infected by one herd and transmit infection to cattle in other herds. When an infectious bovine is introduced to a herd or an infectious badger comes into contact with a herd, there is a risk that infection will be spread to neighbouring herds by badgers. To control bTB spread, we need to evaluate both within- and between-herd transmission.

**Between-herd R**

The average number of neighbouring herds infected by a single newly infected farm is denoted by the between-herd $R$. To calculate the between-herd $R$, a stochastic metapopulation model for each herd and its neighbouring herds was developed with the same model structure as described in figure 3.1 using the SimInf package

in R [141]. All the infection and vital dynamic processes are modelled stochastically using the Gillespie Algorithm, while *M. bovis* dynamic shedding and decay in environment are modelled deterministically using equation 3.1 and 3.2. The spatial structure was accounted for according to equation 3.3 and 3.4. In the Kilkenny area, there are a total of 1335 herds. For each herd, we simulated the transmission between the herd itself, the connected badger territories, and the herds that are directly connected (i.e. those that share a connected badger territories with the initial herd). In total, 1335 different spatial configurations were simulated, each with 200 repetitions.



Parameter estimations obtained in the analysis Section 3.2.2 and 3.2.3 were used in this simulation. At the initial state, one infectious bovine is introduced to a herd. Badgers are considered fully susceptible and there is no contamination in the environment. The resulting distribution for the number of infected neighbouring herds represents the between-herd $R$ distribution. The average number of infected herds is the between-herd $R$.

## 3.3 Results

### 3.3.1 Parameter estimations

The decay rate parameter is estimated as 0.0039 $\text{day}^{-1}$ with CI (0.0036, 0.0041), which means the half-life of *M. bovis* is 178 days ranging from 169 to 192 days. Transmission rate parameters are estimated with a unit of per day for one infectious individual (table 3.2). In addition, our parameter estimation is robust across varying assumptions used to calculate badger prevalence (Supplement 4).

Table 3.2: Parameter estimation

| Parameter | Estimation (per day per E unit) | CI | Transformed (per individual per year) | CI |
|---|---|---|---|---|
| $\beta_{c,c}$ | 1.01e-5 | (9.7e-6, 1.07e-5) | 1.89 | (1.82, 1.97) |
| $\beta_{b,c}$ | 3.977e-6 | (3.78e-6, 4.19e-6) | 0.756 | (0.71, 0.78) |
| $\beta_{b,vb}\frac{N_b}{N_c}$ | 5.14e-5 $\frac{N_b}{N_c}$ | (3.34e-5, 7.28e-5) $\frac{N_b}{N_c}$ | 9.63 $\frac{N_b}{N_c}$ | (6.26, 13.64) $\frac{N_b}{N_c}$ |
| $\beta_{c,vb}\frac{N_b}{N_c}$ | 4.43e-4 $\frac{N_b}{N_c}$ | (2.64e-4, 6.62e-4) $\frac{N_b}{N_c}$ | 82.95 $\frac{N_b}{N_c}$ | (49.62, 124.07) $\frac{N_b}{N_c}$ |
| $\beta_{b,ub}\frac{N_b}{N_c}$ | 9.19e-5 $\frac{N_b}{N_c}$ | (6.44e-5, 1.23e-4) $\frac{N_b}{N_c}$ | 17.22 $\frac{N_b}{N_c}$ | (12.09, 23.21) $\frac{N_b}{N_c}$ |
| $\beta_{c,ub}\frac{N_b}{N_c}$ | 5.07e-4 $\frac{N_b}{N_c}$ | (2.98e-4, 7.62e-4) $\frac{N_b}{N_c}$ | 95.13 $\frac{N_b}{N_c}$ | (55.83, 142.87) $\frac{N_b}{N_c}$ |

We transform $\beta_{c,c}$ to a yearly rate per infected individual ($\frac{\beta_{c,c}\mu}{(-1+e^{-\mu}+\mu)} * 365$) for comparison with other transmission models which use direct contact assumptions. One infectious bovine can infect on average 1.97 cattle per year in a fully susceptible herd with CI (1.82, 1.97). This estimation is slightly lower than estimations in New Zealand, the Netherlands and Argentina ranging from 2.2 to 5.2 per year [142–145].

The transmission rate parameter for badgers ($\beta_{b,vb}$, $\beta_{c,vb}$, $\beta_{b,ub}$, $\beta_{c,vb}$) need to be interpreted with a multiplication of the local relative badger density (See NGM in 2.5), hence they cannot be directly compared with transmission rate parameters for cattle ($\beta_{c,c}$, $\beta_{b,c}$). For example, in an area with $\frac{N_b}{N_c} = 0.01$, an infectious bovine can infect on average 0.95 unvaccinated badgers per year with a CI (0.56, 1.42).

### 3.3.2 Within-herd R

In an isolated farm that does not connect to other farms, the within-herd $R$ can be derived based on the methods presented in Section 3.2.5. When badgers are unvaccinated, the NGM for this farm is $\begin{bmatrix} 0.48 & 0.58 \\ 22.57\frac{N_b}{N_c} & 12.66\frac{N_b}{N_c} \end{bmatrix}$, where $\frac{N_b}{N_c}$ represents the relative badger density in the farm. When badgers are vaccinated, the NGM is $\begin{bmatrix} 0.48 & 0.58 \\ 19.68\frac{N_b}{N_c} & 7.08\frac{N_b}{N_c} \end{bmatrix}$. When an infectious bovine is introduced in this isolated farm, it will infect 0.48 cattle on average during its infectious period. In comparison, when an infectious badger is introduced, it will infect on average 0.58 cattle. The shorter infectious period of cattle than badgers leads to a smaller $R_{c,c}$ than $R_{b,c}$.

However, a relaxation of the test and removal strategy will lead to longer cattle infectious period and will thus increase $R_{c,c}$.

The number of infected badgers in this system depends on the relative badger density ($\frac{N_b}{N_c}$). In addition, the impact of badger vaccination on within-herd $R$ depends on the $\frac{N_b}{N_c}$. For example, in a herd with 100 cattle and 3 unvaccinated badgers, the within-herd $R$ for this local area is 1.07. If all badgers are vaccinated in this local area, the within-herd $R$ is 0.95 (figure 3.3). For example, to control $R$ <1 within an isolated area that accommodate 100 cattle, the relative badger density should be less than 2.6 unvaccinated badgers or 3.4 vaccinated badgers. As the relative badger density and the system $R$ are highly correlated (with a correlation coefficient of 0.999), we fit them into a linear regression. In estimated linear relationships, $R$ increases by 0.134 when the $\frac{N_b}{N_c}$ increases by 0.01 in an unvaccinated area. With all the badgers being vaccinated, this increase in $R$ per 0.01 $\frac{N_b}{N_c}$ is reduced to 0.084.



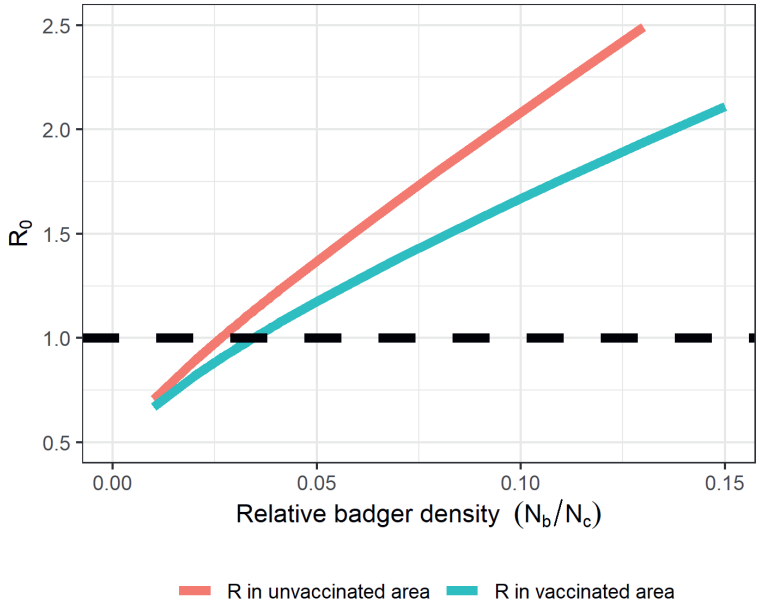


Figure 3.3: Within-herd $R$ in an isolated herd with different relative badger densities ($N_b/N_c$). The pink line represents the within-herd $R$ without badger vaccination and the blue line represents the within-herd $R$ with badger vaccination. The black dashed line represents the threshold $R = 1$.

### 3.3.3 Between-herd R

In real life, herds are not isolated but connected with each other by badger territories. Even if each isolated area has an $R$ below 1, bTB might still spread from one local area to another. Therefore, we used simulations to calculate the average number of herds that get infected if an infectious bovine is introduced or tested positive in an index herd.



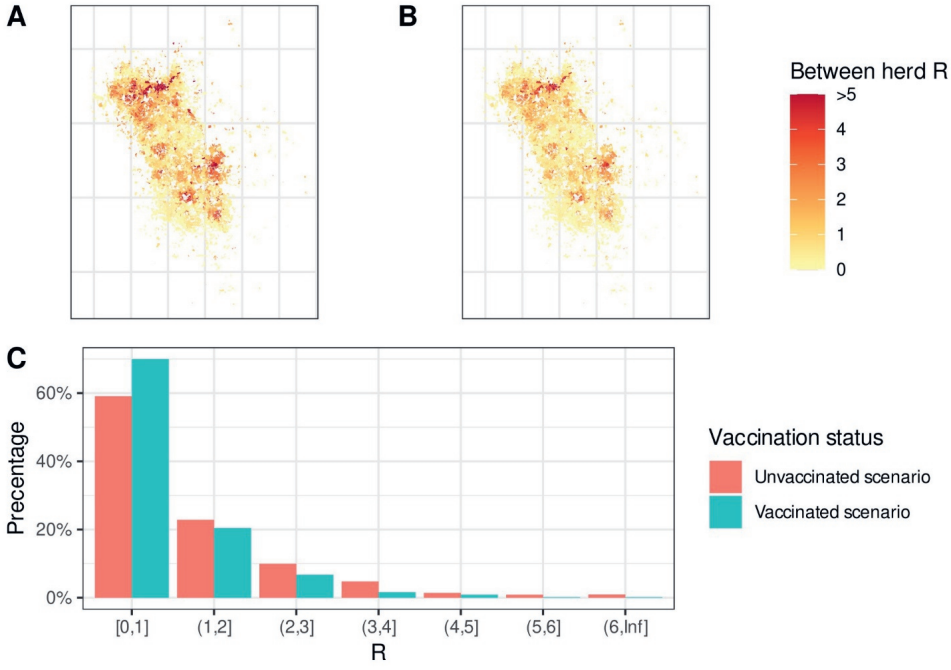


Figure 3.4: Between-herd $R$ maps and $R$ distribution. A) The between-herd $R$ map without any badger vaccination, and B) the between-herd $R$ map with 100% vaccination coverage. Yellow herds represent between-herd $R$ below 1, while orange and red herds represent between-herd $R$ >1. C) The distribution of between-herd $R$ with and without badger vaccination. Each bar represents the percentage of herds falling within a specific between-herd $R$ range. For example, the first bar indicates that 70% herds have between-herd $R$ <1 in vaccination scenario and 60% in un-vaccination scenario.

In between-herd $R$ maps (figure 3.4), herds in yellow are expected to spread bTB to fewer than 1 neighbouring herd, while herds in orange and red are expected to spread to more than 1 neighbouring herd. Red areas are mostly clustered in the north and east side of the study area due to the higher relative density of badgers. Some sporadic red dots lie in the yellow area because of the farm fragmentation, where

high $R$ herds have some land parcels in the low $R$ herd clusters. By comparing the two maps, vaccination reduces the average between-herd $R$ from 1.14 to 0.85. It is worth noting that the average between-herd $R$ is being used to allow a quantitative comparison between maps but does not infer the bTB persistence in a whole area. Despite of a 10% decrease of herds with R>1, there are still 30% herds that can transmit bTB to more than 1 herd with the badger vaccination (figure 3.4C).



## 3.4 Discussion

The quantification of bTB transmission between wildlife and cattle is critical for efforts to eradicate bTB. In Ireland and UK, recent studies have provided evidence that badgers are involved in maintaining bTB transmission; however, a quantitative understanding of how relative badger density influences transmission in this cattle and badger episystem has so far been lacking. To address this gap, this study quantifies the role of badgers, cattle, and the environment in bTB transmission and disentangles how relative badger density may contribute to the spatial heterogeneity in bTB transmission. To achieve this objective, we developed a novel environmental transmission model that incorporates both within-herd/badger territories transmission and between-species transmission. This approach is guided by the overlap of badger territories with cattle herds.

In this two-host transmission system, the partial reproduction ratio $R_{b,c}$ is higher than $R_{c,c}$. This is because the infectious period of badgers is likely longer than cattle given the test and removal policy in cattle being in place. Therefore, any relaxation of the test and removal policy can lead to higher $R_{c,c}$. The partial reproduction ratios $R_{c,(u/v)b}\frac{N_b}{N_c}$ and $R_{b,(u/v)b}\frac{N_b}{N_c}$ depend on the local relative badger density ($\frac{N_b}{N_c}$). As a result, we quantified the relationship between local relative badger density and the $R$ for the system. In unvaccinated areas, within-herd $R$ increases by 0.134 for every 0.01 increase in the $\frac{N_b}{N_c}$. This increase is reduced to 0.084 per 0.01 increase in $\frac{N_b}{N_c}$ when badgers are vaccinated.

Our transmission model adopts a single transmission route incorporating with an environment compartment. We simplified the transmission via droplets, aerosols and faecal to oral as these three transmission routes are intrinsically similar with the only distinction in the duration between the shedding moment and the time

point of inhaling or ingesting *M. bovis*. Shortly after being shed into the environment, *M. bovis* cells may pose an infection risk to other animals. This infection risk decreases over time because viable *M. bovis* decays over time in the environment. We unified these three transmission routes into one and assumed an exponential decay of *M. bovis* with a specified decay rate. This unification simplifies the model structure while still capturing the significance of historic infections. In addition, badger-to-badger transmission via biting may represent a secondary route of infection, which has not been considered in this study. Previous studies have shown that transmission via biting can cause more rapid and progressive infection with generalized pathology [146]. The simplification of transmission routes might lead to an underestimation of badger-to-badger transmission and the overestimation of cattle-to-badger transmission. However, it is not our goal to distinguish badger infection via biting or the other three mechanisms as the data to distinguish the contribution of different mechanisms is lacking.



Previous studies on the within-herd transmission of bTB have exploited either frequency or density-dependent models [142, 144, 147]. A study in US dairy herds found that the frequency-dependent model can predict risk significantly better than a density-dependent model [147]. Additionally, Conlan et al. [26] measured the strength of density dependence of transmission and found a non-linear dependence with herd size. Therefore, our model adopts a frequency-dependent model and uses the number of cattle as a proxy for the area in transmission rates (equation 3.3 and 3.4). This approximation is valid in areas where badger territories and farms dominate a significant portion of the region frequented by badgers, as in this study area. However, when woodlands, river and urban areas constitute a large part of the region, it is important to adjust this proxy to avoid the underestimation of the denominator in badger-to-badger transmission rate that leads to an overestimation of badger-to-badger transmission rate parameter. In addition to using cattle number as a proxy of area, one can consider alternative denominators such as the number of badgers or the sum of cattle and badgers. Our assessment showed that models with $N_c$ or $N_c + N_b$ as the denominator in the transmission rates (equation 3.3 and 3.4) provided similar results in fitting the data (See Supplement 3.5.4)

The significance of the environment in the transmission of *M. bovis* is emphasised

in our model, which estimates a half-life of six months. Our estimation of the half-life of *M. bovis* in the environment is five times higher in comparison to other modelling studies [54], although still within the range of experimental studies [20, 148]. We also conducted a sensitivity analysis of the decay rate using the estimates from [54]. A shorter survival time of *M. bovis* can lead to an increase in transmission rate parameters, but the outcome of this study with respect to NGM, $R$ and threshold for relative badger density remain largely unaffected (See Supplement 3.5.5).



The parameters defining the duration of intermediate stages of the disease (latent periods) were derived from the literature (See Supplement 3.5.1). We did not estimate them from infection data, because previous modelling studies have not been able to distinguish models with differing assumptions regarding these intermediated stages (SORI or SOR model) based on model fit [26]. The most debated parameter is the latent period for cattle. Conventionally, it is believed that *M. bovis* can cause a long latent period similar to human TB. However, an animal challenge study showed that acute infection may occur [149]. In addition, a recent review also suggests that *M. bovis* can frequently causes acute infection in cattle [150]. Therefore, we also assume a short latent period for cattle. In this model, assuming a different latent period for cattle or badgers would impact the transmission rate parameter estimates. However, such a variation would not influence the values for $R$ and NGM since the modifications to these $\beta$ and $\lambda$ would counterbalance each other within the $R$ formula as described in Section 3.2.5. In addition, the sensitivity of tests for cattle and badgers are assumed to be perfect in this model. Infected but undetected animals shed *M. bovis*, which causes an underestimation of environmental contamination. On the other hand, these hidden infections cause an underestimation of the new cases. Both left and right side of the equation 3.7-3.9 were underestimated, whose effects are likely to be cancelled out and therefore have a limited impact on the transmission rate parameter.

In this model, cattle and badgers are assumed to spend their time homogenously distributed within their spatial units. This is a simplification of reality as some parcels of farms might not be used for grazing, or not all of the time, and badgers may spend more time near setts than elsewhere in their territories. However, as

cattle and badger numbers and infection data are available on farm and territory level, we used this as the spatial resolution for our model. Within-farm and within-territory heterogeneity might lead to an underestimation of the actual densities at the location of an infected animal, which in turn leads to an underestimation of the within-herd $R$ by the model. However, heterogeneity in densities may also lead to less overlap in areas used by cattle and badgers, which would have the opposite effect. In addition, assuming that animals are restricted to their spatial units attributes transmission that is actually movement-related to between-species transmission in the model and hence leads to overestimation of the effect of between-species transmission. Future studies could relax this assumption and capture the effect of cattle movements using detailed cattle movement data.

In conclusion, this model disentangles the quantitative relationship between relative badger density and local transmission risks. Estimating transmission rate parameters improves our understanding of badgers as a vector in this two-host system. In addition, the model produces the first between-herd $R$ map for bTB considering badger, cattle, and environment. These $R$ maps identify high-risk areas as clusters of farms with between-herd R>1 and demonstrate how relative badger density determines the local transmission risk. Our results suggest that badger vaccination can maximally reduce the average between-herd $R$ in Kilkenny to 0.85, however, despite this, 30% of herds will still have an $R$ value >1 and so, if infected, have a high potential risk of transmitting bTB to their neighbours. Whether these 30% of herds with a high between-herd $R$ can sustain the bTB spread in a large area, such as the whole Kilkenny area, is unknown and requires further research.

## 3.5 Supplement

### 3.5.1 Model Parameterization

In this section, we describe the details of infectious period, latent period and natural death rate for cattle and badgers (table 3.3).

Table 3.3: Model parameters

| Parameter | Description | Value | Range | Source |
|---|---|---|---|---|
| $1/\gamma_c$ | Infectious period for cattle | 101 days | (30, 225) days | AHCS data |
| $1/\gamma_b$ | Infectious period for badger | 365 days | (117, 1305) days | [151–153] |
| $1/\lambda_c$ | Latent period for cattle | 1.8 s | (1.5, 600) days | [26, 142, 144] |
| $1/\lambda_b$ | Latent period for badger | 90 days | (90, 158) days | [152, 153] |
| $\alpha_c$ | The cattle background death rate | 1/1095 $day^{-1}$ | | [154, 155] |
| $\alpha_b$ | The badger natural death rate | 1/1330 $day^{-1}$ | | [152, 156] |



**Infectious period**

The infectious period of cattle in ROI depends on the test frequency. The onset of the infectious period of a bovine is usually not exactly known. Therefore, we assume that cattle get infected at the middle point of two tests. We extract cattle testing data results in Kilkenny trial area during the vaccination study and calculate the average duration infectious period.

Once badgers get infected, they seem to have a life-long infectiousness. However, the excretion may be intermittent and vary greatly throughout time. The effective duration of infection period can be approximately derived as the average life span of infected animals (excluding the latent period) [152]. The life expectancy after bTB infection varies from 35 days to 3.5 years in in laboratory studies, with the most of badgers survive between one to two years [151, 157]. Another study also found that badgers with bite infection usually have more acute disease progress and the survival of those badgers with bite infection was estimated as 117 days (CI 0 to 341 days) [158]. However, badgers who have apparent respiratory origin infection have a mean survival time of 491 days with CI 253 to 729 days [158].Based on all those information, we assume a one year infection period for badgers.

**Latent period**

The latent period of bTB in badgers is not well understood due to a lack of effective method of detecting *M. bovis* in live animals. Culture and examination methods have been used in some old experimental studies. However, those methods are labour intensive and prone to error, and should be interpreted with caution [152]. Little et al. [151] undertook an animal experiment with a small sample size and used the duration between the first exposure to the first time of recording *M. bovis* excretion. This study found the range of latent period is from 95 days to 158 days, with a comment that the excretion is intermittent. Since the previous badger transmission model assumed a 3-month latent period based on those estimation, we used the same assumption [152].

In cattle, animal challenge study has found a short latent period ~30 days [149] while other models have assumed a lengthy latent period of 6 to 20 months [142, 144]. A more recent modelling study compared two models with long or short latency but could not distinguish the two assumption (SOR and SORI) from within herd transmission data [26]. In SOR model, cattle are infectious once infected, but cattle cannot be detected in occult stage. In this assumption, occult cattle are estimated to become responsive to test cattle in 1.8 days. In the other assumption, infected cattle go through occult, responsive to test and then infectious. In this assumption, cattle's latent period is estimated to be 406 days or 28 days based on different prior information with the similar model fit. As the animal experiments also suggest short latent period, we adopt a short latent period model assuming the latent period as 1.8 days [26].

**Background death rate**

The natural death rate for badgers is calculated from the capture-mark-recapture study conducted in an undisturbed wild population in the west of England [156]. A survival probability each year was reported in the study. We assume an exponential distribution of death and therefore can derive an average lifespan of 1330 days with a natural death rate of 7.52e-4 per day.

The lifespan of cattle varies between farms, herd types and so on. In the Irish farming system, the average lifespan for beef breeds is almost 3 years, being slightly lower than for dairy breeds [154]. Another study suggests that the annual

culling rate is about 20% [155]. Therefore, we assume the background death rate for cattle is about 1/3 per year (9.13e-4 per day).

### 3.5.2 Confidence bounds for partial reproduction ratio

We calculate the confidence bounds for partial reproduction ratios based on the confidence bounds of the transmission rates and the decay rate parameters estimation (table 3.4). The $R_{c,c}$ and $R_{b,c}$ have narrow confidence bounds than other partial $R$ because $R_{c,c}$ and $R_{b,c}$ are estimated from the cattle infection data, which are more abundant than badger infection data.



Table 3.4: Confidence bound for partial reproduction ratios

| $R$ | Value | CI |
|---|---|---|
| $R_{c,c}$ | 0.48 | (0.46, 0.50) |
| $R_{b,c}$ | 0.58 | (0.55, 0.61) |
| $R_{b,vb}$ | 7.08 | (4.60, 10.03) |
| $R_{c,vb}$ | 19.68 | (11.78, 29.44) |
| $R_{b,ub}$ | 12.66 | (8.88, 17.06) |
| $R_{c,ub}$ | 22.57 | (13.24, 33.90) |

### 3.5.3 Smoothing badger prevalence data

Badger infection data were extracted from the badger vaccination trial in Kilkenny. Despite of the intensive data collection, the badger prevalence data are scarce at the resolution in this spatial model. Therefore, we use statistical learning to investigate the association between the spatial location of badger territories, the time and the badger prevalence. With the best-fitted relationship, we can predict the badger in a finer resolution.

Badger annual prevalence at territory level has been calculated and fitted into several spline smooth models. The badger annual prevalence is the response of the model. The coordinates of the centroid of badger territories (x,y) and the time

(day) are the three predictors in statistical model. The predictor (prevalence) has the value from 0 to 1, hence a binomial distribution with a logit link relationship between predictor and response is assumed.

We fit predictors to the observed prevalence data using smoothing spines. The goal was to find a function s() that fits the observed data well, while not overfitting the data. This means to find a function that minimizes $\sum_{i=1}^{n}(y_i - s(x_i))^2 + \lambda \int s''(t)^2 dt$, where $\lambda$ is a tuning parameter and the function s() is the smoothing spline.



The functions for different predictors are additive, hence this statistical learning method is also called generalised additive models (GAM).Five statistical models with different predictors were tested:

Model 1: only time

$$prevalences = s(t)$$

Model 2: time and the vaccination zone

$$prevalence = s(t) + s(zone)$$

Model 3: coordinates (x,y)

$$prevalence = s(x, y)$$

Model 4: coordinates (x,y) and time

$$prevalence = s(x, y) + s(t)$$

Model 5: coordinates (x,y) and time with interaction

$$prevalence = s(x, y, t)$$

From the AIC of these 5 models, the best fit smoothing spline is the Model 5

where the coordinates (x, y) and t are the three predictors with interaction between coordinates and time (x*y*t) (see table 3.5).

Table 3.5: AIC for smoothing models

| Model | df | AIC |
|---|---|---|
| s(t) | 2.0002 | 1771.910 |
| s(t)+ s(zone) | 4.0004 | 1776.133 |
| s(x,y) | 14.0123 | 1745.088 |
| s(x,y) +s(t) | 14.9310 | 1745.659 |
| s(x,y,t) | 72.4936 | 1723.466 |

The predicted prevalence over space is visualized in figure 3.5. The predicted prevalence at each territory varies from 0 to 0.7 with the mean prevalence 0.28 (figure 3.5 B). Temporal prevalence changes in a few example badger territories are presented in figure 3.6.

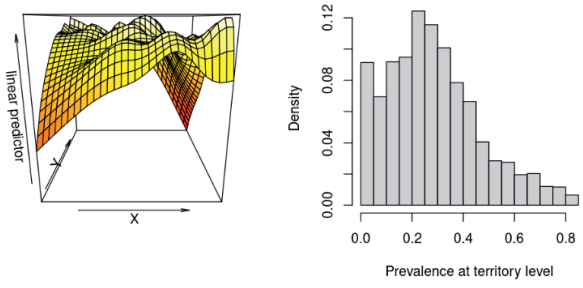


Figure 3.5: The predicted badger prevalence by GAM s(x,y,t) model and the histogram of predicted prevalence at territory level.

### 3.5.4 Model selection on different denominator in infection force

In this paper, we use the total number of cattle to represent a local. Badgers act as vectors that lives in farms but does not determine the area. The model structure

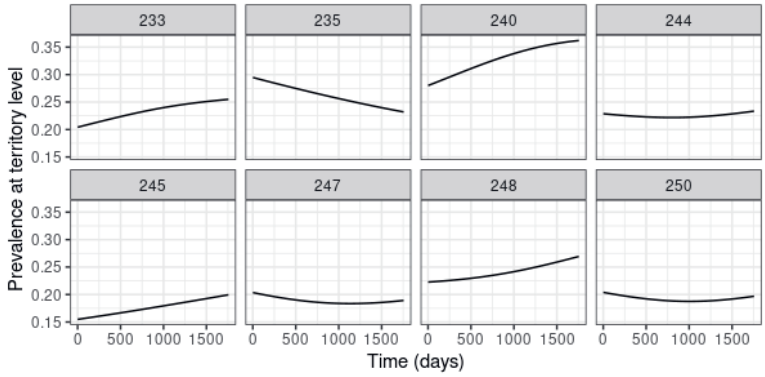


Figure 3.6: An example of the predicted badger prevalence over time at some territories with the value on each panel representing the territory ID.

is similar to vector-borne disease where the number of the host in an area is the denominator ([159, 160]). In our case, the infection force is $\beta \frac{Exposure*S}{N_c}$ for both cattle and badgers. However, ones can assume different assumptions, such as using the number of badger or the cattle and badger number as the representation of this local area, with infection force as $\beta \frac{Exposure*S}{N_b}$ or $\beta \frac{Exposure*S}{N_c+N_b}$ under these two assumption respectively.

We select the three model structures by the goodness of fit. The model 3 ($N_b+N_c$) as denominator is the best fit model structure.

### $N_c$ determines the area

The ordinary differential equations (ODE) version of the transmission model can be written as:

$$\frac{dI_{c(i)}}{dt} = \beta_{c,c} S_{c(i)} \frac{E_{c(i)}}{N_{c(i)}} + \beta_{b,c} S_{c(i)} \frac{\sum_{j=1,..k} E_{b(j)} \frac{A_{(ij)}}{AT_{(j)}}}{N_{c(i)}}$$

$$\frac{dI_{ub(j)}}{dt} = \beta_{b,ub} S_{ub(j)} \frac{E_{ub(j)}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,ub} S_{ub(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} - \alpha_b I_{ub(j)}$$

$$\frac{dI_{vb(j)}}{dt} = \beta_{b,vb} S_{vb(j)} \frac{E_{vb(j)}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,vb} S_{vb(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{\sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} - \alpha_b I_{b(j)}$$

The next generation matrix of this model is:

$$\begin{bmatrix} R_{c,c} & R_{ub,c} & R_{vb,c} \\ R_{c,ub}\frac{N_b}{N_c} & R_{ub,ub}\frac{N_b}{N_c} & R_{vb,ub}\frac{N_b}{N_c} \\ R_{c,vb}\frac{N_b}{N_c} & R_{ub,vb}\frac{N_b}{N_c} & R_{vb,vb}\frac{N_b}{N_c} \end{bmatrix}$$



### $N_b$ determines the area

Compared to Model 1, all the denominator in ODE is changed to $N_b$.

$$\frac{dI_{c(i)}}{dt} = \beta_{c,c} S_{c(i)} \frac{E_{c(i)}}{\sum_{j=1..n} N_{b(j)} \frac{A_{(ij)}}{AT_{(j)}}} + \beta_{b,c} S_{c(i)} \frac{\sum_{j=1,..k} E_{b(j)} \frac{A_{(ij)}}{AT_{(j)}}}{\sum_{j=1..n} N_{b(j)} \frac{A_{(ij)}}{AT_{(j)}}}$$

$$\frac{dI_{ub(j)}}{dt} = \beta_{b,ub} S_{ub(j)} \frac{E_{ub(j)}}{N_{b(i)}} + \beta_{c,ub} S_{ub(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{N_{b(i)}} - \alpha_b I_{ub(j)}$$

$$\frac{dI_{vb(j)}}{dt} = \beta_{b,vb} S_{vb(j)} \frac{E_{vb(j)}}{N_{b(i)}} + \beta_{c,vb} S_{vb(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{N_{b(i)}} - \alpha_b I_{b(j)}$$

The next generation of this model is:

$$\begin{bmatrix} R_{c,c}\frac{N_c}{N_b} & R_{ub,c}\frac{N_c}{N_b} & R_{vb,c}\frac{N_c}{N_b} \\ R_{c,ub} & R_{ub,ub} & R_{vb,ub} \\ R_{c,vb} & R_{ub,vb} & R_{vb,vb} \end{bmatrix}$$

### $N_b$ +$N_c$ determines the area

In the ODE version of transmission model, the denominator is the total number of cattle and badgers.

$$\frac{dI_{c(i)}}{dt} = \beta_{c,c} S_{c(i)} \frac{E_{c(i)}}{\sum_{j=1..n} N_{b(j)} \frac{A_{(ij)}}{AT_{(j)}} + N_{c(i)}} + \beta_{b,c} S_{c(i)} \frac{\sum_{j=1,..k} E_{b(j)} \frac{A_{(ij)}}{AT_{(j)}}}{\sum_{j=1..n} N_{b(j)} \frac{A_{(ij)}}{AT_{(j)}} + N_{c(i)}}$$

$$\frac{dI_{ub(j)}}{dt} = \beta_{b,ub} S_{ub(j)} \frac{E_{ub(j)}}{N_{b(i)} + \sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,ub} S_{ub(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{N_{b(i)} + \sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} - \alpha_b I_{ub(j)}$$

$$\frac{dI_{vb(j)}}{dt} = \beta_{b,vb} S_{vb(j)} \frac{E_{vb(j)}}{N_{b(i)} + \sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} + \beta_{c,vb} S_{vb(j)} \frac{\sum_{i=1,..m} E_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}}{N_{b(i)} + \sum_{i=1..m} N_{c(i)} \frac{A_{(ij)}}{AF_{(i)}}} - \alpha_b I_{b(j)}$$



The next generation matrix for this model is:

$$\begin{bmatrix} R_{c,c} \frac{N_c}{N_b+N_c} & R_{ub,c} \frac{N_c}{N_b+N_c} & R_{vb,c} \frac{N_c}{N_b+N_c} \\ R_{c,ub} \frac{N_b}{N_b+N_c} & R_{ub,ub} \frac{N_b}{N_b+N_c} & R_{vb,ub} \frac{N_b}{N_b+N_c} \\ R_{c,vb} \frac{N_b}{N_b+N_c} & R_{ub,vb} \frac{N_b}{N_b+N_c} & R_{vb,vb} \frac{N_b}{N_b+N_c} \end{bmatrix}$$

The statistic model descripted in 2.3 is used to fit these three models to estimate the parameters. The goodness of fit for these three models was used to select the best fit model (table 3.6)

Table 3.6: Goodness of fit for three transmission model structures

| denominator | Data | Parameters | Estimation | AIC |
|---|---|---|---|---|
| $N_c$ | Cattle | $\beta_{c,c}$ | 1.01e-05 | 15925.2 |
| | | $\beta_{b,c}$ | 3.98e-06 | |
| | Unvac badgers | $\beta_{b,ub}$ | 9.19e-05 | 301.4 |
| | | $\beta_{c,ub}$ | 5.07e-04 | |
| | Vac badgers | $\beta_{b,vb}$ | 5.14e-05 | 253.9 |
| | | $\beta_{c,vb}$ | 4.43e-04 | |
| | Total AIC | | | 16480.5 |
| $N_b$ | Cattle | $\beta_{c,c}$ | 8.63e-09 | 16142.8 |
| | | $\beta_{b,c}$ | 5.77e-08 | |
| | Unvac badgers | $\beta_{b,ub}$ | 5.22e-06 | 261.9 |
| | | $\beta_{c,ub}$ | 1.12e-06 | |
| | Vac badgers | $\beta_{b,vb}$ | 3.37e-06 | 224.4 |
| | | $\beta_{c,vb}$ | 2.17e-06 | |
| | Total AIC | | | 16629.1 |
| $N_c$+$N_b$ | Cattle | $\beta_{c,c}$ | 1.04e-05 | 15896.39 |
| | | $\beta_{b,c}$ | 4.07e-06 | |
| | Unvac badger | $\beta_{b,ub}$ | 9.55e-05 | 298.7 |
| | | $\beta_{c,ub}$ | 4.66e-04 | |
| | Vac badgers | $\beta_{b,vb}$ | 5.59e-05 | 249.6 |
| | | $\beta_{c,vb}$ | 4.22e-04 | |
| | Total AIC | | | 16444.69 |

### 3.5.5 Sensitivity analysis of decay rate

*M. bovis*'s half -life is estimated to 35 days ($\mu = 0.02$) from [54] [161], which is 5 times higher than the estimation in this study (half-life 177 days; $\mu = 0.004$). Therefore, we conduct a sensitivity analysis to investigate how would decay rate parameter influence the result of this study in terms of estimation on transmission rate parameter, $R$, and badger-cattle ratio threshold table 3.7.

Table 3.7: Sensitivity test of decay rate on transmission rate parameter

| | | $\mu = 0.004$ | $\mu = 0.02$ |
|---|---|---|---|
| Data | Parameters | Estimation | Estimation |
| Cattle | $\beta_{c,c}$ | 1.01e-05 | 3.29e-5 |
| | $\beta_{b,c}$ | 3.98e-06 | 2.77e-5 |
| Unvac badgers | $\beta_{b,ub}$ | 9.19e-05 | 5.66e-4 |
| | $\beta_{c,ub}$ | 5.07e-04 | 1.8e-3 |
| Vac badgers | $\beta_{b,vb}$ | 5.14e-05 | 3.4e-4 |
| | $\beta_{c,vb}$ | 4.43e-04 | 1.7e-3 |
| AIC | | 16480.5 | 17531.46 |

Despite the changes in transmission rate parameters, the decay rate parameter has limited impact on the partial $R$ value. From the point estimation, higher decay rate ($\mu$ =0.02) resulted in higher $R_{b,c}$ and $R_{b,b}$. However, the changes in the partial $R$ does not influence much on the $R$ for the system (figure 3.7).

Table 3.8: Sensitivity test of decay rate on NGM

| | $\mu = 0.004$ | $\mu = 0.02$ |
|---|---|---|
| No vac | $\begin{bmatrix} 0.48 & 0.58 \\ 22.57\frac{N_b}{N_c} & 12.66\frac{N_b}{N_c} \end{bmatrix}$ | $\begin{bmatrix} 0.3 & 0.80 \\ 15.28\frac{N_b}{N_c} & 15.83\frac{N_b}{N_c} \end{bmatrix}$ |
| Vac | $\begin{bmatrix} 0.48 & 0.58 \\ 19.68\frac{N_b}{N_c} & 7.08\frac{N_b}{N_c} \end{bmatrix}$ | $\begin{bmatrix} 0.3 & 0.80 \\ 14.89\frac{N_b}{N_c} & 9.22\frac{N_b}{N_c} \end{bmatrix}$ |

### 3.5.6 Code availability

The code for this study can be found in the git (https://git.wur.nl/chang025/btb_transmission_and_r_map). Data has been obtained from DAFM. The restrictions

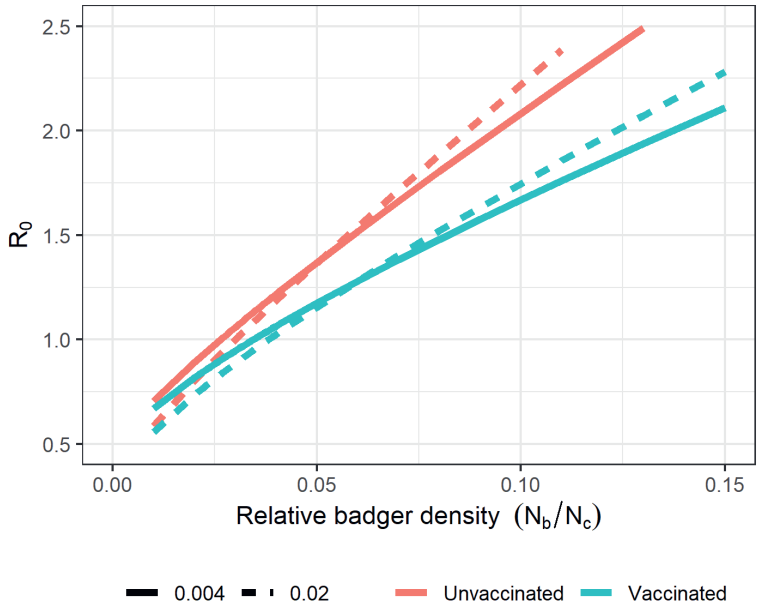


Figure 3.7: Within-herd $R$ in an isolated herd with different relative badger density. A) $\mu = 0.004$; B) $\mu = 0.02$

apply according to the General Data Protection Regulation.

## 3.6 Acknowledgment

We thank Ann Barber and Thomas J. Hagenaars for their very helpful discussions, which led to considerable improvements of the manuscript.

# 4



# Is badger vaccination sufficient to eradicate bTB?

You Chang, Stefan Widgren, Mart C.M. de Jong, Jamie A. Tratalos, Simon J. More, Nienke Hartemink

This chapter is submitted as You Chang, et al. "Is badger vaccination, in combination with existing cattle-based controls, sufficient to eradicate bovine tuberculosis from Ireland? Insights based on a two-host and multi-route transmission model" to Preventive Veterinary Medicine

**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 early 2000s, badger culling was added as an additional control measure in the national programme, with this practice now progressively being replaced by badger vaccination. However, it is unclear whether badger vaccination, in combination with existing cattle-based control measures, 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 current cattle-based control measures, on bTB eradication at a regional level and to assess whether additional interventions are needed. Additionally, we investigate the 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.

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 existing cattle-based control measures, may not be sufficient to achieve eradication in this region. We highlight the need for a comprehensive intervention strategy that simultaneously targets multiple transmission routes.

## 4.1 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*) [162]. The main route for human bTB infection is through the consumption of contaminated milk. Notably, milk pasteurization can reduce this risk, and has resulted in a low number of human cases reported in Europe -- only 88 in 2019 [163]. bTB 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 test-and-removal programme for cattle. 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 [45, 54]. This period of herd restriction, also known as a herd episode, is triggered by a so-called 'bTB breakdown'. Several countries, including Australia, the Netherlands and several northern European countries, have successfully eradicated bTB [164, 165]. 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 [40]. 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 [36, 40, 42–44], and badger culling was subsequently added as an additional control measure in the national eradication programme [36]. However, alternatives to culling are required, given that badgers are protected animals under national legislation [46, 47]. The efficacy of vaccinating badgers with Bacille Calmette-Guérin (BCG) vaccines has been assessed by experimental and field trials, resulting in promising vaccination

efficacy ranging from 36% to 84% [1, 48–50, 115, 135]. 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 [36].

Chapter 3 conducted a follow-up assessment on the impact of badger vaccination on local cattle-badger transmission dynamics in the Kilkenny badger vaccination trial area. This study found that although badger vaccination can reduce the average between-herd reproduction number ($R$) for each herd to below 1, about 30% of herds can still transmit bTB to more than one other farm (that is, between-herd $R > 1$). Consequently, the overall effect of badger vaccination on bTB transmission at a regional level remains uncertain. The question remains as to whether badger vaccination, in combination with existing cattle-based control measures, is sufficient to 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 [20, 148]. 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 [24, 167], 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 [25, 135]. This local transmission can be influenced by the spatial heterogeneity of between-species contacts [25, 124, 135]. 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 [26, 27, 168] In addition, the trade of infected but undetected cattle can introduce infections to previously uninfected herds and areas [26, 169–171]. A quantitative understanding of two-host transmission with multiple transmission routes remains a key knowledge gap [172].

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 [145, 173, 174]. 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 [54, 172]. 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 [1, 52, 175–179], 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 [161, 175, 180]. 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, in addition to current cattle-based control measures, on bTB eradication at a regional level and to assess whether additional interventions are needed. Additionally, we investigate the 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. To achieve this, we expand our local bTB transmission model (Chapter 3) to a multi-host and multi-routes model that includes movement-mediated transmission using actual cattle movement data. In addition to assessing the impact of badger vaccination in addition to existing cattle controls, we also explore other interventions that can strengthen the eradication programme, including badger selective culling, cattle vaccination, improving farm biosecurity, risk-based trading and pre-movement trading. It is important to note that the assessment of these additional interventions is conceptual, and they require further assessment through empirical trials.

## 4.2 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 [103, 141]. Section 4.2.1 described the model, including local transmission, regional transmission, attribution of infection sources, and interventions. Data descriptions are provided in Section 4.2.2. Parameters for the model and sensitivity analysis are presented in Section 4.2.3 and 4.2.4.



### 4.2.1 Model formulation

#### 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. 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 (Chapter 3) There are two types of subpopulations, cattle herds and badger social groups. Each subpopulation has its own spatial unit, which corresponds to a specific location, such as a farm location or a badger territory location (represented in figure 4.1 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 have assumed 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 environment compartments ($E_c$ and $E_b$ for two spatial layers relating to 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 Supplement 4.6.1). Infected animals are considered to shed infectious material immediately after infection (that is, we assumed that there is no latent period). 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 of infection.



In contrast to the previous model (Chapter 3), this model incorporates a range of existing cattle-based control measures that form part of the national bTB eradication programme in Ireland, including a cattle test-and-removal programme and movement restrictions for infected herds. In the model, all herds are scheduled for periodic screening tests using SICCT on a random date with a fixed interval of 365 days. Test outcomes are assumed to follow a binomial distribution, with test sensitivity representing the probability of successfully detecting positive cases. A positive test result occurring in at least one animal in a herd signifies a herd bTB breakdown (that is, the start of a period of herd restriction, during which cattle movements are restricted), triggering the immediate removal of all test-positive cattle in the model. These removed animals are replaced with susceptible cattle to maintain a constant number of cattle in a herd. 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 negative 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, random sample testing of herds, contiguous testing or private test also existed in addition to the annual screening test. Furthermore, the gamma interferon blood test was used to re-test inconclusive cattle [36]. These testing practices were not modelled specifically in the model, but we assumed a test sensitivity of 0.8 (See table 4.1), which is at the higher end of published estimates, to account for their impact.

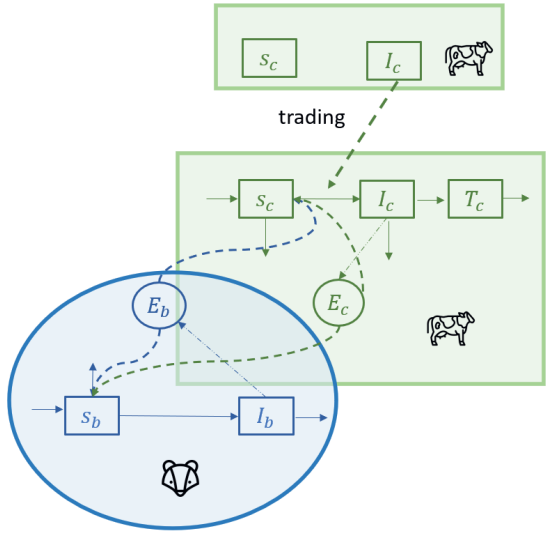


Figure 4.1: A schematic representation of the bTB transmission model, illustrating transmission dynamics within a local area and between-herd transmission via movement.

Badger territory and farm are the two spatial units in the local transmission (blue circle and green rectangle). 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 Supplement 4.6.1.

In the model, infected badgers experience mortality at a rate that is equal to the sum of the bTB-induced death rate and the natural background mortality rate. All deceased badgers are modelled in a "dead" compartment. To maintain a constant population at a regional level, the badgers replenish through transitioning from this "dead" compartment to "susceptible" at a rate equivalent to the death rate. By incorporating these mechanisms, the model allows the potential extinction of badger populations within specific territories, while ensuring a stable overall population within the study area.

**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 (Chapter 3), 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 [181], we have assumed no direct between-territory transmission.



We incorporate movement-mediated transmission into the model 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, similar to 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.

**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 introduced into the herd 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. 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)], [(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 Ec 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)].

**Interventions**

This is a conceptual study and does not directly relate to interventions 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.

Existing cattle-based control measures, which includes test-and-removal and movement restrictions, was considered the default (D) scenario in this study. 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 reducing transmission rate parameters (Chapter 3).

3. Badger vaccination with 100% coverage (BV): All badgers are vaccinated to assess the maximum potential of badger vaccination. (Note: this scenario may not be feasible in reality but is used for exploratory purposes.)

4. Selective culling (SC): Badgers are tested on average once a year and positive badgers are removed [182]. Removed infected badgers are assumed to be replaced by susceptible badgers to maintain a constant badger population.

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): All cattle are vaccinated, assuming a 40% reduction in cattle susceptibility. (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.

**herd level regional R**

We calculate the herd level regional basic reproduction ratio (R) under each intervention scenario using the simulated herd prevalence after reaching equilibrium ($R_{intervention} = \frac{1}{1-HerdPrevalence}$). $R_{intervention}$ 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 ($R_{intervention} > 1$).



### 4.2.2 Data

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

We used data from a previous badger vaccination trial area conducted in Kilkenny County between 2009 and 2012 [1]. 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. 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. The initial value for infectious cattle in the simulation was determined based on the number of cattle that tested positive in 2009.

**Cattle movement data**

Cattle movement data during the study period were extracted from DAFM's Animal Identification and Movement (AIM) database. The trading event via mart are simplified as a trade between farms in the model, which assumes no transmission via mart. Cattle movements were analysed as discrete herd-to-herd pairs and classified as outward movement, representing movements out of a herd, or inward movement, representing movements into a herd. Throughout the four-year duration, 1,335 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.

**Badger data**

The badger data used in this study were the same data as used in (Chapter 3). The badger infection dataset was obtained from [1], 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 [137, 139, 183]. 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.

### 4.2.3 Parameterization

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 constnat parameters by adopting estimations from a previous

local transmission model and from existing literature (see justification of their values and reference in Supplement 4.6.3). 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.

Table 4.1: Constant parameters.

| Parameter (unit per day) | Description | Values |
|---|---|---|
| Parameter estimation based on infection data | | |
| $\beta_{c,c}$ | Transmission rate parameter cattle to cattle | 1e-5 |
| $\beta_{b,c}$ | Transmission rate parameter badger to cattle | 4e-6 |
| $\beta_{b,ub}$ | Transmission rate parameter badger to unvaccinated badger | 9e-5 |
| $\beta_{c,ub}$ | Transmission rate parameter cattle to unvaccinated badger | 5e-4 |
| $\beta_{b,vb}$ | Transmission rate parameter badger to vaccinated badger | 5.1e-4 |
| $\beta_{c,vb}$ | Transmission rate parameter cattle to vaccinated badger | 4.4e-4 |
| $\mu$ | *M. bovis* decay rate parameter | 0.004 |
| $\varphi$ | shedding rate parameter $\frac{\mu^2}{(1-e^{-\mu}+\mu)}$ | 0.002 |
| Parameters derived from literature | | |
| $\gamma_b$ | Infectious badger death rate | 1/365 |
| $\alpha_c$ | Cattle background death rate | 9.13e-4 |
| $\alpha_b$ | Badger natural death rate | 7.52e-4 |
| SE | Sensitivity of the skin test | 0.8 (unitless) |

The local 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% [184].

### 4.2.4 Sensitivity analysis

We conducted a sensitivity analysis on the constant parameters for both parameters estimated from infection data and those derived from the literature. The transmission rate parameters ($\beta s$) and the decay rate parameter ($\mu$) 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 (Chapter 2). Applying this method to bTB transmission resulted in a high persistence of *M. bovis* with $\mu = 0.004$ per day (Chapter 3). In comparison, another modelling study by Brooks-Pollock et al. [54] estimated a lower persistence of *M. bovis* in the environment with fivefold higher $\mu$ (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 [20]. To examine the impact of the assumption about *M. bovis* persistence on the model, we re-estimated all the transmission rate parameters when $\mu$ = 0.02 per day, resulting in higher $\beta$ s compared to the default (high persistence) parameter set. We used $\mu$ = 0.02 and its corresponding re-estimated $\beta$s as a low persistence parameter set in the sensitivity analysis.

Table 4.2: Transmission rate and decay rate parameters for sensitivity analysis under low persistence assumption.

| Parameter (per day) | Low persistence assumption |
|---|---|
| $\beta_{c,c}$ | 3.56e-5 |
| $\beta_{b,c}$ | 2.5e-5 |
| $\beta_{b,ub}$ | 5.3e-4 |
| $\beta_{c,ub}$ | 1.7e-3 |
| $\beta_{b,vb}$ | 3.2e-4 |
| $\beta_{c,vb}$ | 1.6e-3 |
| $\mu$ | 0.02 |
| $\varphi$ | 0.01 |

In addition, we conducted sensitivity analysis for infectious period and latent period of badger and the sensitivity of skin test using one-at-a-time approach, with the range of these parameters shown in table 4.3. Furthermore, a global sensitivity analysis was conducted by drawing 1,000 parameter sets from entire parameter range, and results were shown in Supplement 4.6.4.

Table 4.3: Parameters range for sensitivity analysis.

| Parameter | Range |
|---|---|
| $\gamma_b$ | (1/730, 1/182.5) per day |
| SE | (0.5, 0.95) |
| Latent period of badger | (0, 90) days |



## 4.3 Results

### 4.3.1 The impact of different interventions

We compared the observed infection data from the trial with simulation results under the default scenario (existing cattle control measures, including cattle test-and-removal with 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: high persistence assumption simulations correspond more closely with badger prevalence, while low persistence assumption simulations more accurately reflecting cattle and herd incidence rate (see Supplement 4.6.5). Our model shows that, under the default scenario, herd incidence rates are predicted to be 14% under the assumption of high *M. bovis* persistence (line 1 in figure 4.2A) and 6% under the assumption of low *M. bovis* persistence (line 1 in figure 4.2B).

**Single route intervention**

None of the additional interventions, when considered in isolation but combined with the default scenario, can eradicate bTB. For example, adding badger vaccination to 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 figure 4.2). 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 figure 4.2).

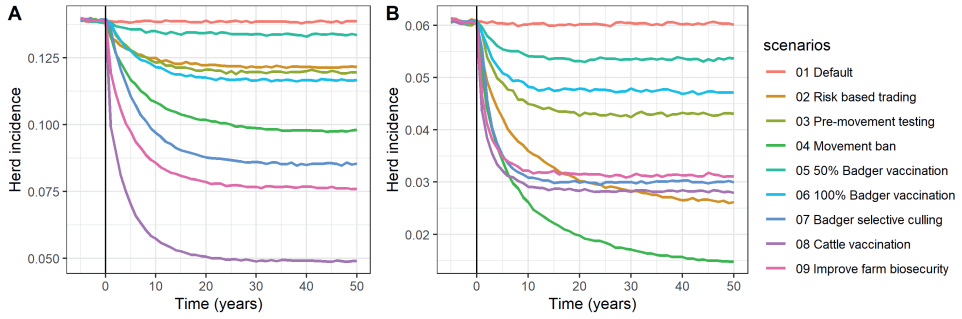


Figure 4.2: The effect of interventions (for lines 02-09, in addition to the default scenario) on herd-level annual incidence under the assumption of high and low *M. bovis* persistence.A) high persistence (*M. bovis* decay rate parameter as 0.004 per day). B) low persistence assumption (*M. bovis* decay 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.



Based to our results, risk-based trading, pre-movement testing and even movement ban, together with existing cattle-based control measures, cannot eliminate bTB (lines 2, 3 and 4 in figure 4.2). 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 figure 4.2B to figure 4.2A). 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 figure 4.2).

### Multi-routes interventions

We also assessed combinations of interventions that target multiple routes. In total, 120 scenarios were simulated, involving 5 measures targeting the badger route, 3 measures targeting the cattle route, and 4 measures targeting the movement route under two parameter sets) (figure 4.3). The default scenario was included with each combination of interventions.

In general, stringent intervention combinations that combine multiple transmission routes can bring $R$ <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 $R$ <1 (figure 4.3B). Un-


Figure 4.3: 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).

der the assumption of high *M. bovis* environmental persistence, however, additional interventions targeting all three routes are needed (figure 4.3A).

### 4.3.2 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 (figure 4.4A) and herd breakdowns (figure 4.4B) 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 figure 4.4.

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%)

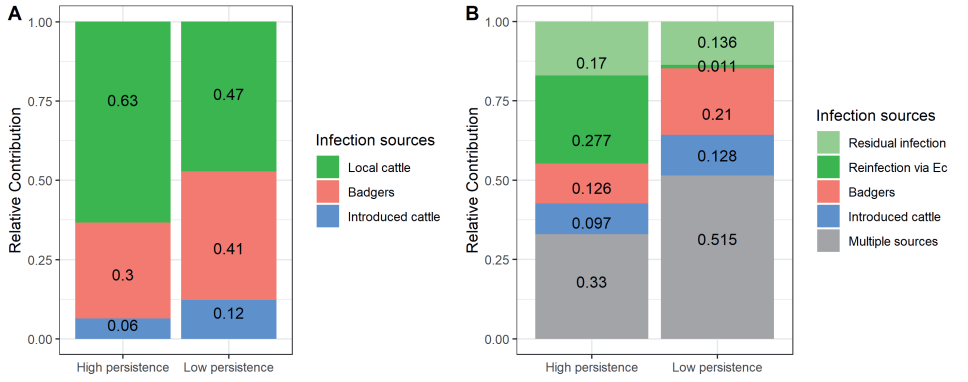


Figure 4.4: Predicted relative contribution of infection sources to cattle infections (A) herd breakdowns (B) under the assumption of high and low *M. bovis* persistence. Colours in bars represent the proportions attributed to each infection source. Note: as shown in figure 4.2, the total number of cattle 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.



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 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.

Table 4.4: 95% confidence bounds for the relative contribution of infection sources.

| Level | Infection sources | High persistence | | Low persistence | |
|---|---|---|---|---|---|
| | | mean | 95% quantiles | mean | 95% quantiles |
| Individual level | Local cattle | 63.4% | (61.8, 64.7%) | 47.3% | (45.1%, 49.5%) |
| | Badgers | 30.2% | (28.7%, 31.8%) | 40.6% | (37.3%, 43.5%) |
| | Introduced cattle | 6.4% | (5.8%, 7.2%) | 12.1% | (10.0%, 15%) |
| Herd level | Residual infection | 17.0% | (15.3, 19.4%) | 13.6% | (11.0%, 16.8%) |
| | Reinfection via Ec | 27.7% | (25.3%, 30.2%) | 1.10% | (0%, 2.16%) |
| | Badgers | 12.6% | (10.3%, 14.7%) | 21.0% | (16.3%, 25.2%) |
| | Introduced cattle | 9.7% | (7.9%, 11.7%) | 12.8% | (9.1%, 18.5%) |
| | Multiple sources | 33% | (29.8%, 36.9%) | 51.5% | (47.5%, 56.7%) |

## 4.4 Discussion

Bovine tuberculosis has a complicated infection ecology and has proved difficult to control in many countries where wildlife contribute to *M. bovis* transmission, including Ireland. The use of existing 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 existing cattle-based control measures – 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. 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 badger vaccination 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.



Our modelling demonstrates that badger vaccination, combined with existing cattle-based control measures, can reduce bTB in cattle but cannot 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 (Chapter 3). 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 R0 to 0.85 (Chapter 3). However, the impact of badger vaccination on a regional level could

be questioned due to the spatial heterogeneity- with 30% of herds between herd R > 1 (Chapter 3). This current study has answered this question, demonstrating that bTB can persist in this area, despite badger vaccination and existing cattle control measures. Under the badger vaccination scenario, the herd-level regional R under the badger vaccination scenario is above 1 (based on the calculation described in 3.2.2). This is not the average between-herd R of all herds (that is, 0.85) but rather the regional R 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 can further spread to low-risk areas through cattle movement or connected badger territories, thus sustaining endemic bTB within a region (that is, regional R>1). This could explain why other models that did not account for spatial heterogeneity often yield more optimistic results for badger vaccination [176, 179]. For example, previous studies based on the same trial have suggested that 40% coverage badger vaccination can eradicate bTB in badgers [1].



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 previous modelling study that found cattle to be the primary source of cattle infections [185]. 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) [126, 127]. 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% [172]. 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 [171, 172, 186]. 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 4.6.4). In newly infected area, 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 4.6.6). Lastly, interventions aimed at different transmission routes, such as badger vaccination or cattle vaccination, can also influence the relative contribution of infection sources.

In this study, the assumptions underpinning local transmission are equivalent to those from a previous study (Chapter 3), where the rationale and impact for these assumptions were extensively discussed. Indirect transmission of bTB via the environment assumes a homogenous distribution of animals within a farm or a territory, resulting in an even distribution of *M. bovis* over each spatial unit. However, this simplification is likely to diverge from the reality, because the distribution of cattle within a farm is likely to vary considerably [187] and badgers are likely to spend more time near setts than in other parts of their territories. Additionally, the direct transmission between badgers via biting is not considered in the current model. These simplifications could lead to an overestimation of inter-species transmission and an underestimation of within-species transmission at local transmission (Chapter 3). To address this concern, an improved understanding is needed of animal movements within herds and territories, as well as direct and indirect contacts between-species.

Our model has assumed that between-herd transmission occurs indirectly via cattle-badger-cattle 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 [181]. 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 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 (Chapter 3), 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 existing cattle-based control measures, cannot 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 is 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 [44, 188]. 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 [189]. 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 [190, 191]. 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 [192].

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 estimation method improved the quantification of environmental transmission, but also might have practical limitations when observations were not frequent enough, especially for endemic diseases (Chapter 2). 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 4.6.4). 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 4.6.4). The transmission rate parameters in this study were estimated from a within-local area transmission model (Chapter 3), where external infectious sources, such as cattle movement, were ignored during parameter estimation. However, this study modelled the transmission route mediated by cattle movement, which could overstimulate the cattle incidence and herd incidence (see supplement 4.6.5).

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 from 2012 to 2016 (Supplement 4.6.5). Conducting long-term badger surveillance to monitor badger population dynamics and bTB prevalence among badgers can improve our understanding of bTB dynamics.



## 4.5 Conclusion

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 existing cattle-based control measures, may not be sufficient to eradicate bTB in this study area. Achieving bTB eradication will require a comprehensive intervention strategy that simultaneously targets multiple transmission routes. 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.

# 4.6 Supplements

## 4.6.1 Compartments and transitions

The stochastic compartments and transitions are listed below:

Table 4.5: Description of compartments in the bTB transmission model.

| Compartments | Description |
|---|---|
| Badgers | |
| $S_b$ | Susceptible badgers |
| $O_b$ | Infected but not infectious badgers (the compartment exist but not in use by assuming a high transition rate from latent to infectious) |
| $O_{cumb}$ | Bookkeeping of the accumulative infected badgers |
| $I_b$ | Infectious badgers |
| $M_b$ | Dead badgers due to bTB |
| $D_b$ | Dead badgers due to natural mortality rate |
| Cattle | |
| $S_c$ | Susceptible cattle |
| $I_c$ | Infectious cattle |
| $I_{cumc}$ | Bookkeeping of the accumulative infectious cattle |
| $trade$ | the number of trade event |
| $I_{mov}$ | Infectious cattle involved in a trade movement (buying in) |
| $I_{mov_{cum}}$ | Bookkeeping of infectious cattle involved in a trade movement |
| $I_{sell}$ | Infectious cattle involved in a trade movement (selling out) |
| $T_{pos}$ | Test positive cattle |
| $T_{pos_{cum}}$ | Bookkeeping of accumulative test positive cattle |

**Replace badgers that die from natural causes with susceptible badgers**

To maintain the stable badger population in the model, we replace badgers that die from natural causes (that is, unrelated to bTB infection) with susceptible badgers, noting that newborn badgers are assumed as susceptible. The replacement rate parameter is set equal to the background mortality rate parameter $\alpha_b$.

$$D_b \xrightarrow{\alpha_b D_b} S_b$$

Replaced bTB- induced dead badgers to susceptible badgers.

Dead badgers caused by bTB are also replaced by new-born susceptible badgers. The replacement rate is equal to the bTB-induced mortality rate parameter $\gamma_b$.

$$M_b \xrightarrow{\gamma_b M_b} S_b$$



**Badger gets infected**

Susceptible badgers can become exposed to the *M. bovis* in the environment through both badger and cattle environmental layers, leading to infection ($O_b$). This exposure occurs within the badger territories (via $\exp_b$) and neighbouring farms that overlap with this badger territory (via $E_{nb}$). The transmission rate parameters are denoted as $\beta_{b,b}$ and $\beta_{c,b}$.

$$S_b \xrightarrow{\frac{\beta_{b,b} S_b \exp_b}{N_c} + \frac{\beta_{c,b} S_b E_{nb}}{N_c}} O_b$$

**Natural death of susceptible badgers**

Susceptible badgers experience mortality at a background rate denoted as $\alpha_b S_b$.

$$S_b \xrightarrow{\alpha_b S_b} D_b$$

**Infected badgers move to infectious badgers**

Infected badgers progress to an infectious badger at a rate $\lambda_b O_b$. While the model structure accommodates a latent period compartment, this study assumes a rapid transition from infection to infectious states, similar to a SI model.

$$O_b \xrightarrow{\lambda_b O_b} I_b$$

**Death of latently infected badgers due to natural causes**

Badgers in the latent period are subject to a background mortality rate $\alpha_b O_b$.

$$O_b \xrightarrow{\alpha_b O_b} D_b$$

**bTB-induced death**

Infectious badgers experience mortality due to bTB at rate denoted as $\gamma_b I_b$.

$$I_b \xrightarrow{\gamma_b I_b} M_b$$

**Death of infectious badgers due to natural causes**

Infectious badger can also experience mortality at a background rate, denoted as $\alpha_b I_b$.

$$I_b \xrightarrow{\alpha_b I_b} D_b$$

**Cattle get infected**

Cattle can be exposed to *M. bovis* in the farm (via $\exp_c$) or the neighbouring badger territories that overlap with this farm (via $E_{nb}$).

$$S_c \xrightarrow{\frac{\beta_{c,c} S_c \exp_c}{N_c} + \frac{\beta_{b,c} S_b E_{nb}}{N_c}} I_c$$

**Trade**

Two compartments $trade$ and $trade_{cum}$ are used to simulate stochastic trade events at a trading rate of $tr_{\sum?}$. The compartment Trade is an integer vector that starting from 0 and increases by 1 unit each time a trade occurs. $trade_{cum}$ is synchronized with the trade compartment at the end of each day. Trade events can only occur if a herd is eligible to trade ($Ttimer > 120$).

$$@ \xrightarrow{(\text{trade} \leq \text{trade}_{\text{cum}} \&\& Sc{>}0 \&\& \text{ Ttimer } {>}120)?\ \text{tr}_{\text{sum}} : 0.0} \text{trade}$$

If a trade event occurs ($trade > trade_{cum}$), the quantities for buying in ($I_{mov}$) and selling ($I_{sell}$) are sampled from a binomial distribution based on the proportion of infected cattle in the selling herd and the number of cows involved in a trade.

**Execute trade**

The increment of Infectious cattle in the buying herd and the decrement of the infectious cattle in the selling herd were also modelled using the transition. These events can only occur when $I_{mov} * S_c > 0$ and $I_{sell} * I_c$. To expedite this transition, a factor of 100 is added to the rate.

$$S_c + I_{mov} \xrightarrow{I_{mov} * S_c * 100} I_c$$

$$I_c + I_{sell} \xrightarrow{I_{sell} * I_c * 100} S_c$$



**Replace test positive cattle**

The cattle testing positive for bTB are culled immediately and subsequently replaced by the susceptible cattle. To expedite this transition, a factor of 100 is added to the rate. This transition can only occur when both $I_c > 0$ and $T_{pos} > 0$.

$$I_c \xrightarrow{I_c * T_{pos} * 100} S_c$$

**Replace cattle that die due to natural causes**

Both susceptible and infectious cattle experience death due to natural causes (ie not related to bTB). We assume that all the new-born cattle are susceptible. Therefore, the process of dying and replacing susceptible cattle cancel out, and only the dead infectious cattle are replaced by susceptible cattle.

$$I_c \xrightarrow{\alpha_c I_c} S_c$$

### 4.6.2 Post-time functions

Post-time function is calculated at end of each time unit (day in this study). Post-time functions define the calculations that are not defined by transition. All the compartment involved in the post-time functions were listed in table 4.6.

Table 4.6: Description of compartments that are involved in post-time functions.

| Compartments | Description |
|---|---|
| $E_b$ | *M. bovis* shed by badger in a badger territory |
| $\exp_b$ | Exposure to the $E_b$ |
| $E_{nb}$ | Exposure to the *M. bovis* shed by the other species in the neighbourhood |
| $E_c$ | *M. bovis* shed by cattle in a farm |
| $\exp_c$ | Exposure to the $E_c$ |
| $trade_{cum}$ | Bookkeeping of trade movements, updated to trade at the end of each day. So $trade_{cum} < trade$ when trade occurs |
| $T_{test}$ | Scheduled time point for the upcoming test |
| $T_{timer}$ | The duration from the last time bTB-positive (based on the test) to today, used for risk-based trading |
| $Partner$ | The selected trading partner |



**Environmental contamination**

The shedding and decay of *M. bovis* are modelled as deterministic processes:

$$\frac{dE_b}{dt} = \varphi I_b - \mu E_b$$
$$\frac{dE_c}{dt} = \varphi I_c - \mu E_c$$

where $\varphi$ is the shedding rate parameter and $\mu$ is the decay rate parameter. The shedding rate parameter is determined by the function $\varphi = \frac{\mu^2}{(-1+e^{-\mu}+\mu)}$ (Chapter 2).

Therefore,

$$E_b = e^{-\mu}E_b + \frac{(1-e^{-\mu}) * \mu}{(-1+e^{-\mu}+\mu)} * I_b$$

$$E_c = e^{-\mu}E_c + \frac{(1-e^{-\mu}) * \mu}{(-1+e^{-\mu}+\mu)} * I_c$$

Two additional compartments, $\exp_b$ and $\exp_c$, are used to calculate the exposure to

*M. bovis* based on the instantaneous value of $E_b$ and $E_c$ (which represent the area under the curve of $E_b$ and $E_c$, respectively). The model uses a day as a time unit, as determined by the parameter unit. As a result, $\exp_b$ and $\exp_c$ calculate daily exposure to *M. bovis*:

$$\exp_b = I_b + \frac{(1 - e^{-\mu})}{\mu} * E_b$$

$$\exp_c = I_c + \frac{(1 - e^{-\mu})}{\mu} * E_c$$



The $\exp_b$ represent the exposure of badgers to *M. bovis* shed by badgers within a badger territory while $\exp_c$ represents the exposure of cattle to *M. bovis* shed by cattle within a farm.

**Exposure to the other species**

Compartment $E_{nb}$ calculates the exposure to *M. bovis* shed by the other species, used in the between-species transmission rate. In a cattle herd, $E_{nb}$ represents the exposure to *M. bovis* shed by neighbouring badgers, while in a badger social group, $E_{nb}$ represents exposure to *M. bovis* shed by neighbouring cattle.

The between-species connection matrix in the ldata is used to calculate $E_{nb}$ for each subpopulation, including both farms and badger territories. In this matrix, each column corresponds to a subpopulation and consists of a string of pairs {“from”, “ratio”}, where the ratio represents the overlapping area as a proportion of the total area of the “from” subpopulation. When there is no connection, the matrix is padded with {-1,0}.

For example, consider two subpopulations, with the first being a farm and the second a badger territory. In the between-species connection matrix, the first column is: {{2, 0.1}, {-1, 0}}, where {2, 0.1} means the subpopulation 1 (the farm) is connected to the subpopulation 2 (the badger territory), and the overlapping area between them accounts for 10% of the total area of subpopulation 2 (badger territory). Therefore, 10% of the $\exp_b$ from the subpopulation 2 (the badger territory) is used when calculating the $E_{nb}$ for the subpopulation 1 (the farm).

While (ldata[i] > 0){ # while loop through all the pair till reach the padding

Extract “from” and “ratio” from ldata;

Extract $\exp_b$ and $\exp_c$ value in the “from” subpopulation;

$E_{nb} += ratio * (\exp_b + \exp_c\}$ content...

In badger subpopulation, $\exp_c$ is 0 and in cattle population, $\exp_b$ is 0. $E_{nb}$ includes all the exposure to *M. bovis* from the other species who share the same area. Therefore, the $\exp_b + \exp_c$ represent $\exp_b$ or $\exp_c$ in the calculation above.

**Trade**

The timing of trade movements is stochastically modelled using compartment $trade$, with the trading rate parameter $tr_{sum}$, as described in Section 4.6.1 Excute trade. Decisions on the source of cattle and the number of cattle involved in a trade are modelled in post-time function using the between-herd connection matrix in the ldata.

In the between-herd matrix, each column corresponds to a subpopulation, consisting of triplets in the format {“from”, “trading rate”, “trading count”}. For example, subpopulation 1 has {{2, 2/365, 2}, {3, 1/365, 1}, {-1, 0, 0}, ..}. This configuration represents that subpopulation 1 buys 2 cows from subpopulation 2 twice a year and 1 cow from subpopulation 3 once a year. The entries {-1, 0, 0} are the padding when no trading connection exists.

When a trade occurs, a decision regarding the selling herd is stochastically modelled based on the competing trading rate among different trading partners. Once the trading partner is determined, the correspondent trading intensity is selected. We then sample from a binomial distribution, with the total count being the “trading count”, and the probability being the prevalence in the “from” subpopulation. The process is used to determine $I_{mov}$ and $I_{sell}$.

In the example above, we first select a trading partner from subpopulation 2 and 3, based on their trading rate 2/365 per day and 1/365 per day respectively. If subpopulation 2 is selected, 2 cows are involved in the trade. We then sample the number of infectious cows among these 2 cows based on the prevalence in the subpopulation 2. If 1 infectious cow is selected, then the subpopulation 1 has $I_{mov} = 1$ and subpopulation 2 has the $I_{sell} = 1$.

**Testing**

Herds are scheduled at a random date for annual tests. Test positive cattle are slaughtered, resulting in herd breakdowns and movement restrictions until two follow-up tests are successfully completed at 60-day intervals [45, 54].

The scheduled testing time is calculated in compartment $T_{test}$. When the scheduled $T_{test}$ is reached, testing occurs. The number of positive cattle ($T_{pos}$) is determined based on the sensitivity of test and the infectious cattle in a herd. If positive cattle are found ($T_{pos} > 0$) or if this is the first re-test ($T_{timer} <= 60$), a new re-test is scheduled 60-day later. Otherwise, a new test with a 365-day interval is scheduled.



**Movement-related interventions**

In this model, interventions targeting movement involve changes in the C code, which are explained in detail here. Interventions targeting badger and cattle routes only involve adjustments of parameters (described in the Supplement 4.6.2).

Under the default scenario, trade movement is only permitted when the selected selling herd is not under herd restriction ($T_{timer} > 120$), otherwise a random herd without restriction is selected as the selling herd. When risk-based trading is implemented in the model, the $T_{timer}$ from the selling herd is compared with $T_{timer}$ from the buying herd. Only buying from herds with lower risk classifiers is allowed. If the selling herd has higher risk (lower $T_{timer}$ value), we randomly select from eligible herds whose $T_{timer}$ is lower than the buying herd. When pre-testing movement is implemented, the selected $I_{mov}$ will be tested unless the herd has been tested in the previous 6 months. Only the test negative cows will be traded. If there are positive cows being tested in $I_{mov}$, a new test will be scheduled in this herd. When movement is banned, then $I_{mov}$ is 0.

### 4.6.3 Detailed parameterization

Table 4.1 in the main body of this paper lists the parameters used in our model. These parameters are derived from the previous study, with some estimated from infection data and others obtained from literatures, whose justification for their values was outlined (Chapter 3).

However, this study has some assumptions that differ slightly from the previous

study. As a result, some parameters required adjustments accordingly. In the following section, we explain the changes made to the parameters and the reasons for these adjustments.

**Infectious period**

In this study, cattle remain infectious until they test positive and are removed, or until they die at the background mortality rate. In contrast, the previous study modelled the removal of infectious cattle by using a bTB-induced mortality rate. The bTB-induced mortality rate was calculated as 1 divided by the average infectious period of cattle using the infection data. Due to the different model structure, the infectious period of cattle is not used in this study.



The infectious period for badgers is assumed as one year, the same as the previous study (Chapter 3). The life expectancy after bTB infection varies from 35 days to 3.5 years in in laboratory studies, with the most of badgers survive between one to two years [151, 157]. Badgers who have apparent respiratory origin infection have a mean survival time of 491 days with CI 253 to 729 days [158]. Based on all those information, we assume a one year infection period for badgers.

**Test sensitivity**

In the previous study, we assumed 100% sensitivity for the diagnostic test (the single intradermal comparative cervical tuberculin (SICCT) test) when estimating transmission rate parameters. We made this choice due to the lack of data regarding residual infection. Infected but undetected animals shed *M. bovis*, leading to an underestimation of environmental contamination. On the other hand, these hidden infections also cause an underestimation of new cases. Therefore, both the left and right sides of the dose-response relationship were underestimated (see equation 4.1), whose effects on transmission rate parameter estimation are likely to be cancelled out. As a result, the assumption of sensitivity of test has minimal impact on the transmission rate parameter estimation in the previous study.

$$P\left(\frac{case}{S}\right) = 1 - e^{(-\beta * exposure)} \tag{4.1}$$

However, in this study, the sensitivity is important and can influence the infec-

tious period of the cattle, which is modelled specifically using scheduled testing timepoints and test sensitivity. The sensitivity analysis has been subject to a wide range of estimates for SICCT sensitivity, from 50 ~ 95% in some other studies [27, 168, 193, 194]. As this model does not model other tests specifically such as random sample testing, contiguous testing, private test, and gamma interferon test for re-test, we assume a sensitivity of 80% with a sensitivity analysis in Supplement 4.6.3.

**Latent period**



In our previous study, we assumed a short latent period of 1.8 days for cattle and 90 days for badgers. We acknowledged that altering this assumption on latent period could change the estimation of the transmission rate parameter but not the reproduction ratio (R). This was because the modifications to both transmission rate parameter and latent period counterbalance each other as we can see from the formula of R. For example, in a Susceptible-Infectious-Susceptible (SIS) model, R is calculated as $\frac{\beta}{\alpha}$, while in a Susceptible-Exposure-Infectious-Susceptible (SEIS) model, it becomes $\frac{\beta}{\alpha}\frac{\alpha}{(\alpha+\gamma)}$ . The estimated transmission rate parameter $\widehat{\beta}$ in a SIS model equals to the $\widehat{\beta}\frac{\alpha}{(\alpha+\gamma)}$ in a SIES model. Distinguishing between transmission rate parameter and latent period based on fitting infection data to transmission models remain challenging [26], while experimental studies can provide more insights.

Sabio et al.[150] conducted a comprehensive review of pathogenicity in animal models and the regulatory mechanisms of pathogens, revealing solid evidence the difference in latency activation between of *M. bovis* and *M. tuberculosis*. The review suggested a lack or lower degree of latency in *M. bovis*, compared to the *M. tuberculosis*. In alignment with this evidence, this study assumes no latent period for cattle and badgers. However, we conducted sensitivity analysis on latent period specifically for badgers in Supplement 4.6.3.

**Transmission rate and decay rate estimations**

This study assumes no latent period, so the transmission rate parameters from previous study (Chapter 3) were adjusted using a factor of $\frac{\alpha}{(\alpha+\gamma)}$ to represent the transmission rate parameter estimation under no latent period assumption. $\frac{\alpha}{(\alpha+\gamma)}$

represents the proportion of animals that survive the latent period.

**Natural death rate for cattle and badgers**

The natural death rate for cattle and badgers were outlined in the previous study (Chapter 3). Our assumption is an average lifespan of 1330 days for badger and 1095 days for cattle.

**Intervention-related parameters**

In this model, some interventions are implemented by changing parameters in this model, such as badger vaccination, cattle vaccination, selective culling, improve farm biosecurity. The parameters were listed here:



Badger vaccination: The impact of badger vaccination on transmission rate parameters were estimated from infection data (Chapter 3). The model does not model vaccinated and unvaccinated badgers explicitly due to insufficient detail vaccination coverage at territory level. The vaccination coverage is modelled as an average reduction on the transmission rate parameters: $\beta_{average} = \beta_{b,vb} * (VC) + \beta_{b,ub}(1-VC)$. Vaccination coverage of 0%, 50% and 100% were used in this study.

Badger selective culling: We assume that badgers are being tested on average once a year, hence the selective culling rate for infectious badgers is 1/365 per day [182].

Cattle vaccination: The efficacy of cattle vaccination has been investigated in the field and in experimental settings, with estimates ranging from 0 to 60% with different standards for direct and indirect vaccine efficacy [192, 195, 196].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).

Improve farm biosecurity: There is limited research on the efficacy of different farm biosecurity strategies. We assume a 50% reduction on badger-to-cattle transmission.

### 4.6.4 Sensitivity analysis

We conduct a sensitivity analysis using a one-at-a-time approach to investigate the influence of uncertainty associated with each parameter on transmission dynamics. It is important to acknowledge that some parameters are not estimated independently; for example, the estimation of transmission rate parameters is

contingent on assumptions regarding the decay rate parameter and latent period. Consequently, an increase in parameter A might be counterbalanced by a decrease in parameter B, resulting in the same simulated herd incidence. This also means that drawing random samples from each parameter's confidence interval without the consideration of correlation between parameters can lead to unreasonably high or low prevalence, compared to observed prevalence.

Therefore, we use one-at-a-time approach to provide an overview of the impact of uncertainty for each parameter on simulation result.The goal of this sensitivity analysis is not to determine which parameter is more influential and has the most uncertainty, but rather to understand how these parameters can influence the simulation results. Lastly, a global sensitivity was conducted to assess the robustness of our conclusions regarding the badger vaccination efficacy. This involved draw random samples from varying parameters across their entire confidence bounds, while only the herd prevalence between 5% to 15% were considered as reasonable parameter sets.

### 4.6.4.1 The sensitivity of diagnostic tests

The sensitivity of screening test is estimated with a wide range from 55% to 95%. Herd incidence varies from 10% to 23% under the high environmental persistence (figure 4.5A) and varies from 4.8% to 14% under the low environmental persistence (figure 4.5B). In general, a lower test sensitivity leads to an average longer infectious period of cattle, hence also a larger contribution of hidden infection, reinfection via cattle (figure 4.6).

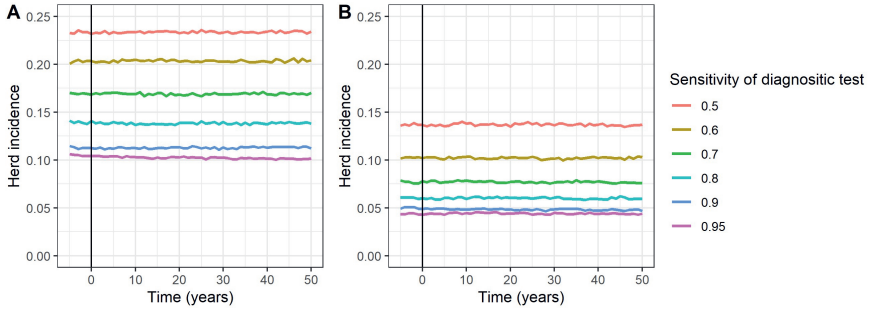


Figure 4.5: Variation in herd incidence across different diagnostic test sensitivities under the default intervention scenario, assuming higher persistence (A) and low persistence (B).

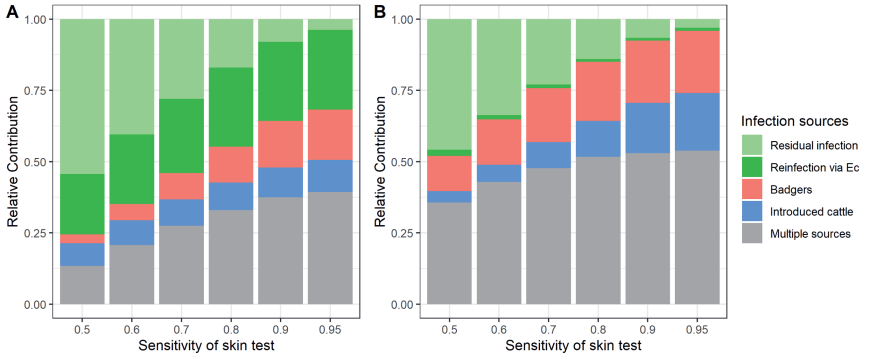


Figure 4.6: Variation in relative contribution of routes to herd breakdowns across different diagnostic test sensitivities under the default intervention scenario, assuming high persistence (A) and low persistence (B).Colours in bars represent the proportions attributed to each infection source.

### 4.6.4.2 Latent period of badgers

The latent periods for both cattle and badgers are assumed to be 0 day in this study, based on a review of pathogenicity in animal models and the regulatory mechanisms of *M. bovis*. While we believe this is highly likely the case for the cattle, it might be less certain for badgers' latent period. The latent period of bTB in badgers is not well understood. Previous animal studies showed a range of 95 to 158 days [151]. Therefore, in this sensitivity analysis, we assumed a badger latent period ranging of 0 to 150 days The impact of this parameter on herd incidence seems to be relatively small, ranging from 12% to 15% under the high persistence scenario and from 5% to 6.8% under the low persistence scenario (figure 4.7). A longer latent period leads to a slightly smaller contribution of badgers (figure 4.8).



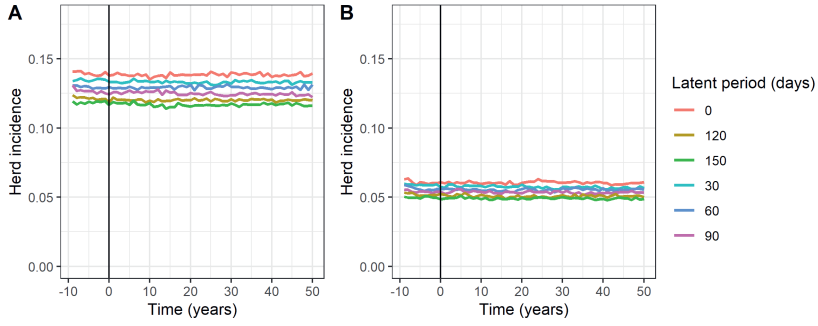


Figure 4.7: Variation in herd incidence across different latent period for badgers under the default intervention scenario, assuming higher persistence scenario (A) and low persistence scenario (B).

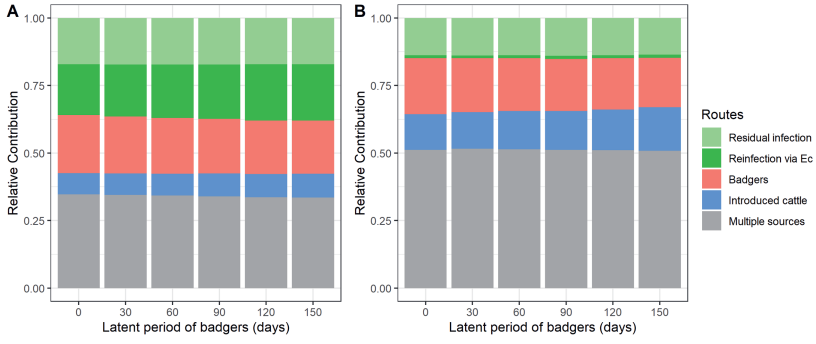


Figure 4.8: Variation in relative contribution of routes to herd breakdowns across different latent period of badgers under the default intervention scenario, assuming high persistence (A) and low persistence (B). Colours in bars represent the proportions attributed to each infection source.

### 4.6.4.3 Infectious period of badger

In this study, the average infectious period of badger is assumed to be 1 year. The life expectancy of infectious badgers can vary from 35 days to 3.5 years and is also influenced by whether the infection was established by biting or respiratory means. Therefore, in the sensitivity analysis, we used a range from 0.5 year to 2 years. A shorter infectious period of badger leads to a lower herd incidence ranging from 8% to 17% under a higher persistence scenario (figure 4.9A) and from 3% to 11% under a low persistence scenario (figure 4.9B). With a longer infectious period for badger, the contribution of badger also increases (figure 4.10).



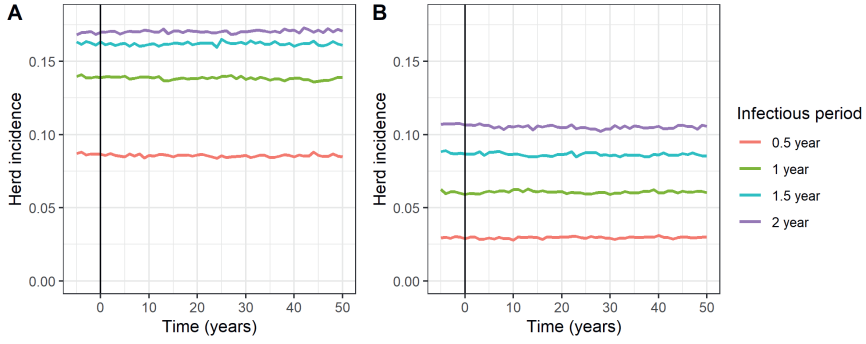


Figure 4.9: Variation in herd incidence across different infectious period for badgers under the default intervention scenario, assuming higher persistence (A) and low persistence (B).

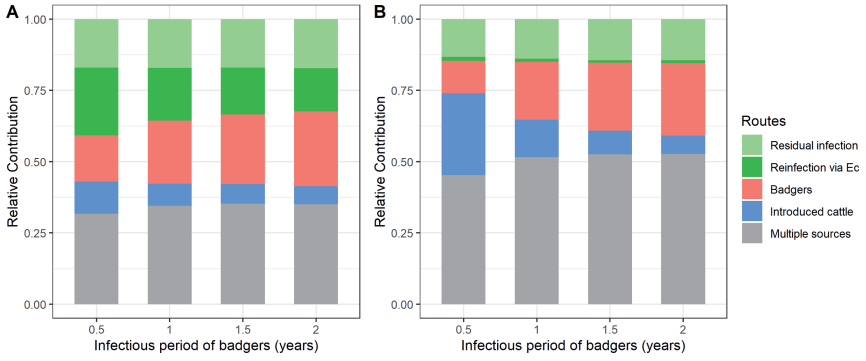


Figure 4.10: Variation in relative contribution of routes to herd breakdowns across different infectious period of badgers under the default intervention scenario, assuming high persistence (A) and low persistence (B).Colours in bars represent the proportions attributed to each infection source.

#### 4.6.4.4 Global sensitivity

We also conduct a global sensitivity analysis on the efficacy of badger vaccination efficacy on eradicating bTB by drawing 1000 parameter sets from the confidence intervals of each parameter (figure 4.11). We consider the runs where herd incidence fell between 5% to 15% prior the badger vaccination as plausible parameter sets. Badger vaccination has a limited impact on controlling bTB. Despite the uncertainties in parameters, our findings remain robust, indicating that badger vaccination is not sufficient to eradicate bTB even when assuming a constant 100% vaccination coverage.



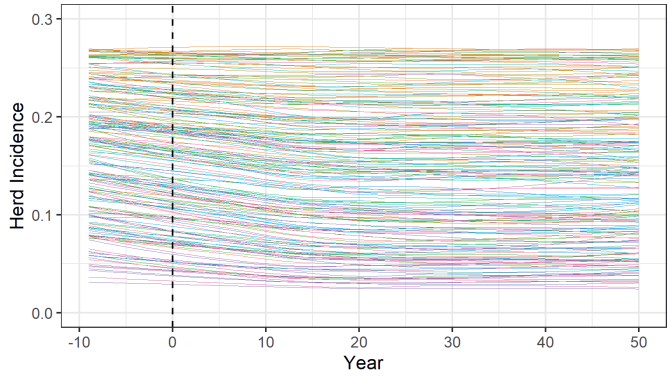


Figure 4.11: The global sensitivity analysis of badger vaccination efficacy on eradicating bTB, with parameters sampling from all the confidence intervals of each parameter. At the year 0, the badger vaccination with 100% coverage is implemented. Each color represents a parameter set, showing the average value of 100 repeats.

### 4.6.5 Rough comparison with observed data

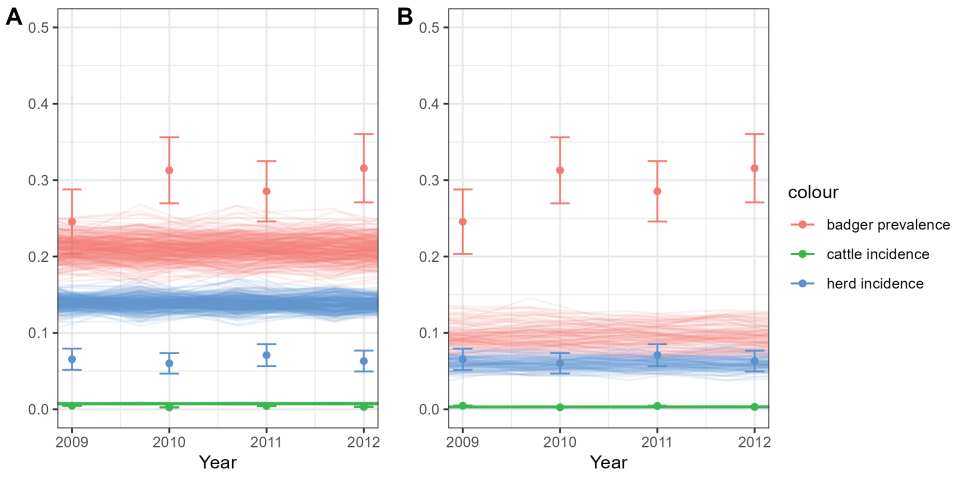


Figure 4.12: Comparison of simulation results and observations under A) high persistence scenario and B) low persistence scenario. The dots denote the observed data points, and the lines donate the simulated results. Red represents badger prevalence. Green represents cattle incidence and blue represents herd incidence.

In the study, the model does not aim to and also cannot repeat the transmission dynamic during the Kilkenny vaccination trial, as the ongoing vaccination progress and the badger population dynamics at the territory-level were not modelled. Therefore, we cannot use the observed data to validate or evaluate the model directly, but a rough comparison is done here. Parameter estimation from the infection data in this study suggested the high persistence. Using these estimated parameters, the model can capture the essence of the observed data with a very low cattle incidence of 0.2% to 0.3% and a much higher badger prevalenceof 20% to 30% (figure 4.12 A).

### 4.6.6 Relative contribution in high and low risk areas

The relative contribution of transmission routes depends on the spatial context. For example, we consider two small areas in Kilkenny study area. In low badger density area, the role of badger (15% at animal level) is less than half of the role in the high badger density area (35%) and also herd-level (9.7% vs 12.4%). Introduced cattle become more important route at herd level in low badger density area (figure 4.13).

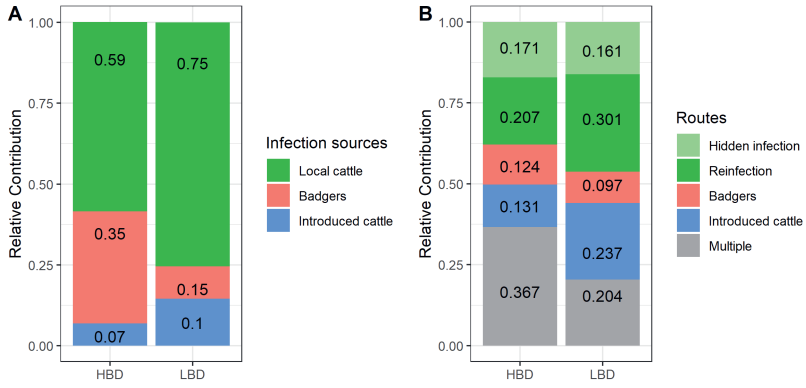


Figure 4.13: The relative contribution of transmission routes to cattle infections (A) herd breakdowns (B) in high badger density area (HBD) and low badger density area (LBD).Colours in bars represent the proportions attributed to each infection source.

### 4.6.7 Code availability

The full model code is available at https://git.wur.nl/chang025/btb.

## 4.7 Acknowledgment

We thank Damien Barrett, Philip Breslin and Andrew Byrne for their helpful discussion and suggestions, which led to considerable improvements of the manuscript.

# 5

# General Discussion

Bovine tuberculosis remains a persistent issue in many countries, including the Republic of Ireland (ROI), despite extensive eradication efforts. European badgers (*Meles meles*) play an important role in maintenance and transmission of bTB in cattle, based on several large-scale badger culling trials in Ireland [40, 42–44]. Badgers are a protected species and culling is therefore not a desirable or feasible long-term control measure. Alternative strategies like badger Bacille Calmette-Guérin (BCG) vaccination have been explored [1, 48–50]. In 2018, badger intra-muscular BCG vaccination was introduced as policy as part of the national eradication program, to progressively replace badger culling. While badger vaccination has since been rolled out across parts of the country, it is unclear whether badger vaccination, implemented nationally in addition to all cattle-based controls that are currently in place, is sufficient to eradicate bTB. This thesis aimed to assess the effectiveness of badger vaccination in the bTB eradication programme and to improve our understanding of transmission between cattle and badgers whilst accounting for spatial heterogeneity. It also aimed to provide evidence-based recommendations to policy makers on whether additional interventions are needed to strengthen the eradication programme.



To improve our understanding of bTB transmission, a statistical method is presented in Chapter 2 to quantify environmental transmission based on infection data. As environmental transmission has been suggested as the main transmission route for between-species transmission, Chapter 2 provides a foundational tool for understanding and quantifying (bTB) environmental transmission. Simulated data from a SIS model with environmental transmission was used to validate this simulation method. In addition, a novel exposure-based method was compared with the trajectory-fitting method, with the former outperforming the latter method, for reasons that are discussed.

In Chapter 3, this statistical method was used to quantify the environmental transmission of bTB between cattle and badgers within a spatial context, using the badger vaccination trial data and comparing vaccinated and unvaccinated areas. We found that *M. bovis* can persist in the environment for an extended period of time, with an estimated half-life period of about 6 months. Estimated parameters were used to calculate within-herd $R_0$ under scenarios with and without vaccination, using the

Next Generation Matrix (NGM) method. Between-herd $R_0$ maps were generated for bTB for the first time. These maps can not only identify high-risk areas for bTB transmission but also evaluate the impact of badger vaccination on the transmission in each local area. Despite vaccination reducing the average between-herd $R_0$ from 1.14 to 0.86, 30% of herds have $R_0 > 1$. Whether these herds with a high between-herd $R_0$ can sustain the bTB spread in the study area is uncertain, and requires further research.

The spread of bTB in a region involves more than transmission to and from badgers; it also involves other factors such as the persistence of *M. bovis* in the environment, the movement of infected cattle, and residual infection in the herd due to imperfect diagnostic tests. Therefore, a dynamic multi-host and multi-route model was developed in Chapter 4 to investigate the regional impact of badger vaccination on cattle incidence. This model showed that spatial heterogeneity complicates bTB control, indicating that badger vaccination, combined with existing cattle-based control measures, may not be sufficient for achieving bTB eradication in this region. The connection between herds, whether via movement or badgers, allows high-risk herds to spread bTB to low-risk herds, sustaining bTB in a region. Consequently, reducing local transmission in high-risk areas via extra control measures targeting badgers and cattle, and interventions to separate high- and low-risk areas, such as risk-informed trading, are suggested to enhance the current eradication strategy.



In the following discussion, I contextualize the main findings of my PhD research within a wider context. In Section 5.1, I integrate the most important findings from Chapter 2 to Chapter 4, using an analytical and broader view. In Section 5.2, I compare and contrast the findings of this thesis with previous work. Section 5.3 offers an outlook on further insights and future research, followed by limitations and conclusions in Section 5.4 and 5.5.

## 5.1 Why badger vaccination seems less effective: all you need to know is $R_0$, but which $R_0$?

The basic reproduction ratio, $R_0$, is the most important quantity in epidemic modelling. It defines the control effort needed to eliminate the infection in a homoge-

neous population. If $R_0$ can be brought below 1, the infection can be eliminated from the population. It is important not to confuse $R_0$ with the effective reproduction ratio $R_e$, which adjusts for the proportion of susceptible individuals in a population ($R_e = R_0 * \frac{S}{N}$). Unlike $R_0$, $R_e$ does not indicate the efforts needed to eliminate an infection. For example, an infection may have an $R_0$ of 5 under SIS model assumptions. At the endemic equilibrium, the prevalence of this disease would fluctuate around 80% and $R_e$ would fluctuate around 1 (since $R_e = R_0 * \frac{S}{N} = 5 * (1 - 80\%) = 1$). However, this equilibrium condition ($R_e \cong 1$) does not imply, given $R_0 = 5$, that disease eradication will be achievable through modest efforts. To assess the effort needed to eliminate an infection, one must examine $R_0$, not $R_e$. Throughout this thesis, I mainly talk about $R_0$. As $R_0$ can differ under different interventions scenarios, I refer to $R_0$ as the basic reproduction ratio in the presence of all existing cattle-based control measures, and $R_{vac}$ as the basic reproduction ratio under the badger vaccination scenario.



Unlike in a homogeneous population, the use of $R_0$ to assess control efforts can become misleading in a heterogeneous population [197]. Heterogeneity can result from different sources, including involvement of different species, local factors leading to spatial variations, or temporal changes. Aggregating $R_0$ in the presence of heterogeneity is challenging. In addition, while $R_0$ is a dimensionless quantity, its interpretation depends on the epidemiological unit in a system. The interpretation of $R_0$ becomes even more challenging when multiple epidemiological units are involved. Combining these two challenges, the understanding of bTB transmission and of the impact of specific interventions offers a perfect illustration of how $R_0$ can be misleading in a spatially heterogenous two-host population.

It is a common belief that the basic reproduction ratios $R_0$ for bTB – whether in cattle, in badgers or in a cattle-badger system under current control measures – are close to 1, which suggests that relatively modest improvements could be sufficient to bring the bTB transmission under control [38, 198]. However, some researchers have noted a discrepancy between the calculation of $R_0$, which suggests modest efforts, and the intensive control indicated by stochastic simulation models and practical experience [178]. The underlying causes of this discrepancy are poorly understood.

In bTB transmission, several types of heterogeneity exist, including the involvement of multiple species, and of multiple epidemiological units. In seeking to understand the impact of badger vaccination on $R_0$ in such a system, it is first important to clarify the efficacy of badger vaccination in reducing badger-to-badger transmission [1]. However, the subsequent steps are challenging, in seeking to translate this efficacy to a reduction in cattle herd incidence within a spatial heterogeneous system. In particular, this process involves aggregating $R_0$ across species, transitioning the epidemiological unit of $R_0$ from the individual animal level to the herd level, and then aggregating herd-level $R_0$ across different spatial context to an "average" $R_0$ (representing a regional summary). To achieve this, three types of $R_0$ were calculated within this thesis, including:

- Within-herd $R_0$ ($R_{0(two-host)}$): This $R_0$ uses animals as the epidemiological unit, which assumes that cattle and badgers are distributed homogeneously across the environment in a local area where a farm and a badger territory completely overlap (figure 3.1 in Chapter 3). This $R_0$ is calculated by using the Next Generation Matrix method, making the transition from a single-host (badger only) to a two-host transmission system.
- Between-herd $R_0$ ( $R_{0(two-host;herdlevel)}$) for each herd: This $R_0$ represents the average number of neighbouring herds that one infected herd can infect, using the herd as the epidemiological unit (figure 3.4 in Chapter 3). Between-herd $R_0$ was calculated by simulating a stochastic two-host transmission model for each local area, which considers each herd with its overlapping territories and connected herds.
- Regional $R_0$ ( $R_{0(two-host;herd\ unit;regional\ level)}$): This $R_0$ represents the average number of herds that a typical infected herd can infect in a region, derived from simulated herd prevalence at the endemic stage (figure 4.2 and figure 4.3 in Chapter 4). It provides a regional summary, accounting for spatial heterogeneity and connectivity between herds, rather than merely averaging the between-herd $R_0$ of each herd.

Due to the complexity of aggregating $R_0$ analytically, many studies, including Chapter 4, used stochastic simulation models to assess the impact of interventions

on herd incidence. Although we estimated that badger vaccination can reduce badger-to-badger transmission by 44% and cattle-to-badger transmission by 13% (Chapter 3), our simulations predicted that badger vaccination can only reduce regional $R_0$ from 1.31 to 1.25 (under the high environmental persistence scenario) or from 1.11 to 1.09 (under the low environmental persistence scenario) (Chapter 4). This regional $R_0$ is not simply the average value of between-herd $R_0$ in the area (the average value of $R_0$ from figure 3.4). The discrepancy between vaccination efficacy and the modest reduction in regional $R_0$ highlights the complexity of translating individual animal-level vaccination efficacy to the impact of vaccination on herd incidence in a spatial heterogenous system.

In the sections below, I will show how badger vaccination effectiveness changes in populations with increased heterogeneities. I use a simplified model to analytically calculate the vaccination impact on $R_0$ under different population assumptions, assuming complete (100%) vaccination coverage. The efficacy of badger vaccination is calculated as the relative reduction in $R_0$, defined as $1-\frac{R_{vac}}{R_0}$. In addition, assessing whether $R_{vac}$ falls below 1 is also important, as it highlights the potential for badger vaccination to eliminate bTB within the population.

### 5.1.1 From single-host to two-host transmission system

In a homogeneous mixing single-host population (figure 5.1A), vaccination has an efficacy of $VE$. An average fraction ($VE$) of the contacts that would have led to infection before vaccination is now prevented from causing infection after vaccination. The basic reproduction ratio after vaccination $R_{vac(single\ host)}$ can be derived as:

$$R_{vac(single\ host)} = (1- VE) * R_{0(single\ host)} \tag{5.1}$$

Vaccine efficacy was estimated as a 44% reduction in the badger-to-badger transmission rate parameter (Chapter 3). Hence the impact of badger vaccination in this population ( $1-\frac{R_{vac}}{R_0}$ ) is 0.44.

When moving to a two-host population (figure 5.1B), the impact of badger vaccination on the whole system depends on the composition of four types of transmissions

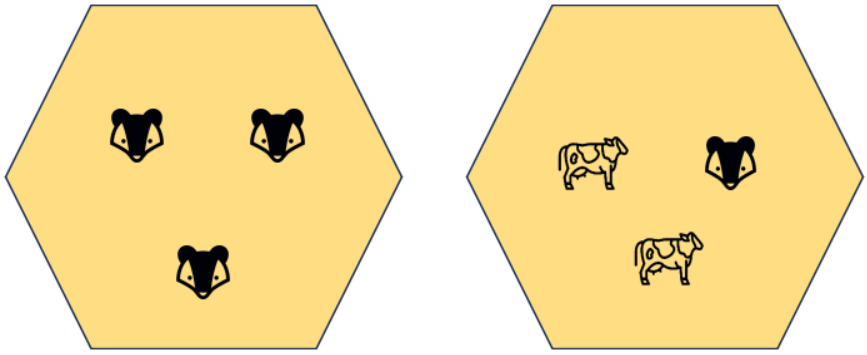

Figure 5.1: Schematic diagrams of A) A homogenous mixing single host population and B) A homogenous mixing two-host population with cattle and badgers



in this system and the local relative badger density (Chapter 3). Four partial reproduction ratios ($R_{c,c}, R_{b,c}, R_{c,b}, R_{b,b}$) represent the partial basic reproduction ratio for the 4 transmission directions, respectively. (Note: $R_{i,j}$ means transmission from host type $i$ to host type $j$). The NGM for the cattle-badger system is shown in equation 5.2 under a no-vaccination scenario and in equation 5.3 under a vaccination scenario. The $R_{0(two\ host)}$ and $R_{vac(two\ host)}$ are the largest eigenvalue of the NGMs, and can be calculated using equation 5.4 (Chapter 3).

$$NGM_{(two\ host)} = \begin{bmatrix} R_{c,c} & R_{b,c} \\ R_{c,b}\frac{N_b}{N_c} & R_{b,b}\frac{N_b}{N_c} \end{bmatrix} = \begin{bmatrix} 0.48 & 0.58 \\ 22.57\frac{N_b}{N_c} & 12.66\frac{N_b}{N_c} \end{bmatrix} \tag{5.2}$$

$$NGM_{vac(two\ host)} = \begin{bmatrix} R_{c,c} & R_{b,c} \\ R_{c,vb}\frac{N_b}{N_c} & R_{b,vb}\frac{N_b}{N_c} \end{bmatrix} = \begin{bmatrix} 0.48 & 0.59 \\ 19.68\frac{N_b}{N_c} & 7.08\frac{N_b}{N_c} \end{bmatrix} \tag{5.3}$$

$$\begin{aligned} R_{(two\ host)} = & \frac{1}{2}\left(R_{c,c} + R_{b,b}\frac{N_b}{N_c}\right) + \\ & \frac{1}{2}\sqrt{\left(R_{c,c} + R_{b,b}\frac{N_b}{N_c}\right)^2 - 4\left(R_{c,c}R_{b,b}\frac{N_b}{N_c} - R_{c,b}\frac{N_b}{N_c}R_{b,c}\right)} \end{aligned} \tag{5.4}$$

Table 5.1 presented the relationship between $R_{vac(two\ host)}$ and $R_{0(two\ host)}$ which

depends on the relative badger to cattle ratio ($\frac{N_b}{N_c}$, where $N_b$ denotes the number of badgers and $N_c$ denote the number of cattle in this local area).

Table 5.1: The impact of badger vaccination in a two-host population.

| $\frac{N_b}{N_c}$ | $R_{0(two\ host)}$ | $R_{vac(two\ host)}$ | Percentage reduction |
|---|---|---|---|
| 0.01 | 0.716 | 0.670 | 6.4% |
| 0.03 | 1.069 | 0.946 | 11.5% |
| 0.06 | 1.528 | 1.280 | 16.2% |
| 0.09 | 1.957 | 1.575 | 19.5% |



Moving from a single host to a two-host system, while badger vaccination can reduce 44% of badger-to-badger transmission and 13% of cattle-to-badger transmission, vaccine efficacy has a lower impact on reducing the two-host system's $R_0$. For example, $R_0$ is reduced 11.5% from 1.082 to as 0.97 when $\frac{N_b}{N_c} = 0.03$. In addition, when relative badger density is high, vaccination cannot bring the $R_{vac}$ below 1. In the following analysis assessing the vaccine impact on R, we adopt a fixed value for the badger density $\frac{N_b}{N_c} = 0.03$.

### 5.1.2 From animal level to herd level

The above-mentioned single-host and two-host transmission systems use animals as the epidemiological unit, whereas livestock infectious diseases are usually assessed at the herd level. For bTB, the EU requires that countries or regions must maintain a herd prevalence below 0.1% for at least 6 years to attain officially tuberculosis-free status [199]. Normally, in a single-host system, if a disease has within-herd $R_0$ (with animal as the epidemiological unit) less than 1, it is highly likely that transmission to other farms will also be less than one farm (between-herd $R_0$<1; herd as the epidemiological unit). This between-herd $R_0$ reflects the average number of herds that a typical infectious herd can infect. However, in a multi-host system where wildlife plays a role and shares habitats with livestock, the between-herd $R_0$ may not be smaller than within-herd transmission. This is observed in bTB, where cattle prevalence is about 0.5% and herd prevalence of bTB is about 4% [200], which means

animal level $R_0$ is 1.005 ($\frac{1}{1-cattle\ prevalence}$) and herd level $R_0$ is 1.07 ($\frac{1}{1-herd\ prevalence}$). Therefore, to assess the impact of vaccination on eradicating bTB, it is essential to understand the vaccine impact on between-herd $R_0$ (that is, using herd as the epidemiological unit).

In a livestock-wildlife transmission system, overlapping habitats usually facilitate transmission between species and among neighbouring herds [201]. In Chapter 3, I used simulation to calculate the between-herd $R_0$ whilst accounting for the heterogeneous spatial structure. There, the real spatial configuration of setts and farms was used, reconstructing the actual overlap as precisely as possible. Here, I use a simplified spatial structure to explain how the impact of vaccination on herd-level $R_0$ can be approximately calculated through analytical methods. In this simplified spatial structure, each badger territory overlaps three separate farms, with each farm sharing one-third of its area with the badger territory (Figure 2). Similarly, each farm overlaps with three badger territories. This spatial structure allows a homogeneous spatial distribution with a consistent $\frac{N_b}{N_c}$ over space, which is set to 0.03 in this example.



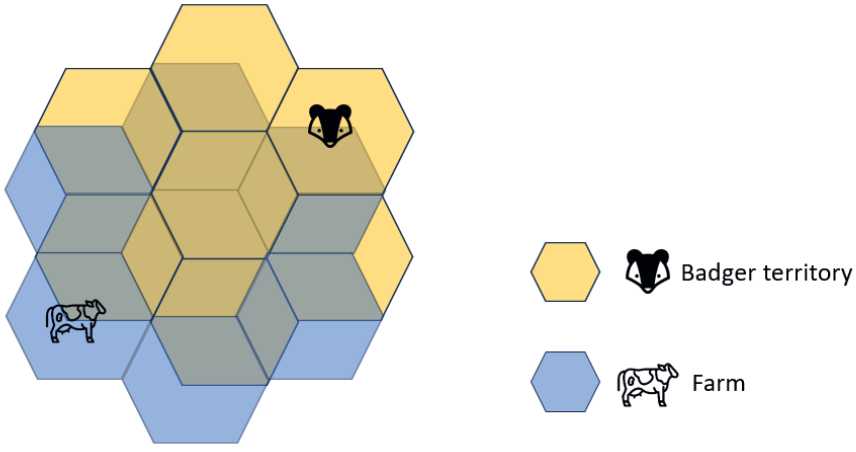


Figure 5.2: A schematic spatial distribution of farms and badger territories. The yellow hexagons delineate badger territories and blue hexagons delineate farm boundaries.

When using herd and territory as epidemiological units, the NGM for this two-host system, with the herd as the epidemiological unit, can be written as:

$$NGM_{(two-host;\ herd\ level)} = \begin{bmatrix} R_{F,F} & R_{T,F} \\ R_{F,T} & R_{T,T} \end{bmatrix} \tag{5.5}$$

$R_{F,F}, R_{T,F}, R_{F,T}, R_{T,T}$ represent four partial basic reproduction ratios for the 4 transmission directions respectively, considering herd/territory as the epidemiological unit. (Note: $R_{i,j}$ means from host type i to host type j). Specifically, $R_{T,F}$ represents the average number of herds that can be infected by an infected badger territory, and $R_{F,T}$ the average number of badger territories that can be infected by an infected herd. These ratios, $R_{T,F}$ and $R_{F,T}$, can be calculated analytically from animal-level transmission dynamics, which I will explain in further detail. However, $R_{F,F}$ and $R_{T,T}$ represent transmission routes between farms and between territories. To estimate these, we need to consider additional transmission routes, including cattle trade movement, the sharing of boundary fences and equipment between neighbouring farms, badger movement between territories and so on. This requires further assumptions and estimations for these transmission routes. To keep the initial model simple, we start with an assumption that there is no cattle movement between farms nor badger movement between territories in this simplified model ($R_{F,F} = 0$ and $R_{T,T} = 0$).



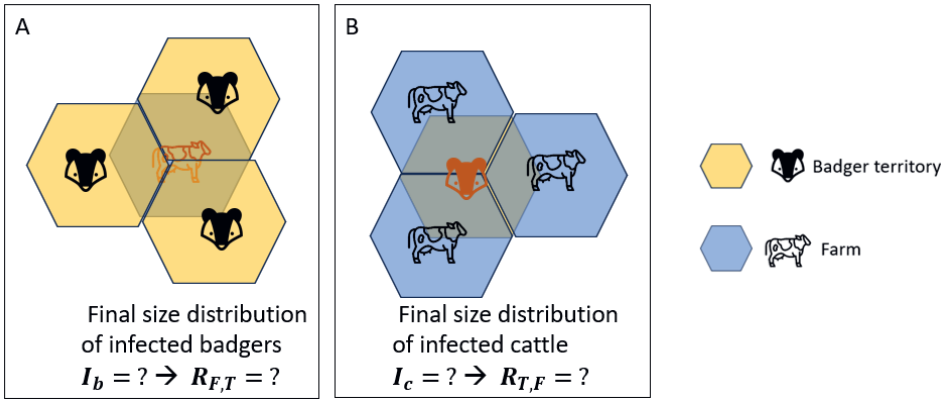


Figure 5.3: Schematic diagrams representing two types of local areas. Local area (A) has an index infected bovine, which can be used to calculate the total infected badgers ($I_b$) using the final size distribution, and to derive the $R_{F,T}$. Similarly, local area (B) has an index infected badger, which can be used to calculate infected cattle ( $I_c$ and $R_{T,F}$. The yellow hexagons delineate badger territories, and the blue hexagons delineate farm territories. Each yellow hexagons contains 3 badgers and each blue hexagons contains 100 cattle.

To calculate $R_{F,T}$, we analyse the transmission within a farm area depicted in Figure 3A, which has a single index infected bovine surrounded by three badger territories. To calculate the total number of infected badgers ($I_b$) in this farm, we assume a homogeneously mixing population consisting of 1 infected bovine, 99 susceptible cattle and 3 susceptible badgers. Then we calculate the distribution of infected territories assuming a binomial distribution. This calculation simplifies the spatial structure by treating badgers as if they were part of a single mixed population, although they originate from three separate territories. This simplification enables the total number of infections to be calculated, which is also known as the "final size distribution" calculation. The detailed algorithm for final size distribution calculation in a two-host system is provided in the Supplement 5.6 and the distribution of the total number of infected badgers $I_b$ is presented in 2.2.



Table 5.2: The distribution of infected badgers ( $I_b$) from a population with 100 cattle and 3 badgers, starting with one index infected bovine. The probability was calculated based on the final size distribution algorithm (see Supplement 5.6)

| Final size $I_b$ | Probability |
|---|---|
| 0 | 0.528 |
| 1 | 0.175 |
| 2 | 0.126 |
| 3 | 0.171 |

The expected number of infected badgers $E(I_b)$ is calculated using the equation:

$$P(I_b = 0) * 0 + P(I_b = 1) * 1 + P(I_b = 2) * 2 + P(I_b = 3) * 3 \tag{5.6}$$

To move the epidemiological unit of analysis from the animal to the herd, we define one infected badger territory as a territory containing at least one infected badger. With this definition, the expected number of infected territories is calculated in four steps:

1. Calculate the expected number of infected badgers using the final size algorithm and equation 5.6, resulting in 0.945.

2. Calculate the probability of each badger getting infected, which is 0.315 (0.94/3).

3. Calculate the probability of no badger being infected in a single territory. Given that a territory is infected if at least one badger is infected, the probability of a territory having no infected badger is 0.685 ( $(1-0.315)^1$).

4. Calculate the probabilities of 0, 1, 2 and 3 territories being infected, assuming a binomial distribution. The probability of $k$ herds getting infected can be derived as:

$$P(k) = \binom{n}{k} (p)^k (1-p)^{n-k} \tag{5.7}$$



Where $n$ is the number of territories being considered, $p$ is the probability of territory not being infected, and $k$ is the number of territories infected. The distribution of infected farms is presented in table 5.3.

Table 5.3: The distribution of infected territories ($I_T$) in a population with 100 cattle and 3 badgers in a farm as shown in figure 5.3, starting with one index infected bovine.

| Final size $I_T$ | Probability | Probability |
|---|---|---|
| 0 | $(0.685)^3$ | 0.321 |
| 1 | $3 * 0.685^2(1-0.685)^1$ | 0.443 |
| 2 | $3 * 0.685^1(1-0.685)^2$ | 0.204 |
| 3 | $(1-0.685)^3$ | 0.031 |

The expected infected herds ($R_{T,F}$) can be estimated as:

$$P(I_T = 0) * 0 + P(I_T = 1) * 1 + (I_T = 2) * 2 + (I_T = 3) * 3 = 0.945.$$

Similarly, to obtain $R_{T,F}$, we can calculate the total number of infected cattle ($I_b\, c$), based on a scenario that includes 1 infected badger, 2 susceptible badgers, and 99 susceptible cattle. (Using 99 instead of 100 to simplify calculations, so each farm has 33 cattle). This can be calculated in four steps:

1. Calculate the expected number of infected cattle using the final size algorithm, which is 1.53.
2. Calculate the probability of each bovine getting infected, which is 0.0155 (1.53/99).
3. Calculate the probability of no bovine being infected in a single herd. A herd is infected when at least one bovine being infected, so the probability of no bovine being infected in a given herd is 0.597 ($(1-0.0157)^{33}$).
4. Calculate the probabilities of 0, 1, 2 and 3 herds being infected, assuming a binomial distribution. The distribution of infected farms is presented in table 5.4.

Table 5.4: The distribution of infected herds ($I_F$) in a population with 100 cattle and 3 badgers, starting with one index infected badger.



| Final size $I_F$ | Probability | Probability |
|---|---|---|
| 0 | $(0.597)^3$ | 0.212 |
| 1 | $3 * 0.597^2(1-0.597)^1$ | 0.430 |
| 2 | $3 * 0.597^1(1-0.597)^2$ | 0.291 |
| 3 | $(1-0.597)^3$ | 0.066 |

The expected infected herds ($R_{T,F}$) can be estimated as:

$$P(I_F = 0) * 0 + P(I_F = 1) * 1 + (I_F = 2) * 2 + (I_F = 3) * 3 = 1.21$$

Applying the transmission rate parameter under the vaccination scenario (see equation 5.3) to the final size distribution, we can derive $R_{T,F}$ and $R_{F,T}$ under the vaccination scenario. $R_{0(two-host;\ herd\ level)}$ and $R_{vac(two-host;\ herd\ level)}$ can be calculated based on equation 5.5, which are shown in table 5.5.

Table 5.5: The herd-level partial R and $R_0$ for the system under un-vaccination $R_{0(two-host;\ herd\ level)}$ and vaccination scenario $R_{vac(two-host;\ herd\ level)}$

| Scenario | $R_{T,F}$ | $R_{F,T}$ | $R_{0(two-host;\ herd\ level)}$ | $R_{vac(two-host;\ herd\ level)}$ |
|---|---|---|---|---|
| Un-vaccination | 0.945 | 1.21 | 1.07 | - |
| Vaccination | 0.836 | 1.14 | - | 0.98 |

When using the herd as the epidemiological unit, badger vaccination can lead to an 8.4% reduction in the herd level $R_{0(two-host)}$ from 1.07 before vaccination to 0.98 after vaccination, under the assumption of $\frac{N_b}{N_c} = 0.03$ see table 5.5. In comparison to the measured vaccine impact in a two-host animal-level transmission system (Section 5.1.1), we can see that the impact of badger vaccination on herd-level R can be less effective under the same badger density.



In addition, if other transmission routes such as cattle movement between herds, sharing equipment and fences between neighbouring herds, and badger movement between territories are considered, for example assuming $R_{F,F} = R_{T,T} = 0.2$, it becomes impossible for badger vaccination to bring $R_{0(two-host;\ herd\ level)}$ below 1. The vaccination impact reduced further to 7% from 1.27 to 1.18 (See table 5.6).

Table 5.6: The herd-level partial R and $R_0$ for the system under the no vaccination scenario $R_{0(two-host;\ herd\ level)}$ and the vaccination scenario $R_{vac(two-host;\ herd\ level)}$, assuming additional transmission routes between herd and territories

| Scenario | $R_{T,F}$ | $R_{F,T}$ | $R_{F,F}$ | $R_{T,T}$ | $R_{0(two-host;\ herd\ level)}$ | $R_{vac(two-host;\ herd\ level)}$ |
|---|---|---|---|---|---|---|
| Un-vaccination | 0.945 | 1.21 | 0.2 | 0.2 | 1.27 | - |
| Vaccination | 0.836 | 1.14 | 0.2 | 0.2 | - | 1.18 |

### 5.1.3 From homogenous spatial structure to heterogeneous spatial structure

In Section5.1.2, we assessed the impact of badger vaccination on herd-level $R_0$, assuming a homogeneous spatial distribution as depicted in figure 5.3. In reality, however, the spatial distribution of farm areas and badger territories varies across space (figure 3.2), and farms often consist of several fragmented parcels that can be spatially dispersed. In addition, the number of badgers in each social group

and herd size also differ. Therefore, in chapter 4, we developed a metapopulation model to assess interventions whilst also considering spatial heterogeneity on transmission dynamics.

In this section, I again use a simplified example to assess the effect of spatial heterogeneity on vaccination assessment. Now, we look at the transmission between herds using a network model where the connection between herds is via badgers, cattle movement, or sharing equipment and fences. To introduce spatial heterogeneity while keeping the model simple, we categorize herds into high-risk herds and low-risk herds based on their between-herd $R_0$ using results of Chapter 3. The average between-herd $R_0$ in the Kilkenny study area was estimated to be 1.14 without badger vaccination. Within this average, 40% of herds – classified as high-risk herds – have their between-herd $R_0$ greater than 1, with an average of 2.23. The remaining 60% of herds – classified as low-risk herds - have between-herd $R_0$ less than 1, with an average of 0.42.



### $R_0$ for the system with spatial heterogeneity

Two herds are connected if they adjacent, overlap with the same badger territory, or have trade movement. As herds are classified into two groups (either high or low risk), we can define the proportion of connection between these two groups of herds:

$e_{ij}$ represents the proportion of edges (connections) that originate from type $i$ to type $j$, with $i$ and $j$ being either high R herds (H) or low R herds (L). In total, thus, there are four types of edges that sum up to 1 ($e_{HH} + e_{LL} + e_{HL} + e_{LH} = 1$).

$e_H$: is the proportion of all edges that originate from high R herds. $e_H = e_{HH} + e_{HL}$

$e_L$: is the proportion of all edges that originate from low R herds. $e_L = e_{LL} + e_{LH}$

The assortativity coefficient $r = \frac{e_{HH} + e_{LL} - (e_H e_H + e_L e_L)}{1 - (e_H e_H + e_L e_L)}$. This measure provides a gauge of how much more (or less) likely nodes are connected with others of the same type compared to a random distribution of edges. If $r = 1$, it indicates that nodes of same type are highly likely to be connected, while $r = 0$ suggests a random pattern of connection.

As I mentioned earlier, high R herds have an average between-herd $R_0$ of 2.23. We assume that the difference between the high R herds and low R herds is only in infectivity of a herd. This means that high R herd can infect 2.23 other herds regardless of whether the connected herds are high R or low R herds. Low R herds can infect 0.42 herds regardless of R status of the connected herd.

$$R_{H,H} = R_{H,L}, \frac{e_{HH}}{e_{HH} + e_{HL}} R_{H,H} + \frac{e_{HL}}{e_{HH} + e_{HL}} R_{H,L} = 2.23 \tag{5.8}$$

$$R_{L,L} = R_{L,H}, \frac{e_{LH}}{e_{LL} + e_{LH}} R_{L,H} + \frac{e_{LL}}{e_{LL} + e_{LH}} R_{L,L} = 0.42 \tag{5.9}$$

With this assumption, we can derive the NGM for these two types of herds as:

$$NGM_{0(herd\ level;\ spatial\ heterogeneity)} = \begin{bmatrix} \frac{e_{HH}}{e_{HH}+ e_{HL}} R_{H,H} & \frac{e_{LH}}{e_{LL}+ e_{LH}} R_{L,H} \\ \frac{e_{HL}}{e_{HH}+ e_{HL}} R_{H,L} & \frac{e_{LL}}{e_{LL}+ e_{LH}} R_{L,L} \end{bmatrix} \tag{5.10}$$

Note: One could also assume that high R herds and low R herds only differ as a result of herd susceptibility. Under that assumption, the NGM would be different, with the first row of the NGM adding up to 2.23 and the second row to 0.42.

The proportion of connections requires more information about the network, but we can analyse the two extreme scenario that set the boundaries for the $R_0$ for this system.

When $r = 0$, the network is random mixing, $e_{HH} = e_H e_H$ and $e_{LL} = e_L e_L$,

$$NGM_{0(herd\ level;\ spatial\ heterogeneity)} = \begin{bmatrix} \frac{0.4*0.4}{0.4*0.4+ 0.4*0.6} 2.23 & \frac{0.4*0.6}{0.4*0.4+ 0.4*0.6} 0.42 \\ \frac{0.4*0.6}{0.4*0.4+ 0.4*0.6} 2.23 & \frac{0.6*0.6}{0.4*0.4+ 0.4*0.6} 0.42 \end{bmatrix} \tag{5.11}$$

$$R_{0(herd\ level;\ spatial\ heterogeneity)} = 1.14$$

When $r = 1$, the network is highly assortative, meaning that high R herds only connect with high R herds $e_{HL} = e_{LH} = 0$,

$$NGM_{0(herd\ level;\ spatial\ heterogeneity)} = \begin{bmatrix} 2.23 & 0 \\ 0 & 0.42 \end{bmatrix} \tag{5.12}$$

$$R_{0(herd\ level;\ spatial\ heterogeneity)} = 2.23$$

When we assume a homogeneous distribution (such as in Section 5.1.2), there is only one type of herds with between-herd $R_0$ of 1.14 and the regional $R_0$ is also 1.14. However, if spatial heterogeneity is also considered (i.e. two type of herds), the dynamics are different. The regional $R_0$ depends on the network of connections between herds. If connections between herds follow random mixing ($r = 0$), the system $R_0$ is still 1.14. In a completely assortative network where high-risk herds only connect to high-risk herds and low risk herds only connect to low-risk herds, regional $R_0$ is 2.23.



**Vaccination impact on $R_0$ for the system**

According to table 5.1, the badger vaccination impact is higher in the relatively high badger density area (High risk herds), while it has limited effect in relatively low badger density area (less than 5% reduction when local $R_0$ < 1). Therefore, we assume that badger vaccination mainly reduces the high-risk herds R. When $r = 0$, the impact of badger vaccination on the NGM is:

$$NGM_{vac(herd\ level;\ regional)} = \begin{bmatrix} \frac{0.4*0.4}{0.4*0.4+\ 0.4*0.6} 2.23(1-VE) & \frac{0.4*0.6}{0.4*0.4+\ 0.4*0.6} 0.42 \\ \frac{0.4*0.6}{0.4*0.4+\ 0.4*0.6} 2.23(1-VE) & \frac{0.6*0.6}{0.4*0.4+\ 0.4*0.6} 0.42 \end{bmatrix} \tag{5.13}$$

$$R_{vac(herd\ level;\ regional)} = 0.4 * 2.23 * (1-VE) + 0.6 * 0.42 = 1.14 - 0.89VE$$

When $r = 1$, the impact of badger vaccination on the NGM is:

$$NGM_{vac(herd\ level;\ regional)} = \begin{bmatrix} 2.23(1-VE) & 0 \\ 0(1-VE) & 0.42 \end{bmatrix} \tag{5.14}$$

$$R_{vac(herd\ level;\ regional)} = 2.23(1-VE)$$

Under a homogeneous distribution assumption in which all herds have between-herd $R_0$ of 1.14, vaccination would reduce $R_0$ to $1.14(1 - VE)$. When introducing spatial heterogenous structure, the impact of badger vaccination is lower than its impact in a homogeneous assumption. For example, in a network with random mixing, $R_{vac(herd\ level;\ regional)}$ is $1.14 - 0.89VE$ (see equation 5.13), which is $0.25VE$ higher than the vaccine impact without spatial heterogeneity ($1.14(1 - VE)$). When the connection is more assortative, $R_{vac(herd\ level;\ regional)} = 2.23(1-VE)$ (equation 5.14), which is almost twice the value of $R_0$ under homogenous spatial distribution.

## 5.2 Comparison with other studies:

### 5.2.1 Badger vaccination impact

Several studies have been conducted to investigate the impact of badger vaccination, however, very few have used both mathematical modelling and analysis of observational studies. Initially, the lack of empirical data from vaccination trials required reliance on mathematical models with assumed vaccination efficacies. These early models assumed a full vaccination efficacy with a certain level of vaccination coverage, such as protecting 50%~80% of the population [175], and a wide range scenario analysis assuming protection of 10% or 80% of the population [176]. Later models also considered partial vaccination protection [177, 179, 202], basing vaccine efficacy on reduced detection of *M. bovis* in excretions [203] or tissues [50], or on reduction in transmission rate parameter [52].

In parallel to model simulations, several badger BCG vaccination trials were conducted in the 2010s to assess the impact of badger vaccination on bTB control. These included trials in Gloucestershire, England [204], Wales [205]; the Test-Vaccinate or Remove trial in Northern Ireland [182, 206]; the Kilkenny trial [1, 49] and the Non-Inferiority trial [115] in Republic of Ireland. Except for Aznar [1], most studies

from these trials were merely observational and compared the difference in herd incidence or badger incidence between vaccination and buffer areas. Although these observational studies provide some insights into the impact of badger vaccination, they can generate misleading results given that the analysis of these observational studies could not account for differences in local transmission dynamics between areas.

As more field trials began to provide valuable data, the integration of these observed data into mathematical modelling became more important. Aznar et al. [1] made an important step in combining empirical observations with mathematical modelling to understand the badger vaccine impact. By developing a badger transmission model, they estimated vaccination efficacy at 59% (8.8~83%) using badger infection data from the Kilkenny trial. Building on this foundation, this thesis deepens our understanding of badger vaccination impact by developing a two-host transmission model. Using both badger infection data from the Kilkenny trial and corresponding cattle surveillance data, this study estimated a 44% reduction in the badger-to-badger transmission rate parameter and a 13% reduction in the cattle-to-badger transmission rate parameter. The estimations from the studies in this thesis are slightly lower than Aznar's estimation, but not significantly. The difference in badger vaccination efficacy estimation between this thesis (Chapter 3) and Aznar et al.[1] is reasonable as the earlier work ignored local cattle infection. The impact of vaccination impact estimated from their single-host transmission model can be partly explained by the differences in local cattle infection.



### 5.2.2 NGM and R

As I discussed in Section 5.1, the basic reproduction ratio can have different meanings when using different epidemiological units and different assumptions about populations. Therefore, caution is needed when comparing different $R_0$.

Several estimations for the basic reproduction ratio were based on single-host transmission models, assuming no external infection source. Therefore, these $R_0$s consider within-species transmission as well as transmission from other hosts, which should be higher than partial $R_0$ for within-species transmission ($R_{cc}$ and $R_{bb}$) as estimated in Chapter 3. For example, $R_0$ for cattle was estimated from 0.5 to

4.9, either via density-dependent or frequency-dependent models [26, 142, 180, 207]. $R_0$ for badger is mostly calculated using observed badger prevalence ($\frac{1}{1-prevalence}$), from 1.03 to 1.46 [1, 175, 208, 209].

A few studies have calculated the basic reproduction ratio in a two-host system using the Next Generation Matrix (NGM) method. Brooks-Pollock and Wood et al [161] and Aznar et al [1] provided a conceptual framework for using NGMs to study badger-cattle transmission dynamics but did not identify four partial basic reproduction ratios ($R_{c,c}, R_{b,c}, R_{c,b}, R_{b,b}$). As Brooks-Pollock and Wood [161] assumed high within-species transmission ($R_{b,b}$ and $R_{c,c}$ close to 1), it is not surprising that this study concluded that there would be limited impact of badger controls on bTB in cattle. Aznar et al [1] listed all possible NGMs and suggested that 40% of vaccination coverage may be sufficient to bring system $R_0$ below 1. However, Aznar's NGM used a mixture of epidemiological units, animal level for badgers and herd level for cattle. As a consequence of this mixing of epidemiological units in the NGM, badger vaccination efficacy would directly impact between-herd transmission, which might be an oversimplification of the challenges as described in Section 5.1. In addition, Bouchez-Zacria et al. [210] estimated four partial reproduction $R_0$ at the herd level, by estimating transmission rate parameters (using animals as the epidemiological unit) from infection data and using simulations to aggregate herd level $R$. Although the epidemiological units are different from the NGM in Chapter 3, this study similarly identified high intra-species transmission (with estimated $R_{b,c} = 0.21 \sim 1.09$, $R_{c,b} = 0.38 \sim 1.45$) and low within-species transmission ($R_{c,c} = 0.24 \sim 0.74$, $R_{b,b} = 0.08 \sim 0.41$), which suggests that badger-cattle could be a maintenance-community in some areas [210].

### 5.2.3 Insights into transmission directions

In addition to insights from the NGM (Chapter 3), the meta-population model in Chapter 4 also provides insights into transmission dynamics and the evolving directions of transmission. For example, let us start from a 'clean' area where *M. bovis* has not been found in cattle and badgers. The cattle trade movement introduces bTB infection to a herd, leading to cattle-to-cattle transmission within a herd. Then, the infections may spread to local badgers and neighbouring herds, thus establishing infection in this local area. The likelihood and speed of this

spread depend on the local spatial structure of farms and badger territories, and the relative density of badgers. During this initial establishment phase, transmission mainly occurs from cattle to cattle, and from cattle to badgers, as the local badger prevalence is low in this clean area. Then bTB circulates in this local area until herd breakdowns. After herd breakdowns are lifted, most infected cattle are removed and the direction of transmission shifts as the local cattle prevalence is low. Infected badgers start to transmit bTB back to cattle, thus sustaining the circulation of *M. bovis* in the area. In this spillover phase, we mostly see badger-to-badger and badger-to-cattle transmissions. If cattle become infected, cattle-to-cattle transmission can amplify transmission, triggering recurrent breakdowns and moving from a spillover to an establishment phase.

A recent study in a previous clean area [25] supports this concept as it showed the important role of early amplification of *M. bovis* by transmission between cattle farms in establishing bTB in the local badger population, which then passed it back to cattle. Therefore, besides the impact of spatial heterogeneity on transmission direction, transmission directions also evolve over time (as captured by Chapter 4). This change is driven by the introduction of new infections into an area and the implementation of test-and-removal. These two processes result in the dynamics of local transmission alternating between the establishment and spillover phases. This cycle between phases can take a few years, based on another modelling study [210]. This hypothesis could provide an explanation for different patterns of transmission directions in phylodynamic studies, including a predominance of cattle-to-badger (as opposed to badger-to-cattle) transmission in some studies [25, 127] and badger-to-cattle transmission in others [124, 126, 211]. Further phylodynamic studies could aim to validate this hypothesis.



## 5.3 Further insights and future research

Modelling for public health operates in a circular manner [212], and this way of looking at the role of modelling is also applicable to bTB control. The policy question of how badger vaccination impacts bTB control defined the objective of our modelling. Based on our current understanding of badger-cattle transmission dynamics, I developed a model and fitted that model to available data. This then

provides scientific insights into the badger vaccination impacts. Firstly, we verified the results from previous research that badger vaccination can reduce local transmission, and badger vaccination should be incorporated within the national eradication programme [1]. However, we also noted new insights that badger vaccination may not be sufficient to control local transmission in high-risk areas. Such high-risk areas can spread bTB to low-risk areas and sustain infection at a regional level.

Based on this understanding, we recommend more stringent interventions in high-risk areas in addition to badger vaccination and cattle test-and-removal. Options include extra intervention in badgers such as badger selective culling, and additional cattle-focused interventions such as cattle vaccination. Lastly, we also recommend the creation of barriers between high-risk areas and low-risk areas, for example, through risk-based trading.



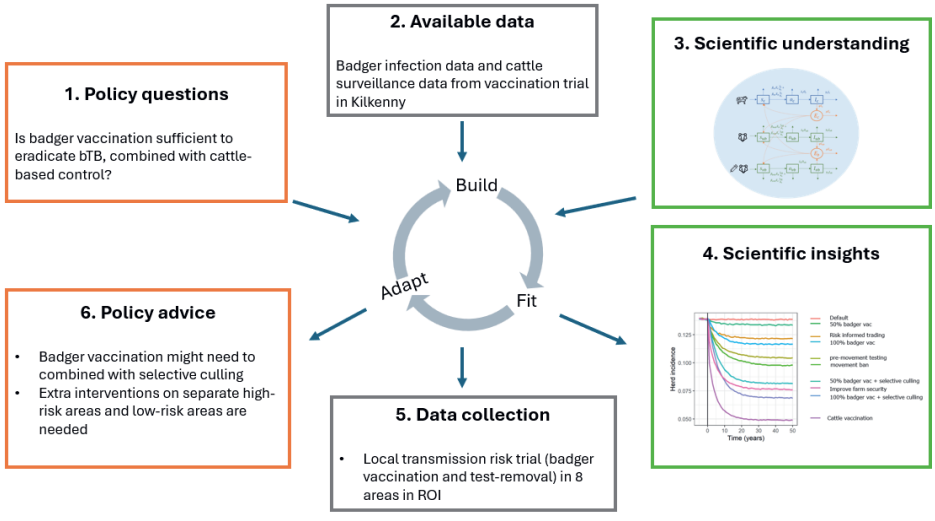


Figure 5.4: Model for bTB control inspired by Heesterbeek et al.[212].

Insights and recommendations derived from this study can be validated by further data collection in other areas and by future empirical trials. Recently, a new badger vaccination trial (Local transmission risk trial) has been conducted across eight different areas in Ireland, with serological samples currently being analysed. This data can refine this transmission model, generating more insights and policy

recommendations regarding badger vaccination and selective culling. Field trials of cattle vaccination combined with the development of DIVA (Differentiating Infected from Vaccinated Animals) diagnostic technologies are taking place in UK [213]. In addition, the impacts of risk-based trading and different farm biosecurity measures, including badger-proof fencing, require further investigation via empirical trials.

In addition, future research should also improve our understanding of other perspectives relevant to bTB control. In a two-host transmission system, long-term monitoring of badger population and badger prevalence is as important as cattle surveillance. The use of deep learning to analyse camera footage may allow us to conduct long-term monitoring of badger populations in a less intrusive and more cost-effective way. Fundamental studies, such as aerosol sampling in farms or experiments on whether *M. bovis* can be re-aerosolized in farm settings, can deepen our knowledge of *M. bovis* transmission and identify farm-level hotspots for improving farm biosecurity. Integration of Whole Genome Sequencing and transmission models can reduce uncertainties in transmission mechanisms and validate our hypotheses about the changes in transmission directions during the phases of spillover and establishment. Lastly, although this study did not consider other bTB hosts, other wildlife such as deer can make the transmission system even more persistent in certain areas. This should be addressed by adapting models based on data collected from those areas.



## 5.4 Limitations

This thesis assumed a homogeneous distribution of pathogens within a spatial unit due to limitations relating to the resolution of available data (Chapter 3 and 4), which simplifies the realistic distribution of cattle within a farm and badgers within a territory [187]. Additionally, it does not include all the potential transmission routes, such as badger-to-badger transmission via biting, between-territory transmission via badger movement, and between-herd transmission via sharing of equipment and boundary fences. These simplifications could underestimate the within-species transmission and overestimate between-species transmission, potentially leading to an overestimation of of the impact of badger vaccination. Given this direction of bias, this thesis can robustly conclude that badger vaccination combined with

existing cattle-based control is not sufficient for bTB control, which highlights the need for a comprehensive intervention strategy that simultaneously targets multiple transmission routes.

As the main goal of the thesis is to understand cattle-badger transmission in a spatial context and assess the impact of badger vaccination, we assumed the relative density ($\frac{N_b}{N_c}$) between two hosts as the main driver of spatial heterogeneity. Thus, areas of high relative density are also high-risk areas in this thesis. While no significant association was found between $\frac{N_b}{N_c}$ (when calculating $N_b$ at territory scale) and cattle incidence data in this study area, a significant association was observed between the number of badger setts and cattle incidence within a farm. Although sett-level data may have potentially better identified local risk, Chapter 3 and 4 used a territory scale for badgers due to data limitations. Therefore, it was not surprising to observe no significant association between the simulated cattle incidence at the farm and territory scale from Chapter 4 and the observed data. Further studies that aim to improve understanding of local transmission would benefit from finer resolution data within territories and within farms. Based on the location and duration of where animals stay, dispersal kernels could be implemented to identify high-risk areas within a local area [214], which can also provide insight into how farm biosecurity could be improved. Despite these limitations in data resolution, the insights on two-host transmission and badger vaccination assessment gained from this thesis remain valid.

## 5.5 Conclusion

In Ireland, the implementation of badger BCG vaccination into the bTB eradication programme is an important step towards bTB eradication. Badger vaccination has been shown to reduce badger-to-badger by 44% and cattle-to-badger transmission by 13%. We demonstrated that although badger vaccination, combined with cattle test-and-removal, is sufficient to bring local R below 1 in some areas, it is not sufficient to control bTB in high-areas. More importantly, the spread between high-risk areas and low-risk areas can sustain the bTB at a regional level. Therefore, we recommend more stringent controls targeting cattle and/or badgers, and also interventions such as risk-based trading to stop the spread of infection from high-

risk areas to low-risk areas. Finally, it is important for policymakers to set realistic expectations for the badger vaccination programme, recognizing its limitations in controlling bTB, and acknowledging the necessity of implementing additional controls.

## 5.6 Supplements

### 5.6.1 Final size distribution

The final size distribution for single host has been described in details in other paper [66, 215], where transmission chains for a population with 5 infectious and 5 susceptible individuals are listed as an example (figure 5.5).

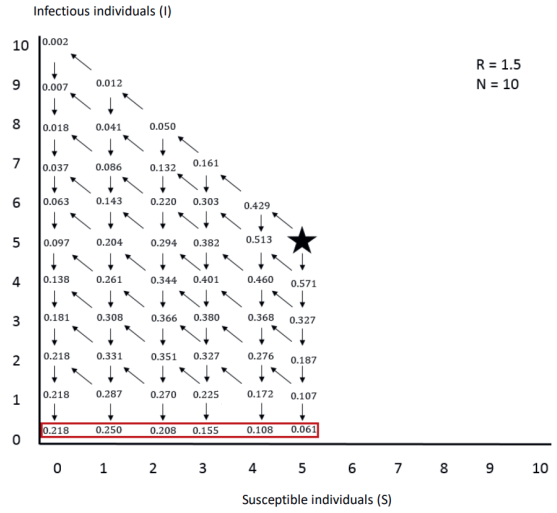


Figure 5.5: The probabilities for all possible transmission chains for a population of 10 individuals starting with 5 susceptible and 5 infectious individuals with a basic reproduction ratio of 1.5. [216]. The star represents the initial point.

In a two-host system, it is harder to plot the transmission chain, which has 4 dimensions. However, we can still write an algorithm to calculate the probabilities of each transition. In a two-host transmission chain, there are 6 types of events. The probability of each event is calculated as follows:

The probability of escaping infection in type 1:

$$\frac{\alpha_1 I_1}{\frac{\beta_{11} * I_1 S_1}{N_1} + \frac{\beta_{12} * I_1 S_2}{N_1} + \alpha_1 I_1} * \frac{I_1}{I_1 + I_2} = \frac{N_1}{R_{11} S_1 + R_{12} S_2 + N_1} * \frac{I_1}{I_1 + I_2}$$

The probability of escaping infection in type 2:

$$\frac{\alpha_2 I_2}{\frac{\beta_{21} * I_2 S_1}{N_1} + \frac{\beta_{22} * I_2 S_2}{N_1} + a_2 I_1} * \frac{I_2}{I_1 + I_2} = \frac{N_1}{R_{21} S_1 + R_{22} S_2 + N_1} * \frac{I_1}{I_1 + I_2}$$

The probability of type 1 getting infected by type 1:

$$\frac{\frac{\beta_{11} * I_1 S_1}{N_1}}{\frac{\beta_{11} * I_1 S_1}{N_1} + \frac{\beta_{12} * I_1 S_2}{N_1} + \alpha_1 I_1} * \frac{I_1}{I_1 + I_2} = \frac{R_{11} S_1}{R_{11} S_1 + R_{12} S_2 + N_1} * \frac{I_1}{I_1 + I_2}$$

The probability of type 1 getting infected by type 2:

$$\frac{\frac{\beta_{12} * I_1 S_2}{N_1}}{\frac{\beta_{11} * I_1 S_1}{N_1} + \frac{\beta_{12} * I_1 S_2}{N_1} + \alpha_1 I_1} * \frac{I_1}{I_1 + I_2} = \frac{R_{12} S_2}{R_{11} S_1 + R_{12} S_2 + N_1} * \frac{I_1}{I_1 + I_2}$$

The probability of type 2 getting infected by type 1:

$$\frac{\frac{\beta_{21} * I_2 S_1}{N_1}}{\frac{\beta_{21} * I_2 S_1}{N_1} + \frac{\beta_{22} * I_2 S_2}{N_1} + a_2 I_1} * \frac{I_2}{I_1 + I_2} = \frac{R_{21} S_1}{R_{21} S_1 + R_{22} S_2 + N_1} * \frac{I_1}{I_1 + I_2}$$

The probability of type 2 getting infected by type 2:

$$\frac{\frac{\beta_{22} * I_2 S_2}{N_1}}{\frac{\beta_{21} * I_2 S_1}{N_1} + \frac{\beta_{22} * I_2 S_2}{N_1} + a_2 I_1} * \frac{I_2}{I_1 + I_2} = \frac{R_{22} S_2}{R_{21} S_1 + R_{22} S_2 + N_1} * \frac{I_1}{I_1 + I_2}$$

The algorithm for calculating the probability of the final outcomes:

Table 5.7: The algorithm.

| | |
|---|---|
| Program | Calculate the final size distribution of infections in two-host SIR |
| Input | $N_1$ the total population of host 1, $N_2$ the total population of host 2. Initial status $i_1$,$s_1$,$i_2$,$s_2$. Four partial reproduction ratios $R_{11}, R_{21}, R_{12}, R_{22}$ |
| Initialization | Create a 4-dimentional array "A" with dimensions ($N_1$+1, $N_1$+1, $N_2$+1, $N_2$+1) and initialize all elements to 0. Set the initial starting point to 1. |
| Nested loops for iteration | • For "$s_1$" from "$S_1$" to "0"<br>– For "$i_1$" from "$N_1 - s_1$" to "0"<br>◇ For "$s_2$" from "S2" to "0"<br>· For "$i_2$" from "$N_2$-$s_2$" to "0"<br>· $I_1$ recovery: if "$i_1 > 0$", calculate the recovery of $i_1$ and update A.<br>· $I_2$ recovery: if "$i_2 > 0$", calculate the recovery of $i_2$ and update A.<br>· $I_1$ infection by $i_1$: if "$i_1 > 0$", calculate the infection of $i_1$ by $i_1$ and update A.<br>· $I_2$ infection by $i_1$: if "$i_1 > 0$", calculate the infection of $i_2$ by $i_1$ and update A.<br>· $I_1$ infection by $i_2$: if "$i_2 > 0$", calculate the infection of $i_1$ by $i_2$ and update A.<br>· $I_2$ infection by $i_2$: if "$i_2 > 0$", calculate the infection of $i_1$ by $i_2$ and update A. |
| Return the array | Return(A) |

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# Summary

Despite extensive control measures, *Mycobacterium bovis*, the causative agent of bovine tuberculosis, persistently infects about 0.5% of the Irish national cattle population annually. Until recent decades, it has became clear that eradication of bTB in cattle requires addressing multiple hosts, including both cattle and badgers. As badgers are protected animals, badger culling is not a desirable long-term control measure and is being progressively phased out by badger vaccination. However, it remains unclear whether badger vaccination, combined with existing cattle-based control is sufficient to eradicate bTB or whether additional interventions are required to strengthen the eradication programme.

The assessment of badger vaccination on reducing bTB in cattle is challenging due to the involvement of multiple hosts and transmission routes. At a local scale, *M. bovis* can be shed into the environment, where it may survive for an extended period. Therefore, cattle reinfection can occur even after the removal of infected cattle. In addition, badgers usually reside on farms and move between farms, sharing contaminated environments with cattle. Badgers can become infected by one herd and subsequently spread bTB to neighbouring herds. Infected cattle might remain undetected within the herd due to imperfect diagnostic tests, potentially continuing to shed of *M. bovis*. In addition, the trade of infected but undetected cattle can introduce infection to previously uninfected areas. Although badger vaccination efficacy has been estimated on at the badger population level, understanding its influence on cattle bTB requires consideration of all the mentioned factors.

Therefore, the overall objective of this thesis was to assess the effectiveness of badger vaccination in the bTB eradication programme in order to support policy-making. In addition, this thesis aimed to improve our understanding of transmission between cattle and badgers, accounting for spatial heterogeneity and different transmission routes. The overall objective of this thesis was divided into the following

three sub-objectives:

1. Develop a method to quantify environmental transmission using infection data.
2. Quantify the transmission between cattle and badgers via environment considering the spatial context, and assess the impact of badger vaccination on local transmission.
3. Develop decision support tools for assessing interventions at a regional level, and assessing the impact of (combinations of) badger vaccination and other additional measures.

In Chapter 2, a novel method to quantify environmental transmission was developed, laying the foundation for understanding and quantifying bTB environmental transmission. While bTB transmission between cattle and badgers has been suggested mainly via environmental transmission, it had yet to be quantified. This novel method can estimate back transmission rate and decay rate parameters simultaneously using infection data. The method was validated using simulated data, showing its ability to quantify environmental transmission at both the transient phase and the endemic equilibrium.

In Chapter 3, the impact of badger vaccination was assessed at the local level by analysing both cattle and badger infection data during the badger vaccination trial in County Kilkenny. I developed an environmental transmission model to understand bTB transmission between cattle and badgers within a local area, comparing vaccinated and unvaccinated areas. A local area is defined as a farm with overlapping badger territories and connected farms. The statistical method from Chapter 2 was used to estimate transmission rate and decay rate parameters and calculate within-herd and between-herd $R_0$ under scenarios with and without vaccination. Between-herd $R_0$ maps were generated for bTB for the first time, which can identify the high-risk areas for bTB transmission and evaluate the badger vaccination impact on that transmission in each local area. Despite vaccination reducing the average between-herd $R_0$ from 1.14 to 0.86, 30% of herds have $R_0 > 1$, indicating that potentially bTB can be sustained in parts of a region.

In Chapter 4, the impact of badger vaccination was assessed at the regional level in the Kilkenny study area. I developed a dynamic multi-host and multi-route transmission model. Transmission to and from badgers, 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 are all considered in this model. This model presents how spatial heterogeneity could pose challenges in bTB control, suggesting that badger vaccination, combined with the existing cattle-based control, is not sufficient to eradicate bTB in this region. Additional interventions that simultaneously target multiple transmission routes, in cattle, badgers and movement, are required. Overall, in Chapter 5, I discussed why badger vaccination might be less effective than it seems (based on its vaccination efficacy). I used simplified models to show how vaccination efficacy becomes less effective from a homogeneous system to a more complex heterogeneous system, involving mutidimensional heterogeneity. Based on this thesis, I recommend more stringent interventions that target cattle, badgers and movement, in order to achieve bTB eradication.

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# About the Author

You Chang was born in Wuhan, China, on October 30, 1994. From a young age, she had a passion for maths and biology, dreaming of exploring the world beyond China. In 2012, she began her studies in veterinary medicine at Huazhong Agricultural University, graduating in 2017.

After completing her undergraduate studies, she moved to the Netherlands to pursue a master's degree at Wageningen University, where she graduated cum laude in 2019. Her education there deepened her interest in mathematical modelling, statistics and programming.

In 2019, You Chang started her PhD in the QVE group at Wageningen University. She studied environmental transmission of bovine tuberculosis (bTB) between cattle and badgers, and investigated the impact of badger vaccination on bTB eradication. In 2020, when the pandemic started, You Chang began research on indoor transmission of SARS-CoV-2, focusing on how human behaviors and virus characteristics influence pathogen transmission and the effectiveness of non-pharmaceutical interventions in indoor spaces.

In 2023, she was awarded a WIAS fellowship grant, allowing her to visit the Swedish Veterinary Agency for three months. In 2024, she presented her PhD findings at the annual conference of the Society of Veterinary Epidemiology and Preventive Medicine (SVEPM), where she received the award for best oral presentation. Since May 2024, she has been working as a postdoctoral researcher at the University of Copenhagen, continuing her passion for infectious disease modelling.

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# WIAS Training and education statement


## **The basic package** (3 ECTS)

| | |
|---|---|
| WIAS course: Introduction day | 2019 |
| WGS course: Scientific Integrity & Ethics and Animal Science | 2019 |
| WIAS course: Personal Effectiveness | 2019 |

## **Disciplinary Competences** (10,9 ECTS)

| | |
|---|---|
| Writing a WIAS research proposal | 2019 |
| R and Big Data | 2019 |
| Geostatistics | 2019 |
| WIAS course: Statistics for Data Science | 2022 |
| WIAS course: Image and Video Analysis | 2023 |

## **Professional Competences** (6,9 ECTS)

| | |
|---|---|
| WGS course: PhD competence assessment | 2019 |
| WGS course: Scientific Writing | 2022 |
| WGS course: Mobilising your Scientific Network | 2023 |
| WGS course: Searching and Organising Literature | 2022 |
| WGS course: Critical Thinking and Argumentation | 2022 |
| WGS course: Career Orientation | 2023 |
| WGS course: Scientific Artwork | 2023 |

## **Presentation Skills** (4 ECTS)

| | |
|---|---|
| WIAS annual conference (oral, poster) | 2021-2022 |
| Epidemics 8th, 9th (poster) | 2021, 2023 |
| *M. bovis* confernece (poster) | 2022 |
| SVEPM (oral) | 2024 |

## **Teaching competences** (6 ECTS)

| | |
|---|---|
| Supervising 4 master students | 2019-2023 |
| Teaching assistant for QVE-30806 MIDA course | 2020-2023 |

# Colophon

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