Modelling the Transmission Dynamics of Bluetongue Disease with Controls, Stochasticity and Migration in Patchy Environments

by

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Declaration

I, **Mugabi Francis**, do hereby declare that this is my original research and to the best of my knowledge it has never been submitted for a degree at any other university.

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This thesis has been under our supervision and has our approval for submission.

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Dedication

This thesis is dedicated to my wife Amooti Margaret Mugabi, daughter Gabriella Blessing Mugabi, Mummy Kelly Akiiki, father Araali Kanywa (RIP) and mother Amooti Kanywa (RIP).

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With a grateful heart, I give thanks to my Lord and Saviour Jesus Christ for the blessing of good health, knowledge and strength that enabled me to do this work. Lord, may your holy name be glorified forever!

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Abstract

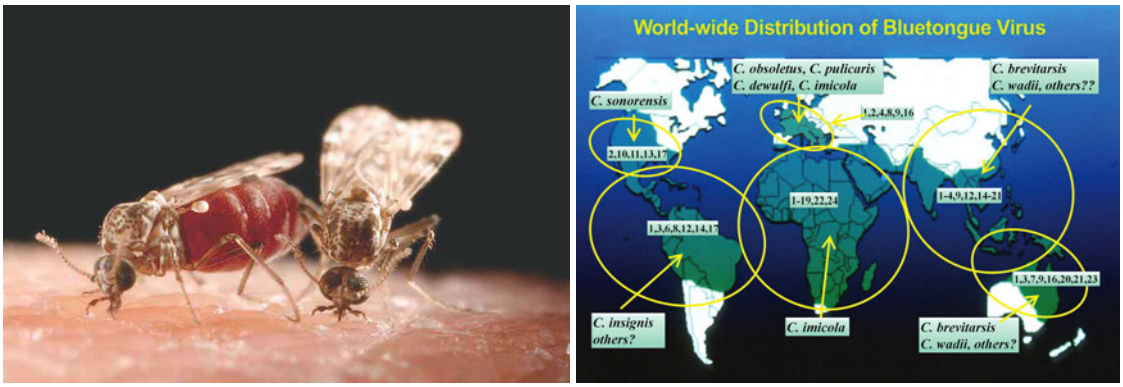
In this thesis, a single serotype ($j = 1$) and patch ($i = 1$) ordinary difference equation (ODE) model is formulated and analysed for the effects of direct and transplacental transmission on the probability of bluetongue virus (BTV) persistence. Using the next generation approach, the basic reproduction number ($\mathscr{R}_0$) is determined. When $\mathscr{R}_0 < 1$, the model exhibits a backward bifurcation indicating that the virus persists. When $\mathscr{R}_0 > 1$, a continuous-time Markov chain (CTMC) model derived from the ODE model is used to estimate the probability of BTV persistence. By approximating the CTMC model with a multitype branching process, it is shown that both direct and transplacental transmission can have a large effect on the probability of persistence in regions with temperature $T < 12^{\circ}C$ and a small effect for those with $T > 12^{\circ}C$. The ODE and CTMC models are extended to include r serotypes and n patches with the aim of determining the effects of midge movement on the outbreak and coexistence of multiple BTV serotypes in an environment divided into patches depending on the risk of infection. An estimate for the probability of a major outbreak of two BTV serotypes in two patches is obtained by approximating the CTMC model with a multitype branching process. It is shown that without movement a major outbreak occurs in the high-risk patch, but with cattle or midge movement it occurs in both patches. When a major outbreak occurs, numerical simulations of the ODE model illustrate possible coexistence in both patches if the patches are connected by midge or cattle movement. The multi-patch single-serotype ODE model is then modified as an optimal control problem to evaluate the effectiveness of vaccination, quarantine, insecticide spraying and the use of repellent control strategies in reducing the within- and between-patches transmission. By using optimal control theory, the effectiveness of these strategies is established. In a single patch, vaccination, insecticide spraying and the use of a repellent are all highly effective in minimising transmission, but the most cost-effective is vaccination. In patches connected by host and midge movements, if any of these controls is applied in the high-risk patch, a disease-free status is achieved in both patches, but if implemented in the low-risk patch, it is not attained in any patch. If hosts and midges move, quarantine has no effect, but for no midge movement, the effect can be large in the low-risk patch if it's internally imposed.

Chapter 1
Introduction

1.1 Characteristics, Distribution and Consequences of Bluetongue Virus

Bluetongue (BT) is an infectious and non-zoonotic viral disease of domestic and wild ruminants. It is mainly spread by the bites of *Culicoides* midges (Figure 1.1 (a)) and caused by the bluetongue virus (BTV) [121]. Twenty-eight different BTV serotypes (BTV-1 to BTV-28) are currently responsible for causing the disease worldwide [22]. The major symptoms of BT disease include: high fever, excessive salivation, swelling of the face and tongue (the tongue turns blue in colour) and nasal discharge [65]. Clinical signs are mostly observed in sheep whereas cattle are the major reservoirs and amplification hosts for the virus [121]. The mortality rate is usually low, but morbidity rate of the disease is high. The animals that survive the infection recover slowly taking several months.

Bluetongue was first described as a disease of cattle and sheep by the French biologist Francois de Vaillant in the late 18th century [45]. Approximately 40 years later, the symptoms of the disease were identified in imported sheep by farmers in South Africa [97]. In 1905, based on the clinical signs of the disease which make the tongue of the infected sheep develop a blue colour, Spreull suggested that the disease be called Bluetongue which is a name used to date [97]. After importation of infected sheep in South Africa in 1900, BT spread rapidly throughout Africa and consequently to Middle East, Europe, America, Australia and Asia. Bluetongue virus has been isolated on all continents of the world except Antarctica [90] (Figure 1.1 (b)) and among all *arboviruses* (arthropod-borne viruses) BTV is the most widely distributed in all affected countries.



(a) (b)

Figure 1.1: The *Culicoides* midges (a) and the map of worldwide distribution of BTV serotypes with their primary *Culicoides* midges (b). Sub-figures (a) and (b), respectively, are reproduced from Wilson et al. [120] and Tabachnick [103].

Bluetongue is regarded by the World Organisation for Animal Health (OIE) as one of the most serious livestock diseases in the world in terms of its economic impact [91]. In 1956, a severe outbreak of BTV, with a mortality rate of up to 75%, killed approximately 179,000 sheep in the Iberian Peninsula [64]. This massive killing of sheep by BTV demonstrated the threat which the virus can pose to BTV-free regions. From this event the OIE classified BT as a list **A** disease in the mid 1960*s*. This classification has for many years led to the imposition of strict export and import regulations on animals and their products from BTV-affected regions. Surprisingly, the import and export regulatory measures have had a more serious economic impact on the worldwide livestock industry, especially the BTV-affected countries, than the disease itself [44].

The annual economic impact worldwide of BTV in terms of visible production losses and vaccination costs in endemic regions is estimated to be US$ 3 billion [104]. The economic impact of BTV outbreaks can be direct and/or indirect [83]. Direct impacts consist of losses in milk production, reduced meat production, retarded animal growth, abortion of fetuses, delayed breeding and high mortality rates especially in improved sheep breeds, while indirect impacts are related to market restrictions and costs of control [83]. Market restrictions result in loss of income to farmers due to reduced local and international sales of animals. There are also losses of government revenues attributed to heavy restrictions on trade of animals and their products such as semen, milk, meat, regular butter, hides and skins [83].

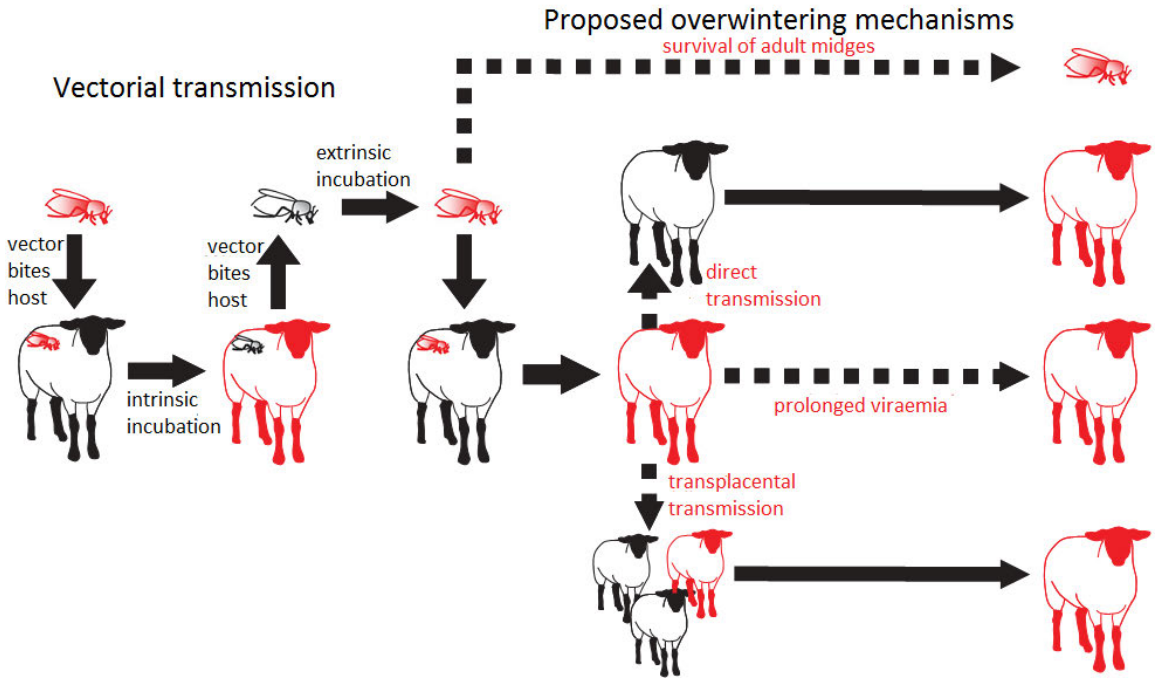


Figure 1.2: Transmission routes and proposed overwintering mechanisms for BTV. Figure reproduced from Wilson et al. [121].

1.2 Transplacental and Direct Transmission as Mechanisms for BTV Persistence in Temperate and Tropical Regions

Bluetongue virus can be transmitted either horizontally through biting of a susceptible animal by an infected adult female midge [29] or transplacentally from an infected mother to the fetus [33, 73, 94, 111 – 113] . Studies also show that some serotypes of BTV such as BTV-1 [92], BTV-2 [87], BTV-8 [72, 87, 111], BTV-11 [69], BTV-26 [13]) and BTV-27 [22] can be transmitted directly from an infected host to a susceptible host. Under horizontal (vectorial) transmission, when a midge bites an infected animal, the virus passes to the midge in the blood meal and the virus replicates in the midge. The time it takes the virus to complete the replication process in the midge is known as the extrinsic incubation period. After this period, when the midge bites another susceptible animal the virus is transmitted and the infectious cycle continues as shown in Figure 1.2. The time it takes a virus to replicate in the midge depends on the ambient temperature. For temperatures below $12^{\circ}C$ the replication of the virus stops [117] and this is important in temperate regions.

In temperate regions, due to very low temperatures the activities of the midges and BTV replication within these vectors cease and as a result the transmission is interrupted during winter for several months. However, outbreaks of BTV have been reported after interruptions for periods far longer than the adult life span of the midges and the normal duration of the infectious viraemia in the host [120]. The persistence of the virus from winter to another season is known as overwintering. Various mechanisms for BTV overwintering such as transplacental transmission, direct transmission, prolonged viraemia in animal hosts and vectors, persistence in alternative vectors such as ticks and survival of adult midges have been proposed [120] (see Figure 1.2). However, the effects of these mechanisms especially transplacental and direct transmission on the probability of BTV persistence during winter are not fully understood [78]. Therefore, in this study the effects of these routes on the probability of BTV persistence in temperate regions during winter (periods of no or low midge activity (PLMA)) are explored.

On the other hand, in periods of high midge activity (PHMA), the case in tropical regions (warmer climates), the transmission of the virus is thought to occur mainly through the vectorial route and any other routes are considered minor [111]. The control measures are therefore focused on the vectorial route. However, despite the presence of the control interventions against the virus such as vaccination, quarantine, use of insecticides and among others, the virus has become endemic with outbreaks being recorded at any time of the year [89]. Extra efforts are needed to control diseases that are transmitted through more than one route [12]. Persistence of BTV in warmer regions despite the use of control measures could be as a result of focusing the controls primarily on vectorial transmission and neglecting other routes of transmission such as the transplacental and direct routes. The effects of these different routes on the persistence of BTV in tropical regions are not completely clear [89]. Thus, in this study the effects of the different transmission routes on the probability of BTV persistence in PHMA are investigated. The results could assist in showing which efforts are required to better control the disease.

Both deterministic [29, 49, 53, 80] and stochastic [39, 51, 100, 101] mathematical models have been used to study the transmission dynamics of BTV. However, none of these models have been developed to determine the effects of transplacental and direct transmission on the probability of BTV persistence in temperate and/or tropical regions. Therefore, based on

the model by O'Farrell and Gourley [80], a deterministic model for the transmission dynamics of BTV is formulated by incorporating transplacental and direct transmission in the host population. To determine the effects of the aforementioned routes on probability of BTV persistence, the deterministic model is transformed into a stochastic model [5, 61, 70].

1.3 Wind-Aided Midge Movement as a Mechanism for Coexistence of Multiple BTV Serotypes in Patchy Environments

Multiple BTV serotypes often coexist in the same geographical environment in different parts of the world [23, 30]. Coexistence can enhance the reassortment (combination) of different serotypes resulting in resistant ones which persist despite wide-spread vaccination and treatment [30]. Besides reassortment, coexistence makes vaccination (the most effective tool for the control of BT disease) less effective since the vaccine is serotype-specific [64]. Understanding the mechanisms behind the coexistence of multiple BTV serotypes in patchy (different) environments is essential for the control of the disease.

Various studies have shown that mechanisms, such as partial cross-immunity [27], co-infection [67, 68], different transmission modes [36], density dependent mortality of hosts [6] and superinfection [41, 57] can enable the coexistence of multiple serotypes or strains. Qiu et al. [86] described a vector-host model with multiple strains in n patches connected by host migration. They showed that spatial heterogeneity can also lead to the coexistence of multiple strains in a given environment. In their study, vector migration was neglected on account that vectors are arthropods which move for a short distance in their lives. However, according to Hendrickx et al. [54] and Ducheyne et al. [38], respectively, under passive wind-mediated flight, midges can be transported by wind over distances up to 150 km on land and 700 km on water. The long distance movement of midges by the help of wind is not accidental; it is actively initiated and maintained by the midges [88]. Even in strong winds the midges can actively choose to terminate their flight by ceasing to move their wings which results in landing [38]. Moreover, using a mathematical model, Fitzgibbon et al. [42] were able to show that the long-range movement of midges with the help of wind can enhance the spread of BTV to hosts in distant places. Thus, the role of midge movement in the spread of BTV serotypes among patches cannot be ignored. What remains to be understood, as considered

here, is whether long range movement of midges by help of wind has an effect on the outbreak and coexistence of multiple competing BTV serotypes and whether coexistence can be maintained if demographic and movement variability are considered.

1.4 Control Measures for BTV Transmission in Patchy Environments

The mechanisms for the introduction of BTV from endemic to disease-free areas include movements of infected animals and the passive flight of infected midges by wind [42]. Controlling BTV outbreaks locally and globally are a big concern to the ruminant livestock sector. With transport advancement and increased climate shifts, infected animals and midges can easily spread the virus from one region (patch) to other regions (patches) [54]. Hence, a better understanding of the potential strategies for the management of BTV outbreaks on a global level is crucial for disease control.

The four main control methods against BTV transmission are vaccination of susceptible hosts; quarantining animals from infected regions; controlling the midge population through insecticide spraying; and minimising the biting rate of midges through the use of a repellent [64]. Other measures of containing the disease are methods used by farmers to stop midges making contact with animals such as housing the animals between dusk and dawn when the vectors are most active; covering the animal houses with nets; destroying the midge breeding sites like dung heaps and standing pools of water; and trapping of adult midges or the use of decoy animal hosts [64].

Vaccination remains the most effective strategy for the control of BTV outbreaks [52]. However, the coexistence of multiple serotypes in some regions of the world makes the strategy less effective since the vaccine is serotype-specific and there is no cross-cutting immunity among serotypes. Host and midge movements can easily spread different BTV serotypes from one place to another. Due to coexistence of multiple serotypes, the available BTV vaccines are expensive and may not be affordable to farmers [52]. This makes the vaccination strategy less effective as it may not be applied in time due to lack of funds. For instance, in northern Europe it took almost 18 months from the time of introduction of BTV in 2006 to the time of application of a vaccine in the field [26]. During such a time lag, the method that is usually applied to control the spread of the disease is quarantine [34, 52]. This method

restricts the movement of animals from infected to disease-free places. Quarantine has limitations as it cannot control internal outbreaks in the affected areas and movement restrictions often cannot be implemented effectively due to limited funding to pay enforcement officers. Furthermore, wind-aided midge movement can affect the effectiveness of this control measure as it may make it hard to estimate the radius of the restriction zones. In addition to the use of quarantine and vaccination, insecticide spraying and/or the use of a repellent complete an integrated control programme against BTV transmission [25, 113].

The use of a repellent has been recommended to reduce the attack rate of midges [113]. Repellents are substances applied to the skin, walls for animal housings, ear tags and collars to prevent animal-midge contact. The use of a repellent in animals is difficult and limited by the tiresome daily application regimen and the insufficient information regarding the withdrawal period [64]. In addition to the use of a repellent, insecticides can be used to minimise the population of adult midges which reduces the risk of BTV transmission [64]. Different insecticide compounds in the form of endo- and ecto-parasites can be used to kill midges [64]. Insecticides such as fenvalerate pyrethroid, permethrin, alpha-cypermethrin and cypermethrin have been shown to significantly reduce the population of midges [113]. However, the perceived negative impacts of these insecticides on the environment and humans [25], the requirement for continuous application, the vast areas involved and the rapid wind-aided midge movements can all limit the effectiveness of this control measure. Thus, in environments connected by host and/or midge movements, it is important to determine the locations and times for which these control strategies might be most effective (optimal) in minimising the spread of BTV from one patch to another.

Mathematical models can provide insights into the transmission dynamics of infectious diseases and the design of control programs. They can be used to identify critical intervention values which are aimed at minimising the disease-induced mortality rates [58]. Spatial and non-spatial mathematical models have been developed to explore the within- and between-farms transmission dynamics of BTV and their control by vaccination [15, 48, 50, 98, 100, 102] and by quarantine [15, 18, 35, 40, 47, 51, 101 – 103, 109] . These models considered vectorial transmission, but none investigated the effects of vector-based control strategies such as insecticide spraying and the use of a repellent [32]. Also in these models, fixed control parameters were considered, but in reality these may not be independent of time. In this study, a multi-patch deterministic control model is formulated and used to determine the

effectiveness of time-dependent host-based (vaccination and quarantine) and vector-based (insecticide spraying and the use of a repellent) control parameters in reducing BTV transmission in patchy environments connected by host and midge movements.

1.5 Problem Statement

Bluetongue is a very costly livestock disease worldwide in terms of mortality, morbidity and control. Efforts to control it are in place, but it has persisted sometimes with multiple serotypes in different regions (patches). Transplacental transmission, direct transmission, host movement and wind-aided midge movement have been proposed as mechanisms that facilitate its persistence, but to date, their effects on the probability of persistence are not fully understood. In addition, vaccination, quarantine, insecticide spraying and the use of a repellent are known control tools for BTV transmission, but their effectiveness in patchy environments connected by host and midge movements are not quantified. In this study, mathematical models for the transmission dynamics of multiple serotypes in patchy environments are formulated and analysed for the effects of these mechanisms on the probability of BTV persistence. They are also analysed for the effectiveness of the aforementioned control measures in reducing within- and between-patches transmission. The results of the study will help to determine the best control strategies for reducing BTV transmission on a local and global scale.

1.6 Objectives of the Study

The main and specific objectives of the study are presented.

1.6.1 Main Objective

To formulate deterministic and/or stochastic models for determining the mechanisms for persistence and the control strategies of BTV transmission in patchy environments.

1.6.2 Specific Objectives

(i) To determine the effects of direct and transplacental transmission on the probability of BTV persistence in temperate and tropical regions.

(ii) To determine the effects of wind-aided midge movement on the outbreak and coexistence of multiple BTV serotypes in patchy environments.

(iii) To determine the effectiveness of host-based and vector-based control strategies in reducing the transmission of BTV in patchy environments.

1.7 Significance of the Study

The results of the study are expected to benefit farmers with animals susceptible to BTV, veterinary officials, the Food and Agriculture Organisation (FAO), government departments in charge of animal husbandry and other policy makers in: budgeting, planning, policy formulation and making informed decisions relating to the control of BTV transmission locally and globally. The results of the study are also expected to guide future research in related fields.

1.8 Layout of the Thesis

This thesis has 6 chapters. Chapter 1 presented an introduction, problem statement, objectives and significance of the study. Chapter 2 highlights some existing literature on the transmission and control of BTV in patchy environments. In Chapter 3, the effects of transplacental and direct transmission on the probability of BTV persistence in temperate and tropical regions are determined. In Chapter 4, the effects of wind-aided midge movement on the outbreak and coexistence of multiple BTV serotypes are established. In Chapter 5, the effectiveness of vaccination, quarantine, insecticide spraying and the use of a repellent in reducing the within- and between-patches transmission of BTV are explored. The discussions, conclusions and recommendations of the study are presented in Chapter 6.

Chapter 2
Literature Review

In this chapter, English written published articles on BTV transmission, persistence and control worldwide are considered. The considered articles were obtained by searching PubMed, Google Scholar and Scopus databases using the terms “transplacental” or “vertical transmission of BTV”, “direct” or “contact transmission of BTV”, “models for BTV transmission”, “wind-aided midge movement” and “midge control measures”. The “all fields” option was used to enable retrieval of articles in which the search terms appeared in the abstracts, titles and/or keywords. Duplicates and those deemed irrelevant to the topic were excluded. The reference lists for the articles that were thought relevant to the research topic were scanned for additional literature. Full text reading was done for the selected articles to establish the final list of the studies for inclusion in the literature review. Based on the findings of these publications in relation to our research objectives, the articles that were deemed relevant are included in the following sections of this chapter.

2.1 Transmission of BTV

Bluetongue disease is mainly spread by adult female midges that belong to the *Culicoides* genus [37]. Only female midges can spread or acquire BTV by feeding on host blood, food necessary for their eggs to maturate [120]. In 1944, Du Toit [37] used light traps to capture midges at night so as to demonstrate that BTV could be induced in susceptible sheep that were inoculated with wild caught midges. Du Toit finally ascertained that midges were biological vectors for BTV by demonstrating that the midges which were fed on BTV-infected sheep could spread the disease to BTV-free sheep. Bluetongue virus has also been isolated from ticks and mosquitoes [120]. However, these are characterised as mechanical vectors and their role in the transmission of BTV is negligible [120].

Infection of pregnant animals by BTV can result in vertical transmission. Saminathan et al. [92] demonstrated transplacental transmission of BTV in mice. In United States of America (U.S.A) and South Africa, experimental studies on BTV-infected pregnant cattle and sheep

showed that transplacental foetal infection due to BTV is possible [63]. De Clercq et al. [33] highlighted the fact that vertically infected calves have the potential of introducing infection into BTV-free areas where midges are active. In addition, their study showed that of the infected dams, 10% of births result in transplacental BTV infection. Other studies that demonstrated transplacental transmission of different BTV serotypes include [11, 73, 88, 111 – 113] . On the other hand, vertical transmission does not take place in midges. A study carried out by White et al. [118] found fragments of BTV RNA in pools of larvae from infected midges, but no live virus indicating that the offspring of infected midges do not carry BTV. These studies provide evidence and extent at which infections through this route can occur in hosts, but its probability in generating an outbreak is not quantified.

Bluetongue disease can be transmitted directly from one host to another even in the absence of midges [110]. Menzies et al. [72] provide evidence for direct transmission of BTV-8 in cattle possibly through ingestion of contaminated placentas. Rasmussen et al. [87] and Backx et al. [11], respectively, demonstrated that under experimental conditions BTV-2 and BTV-8 can be transmitted orally from one animal to another. Batten et al. [13] and Bréard et al. [22] described direct contact transmission of BTV-26 and BTV-27, respectively, in goats under experimental conditions. In an experimental setting, van der Sluijs et al. [110] and López-Olvera et al. [62], respectively, showed that BTV-1 can be transmitted through direct contact in sheep and red deer. These studies indicate the significance of the direct route in the transmission of BTV.

2.2 Models for Transmission Dynamics of BTV

Gubbins et al. [49] formulated a deterministic model and used it to compute the basic reproduction number ($\mathscr{R}_0$) for BTV in a population comprising of sheep and cattle as host species. By definition, $\mathscr{R}_0$ is the average number of infections produced by an infectious individual introduced into a totally susceptible population [108]. Using uncertainty and sensitivity analyses based on the Latin Hypercube Sampling method, Gubbins et al. showed that temperature and the probabilities of BTV transmission from midges to host and from host to midges are the most important parameters in determining the magnitude of $\mathscr{R}_0$. Ward and Carpenter [115] used simulation transition models to analyse the ability of the disease to spread but only in given climatic conditions. A model for the time evolution of bluetongue in sheep and cattle has been presented and analysed in [46] using delay differential equations. Hartemink

et al. [53] integrated vector-abundance data with statistical methods and modelled $\mathscr{R}_0$ to create regional prediction maps of BTV abundance. Using the maps, the areas in Netherlands at higher risk for an outbreak after an introduction of the virus were identified. The effect of seasonality has also been investigated using delay differential equations [80]. The key findings in this study include the need for prompt diagnosis of latently infected animals, appropriate control actions before an animal turns infectious and the need for mitigation measures that reduce midge bites. All these studies did not consider transplacental and/or direct (host-to-host) transmission.

Charron et al. [29] developed a deterministic model to study the seasonal spread and control of BT disease in cattle. In their model, transplacental (vertical) and pseudo-vertical transmission (infection just after birth due to the contact between a susceptible newborn calf and its infected mother) were considered. However, the effects of these routes on the spread of BTV were not assessed [32]. Also, that study did not consider the possibility of direct transmission. In our study, the effects of transplacental and direct transmission on the probability of BTV persistence are explored.

2.3 Effects of Transplacental and Direct Transmission on the Probability of BTV Persistence in Temperate and Tropical Regions

Numerous deterministic mathematical models have been developed to study the transmission dynamics of BTV [29, 46, 49, 53, 80, 115, 116]. The prediction of disease extinction and persistence in these studies is based on $\mathscr{R}_0$. The predictions of these models is valid for $\mathscr{R}_0 > 1$ when the epidemic and population sizes are large [5, 66]. However, when the outbreak is initiated by a small number of hosts or vectors, this prediction may not be valid [5, 70]. In situations of small numbers for the initial conditions, stochastic models are more realistic than deterministic models [5, 70]. Thus, due to the small number of infections caused by direct and transplacental transmission, stochastic models are used to study their effects on the probability of BTV persistence.

In a study by Whittle [119], it was shown that for a Susceptible-Infectious-Recovered (*SIR*) model, the probability of extinction of an epidemic can be determined from $\mathscr{R}_0$. If $\mathscr{R}_0 > 1$,

this probability can be approximated as $(1/\mathscr{R}_0)^{i_0}$, where i_0 is the initial number of infectious hosts [5, 66]. The corresponding probability of persistence is approximated by $1-(1/\mathscr{R}_0)^{i_0}$. This approximation is valid only for disease models with one infectious group. For epidemics with multiple infectious groups, a major outbreak can result from each class within the population. In such circumstance, the probability of a major outbreak depends on the initial number of individuals in each infectious group [5, 70]. Bluetongue disease can be transmitted directly, vertically and horizontally (from vector to host); both infectious hosts and midges represent sources of infection for their susceptible counterparts. Thus, for a BTV model, hosts and midges are regarded as different infectious groups and the probability of persistence can be approximated using the multitype branching process [5, 60, 66].

Stochastic mathematical models have been used to study the transmission dynamics of BTV [38, 49, 102 – 104] . However, none of these models have been developed to assess the impacts of direct and transplacental transmission on the probability of BTV persistence. Napp et al. [78] used a stochastic risk assessment model to explore the probability of BTV overwintering in Germany between 2006 and 2007 by horizontal transmission. The horizontal transmission was considered to occur through long term persistence of the virus in either adult vectors or hosts. The results of their study showed that the likelihood of overwintering by these mechanisms is too low to explain the 2006/2007 BTV re-emergence in Germany. They concluded that other mechanisms not considered in their model could have played a significant role in the virus overwintering/persistence. Therefore, in Chapter 3 of this study, deterministic and stochastic models are formulated and used to explore the effects of direct and transplacental transmission on the probability of BTV persistence in temperate and tropical regions.

2.4 Effects of Wind-Aided Midge Movements on the Coexistence of Multiple BTV Serotypes in Patchy Environments

Qiu et al. [86] used a multi-patch multi-strain host-vector model to study the effect of host movement in patchy environments on the coexistence of multiple strains. They showed that host movement can lead to the coexistence of multiple strains. However, in their study, vector movement was not considered. They assumed that vectors are arthropods which move

for a short distance in their life time, however, with increased climate shifts, vectors such as midges can easily be moved by wind from one place to another [54]. In fact, wind-aided midge movement has been implicated as the cause of the introduction of BTV to Portugal from Morocco [84], to Florida in U.S.A from Cuba [94], to Montana in U.S.A from Mexico [95] and to Cyprus from Syria [84]. Using a formal trajectory analysis Alba et al. [1] explored the possibility of the introduction of infected *Culicoides* midges by help of wind from Sardinia to the Balearic Islands during the 2000 BTV outbreaks. They were able to match the outbreaks on the Balearic Islands with those previously experienced in Sardinia. In Bulgaria and Greece, Ducheyne et al. [38] using forward and backward wind trajectory analysis found that two BTV epidemics involving multiple serotypes were linked to long-range wind-aided midge movements. Using a wind density model, Hendrickx et al. [54] quantified the airborne spread of midges during a 2006 North-western Europe BTV epidemic. They gave evidence supporting the possibility of long-range spreading of midges by wind, over land, of up to 150 km. According to Reynolds et al. [88], passive movement of midges by wind is not accidental; it is actively initiated and maintained by the midges.

Sedda et al. [93] used a stochastic model to study the effects of wind-aided midge movement on the spread of BTV in Europe. Burgin et al. [24] described an atmospheric dispersion model to explore the effect of wind on the transmission of BTV in sheep. Fitzgibbon et al. [42] used a system of partial differential equations to demonstrate that the long-range movement of midges facilitated the 2000 BTV outbreak transmission in sheep to distant places in Europe. All these studies stress the significance of wind-aided midge movement in the spread of BTV, but they do not explain its effects on the coexistence of multiple serotypes. Szmaragd et al. [101] developed a stochastic farm level model to explain the within- and between-farms transmission of BTV. The transmission dynamics between the farms were captured by a generic kernel which included both vector and animal movements. In their study the recommendation was made to include the virus strains so as to understand better the transmission dynamics of the disease. Thus, in Chapter 4 of this study, multi-patch multi-serotype deterministic and stochastic models are formulated and used to determine the effects of wind-aided midge movement on the outbreak and coexistence of multiple BTV serotypes in patchy environments.

2.5 Control Strategies for BTV Transmission in Patchy Environments

Spatial and non-spatial mathematical models have been developed to explore the dynamics and control of within- and between-farms transmission of BTV. Based on the model in [49], Szmaragd et al. [101] formulated a stochastic spatially-explicit farm-level model for Great Britain in the period 2006/07 and used it to investigate the impacts of movement restriction (quarantine) on restricting the disease. Sumner et al. [99] using methods from [101] also studied the impact of quarantine. Other authors that investigated the impact of quarantine also show the importance of considering restricting animal movement for limiting the spread of the disease [18, 35, 40, 107]. The formulation of within-farm transmission given in [101] was modified by Szmaragd et al. [102] to understand different vaccination scenarios in Great Britain. Vaccination was assumed to reduce the probability of host and midge infection. The model by Szmaragd et al. [102] was then used by the authors in [50, 98] to study vaccination strategies in other settings.

The impact of vaccination on between-farms transmission was studied by Græsbøll et al. [48] who modified the methods in their previous study [47] by the addition of eight vaccination strategies. They assumed that vaccination offers 100% immunity. In [15, 100], the authors investigated the impact of both quarantine and vaccination. However, all these reviewed models consider vectorial transmission, and none investigated the effects of vector-based control strategies such as insecticide spraying or the use of a repellent [32]. Also in these models, fixed control parameters were considered, but in reality they may not be independent of time. Further in these studies, disease spread between farms was modelled by transmission kernels of different forms (Gaussian, exponential or fat-tailed) depending on the distance between farms. The predictions and the effectiveness of control measures of these models critically depend on the shape of the transmission kernel [101]. For instance, Szmaragd et al. [101] demonstrated that for a Gaussian kernel, movement restrictions have little impact on BTV spread and are not necessary, whereas for a fat-tailed kernel, such restrictions are effective.

Charron et al. [29] developed a deterministic model for BTV-8 transmission and using sensitivity index analysis it was found that the parameters which influenced $\mathscr{R}_0$ most were the biting and fertility rates of the midge. Thus, a vector control intervention that directly kills adult midges or interrupts their feeding cycle can reduce the transmission of BTV. A study by Ve-

nail et al. [112] determined the susceptibility of European *Culicoides* midges to deltamethrin insecticides sprayed on sheep. They demonstrated a mortality rate of up to 49% after 4 days of application. Under field conditions, Murchie et al. [77] showed that pour-on applications of deltamethrin to cattle have a significant negative effect on the population of adult midges and could reduce the risk of BTV transmission. Other authors that demonstrated the effects of insecticide spraying on midge populations under both field and laboratory conditions include those in [16, 21, 34, 52]. Experimental studies have also been used to investigate the effects of repellents on limiting host-midge contacts. In a study based in northern Spain, a 15% N, N-diethyl-3-methylbenzamide (DEET), a mix of lemon eucalyptus oil and a mixture of fatty acids were shown to have large repellent effects against midges [52]. In South Africa, Venter et al. [113] demonstrated that a combination of three organic fatty acids (octanoic, nonanoic and decanoic) is effective at reducing the attack rate of midges. Page et al. [82] also showed that DEET has a significant repellent effect against *Culicoides* species. All these articles on the use of insecticides or repellents to control the population or activity of midges are experimental studies.

In Chapter 5 of this study, a multi-patch model is formulated and analysed for the effectiveness of vaccination, quarantine, insecticide spraying and the use of a repellent in reducing BTV transmission in patchy environments connected by host and/or midge movements. Unlike the models in [15, 18, 35, 40, 47, 48, 50, 51, 100 – 104, 109] where BTV spread between farms was modelled by transmission kernels, in this thesis, a deterministic model in a metapopulation setting [10, 31, 86, 114] is used. Also different from these models, time-dependent control parameters of quarantine and vaccination are considered.

Chapter 3
Effects of Transplacental and Direct Transmission on the Probability of BTV Persistence in Temperate and Tropical Regions

In this chapter, based on the model by O'Farrell and Gourley [80], a deterministic mathematical model (basic model) for the transmission dynamics of BTV is formulated. The basic model is transformed to include vertical and direct transmission based on the study by De Clercq et al. [33]. Qualitative analyses of the model are done in order to investigate the existence and stability of disease-free and endemic equilibrium points. To capture the effects of small numbers of infectious individuals introduced into the cattle-midge population through transplacental and direct transmission, the deterministic basic model is transformed into a continuous-time Markov chain (CTMC) stochastic model by referring to the work by Allen and Kirupaharan [5]. Using the CTMC model and a multiple branching process approximation, the effects of transplacental and direct transmission on the probability of BTV persistence in temperate and tropical regions are explored. The content in this chapter, coauthored with Kevin J. Duffy, Joseph Y.T. Mugisha and Obiora C. Collins has been published in the journal of *Results in Applied Mathematics* [75].

3.1 The BTV Deterministic Model

In this model, cattle are considered since they are the major reservoirs and amplification hosts for BTV [121]. However, the model can be applicable to other susceptible hosts. The cattle population $N_c(t)$ is divided into four epidemiological sub-population classes: Susceptible $S_c(t)$, Exposed $E_c(t)$, Infectious $I_c(t)$ and Recovered $R(t)$. Hence, $N_c(t) = S_c(t) + E_c(t) + I_c(t) + R(t)$. The midge (vector) population $N_m(t)$ is divided into three sub-classes: Susceptible $S_m(t)$, Exposed $E_m(t)$ and Infectious $I_m(t)$. Thus, $N_m(t) = S_m(t) + E_m(t) + I_m(t)$. In the cattle population, recruitment is by birth. It is assumed that recruitment is at rates Λ (constant) and b, respectively, from non-infectious and infectious cattle. It is assumed that the

progeny of $E_c(t)$ are all susceptible, since in this class the animals are not yet infectious. Of the progeny of $I_c(t)$, it is assumed that a fraction ϕ are infectious and the remaining fraction $(1-\phi)$ are susceptible to BTV infection. Direct host to host transmission is due to contact of susceptible and infectious animals at a rate β. It is assumed that this transmission process follows the law of mass action. Therefore, the force of infection under direct transmission is given by $\beta S_c I_c$.

Under horizontal vector transmission of BTV, susceptible midges become infected by biting infectious cattle, while susceptible cattle are infected after being bitten by infectious midges. The horizontal vector transmission of BTV in cattle is modelled using the incidence term $\frac{apS_cI_m}{N_c}$ that denotes the rate at which susceptible cattle $S_c(t)$, get infected by infectious midges $I_m(t)$. Similarly, the transmission of BTV in midges is given by $\frac{aqS_mI_c}{N_c}$ which refers to the rate at which susceptible midges $S_m(t)$ become infected by infectious cattle $I_c(t)$, p is the probability that a bite from an infectious midge leads to infection of the susceptible cattle, a is the biting rate of female midges and q is the probability that a bite from a susceptible midge to an infectious cow leads to infection of the midge. The terms ap and aq are a measure of the conservation of bites through the biting rate a. Upon infection, the cow is now exposed to BTV and moves to class $E_c(t)$. At the end of the intrinsic incubation period of $1/\sigma_c$ days, the cow becomes symptomatic and moves to class $I_c(t)$, where it can die due to BTV at a rate ν or may recover at a rate γ to join the recovered class $R(t)$. While in $R(t)$, the cow gains temporary immunity after which it moves back to $S_c(t)$ at a rate ω and the cycle continues. All the animal sub-groups are subjected to a per capita natural mortality rate μ_c.

For the midge population, it is assumed that susceptible midges are recruited at a constant birth rate π. Susceptible midges which are infected move to the exposed class $E_m(t)$ and progress to the infectious class $I_m(t)$ after the end of the extrinsic incubation period at a rate σ_m. Midges do not recover from BTV. All midges, whatever their status are subject to a per capita natural mortality rate μ_m.

The dynamics of BTV as facilitated by the infected cattle and midges are represented by the compartmental diagram in Figure 3.1.

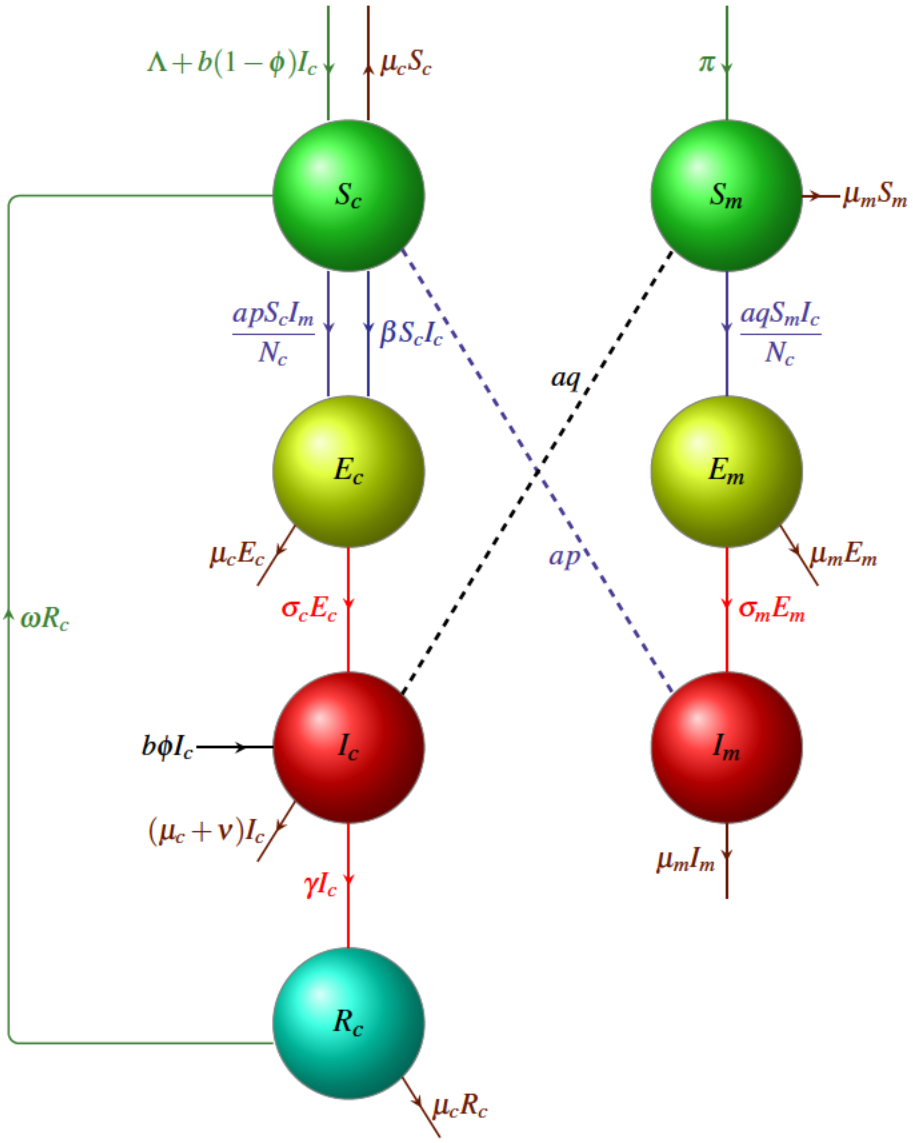


Figure 3.1: Compartmental diagram for the transmission dynamics of BTV in cattle-midge population.

From Figure 3.1, the system of ordinary differential equations describing the dynamics of BTV in cattle-midge population is given by:

$$
\begin{aligned}
\frac{dS_c}{dt} &= \Lambda + b(1-\phi)I_c + \omega R_c - \frac{apS_cI_m}{N_c} - \beta I_c S_c - \mu_c S_c, \\
\frac{dE_c}{dt} &= \frac{apS_cI_m}{N_c} + \beta I_c S_c - (\mu_c + \sigma_c)E_c, \\
\frac{dI_c}{dt} &= \sigma_c E_c + b\phi I_c - (\mu_c + \nu + \gamma)I_c, \\
\frac{dR_c}{dt} &= \gamma I_c - (\omega + \mu_c)R_c, \\
\frac{dS_m}{dt} &= \pi - \frac{aqS_mI_c}{N_c} - \mu_m S_m, \\
\frac{dE_m}{dt} &= \frac{aqS_mI_c}{N_c} - (\sigma_m + \mu_m)E_m, \\
\frac{dI_m}{dt} &= \sigma_m E_m - \mu_m I_m.
\end{aligned} \tag{3.1}
$$

The initial conditions are such that $S_c(0) > 0$, $E_c(0) \geq 0$, $I_c(0) \geq 0$, $R_c(0) \geq 0$, $S_m(0) > 0$, $E_m(0) \geq 0$ and $I_m(0) \geq 0$. The parameters and their values are presented in Table 3.3.

The equations for the rates of change of the total cattle and midge populations, respectively, are given by

$$\frac{dN_c}{dt} = \Lambda - \mu_c N_c + (b - \nu)I_c \tag{3.2}$$

and

$$\frac{dN_m}{dt} = \pi - \mu_m N_m. \tag{3.3}$$

3.1.1 Feasible Region and the Disease-Free Equilibrium Point (E_0)

To determine whether the model is biologically meaningful, positivity and boundedness are analysed.

Theorem 3.1. *The solutions $S_c(t)$, $E_c(t)$, $I_c(t)$, $R_c(t)$, $S_m(t)$, $E_m(t)$ and $I_m(t)$ of the model* (3.1) *with non-negative initial data, remain non-negative for all time $t > 0$.*

Proof. Suppose that $t_1 = \sup\{t > 0 : S_c(t) > 0, E_c(t) > 0, I_c(t) > 0, R_c(t) > 0,$

$S_m(t) > 0, E_m(t) > 0, I_m(t) > 0\big\} > 0$. It follows from (3.1) that,

$$\begin{aligned}\frac{dS_c}{dt} =& \Lambda + b(1-\phi)I_c + \omega R_c - \frac{apS_cI_m}{N_c} - \beta I_c S_c - \mu_c S_c \\ &\geq \Lambda - \frac{apS_cI_m}{N_c} - \beta I_c S_c - \mu_c S_c,\end{aligned}$$

which can be written as

$$\begin{aligned}&\frac{d}{dt}\left(S_c(t)exp\left[\mu_c t + \int_0^t (\frac{apI_m}{N_c} + \beta I_c)(u)du\right]\right) \geq \quad \Lambda exp\left[\mu_c t \right. \\ &\left. + \int_0^t (\frac{apI_m}{N_c} + \beta I_c)(u)du\right].\end{aligned}$$

Hence,

$$\begin{aligned}&S_c(t_1)exp\left[\mu_c t_1 + \int_0^{t_1} (\frac{apI_m}{N_c} + \beta I_c)(u)du\right] \\ &- S_c(0) \geq \int_0^{t_1} \left(\Lambda exp\left[\mu_c y + \int_0^y (\frac{apI_m}{N_c} + \beta I_c)(u)du\right]\right)dy,\end{aligned}$$

so that

$$\begin{aligned}S_c(t_1) \geq& S_c(0)exp\left[-\mu_c t_1 - \int_0^{t_1} (\frac{apI_m}{N_c} + \beta I_c)(u)du\right] \\ &+ exp\left[-\mu_c t_1 - \int_0^{t_1} (\frac{apI_m}{N_c} + \beta I_c)(u)du\right] \\ &\int_0^{t_1} \left(\Lambda exp\left[\mu_c y + \int_0^y (\frac{apI_m}{N_c} + \beta I_c)(u)du\right]\right)dy > 0.\end{aligned}$$

Similarly, it can be shown that $E_c(t) \geq 0$, $I_c(t) \geq 0$, $R_c(t) \geq 0$, $S_m(t) > 0$, $E_m(t) \geq 0$ and $I_m(t) \geq 0$ for all $t > 0$.

□

Therefore, all solutions to the model (3.1) remain non-negative for all non-negative initial conditions.

Theorem 3.2. *The feasible region*

$$\Omega = \left\{(S_c, E_c, I_c, R_c, S_m, E_m, I_m) \in \mathbb{R}_+^7 | N_c \leq \frac{\Lambda}{\mu_c}, N_m \leq \frac{\pi}{\mu_m}\right\}$$

is positively invariant with respect to the model (3.1).

Proof. From (3.2), it can be noted that the total cattle population size $N_c(t)$ is variable. In the absence of the disease,

$$\frac{dN_c}{dt} = \Lambda - \mu N_c.$$

This gives a solution of

$$N_c(t) = \frac{\Lambda}{\mu_c} + \left(N_c(0) - \frac{\Lambda}{\mu_c}\right)e^{-\mu_c t},$$

which implies that

$$\limsup_{t\to\infty} N_c(t) \leq \frac{\Lambda}{\mu_c}.$$

Hence,

$$\Omega_{N_c} = \left\{N_c(t) \in \mathbb{R}_+ : N_c(t) \leq \frac{\Lambda}{\mu_c}\right\}.$$

From (3.3),

$$\frac{dN_m}{dt} = \pi - \mu_m N_m.$$

Upon integration,

$$N_m(t) = \frac{\pi}{\mu_m} + \left(N_m(0) - \frac{\pi}{\mu_m}\right)e^{-\mu_m t},$$

which implies that

$$\limsup_{t\to\infty} N_m(t) \leq \frac{\pi}{\mu_m}.$$

Thus,

$$\Omega_{N_m} = \left\{N_m(t) \in \mathbb{R}_+ : N_m(t) \leq \frac{\pi}{\mu_m}\right\}.$$

Therefore, the feasible region

$$\Omega = \left\{(S_c, E_c, I_c, R_c, S_m, E_m, I_m) \in \mathbb{R}_+^7 | N_c \leq \frac{\Lambda}{\mu_c}, N_m \leq \frac{\pi}{\mu_m}\right\}$$

is positively invariant with respect to the model (3.1). □

In this region, the model can be considered as being epidemiologically meaningful, positively invariant and mathematically well-posed [55]. Thus, every solution of the system with initial conditions in Ω always remains in Ω for all $t > 0$.

Let $E_0 = (S_c^0, E_c^0, I_c^0, R_c^0, S_m^0, E_m^0, I_m^0)$ be the disease-free equilibrium point of the model

(3.1) where $S_c^0 > 0$, $E_c^0 = 0$, $I_c^0 = 0$, $R_c^0 = 0$, $S_m^0 > 0$, $E_m^0 = 0$ and $I_m^0 = 0$. Solving the model (3.1) at E_0 gives,

$$E_0 = (S_c^0, E_c^0, I_c^0, R_c^0, S_m^0, E_m^0, I_m^0) = \left(\frac{\Lambda}{\mu_c}, 0, 0, 0, \frac{\pi}{\mu_m}, 0, 0\right).$$

3.1.2 Local Stability of E_0

The local stability of E_0 is explored using the next-generation operator method [108]. Consider the disease compartments $E_c(t)$, $I_c(t)$, $E_m(t)$ and $I_m(t)$ of the model (3.1). From the model (3.1), it can be observed that the rate of appearance of new infections into the disease compartments is given by

$$\mathscr{F} = \begin{pmatrix} \frac{apS_cI_m}{N_c} + \beta S_c I_c \\ b\phi I_c \\ \frac{aqS_mI_c}{N_c} \\ 0 \end{pmatrix},$$

the rate of transfer of individuals into the disease compartments by

$$\mathscr{V}^+ = \begin{pmatrix} 0 \\ \sigma_c E_c \\ 0 \\ \sigma_m E_m \end{pmatrix},$$

and the rate of transfer of individuals out of the disease compartments by

$$\mathscr{V}^- = \begin{pmatrix} (\sigma_c + \mu_c)E_c \\ (\nu + \mu_c + \gamma)I_c \\ (\mu_m + \sigma_m)E_m \\ \mu_m I_m \end{pmatrix}.$$

Then, it follows that

$$\mathscr{V} = \mathscr{V}^- - \mathscr{V}^+ = \begin{pmatrix} (\sigma_c + \mu_c)E_c \\ (\nu + \mu_c + \gamma)I_c - \sigma_c E_c \\ (\mu_m + \sigma_m)E_m \\ \mu_m I_m - \sigma_m E_m \end{pmatrix}.$$

The Jacobian, F of $\mathscr{F}$ at disease-free is given by

$$\mathrm{F} = \begin{pmatrix} 0 & \frac{\beta\Lambda}{\mu_c} & 0 & ap \\ 0 & b\phi & 0 & 0 \\ 0 & \frac{aq\pi\mu_c}{\Lambda\mu_m} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \tag{3.4}$$

and the Jacobian, V of $\mathscr{V}$ at disease-free by

$$\mathrm{V} = \begin{pmatrix} \sigma_c + \mu_c & 0 & 0 & 0 \\ -\sigma_c & \mu_c + \nu + \gamma & 0 & 0 \\ 0 & 0 & (\mu_m + \sigma_m) & 0 \\ 0 & 0 & -\sigma_m & \mu_m \end{pmatrix}. \tag{3.5}$$

Since the Jacobian (3.5) is non-singular, its inverse is given by

$$\mathrm{V}^{-1} = \begin{pmatrix} \frac{1}{\sigma_c+\mu_c} & 0 & 0 & 0 \\ \frac{\sigma_c}{(\sigma_c+\mu_c)(\mu_c+\nu+\gamma)} & \frac{1}{(\mu_c+\nu+\gamma)} & 0 & 0 \\ 0 & 0 & \frac{1}{\sigma_m+\mu_m} & 0 \\ 0 & 0 & \frac{\sigma_m}{\mu_m(\sigma_m+\mu_m)} & \frac{1}{\mu_m} \end{pmatrix}. \tag{3.6}$$

The product of (3.4) and (3.6) gives

$$\mathrm{FV}^{-1} = \begin{pmatrix} \frac{\beta\Lambda\sigma_c}{\mu_c} & \frac{\beta\Lambda}{\mu_c(\mu_c+\nu+\gamma)} & \frac{ap\sigma_m}{\mu_m(\sigma_m+\mu_m)} & \frac{ap}{\mu_m} \\ \frac{b\phi\sigma_c}{(\sigma_c+\mu_c)(\mu_c+\nu+\gamma)} & \frac{b\phi}{(\mu_c+\nu+\gamma)} & 0 & 0 \\ \frac{aq\pi\mu_c\sigma_c}{\Lambda\mu_m(\mu_c+\sigma_c)(\mu_c+\nu+\gamma)} & \frac{aq\pi\mu_c}{\Lambda\mu_m(\mu_c+\nu+\gamma)} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The eigenvalues of FV^{-1} are 0, 0, $\frac{\mathscr{R}_{vd} - \sqrt{\mathscr{R}_{vd}^2 + 4\mathscr{R}_m}}{2}$ and $\frac{\mathscr{R}_{vd} + \sqrt{\mathscr{R}_{vd}^2 + 4\mathscr{R}_m}}{2}$, where

$$\begin{aligned} \mathscr{R}_{vd} =& \frac{\beta\Lambda\sigma_c + (\mu_c + \sigma_c)b\phi\mu_c}{\mu_c(\mu_c+\sigma_c)(\mu_c+\nu+\gamma)} \\ =& \mathscr{R}_v + \mathscr{R}_d, \end{aligned} \tag{3.7}$$

$$\mathscr{R}_v = \frac{b\phi}{(\mu_c + \nu + \gamma)}, \tag{3.8}$$

$$\mathscr{R}_d = \frac{\beta\Lambda\sigma_c}{\mu_c(\mu_c + \sigma_c)(\mu_c + \nu + \gamma)} \tag{3.9}$$

and

$$\mathscr{R}_m = \frac{a^2 pq\pi\mu_c\sigma_c\sigma_m}{\Lambda\mu_m^2(\mu_c + \sigma_c)(\mu_m + \sigma_m)(\mu_c + \nu + \gamma)}. \tag{3.10}$$

The dominant eigenvalue for FV^{-1} is the basic reproduction number denoted by $\mathscr{R}_0$ [76]. Therefore,

$$\mathscr{R}_0 = \frac{\mathscr{R}_{vd} + \sqrt{\mathscr{R}_{vd}^2 + 4\mathscr{R}_m}}{2}. \tag{3.11}$$

The threshold quantity $\mathscr{R}_0$ is the reproduction number for the BTV model (3.1). It measures the average number of secondary cases generated by a single BTV infected cow or midge in a population throughout its life time. In epidemics, $\mathscr{R}_0$ is useful in describing the magnitude of transmission. If $\mathscr{R}_0 > 1$, then the outbreak generates an epidemic; whereas, if $\mathscr{R}_0 < 1$, then the infection will disappear from the population [12]. The quantities $\mathscr{R}_{vd}$ and $\mathscr{R}_m$, respectively, are the basic reproduction numbers corresponding to the host-to-host and the vector-to-host transmissions. From (3.7), the terms $\mathscr{R}_v$ and $\mathscr{R}_d$ can be interpreted as the basic reproduction numbers corresponding to the transplacental and direct transmission, respectively. From Theorem 2 of [108] the following result is established.

Result 3.1. *The disease-free equilibrium point is locally asymptotically stable in* Ω *whenever* $\mathscr{R}_0 < 1$ *and unstable if* $\mathscr{R}_0 > 1$.

The epidemiological implication of Result 3.1 is that if the initial sub-populations of the model (3.1) are in the basin of attraction of the disease-free equilibrium point E_0, then BTV can be effectively controlled if $\mathscr{R}_0 < 1$. However, this equilibrium point may not be stable globally when $\mathscr{R}_0 < 1$ owing to the possibility of backward bifurcation. The existence of the backward bifurcation is analysed in the next subsection.

3.1.3 Existence of the Backward Bifurcation

Backward bifurcation occurs when a stable disease-free equilibrium point co-exists with a stable endemic equilibrium point for $\mathscr{R}_0 < 1$. The epidemiological significance of the back-

ward bifurcation is that the requirement of having $\mathscr{R}_0$ less than unity though necessary is no longer enough for the control of the disease.

Theorem 3.3. *The model* (3.1) *undergoes a backward bifurcation at* $\mathscr{R}_0 = 1$.

Proof. Let $E_1 = (S_c^*, E_c^*, I_c^*, R_c^*, S_m^*, E_m^*, I_m^*)$ be the endemic equilibrium point where $0 < S_c^*, 0 < E_c^*, 0 < I_c^*, 0 < R_c^*, 0 < S_m^*, 0 < E_m^*$ and $0 < I_m^*$. Solving the model (3.1) at E_1 gives,

$$\begin{aligned}
S_c^* =& \frac{\Lambda(\mu_c+\sigma_c)(\mu_c+\nu+\gamma)(\mu_c+\omega)(1-R_v)}{A(\lambda_c^*+\lambda_d^*)+\mu_c B(1-R_v)},\\
E_c^* =& \frac{\Lambda(\mu_c+\nu+\gamma)(\mu_c+\omega)(1-R_v)(\lambda_c^*+\lambda_d^*)}{A(\lambda_c^*+\lambda_d^*)+\mu_c B(1-R_v)},\\
I_c^* =& \frac{\Lambda\sigma_c(\mu_c+\omega)(\lambda_c^*+\lambda_d^*)}{A(\lambda_c^*+\lambda_d^*)+\mu_c B(1-R_v)},\\
R_c^* =& \frac{\Lambda\sigma_c\gamma(\lambda_c^*+\lambda_d^*)}{A(\lambda_c^*+\lambda_d^*)+\mu_c B(1-R_v)},\\
S_m^* =& \frac{\Pi}{\mu_m+\lambda_m^*},\ E_m^* = \frac{\Pi\lambda_m^*}{(\mu_m+\sigma_m)(\mu_m+\lambda_m^*)},\\
I_m^* =& \frac{\Pi\sigma_m\lambda_m^*}{\mu_m(\mu_m+\sigma_m)(\mu_m+\lambda_m^*)},
\end{aligned} \tag{3.12}$$

where $A = B(1-R_v) - b(1-\phi)\sigma_c(\mu_c+\omega) - \omega\gamma\sigma_c$, $B = (\mu_c+\omega)(\mu_c+\sigma_c)(\mu_c+\nu+\gamma)$,

$$\lambda_d^* = \beta I_c^*, \tag{3.13}$$

$$\lambda_c^* = \frac{apI_m^*}{S_c^*+E_c^*+I_c^*+R_c^*}, \tag{3.14}$$

and

$$\lambda_m^* = \frac{aqI_c^*}{S_c^*+E_c^*+I_c^*+R_c^*}. \tag{3.15}$$

Substituting (3.12), (3.13) and (3.14) into (3.15) gives a polynomial

$$\lambda_m^*\left(d_3(\lambda_m^*)^3 + d_2(\lambda_m^*)^2 + d_1\lambda_m^* + d_0\right) = 0, \tag{3.16}$$

where

$$
\begin{aligned}
d_3 =& \mu_c B(1-\mathscr{R}_v)\Big\{ ap\sigma_m\pi\big(\Lambda C - F_3 - B(1-\mathscr{R}_v)C\Lambda\big)F_3^3 \\
&+ \Lambda B\Big[\mu_c\big((1-\mathscr{R}_{vd})F_3 + C\Lambda\mathscr{R}_d\big)\big\{\mu_c\Lambda B(1-\mathscr{R}_v)\big(\mu_m\Lambda B(1-\mathscr{R}_v) \\
&+ \sigma_c(\mu_c+\omega+\gamma)\big)\big\} - \Lambda\mu_m(\mu_m+\sigma_m)(\Lambda C - F_3)\Big]\Big\}, \\
d_2 =& \mu_c(\Lambda B)^2(1-\mathscr{R}_v)\Big\{\mu_m(\mu_m+\sigma_m)\big[(1-\mathscr{R}_{vd})F_3 + \Lambda\mathscr{R}_d C\big]\big[\sigma_c(\mu_c+\omega) \\
&aq\mu_c\Lambda - \mu_m(\Lambda C - F_3)\big] + aq\sigma_c\mu_m\Lambda(\mu_m+\sigma_m)(\mu_c+\omega)(1-\mathscr{R}_{vd}) \\
&\Big[\Lambda\mu_c B(1-\mathscr{R}_v)\big((\mu_c+\omega)(\mu_c+\nu+\gamma)(1-\mathscr{R}_v) + \sigma_c(\mu_c+\omega+\gamma)\big) \\
&- (\Lambda C - F_3)\Big]\Big\} - ap\sigma_m\pi\mu_c\Lambda B(1-\mathscr{R}_v)\Big\{aq\sigma_c(\mu_c+\omega)\mu_c F_3^2 \\
&+ \big[\Lambda B(1-\mathscr{R}_v)C - (\Lambda C - F_3)\big]\big[2aq\sigma_c\mu_c(\mu_c+\omega)F_3 - C\big]\Big\}, \\
d_1 =& aq\sigma_c\big(\Lambda\mu_c\big)^2(\mu_c+\omega)B(1-\mathscr{R}_v)\Big\{\Big[ap\sigma_m\pi C \\
&+ \Lambda\mu_m(\mu_m+\sigma_m)B\Big(\mu_m\big[(1-\mathscr{R}_{vd})F_3 + \Lambda\mathscr{R}_d C\big] \\
&+ (1-\mathscr{R}_{vd})\big[aq\sigma_c(\mu_c+\omega)\Lambda - \mu_m(\Lambda C - F_3)\big]\Big)\Big] \\
&- pq\sigma_m\pi\sigma_c a^2\mu_c(\mu_c+\omega)\Big[3F_3 + \big[B(1-\mathscr{R}_v)-1\big]\Lambda C\Big]\Big\}, \\
d_0 =& \mu_c(\mu_m+\sigma_m)\big\{aq\sigma_c\mu_c\mu_m\Lambda^2(\mu_c+\omega)\big\}^2(1-\mathscr{R}_v)(1-\mathscr{R}_0),
\end{aligned}
$$

$C = (\mu_c+\omega)(\mu_c+\sigma_c)(\mu_c+\nu+\gamma)(1-\mathscr{R}_v) - \sigma_c\big\{\omega\gamma + (\mu_c+\omega)b(1-\phi)\big\}$ and
$F_3 = \Lambda\big[C - \mu_c\big\{(\mu_c+\omega)(\mu_c+\nu+\gamma)(1-\mathscr{R}_v) + \sigma_c(\mu_c+\omega+\gamma)\big\}\big]$.

From (3.16), the root $\lambda_m^* = 0$ corresponds to the disease-free equilibrium point whose stability has been discussed in Subsection 3.1.2. To check for the occurrence of backward bifurcation, (3.16) is analysed for the existence of multiple non-zero endemic equilibria points (positive roots) when $\mathscr{R}_0 < 1$. The number of positive roots for (3.16) are determined by the sign of the coefficients d_0, d_1, d_2 and d_3. The sign of d_0 depends on $\mathscr{R}_0$, d_0 is positive (negative) when $\mathscr{R}_0$ is less (greater) than unity. The possible number of positive roots for (3.16) are summarised in Table 3.1.

Table 3.1: Number of positive roots for (3.16).

Case	d_3	d_2	d_1	d_0	$\mathscr{R}_0$	Number of signs	Number of possible positive roots
1	-	-	-	-	$\mathscr{R}_0 > 1$	0	0
	-	-	-	+	$\mathscr{R}_0 < 1$	1	1
2	+	+	+	-	$\mathscr{R}_0 > 1$	1	1
	+	+	+	+	$\mathscr{R}_0 < 1$	0	0
3	+	-	-	-	$\mathscr{R}_0 > 1$	1	1
	+	-	-	+	$\mathscr{R}_0 < 1$	2	2,0
4	+	+	-	-	$\mathscr{R}_0 > 1$	1	1
	+	+	-	+	$\mathscr{R}_0 < 1$	2	2,0
5	-	+	-	-	$\mathscr{R}_0 > 1$	2	2,0
	-	+	-	+	$\mathscr{R}_0 < 1$	3	3,1
6	+	-	+	-	$\mathscr{R}_0 > 1$	3	3,1
	+	-	+	+	$\mathscr{R}_0 < 1$	2	2,0
7	-	+	+	-	$\mathscr{R}_0 > 1$	2	2,0
	-	+	+	+	$\mathscr{R}_0 < 1$	1	1
8	-	-	+	-	$\mathscr{R}_0 > 1$	2	2,0
	-	-	+	+	$\mathscr{R}_0 < 1$	1	1

From Table 3.1, the following result has been established.

Result 3.2. *The model* (3.1) *has*

(i) *more than one endemic equilibria points if* $\mathscr{R}_0 < 1$ *and whenever cases* $3-6$ *hold,*

(ii) *a unique endemic equilibrium point if* $\mathscr{R}_0 > 1$ *and whenever cases* $2-4$ *hold,*

(iii) *more than one endemic equilibria points if* $\mathscr{R}_0 > 1$ *and whenever cases* $5-8$ *hold.*

The possible existence of multiple endemic equilibria in $item(i)$ of Result 3.2 shows the likelihood for the occurrence of the backward bifurcation in the model (3.1). This is further explored by using the Center Manifold Theorem (Theorem A.1 in the appendix) [28]. To apply this theorem, the following simplifications and change of variables are made first. Let $S_c = x_1, E_c = x_2, I_c = x_3, R_c = x_4, S_m = x_5, E_m = x_6, I_m = x_7$ and $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^T$, then (3.1) can be written in the form $\frac{dX}{dt} = F(X)$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)^T$, as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Lambda + b(1-\phi)x_3 + \omega x_4 - \frac{apx_1x_7}{N_c} - \beta x_1 x_3 - \mu_c x_1, \\
\frac{dx_2}{dt} &= f_2 = \frac{apx_1x_7}{N_c} + \beta x_1 x_3 - (\mu_c + \sigma_c)x_2, \\
\frac{dx_3}{dt} &= f_3 = \sigma_c x_2 + b\phi x_3 - (\mu_c + \nu + \gamma)x_3, \\
\frac{dx_4}{dt} &= f_4 = \gamma x_3 - (\omega + \mu_c)x_4, \\
\frac{dx_5}{dt} &= f_5 = \pi - \frac{aqx_5x_3}{N_c} - \mu_m x_5, \\
\frac{dx_6}{dt} &= f_6 = \frac{aqx_5x_3}{N_c} - (\sigma_m + \mu_m)x_6, \\
\frac{dx_7}{dt} &= f_7 = \sigma_m x_6 - \mu_m x_7,
\end{aligned}
\tag{3.17}
$$

where $N_c = x_1 + x_2 + x_3 + x_4$. The Jacobian matrix of (3.17) at E_0 is given by

$$
\begin{pmatrix}
-\mu_c & 0 & J_1 & \omega & 0 & 0 & -ap \\
0 & -J_2 & \frac{\beta\Lambda}{\mu_c} & 0 & 0 & 0 & ap \\
0 & \sigma_c & J_3 & 0 & 0 & 0 & 0 \\
0 & 0 & \gamma & -J_4 & 0 & 0 & 0 \\
0 & 0 & -J_5 & 0 & -\mu_m & 0 & 0 \\
0 & 0 & J_5 & 0 & 0 & -J_6 & 0 \\
0 & 0 & 0 & 0 & 0 & \sigma_m & -\mu_m
\end{pmatrix},
\tag{3.18}
$$

where $J_1 = b(1-\phi) - \dfrac{\beta\Lambda}{\mu}$, $J_2 = (\mu_c + \sigma_c)$, $J_3 = b\phi - (\mu_c + \nu + \gamma)$, $J_4 = (\mu_c + \omega)$, $J_5 = \dfrac{aq\pi\mu_c}{\Lambda\mu_m}$ and $J_6 = (\mu_m + \sigma_m)$.

Let α^* be the bifurcation parameter and consider the case of $\alpha^* = q$. From (3.11) when $\mathscr{R}_0 = 1$, q is determined as

$$
q = \frac{\mu_m^2\Lambda(\sigma_m + \mu_m)(\sigma_c + \mu_c)(\mu_c + \nu + \gamma)(1 - \mathscr{R}_{vd})}{a^2 p\mu_c\pi\sigma_c\sigma_m}.
$$

The Jacobian matrix for the transformed system with α^* has a simple zero eigenvalue [28]. Therefore, the Centre Manifold Theorem can be used to analyze the stability of the system near α^*. The Jacobian matrix (3.18) has left and right eigenvectors associated with a simple zero eigenvalue. Let the left and right eigenvectors, respectively, be denoted by m and n. The left eigenvector is given by $n = (n_1, n_2, n_3, n_4, n_5, n_6, n_7)$, where

$$\begin{pmatrix} n_1 & n_2 & n_3 & n_4 & n_5 & n_6 & n_7 \end{pmatrix} \begin{pmatrix} -\mu_c & 0 & J_1 & \omega & 0 & 0 & -ap \\ 0 & -J_2 & \frac{\beta\Lambda}{\mu_c} & 0 & 0 & 0 & ap \\ 0 & \sigma_c & J_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -J_4 & 0 & 0 & 0 \\ 0 & 0 & -J_5 & 0 & -\mu_m & 0 & 0 \\ 0 & 0 & J_5 & 0 & 0 & -J_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_m & -\mu_m \end{pmatrix} = 0. \quad (3.19)$$

Solving (3.19) gives,

$$\begin{aligned} n_1 =& 0, \\ n_2 =& n_2 > 0, \\ n_3 =& \frac{(\mu_c + \sigma_c)}{\sigma_c} n_2 > 0, \\ n_4 =& 0, \\ n_5 =& 0, \\ n_6 =& \frac{ap\sigma_m}{\mu_m(\mu_m + \sigma_m)} n_2 > 0, \\ n_7 =& \frac{ap}{\mu_m} n_2 > 0. \end{aligned} \quad (3.20)$$

The right eigenvector denoted by $m = (m_1, m_2, m_3, m_4, m_5, m_6, m_7)^T$ is obtained from

$$\begin{pmatrix} -\mu_c & 0 & J_1 & \omega & 0 & 0 & -ap \\ 0 & -J_2 & \frac{\beta\Lambda}{\mu_c} & 0 & 0 & 0 & ap \\ 0 & \sigma_c & J_3 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & -J_4 & 0 & 0 & 0 \\ 0 & 0 & -J_5 & 0 & -\mu_m & 0 & 0 \\ 0 & 0 & J_5 & 0 & 0 & -J_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_m & -\mu_m \end{pmatrix} \begin{pmatrix} m_1 \\ m_2 \\ m_3 \\ m_4 \\ m_5 \\ m_6 \\ m_7 \end{pmatrix} = 0.$$

This gives

$$
\begin{aligned}
m_1 =& \frac{\omega\gamma\sigma_c + b(1-\phi)(\mu_c+\omega)\sigma_c - (\mathscr{R}_m+\mathscr{R}_d)(\mu_c+\sigma_c)(\mu_c+\nu+\gamma)(\mu_c+\omega)}{\mu_c\sigma_c} m_3, \\
m_2 =& \frac{(\mu_c+\nu+\gamma)(1-\mathscr{R}_v)}{\sigma_c} m_3 > 0, \\
m_3 =& m_3 > 0, \\
m_4 =& \frac{\gamma}{(\mu_c+\omega)} m_3 > 0, \\
m_5 =& \frac{-aq\mu_c\pi}{\mu_m^2\Lambda} m_3 < 0, \\
m_6 =& \frac{aq\mu_c\pi}{\mu_m\Lambda(\mu_m+\sigma_m)} m_3 > 0, \\
m_7 =& \frac{aq\mu_c\pi\sigma_m}{\mu_m^2\Lambda(\mu_m+\sigma_m)} m_3 > 0.
\end{aligned} \tag{3.21}
$$

The stability of the system around the equilibrium point is determined by the sign of the bifurcation coefficients A and B, where

$$
A = \sum_{k,i,j=1}^{6} n_k m_i m_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j} \tag{3.22}
$$

and

$$
B = \sum_{k,i=1}^{6} n_k m_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \alpha^*}. \tag{3.23}
$$

From (3.20), (3.21) and (3.22), the only non-vanishing partial derivatives at the disease-free equilibrium point are for $k = 2$ and $k = 6$.
When $k = 2$,

$$
\begin{aligned}
\frac{\partial^2 f_2(0,0)}{\partial x_2 \partial x_7} &= \frac{\partial^2 f_2(0,0)}{\partial x_7 \partial x_2} = \frac{-ap}{x_1}, \\
\frac{\partial^2 f_2(0,0)}{\partial x_3 \partial x_7} &= \frac{\partial^2 f_2(0,0)}{\partial x_7 \partial x_3} = \frac{-ap}{x_1}, \\
\frac{\partial^2 f_2(0,0)}{\partial x_4 \partial x_7} &= \frac{\partial^2 f_2(0,0)}{\partial x_7 \partial x_4} = \frac{-ap}{x_1}, \\
\frac{\partial^2 f_2(0,0)}{\partial x_1 \partial x_3} &= \frac{\partial^2 f_2(0,0)}{\partial x_3 \partial x_1} = \beta x_1
\end{aligned}
$$

and

$$\frac{\partial^2 f_2(0,0)}{\partial x_7^2} = \frac{-2ap}{x_1}.$$

When $k = 6$,

$$\frac{\partial^2 f_6(0,0)}{\partial x_1 \partial x_3} = \frac{\partial^2 f_6(0,0)}{\partial x_3 \partial x_1} = \frac{-aqx_5}{x_1^2},$$
$$\frac{\partial^2 f_6(0,0)}{\partial x_2 \partial x_3} = \frac{\partial^2 f_6(0,0)}{\partial x_3 \partial x_2} = \frac{-aqx_5}{x_1^2},$$
$$\frac{\partial^2 f_6(0,0)}{\partial x_3^2} = \frac{-2aqx_5}{x_1^2},$$
$$\frac{\partial^2 f_6(0,0)}{\partial x_3 \partial x_4} = \frac{\partial^2 f_6(0,0)}{\partial x_4 \partial x_3} = \frac{-aqx_5}{x_1^2}$$

and

$$\frac{\partial^2 f_6(0,0)}{\partial x_3 \partial x_5} = \frac{\partial^2 f_6(0,0)}{\partial x_5 \partial x_3} = \frac{aq}{x_1}.$$

Thus,

$$A = \frac{2(\mu_c + \sigma_c)(\mu_c + \nu + \gamma) n_2 m_3^2}{\Lambda \mu_m \mu_c ap \sigma_c^2 (\mu_c + \omega)} \Big\{ T - Q \Big\},$$

where

$$T = \Big\{ ap\mu_m(\mu_c + \omega) \Big[\mu_c W \mathscr{R}_m (\mathscr{R}_d + \mathscr{R}_m) + \Lambda \sigma_c \mathscr{R}_d \big\{ \omega\gamma + b(1-\phi)(\mu_c + \omega) \big\} \Big],$$

$$\begin{aligned} Q =& \mu_c \mathscr{R}_m \Big[2\mu_c \mu_m ap \big\{ (\mu_c + \omega)(\mu_c + \nu + \gamma)(1 - \mathscr{R}_v) + \sigma_c(\mu_c + \omega + \gamma) \big\} \\ &+ ap\mu_m \sigma_c (\mu_c + \omega) \big\{ \omega\gamma + b(1-\phi)(\mu_c + \omega) \big\} \\ &+ a^2 pq \mu_c \sigma_c (\mu_c + \omega) + \mu_c \mu_m W \mathscr{R}_m \Big] + \mu_m ap \Lambda (\mu_c + \omega) W \mathscr{R}_d (\mathscr{R}_d + \mathscr{R}_m) \Big\} \end{aligned}$$

and

$$W = (\mu_c + \omega)(\mu_c + \sigma_c)(\mu_c + \nu + \gamma).$$

From (3.23), it is clear that the only non-vanishing partial derivative at the disease-free equilibrium is for $k = 6$ when $i = 3$, that is,

$$\frac{\partial^2 f_6(0,0)}{\partial x_3 \partial q} = \frac{a x_5}{x_1} = \frac{a\mu_c \pi}{\mu_m \Lambda}.$$

Thus,

$$B = \frac{a\mu_c \pi}{\mu_m \Lambda} n_6 m_3 = \frac{a^2 p \mu_c \pi \sigma_m}{\mu_m^2 \Lambda(\mu_m + \sigma_m)} n_2 m_3 > 0.$$

Since $B > 0$, by the Center Manifold Theorem (Theorem A.1), the BTV model (3.1) undergoes a backward bifurcation at $\mathscr{R}_0 = 1$ whenever $A > 0$.

□

The basic reproduction number ($\mathscr{R}_0$) has been used to determine the disease extinction and persistence of the deterministic model (3.1). When $\mathscr{R}_0 < 1$, the disease-free and endemic equilibria points coexist. This implies that the disease persists or goes extinct, respectively, if the initial sub-populations are high or low. If $\mathscr{R}_0 > 1$, an endemic equilibrium point exists implying a major outbreak. However, if there are only a small number of infectious individuals prior to a major outbreak there is a possibility of disease extinction. This is known as the stochastic fade-out of the disease epidemic [61]. In this case, a stochastic model with discrete individuals is more realistic than an ODE model [61]. Thus, to determine the effects of transplacental and direct transmission when the number of infectious midges is very small, for example due to harsh winter weather, a stochastic version of the deterministic model (3.1) is derived and analysed in Section 3.2.

3.2 The BTV Stochastic Epidemic Model

For the deterministic model, time is continuous and the state variables are discrete. Therefore, a continuous-time Markov chain (CTMC) is used to derive a stochastic version of the basic model (3.1) [70]. The stochastic model takes into account the demographic (birth and death) variability. This stochastic process is defined by probabilities for different events over a small time interval Δt. For each state variable in the model (3.1), there are two possible events, birth/flow-in and death/removal. The corresponding rates in the model (3.1) are replaced in the stochastic version by the event probabilities in time Δt [70].

Table 3.2: State transitions and rates of occurrence for the CTMC model.

Event	State transition	Transition rate
Birth of S_c	$S_c \to S_c + 1$	$\Lambda + b(1-\phi)I_c$
Death of S_c	$S_c \to S_c - 1$	$\mu_c S_c$
Vectorial transmission	$(S_c, E_c) \to (S_c - 1, E_c + 1)$	$\frac{apS_cI_m}{N_c}$
Direct transmission	$(S_c, E_c) \to (S_c - 1, E_c + 1)$	$\beta I_c S_c$
Death of E_c	$E_c \to E_c - 1$	$\mu_c E_c$
E_c becoming I_c	$(E_c, I_c) \to (E_c - 1, I_c + 1)$	$\sigma_c E_c$
Vertical transmission	$I_c \to I_c + 1$	$b\phi I_c$
Death of I_c	$I_c \to I_c - 1$	$(\mu_c + \nu)I_c$
Recovery of I_c	$(I_c, R_c) \to (I_c - 1, R_c + 1)$	γI_c
Death of R_c	$R_c \to R_c - 1$	$\mu_c R_c$
Loss of immunity by R_c	$(S_c, R_c) \to (S_c + 1, E_c - 1)$	ωR_c
Birth of midges	$S_m \to S_m + 1$	π
Death of S_m	$S_m \to S_m - 1$	$\mu_m S_m$
Infection of S_m	$(S_m, E_m) \to (S_m - 1, E_m + 1)$	$\frac{aqS_mI_c}{N_c}$
Death of E_m	$E_m \to E_m - 1$	$\mu_m E_m$
E_m becoming I_m	$(E_m, I_m) \to (E_m - 1, I_m + 1)$	$\sigma_m E_m$
Death of I_m	$I_m \to I_m - 1$	$\mu_m I_m$

3.2.1 Model Formulation

Let time be continuous, $t \in [0, \infty)$ and let $S_c(t)$, $E_c(t)$, $I_c(t)$, $R_c(t)$, $S_m(t)$, $E_m(t)$ and $I_m(t)$, respectively, be discrete random variables for the number of susceptible cattle, exposed cattle, infectious cattle, recovered cattle, susceptible midges, exposed midges and infectious midges with finite state space,

$$S_c(t), E_c(t), I_c(t), R_c(t), S_m(t), E_m(t), I_m(t) \in \{0, 1, 2, ..., P\},$$

where P is a positive integer and represents the maximum size of the populations in a finite space [70]. For CTMC models, the transition from one state to a new state may occur at any time t [66]. The state transitions and their rates of occurrence for the CTMC model are presented in the Table 3.2.

3.2.2 Galton-Watson Branching Process

The probability of disease persistence or extinction from the CTMC model near the disease-free equilibrium point can be approximated by applying branching process theory a technique from probability theory. To calculate these probabilities the Galton-Watson branching process (GWbp) is used to approximate the dynamics of the nonlinear CTMC near the disease-free equilibrium point (see [5] for a description of the method). If the number of infections caused by transplacental and direct transmission are known, then by GWbp theory the probability of BTV persistence (a major outbreak) can be approximated. The GWbp theory is only applied to infected populations and it assumes that non-infected populations are at the disease-free equilibrium point [61]. Since for BTV there are four sources of infection, that is, exposed cattle, infectious cattle, exposed midges and infectious midges a multitype GWbp is used. Using this theory the offspring probability generating functions (pgfs) for the birth and death/recovery of the infected populations (E_c, I_c, E_m and I_m) can be defined [61]. The pgfs are used to calculate the probability of a major outbreak or disease extinction [61]. The pgf for n variables takes the form

$$g_i(x_1,x_2,\ldots,x_n) = \sum_{k_n=0}^{\infty}\sum_{k_{n-1}=0}^{\infty}\cdots\sum_{k_1=0}^{\infty} P_i(k_1,k_2,\ldots,k_n)x_1^{k_1}x_2^{k_2}\ldots x_n^{k_n}, \tag{3.24}$$

where $P_i(k_1,k_2,\ldots,k_n) = \text{prob}(Z_{i1}=k_1,Z_{i2}=k_2,\ldots,Z_{in}=k_n)$ is the probability that one infected individual of type i gives birth to k_j individuals of type j [70]. When the initial cattle and midge populations are near the disease-free equilibrium point, $S_c(0) \approx N_c(0) = S_c^0$ and $S_m(0) \approx N_m(0) = S_m^0$, the specific offspring pgfs for E_c, I_c, E_m and I_m can be defined using (3.24) and the rates in the Table 3.2 [61].

The offspring pgf for an exposed cow given that $E_c(0)=1$, $I_c(0)=0$, $E_m(0)=0$ and $I_m(0)=0$ is

$$g_1(x_1,x_2,x_3,x_4) = \frac{\sigma_c x_2 + \mu_c}{\sigma_c + \mu_c}. \tag{3.25}$$

The term $\sigma_c/(\sigma_c+\mu_c)$ represents the probability that an exposed cow survives natural mortality and becomes infectious which results in one infectious cow, zero exposed cows, zero exposed midges and zero infectious midges. The term $\mu_c/(\sigma_c+\mu_c)$ can be interpreted as the probability that an exposed cow dies due to natural mortality before becoming infectious.

The offspring pgf for an infectious cow given that $E_c(0) = 0$, $I_c(0) = 1$, $E_m(0) = 0$ and $I_m(0) = 0$ is

$$g_2(x_1, x_2, x_3, x_4) = \frac{\hat{\beta}_2 x_2 x_3 + b\phi x_2^2 + \hat{\beta}_1 x_1 x_2 + \gamma + \nu + \mu_c}{\hat{\beta}_2 + b\phi + \hat{\beta}_1 + \gamma + \nu + \mu_c}, \tag{3.26}$$

where $\hat{\beta}_1 = \beta S_c^0$ and $\hat{\beta}_2 = \frac{aqS_m^0}{S_c^0}$.

The term $\hat{\beta}_2/(\hat{\beta}_2 + b\phi + \hat{\beta}_1 + \gamma + \nu + \mu_c)$ represents the probability that an infectious cow infects a susceptible midge which results in one infectious cow and one exposed midge. The term $b\phi/(\hat{\beta}_2 + b\phi + \hat{\beta}_1 + \gamma + \nu + \mu_c)$ represents the probability that an infectious cow through transplacental transmission gives birth to an infectious calf which results in two infectious cows. The term $\hat{\beta}_1/(\hat{\beta}_2 + b\phi + \hat{\beta}_1 + \gamma + \nu + \mu_c)$ can be interpreted as the probability that a susceptible cow becomes exposed through direct transmission which results in one exposed cow and one infectious cow. The term $(\gamma + \nu + \mu_c)/(\hat{\beta}_2 + b\phi + \hat{\beta}_1 + \gamma + \nu + \mu_c)$ represents the probability that an initially infectious cow is lost through death (natural or disease related mortality) or recovery before transmitting the disease resulting in zero exposed cows, zero infectious cows, zero exposed midges and zero infectious midges.

The offspring pgf for an exposed midge given that $E_c(0) = 0$, $I_c(0) = 0$, $E_m(0) = 1$ and $I_m(0) = 0$ is

$$g_3(x_1, x_2, x_3, x_4) = \frac{\sigma_m x_4 + \mu_m}{\sigma_m + \mu_m}. \tag{3.27}$$

The term $\sigma_m/(\sigma_m + \mu_m)$ represents the probability that an exposed midge survives natural mortality and becomes infectious which results in one infectious midge, zero exposed cows, zero exposed midges and zero infectious cows. The term $\mu_m/(\sigma_m + \mu_m)$ can be interpreted as the probability that an exposed midge dies due to natural mortality before becoming infectious.

The offspring pgf for an infectious midge given that $E_c(0) = 0$, $I_c(0) = 0$, $E_m(0) = 0$ and $I_m(0) = 1$ is

$$g_4(x_1, x_2, x_3, x_4) = \frac{apx_1 x_4 + \mu_m}{ap + \mu_m}. \tag{3.28}$$

The term $ap/(ap + \mu_m)$ represents the probability that an infectious midge infects a susceptible cow and the initial midge does not die which results in one exposed cow and one

infectious midge. The term $\mu_m/(ap+\mu_m)$ can be interpreted as the probability that an infectious midge dies due to natural mortality before transmitting the disease.

The expectation matrix of the offspring pgfs is given by

$$\mathbb{E} = \begin{pmatrix} \frac{\partial g_1}{\partial x_1} & \frac{\partial g_2}{\partial x_1} & \frac{\partial g_3}{\partial x_1} & \frac{\partial g_4}{\partial x_1} \\ \frac{\partial g_1}{\partial x_2} & \frac{\partial g_2}{\partial x_2} & \frac{\partial g_3}{\partial x_2} & \frac{\partial g_4}{\partial x_2} \\ \frac{\partial g_1}{\partial x_3} & \frac{\partial g_2}{\partial x_3} & \frac{\partial g_3}{\partial x_3} & \frac{\partial g_4}{\partial x_3} \\ \frac{\partial g_1}{\partial x_4} & \frac{\partial g_2}{\partial x_4} & \frac{\partial g_3}{\partial x_4} & \frac{\partial g_4}{\partial x_4} \end{pmatrix} \text{ evalauted at } (1,1,1,1). \tag{3.29}$$

Therefore, from (3.25), (3.26), (3.27), (3.28) and (3.29),

$$\mathbb{E} = \begin{bmatrix} 0 & \frac{\hat{\beta}_1}{\hat{\beta}_2+b\phi+\hat{\beta}_1+\gamma+\nu+\mu_c} & 0 & \frac{ap}{ap+\mu_m} \\ \frac{\sigma_c}{\sigma_c+\mu_c} & \frac{\hat{\beta}_2+2b\phi+\hat{\beta}_1}{\hat{\beta}_2+b\phi+\hat{\beta}_1+\gamma+\nu+\mu_c} & 0 & 0 \\ 0 & \frac{\hat{\beta}_2}{\hat{\beta}_2+b\phi+\hat{\beta}_1+\gamma+\nu+\mu_c} & 0 & 0 \\ 0 & 0 & \frac{\sigma_m}{\sigma_m+\mu_m} & \frac{ap}{ap+\mu_m} \end{bmatrix} = \begin{bmatrix} E_1 & E_2 \\ E_3 & E_4 \end{bmatrix}, \tag{3.30}$$

where E_1, E_2, E_3 and E_4, respectively, are 2 by 2 matrices in the upper left, upper right, lower left and lower right corners of $\mathbb{E}$. The entries E_{11}, E_{21}, E_{31} and E_{41}, respectively, represent the expected number of exposed cattle, infectious cattle, exposed midges and infectious midges produced by one exposed cow. E_{12}, E_{22}, E_{32} and E_{42}, respectively, represent the expected number of exposed cattle, infectious cattle, exposed midges and infectious midges produced by one infectious cow. E_{13}, E_{23}, E_{33} and E_{43}, respectively, represent the expected number of exposed cattle, infectious cattle, exposed midges and infectious midges produced by one exposed midge. Similarly, E_{14}, E_{24}, E_{34} and E_{44}, respectively, represent the expected number of exposed cattle, infectious cattle, exposed midges and infectious midges produced by one infectious midge. The magnitude of $\rho(\mathbb{E})$ determines whether the probability of the disease extinction is equal to or less than unity [5]. If $\rho(\mathbb{E}) \leq 1$ (subcritical and critical), the probability of the disease extinction is one, that is,

$$\lim_{t\to\infty} Prob\{\vec{I}(t) = \vec{0}\} = 1,$$

where $\vec{I}(t) = (E_c(t), I_c(t), E_m(t), I_m(t))^T$ and T means transpose. If $\rho(\mathbb{E}) > 1$ (supercritical), there exists a fixed point $(x_1, x_2, x_3, x_4) \in (0,1)^4$ of the offspring pgfs, $g_i(x_1, x_2, x_3, x_4) = x_i$ for $i = 1, 2, 3, 4$ such that the respective probability of the disease extinction is given by

$$\mathbb{P}_0 = \lim_{t \to \infty} Prob\{\vec{I}(t) = \vec{0}\} = x_1^{e_c} x_2^{i_c} x_3^{e_m} x_4^{i_m} < 1, \tag{3.31}$$

where $e_c = E_c(0)$, $i_c = I_c(0)$, $e_m = E_m(0)$ and $i_m = I_m(0)$ [5]. The value of x_1, x_2, x_3 and x_4, respectively, is the probability of disease extinction for E_c, I_c, E_m and I_m. The probability of a major outbreak or persistence $\mathbb{P}_m = 1 - \mathbb{P}_0$. The matrix (3.30) satisfies $\rho(\mathbb{E}) < 1$ if and only if the following conditions hold.

$$trace(E_i) < 1 + det(E_i) < 2, \ \ \forall\, i = 1, 2, 3, 4. \tag{3.32}$$

From (3.30) it can easily be seen that $det(E_i) = trace(E_i) = 0$ for $i = 2, 3$, hence (3.32) hold for E_2 and E_3. Again from (3.30)

$$\begin{aligned}
det(E_1) =& \frac{-\Lambda \mu_m \mu_c (\mu_c + \nu + \gamma) \mathscr{R}_d}{\Lambda \mu_m \mu_c (\mu_c + \nu + \gamma)(1 + \mathscr{R}_v) + aq\pi\mu_c^2 + \beta\Lambda^2\mu_m} < 1, \\
det(E_4) =& \frac{-\sigma_m}{\sigma_m + \mu_m} < 1, \\
trace(E_1) =& \frac{aq\pi\mu_c^2 + \Lambda\mu_m(2b\phi\mu_c + \beta\Lambda)}{\Lambda \mu_m \mu_c (\mu_c + \nu + \gamma)(1 + \mathscr{R}_v) + aq\pi\mu_c^2 + \beta\Lambda^2\mu_m}, \\
trace(E_4) =& \frac{ap}{ap + \mu_m}.
\end{aligned}$$

Thus, the second inequality of (3.32) ($det(E_i) < 1$, $i = 1, 4$) is satisfied. After some algebraic manipulations it can be shown that the first inequality of (3.32), $trace(E_1) - det(E_1) < 1$ for E_1 holds iff $(\mathscr{R}_v + \mathscr{R}_d) < 1$ and $trace(E_4) - det(E_4) < 1$ for E_4 holds iff $\frac{ap\sigma_m}{\mu_m^2} < 1$. The quantities $\mathscr{R}_v$ and $\mathscr{R}_d$, respectively, are basic reproduction numbers for transplacental and direct transmission. Therefore, $\rho(\mathbb{E}) < 1$ iff $(\mathscr{R}_v + \mathscr{R}_d) < 1$ and $\frac{ap\sigma_m}{\mu_m^2} < 1$. This shows that in the presence of transplacental and direct transmission the disease cannot be eliminated from the animal community by only targeting the midges.

The matrix (3.30) is reducible implying that there is not necessarily a unique fixed point $\mathbf{x} \in (0,1)^4$ when $\rho(E) > 1$ [5]. If $(\mathscr{R}_v + \mathscr{R}_d) > 1$ and $\frac{ap\sigma_m}{\mu_m^2} > 1$, the fixed points of the offspring pgfs can be determined by setting $g_i(x_1, x_2, x_3, x_4) = x_i$ for $i = 1, 2, 3, 4$ and solving for x_i. Thus, from (3.25), (3.26), (3.27) and (3.28),

$$
\begin{aligned}
x_1 =& \frac{(\sigma_c x_2 + \mu_c)}{(\sigma_c + \mu_c)}, \\
x_3 =& \frac{\mu_m \sigma_m (\mu_c + \sigma_c) + \mu_m \big[(\mu_m + ap)(\mu_c + \sigma_c) - ap(\sigma_c x_2 + \mu_c)\big]}{(\mu_m + \sigma_m)\big[(\mu_m + ap)(\mu_c + \sigma_c) - ap(\sigma_c x_2 + \mu_c)\big]}, \\
x_4 =& \frac{\mu_m (\mu_c + \sigma_c)}{(\mu_m + ap)(\mu_c + \sigma_c) - ap(\sigma_c x_2 + \mu_c)}
\end{aligned} \tag{3.33}
$$

and x_2 satisfies the cubic equation given by

$$
a_3 x_2^3 + a_2 x_2^2 + a_1 x_2 + a_0 = 0, \tag{3.34}
$$

where

$$
\begin{aligned}
a_3 =& ap\sigma_c(\mu_m + \sigma_m)(\mu_c + \sigma_c)(\mu_c + \nu + \gamma)\mathscr{R}_{vd}, \\
a_2 =& -(\mu_m + \sigma_m)(\mu_c + \sigma_c)(\mu_c + \nu + \gamma)\big[ap\sigma_c(1 + 2\mathscr{R}_{vd}) \\
& + \mathscr{R}_0 \mu_m(\mu_c + \sigma_c)\big], \\
a_1 =& (\mu_m + \sigma_m)(\mu_c + \sigma_c)(\mu_c + \nu + \gamma)\big[(1 + \mathscr{R}_{vd})\big(ap\sigma_c + \mu_m(\mu_c \\
& + \sigma_c)\big) - \mu_m(\mu_c + \sigma_c)\mathscr{R}_m\big], \\
a_0 =& -(\mu_c + \nu + \gamma)(\mu_c + \sigma_c)(\mu_m + \sigma_m)\big[ap\sigma_c + \mu_m(\mu_c + \sigma_c)\big]
\end{aligned}
$$

with $\mathscr{R}_{vd}$, $\mathscr{R}_m$ and $\mathscr{R}_0$, respectively, being defined as in (3.7), (4.6) and (3.11). The analytical expressions for the fixed points x_1, x_2, x_3 and x_4 cannot easily be obtained. Thus, these fixed points will be determined numerically using (3.33) and (3.34). Considering (3.33) and (3.34) numerically one of the fixed points $(x_1, x_2, x_3, x_4) = (1, 1, 1, 1)$ always exists and the other fixed points lie in the set $(0, 1]^4$ for $\rho(\mathbb{E}) > 1$.

3.3 Numerical Results

In this section, the extinction probabilities x_1, x_2, x_3 and x_4 are computed numerically and used to determine the effects of transplacental and direct transmission on the probability of BTV persistence in temperate and tropical regions. It is assumed that persistence occurs if the probability of a major outbreak $\mathbb{P}_m = 1 - \mathbb{P}_0 \geq 0.5$, where $\mathbb{P}_0$ is defined as in (3.31).

3.3.1 Effects of Transplacental and Direct Transmission on the Probability of BTV Persistence in Temperate Regions

To study the effects of these routes on the probability of BTV persistence in PLMA, the following cases are considered:

(a) When there is only transplacental transmission ($\mathscr{R}_v > 1$, $\mathscr{R}_d = 0$ and $\mathscr{R}_m < 1$).

(b) When there is only direct transmission ($\mathscr{R}_v = 0$, $\mathscr{R}_d > 1$ and $\mathscr{R}_m < 1$).

(c) When there is transplacental and direct transmission ($\mathscr{R}_v > 1$, $\mathscr{R}_d > 1$ and $\mathscr{R}_m < 1$).

In all cases we take $\mathscr{R}_m < 1$, a case for the PLMA. To obtain the conditions for the PLMA the equations $a = 0.0002T(T-3.7)(41.9-T)^{\frac{1}{2.7}}$ [49], $\sigma_m = 0.0003T(T-10.4)$ [49] and $\mu_m = 0.009e^{0.16T}$ [43] where T is temperature in degrees Celsius are used. When $T < 12^{\circ}C$, replication of BTV and the midge activity cease [117]. Therefore, we set T below $12^{\circ}C$, that is $T = 11^{\circ}C$ to obtain the conditions for PLMA. This leads to $a = 0.0572$, $\sigma_m = 0.0020$ and $\mu_m = 0.0523$. Other parameter values are presented in Table 3.3.

In item (a) let the direct transmission rate $\beta = 0$, that is, no direct transmission. This yields $\mathscr{R}_v = 1.8362$, $\mathscr{R}_d = 0$ and $\mathscr{R}_m = 0.3052$. The fixed point (0.4924, 0.4921, 0.9867, 0.6417) calculated from (3.33) and (3.34) is used to determine the probability of BTV extinction $\mathbb{P}_0$. For item (b), setting the proportion of transplacental transmission $\phi = 0$ such that $\mathscr{R}_v = 0$, $\mathscr{R}_d = 2.4799$ and $\mathscr{R}_m = 0.3052$, the fixed point (0.3762, 0.3758, 0.9849, 0.5931) determined from (3.33) and (3.34) is used to calculate $\mathbb{P}_0$. In item (c), using the parameter values as given in Table 3.3 such that $\mathscr{R}_v = 1.8362$, $\mathscr{R}_d = 2.4799$ and $\mathscr{R}_m = 0.3052$, the fixed point (0.2236, 0.2232, 0.9829, 0.5394) obtained from (3.33) and (3.34) is used to calculate $\mathbb{P}_0$. Table 3.4 provides a summary of the probability of BTV extinction for the branching processes based on small initial values of the exposed cattle $E_c(0) = e_c$ and infectious cattle $I_c(0) = i_c$. The results in the Table 3.4 are depicted in Figure 3.2 for easy visualisation.

In PLMA such as in winter (Figure 3.2 and Table 3.4), for any pair of initial conditions and a transmission route, $\mathbb{P}_0 < 0.5$ which implies a persistence probability $\mathbb{P}_m \geq 0.5$. Also, direct transmission (item (ii)) yields a smaller probability of extinction than transplacental transmission (item (i)) indicating that BTV is most likely to persist by direct transmission rather than transplacental transmission. When both routes are present (item (iii)) the probability of extinction becomes significantly small ($\mathbb{P}_m > 0.7$).

Table 3.3: Parameter values of the model (3.1). The unit of time is one day.

Parameter	Description	Baseline value	Range	Reference
Λ	Recruitment rate from non-infectious cattle	0.2	0.1-0.2	[12]
b	Recruitment rate from infectious cattle	0.2	0.1-0.2	Assumed
ϕ	Proportion of transplacental transmission	0.37	0.1-0.37	[33]
ω	Rate of immunity loss	0.01	0-0.01	Estimated
μ_c	Host natural mortality rate	0.0002	0.0002-0.001	[7]
a	Midge biting rate	0.2757	$0.0572_l - 0.2757_h$	[49]
p	Probability that a midge infects a host	1.0	0.8-1.0	[53]
q	Probability that a host infects a midge	0.15	0.01-0.2	[26]
β	Direct transmission rate	0.0001	0.0001-0.0002	Assumed
σ_c	Host rate of becoming infectious	0.2778	$0.0556 - 0.5000$	[91]
ν	Disease-induced mortality rate	0.0001	0-0.0001	[101]
γ	Host recovery rate	0.04	$0.0167 - 0.1$	[53]
π	Midge recruitment rate	13748	$1830.5_l - 13748_h$	Estimated
μ_m	Midge natural mortality rate	0.3928	$0.0523_l - 0.3928_h$	[43]
σ_m	Midge rate of becoming infectious	0.0935	$0.0020_l - 0.0935_h$	[49]

The values with subscripts l and h are determined at $T = 11^{\circ}C$ and $T = 23.6^{\circ}C$, respectively, using $a = 0.0002T(T-3.7)(41.9-T)^{\frac{1}{2.7}}$, $\sigma_m = 0.0003T(T-10.4)$ and $\mu_m = 0.009e^{0.16T}$ [49]. It is assumed that the disease-induced immunity lasts for at least 6 months, thus, $\omega = 1/180$ (doesn't affect $\mathscr{R}_0$ or $\mathbb{P}_0$). The values of Λ, Π and b are set such that $\frac{\Lambda}{\mu_c} \approx 1,000$, $\frac{\pi}{\mu_m} \approx 35,000$ and $b = \Lambda$. Due to lack of data, β is chosen arbitrarily (for illustration).

Table 3.4: The effects of ϕ and β on the probability of BTV extinction in the PLMA. The parameter values are as given in the Table 3.3. The initial conditions used are $E_c(0) = e_c$, $I_c(0) = i_c$, $E_m(0) = 0$ and $I_m(0) = 0$.

		(a)	(b)	(c)
Initial conditions		$\mathscr{R}_v > 1$, $\mathscr{R}_d = 0$,	$\mathscr{R}_v = 0$, $\mathscr{R}_d > 1$,	$\mathscr{R}_v > 1$, $\mathscr{R}_d > 1$,
e_c	i_c	$\mathbb{P}_0$	$\mathbb{P}_0$	$\mathbb{P}_0$
1	0	0.4924	0.3762	0.2236
0	1	0.4921	0.3758	0.2232
1	1	0.2423	0.1414	0.0499
2	0	0.2425	0.1415	0.0500
0	2	0.2422	0.1412	0.0498
1	2	0.1193	0.0531	0.0111
2	1	0.1193	0.0532	0.0112
2	2	0.0587	0.0200	0.0025

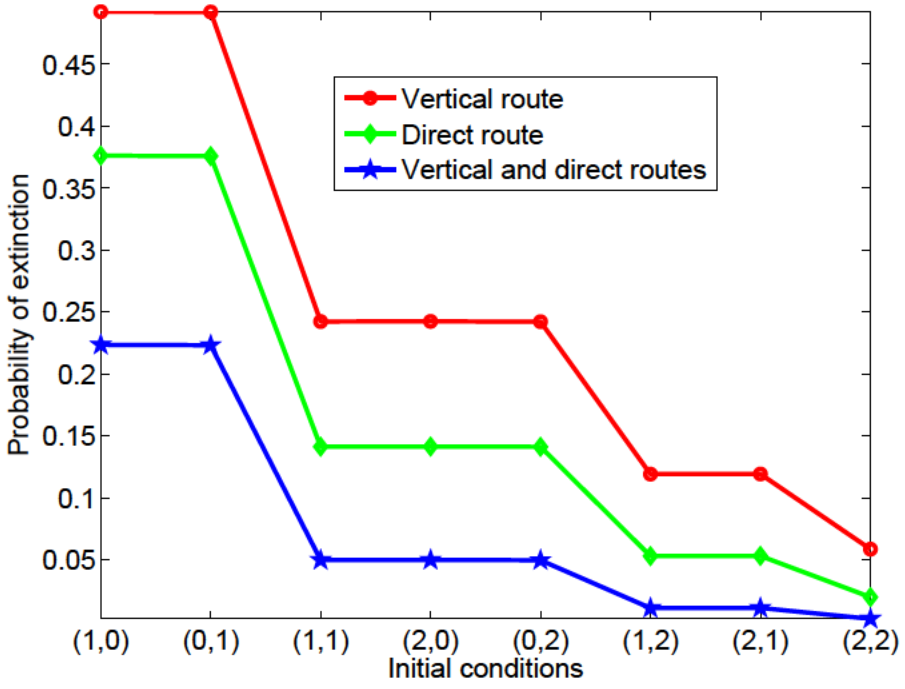


Figure 3.2: The effects of ϕ and β on the probability of BTV extinction in the PLMA.

The steep slopes of Figure 3.2 indicate that the effect of transplacental and direct transmission on the probability of BTV persistence increases with an increase in the initial conditions present at the beginning of an epidemic. The gentle slopes show that the exposed and infectious hosts almost play the same role on the probability of BTV persistence.

3.3.2 Effects of Transplacental and Direct Transmission on the Probability of BTV Persistence in Tropical Regions

Here we analyse the effects of these routes on the probability of BTV persistence or extinction in periods of high midge activity (PHMA), which applies especially in tropical regions where the disease is endemic and transmission is thought to occur mainly through vectorial transmission (host-to-midge and midge-to-host pathways). To explore the effects of these routes on the probability of persistence in PHMA, the following cases are considered based on the transmission behaviour of the different BTV serotypes:

(i) When there is only vectorial transmission ($\mathscr{R}_v = 0 = \mathscr{R}_d$ and $\mathscr{R}_m > 1$).

(ii) When there is vectorial and direct transmission ($\mathscr{R}_v = 0$, $\mathscr{R}_d > 1$ and $\mathscr{R}_m > 1$).

(iii) When there is vectorial and transplacental transmission ($\mathscr{R}_v > 1$, $\mathscr{R}_d = 0$ and $\mathscr{R}_m > 1$).

(iv) When there is vectorial, direct and transplacental transmission ($\mathscr{R}_v > 1$, $\mathscr{R}_d > 1$ and $\mathscr{R}_m > 1$).

In all cases we take $\mathscr{R}_m > 1$, that is the case for PHMA where the vectorial route is thought to be the main route of transmission. To achieve the conditions for PHMA the equations $a = 0.0002T(T-3.7)(41.9-T)^{\frac{1}{2.7}}$, $\sigma_m = 0.0003T(T-10.4)$ and $\mu_m = 0.009e^{0.16T}$ are used. According to Gubbins et al. [49], $\mathscr{R}_0$ is maximum in the temperature range of $23-25^{\circ}C$ and according to Brand and Keeling [19] the temperature that maximizes the probability of a midge surviving a single day and taking a blood meal is $T = 23.6^{\circ}C$. Therefore, to attain these conditions for the PHMA, T is set to $23.6^{\circ}C$. This forces $a = 0.2757$, $\mu_m = 0.3928$ and $\sigma_m = 0.0935$. Using these values and those in the Table 3.3 results in $\mathscr{R}_m = 4.8371$, $\mathscr{R}_v = 1.8362$ and $\mathscr{R}_d = 2.4799$. The observation that the vectorial route is dominant in the PHMA is not violated.

Table 3.5: The effects of ϕ and β on the probability of BTV extinction in the PHMA. The parameter values used are as given in Table 3.3. The initial conditions used are $E_c(0) = e_c$, $I_c(0) = i_c$, $E_m(0) = e_m$ and $I_m(0) = i_m$.

				(i)	(ii)	(iii)	(iv)
Initial conditions				$\mathscr{R}_v = 0$, $\mathscr{R}_d = 0$	$\mathscr{R}_v = 0$, $\mathscr{R}_d > 1$	$\mathscr{R}_v > 1$, $\mathscr{R}_d = 0$	$\mathscr{R}_v > 1$, $\mathscr{R}_d > 1$
e_c	i_c	e_m	i_m	$\mathbb{P}_0$	$\mathbb{P}_0$	$\mathbb{P}_0$	$\mathbb{P}_0$
1	0	0	0	0.3074	0.1806	0.2029	0.1369
0	1	0	0	0.3070	0.1801	0.2024	0.1364
0	0	1	0	0.9371	0.9298	0.9310	0.9275
0	0	0	1	0.6729	0.6349	0.6413	0.6228
2	0	0	0	0.0945	0.0326	0.0412	0.0186
0	2	0	0	0.0942	0.0324	0.0410	0.0187
0	0	2	0	0.8782	0.8645	0.8668	0.8603
0	0	0	2	0.4528	0.4031	0.4031	0.3879

Utilising (3.33) and (3.34) and the parameter values in Table 3.3, the fixed points (0.3074, 0.3070, 0.9371, 0.6729), (0.1806, 0.1801, 0.9298, 0.6349), (0.2029, 0.2024, 0.9310, 0.6413) and (0.1369, 0.1364, 0.9275, 0.6228), for items (i), (ii), (iii) and (iv) described above, are used to determine $\mathbb{P}_0$ in the PHMA.

Table 3.5 provides a summary of the probability of BTV extinction for the branching processes based on small initial values of the exposed cattle $E_c(0) = e_c$, infectious cattle $I_c(0) = i_c$, exposed midge $E_m(0) = e_m$ and the infectious midge $I_m(0) = i_m$. The results in the Table 3.5 are shown in the Figure 3.3 for easy visualisation. From Figure 3.3, in the PHMA transplacental and direct transmission have a small effect on $\mathbb{P}_0$ when the disease is initiated by a host and a very small effect when the disease is introduced by a midge at the beginning of an epidemic. The dynamics of disease are mostly driven by the vectorial transmission. For vectorial transmission (item (i)), the probability of BTV extinction is low ($\mathbb{P}_0 = 0.3070$) or high ($\mathbb{P}_0 = 0.6729$) if the disease emerges from an infectious host or an infectious midge at the beginning of an epidemic. The two peaks indicate that the probability of the disease extinction is highest if the disease is introduced by an exposed midge.

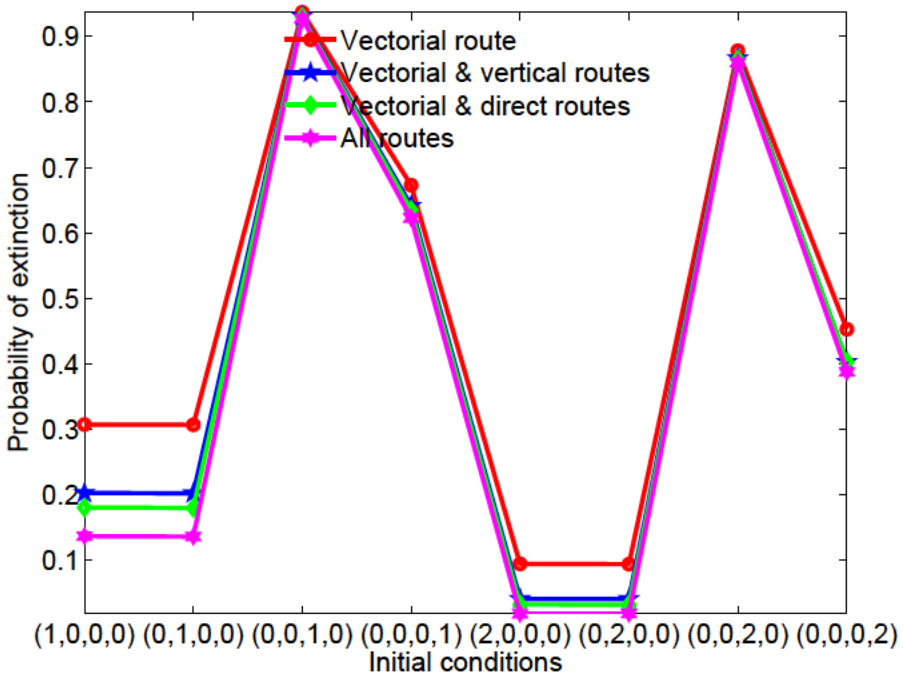


Figure 3.3: The effects of ϕ and β on the probability of BTV extinction in the PHMA.

3.3.3 Effects of Temperature on the Probability of BTV Extinction for PLMA and PHMA

To understand further the effects of transplacental and direct transmission on the probability of disease extinction in periods of either high or low midge activity the probabilities of disease extinction are plotted against temperature in Figure 3.4. The baseline parameter values given in the Table 3.3 are used except the values of a, σ_m and μ_m are varied in the temperature range of 0 to 35$^\circ C$. The initial values used are $E_c(0) = 0$, $I_c(0) = 1$, $E_m(0) = 0$ and $I_m(0) = 0$ (Figure 3.4 (a)) and $E_c(0) = 0$, $I_c(0) = 0$, $E_m(0) = 0$ and $I_m(0) = 1$ (Figure 3.4 (b)). For Figures 3.4 (c) and (d) initial values are indicated in the legend with e_c and e_m set to zero.

From Figure 3.4 (a), without transplacental and direct transmission the probability of BTV extinction is 1 for $T \leq 12^\circ C$. When the transplacental route is present the probability of extinction drops from 1 to 0.55 for $T \leq 10^\circ C$. Again from this figure, BTV persistence can easily take place with a probability of 0.58 when direct transmission is present at the beginning of an epidemic. The worst scenario (a persistence probability of 0.78 for $T \leq 10^\circ C$) is obtained when both routes are present in addition to the vectorial route.

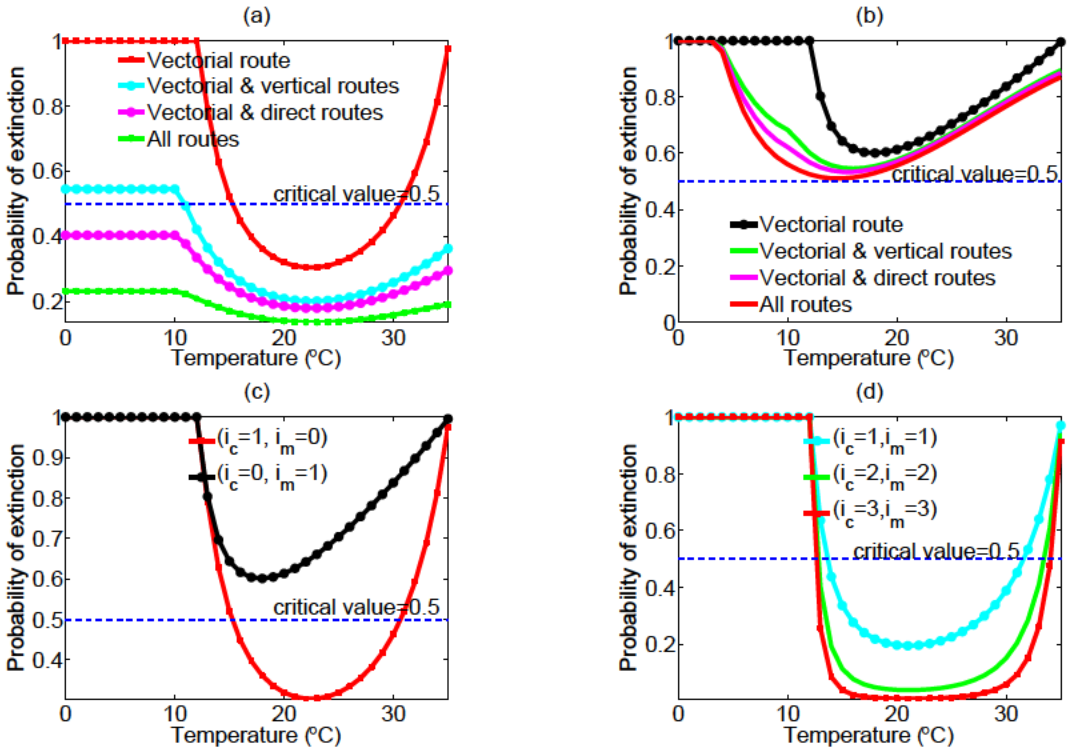


Figure 3.4: Effects of temperature on the probability of BTV extinction. In Figure 3.4 (a) the disease is initiated by the host, in Figure 3.4 (b) the disease is initiated by the vector, in Figure 3.4 (c) the host-to-midge and midge-to-host pathways are compared and in Figure 3.4 (d) the disease is initiated by both hosts and midges.

From Figure 3.4 (b), with only vectorial transmission, a major outbreak cannot happen for $T \leq 12°C$. From Figures 3.4 (a) and (b) it is clear that without transplacental and direct transmission, whether the disease is initiated by the host or the vector, transmission cannot take place when the temperature falls below $12°C$. Also from Figure 3.4 (b), transplacental and direct transmission cannot cause a major outbreak for temperatures below or equal to $3°C$ if the source of the infection is a midge.

From Figure 3.4 (c), the effects of host-to-midge (red line) and midge-to-host (black line) pathways are compared. The difference between the two pathways occurs at a temperature of $12°C$, after this value $\mathbb{P}_0$ decreases to the minimum value of 0.6 for $T \in [16, 20]$ or 0.3 for $T \in [20, 25]$, respectively, if the disease is initiated by the midge or host.

The effect of the initial conditions on the temperature range for the minimum probability

of extinction or maximum probability of a major outbreak is presented in Figure 3.4 (d). It is clear that depending on the initial conditions without transplacental and direct transmission the temperature range for minimum $\mathbb{P}_0$ is 13 to 34°C.

3.3.4 Sensitivity Analysis for PLMA and PHMA

Here we carry out the effect of transplacental and direct transmission on $\mathscr{R}_0$ in PLMA and PHMA using sensitivity analysis. Sensitivity analysis is a means of determining the relative importance of each model parameter on a given response function which in this case is taken to be $\mathscr{R}_0$. Thus, in addition to finding the effects of these routes on $\mathscr{R}_0$, the effects of other parameters in the model (3.1) on $\mathscr{R}_0$ are also determined. The analysis here will help to determine where to best allocate resources which are scarce in times of PLMA and PHMA by focusing control measures on the parameters with the highest influence.

The Latin Hypercube Sampling (LHS) method is used for the sensitivity analysis. This method requires defining a range and baseline value for each model parameter and generating N multiple runs for $\mathscr{R}_0$ [17, 71]. The ranges for the temperature-dependent parameters a, σ_m and μ_m for PLMA and PHMA, respectively, are taken from the temperature ranges of $[0,12]$ and $[20,25]$. These ranges are determined from Figure 3.4 (c) corresponding to maximum (for PLMA) and minimum (for PHMA) probabilities of BTV extinction. All the parameters are assumed to follow a uniform distribution [96]. From the LHS method the partial rank correlation coefficients (PRCCs) of the model (3.1) for PLMA and PHMA are calculated (Table 3.6) and depicted in the Figures 3.5 and 3.6, respectively. The sign and magnitude of the PRCC determines the effect of that parameter on the transmission of the disease. A parameter with a negative or positive PRCC value, respectively, has the potential of minimising the infection when increased or decreased. The parameters with PRCC values greater than 0.5 or less than -0.5 are the most sensitive to $\mathscr{R}_0$ [106].

From Table 3.6 and Figure 3.5, the parameters with the highest influence on $\mathscr{R}_0$ in the PLMA are the direct transmission rate β, proportion of transplacental transmission rate ϕ, cattle recovery rate γ and the cattle recruitment rates, Λ (from non-infectious individuals) and b (from infectious individuals). Apart from γ all the other aforementioned parameters have positive PRCC values.

Table 3.6: PRCC values of the ODE model parameters for PLMA and PHMA based on $N = 1000$ runs. The parameter ranges used are as in the Table 3.3 with $a \in [0, 0.0701]$, $\sigma_m \in [0, 0.0058]$ and $\mu_m \in [0.0090, 0.0614]$ for PLMA and $a \in [0.2045, 0.3035]$, $\sigma_m \in [0.0576, 0.1095]$ and $\mu_m \in [0.2208, 0.4914]$ for PHMA.

Parameter	PRCC value for PLMA	PRCC value for PHMA
Λ	0.51887	-0.5195
b	0.5801	0.0775
ϕ	0.5804	0.0764
μ_c	-0.0103	-0.0077
a	0.3192	0.5762
p	0.0363	0.1337
q	0.8386	0.8386
β	0.840	0.0088
σ_c	0.0071	0.0165
ν	-0.0108	-0.0145
γ	-0.9683	-0.7073
π	0.6466	0.6466
μ_m	-0.2841	-0.9215
σ_m	0.3968	0.1724

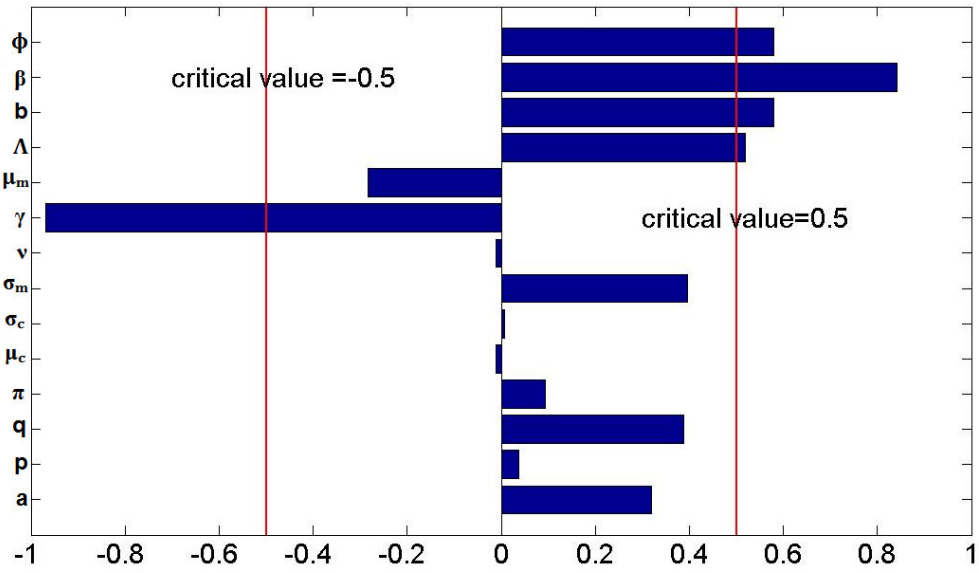


Figure 3.5: Tornado plot for sensitivity indices for PLMA.

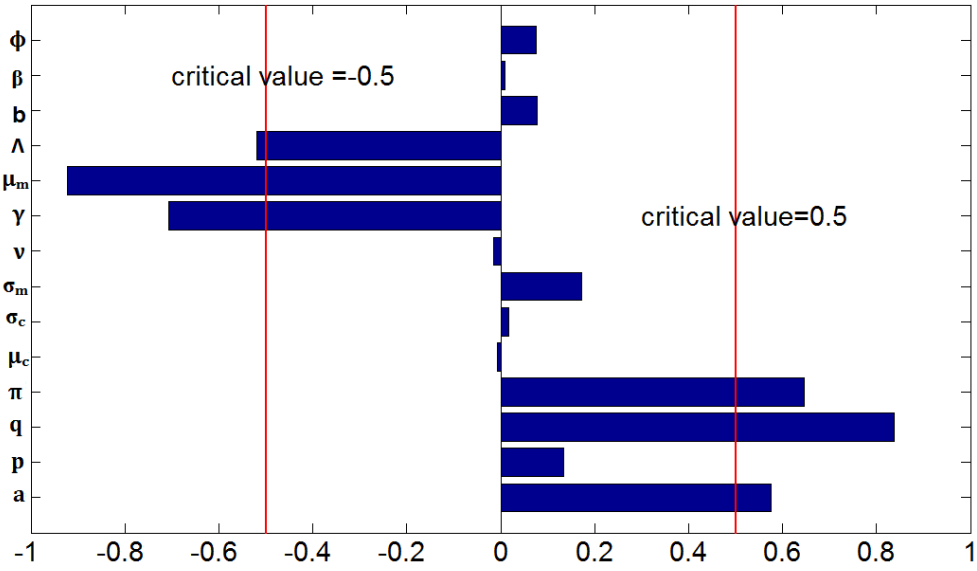


Figure 3.6: Tornado plot for sensitivity indices for PHMA.

From Table 3.6 and Figure 3.6, the parameters with the highest influence on $\mathscr{R}_0$ in the PHMA are the host recruitment rate Λ, Probability of a midge infection by an infectious host q, midge recruitment rate π, midge natural mortality rate μ_m, midge biting rate a and the host recovery rate γ. The parameters a, π and q have positive PRCC values while Λ, μ_m and γ have negative PRCC values. Results of Figures 3.5 and 3.6 further show that in the PLMA and PHMA transplacental and direct transmission play a major and a minor role, respectively, on the persistence of the disease.

3.4 Discussion

In this chapter, a deterministic model for the transmission dynamics of BTV was formulated and analysed. The model was shown to exhibit a backward bifurcation, where the stable disease-free and endemic equilibrium points co-exist, when the basic reproduction number is less than unity. In this case, control measures for BTV depend on the initial conditions and are likely to be more effective if the disease originates in small populations. Thus, for better results control measures against the disease should be applied in early stages of an epidemic. Based on the same assumptions as the deterministic model a continuous-time Markov chain (CTMC) model was formulated to capture the effects of small numbers of infectious individuals introduced into the cattle-midge population. Multitype Galton-Watson branching process theory was used to approximate the nonlinear CTMC model near the disease-free

equilibrium point and to estimate the effects of transplacental and direct transmission on the probability of BTV persistence in temperate and tropical regions.

In periods of low midge activity such as in winter (Figure 3.2 and Table 3.4), for a single temperature $T = 11°C$ and any pair of initial conditions both transplacental and direct transmission lead to a high probability of BTV persistence ($\mathbb{P}_m > 0.5$). This implies that BTV persistence can easily take place when either of the routes is present at the beginning of an epidemic. Also, direct transmission resulted in a higher probability of persistence than transplacental transmission. The highest probability ($\mathbb{P}_m > 0.7$) was obtained when both routes were considered at the beginning of an epidemic. Since the current BTV serotypes have a high potential of reassortment in the field [14], this result indicates that reassortment of a BTV serotype that is directly transmitted such as BTV-26 and the one that is transplacentally transmitted such as BTV-8 may result into a new serotype that can easily overwinter. It also emphasises the conclusion made by Menzies et al. [72], an experimental study that showed evidence of transplacental and direct transmission of BTV in cattle that caution is needed when moving pregnant animals that are BTV positive into regions which are free from the virus.

The effects of transplacental and direct transmission on the probability of BTV persistence increased with an increase in the initial conditions present at the beginning of an epidemic (Figure 3.2 and Table 3.4). This result indicates that control measures against the disease targeting these routes can work effectively if they are implemented in the early stages of an epidemic when the number of infectious individuals is still small. Also, the exposed and the infectious hosts result in similar probabilities of bluetongue virus persistence and thus can be seen as playing similar roles in this process. This result emphasises the importance of screening cattle at border points regardless of their physical health appearance to avoid movement of the BTV exposed cattle into BTV-free regions as the effect on the probability of bluetongue virus persistence can then be high.

When the temperature was varied in the range $[0, 35°C]$, it was shown that without transplacental and direct transmission, whether the disease is initiated by the host or the midge, the probability of BTV extinction is 1.0 for $T \leq 12°C$ (Figure 3.4 (a) and (b)). This is due to the fact that below this temperature midge activities cease [117]. This result depends on the assumption that no midge hides in animal shelters during harsh temperature conditions. A

midge can hide in animal shelters during winter (endophilic behaviour) [120], but research carried out by Napp et al. [78] showed that the possibility of BTV persistence by the small numbers of midge which survive during winter, probably hiding in farm buildings, is very small and couldn't explain the BTV persistence found in Germany between 2006 and 2007. This indicates that the small numbers of midge that survive winter by hiding in animal shelters may have little effect on our result. Thus, bluetongue virus persistence cannot take place by a vectorial route for $T \leq 12^{\circ}C$.

For periods of high midge activity, transplacental and direct transmission have a small effect on the probability of BTV persistence (Figure 3.3 and Table 3.5). This implies that in tropical regions the dynamics of BTV are mostly driven by the vectorial transmission route. This is in agreement with the study by van der Sluijs et al. [111] where it was pointed out that the role of transplacental and direct routes on the transmission of BTV is limited in tropical regions. Also from Figure 3.3, the probability of BTV extinction is low ($\mathbb{P}_0 = 0.3070$) if the disease emerges from an infectious host and high ($\mathbb{P}_0 = 0.6729$) if it emerges from an infectious midge. Thus, for vectorial transmission the host-to-midge route is more dominant than the midge-to-host route. This result can be explained by the fact that an infectious cow before its recovery can be in a position to infect many midges continuously which in turn can infect many susceptible cattle thereby reducing the probability of BTV extinction. In addition, cattle are the main reservoirs for BTV and they can be viremic for long periods of time, up to 100 days [105] leading to a low probability of disease extinction. Hence, for periods of high midge activity control efforts that target the hosts are likely to yield better results than those that target midges. Without transplacental and direct transmission the temperature range for minimum probability of extinction is 13 to $34^{\circ}C$ (see Figure 3.4 (d)). The same temperature range of 13 to $34^{\circ}C$ is noted in the study by Braverman and Chechik [20] as the range for maximum midge activities. Therefore, in periods of high midge activity (tropical regions) this is the range for maximum application of control measures against the disease.

For periods of low midge activity, persistence can be avoided if the direct transmission rate (β), proportion of transplacental transmission (ϕ) and the host recruitment rates (Λ and b) are reduced and/or the recovery rate (γ) is increased (see Table 3.6 and Figure 3.5). The rates β, ϕ, Λ and b can all be decreased by vaccination. β can also be decreased by any other means that limits the physical contact of animals such as quarantine. The decrease of Λ and b by vaccination emphasises the need of vaccinating the animals after birth and before recruitment

into the farm. There are no control measures which directly increase the recovery rate since the disease has no cure. However, antibiotics to treat the clinical signs and prevent the secondary infections can be used to increase γ indirectly.

Control measures that simultaneously decrease the midge biting rate (a), recruitment rate (π) and the probability of transmission from host to midge (q) while increasing the midge mortality rate (μ_m) and the cattle recovery rate (γ) can greatly reduce the chances of BTV persistence in the periods of high midge activity (see Table 3.6 and Figure 3.6). The midge biting rate can be reduced by the use of a repellent and any other mechanism that limits the access of midges to animals such as stabling animals in houses between dusk and dawn when the midge activity is highest and use of nets to cover animal shelters. Recruitment of midges can be reduced by using larvicides to kill the midges in the aquatic stage, destroying the breeding places such as stagnant pools of water, dung hips and the bushes around animal shelters. Transmission from host to midges can be reduced by vaccination of susceptible animals. The midge mortality rate can be increased by using fungi [8] and insecticides [56] which directly kill the adult midges.

Chapter 4
Effects of Wind-aided Midge Movement on the Outbreak and Coexistence of Multiple Bluetongue Virus Serotypes in Patchy Environments

Following Qiu et al. [86], the deterministic model (3.1) in Chapter 3 is transformed into a multi-patch multi-serotype deterministic model. However, in a deterministic model the probability of a major outbreak of multiple serotypes cannot be determined [3]. Thus, a continuous-time Markov chain (CTMC) stochastic model is derived from the deterministic model. Stochastic models give extra information about the disease dynamics at the beginning and during an outbreak that cannot be provided by deterministic models [60]. The probability of a major outbreak of multiple BTV serotypes is computed using a multitype branching process approximation of the CTMC model [60]. There are two different outcomes of a major outbreak for a CTMC model, either competitive exclusion (persistence of only one serotype) or coexistence of multiple serotypes [2]. Using numerical simulations, the two outcomes of the major outbreak for the CTMC are predicted by the ODE model. To the best of our understanding, our CTMC model is the first one of its kind to study the outbreak and coexistence of multiple serotypes or strains in patchy environments connected by cattle (host) and midge (vector) movements and thus a methodological advancement in this field. The version of this chapter, co-authored with Kevin J. Duffy, Joseph Y.T. Mugisha and Obiora C. Collins has been published in *Mathematical Biosciences* [73].

4.1 Deterministic Model for Multiple BTV Serotypes in Patchy Environments

In this section, the BTV model (3.1) in Chapter 3 is extended to include r different serotypes and n discrete patches connected by cattle and/or midge movements. It is also an extension of the model in [86] by including vector (midge) migration and exposed classes in the host (cattle) and vector populations. Since the study seeks to determine the effects of wind-aided midge movements on the probability of coexistence of multiple BTV serotypes, only vectorial transmission is considered. In this model, the cattle population $N_{ci}(t)$ in patch i is divided into $3r+1$ epidemiological sub-population classes: Susceptible $S_{ci}(t)$, Exposed $E^j_{ci}(t)$, Infectious $I^j_{ci}(t)$ and Recovered $R^j_{ci}(t)$ with strain j, $j = 1,2,...,r$. The midge population $N_{mi}(t)$ in patch i is divided into $2r+1$ subclasses: Susceptible $S_{mi}(t)$, Exposed $E^j_{mi}(t)$ and Infectious $I^j_{mi}(t)$ with strain j, $j = 1,2,...r$. We assume that there is cross-immunity among serotypes. Otherwise, there will be co-infection which has been shown to enable the coexistence of multiple strains [67, 68]. If the n patches are connected and the cattle and midges can move at rates $c_{ki} \geq 0$ and $m_{ki} \geq 0$ from patch i to patch k, where $i \neq k$, then the dynamics of BTV transmission in patch i with r serotypes can be described by the following system of $5r+2$ equations:

$$
\begin{aligned}
\frac{dS_{ci}}{dt} =& \Lambda_i + \sum_{j=1}^{r} \omega_i^j R_{ci}^j - a_i \sum_{j=1}^{r} \left(p_j I_{mi}^j\right) \frac{S_{ci}}{N_{ci}} - \mu_{ci} S_{ci} + \sum_{k=1,k\neq i}^{n} c_{ik} S_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki} S_{ci}, \\
\frac{dE_{ci}^j}{dt} =& a_i p_j I_{mi}^j \frac{S_{ci}}{N_{ci}} - (\mu_{ci} + \sigma_{ci}^j) E_{ci}^j + \sum_{k=1,k\neq i}^{n} c_{ik} E_{ck}^j - \sum_{k=1,k\neq i}^{n} c_{ki} E_{ci}^j, \\
\frac{dI_{ci}^j}{dt} =& \sigma_{ci}^j E_{ci}^j - (\mu_{ci} + \nu_i^j + \gamma_i^j) I_{ci}^j + \sum_{k=1,k\neq i}^{n} c_{ik} I_{ck}^j - \sum_{k=1,k\neq i}^{n} c_{ki} I_{ci}^j, \\
\frac{dR_{ci}^j}{dt} =& \gamma_i^j I_{ci}^j - (\omega_i^j + \mu_{ci}) R_{ci}^j + \sum_{k=1,k\neq i}^{n} c_{ik} R_{ck}^j - \sum_{k=1,k\neq i}^{n} c_{ki} R_{ci}^j, \\
\frac{dS_{mi}}{dt} =& \pi_i - a_i \sum_{j=1}^{r} \left(q_j I_{ci}^j\right) \frac{S_{mi}}{N_{ci}} - \mu_{mi} S_{mi} + \sum_{k=1,k\neq i}^{n} m_{ik} S_{mk} - \sum_{k=1,k\neq i}^{n} m_{ki} S_{mi}, \\
\frac{dE_{mi}^j}{dt} =& a_i q_j I_{ci}^j \frac{S_{mi}}{N_{ci}} - (\sigma_{mi}^j + \mu_{mi}) E_{mi}^j + \sum_{k=1,k\neq i}^{n} m_{ik} E_{mk}^j - \sum_{k=1,k\neq i}^{n} m_{ki} E_{mi}^j, \\
\frac{dI_{mi}^j}{dt} =& \sigma_{mi}^j E_{mi}^j - \mu_{mi} I_{mi}^j + \sum_{k=1,k\neq i}^{n} m_{ik} I_{mk}^j - \sum_{k=1,k\neq i}^{n} m_{ki} I_{mi}^j,
\end{aligned}
\tag{4.1}
$$

with $N_{ci} = S_{ci} + \sum_{j=1}^{r}(E_{ci}^{j} + I_{ci}^{j} + R_{ci}^{j})$, $N_{mi} = S_{mi} + \sum_{j=1}^{r}(E_{mi}^{j} + I_{mi}^{j})$, $i \in \{1,2,...,n\}$ and $j = 1,2,...,r$. In (4.1), Λ_i and π_i, respectively, are cattle and midge recruitment rates (by birth); p_j is the probability that a bite from an infectious midge leads to infection of a susceptible cow; a_i is the biting rate of female midges; q_j is the probability that a bite from a susceptible midge to an infectious cow leads to infection of the midge; ν_i^j is the disease related mortality rate of cattle; γ_i^j is the recovery rate of an infected cow; ω_i^j is the rate of loss of disease-induced immunity; μ_{ci} and μ_{mi}, respectively, are the natural mortality rates of cattle and midges; σ_{ci}^j and σ_{mi}^j, respectively, are the rates that exposed cattle and midges become infectious.

Adding the cattle equations of (4.1),

$$\frac{dN_{ci}(t)}{dt} = \Lambda_i - \nu_i^j I_i^j + \sum_{k=1,k\neq i}^{n} c_{ik}N_{ck}(t) - \big(\mu_{ci} + \sum_{k=1,k\neq i}^{n} c_{ki}\big)N_{ci}(t). \tag{4.2}$$

Similarly, adding the midge equations of (4.1),

$$\frac{dN_{mi}(t)}{dt} = \pi_i + \sum_{k=1,k\neq i}^{n} m_{ik}N_{mk}(t) - \big(\mu_{mi} + \sum_{k=1,k\neq i}^{n} m_{ki}\big)N_{mi}(t). \tag{4.3}$$

It can be verified that all solutions of (4.1) with positive initial conditions remain positive for all time $t > 0$. From (4.2), $\limsup_{t\to\infty} N_{ci}(t) \leq \Lambda_i/(\mu_{ci} + \sum_{k=1,k\neq i}^{n} c_{ki}) := \bar{N}_{ci}$ and from (4.3) $\limsup_{t\to\infty} N_{mi}(t) \leq \pi_i/(\mu_{mi}$
$+ \sum_{k=1,k\neq i}^{n} m_{ki}) := \bar{N}_{mi}$. Let $L_i^j = (E_{ci}^j, I_{ci}^j, R_{ci}^j, E_{mi}^j, I_{mi}^j)$ for $i \in \{1,2,...,n\}$ and $j = 1,2,...,r$. Then, the feasible region

$$\Omega_i = \left\{ (S_{ci}, S_{mi}, L_i^1, L_i^2, ..., L_i^r) \in \mathbb{R}_+^{(5r+2)} | N_{ci} \leq \bar{N}_{ci}, N_{mi} \leq \bar{N}_{mi} \right\}$$

is positively invariant with respect to the model (4.1). Thus, the model (4.1) is epidemiologically feasible and mathematically well-posed [55]. From (4.1), the mobility matrix for cattle movement is given by $M_c(i,k) = c_{ik}$ for $i \neq k$ and $M_c(i,i) = -\sum_{k=1,k\neq i}^{n} c_{ki}$. This implies that

$$M_c = \begin{bmatrix} -\sum_{k=1}^{n} c_{k1} & c_{12} & \cdots & c_{1n} \\ c_{21} & -\sum_{k=1}^{n} c_{k2} & \cdots & c_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ c_{n1} & c_{n2} & \cdots & -\sum_{k=1}^{n} c_{kn} \end{bmatrix}. \tag{4.4}$$

Similarly, for the midge $M_m(i,k) = m_{ik}$ for $i \neq k$ and $M_m(i,i) = -\sum_{k=1,k\neq i}^{n} m_{ki}$. This leads to

$$M_m = \begin{bmatrix} -\sum_{k=1}^{n} m_{k1} & m_{12} & \cdots & m_{1n} \\ m_{21} & -\sum_{k=1}^{n} m_{k2} & \cdots & m_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ m_{n1} & m_{n2} & \cdots & -\sum_{k=1}^{n} m_{kn} \end{bmatrix}. \tag{4.5}$$

4.1.1 Basic Reproduction Numbers

Without movement, the (4.1) has n isolated patches. For any serotype in an isolated patch i, its disease-free equilibrium point is given by $(S_{ci}^0, 0, 0, 0, S_{mi}^0, 0, 0)$. The local stability of this equilibrium point is governed by the basic reproduction number, $\mathscr{R}_0$ (see [108] for the definition). If $\mathscr{R}_0 < 1$ it is locally-asymptotically stable, whereas it is unstable if $\mathscr{R}_0 > 1$. Using the next generation operator method [108], the basic reproduction number for serotype j in an isolated patch i (see [108] for the derivation) is given by

$$\mathscr{R}_{0i}^j = \sqrt{\frac{{}^2a_i^2 p_j q_j \sigma_{ci}^j \sigma_{mi}^j}{\mu_{mi}(\mu_{ci}+\sigma_{ci}^j)(\mu_{mi}+\sigma_{mi}^j)(\mu_{ci}+\nu_i^j+\gamma_i^j)} \left(\frac{S_{mi}^0}{S_{ci}^0}\right)}, \tag{4.6}$$

where $\dfrac{S_{mi}^0}{S_{ci}^0} = \dfrac{\pi_i \mu_{ci}}{\Lambda_i \mu_{mi}}$ for $i \in \{1,2,...,n\}$ and $j \in \{1,2,...,r\}$.

To determine the basic reproduction number for any serotype j, $j \in \{1,2,...,r\}$ over the entire patch system, set $L_{ci}^j = (E_{ci}^j, I_{ci}^j, R_{ci}^j)$ and $L_{mi}^j = (E_{mi}^j, I_{mi}^j)$ for $i = 1,2,...,n$. Then, $(S_{c1}^0, L_{c1}^{j0}, S_{m1}^0, L_{m1}^{j0}, ..., S_{cn}^0, L_{cn}^{j0}, S_{mn}^0, L_{mn}^{j0})$ is the disease-free equilibrium point of the model (4.1) where $L_{ci}^{j0} = 0 = L_{mi}^{j0}$, $S_{ci}^0 > 0$ and $S_{mi}^0 > 0$. For instance, if there are two patches, the model (4.1) has a unique disease free-equilibrium point given by $(S_{c1}^0, 0, 0, 0, S_{m1}^0, 0, 0, S_{c2}^0, 0, 0, 0, S_{m2}^0, 0, 0)$, where

$$\begin{aligned} S_{ci}^0 &= \frac{\Lambda_i(\mu_{ck}+c_{ik}) + c_{ik}\Lambda_k}{\mu_{ci}(\mu_{ck}+c_{ik}) + c_{ki}\mu_{ck}},\ i = 1,2,\ k = 1,2,\ i \neq k, \\ S_{mi}^0 &= \frac{\pi_i(\mu_{mk}+u_{2k}+m_{ik}) + m_{ik}\pi_k}{\mu_{mi}(\mu_{mk}+u_{2k}+m_{ik}) + m_{ki}(\mu_{mk}+u_{2k})}. \end{aligned} \tag{4.7}$$

Consider the infected classes, E_{ci}^j, I_{ci}^j, E_{mi}^j and I_{mi}^j, $i = 1,2,...,n$ of (4.1). Using the next generation operator method [108], it follows from [108] that the matrices F^j and V^j for the new infection and transfer terms, respectively, are given by

$$F^j = \begin{bmatrix} 0 & 0 & 0 & F_{14}^j \\ 0 & 0 & 0 & 0 \\ 0 & F_{32}^j & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{4.8}$$

and

$$V^j = \begin{bmatrix} V_{11}^j & 0 & 0 & 0 \\ -V_{21}^j & V_{22}^j & 0 & 0 \\ 0 & 0 & V_{33}^j & 0 \\ 0 & 0 & -V_{43}^j & V_{44}^j \end{bmatrix}, \tag{4.9}$$

where $F_{14}^j = \text{diag}[a_i p_j]$, $F_{32}^j = \text{diag}[a_i q_j S_{mi}^0 / S_{ci}^0]$, $V_{21}^j = \text{diag}[\sigma_{ci}^j]$, $V_{43}^j = \text{diag}[\sigma_{mi}^j]$, $V_{11}^j = \text{diag}[\sigma_{ci}^j + \mu_{ci}] - M_c$, $V_{22}^j = \text{diag}[\mu_{ci} + \nu_i^j + \gamma_i^j] - M_c$, $V_{33}^j = \text{diag}[\mu_{mi} + \sigma_{mi}^j] - M_m$ and $V_{44}^j = \text{diag}[\mu_{mi}] - M_m$ with M_c and M_m, respectively, being defined as in (4.4) and (4.5).

From [108], the basic reproduction number for (4.1) is determined from (4.8) and (4.9) and is given by

$$\mathscr{R}_0^j = \rho(F^j (V^j)^{-1}), \tag{4.10}$$

where $\rho(A)$ represents the dominant eigenvalue of the matrix A.

The disease-free equilibrium point of the entire system is locally stable when $\mathscr{R}_0^j < 1$ and unstable if $\mathscr{R}_0^j > 1$ for all $1 \leq j \leq r$. This result is governed by $\mathscr{R}_0^j$, $j = 1, 2, ..., r$, which depend on demographic, disease and movement parameters [9]. These vary from patch to patch. In the next section, a model (CTMC) that accounts for demographic and movement variability is formulated.

4.2 Stochastic Model for Multiple BTV Serotypes in Patchy Environments

Here a CTMC stochastic model for (4.1) is derived. For simplicity, the same notation for the random variables and parameters as used in (4.1) is maintained. Let

$$\vec{Y}(t) = \big(S_{c1}(t), E^j_{c1}(t), I^j_{c1}(t), R^j_{c1}(t), S_{m1}(t), E^j_{m1}(t), I^j_{m1}(t), ..., S_{cn}(t), E^j_{cn}(t), I^j_{cn}(t),$$
$$R^j_{cn}(t), S_{mn}(t), E^j_{mn}(t), I^j_{mn}(t)\big), \quad j = 1, 2, ..., r,$$

represent a discrete valued random vector where $S_{ci}(t), E^j_{ci}(t), I^j_{ci}(t), R^j_{ci}(t), S_{mi}(t)$, $E^j_{mi}(t), I^j_{mi}(t) \in \{0, 1, 2, ..., P\}$ for $i \in \{1, 2, ..., n\}$, $j \in \{1, 2, ..., r\}$ and P is a positive integer denoting the maximum possible size of the population in a finite space [66]. The state transitions and their rates of occurrence for the multi-serotype CTMC BTV model in patchy environments are depicted in Table 4.1. From the Markov assumption, the inter-event time is exponentially distributed [60, 61] with parameter

$$\begin{aligned}\phi(\vec{Y}(t)) = \sum_{i=1}^{n} \Big[&\Lambda_i + \mu_{ci} N_{ci} + \sum_{j=1}^{r} (\sigma^j_{ci} E^j_{ci} + \sigma^j_{mi} E^j_{mi} + (\nu^j_i + \gamma^j_i) I^j_{ci} + \omega R^j_{ci}) \\ &+ \frac{a_i \sum_{j=1}^{r} \left(p_j S_{ci} I^j_{mi} + q_j S_{mi} I^j_{ci}\right)}{N_{ci}} + \pi_i + \mu_{mi} N_{mi} + \sum_{k=1, k\neq i}^{n} \left(c_{ki} N_{ci} + m_{ki} N_{mi}\right) \Big].\end{aligned} \tag{4.11}$$

4.2.1 Multitype Branching Process Approximation

To determine the probability of a major outbreak of multiple BTV serotypes, the multitype Galton-Watson branching processes is used to approximate the nonlinear CTMC model near the disease-free equilibrium [60, 61]. This process assumes that the transition rates are linear [60, 61]. It is only applied to the infected individuals, the recovered and susceptible individuals are assumed to be at disease-free equilibrium point [60, 61, 66]. Since the multitype branching process is time-homogeneous, linear near the disease-free equilibrium point, and deaths and births are independent, the offspring probability generating functions (pgfs) for the birth and death of infected individuals can be defined [60, 61, 66]. Here, birth means a new infection and offspring denotes the number of new infections that each infected individual produces [66]. The pgfs can be used to calculate the probability of disease extinction [61, 66], which in turn can be used to determine the probability of an outbreak of multiple serotypes. Let $I^j_i = (E^j_{ci}, I^j_{ci}, E^j_{mi}, I^j_{mi})^T$ be a vector of infected cattle and midges in patch i. Assume that infected cattle or midges of type u in patch i with serotype j, I^j_u, give birth to cattle or midges of type v in patch k, I^j_v and that the number of offspring produced by a cow or a midge of type u does not depend on the number of offspring produced by other cows or midges of type u or type v, $u \neq v$ (they are independent) [60, 66]. Also, cows or midges of type u have the same offspring pgf [66].

Table 4.1: State transitions and rates for the multi-serotype CTMC BTV model in patchy environments.

Event	State transition ($\vec{Y}(t+\Delta t)$)	Transition rate (λ)
Birth of S_{ci}	$S_{ci} \to S_{ci}+1$	Λ_i
Death of S_{ci}	$S_{ci} \to S_{ci}-1$	$\mu_{ci}S_{ci}$
Infection of S_{ci} by serotype j	$(S_{ci}, E^j_{ci}) \to (S_{ci}-1, E^j_{ci}+1)$	$\frac{a_i p_j S_{ci} I^j_{mi}}{N_{ci}}$
Death of E^j_{ci}	$E^j_{ci} \to E^j_{ci}-1$	$\mu_{ci}E^j_{ci}$
E^j_{ci} becoming I^j_{ci}	$(E^j_{ci}, I^j_{ci}) \to (E^j_{ci}-1, I^j_{ci}+1)$	$\sigma^j_{ci}E^j_{ci}$
Death of I^j_{ci}	$I^j_{ci} \to I^j_{ci}-1$	$(\mu_{ci}+\nu^j_i)I^j_{ci}$
Recovery of I^j_{ci}	$(I^j_{ci}, R^j_{ci}) \to (I^j_{ci}-1, R^j_{ci}+1)$	$\gamma^j_i I^j_{ci}$
Death of R^j_{ci}	$R^j_{ci} \to R^j_{ci}-1$	$\mu_{ci}R^j_{ci}$
Loss of immunity	$(S_{ci}, R^j_{ci}) \to (S_{ci}+1, R^j_{ci}-1)$	ωR^j_{ci}
Birth of midges	$S_{mi} \to S_{mi}+1$	π_i
Death of S_{mi}	$S_{mi} \to S_{mi}-1$	$\mu_{mi}S_{mi}$
Infection of S_{mi} by serotype j	$(S_{mi}, E^j_{mi}) \to (S_{mi}-1, E^j_{mi}+1)$	$\frac{a_i q_j S_{mi} I^j_{ci}}{N_{ci}}$
Death of E^j_{mi}	$E^j_{mi} \to E^j_{mi}-1$	$\mu_{mi}E^j_{mi}$
E^j_{mi} becoming I^j_{mi}	$(E^j_{mi}, I^j_{mi}) \to (E^j_{mi}-1, I^j_{mi}+1)$	$\sigma^j_{mi}E^j_{mi}$
Death of I^j_{mi}	$I^j_{mi} \to I^j_{mi}-1$	$\mu_{mi}I^j_{mi}$
Movement of S_{ci} to k	$(S_{ci}, S_{ck}) \to (S_{ci}-1, S_{ck}+1)$	$c_{ki}S_{ci}$
Movement of E^j_{ci} to k	$(E^j_{ci}, E^j_{ck}) \to (E^j_{ci}-1, E^j_{ck}+1)$	$c_{ki}E^j_{ci}$
Movement of I^j_{ci} to k	$(I^j_{ci}, I^j_{ck}) \to (I^j_{ci}-1, I^j_{ck}+1)$	$c_{ki}I^j_{ci}$
Movement of R^j_{ci} to k	$(R^j_{ci}, R^j_{ck}) \to (R^j_{ci}-1, R^j_{ck}+1)$	$c_{ki}R^j_{ci}$
Movement of S_{mi} to k	$(S_{mi}, S_{mk}) \to (S_{mi}-1, S_{mk}+1)$	$m_{ki}S_{mi}$
Movement of E^j_{mi} to k	$(E^j_{mi}, E^j_{mk}) \to (E^j_{mi}-1, E^j_{mk}+1)$	$m_{ki}E^j_{mi}$
Movement of I^j_{mi} to k	$(I^j_{mi}, I^j_{mk}) \to (I^j_{mi}-1, I^j_{mk}+1)$	$m_{ki}I^j_{mi}$

The expression $\lambda\Delta t + o(\Delta t)$ is the infinitesimal transition probability for the change $\Delta\vec{Y}(t) = \vec{Y}(t+\Delta t) - \vec{Y}(t)$.

Define $\{Z^j_{vu}\}_{v=1}^{4n}$ as the offspring random variables for type u, $u = 1,2,3,4$ in n patches, where Z^j_{vu} denotes the number of offspring of type v produced by cows or midges of type u [60, 61, 66]. Further, let the probability that an infected cow or midge of type u gives birth to w^j_v cows or midges of type v be

$$P^j_{ui}(w^j_1,...,w^j_{4n}) = \text{prob}(Z^j_{1u} = w^j_1,...,Z^j_{4nu} = w^j_{4n}).$$

Then, the offspring pgf for cows or midges of type u given that $I^j_u(0) = 1$ and $I^j_v(0) = 0$, $u \neq v$, $g^j_{ui} : [0,1]^{4n} \to [0,1]$ is

$$g^j_{ui}(x^j_{11},x^j_{21},x^j_{31},x^j_{41},...,x^j_{1n},x^j_{2n},x^j_{3n},x^j_{4n}) = \sum_{w^j_{4n}=0}^{\infty} .... \sum_{w^j_1=0}^{\infty} P^j_{ui}(w^j_1,w^j_2, \\ ...,w^j_{4n})(x^j_{11})^{w^j_1}(x^j_{21})^{w^j_2}...(x^j_{4n})^{w^j_{4n}}, \tag{4.12}$$

for $x^j_{uk} \in \mathbb{R}$, $i \in \{1,2,...,n\}$, $k = 1,2,...,n$ and $j \in \{1,2,...,r\}$.

When the cattle and midge populations initially are near the disease-free equilibrium point, $S_{ci}(0) \approx N_{ci}(0) = S^0_{ci}$ and $S_{mi}(0) \approx N_{mi}(0) = S^0_{mi}$, then the specific offspring pgfs for E^j_{ci}, I^j_{ci}, E^j_{mi} and I^j_{mi} can be defined using (4.12) and the rates in Table 4.1 [61].

The offspring pgf for an exposed cow such that $E^j_{ci}(0) = 1$, $I^j_{ci}(0) = 0$, $E^j_{mi}(0) = 0$ and $I^j_{mi}(0) = 0$ is given by

$$g^j_{1i}(x^j_{11},x^j_{21},x^j_{31},x^j_{41},...,x^j_{1n},x^j_{2n},x^j_{3n},x^j_{4n}) = \frac{\sigma^j_{ci}x^j_{2i} + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki}x^j_{1k}}{\sigma^j_{ci} + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki}}. \tag{4.13}$$

The term $\sigma^j_{ci}/(\sigma^j_{ci} + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki})$ denotes the probability that an exposed cow of serotype j in patch i becomes infectious resulting in one infectious cow of serotype j in patch i, x^j_{2i}. The term $\mu_{ci}/(\sigma^j_{ci} + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki})$ represents the probability that an exposed cow in patch i is lost due to natural mortality which results in zero infectious individuals, x^0_{2i}. The term $c_{ki}/(\sigma^j_{ci} + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki})$ is the probability that an exposed cow of serotype j moves from patch i to k which results in one exposed cow of serotype j in patch k and zero exposed cow in patch i, $x^j_{1k}x^0_{1i}$.

The offspring pgf for an infectious cow such that $E^j_{ci}(0) = 0$, $I^j_{ci}(0) = 1$, $E^j_{mi}(0) = 0$ and $I^j_{mi}(0) = 0$ is given by

$$g^j_{2i}(x^j_{11},x^j_{21},x^j_{31},x^j_{41},...,x^j_{1n},x^j_{2n},x^j_{3n},x^j_{4n}) = \frac{\beta^j_i x^j_{2i}x^j_{3i} + \gamma^j_i + \nu^j_i + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki}x^j_{2k}}{\beta^j_i + \gamma^j_i + \nu^j_i + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki}}, \tag{4.14}$$

where $\beta_i^j = \frac{a_i q_j S_{mi}^0}{S_{ci}^0}$.

The term $\beta_i^j/(\beta_i^j + \gamma_i^j + \nu_i^j + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki})$ indicates the probability that an infectious cow of serotype j in patch i infects a susceptible midge resulting in one infectious cow and one exposed midge, $x_{2i}^j x_{3i}^j$. The term $(\gamma_i^j + \nu_i^j + \mu_{ci})/(\beta_i^j + \gamma_i^j + \nu_i^j + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki})$ represents the probability that an initially infectious cow is lost through death (natural or disease related mortality) or recovers before transmitting the disease resulting in zero infectious cow and zero exposed midge, $x_{2i}^0 x_{3i}^0$. The term $c_{ki}/(\beta_i^j + \gamma_i^j + \nu_i^j + \mu_{ci} + \sum_{k=1,k\neq i}^n c_{ki})$ is the probability that an infectious cow of serotype j moves from patch i to k which results in one infectious cow of serotype j in patch k and zero infectious cows in patch i, $x_{2k}^j x_{2i}^0$.

The offspring pgf for an exposed midge such that $E_{ci}^j(0) = 0$, $I_{ci}^j(0) = 0$, $E_{mi}^j(0) = 1$ and $I_{mi}^j(0) = 0$ is given by

$$g_{3i}^j(x_{11}^j, x_{21}^j, x_{31}^j, x_{41}^j, ..., x_{1n}^j, x_{2n}^j, x_{3n}^j, x_{4n}^j) = \frac{\sigma_{mi}^j x_{4i}^j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki} x_{3k}^j}{\sigma_{mi}^j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki}}, \tag{4.15}$$

where $i = 1, 2, ..., n$, $k = 1, 2, ..., n$ and $i \neq k$. The term $\sigma_{mi}^j/(\sigma_{mi}^j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki})$ represents the probability that an exposed midge of serotype j in patch i survives natural mortality and becomes infectious resulting in one infectious midge, x_{4i}^j. The term $\mu_{mi}/(\sigma_{mi}^j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki})$ represents the probability that an exposed midge in patch i dies naturally before becoming infectious which results in zero infectious midge, x_{4i}^0. The term $m_{ki}/(\sigma_{mi}^j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki})$ represents the probability that an exposed midge of serotype j with the help of wind successfully moves from patch i to k which results in one exposed midge of serotype j in patch k and zero exposed midge in patch i, $x_{3k}^j x_{3i}^0$.

The offspring pgf for an infectious midge such that $E_{ci}^j(0) = 0$, $I_{ci}^j(0) = 0$, $E_{mi}^j(0) = 0$ and $I_{mi}^j(0) = 1$ is given by

$$g_{4i}^j(x_{11}^j, x_{21}^j, x_{31}^j, x_{41}^j, ..., x_{1n}^j, x_{2n}^j, x_{3n}^j, x_{4n}^j) = \frac{a_i p_j x_{1i}^j x_{4i}^j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki} x_{4k}^j}{a_i p_j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki}}. \tag{4.16}$$

The term $a_i p_j/(a_i p_j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki})$ denotes the probability that an infectious midge infects a susceptible cow resulting in one exposed cow and one infectious midge, $x_{1i}^j x_{4i}^j$. The term $\mu_{mi}/(a_i p_j + \mu_{mi} + \sum_{k=1,k\neq i}^n m_{ki})$ represents the probability that an infectious midge dies

before infecting a susceptible cow which results in zero exposed cow and zero infectious midge $x_{1i}^0 x_{4i}^0$. The term $m_{ki}/(a_i p_j + \mu_{mi} + \sum_{k=1,k\neq i}^{n} m_{ki})$ represents the probability that an infectious midge of serotype j with the help of wind successfully moves from patch i to k which results in one infectious midge of serotype j in patch k and zero infectious midge in patch i, $x_{4k}^j x_{4i}^0$.

From (4.12), the $n \times n$ nonnegative matrix $\mathbb{M}^j = [e_{ik}^j]$ is referred to as the expectation matrix of the offspring pgfs and each entry e_{ik}^j gives the expected number of offspring of type v and serotype j in patch k produced by a cow or a midge of type u with serotype j in patch i [60, 66]. The entry e_{ik}^j is obtained from (4.17) below.

$$e_{ik}^j = \left.\frac{\partial g_{ui}^j}{\partial x_{uk}^j}\right|_{\vec{x}=\vec{1}}. \tag{4.17}$$

From the equations (4.13), (4.14), (4.15), (4.16) and (4.17),

$$\mathbb{M}^j = \begin{bmatrix} M_1 & 0 & 0 & M_2 \\ M_3 & M_4 & 0 & 0 \\ 0 & M_5 & M_6 & 0 \\ 0 & 0 & M_7 & M_8 \end{bmatrix}, \tag{4.18}$$

where $M_1 = \left[\frac{c_{ik}}{A_i^j}\right]$, $M_2 = \text{diag}\left[\frac{a_i p_j}{D_i^j}\right]$, $M_3 = \text{diag}\left[\frac{\sigma_{ci}^j}{A_i^j}\right]$, $M_4 = \text{diag}\left[\frac{\beta_i^j}{B_i^j}\right] + \left[\frac{c_{ik}}{B_i^j}\right]$, $M_5 = \text{diag}\left[\frac{\beta_i^j}{B_i^j}\right]$, $M_6 = \left[\frac{m_{ik}}{C_i^j}\right]$, $M_7 = \text{diag}\left[\frac{\sigma_{mi}^j}{C_i^j}\right]$, $M_8 = \text{diag}\left[\frac{a_i p_j}{D_i^j}\right] + \left[\frac{m_{ik}}{D_i^j}\right]$, $A_i^j = \sigma_{c1}^j + \mu_{c1} + \sum_{k=1,k\neq i}^{n} c_{ki}$, $B_i^j = \beta_1^j + \gamma_1^j + \nu_1^j + \mu_{c1} + \sum_{k=1,k\neq i}^{n} c_{ki}$, $C_i^j = \sigma_{mi}^j + \mu_{mi} + \sum_{k=1,k\neq i}^{n} m_{ki}$ and $D_i^j = a_i p_j + \mu_{mi} + \sum_{k=1,k\neq i}^{n} m_{ki}$ for $j \in \{1,2,...,r\}$ and $i \in \{1,2,...,n\}$.

The spectral radius of (4.18), $\rho(\mathbb{M}^j)$ for the CTMC model has similar roles in disease transmission as the deterministic threshold $\mathscr{R}_0^j$ given in (5.6) [60, 61, 66]. Their relationship is given by:

$$\mathscr{R}_0^j < 1, = 1, > 1 \text{ iff } \rho(\mathbb{M}^j) < 1, = 1, > 1.$$

The magnitude of $\rho(\mathbb{M}^j)$ determines the probability of a major outbreak or extinction of the disease [61, 66]. If $\rho(\mathbb{M}^j) \leq 1$ (critical and subcritical case), the probability of extinction is one [60, 61, 66]. Thus,

$$\lim_{t\to\infty} Prob\{\vec{I}^j(t)=\vec{0}\}=1,$$

where $\vec{I}^j(t)=(E^j_{ci}(t),I^j_{ci}(t),E^j_{mi}(t),I^j_{mi}(t))^T$ and T represents the transpose. On the other hand, if $\rho(\mathbb{M}^j)>1$ (supercritical case), there exists a fixed point $(x^j_{11},\ x^j_{21},...,x^j_{3n},\ x^j_{4n})\in(0,1)^{4n}$ of the offspring pgfs (4.13) – (4.16), $g^j_{ui}\ (x^j_{11},\ x^j_{21},...,x^j_{3n},\ x^j_{4n})=x^j_{ui}$ for $j\in\{1,2,...,r\}$, $u=1,2,3,4$, $i\in\{1,2,...,n\}$ such that the multipatch probability of extinction of any serotype j is given by

$$\mathbb{P}^j=\lim_{t\to\infty} Prob\{\vec{I}^j(t)=\vec{0}\}=(x^j_{11})^{e^j_{c1}}(x^j_{21})^{h^j_{c1}}...(x^j_{3n})^{e^j_{mn}}(x^j_{4n})^{h^j_{mn}}<1,$$

where $e^j_{ci}=E^j_{ci}(0)$, $h^j_{ci}=I^j_{ci}(0)$, $e^j_{mi}=E^j_{mi}(0)$ and $h^j_{mi}=I^j_{mi}(0)$.

For any patch i the probability of extinction for a serotype j is

$$\mathbb{P}^j_i=\lim_{t\to\infty} Prob\{\vec{I}^j_i(t)=\vec{0}\}=(x^j_{1i})^{e^j_{ci}}(x^j_{2i})^{h^j_{ci}}(x^j_{3i})^{e^j_{mi}}(x^j_{4i})^{h^j_{mi}}<1.$$

The fixed points $(x^j_{1i},x^j_{2i},x^j_{3i},x^j_{4i})$ for $j\in\{1,2,...,n\}$ and $i=1,2,...,n$ are obtained by solving,

$$\begin{aligned}
x^j_{1i}&=\frac{\sigma^j_{ci}x^j_{2i}+\mu_{ci}+\sum_{k=1,k\neq i}^{n}c_{ki}x^j_{1k}}{\sigma^j_{ci}+\mu_{ci}+\sum_{k=1,k\neq i}^{n}c_{ki}},\\
x^j_{2i}&=\frac{\beta^j_i x^j_{2i}x^j_{3i}+\gamma^j_i+\nu^j_i+\mu_{ci}+\sum_{k=1,k\neq i}^{n}c_{ki}x^j_{2k}}{\beta^j_i+\gamma^j_i+\nu^j_i+\mu_{ci}+\sum_{k=1,k\neq i}^{n}c_{ki}},\\
x^j_{3i}&=\frac{\sigma^j_{mi}x^j_{4i}+\mu_{mi}+\sum_{k=1,k\neq i}^{n}m_{ki}x^j_{3k}}{\sigma^j_{mi}+\mu_{mi}+\sum_{k=1,k\neq i}^{n}m_{ki}},\\
x^j_{4i}&=\frac{a_i p_j x^j_{1i}x^j_{4i}+\mu_{mi}+\sum_{k=1,k\neq i}^{n}m_{ki}x^j_{4k}}{a_i p_j+\mu_{mi}+\sum_{k=1,k\neq i}^{n}m_{ki}}.
\end{aligned}\tag{4.19}$$

To determine the probability of a major outbreak of multiple serotypes, consider two serotypes, a and b and two patches, 1 and 2. Let $\mathbb{P}_1$ and $\mathbb{P}_2$ be the outbreak probabilities for the two serotypes in patch 1 and patch 2, respectively, then

$$\mathbb{P}_i=\lim_{t\to\infty} Prob\{\vec{I}^a_i(t)>\vec{0}\ \text{ and }\ \vec{I}^b_i(t)>\vec{0}\},\quad i=1,2.$$

$\mathbb{P}_i$ is calculated from the extinction probabilities for serotypes a and b, or both in patch i.

$$\mathbb{P}_i^a = \lim_{t\to\infty} Prob\{\vec{I}_i^a(t) = \vec{0}\},\ \ \mathbb{P}_i^b = \lim_{t\to\infty} Prob\{\vec{I}_i^b(t) = \vec{0}\},$$

and

$$\mathbb{P}_i^{ab} = \lim_{t\to\infty} Prob\{\vec{I}_i^a = \vec{0} \text{ and } \vec{I}_i^b = \vec{0}\}, \quad i = 1,2.$$

Using the coexistence expression given in [3, 59],

$$\mathbb{P}_i = 1 - [\mathbb{P}_i^a + \mathbb{P}_i^b - \mathbb{P}_i^{ab}], \quad i = 1,2. \tag{4.20}$$

The probability of a major outbreak of two BTV serotypes can be determined from (4.20). In the next section the effects of cattle and midge movements on the probability of a major outbreak of two BTV serotypes in two patches are explored numerically.

4.3 Numerical Explorations of the Dynamics of Two BTV Serotypes in Two Patches

For simplicity, two patches, patch 1 and patch 2 and two serotypes, a and b are considered. Serotype a is assumed to be more (less) dominant than b in patch 1 (patch 2) ($\mathscr{R}_{01}^a > \mathscr{R}_{01}^b > 1$ and $\mathscr{R}_{02}^a < \mathscr{R}_{02}^b < 1$). The reason for this assumption is that if one serotype dominates in both patches, then coexistence cannot take place [4]. By this assumption patch 1 is at a higher risk of infection than patch 2. Thus, we refer to patch 1 as a high-risk patch and patch 2 as a low-risk patch. Table 4.2 lists the model parameter values for serotypes a and b in patch 1 and patch 2. In this table, parameters a_i, μ_{mi}, μ_{ci}, π_i and Λ_i are only patch dependent, whereas q_j and p_j are only serotype dependent. The rest apart from movement parameters are both serotype and patch dependent. For lack of data, σ_{mi}^j, σ_{ci}^j, and ν_i^j are assumed to be only patch dependent. The recovery rate γ_i^j is taken to be serotype and patch dependent. Temperatures $T = 14°C$ and $T = 23.6°C$ are used to estimate the values of a_i, σ_{mi} and μ_{mi} (see the caption of Table 4.2) in low and high-risk patches, respectively. According to Gubbins *et al.* [49], for cattle $\mathscr{R}_0 < 1$ for $T \in [10,15]$ and $\mathscr{R}_0 > 1$ (peaks) for $T \in [20,25]$. The unit of time for the parameter values is one day. The assumed and estimated values are for illustration purposes only. For the values in Table 4.2, the patch serotype-specific reproduction numbers are $\mathscr{R}_{01}^a = 2.25$, $\mathscr{R}_{01}^b = 1.59$, $\mathscr{R}_{02}^a = 0.41$ and $\mathscr{R}_{02}^b = 0.70$.

Table 4.2: Parameter values of the model (4.1) for $i = 1, 2$. The values in parentheses are for patch 2.

Parameter for patch dependent	Baseline value	Reference
Λ_i	1.6	Estimated
μ_{ci}	0.0002	[7]
a_i	$0.28(0.1)$	[49]
σ_{ci}	$0.5(0.06)$	[91]
ν_i	0.0001	[101]
π_i	$27494(59178)$	Estimated
μ_{mi}	$0.39(0.08)$	[49]
σ_{mi}	$0.09(0.02)$	[49]
ω_i	0.01	Estimated
serotype dependent		
p_a	0.8	[53]
p_b	0.8	[53]
q_a	0.2	[26]
q_b	0.1	Assumed
γ_i^a	$0.01(0.1)$	Assumed
γ_i^b	$0.01(0.03)$	Assumed

The values of a_i, σ_{mi} and μ_{mi} are estimated at $T = 14^\circ C$ (in patch 2) and $T = 23.6^\circ C$ (in patch 1) using $a_i = 0.0002T(T-3.7)(41.9-T)^{\frac{1}{2.7}}$, $\sigma_{mi} = 0.0003T(T-10.4)$ and $\mu_{mi} = 0.009e^{0.16T}$ [49]. The values of Λ_i and π_i are estimated such that $\frac{\Lambda_i}{\mu_{ci}} \approx 8000$ and $\frac{\pi_i}{\mu_{mi}} \approx 70000$. We consider $\gamma_1^a = \gamma_1^b = \frac{1}{100}$ (Duration of viraemia in cattle is up to 100 days [105]). The rates γ_2^a and γ_2^b are assumed from the range $0.0167 - 0.1$ [53] and q_b from $0.01 - 0.2$ [26].

4.3.1 Effects of Infected Cattle or Midge Movement on the Outbreak of Multiple Serotypes

Directed movement of infected cattle or midges between a low-risk and a high-risk patch are considered. Susceptible sub-populations are assumed not to have an effect on the spread of the disease and as such their movement rates are set to a constant value. Four cases, outlined below, are studied to establish the effects of infected cattle or midge movement on

the probability of a major outbreak of two BTV serotypes in two patches.

(i) No cattle and midge movement ($c_{12} = c_{21} = 0$ and $m_{12} = m_{21} = 0$).

(ii) Cattle or midge movement at equal rates ($c_{12} = c_{21}$ or $m_{12} = m_{21}$).

(iii) Cattle or midge movement greater towards a high than a low-risk patch ($c_{12} > c_{21}$ or $m_{12} > m_{21}$).

(iv) Cattle or midge movement greater towards a low than a high-risk patch ($c_{21} > c_{12}$ or $m_{21} > m_{12}$).

Let the initial conditions be given as $S_{ci}(0) = 8000$, $S_{mi}(0) = 70000$, $R^b_{ci}(0) = R^a_{ci}(0) = 0$, $E^b_{ci}(0) = E^a_{ci}(0) = e_c$, $I^b_{ci}(0) = I^a_{ci}(0) = h_c$, $E^b_{mi}(0) = E^a_{mi}(0) = e_m$ and $I^b_{mi}(0) = I^a_{mi}(0) = h_m$, $i = 1,2$. Utilising (4.19) and the parameter values in Table 4.2, the fixed points for serotypes a and b in the high and low-risk patches are obtained based on the above cases. For case (i), the fixed points (0.2784,0.2781,0.7117,0.7117) and (0.5059,0.5057,0.7828,0.7828) for serotypes a and b, respectively, in the high-risk patch are used to obtain $\mathbb{P}^a_1$, $\mathbb{P}^b_1$ and $\mathbb{P}^{ab}_1$ as follows:

$$\begin{aligned}
\mathbb{P}^a_1 =& 0.2784^{e_c} \times 0.2781^{h_c} \times 0.7117^{e_m} \times 0.7117^{h_m} \quad \text{(Extinction of } a\text{)},\\
\mathbb{P}^b_1 =& 0.5059^{e_c} \times 0.5057^{h_c} \times 0.7828^{e_m} \times 0.7828^{h_m} \quad \text{(Extinction of } b\text{)},\\
\mathbb{P}^{ab}_1 =& \mathbb{P}^a_1 \times \mathbb{P}^b_1 \quad \text{(Extinction of } a \text{ and } b\text{)}.
\end{aligned}$$

Then, the probability of a major outbreak of two serotypes in the high-risk patch is given by

$$\mathbb{P}_1 = \quad 1 - [\mathbb{P}^a_1 + \mathbb{P}^b_1 - \mathbb{P}^{ab}_1].$$

Similarly, from (4.19), the fixed point (1,1,1,1) for both a and b in the low-risk patch is used to determine $\mathbb{P}_2$. The branching process probabilities $\mathbb{P}_1$ and $\mathbb{P}_2$ for the above cases and different initial conditions are summarised in Tables 4.3 and 4.4. To verify the branching process results, the probabilities of a major outbreak for the nonlinear CTMC model are obtained numerically. Let P^a_i, P^b_i and P^{ab}_i be numerical approximation probabilities based on 10,000 sample paths of the nonlinear CTMC model for which the sums $(E^a_{ci} + I^a_{ci} + E^a_{mi} + I^a_{mi})$, $(E^b_{ci} + I^b_{ci} + E^b_{mi} + I^b_{mi})$ and $(E^a_{ci} + I^a_{ci} + E^a_{mi} + I^a_{mi} + E^b_{ci} + I^b_{ci} + E^b_{mi} + I^b_{mi})$, respectively, hit zero prior to time $t = 2000$ days, then the numerical probabilities of a major outbreak (P_i) are obtained from (4.20) and given by

$$P_i = \quad 1 - [P^a_i + P^b_i - P^{ab}_i], \quad i = 1,2.$$

Table 4.3: Effects of infected midge movement on the probability of a major outbreak ($\mathbb{P}_i$ or P_i, $i = 1,2$) of two BTV serotypes in two patches. The probabilities $\mathbb{P}_i$ are calculated from the branching process using (4.20) and P_i are numerical approximations based on 10,000 sample paths of the CTMC model. For all cases, $P_2 \leq 0.0001$. The parameter values used are given in Table 4.2 with initial conditions $S_{ci}(0) = 8000$, $S_{mi}(0) = 70000$, $R^b_{ci}(0) = R^a_{ci}(0) = 0$, $E^b_{ci}(0) = E^a_{ci}(0) = e_c$, $I^b_{ci}(0) = I^a_{ci}(0) = h_c$, $E^b_{mi}(0) = E^a_{mi}(0) = e_m$ and $I^b_{mi}(0) = I^a_{mi}(0) = h_m$, $i = 1,2$.

				(i)			(ii)		
Initial conditions				$m_{12} = m_{21} = 0$, $c_{12} = c_{21} = 0$			$m_{12} = 0.002$ $m_{21} = 0.002$		
e_c	h_c	e_m	h_m	$\mathbb{P}_1$	P_1	$\mathbb{P}_2$	$\mathbb{P}_1$	P_1	$\mathbb{P}_2$
1	0	0	0	0.3566	0.3563	0	0.3534	0.3532	0
0	1	0	0	0.3568	0.3569	0	0.3537	0.3535	0
0	0	1	0	0.0023	0.0023	0	0.0023	0.0022	0
0	0	0	1	0.0626	0.0628	0	0.0617	0.0613	0.0001
1	1	1	1	0.7660	0.7665	0	0.7626	0.7629	0.0006
2	0	0	0	0.7002	0.7000	0	0.6827	0.6823	0.0001
0	2	0	0	0.7005	0.7003	0	0.6830	0.6834	0.0001
0	0	2	0	0.0105	0.0109	0	0.0086	0.0079	0
0	0	0	2	0.2221	0.2227	0	0.1888	0.1882	0.0005
				(iii)			(iv)		
Initial conditions				$m_{12} = 0.003$ $m_{21} = 0.001$			$m_{12} = 0.001$ $m_{21} = 0.003$		
e_c	h_c	e_m	h_m	$\mathbb{P}_1$	P_1	$\mathbb{P}_2$	$\mathbb{P}_1$	P_1	$\mathbb{P}_2$
1	0	0	0	0.3550	0.3548	0.0001	0.3516	0.3512	0
0	1	0	0	0.3553	0.3556	0.0001	0.3519	0.3517	0
0	0	1	0	0.0023	0.0023	0	0.0022	0.0019	0
0	0	0	1	0.0622	0.0627	0.0003	0.0613	0.0618	0
1	1	1	1	0.7643	0.7640	0.0013	0.7606	0.7604	0.0002
2	0	0	0	0.6846	0.6842	0.0002	0.6807	0.6811	0
0	2	0	0	0.6849	0.6847	0.0002	0.6810	0.6813	0
0	0	2	0	0.0087	0.0081	0.0001	0.0085	0.0080	0
0	0	0	2	0.1900	0.1905	0.0011	0.1876	0.1875	0.0001

Table 4.4: Effects of infected cattle movement on the probability of a major outbreak ($\mathbb{P}_i$ or P_i, $i = 1,2$) of two BTV serotypes in two patches. The probabilities $\mathbb{P}_i$ are calculated from the branching process using (4.20) and P_i are numerical approximations based on 10,000 sample paths of the CTMC model. The parameter values used are given in Table 4.2. The initial conditions are the same as in Table 4.3.

				(ii)				(iii)	
Initial conditions				$c_{12} = 0.002$ $c_{21} = 0.002$				$c_{12} = 0.003$ $c_{21} = 0.001$	
e_c	h_c	e_m	h_m	$\mathbb{P}_1$	P_1	$\mathbb{P}_2$	P_2	$\mathbb{P}_1$	P_1
1	0	0	0	0.2851	0.2856	0.0026	0.0021	0.3210	0.3216
0	1	0	0	0.2874	0.2870	0.0009	0.0004	0.3224	0.3227
0	0	1	0	0.0019	0.0021	0	0.0001	0.0021	0.0023
0	0	0	1	0.0527	0.0523	0.0020	0.0026	0.0578	0.0574
1	1	1	1	0.6885	0.6881	0.0163	0.0171	0.7300	0.7305
2	0	0	0	0.5967	0.5962	0.0097	0.0085	0.6440	0.6447
0	2	0	0	0.5996	0.5998	0.0035	0.0032	0.6455	0.6451
0	0	2	0	0.0074	0.0069	0.0002	0.0005	0.0081	0.0088
0	0	0	2	0.1645	0.1643	0.0078	0.0069	0.1782	0.1776

				(iv)					
Initial conditions						$c_{12} = 0.001$ $c_{21} = 0.003$			
e_c	h_c	e_m	h_m	$\mathbb{P}_2$	P_2	$\mathbb{P}_1$	P_1	$\mathbb{P}_2$	P_2
1	0	0	0	0.0057	0.0056	0.2484	0.2480	0.0006	0.0009
0	1	0	0	0.0020	0.0024	0.2514	0.2519	0.0002	0.0005
0	0	1	0	0.0001	0.0002	0.0017	0.0013	0	0.0001
0	0	0	1	0.0043	0.0041	0.0473	0.0478	0.0005	0.0007
1	1	1	1	0.0339	0.0335	0.6397	0.6391	0.0044	0.0050
2	0	0	0	0.0210	0.0211	0.5433	0.5430	0.0025	0.0019
0	2	0	0	0.0075	0.0070	0.5474	0.5475	0.0009	0.0004
0	0	2	0	0.0004	0.0002	0.0067	0.0062	0	0.0001
0	0	0	2	0.0162	0.0163	0.1493	0.1480	0.0021	0.0018

The values of P_i based on the above cases and different initial conditions are given in Tables 4.3 and 4.4. From Table 4.3, a case with no cattle and/or midge movement (case *i*), results

in a major outbreak of two serotypes in the high-risk patch and no outbreak in the low-risk patch ($\mathbb{P}_1 > 0$ and $\mathbb{P}_2 = 0$). There is a larger probability of a major outbreak if the serotypes are introduced by a cow than by a midge. Also, infectious cattle and midges result in larger probabilities of outbreak than their exposed counterparts.

For cases $(ii) - (iv)$ in Tables 4.3 and 4.4, infected cattle or midge movements result in outbreaks in both patches. The probability of an outbreak decreases in the high-risk patch, but increases in the low-risk patch. The probability of a major outbreak is least in both patches if movement is greater towards the low-risk patch ($c_{21} > c_{12}$ or $m_{21} > m_{12}$). In all cases the probability of an outbreak depends on the initial conditions at the beginning of the outbreak. The value $\mathbb{P}_i$ for the linear model calculated from the branching process near the disease-free equilibrium is a good approximation of the probability of a major outbreak of two BTV serotypes for the nonlinear CTMC model.

The results for the outbreak of two serotypes of the CTMC model in Tables 4.3 and 4.4 have two outcomes, either competitive exclusion or coexistence [2]. These outcomes can be predicted by the deterministic model [2]. Using the numerical results of the ODE model (4.1) and the CTMC model, the outcomes of a major outbreak (competitive exclusion or coexistence) for the different cases studied in Tables 4.3 and 4.4 are depicted in Figures 4.1-4.3 and B.1-B.3 in the appendix and Tables 4.5-4.7.

When the patches are not connected (case (i), Table 4.3), the ODE model (4.1) predicts competitive exclusion in both patches with the persistence of serotype a in the low-risk patch and serotype b in the high-risk patch (Figure 4.1 and Table 4.5). For the CTMC, one sample path depicted in Figure 4.1, the mean and median calculated from 10,000 sample paths of the infected population sizes at t=2000 days (Table 4.5) show coexistence in the high-risk patch and competitive exclusion with the persistence of serotype b in the low-risk patch. The mean and median population sizes for the CTMC model are closer to the values of the population sizes for the ODE model in the low-risk patch (when $\mathscr{R}_{02}^a$ and $\mathscr{R}_{02}^b < 1$).

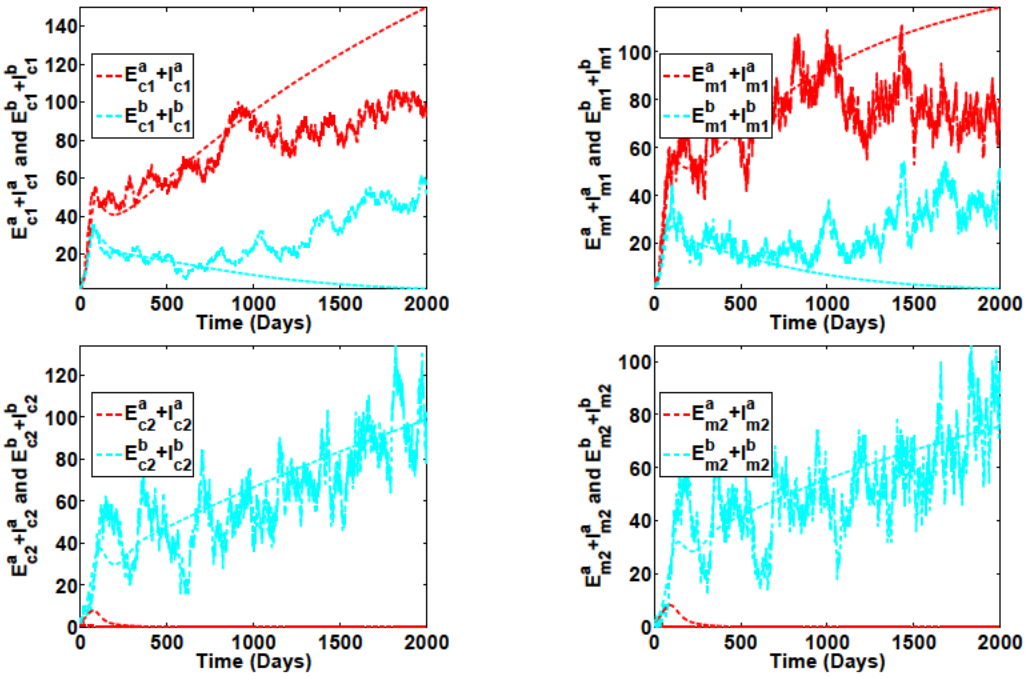


Figure 4.1: One sample path of the CTMC model and the ODE solution (smooth curve) for serotypes a and b in two patches without cattle and/or midge movements indicating competitive exclusion in both patches for the ODE model, coexistence in patch 1 and competitive exclusion in patch 2 for the CTMC model. The parameter values used are given in Table 4.2 with initial conditions $S_{ci}(0) = 8000$, $S_{mi}(0) = 70000$, $R^b_{ci}(0) = R^a_{ci}(0) = 0$, $E^b_{ci}(0) = E^a_{ci}(0) = 1$, $I^b_{ci}(0) = I^a_{ci}(0) = 1$, $E^b_{mi}(0) = E^a_{mi}(0) = 1$ and $I^b_{mi}(0) = I^a_{mi}(0) = 1$, $i = 1, 2$.

When the patches are connected by infected midge movement as in cases (ii)-(iv) in Table 4.3, both models predict coexistence in both patches by t=2000 days (Figure 4.2 and Table 4.6). In Figure B.2, the probability distributions of the infected population sizes for the CTMC model are skewed to the right for serotype a in both patches and to the left for serotype b in the high-risk patch. In the low-risk patch, serotype b approximates a normal distribution.

When the patches are considered to be connected by infected cattle movement as in cases (ii)-(iv) in Table 4.4, the ODE model predicts coexistence in both patches, but the CTMC model predicts competitive exclusion in both patches with the extinction of serotype a (Figure 4.3 and Table 4.7). In both patches the probability distributions of the infected population sizes are skewed to the right for serotype a and approximately normal for serotype b (Figure B.3).

Table 4.5: Population sizes in Figure 4.1 at t=2000 days. For the CTMC model, computations of the mean, the median and the histograms (Figure B.1) are based on 10,000 sample paths. The values are for serotype a and, in the parentheses, for serotype b.

	Patch 1		Patch 2	
	Cattle	Midge	Cattle	Midge
Mean size	76.5(75)	60.4(59.3)	1.5(56.8)	1.2(51.4)
Median size	76(74)	60(58)	0(60)	0(54)
ODE size	150(1.7)	118.6(1.1)	0(61.4)	0(55.8)

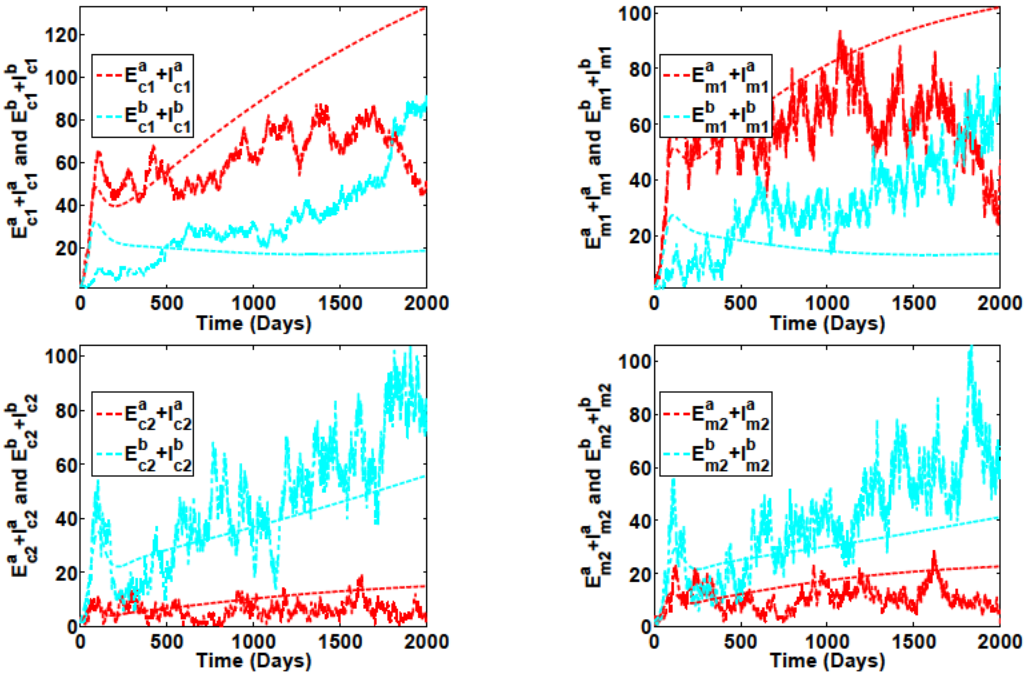


Figure 4.2: One sample path of the CTMC model and the ODE solution (smooth curve) for serotypes a and b in two patches with equal midge movement rates and no cattle movement (case (ii) in Table 4.3) indicating coexistence in both patches for both models. Similar trends are obtained if cases (iii) and (iv) in Table 4.3 are considered. Parameter values and initial conditions are the same as in Figure 4.1, except for $m_{12} = m_{21} = 0.002$.

Table 4.6: Population sizes in Figure 4.2 at t=2000 days. For the CTMC model, computations of the mean, the median and the histograms (Figure B.2) are based on 10,000 sample paths. The values are for serotype a and, in the parentheses, for serotype b.

	Patch 1		Patch 2	
	Cattle	Midge	Cattle	Midge
Mean size	43.5(107.8)	31.9(81.9)	3.5(55.6)	5.3(53.9)
Median size	38(111)	28(84)	2(56)	4(54)
ODE size	132.7(18.8)	102(13.5)	15(34.8)	22.7(30.9)

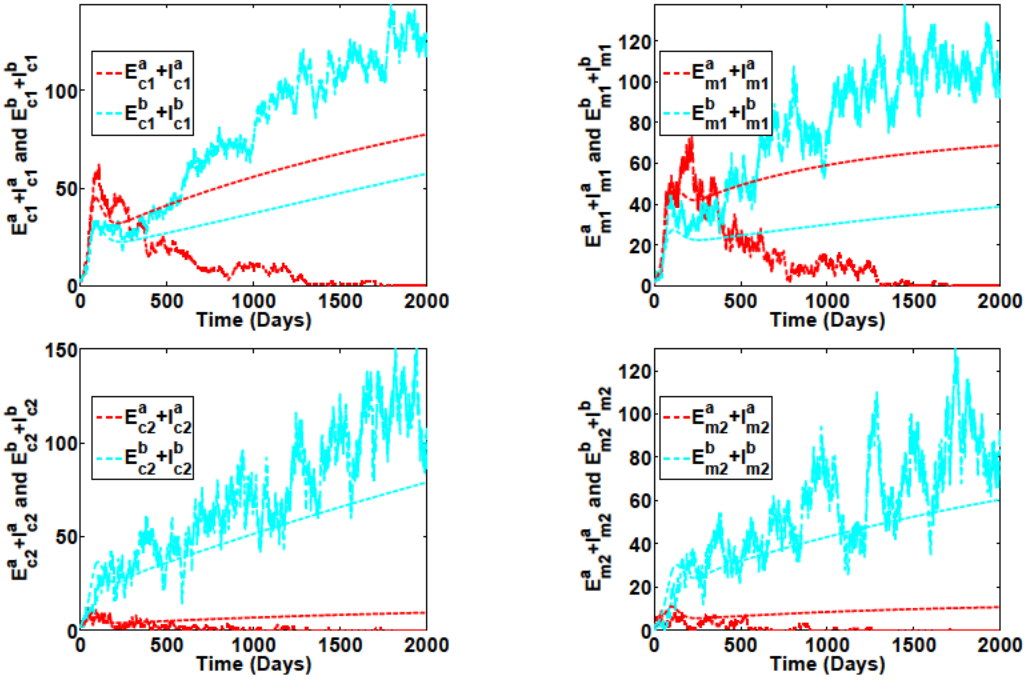


Figure 4.3: One sample path of the CTMC model and the ODE solution (smooth curve) for serotypes a and b in two patches with equal cattle movement rates and no midge movement (case (ii) in Table 4.4) indicating coexistence and competitive exclusion in both patches for the ODE model and the CTMC model, respectively. Similar trends are obtained if cases (iii) and (iv) in Table 4.4 are considered. Parameter values and initial conditions are the same as in Figure 4.1, except for $c_{12} = c_{21} = 0.002$.

Table 4.7: Population sizes in Figure 4.3 at t=2000 days. For the CTMC model, computations of the mean, the median and the histograms (Figure B.3) are based on 10,000 sample paths. The values are for serotype a and, in the parentheses, for serotype b.

	Patch 1		Patch 2	
	Cattle	Midge	Cattle	Midge
Mean	5.8(131)	5(108.9)	0.6(65.6)	0.5(59.4)
Median	0(132)	0(110)	0(66)	0(59)
ODE final size	77.5(57.4)	68.8(38.8)	9.5(48.7)	10.8(44.7)

4.3.2 Effects of Susceptible Cattle or Midge Movement on the Outbreak of Multiple Serotypes

Previous studies such as those in [60, 114] have shown that the dispersal rates of susceptible individuals do not influence the extinction or persistence of a disease in patchy environments. All these articles considered directly transmitted diseases where the basic reproduction number does not depend on the movement rates. For vector-borne diseases the basic reproduction number for any patchy and serotype, $\mathscr{R}_{0i}^{j} \propto (S_{mi}^{0}/S_{ci}^{0})^2$ (see (4.6)). When the patches are connected by cattle and/or midge movement (see (4.7)), S_{mi}^{0} and S_{ci}^{0} depend on the movement rates. Since the probability of a major outbreak depends on the reproduction number, the movement rates for susceptible cattle or midges can have an effect on the probability of a major outbreak of two BTV serotypes in patchy environments. To explore this effect, the values of $\mathbb{P}_i$ for different initial conditions are determined from (4.20) and summarised in Table 4.8.

From Table 4.8, directed movement of susceptible cattle or midge has a large effect on the probability of a major outbreak of BTV serotypes in patchy environments. For susceptible cattle movement, the probability of a major outbreak increases or decreases in the high-risk patch if movement increases towards the low-risk or high-risk patch, respectively. On the other hand for susceptible midge movement, the probability of a major outbreak increases or decreases in the high-risk patch if the movement rate increases in the direction of the high-risk or low-risk patch, respectively. For identical movement rates ($c_{12} = c_{21}$ or $m_{12} = m_{21}$), susceptible cattle or midges do not have any effect on the probability of a major outbreak of BTV serotypes. In all cases the probability of a major outbreak is zero in the low-risk patch.

Table 4.8: Effects of susceptible midge or cattle movement on the probability of a major outbreak ($\mathbb{P}_i$ or P_1, $i = 1,2$) of two BTV serotypes in two patches. The probabilities $\mathbb{P}_i$ are calculated from the branching process using (4.20) and P_i are numerical approximations based on 10,000 sample paths of the CTMC model. For all cases, $\mathbb{P}_2 = P_2 = 0$. The parameter values used are given in Table 4.2. The initial conditions are the same as in Table 4.3.

				(i)		(ii)	
Initial conditions				$c_{12} = 0.003$, $c_{21} = 0.001$		$c_{12} = 0.001$ $c_{21} = 0.003$	
e_c	h_c	e_m	h_m	$\mathbb{P}_1$	P_1	$\mathbb{P}_1$	P_1
1	0	0	0	0.1902	0.1900	0.6009	0.6003
0	1	0	0	0.1903	0.1905	0.6014	0.6012
0	0	1	0	0.0014	0.0015	0.0034	0.0031
0	0	0	1	0.0380	0.0391	0.0918	0.0915
1	1	1	1	0.5435	0.5438	0.9290	0.9258
2	0	0	0	0.4467	0.4463	0.8942	0.8944
0	2	0	0	0.4469	0.4471	0.8945	0.8949
0	0	2	0	0.0054	0.0052	0.0128	0.0127
0	0	0	2	0.1228	0.1225	0.2642	0.2640
				(iii)		(iv)	
Initial conditions				$m_{12} = 0.003$ $m_{21} = 0.001$		$m_{12} = 0.001$ $m_{21} = 0.003$	
e_c	h_c	e_m	h_m	$\mathbb{P}_1$	P_1	$\mathbb{P}_1$	P_1
1	0	0	0	0.3586	0.3584	0.3544	0.3540
0	1	0	0	0.3589	0.3592	0.3547	0.3546
0	0	1	0	0.0023	0.0026	0.0023	0.0031
0	0	0	1	0.0629	0.0623	0.0623	0.0625
1	1	1	1	0.7681	0.7685	0.7639	0.7637
2	0	0	0	0.6888	0.6880	0.6839	0.6834
0	2	0	0	0.6891	0.6899	0.6843	0.6841
0	0	2	0	0.0088	0.0076	0.0088	0.0080
0	0	0	2	0.1918	0.1912	0.1903	0.1900

4.3.3 Sensitivity Analysis

Sensitivity analysis is carried out to determine the effects of variations of the parameters of the CTMC model on the probability of a major outbreak ($\mathbb{P}_1$) of two BTV serotypes in the high-risk patch. The Latin hypercube sampling (LHS) method is used for this analysis [17, 71]. The LHS method requires defining a baseline value and the range for each model parameter and generating N multiple runs for the model outcome which in this case is chosen to be $\mathbb{P}_1$ [17, 71]. The value of N is determined such that the inequality $N > (4/3)K$ is satisfied, where K is the number of uncertain model parameters [17, 71]. The lower and upper values of the parameter ranges are determined by arbitrarily decreasing and increasing, respectively, the baseline values in Table 4.2 by 25%. It is assumed that the model parameters follow a uniform distribution. The strength of $\mathbb{P}_1$ sensitivity to parameter variations is determined by the sign and magnitude of the partial rank correlation coefficients (PRCCs) [17]. A parameter with a positive or negative PRCC value, respectively, has the ability of reducing $\mathbb{P}_1$ when decreased or increased. Parameters with PRCC values greater than 0.5 or less than -0.5 are considered the most sensitive to $\mathbb{P}_1$ [106]. Using the LHS method, the PRCCs of the CTMC model parameters are calculated from the branching process using (4.20), summarised in Table 4.9 and depicted in Figure 4.4.

From Table 4.9 and Figure 4.4, the parameters with the highest influence on $\mathbb{P}_1$ are the midge natural mortality rate (μ_{m1}) and the midge biting rate (a_1). Other parameters with an influence are the cattle natural mortality rate (μ_{c1}), cattle recruitment rate (Λ_1), midge recruitment rate (π_1), midge extrinsic incubation period ($1/\sigma_{m1}$), probability of serotype b transmission by cattle (q_b) and the cattle recovery rate from serotype b (γ_1^b). The parameters μ_{m1}, Λ_1 and γ_1^b have negative PRCC values while a_1, μ_{c1}, σ_{m1}, π_1 and q_b have positive PRCC values.

4.4 Discussion

The aim of the study in this chapter was to determine whether wind-aided midge movement has an effect on the outbreak and coexistence of multiple BTV serotypes and whether coexistence can be maintained if demographic and movement variability are considered. For that aim, deterministic and stochastic (CTMC) models for the transmission dynamics of BTV with multiple serotypes in patchy environments connected by cattle and midge movements were formulated and analysed. For numerical results, two patches (high-risk and low-risk) and two serotypes (a and b) were considered.

Table 4.9: PRCC values of the CTMC model parameters in the high-risk patch calculated from the branching process and based on $N = 1000$ runs. Parameter ranges used are obtained by varying the baseline values in Table 4.2 by $\pm 25\%$. The initial conditions used are $E^a_{c1}(0) = E^b_{c1}(0) = 1$, $I^a_{c1}(0) = I^b_{c1}(0) = 1$, $E^a_{m1}(0) = E^b_{m1}(0) = 1$ and $I^a_{m1}(0) = I^b_{m1}(0) = 1$.

Parameter	PRCC value
Λ_1	-0.7888
μ_{c1}	0.7562
a_1	0.9297
σ_{c1}	0.0838
ν_1	-0.1095
π_1	0.7796
μ_{m1}	-0.9661
σ_{m1}	0.6351
p_a	0.0462
p_b	0.3175
q_a	0.3468
q_b	0.6746
γ^a_1	-0.1464
γ^b_1	-0.7092

Multitype branching process theory was used to approximate the nonlinear CTMC model near the disease-free equilibrium point and to estimate the effects of wind-aided midge movement on the probability of a major outbreak ($\mathbb{P}_i$, $i = 1,2$) for serotypes a and b in high and low-risk patches. From Table 4.3 (case (i)), without cattle and/or midge movement between patches, the probability of a major outbreak in the high-risk patch is greater than zero ($\mathbb{P}_1 > 0$), whereas in the low-risk patch it is zero ($\mathbb{P}_2 = 0$). This is due to the fact that the probability of a major outbreak of multiple strains in any given patch largely depends on the basic reproduction number [3, 59]. In both patches, the probability of a major outbreak is more likely if the serotypes are introduced by infected cattle as opposed to infected midges. This is the case because cattle are the major reservoirs and amplification hosts for the virus and they can be viraemic for long periods of time, up to 100 days [105]. Thus, control measures targeting cattle will yield better results than those targeting midges. The probability of a major outbreak $\mathbb{P}_1$ increased with increasing initial conditions at the beginning of the outbreak. Therefore, a major outbreak of multiple BTV serotypes can easily be avoided

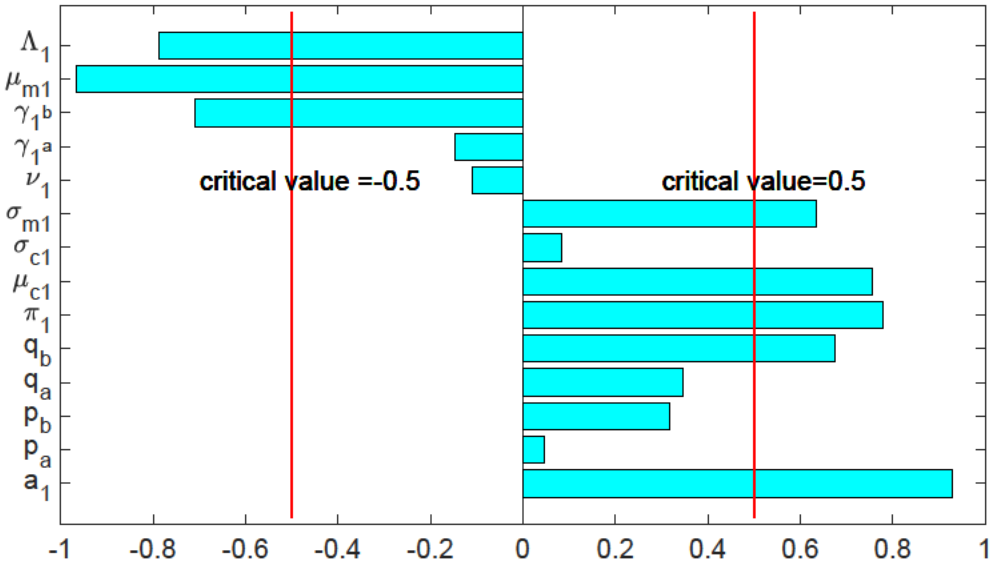


Figure 4.4: Effects of varying the baseline parameter values in Table 4.2 by $\pm 25\%$ on the probability of the major outbreak ($\mathbb{P}_1$) of two BTV serotypes for the high-risk patch calculated from the branching process. The same trends are expected in the low-risk patch. The values depicted in this figure are given in Table 4.9.

if the control measures are implemented in the early stages of the epidemic. Numerical simulations of the ODE model in Figure 4.1 show that without cattle and midge movement, competitive exclusion is the only outcome of the outbreak results for the CTMC model given in Table 4.3 (case (i)). This implies that without cattle or midge movement coexistence cannot take place in patchy environments.

When the two patches were considered to be connected by infected midge or cattle movement (Table 4.3 or 4.4), the probability of a major outbreak decreased in the high-risk patch and increased in the low-risk patch. The least probability in both patches was obtained if movement of infected cattle or midge was considered to be greater towards the low-risk patch. Thus, allowing movement of infected cattle out of the high-risk patch while restricting movement into the patch is a good control strategy for the outbreak of two (multiple) BTV serotypes in both patches. This can be achieved by isolation and careful boarder screening of the infected animals. On the other hand, midge movement cannot be restricted, but vector control measures (killing or trapping the midges) applied at the high-risk patch can lessen the risk of BTV transmission to the low-risk patch by reducing the number of midges moving from that patch, as well as minimising outbreaks at the high-risk patch itself.

Numerical simulations of the ODE model show that when infected cattle or midges move between patches, coexistence takes place in both patches (Figures 4.2 and 4.3). However, the results of the CTMC model show that this coexistence is lost rapidly in both patches if cattle movement is considered. With midge movement it is lost gradually, especially in the high-risk patch. Thus, wind-aided midge movement can enable the coexistence of multiple BTV serotypes in patchy environments which can be maintained for some time (at least 2000 days) if demographic and movement variability are considered. For infected cattle movement, our results for the ODE model are in agreement with the study by Qiu *et al*. [86] where it was shown that for n patches connected by host movement, coexistence takes place in all n patches.

From Table 4.8, susceptible cattle or midge movement has a large impact on the probability of a major outbreak of two BTV serotypes in the high-risk patch ($\mathbb{P}_1$) and a zero impact in the low-risk patch ($\mathbb{P}_2$). For susceptible cattle, $\mathbb{P}_1$ increases if movement is greater towards the low-risk patch, and reduces if movement is increased in the direction of the high-risk patch. For susceptible midges, $\mathbb{P}_1$ increases if movement is greater towards the high-risk patch, and decreases if movement is increased in the direction of the low-risk patch. This is due to the fact that for a serotype to successfully invade a patch, the ratio of vectors to hosts (S^0_{mi}/S^0_{ci}) needs to be sufficiently large so that double bites are common [85]. Therefore, restricting movement of susceptible cattle out of the high-risk patch while allowing more to come in can be a good control strategy for the persistence of two BTV serotypes in that patch.

From Figure 4.4 and Table 4.9, sensitivity analysis based on Latin hypercube sampling method identified midge mortality rate (μ_m) and biting rate (a) as the most important parameters in determining the magnitude of the probability of a major outbreak of two BTV serotypes. These parameters have been shown by other studies as critical in the transmission of BTV [49], mostly because the biting rate influences the process of transmission from midge to cattle and from cattle to midge and the mortality rate determines the probability of the midge surviving the extrinsic incubation period ($1/\sigma_m$). The negative PRCC of μ_m and the positive PRCC of a imply that the control measures that increase and decrease these parameters, respectively, can greatly reduce the probability of a major outbreak. Control measures such as the use of fungi [8] and insecticide spraying [56] can increase μ_m. The biting rate can be reduced by the use of repellents and stabling animals in shelters between dusk and

dawn [64]. Both μ_m and a increase with temperature [49] which indicates that seasonal variations in temperature, rainfall and/or humidity can affect the activity of the midge, including movement. Nipa and Allen [79] showed that seasonal variation in dispersal and transmission rates affect the probability of a disease outbreak in patchy environments. Therefore, seasonal variations in μ_m and a and other model parameters may intensify or reduce the effects of wind-aided midge movement on the probability of a major outbreak and consequently the coexistence of multiple BTV serotypes. Also, from Figure 4.4, the probability of a major outbreak is more sensitive to the parameters for the less dominant serotype. Thus, to prevent a major outbreak of two BTV serotypes, the control strategies should target all serotypes, but not only the dominant one.

Chapter 5
Optimal Control Analysis of BTV Transmission in Patchy Environments

In this chapter a multi-patch control deterministic model, based on the single-serotype multi-patch model (4.1) in Chapter 4, is formulated by incorporating four time-dependent control variables; two host-based controls (vaccination and quarantine) and two vector-based controls (insecticide spraying and the use of a repellent). Using optimal control theory the effectiveness of these parameters in reducing the spread of BTV in patchy environments is determined. The study in this chapter, co-authored with Kevin J. Duffy, Joseph Y.T. Mugisha and Obiora C. Collins has been published in the *Journal of Applied Mathematics and Computing* [74].

5.1 Model Formulation and Analysis

The single-serotype ($r = 1$) model (4.1) in Chapter 4 is extended to include $x_{1i}(t)$, $x_{2i}(t)$, $x_{3i}(t)$ and $x_{4i}(t)$ time-dependent preventive efforts to curtail the spread of BTV in patchy environments. The control function $x_{1i}(t) \in [0,1]$ is aimed at reducing the biting rate a_i of midges. This can be done for example through using repellents. The control $x_{2i}(t) \in [0,1]$ is aimed at decreasing the population of midges. This involves killing the midges through insecticide spraying. Control $x_{3i}(t) \in [0,1]$ is aimed at increasing the number of hosts in the immune class. This can be achieved by vaccinating susceptible hosts. Finally, control $x_{4i}(t) \in [0,1]$ is aimed at minimising the number of hosts moving into patch i from any other patch. This can be attained by the quarantine strategy. The notation for the variables and parameters as used in model (4.1) are maintained. The modified model is given by the following equations:

$$
\begin{aligned}
\frac{dS_{ci}}{dt} =& \Lambda_i + \omega_i R_{ci} - (1-x_{1i}) a_i p I_{mi} \frac{S_{ci}}{N_{ci}} - (\mu_{ci} + x_{3i}) S_{ci} \\
&+ (1-x_{4i}) \Bigg\{ \sum_{k=1,k\neq i}^{n} c_{ik} S_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki} S_{ci} \Bigg\}, \\
\frac{dE_{ci}}{dt} =& (1-x_{1i}) a_i p I_{mi} \frac{S_{ci}}{N_{ci}} - (\mu_{ci} + \sigma_{ci}) E_{ci} + (1-x_{4i}) \Bigg\{ \sum_{k=1,k\neq i}^{n} c_{ik} E_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki} E_{ci} \Bigg\}, \\
\frac{dI_{ci}}{dt} =& \sigma_{ci} E_{ci} - (\mu_{ci} + \nu_i + \gamma_i) I_{ci} + (1-x_{4i}) \Bigg\{ \sum_{k=1,k\neq i}^{n} c_{ik} I_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki} I_{ci} \Bigg\}, \\
\frac{dR_{ci}}{dt} =& x_{3i} S_{ci} + \gamma_i I_{ci} - (\omega_i + \mu_{ci}) R_{ci} + (1-x_{4i}) \Bigg\{ \sum_{k=1,k\neq i}^{n} c_{ik} R_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki} R_{ci} \Bigg\}, \\
\frac{dS_{mi}}{dt} =& \pi_i - (1-x_{1i}) a_i q I_{ci} \frac{S_{mi}}{N_{ci}} - (\mu_{mi} + x_{2i}) S_{mi} + \sum_{k=1,k\neq i}^{n} m_{ik} S_{mk} - \sum_{k=1,k\neq i}^{n} m_{ki} S_{mi}, \\
\frac{dE_{mi}}{dt} =& (1-x_{1i}) a_i q I_{ci} \frac{S_{mi}}{N_{ci}} - (\sigma_{mi} + \mu_{mi} + x_{2i}) E_{mi} + \sum_{k=1,k\neq i}^{n} m_{ik} E_{mk} - \sum_{k=1,k\neq i}^{n} m_{ki} E_{mi}, \\
\frac{dI_{mi}}{dt} =& \sigma_{mi} E_{mi} - (\mu_{mi} + x_{2i}) I_{mi} + \sum_{k=1,k\neq i}^{n} m_{ik} I_{mk} - \sum_{k=1,k\neq i}^{n} m_{ki} I_{mi},
\end{aligned}
\tag{5.1}
$$

with $N_{ci} = S_{ci} + E_{ci} + I_{ci} + R_{ci}$, $N_{mi} = S_{mi} + E_{mi} + I_{mi}$ and $i \in \{1, 2, \ldots, n\}$. The initial conditions are such that $S_{ci}(0) > 0$, $E_{ci}(0) \geq 0$, $I_{ci}(0) \geq 0$, $R_{ci}(0) \geq 0$, $S_{mi}(0) > 0$, $E_{mi}(0) \geq 0$ and $I_{mi}(0) \geq 0$.

5.1.1 Basic Model Properties

Positivity and boundedness analysis are carried out to show that the model (5.1) is biologically meaningful.

Theorem 5.1. *The solutions $S_{ci}(t)$, $E_{ci}(t)$, $I_{ci}(t)$, $R_{ci}(t)$, $S_{mi}(t)$, $E_{mi}(t)$ and $I_{mi}(t)$ of the model* (5.1) *with non-negative initial conditions, remain non-negative for all time $t > 0$.*

Proof. Suppose that $t_1 = \sup\big\{t > 0 : S_{ci}(t) > 0, E_{ci}(t) > 0, I_{ci}(t) > 0, R_{ci}(t) > 0, S_{mi}(t) > 0, E_{mi}(t) > 0, I_{mi}(t) > 0\big\} > 0$ for all $i \in \{1, 2, \ldots, n\}$. The first equation of the model (5.1)

$$\frac{dS_{ci}}{dt} = \Lambda_i + \omega_i R_{ci} - (1-x_{1i})a_i p I_{mi}\frac{S_{ci}}{N_{ci}} - (\mu_{ci}+x_{3i})S_{ci}$$
$$+ (1-x_{4i})\left\{\sum_{k=1,k\neq i}^{n} c_{ik}S_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki}S_{ci}\right\} \geq \Lambda_i - (1-x_{1i})a_i p I_{mi}\frac{S_{ci}}{N_{ci}}$$
$$- \left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}S_{ci},$$

from which it follows that,

$$\frac{d}{dt}\left(S_{ci}(t)exp\left[\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t + \int_0^t (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right]\right)$$
$$\geq \Lambda_i exp\left[\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t + \int_0^t (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right].$$

Hence,

$$S_{ci}(t_1)exp\left[\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t_1 + \int_0^{t_1} (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right]$$
$$- S_{ci}(0) \geq \int_0^{t_1}\left(\Lambda_i exp\left[\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t\right.\right.$$
$$\left.\left.+\int_0^y (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right]\right)dy,$$

so that

$$S_{ci}(t_1) \geq S_{ci}(0)exp\left[-\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t_1 - \int_0^{t_1} (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right]$$
$$+ exp\left[-\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t_1 - \int_0^{t_1} (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right]$$
$$\int_0^{t_1}\left(\Lambda_i exp\left[\left\{\mu_{ci}+x_{3i}+(1-x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\}t\right.\right.$$
$$\left.\left.+\int_0^y (1-x_{1i})a_i p\frac{I_{mi}}{N_{ci}}(u)du\right]\right)dy > 0.$$

Similarly, it can be shown that $E_{ci}(t) \geq 0$, $I_{ci}(t) \geq 0$, $R_{ci}(t) \geq 0$, $S_{mi}(t) > 0$, $E_{mi}(t) \geq 0$, and $I_{mi}(t) \geq 0$ for all $i \in \{1,2,\ldots,n\}$ and $t > 0$. □

Therefore, all solutions of the model (5.1) remain non-negative for all non-negative initial conditions.

Theorem 5.2. *The solutions of the model* (5.1) *with non-negative initial conditions are bounded.*

Proof. Calculating the overall host equations of (5.1),

$$\frac{dN_{ci}}{dt} = \Lambda_i - \nu_i I_i + (1 - x_{4i})\left\{ \sum_{k=1,k\neq i}^{n} c_{ik}N_{ck} - \sum_{k=1,k\neq i}^{n} c_{ki}N_{ci} \right\} - \mu_{ci}N_{ci}. \tag{5.2}$$

Let $N_c = \sum_{i=1}^{n} N_{ci}$, $\Lambda = \sum_{i=1}^{n} \Lambda_i$ and $\mu_c = \min\{\mu_{ci}, i = 1,2,\ldots,n\}$. Now from (5.2),

$$\frac{dN_c}{dt} = \sum_{i=1}^{n} \left(\Lambda_i - \nu_i I_i - \mu_{ci}N_{ci} \right) \leq \Lambda - \mu_c N_c.$$

Thus, $\limsup_{t\to\infty} N_c \leq \frac{\Lambda}{\mu_c}$.

Similarly, adding the midge equations of (5.1),

$$\frac{dN_{mi}}{dt} = \pi_i + \sum_{k=1,k\neq i}^{n} m_{ik}N_{mk} - \left(\mu_{mi} + \sum_{k=1,k\neq i}^{n} m_{ki} \right) N_{mi}. \tag{5.3}$$

Let $N_m = \sum_{i=1}^{n} N_{mi}$, $\pi = \sum_{i=1}^{n} \pi_i$ and $\mu_m = \min\{\mu_{mi}, i = 1,2,\ldots,n\}$. Then equation (5.3) gives $\frac{dN_m}{dt} \leq \pi - \mu_m N_m$. Hence, $\limsup_{t\to\infty} N_m \leq \frac{\pi}{\mu_m}$. □

Therefore, all solutions of the model (5.1) with non-negative initial conditions are bounded.

The feasible region

$$\Omega = \left\{ (L_1, L_2, \ldots, L_n) \in \mathbb{R}_+^{7n} | N_c \leq \frac{\Lambda}{\mu_c}, N_m \leq \frac{\pi}{\mu_m} \right\},$$

where $L_i = (S_{ci}, E_{ci}, I_{ci}, R_{ci}, S_{mi}, E_{mi}, I_{mi})$, $i = 1,2,\ldots,n$ is positively invariant with respect to the model (5.1). Thus, in the region Ω, the model (5.1) is mathematically well-posed and epidemiologically feasible [96].

5.1.2 Equilibria and the Basic Reproduction Numbers

The disease-free equilibrium point (E_{0i}) of the model (5.1) with fixed controls and without host and midge movement is given by

$$E_{0i} = \left(\frac{\Lambda_i(\omega_i + \mu_{ci})}{\mu_{ci}(\omega_i + \mu_{ci} + x_{3i})}, 0, 0, \frac{\Lambda_i x_{3i}}{\mu_{ci}(\omega_i + \mu_{ci} + x_{3i})}, \frac{\pi_i}{(\mu_{mi} + x_{2i})}, 0, 0 \right).$$

Using the next generation operator method [108], the local stability of E_{0i} is determined. Maintaining the notation in [108], the matrices F_i and V_i for the new infection and transfer terms are respectively given by

$$\mathrm{F}_i = \begin{pmatrix} 0 & 0 & 0 & (\frac{(1-x_{1i})a_i p(\omega_i + \mu_{ci})}{(\omega_i + \mu_{ci} + x_{3i})} \\ 0 & 0 & 0 & 0 \\ 0 & \frac{(1-x_{1i})a_i q \pi_i \mu_{ci}}{\Lambda_i(\mu_{mi} + x_{2i})} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{5.4}$$

and

$$\mathrm{V}_i = \begin{pmatrix} \sigma_{ci} + \mu_{ci} & 0 & 0 & 0 \\ -\sigma_{ci} & \mu_{ci} + \nu_i + \gamma_i & 0 & 0 \\ 0 & 0 & \mu_{mi} + x_{2i} + \sigma_{mi} & 0 \\ 0 & 0 & -\sigma_{mi} & \mu_m + x_{2i} \end{pmatrix}. \tag{5.5}$$

From (5.4) and (5.5), the basic reproduction number $\mathscr{R}_{0i}$ of the model (5.1) in any isolated/closed patch i is given by

$$\begin{aligned} \mathscr{R}_{0i} =& \rho(F_i V_i^{-1}) \\ =& \sqrt{\frac{(1-x_{1i})^2 a_i^2 p_j q_j \pi_i \mu_{ci} \sigma_{ci} \sigma_{mi} (\omega_i + \mu_{ci})}{A_i (\mu_{mi} + x_{2i})^2 (\mu_{mi} + x_{2i} + \sigma_{mi})(\omega_i + \mu_{ci} + x_{3i})}}, \end{aligned}$$

where $A_i = \Lambda_i(\mu_{ci} + \sigma_{ci})(\mu_{ci} + \nu_i + \gamma_i)$, $i \in \{1, 2, \ldots, n\}$ and $\rho(F_i V_i^{-1})$ is the spectral radius of $F_i V_i^{-1}$.

The disease-free equilibrium point (E_{0i}) is locally asymptotically stable when $\mathscr{R}_{0i} < 1$ and if $\mathscr{R}_{0i} > 1$ for all $i \in \{1, 2, \ldots, n\}$, there exists an endemic equilibrium point (S_{ci}^*, E_{ci}^*, I_{ci}^*, R_{ci}^*, S_{mi}^*, E_{mi}^*, I_{mi}^*) which is also locally asymptotically stable. For the detailed analytical analysis of the model (5.1) with fixed controls in an isolated patch, see a study in Chapter 3.

For the entire patch system, let L_{ci} =(E_{ci}, I_{ci}) and L_{mi} =(E_{mi}, I_{mi}) for $i = 1, 2, \ldots, n$. Then, E_0 = (S_{c1}^0, L_{c1}^0, R_{c1}^0, S_{m1}^0, L_{m1}^0, …, S_{cn}^0, L_{cn}^0, R_{cn}^0, S_{mn}^0, L_{mn}^0) is the disease-free equilibrium point of

the model (5.1), where $L_{ci}^0 = 0 = L_{mi}^0$, $S_{ci}^0 > 0$, $R_{ci}^0 > 0$ and $S_{mi}^0 > 0$.

Considering the infected classes, E_{ci}, I_{ci}, E_{mi} and I_{mi}, $i = 1,2,\ldots,n$ of the model (5.1), it follows from [108] that

$$F = \begin{bmatrix} 0 & 0 & 0 & F_{14} \\ 0 & 0 & 0 & 0 \\ 0 & F_{32} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$V = \begin{bmatrix} V_{11} & 0 & 0 & 0 \\ -V_{21} & V_{22} & 0 & 0 \\ 0 & 0 & V_{33} & 0 \\ 0 & 0 & -V_{43} & V_{44} \end{bmatrix},$$

where $F_{14} = \text{diag}\big[(1-x_{1i})a_i p S_{ci}^0/N_c\big]$, $F_{32} = \text{diag}\big[(1-x_{1i})a_i q S_{mi}^0/N_c\big]$, $V_{21} = \text{diag}\big[\sigma_{ci}\big]$, $V_{43} = \text{diag}\big[\sigma_{mi}\big]$, $V_{11} = \text{diag}\big[\sigma_{ci} + \mu_{ci}\big] - M_c$, $V_{22} = \text{diag}\big[\mu_{ci} + \nu_i + \gamma_i\big] - M_c$, $V_{33} = \text{diag}\big[\mu_{mi} + x_{2i} + \sigma_{mi}\big] - M_m$ and $V_{44} = \text{diag}\big[\mu_{mi} + x_{2i}\big] - M_m$. M_c and M_m, respectively, are defined by $M_c(i,k) = c_{ik}$ and $M_m(i,k) = m_{ik}$ for $i \neq k$ and $M_c(i,i) = -\sum_{k=1,k\neq i}^{n} c_{ki}$ and $M_m(i,i) = -\sum_{k=1,k\neq i}^{n} m_{ki}$ for $i = k$.

Thus, the basic reproduction number of the model (5.1) is given by

$$\mathscr{R}_0 = \rho(FV^{-1}). \tag{5.6}$$

The disease-free equilibrium point (E_0) of the entire patch system is locally asymptotically stable when $\mathscr{R}_0 < 1$ and unstable for $\mathscr{R}_0 > 1$, implying an existence of the endemic equilibrium point.

To obtain the disease-free equilibrium points E_{0i} and E_0 and their associated basic reproduction numbers $\mathscr{R}_{0i}$ and $\mathscr{R}_0$, fixed control parameters are considered. But in reality, these parameters may not be independent of time. Also, controlling at fixed values is difficult and costly. In the section that follows, by using optimal control theory, the model (5.1) with time-dependent controls is analysed to determine the optimal control strategies for BTV transmission in patchy environments.

5.2 Optimal Control Analysis

In this section, optimal control analysis is carried out to determine the most effective control strategy for minimising the number of hosts getting infected with BTV in patchy environments. The control strategy is effective over the entire patch system if it minimises the following objective function:

$$J(x_1,x_2,\ldots,x_n)=\int_0^T\sum_{i=1}^{n}\left\{A_{1i}I_{ci}(t)+A_{2i}x_{1i}^2+A_{3i}x_{2i}^2+A_{4i}x_{3i}^2+A_{5i}x_{4i}^2\right\}dt \tag{5.7}$$

subject to the model (5.1), where $x_i=(x_{1i},x_{2i},x_{3i},x_{4i})$ for $i=1,2,\ldots,n$. Here A_{ui}, $u=1,2,\ldots,5$ are positive weights attached to the advantages of controlling hosts infected with BTV over a finite period of time T [76]. Weight A_{1i} is a direct cost associated with reducing the number of infectious hosts in patch i. It represents the cost of buying the vaccine, insecticides, repellents, test kits and among others. Weights A_{2i}, A_{3i}, A_{4i} and A_{5i} are relative cost weights for enforcing control strategies x_{1i}, x_{2i}, x_{3i} and x_{4i}, they include costs of labour hired to apply the repellents, spray the insecticides, vaccinate the hosts and implement the quarantine, respectively, in patch i.

The goal is to minimise the number of infectious hosts while minimising the control costs. For this goal, we require controls $x_1^*,x_2^*,\ldots,x_n^*$ such that

$$J(x_1^*,x_2^*,\ldots,x_n^*)=min\left\{J(x_1,x_2,\ldots,x_n)|\ x_1,x_2,\ldots,x_n\in X\right\} \tag{5.8}$$

subject to the model (5.1), where

$$X=\left\{\left(x_1(t),x_2(t),\ldots,x_n(t)\right)\in\left[L^2(0,T)\right]^{4n}|\ 0\le x_1,x_2,\ldots,x_n\le 1,t\in[0,T]\right\}.$$

Pontryagin's maximum principle provides the necessary conditions for an optimal control. They include proving the existence of the optimal control and determining the optimality system [31, 76].

5.2.1 Existence of the Optimal Control

Let $x=(x_1,x_2,\ldots,x_n)\in\left[L^2(0,T)\right]^{4n}$ and $I=(I_{c1},I_{c2},\ldots,I_{cn})$. Hence, a reduced function corresponding to (5.7) is given by

$$J(x,I^x) = \int_0^T \sum_{i=1}^{n} \left\{ A_{1i} I_{ci}(t) + A_{2i} x_{1i}^2 + A_{3i} x_{2i}^2 + A_{4i} x_{3i}^2 + A_{5i} x_{4i}^2 \right\} dt, \;\; x \in X.$$

Lemma 5.1. *Set X is convex and closed.*

Proof. To prove that X is a closed set, assume that $x_{m\in\mathbb{N}} \longrightarrow x^*$ in $L^2(0,T)$ for $x_m \in X$, but $x^* \notin X$, that is, $x^* < 0$ or $x^* > 1$ on a set of positive measure. Then taking $x^* < 0$, from Lebesgue measure methods there exists $\varepsilon > 0$ and a positive measure set $(0,t) \subset (0,T)$ such that $x^* \leq 0 - \varepsilon$ on $(0,t)$ [76]. This implies that

$$\int_0^T (x_m - x^*)^2 dt \geq \int_0^t (x_m - x^*)^2 dt \geq \int_0^t (0 - x^*)^2 dt \geq \int_0^t \varepsilon^2 dt > 0,$$

a contradiction. Thus, set X is closed.

To prove convexity of set X, it suffices to show that if X is a convex set and $x_1, x_2, \ldots, x_n \in X$, then any convex combination $\sum_{i=1}^n \phi_i x_i$ for $\sum_{i=1}^n \phi_i = 1$, $\phi_1, \phi_2, \ldots, \phi_n \geq 0$ is also contained in X.

The proof is by induction. For $i = 1$, since $x_1 \in X$ then $\phi_1 x_1 \in X$. For $i = 2$, since $(x_1, x_2) \in X$,

$$0 \leq x_1 \leq 1, \tag{5.9}$$

and

$$0 \leq x_2 \leq 1. \tag{5.10}$$

Multiplying (5.9) by ϕ_1 and (5.10) by ϕ_2 gives

$$0 \leq \phi_1 x_1 \leq \phi_1, \tag{5.11}$$

and

$$0 \leq \phi_2 x_2 \leq \phi_2. \tag{5.12}$$

Adding up equations (5.11) and (5.12),

$$0 \leq \phi_1 x_1 + \phi_2 x_2 \leq 1.$$

Thus, $\phi_1 x_1 + \phi_2 x_2 \in X$.
For $i = n - 1$, suppose that $\sum_{i=1}^{n-1} \phi_i x_i \in X$. By the inductive hypothesis,

$$w = \frac{\phi_1 x_1}{\sum_{i=1}^{n-1}\phi_i} + \frac{\phi_2 x_2}{\sum_{i=1}^{n-1}\phi_i} + \ldots + \frac{\phi_{n-1} x_{n-1}}{\sum_{i=1}^{n-1}\phi_i} \in X. \tag{5.13}$$

For $i = n$,

$$\sum_{i=1}^{n} \phi_i x_i = \sum_{i=1}^{n-1} \phi_i x_i + \phi_n x_n. \tag{5.14}$$

From (5.13), $\sum_{i=1}^{n-1} \phi_i x_i = w \sum_{i=1}^{n-1} \phi_i$. Then (5.14) gives

$$\sum_{i=1}^{n} \phi_i x_i = w \sum_{i=1}^{n-1} \phi_i + \phi_n x_n. \tag{5.15}$$

Since $x_n \in X$ it follows that the RHS of (5.15) is a convex combination of two points of X. Thus, $w\sum_{i=1}^{n-1} \phi_i + \phi_n x_n \in X$ and hence, X is convex.

□

Theorem 5.3. *There exists an optimal control pair* (x^*, I^{x^*}) *to the optimization problem* (5.8).

Proof. Set

$$b = \sup_{x \in X} J(x, I^x).$$

This implies, for any $m \in \mathbb{N}$, there exists $x_m \in X$ so that

$$b - \frac{1}{m} < J(x_m, I^{x_m}) \leq b. \tag{5.16}$$

As set X is a bounded subset of $L^2(0,T)$, it follows from Bolzano-Weierstrass theorem, that there exists a subsequence $\{x_{m_r}\}_{r \in \mathbb{N}}$ such that

$$x_{m_r} \longrightarrow x^*, \tag{5.17}$$

weakly in $L^2(0,T)$. From Theorem 5.2 it is observed that the set of state variables is bounded. Thus, there exists a subsequence $\{I^{x_{m_r}}\}_{r \in \mathbb{N}}$ such that

$$I^{x_{m_r}} \longrightarrow I^{x^*} \text{ in } C([0,T]). \tag{5.18}$$

From (5.16),

$$b - \frac{1}{m} < \int_0^T \sum_{i=1}^{n} \left\{ A_{1i} I_{ci}^{x_{m_r}}(t) + A_{2i} x_{1im_r}^2 + A_{3i} x_{2im_r}^2 + A_{4i} x_{3im_r}^2 + A_{5i} x_{4im_r}^2 \right\} dt \leq b. \tag{5.19}$$

By (5.17) and (5.18), passing to the limit in (5.19),

$$b=\int_0^T\sum_{i=1}^{n}\left\{A_{1i}I_{ci}^{x^*}(t)+A_{2i}(x_{1i}^*)^2+A_{3i}(x_{2i}^*)^2+A_{4i}(x_{3i}^*)^2+A_{5i}(x_{4i}^*)^2\right\}dt,$$

that is, $\left((x_{1i}^*,x_{2i}^*,x_{3i}^*,x_{4i}^*),I^{x^*}\right)$, $i=1,2,\ldots,n$ is an optimal pair where x_{1i}^*, x_{2i}^*, x_{3i}^* and x_{4i}^* are optimal controls for (5.8). □

5.2.2 Optimality System

This is used to compute values for the optimal control pair. To determine the optimality system, we start by stating the Hamiltonian as follows:

$$\begin{aligned}
\mathscr{H}=\sum_{i=1}^{n}\Bigg[&A_{1i}I_{ci}(t)+A_{2i}x_{1i}^2+A_{3i}x_{2i}^2+A_{4i}x_{3i}^2+A_{5i}x_{4i}^2\\
&+\lambda_{1i}\Bigg(\Lambda_i+\omega_iR_{ci}-(1-x_{1i})a_ipI_{mi}\frac{S_{ci}}{N_{ci}}-(\mu_{ci}+x_{3i})S_{ci}\\
&+(1-x_{4i})\Bigg\{\sum_{k=1,k\neq i}^{n}c_{ik}S_{ck}-\sum_{k=1,k\neq i}^{n}c_{ki}S_{ci}\Bigg\}\Bigg)\\
&+\lambda_{2i}\Bigg((1-x_{1i})a_ipI_{mi}\frac{S_{ci}}{N_{ci}}-(\mu_{ci}+\sigma_{ci})E_{ci}\\
&+(1-x_{4i})\Bigg\{\sum_{k=1,k\neq i}^{n}c_{ik}E_{ck}-\sum_{k=1,k\neq i}^{n}c_{ki}E_{ci}\Bigg\}\Bigg)\\
&+\lambda_{3i}\Bigg(\sigma_{ci}E_{ci}-(\mu_{ci}+\nu_i+\gamma_i)I_{ci}\\
&+(1-x_{4i})\Bigg\{\sum_{k=1,k\neq i}^{n}c_{ik}I_{ck}-\sum_{k=1,k\neq i}^{n}c_{ki}I_{ci}\Bigg\}\Bigg)\\
&+\lambda_{4i}\Bigg(x_{3i}S_{ci}+\gamma_iI_{ci}-(\omega_i+\mu_{ci})R_{ci}\\
&+(1-x_{4i})\Bigg\{\sum_{k=1,k\neq i}^{n}c_{ik}R_{ck}-\sum_{k=1,k\neq i}^{n}c_{ki}R_{ci}\Bigg\}\Bigg)\\
&+\lambda_{5i}\Bigg(\pi_i-(1-x_{1i})a_iqI_{ci}\frac{S_{mi}}{N_{ci}}-(\mu_{mi}+x_{2i})S_{mi}\\
&+\sum_{k=1,k\neq i}^{n}m_{ik}S_{mk}-\sum_{k=1,k\neq i}^{n}m_{ki}S_{mi}\Bigg)
\end{aligned}$$

$$
\begin{aligned}
&+\lambda_{6i}\Bigg((1-x_{1i})a_i q I_{ci}\frac{S_{mi}}{N_{ci}}-(\sigma_{mi}+\mu_{mi}+x_{2i})E_{mi}\\
&+\sum_{k=1,k\neq i}^{n} m_{ik}E_{mk}-\sum_{k=1,k\neq i}^{n} m_{ki}E_{mi}\Bigg)+\lambda_{7i}\Bigg(\sigma_{mi}E_{mi}\\
&-(\mu_{mi}+x_{2i})I_{mi}+\sum_{k=1,k\neq i}^{n} m_{ik}I_{mk}-\sum_{k=1,k\neq i}^{n} m_{ki}I_{mi}\Bigg)\Bigg],
\end{aligned}
\tag{5.20}
$$

where $\lambda_{ji},\ j=1,2,\ldots,7,\ i\in\{1,2,\ldots,n\}$ are co-state variables corresponding to S_{ci}, E_{ci}, I_{ci}, R_{ci}, S_{mi}, E_{mi} and I_{mi}, respectively. The Hamiltonian (5.20) is used to derive the adjoint equations of the control problem (5.8) by using Theorem 5.4.

Theorem 5.4. *Let x_{1i}^*, x_{2i}^*, x_{3i}^*, x_{4i}^* be optimal controls for* (5.7) *with corresponding optimal states $S_{ci}^{x^*}$, $E_{ci}^{x^*}$, $I_{ci}^{x^*}$, $R_{ci}^{x^*}$, $S_{mi}^{x^*}$, $E_{mi}^{x^*}$ and $I_{mi}^{x^*}$ of the model* (5.1) *that minimises* (5.7) *over X. Then, there exist co-state variables λ_{ji}, $i=1,2,\ldots,n$, $j=1,2,\ldots,7$ satisfying:*

$$
\begin{aligned}
\frac{\partial\lambda_{1i}}{\partial t}=&\frac{(1-x_{1i})a_i}{N_{ci}^2}\Bigg\{pI_{mi}(N_{ci}-S_{ci})(\lambda_{1i}-\lambda_{2i})+qI_{ci}S_{mi}(\lambda_{6i}-\lambda_{5i})\Bigg\}\\
&+\lambda_{1i}\Bigg\{\mu_{ci}+(1-x_{4i})\sum_{k=1,k\neq i}^{n}c_{ki}\Bigg\}+(\lambda_{1i}-\lambda_{4i})x_{3i},\\
\frac{\partial\lambda_{2i}}{\partial t}=&\frac{(1-x_{1i})a_i}{N_{ci}^2}\Bigg\{pI_{mi}S_{ci}(\lambda_{2i}-\lambda_{1i})+qI_{ci}S_{mi}(\lambda_{6i}-\lambda_{5i})\Bigg\}\\
&+\lambda_{2i}\Bigg\{\mu_{ci}+\sigma_{ci}+(1-x_{4i})\sum_{k=1,k\neq i}^{n}c_{ki}\Bigg\}-\lambda_{3i}\sigma_{ci},\\
\frac{\partial\lambda_{3i}}{\partial t}=&-A_{1i}+\frac{(1-x_{1i})a_i}{N_{ci}^2}\Bigg\{pI_{mi}S_{ci}(\lambda_{2i}-\lambda_{1i})+qS_{mi}(N_{ci}-I_{ci})(\lambda_{5i}-\lambda_{6i})\Bigg\}\\
&+\lambda_{3i}\Bigg\{\mu_{ci}+\nu_i+\gamma_i+(1-x_{4i})\sum_{k=1,k\neq i}^{n}c_{ki}\Bigg\}-\lambda_{4i}\gamma_i,\\
\frac{\partial\lambda_{4i}}{\partial t}=&\frac{(1-x_{1i})a_i}{N_{ci}^2}\Bigg\{pI_{mi}S_{ci}(\lambda_{2i}-\lambda_{1i})+qI_{ci}S_{mi}(\lambda_{6i}-\lambda_{5i})\Bigg\}\\
&+\lambda_{4i}\Bigg\{\mu_{ci}+\omega_i+(1-x_{4i})\sum_{k=1,k\neq i}^{n}c_{ki}\Bigg\}-\lambda_{1i}\omega_i,\\
\frac{\partial\lambda_{5i}}{\partial t}=&\frac{(1-x_{1i})a_i}{N_{ci}}qI_{ci}(\lambda_{5i}-\lambda_{6i})+\lambda_{5i}\Bigg\{\mu_{mi}+x_{2i}+\sum_{k=1,k\neq i}^{n}m_{ki}\Bigg\},
\end{aligned}
$$

$$\frac{\partial \lambda_{6i}}{\partial t} = \lambda_{6i}\left\{\mu_{mi} + \sigma_{mi} + x_{2i} + \sum_{k=1,k\neq i}^{n} m_{ki}\right\} - \lambda_{7i}\sigma_{mi},$$
$$\frac{\partial \lambda_{7i}}{\partial t} = \lambda_{7i}\left\{\mu_{mi} + x_{2i} + \sum_{k=1,k\neq i}^{n} m_{ki}\right\} + (\lambda_{1i} - \lambda_{2i})(1 - x_{1i})a_i p\frac{S_{ci}}{N_{ci}},$$

with transversality condition $\lambda_{ji}(T) = 0$, $i = 1,2,\ldots,n$, $i = 1,2,\ldots,7$ *and the following characterization:*

$$x_{1i}^{*} = \max\{0, \min(1, \hat{x}_{1i}(t))\},\ x_{2i}^{*} = \max\{0, \min(1, \hat{x}_{2i}(t))\},$$
$$x_{3i}^{*} = \max\{0, \min(1, \hat{x}_{3i}(t))\},\ x_{4i}^{*} = \max\{0, \min(1, \hat{x}_{4i}(t))\},$$

where $\hat{x}_{1i} = \left[a_i S_{ci} p I_{mi}(\lambda_{2i} - \lambda_{1i}) + a_i S_{mi} q I_{ci}(\lambda_{6i} - \lambda_{5i})\right]/2A_{2i}N_{ci}$, $\hat{x}_{2i} = \left[(\lambda_{5i}S_{mi} + \lambda_{6i}E_{mi} + \lambda_{7i}I_{mi})\right]/2A_{3i}$, $\hat{x}_{3i} = \left[(\lambda_{1i} - \lambda_{4i})S_{ci}\right]/2A_{4i}$,
$\hat{x}_{4i} = \left[\sum_{k=1,k\neq i}^{n} c_{ik}B_{ik} - \sum_{k=1,k\neq i}^{n} c_{ki}C_i\right]/2A_{5i}$, $B_{ik} = \lambda_{1i}S_{ck} + \lambda_{2i}E_{ck} + \lambda_{3i}I_{ck} + \lambda_{4i}R_{ck}$ *and* $C_i = \lambda_{1i}S_{ci} + \lambda_{2i}E_{ci} + \lambda_{3i}I_{ci} + \lambda_{4i}R_{ci}$.

Proof. Pontryagin's maximum principle guarantees the existence of λ_{ji}, satisfying

$$\begin{aligned}
&\frac{\partial \lambda_{1i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial S_{ci}},\ \frac{\partial \lambda_{2i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial E_{ci}},\ \frac{\partial \lambda_{3i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial I_{ci}},\ \frac{\partial \lambda_{4i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial R_{ci}},\\
&\frac{\partial \lambda_{5i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial S_{mi}},\ \frac{\partial \lambda_{6i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial E_{mi}},\ \frac{\partial \lambda_{7i}}{\partial t} = -\frac{\partial \mathscr{H}}{\partial I_{mi}},\\
&\lambda_{ji}(T) = 0,\ \ j = 1,2,\ldots,7,\ \ i = 1,2,\ldots,n.
\end{aligned} \tag{5.21}$$

From (5.20) and (5.21),

$$\begin{aligned}
\frac{\partial \lambda_{1i}}{\partial t} =& \frac{(1 - x_{1i})a_i}{N_{ci}^2}\left\{pI_{mi}(N_{ci} - S_{ci})(\lambda_{1i} - \lambda_{2i}) + qI_{ci}S_{mi}(\lambda_{6i} - \lambda_{5i})\right\}\\
&+ \lambda_{1i}\left\{\mu_{ci} + (1 - x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\} + (\lambda_{1i} - \lambda_{4i})x_{3i},\\
\frac{\partial \lambda_{2i}}{\partial t} =& \frac{(1 - x_{1i})a_i}{N_{ci}^2}\left\{pI_{mi}S_{ci}(\lambda_{2i} - \lambda_{1i}) + qI_{ci}S_{mi}(\lambda_{6i} - \lambda_{5i})\right\}\\
&+ \lambda_{2i}\left\{\mu_{ci} + \sigma_{ci} + (1 - x_{4i})\sum_{k=1,k\neq i}^{n} c_{ki}\right\} - \lambda_{3i}\sigma_{ci},
\end{aligned}$$

$$
\begin{aligned}
\frac{\partial \lambda_{3i}}{\partial t} =& -A_{1i} + \frac{(1-x_{1i})a_i}{N_{ci}^2}\left\{ pI_{mi}S_{ci}(\lambda_{2i}-\lambda_{1i}) + qS_{mi}(N_{ci}-I_{ci})(\lambda_{5i}-\lambda_{6i}) \right\} \\
&+ \lambda_{3i}\left\{ \mu_{ci} + \nu_i + \gamma_i + (1-x_{4i}) \sum_{k=1,k\neq i}^{n} c_{ki} \right\} - \lambda_{4i}\gamma_i, \\
\frac{\partial \lambda_{4i}}{\partial t} =& \frac{(1-x_{1i})a_i}{N_{ci}^2}\left\{ pI_{mi}S_{ci}(\lambda_{2i}-\lambda_{1i}) + qI_{ci}S_{mi}(\lambda_{6i}-\lambda_{5i}) \right\} \\
&+ \lambda_{4i}\left\{ \mu_{ci} + \omega_i + (1-x_{4i}) \sum_{k=1,k\neq i}^{n} c_{ki} \right\} - \lambda_{1i}\omega_i, \\
\frac{\partial \lambda_{5i}}{\partial t} =& \frac{(1-x_{1i})a_i}{N_{ci}} qI_{ci}(\lambda_{5i}-\lambda_{6i}) + \lambda_{5i}\left\{ \mu_{mi} + x_{2i} + \sum_{k=1,k\neq i}^{n} m_{ki} \right\}, \\
\frac{\partial \lambda_{6i}}{\partial t} =& \lambda_{6i}\left\{ \mu_{mi} + \sigma_{mi} + x_{2i} + \sum_{k=1,k\neq i}^{n} m_{ki} \right\} - \lambda_{7i}\sigma_{mi}, \\
\frac{\partial \lambda_{7i}}{\partial t} =& \lambda_{7i}\left\{ \mu_{mi} + x_{2i} + \sum_{k=1,k\neq i}^{n} m_{ki} \right\} + (\lambda_{1i}-\lambda_{2i})(1-x_{1i})a_i p\frac{S_{ci}}{N_{ci}},
\end{aligned}
\tag{5.22}
$$

with transversality condition $\lambda_{ji}(T) = 0$, $j = 1,2,\ldots,7$, $i = 1,2,\ldots,n$.

Differentiating (5.20) with respect to the admissible controls, gives

$$
\begin{aligned}
\frac{\partial \mathscr{H}}{\partial x_{1i}} =& 2A_{2i}x_{1i} + a_i\frac{S_{ci}}{N_{ci}} pI_{mi}(\lambda_{1i}-\lambda_{2i}) + a_i\frac{S_{mi}}{N_{ci}} qI_{ci}(\lambda_{5i}-\lambda_{6i}), \\
\frac{\partial \mathscr{H}}{\partial x_{2i}} =& 2A_{3i}x_{2i} - (\lambda_{5i}S_{mi} + \lambda_{6i}E_{mi} + \lambda_{7i}I_{mi}), \\
\frac{\partial \mathscr{H}}{\partial x_{3i}} =& 2A_{4i}x_{3i} + (\lambda_{4i}-\lambda_{1i})S_{ci}, \\
\frac{\partial \mathscr{H}}{\partial x_{4i}} =& 2A_{5i}x_{4i} + \lambda_{1i}\left\{ \sum_{k=1,k\neq i}^{n} c_{ki}S_{ci} - \sum_{k=1,k\neq i}^{n} c_{ik}S_{ck} \right\} \\
&+ \lambda_{2i}\left\{ \sum_{k=1,k\neq i}^{n} c_{ki}E_{ci} - \sum_{k=1,k\neq i}^{n} c_{ik}E_{ck} \right\} + \lambda_{3i}\left\{ \sum_{k=1,k\neq i}^{n} c_{ki}I_{ci} - \sum_{k=1,k\neq i}^{n} c_{ik}I_{ck} \right\} \\
&+ \lambda_{4i}\left\{ \sum_{k=1,k\neq i}^{n} c_{ki}R_{ci} - \sum_{k=1,k\neq i}^{n} c_{ik}R_{ck} \right\},
\end{aligned}
\tag{5.23}
$$

for $i = 1,2,\ldots,n$.

Solving the system (5.23) by setting its right-hand side to zero, the possible values $\hat{x}_{1i}$, $\hat{x}_{2i}$, $\hat{x}_{3i}$ and $\hat{x}_{4i}$ of the optimal controls x_{1i}^*, x_{2i}^*, x_{3i}^* and x_{4i}^* are given by

$$\hat{x}_{1i} = \frac{a_i S_{ci} p I_{mi}(\lambda_{2i} - \lambda_{1i}) + a_i S_{mi} q I_{ci}(\lambda_{6i} - \lambda_{5i})}{2A_{2i} N_{ci}},$$
$$\hat{x}_{2i} = \frac{(\lambda_{5i} S_{mi} + \lambda_{6i} E_{mi} + \lambda_{7i} I_{mi})}{2A_{3i}},$$
$$\hat{x}_{3i} = \frac{(\lambda_{1i} - \lambda_{4i}) S_{ci}}{2A_{4i}},$$
$$\hat{x}_{4i} = \frac{\sum_{k=1,k\neq i}^{n} c_{ik} B_{ik} - \sum_{k=1,k\neq i}^{n} c_{ki} C_i}{2A_{5i}},$$

where $B_{ik} = \lambda_{1i} S_{ck} + \lambda_{2i} E_{ck} + \lambda_{3i} I_{ck} + \lambda_{4i} R_{ck}$ and $C_i = \lambda_{1i} S_{ci} + \lambda_{2i} E_{ci} + \lambda_{3i} I_{ci} + \lambda_{4i} R_{ci}$ for $i = 1, 2, \ldots, n$.

Standard arguments on the controls [76, 81] are such that

$$x_{vi}^{*} = \begin{cases} 0 & \text{if } \hat{x}_{vi} \leq 0, \\ \hat{x}_{vi} & \text{if } 0 < \hat{x}_{vi} < 1, \\ 1 & \text{if } \hat{x}_{vi} \geq 1, \end{cases} \tag{5.24}$$

where $v = 1, 2, 3, 4$ and $i = 1, 2, \ldots, n$. The value $x_{vi}^{*} = 1$ is a characteristic of a perfectly effective control strategy.

From (5.24),

$$\begin{aligned} x_{1i}^{*} &= \max\{0, \min(1, \hat{x}_{1i}(t))\}, \; x_{2i}^{*} = \max\{0, \min(1, \hat{x}_{2i}(t))\}, \\ x_{3i}^{*} &= \max\{0, \min(1, \hat{x}_{3i}(t))\}, \; x_{4i}^{*} = \max\{0, \min(1, \hat{x}_{4i}(t))\}. \end{aligned} \tag{5.25}$$

□

The model (state system) (5.1) with its initial conditions, the co-state system (5.22) with its transversality conditions and the optimality condition (5.25) form the optimality system. The solutions of the state (5.1) and co-state (5.22) systems, respectively, are obtained by using Runge-Kutta fourth order schemes forward and backward in time [76].

Let the solutions of (5.1), (5.22) and (5.25), respectively, be given by

$$
\begin{aligned}
Y_i^k =& \big\{S_{ci}(t_k), E_{ci}(t_k), I_{ci}(t_k), R_{ci}(t_k), S_{mi}(t_k), E_{mi}(t_k), I_{mi}(t_k)\big\},\\
\lambda_i^{l+1-k} =& \big\{\lambda_{1i}(t_{l+1-k}), \lambda_{2i}(t_{l+1-k}), \lambda_{3i}(t_{l+1-k}), \lambda_{4i}(t_{l+1-k}), \lambda_{5i}(t_{l+1-k}),\\
& \lambda_{6i}(t_{l+1-k}), \lambda_{7i}(t_{l+1-k})\big\} \text{ and}\\
x_i^k =& \big\{x_{1i}^*(t_k), x_{2i}^*(t_k), x_{3i}^*(t_k), x_{4i}^*(t_k)\big\},
\end{aligned}
$$

$i = 1, 2, \ldots, n$, $t_k = kh$, $k = 0, 1, 2, \ldots, l+1$, $h = (T-0)/l$ (step size) and l is the number of sub-intervals for the interval $[0, T]$. Then the algorithm for obtaining the optimal control [76] is given by

Algorithm 1 The algorithm for obtaining optimal control.

A0: Choose $x_i^k \in X$ and Y_i^k;
Set $k := 0$.

A1: Compute Y_i^{k+1} the solution to (5.1) corresponding to Y_i^k and x_i^k.

A2: Compute λ_i^{l-k} the solution to (5.22) corresponding to $\lambda_i^{(l+1)} = 0$, Y_i^{k+1} and x_i^k.

A3: Using λ_i^{l-k} and Y_i^{k+1} update (5.25) to obtain x_i^{k+1}.

A4: If $\|x_i^{k+1} - x_i^k\| < \varepsilon$, then STOP ($x_i^{k+1}$ is the optimal control) else $k := k+1$; go to **A1**.
Here ε is an arbitrary small positive number.

Using Algorithm 1 the optimality system is solved numerically in the next section to obtain the optimal control for BTV spread in patchy environments.

5.3 Numerical Results

Isolated and connected patches are considered. For isolated patches, the movement parameters for hosts and midges are assumed to be zero. For patches connected by host and/or midge movement, two patches ($i = 1, 2$) denoted by patch 1 and patch 2 are considered. We assume that the virus is endemic in patch 1 (high-risk patch, $\mathscr{R}_{01} > 1$) and not yet endemic in patch 2 (low-risk patch, $\mathscr{R}_{02} < 1$). The parameter values used are given in Table 4.3 with $p = 1.0$, $q = 0.2$, $\gamma_1 = 0.0167$ and $\gamma_2 = 0.1$. For illustration, the weighting factors used are $A_{11} = A_{12} = 1000$, $A_{21} = A_{22} = 1$, $A_{31} = A_{32} = 1$, $A_{41} = A_{42} = 1$ and $A_{51} = A_{52} = 1$. The initial conditions are $S_{c1} = S_{c2} = 8000$, $E_{c1} = E_{c2} = 1$, $I_{c1} = I_{c2} = 1$, $R_{c1} = R_{c2} = 0$,

$S_{m1} = S_{m2} = 100000$, $E_{m1} = 1 = E_{m2}$ and $I_{m1} = 1 = I_{m2}$. The patch specific basic reproduction numbers are $\mathscr{R}_{01} = 2.3862$ and $\mathscr{R}_{02} = 0.5492$.

5.3.1 Effects of Using Repellents, Insecticide Spraying or Vaccination in an Isolated Patch

The effects of using a repellent (x_{1i}), insecticide spraying (x_{2i}) or vaccination (x_{3i}) on the spread of BTV in the high-risk patch are studied in Figure 5.1. One control at a time is used to minimise the objective function (5.7). The effect of using quarantine (x_{4i}) is not studied since it is assumed that there is no host movement. From Figures 5.1 (a) and (b), without control the trajectories for infected hosts and midges increase to 30 and 52, respectively in 60 days from the beginning of the outbreak, but with optimal vaccination, insecticide spraying or the use of a repellent they converge to zero. For infected midges, the trajectories converge to zero in 4 and 11 days when repellents and insecticides are applied, respectively, and to 2 in 60 days when vaccination strategy is implemented. In Figure 5.1 (c), both vaccination, insecticide spraying and use of a repellent controls begin and stay at the upper bound of 100% before dropping to zero in 56, 57 and 58 days, respectively. In Figure 5.1, both controls can optimise the objective function (5.7). Thus, to determine the most optimal strategy we carry out the cost-effectiveness analysis.

5.3.2 Cost-Effectiveness Analysis in an Isolated Patch

To determine the most cost-effective control strategy, the Incremental Cost-Effectiveness Ratio (ICER) for each control strategy is calculated [81]. A strategy with the least ICER is the most cost-effective (optimal). The ICER formula is given by

$$ICER = \frac{\text{difference in intervention costs}}{\text{difference in the total number of infections averted}}. \tag{5.26}$$

The total number of infections averted is computed by estimating the difference between the total number of infection cases with and without control. The integrand of the objective function (5.7) gives the intervention costs. From the simulation results depicted in Figure 5.1 the strategies are ranked in order of increasing effectiveness in Table 5.1.

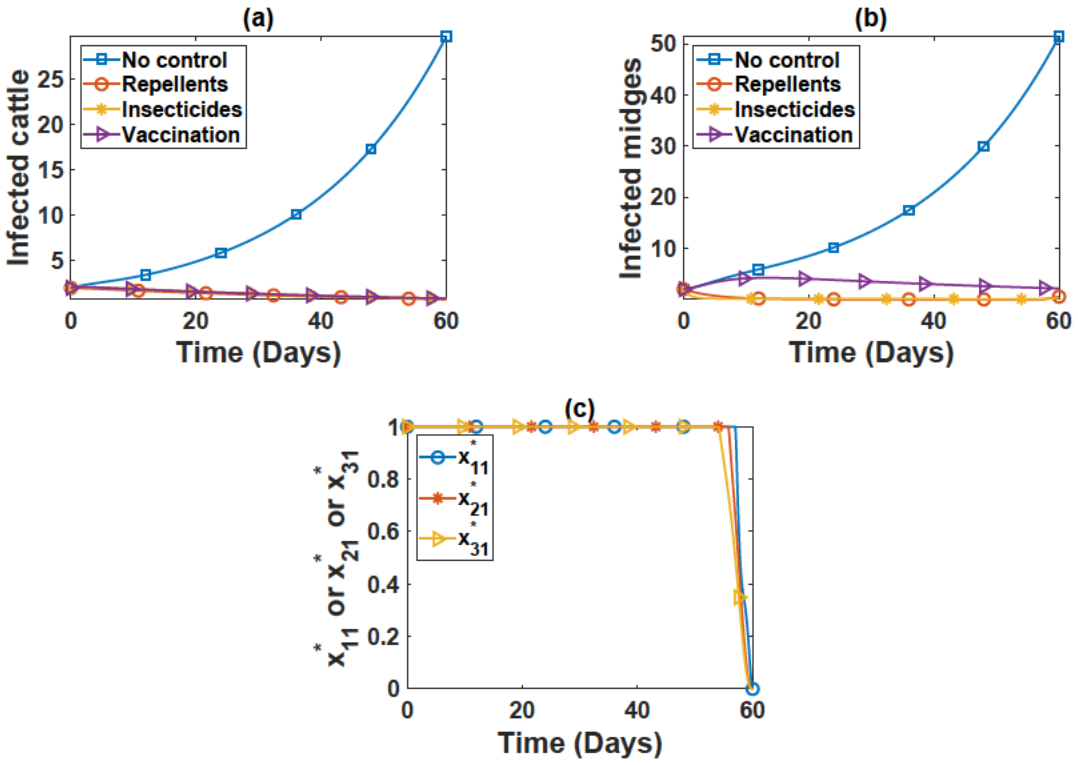


Figure 5.1: Effects of vaccination (x_{31}), insecticide spraying (x_{21}) or the use of a repellent (x_{11}) on infected hosts (a) and infected midges (b) in an isolated patch. The control profiles are illustrated in (c). The parameter values used are in Table 4.3 with the movement parameters set to zero. The weighting factors and the initial conditions are as stated in the text.

Table 5.1: Incremental cost-effectiveness ratios for an isolated patch.

Control strategy	Total infections averted	Total cost	ICER
Vaccination (V)	4440.0	28.5472	0.0064
Insecticide spraying (I)	4440.4	28.7969	0.6243
Use of a repellent (R)	4505.8	29.0266	0.0035

Table 5.2: Incremental cost-effectiveness ratios for an isolated patch after excluding insecticide spraying strategy.

Control strategy	Total infections averted	Total cost	ICER
Vaccination (V)	4440.4	28.5472	0.0064
Use of a repellent (R)	4505.8	29.0266	0.0073

In Table 5.1, the ratios are computed as below.

$$\begin{aligned} ICER(V) &= \frac{28.5472}{4440.0}, \\ ICER(I) &= \frac{28.7969 - 28.5472}{4440.4 - 4440.0}, \\ ICER(R) &= \frac{29.0266 - 28.7969}{4505.8 - 4440.4}. \end{aligned}$$

From Table 5.1, insecticide spraying strategy has the greatest ICER. Therefore, it is excluded from the set of control alternatives. The ratios for the other two strategies are recalculated and given in Table 5.2. From Table 5.2, vaccination strategy has the least ICER and thus most cost-effective as compared to the use of a repellent strategy.

5.3.3 Effects of Using Repellents in Connected Patches

The repellent control strategy (x_{1i}) applied in a low or high-risk patch is used to optimise the objective function (5.7). The results of this strategy are illustrated in Figure 5.2. In Figures 5.2 (a)-(d), with the control in the high-risk patch, the numbers of infected hosts and midges decrease to zero in both patches. When the control is applied in the low-risk patch, the numbers of infected populations significantly reduce in both patches, but do not drop to zero. In Figure 5.2 (e), the control in the high-risk patch is at the upper bound of 100% for 174 days before dropping gradually to the lower bound of 0% on the 180th day. When applied in the low-risk patch, the control starts and stays at the upper bound of 100% throughout the intervention period.

5.3.4 Effects of Insecticide Spraying in Connected Patches

With this strategy, the control on insecticide spraying (x_{2i}) is used to minimise the objective function (5.7), while the other controls are set to zero. The effects of this strategy in low and high-risk patches are given in Figure (5.3).

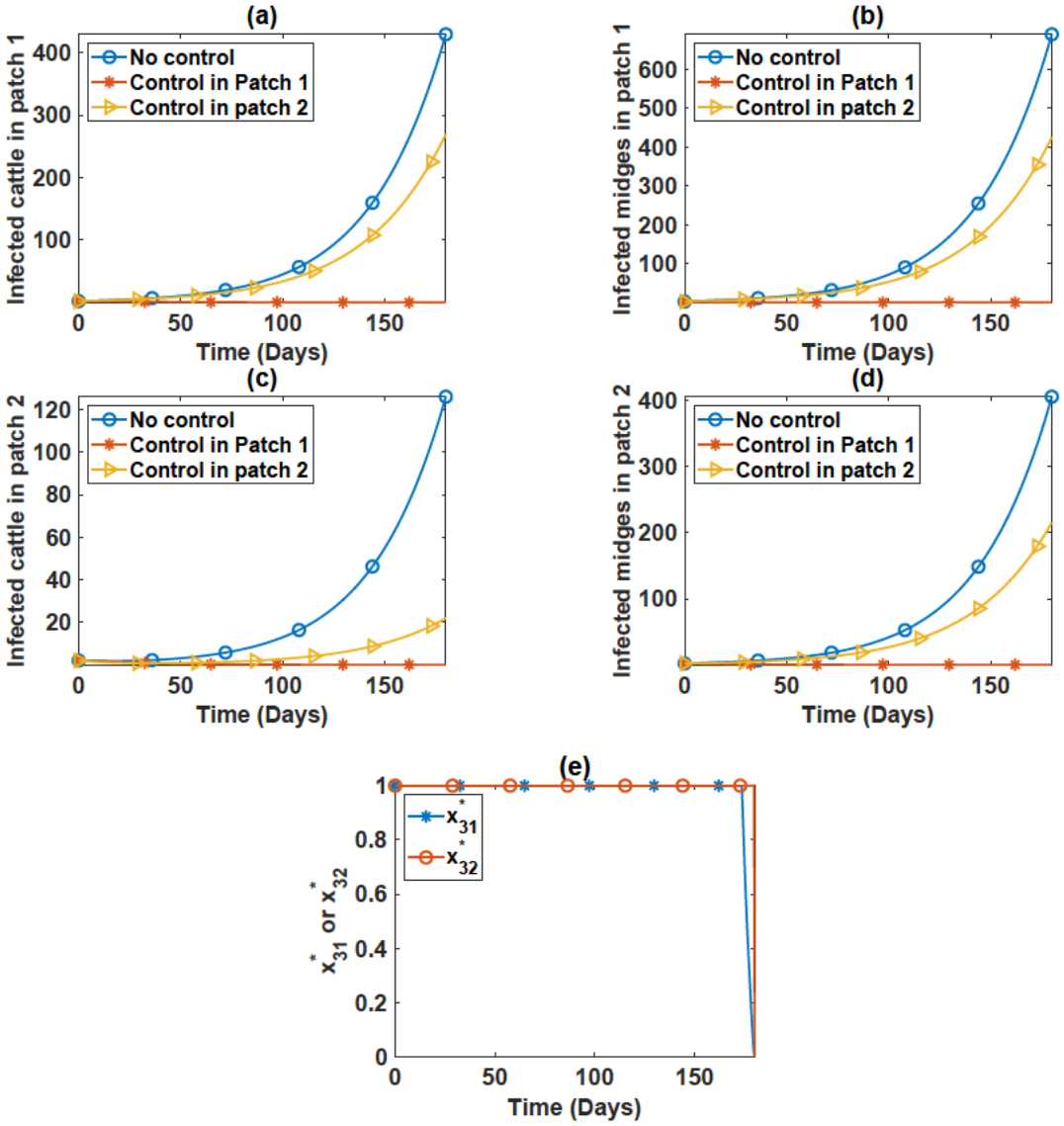


Figure 5.2: Effects of using a repellent on infected cattle and midges, respectively, illustrated in (a) and (b) for patch 1 and in (c) and (d) for patch 2. The patch control profiles are presented in (e). The parameter values used are in Table 4.3 with $c_{12} = c_{21} = 0.01$ and $m_{12} = m_{21} = 0.1$. The weighting factors and the initial conditions are as stated in the text.

If the strategy of insecticide spraying is applied in the low-risk patch, the number of infected cattle and midges in the high-risk patch drops from 430 to 10 and from 691 to 11, respectively over 180 days (Figures 5.3 (a) and (b)). Whereas in the low-risk patch, the number of cattle drops from 127 to 10 over 180 days and midges from 406 to 2 over 5 days (Figures 5.3 (c) and (d)).

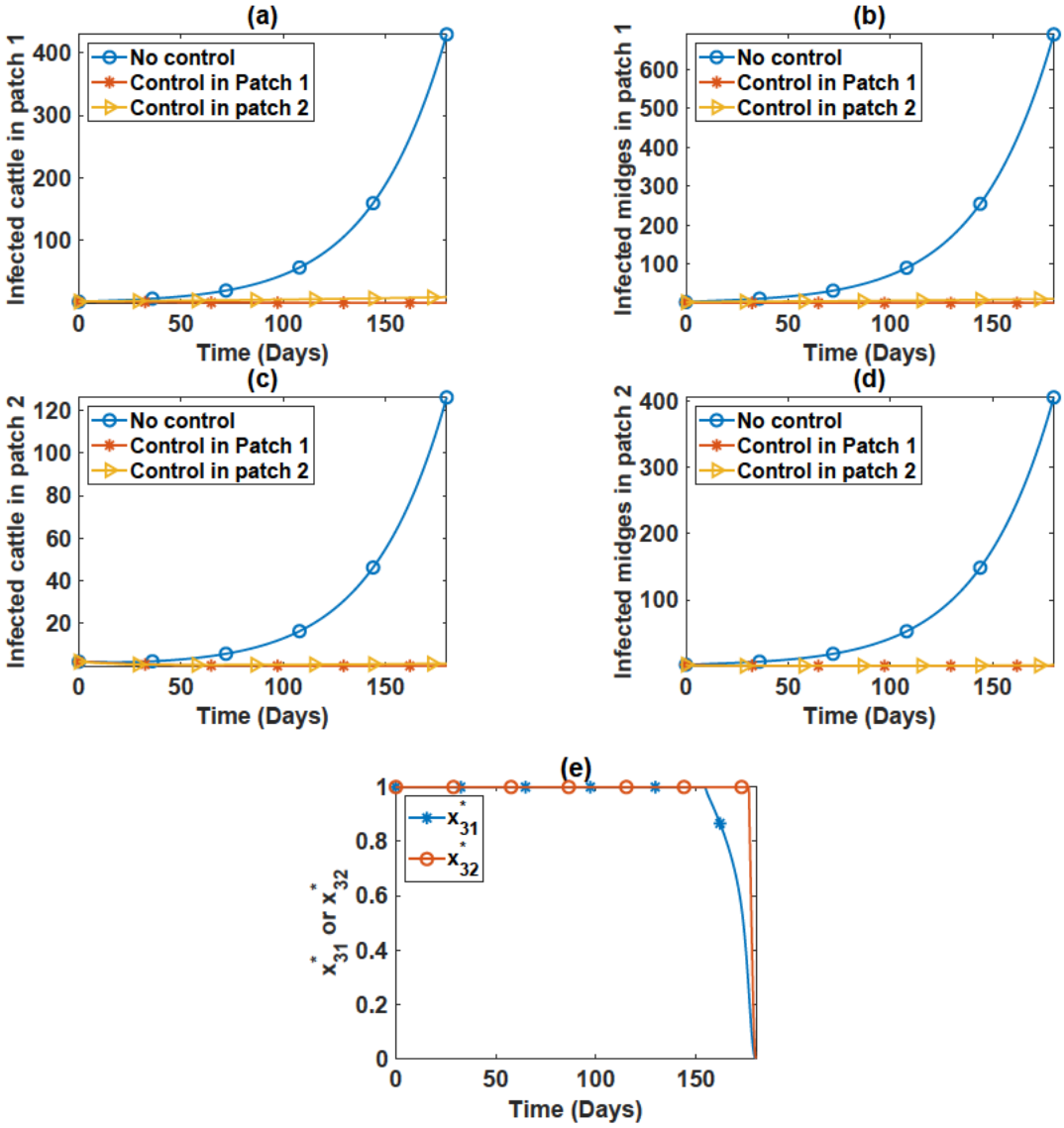


Figure 5.3: Effects of insecticide spraying on infected hosts and midges, respectively, illustrated in (a) and (b) for patch 1 and in (c) and (d) for patch 2. The patch control profiles are presented in (e). The parameter values used are in Table 4.3 with $c_{12} = c_{21} = 0.01$ and $m_{12} = m_{21} = 0.1$. The weighting factors and the initial conditions are as stated in the text.

If applied in the high-risk patch, the number of infected hosts and midges, respectively, reduce from 430 to zero over 38 days and from 691 to zero over 35 days in the high-risk patch (Figures 5.3 (a) and (b)). In the low-risk patch (Figures 5.3 (c) and (d)), infected hosts decrease from 127 to zero over 57 days and midges from 406 to zero over 18 days. The control in both patches starts and stays at the upper bound of 100% before dropping to the

lower bound of 0% on the 155th and 177th day in the high and low-risk patch, respectively (Figure 5.3 (e)).

5.3.5 Effects of Vaccination in Connected Patches

With this strategy, only a vaccination control (x_{3i}) is used to optimise the objective function (5.7). All other controls are set to zero. The results of this strategy are depicted in Figure 5.4. From Figures 5.4 (a)-(d), without vaccination the disease approaches an endemic equilibrium point in both patches. With vaccination in the high-risk patch, the trajectories of infected hosts and midges in both patches approach a disease-free equilibrium point. If applied in the low-risk patch, the numbers of infected hosts and midges significantly reduce in both patches, but a disease-free status is not attained in any patch. In Figure 5.4 (e), the control starts and is maintained at the upper bound of 100% before dropping to the lower bound of 0% in 159 and 174 days if applied in high and low-risk patches, respectively.

5.3.6 Effects of Quarantine in Connected Patches

To study the effects of quarantine (x_{4i}), the following cases are considered:

(i) The patches are connected by host and midge movement.

(ii) The patches are connected by only host movement.

For case **(i)**, the effects of quarantine on the control of BTV incidence in patchy environments are shown in Figure 5.5. In Figures 5.5 (a)-(d), when quarantine is imposed in the high-risk patch its effects on the spread of the disease are insignificant in both patches. If applied in the low-risk patch, there is a small effect on the transmission of BTV in all patches.

For case **(ii)**, the effects of quarantine on the spread of BTV between patches are depicted in Figure 5.6. From Figures 5.6 (a)-(d), in a situation of no midge movement, a case for patches which are very far from each other, quarantine imposed in the high-risk patch has no effect on the spread of BTV between patches. If applied in the low-risk patch, the benefits of quarantine in the low-risk patch are high and very low in the high-risk patch.

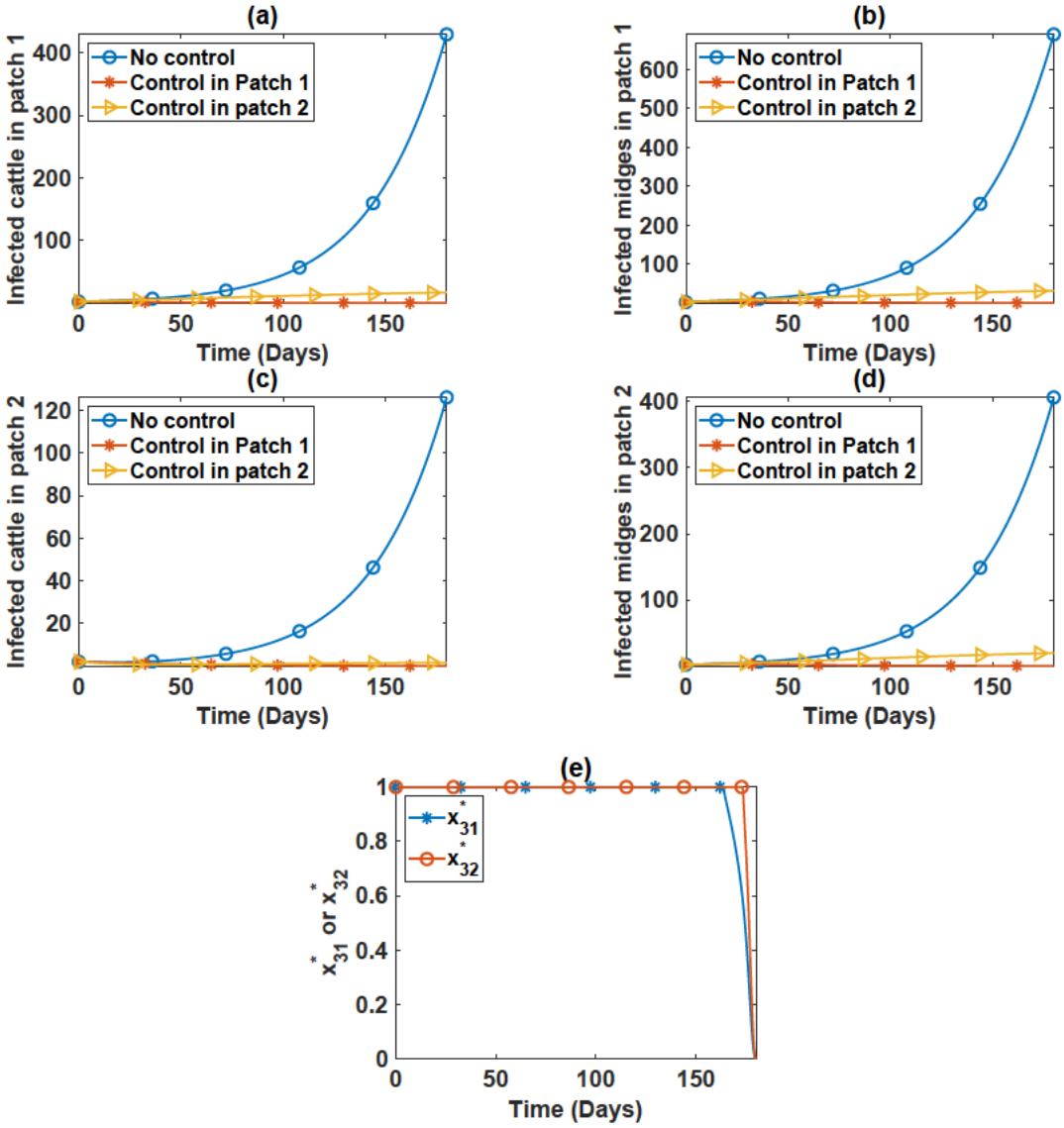


Figure 5.4: Effects of vaccination on infected hosts and midges, respectively, illustrated in (a) and (b) for patch 1 and in (c) and (d) for patch 2. The patch control profiles are presented in (e). The parameter values used are in Table 4.3 with $c_{12} = c_{21} = 0.01$ and $m_{12} = m_{21} = 0.1$. The weighting factors and the initial conditions are as stated in the text.

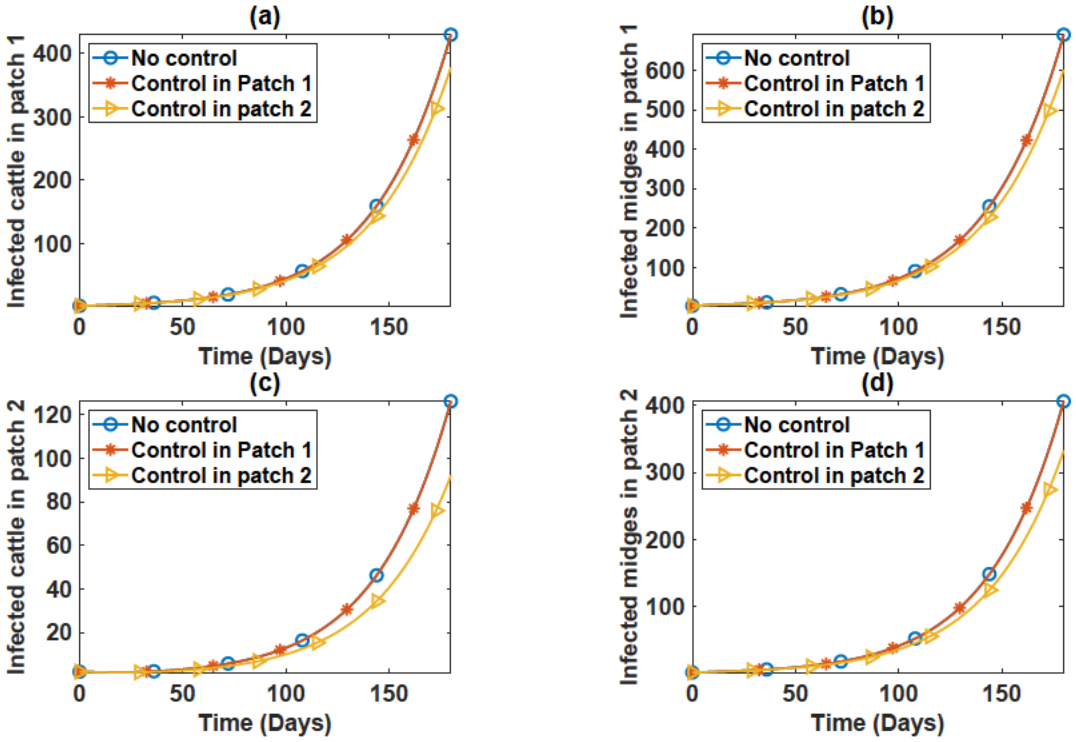


Figure 5.5: Effects of quarantine on infected hosts and midges, respectively, illustrated in (a) and (b) for patch 1 and in (c) and (d) for patch 2. The parameter values used are in Table 4.3 with $c_{12} = c_{21} = 0.01$ and $m_{12} = m_{21} = 0.1$. The weighting factors and the initial conditions are as stated in the text.

5.3.7 Cost-Effectiveness Analysis in Connected Patches

To carry out the cost-effectiveness analysis in connected patches, the following cases are considered:

(i) Controls applied in the high-risk patch.

(ii) Controls applied in the low-risk patch.

The quarantine strategy is not considered in the analysis since it has a little effect on the spread of the disease. Based on the results of Figures 5.2-5.4 and Equation (5.26), the ICERs for case **(i)** are given in Table 5.3.

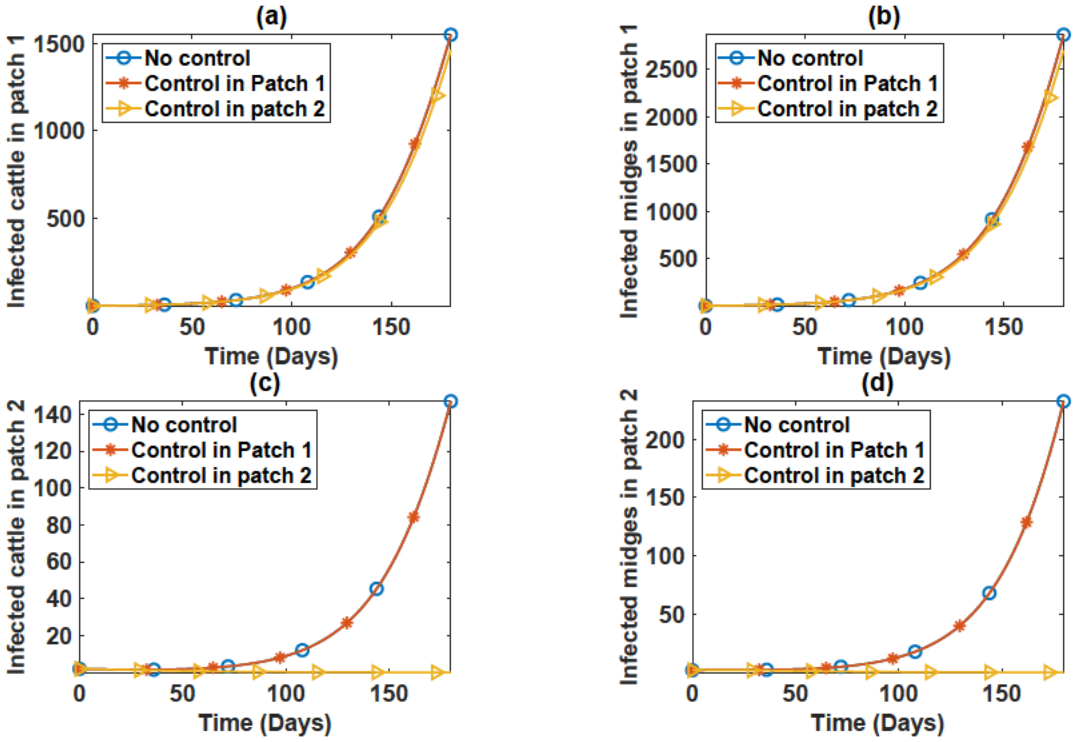


Figure 5.6: Effects of quarantine in the absence of midge movement on infected hosts and midges, respectively, illustrated in (a) and (b) for patch 1 and in (c) and (d) for patch 2. The parameter values used are in Table 4.3 with $c_{12} = c_{21} = 0.01$ and $m_{12} = m_{21} = 0$. The weighting factors and the initial conditions are as stated in the text.

Table 5.3: Incremental cost-effectiveness ratios for case **(i)**.

Control strategy	Total infections averted	Total cost	ICER
Vaccination (V)	54598	86.4187	0.0016
Use of a repellent (R)	54776	88.2862	0.01049
Insecticide spraying (I)	54784	85.8910	-0.2994

From Table 5.3, the use of a repellent strategy is excluded from the set of control alternatives due to its high ICER as compared to the rest. The ratios are recalculated for vaccination and insecticide spraying strategies and the results are given in Table 5.4.

Table 5.4: Incremental cost-effectiveness ratios for case **(i)** excluding the use of a repellent strategy.

Control strategy	Total infections averted	Total cost	ICER
Vaccination (V)	54598	86.4187	0.0016
Insecticide spraying (I)	54784	85.8910	-0.0028

Table 5.5: Incremental cost-effectiveness ratios for case **(ii)**.

Control strategy	Total infections averted	Total cost	ICER
Use of a repellent (R)	23938	89.9100	0.0038
Vaccination (V)	49593	88.4292	-0.0001
Insecticide spraying (I)	52199	88.9607	0.0002

Table 5.6: Incremental cost-effectiveness ratios for case **(ii)** excluding the use of a repellent strategy.

Control strategy	Total infections averted	Total cost	ICER
Vaccination (V)	49593	88.4292	0.0018
Insecticide spraying (I)	52199	88.9607	0.0002

From Table 5.4, insecticide spraying strategy has the least ICER. For case **(ii)**, using the results of Figures 5.2-5.4 and Equation (5.26), the ICERs are given in Table 5.5. From Table 5.5, the use of a repellent has the greatest ICER. The ratios for the other two strategies are recalculated and recorded in Table 5.6. From Table 5.6, insecticide spraying strategy has the least ICER.

5.4 Discussion

In this chapter, the optimal control strategies for bluetongue virus transmission in patchy environments are determined. Based on a single-serotype BTV transmission model analysed in Chapter 4, a multi-patch model (5.1) that incorporates host-based (vaccination and quarantine) and vector-based (insecticide spraying and the use of a repellent) control measures is formulated. A strategy is optimal if it minimises the number of infected hosts and the cost

of control. Thus, a minimisation problem (5.8) of the model (5.1) is derived. Using Pontryagin's Maximum Principle, the analytical and numerical results of the minimisation problem (5.8) are obtained. For numerical results, isolated (single) and connected (low and high-risk) patches are considered.

In an isolated patch, it is possible to attain disease-free status when vaccination, insecticide spraying or a repellent strategy is used. To achieve this status, 100% coverage and efficacy are required for 56, 57 or 58 days if vaccination, insecticide spraying or the use of a repellent strategy is applied, respectively. For vaccination, the results are in line with a study by Charron et al. [29] where it was shown that a perfect vaccine (with 100% efficacy) is necessary to ensure no BTV outbreaks in a population, otherwise the virus cannot be eliminated. The results for insecticide spraying strategy are consistent with a study by Okosun et al. [81] where it was shown that 100% effort is required for 57 days to eliminate malaria from the human population. From the results of the cost-effectiveness analysis, vaccination is the most cost-effective strategy followed by the use of a repellent. These results imply that if resources are available any of these control measures can be used in isolated communities to control internal BTV outbreaks, but if the resources are limited, a vaccination strategy is recommended.

In patches connected by host and/or midge movement, if vaccination, insecticide spraying or the use of a repellent strategy is applied in the high-risk patch, a disease-free status is achieved in both patches. However, if any of these strategies is implemented in the low-risk patch the numbers of infected hosts and midges are reduced in both patches, but a disease-free status is not obtained in any patch. From the results of the cost-effectiveness analysis, insecticide spraying is the most cost-effective strategy followed by vaccination regardless of the patch of implementation. Thus, in communities linked by migration, vaccinating animals, killing midges or the use of a repellent in a community with a high risk of infection is enough to control BTV outbreaks in both communities. On the other hand, controlling in a region with a low risk of infection is not enough to stop the spread of the virus in a high-risk region. Therefore, insecticide spraying or any strategy that targets the life expectancy of adult midges in a high-risk patch is the most recommended strategy for reducing BTV transmission in patchy environments.

In a situation of host and midge movement, quarantine imposed in the high-risk patch has no effect in both patches. If imposed in the low-risk patch a small effect is observed in the

low-risk patch and a very small effect in the associated high-risk patch. Without midge movement, a case for patches very far away from each other, quarantine applied to the high-risk patch has insignificant effects in both patches, but if implemented in the low-risk patch, the effects are small in the high-risk patch and large in the low-risk patch. This indicates that if the introduction of the virus in a low-risk patch is by host movement, internally imposed quarantine can be crucial in controlling the outbreaks, but if the virus has already spread into the community with high numbers of internal infections then quarantine is not necessary. Also, for vector-borne diseases, quarantine may not be a good strategy for controlling outbreaks especially when the vectors can move (actively or passively) from one place to another. For directly transmitted diseases such as foot and mouth disease, this strategy can be effective in controlling outbreaks in low-risk areas [101].

Chapter 6
Conclusions and Recommendations

6.1 Conclusions

6.1.1 On the Effects of Transplacental and Direct Transmission on the Probability of BTV Persistence

Single-serotype deterministic and CTMC models for a single-patch were formulated to study the effects of transplacental and direct transmission on the probability of BTV persistence in temperate and tropical regions. For the deterministic model, persistence and its control depend on the initial conditions. For a CTMC model, both transplacental and direct transmission can have a large positive effect on the probability of BTV persistence in temperate regions. The effect is exacerbated if initial conditions are larger, and it is highest when both mechanisms are present at the beginning of the epidemic. This increased probability of BTV persistence can be averted by decreasing direct transmission, the proportion of transplacental transmission and the host recruitment rates while increasing the recovery rate. In tropical regions, the routes under consideration have a small effect on the probability of BTV persistence and the dynamics of the disease are mainly governed by vectorial transmission. In vectorial transmission, the probability of persistence is larger if the disease emerges from an infectious host as opposed to an infectious midge and as such the control measures suggested in this thesis are likely to be more effective if they are focused on the host.

6.1.2 On the Effects of Wind-Aided Midge Movement on the Outbreak and Coexistence of Multiple BTV Serotypes

Multi-serotype ODE and CTMC models for patchy environments connected by cattle or midge movement were formulated and analysed to determine the effects of midge movement, demographic and midge-movement variability on the outbreak and coexistence of multiple BTV serotypes. It was shown that without movement a major outbreak occurs in the high-risk patch, but with infected cattle or midge movement it occurs in both patches. With susceptible

cattle or midge movement, it occurs only in the high-risk patch. When a major outbreak occurs, numerical simulations of the ODE model illustrate possible coexistence in both patches if the patches are connected by infected midge or cattle movement. Results of the CTMC model show that this coexistence can be maintained for a long period of time ($t \geq 2000$ days) when demographic and midge-movement variability are considered. Sensitivity analysis, based on the Latin hypercube sampling method, identified midge mortality and biting rates as being the most important parameters in determining the magnitude of the probability of a major outbreak and as such the control measures suggested in this study are likely to be more effective if they are focused on these parameters.

6.1.3 On the Control Measures for BTV Transmission in Patchy Environments

A single-serotype deterministic model for patchy environments was used to study the effectiveness of four time-dependent control parameters, vaccination, quarantine, insecticide spraying and the use of a repellent, in reducing the within-patches and between-patches BTV transmissions. In a single patch, vaccination, insecticide spraying and the use of a repellent are all highly effective in reducing transmission, but the most cost-effective is vaccination. In patches connected by host and midge movements, these control strategies are more effective in minimising between-patches transmission if applied in a high-risk than in a low-risk patch and the most cost-effective strategy is insecticide spraying. With host and midge movement, quarantine has no effect, but for no midge movement, the effect can be large in a low-risk patch if it is internally imposed. Although cattle and midges as hosts and vectors for BTV were considered in this thesis, the models and techniques used could be applicable to other susceptible hosts and vectors, and related viruses such as Akabane, African horse sickness and Schmallenberg.

6.2 Recommendations

Based on the findings of this study, the following recommendations are made:

(i) The control measures for BTV depend on the initial conditions and are likely to be more effective if the disease originates in small populations. Thus, for better results the control measures against the disease should be applied in the early stages of an epidemic.

(ii) Transplacental and/or direct transmission have a low probability of BTV extinction ($\mathbb{P}_0 < 0.5$) in periods of low midge activity. Therefore, care should be taken when moving pregnant animals from BTV-infected into BTV-free regions.

(iii) The exposed and the infectious hosts result in similar probabilities of BTV extinction. Thus, all susceptible animals from BTV-infected areas should always be screened at the border points regardless of their physical health appearance to avoid movement of exposed animals into BTV-free areas.

(iv) In endemic areas, the probability of BTV extinction is low ($\mathbb{P}_0 = 0.3070$) if the disease emerges from an infectious host and high ($\mathbb{P}_0 = 0.6729$) if it emerges from an infectious midge. Hence, for better results the control efforts should be focused on the hosts more than on the midges.

(v) For periods of low midge activity, control measures against BTV incidence should be focused on reducing direct transmission (β), the proportion of transplacental transmission (ϕ) and host recruitment rates (Λ and b) and on increasing the recovery rate (γ). For periods of high midge activity, control measures should be focused on reducing the midge biting rate (a), recruitment rate (π) and the probability of transmission from host to midge (q) and on increasing the midge mortality rate (μ_m) and the recovery rate (γ).

(vi) Vaccination and insecticide spraying are the most cost-effective strategies in isolated and connected patches, respectively, and these are recommended for reducing internal and between-patches transmission of BTV.

(vii) For better management of outbreaks and coexistence of multiple BTV serotypes in communities linked by cattle and/or midge movements, control measures targeting the midge mortality and biting rates should be applied at a community with the high risk of infection.

6.3 Future Work

There are still many interesting areas of investigation for both the deterministic and CTMC models formulated in this study. A few possible areas of study follow.

(i) For temperate regions, our work does not include the persistence (overwintering) of any possible BTV serotypes that are not vertically or directly transmitted. Other mecha-

nisms could also play a role on the overwintering of the virus and their determination remains an open problem.

(ii) Due to lack of data, the optimal control weighting factors and some parameters (see Tables 3.3 and 4.2) were estimated. Thus, further studies, especially experimental ones, that can determine more accurate estimates can improve model predictions for BTV persistence, coexistence and control. To improve the parameter estimation process and model predictions, identifiability analysis of the model parameters can also be carried out.

(iii) The analytical results for the global stability of the endemic equilibrium point of model (4.1) requires further work.

(iv) For the CTMC models in chapters 3 and 4, the asymptotic properties such as the expected duration and the final size of an epidemic could be determined.

(v) For the control model (5.1), it is assumed that there is a single serotype, but multiple serotypes with different vaccine immunities can coexist in nature [30]. Thus, a control model with multiple serotypes can be explored.

(vi) In Chapter 5, quarantine is considered as only a restriction of animal movement from one patch to another, but other forms of movement restrictions such as isolation of infected hosts can be investigated.

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Appendix A
The Center Manifold Theorem

The following theorem is based on a study by Castillo-Chavez and Song [28]. It is used to prove the existence of backward bifurcation of the model (3.1) when $\mathscr{R}_0 < 1$.

Theorem A.1. *Consider the following general system of ordinary differential equations with a parameter ϕ:*

$$\frac{dx}{dt} = f(x,\phi), \;\; f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n, \;\; \textit{and} \;\; f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{A.1}$$

where 0 is an equilibrium point of the system (that is, $f(0,\phi) \equiv 0$ for all ϕ) and assume

B1: $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0) \right)$ *is the linearisation matrix of the system* (A.1) *around the equilibrium* 0 *with ϕ evaluated at* 0*. Zero is a simple eigenvalue of A and all other eigenvalues of A have negative real parts;*

B2: *Matrix A has a non-negative right eigenvector m and a left eigenvector n each corresponding to the zero eigenvalue.*

Let f_k be the k^{th} component of f and

$$\begin{aligned} a &= \sum_{k,i,j=1}^{5} n_k m_i m_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}, \\ b &= \sum_{k,i=1}^{5} n_k m_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \phi^*}. \end{aligned}$$

The local dynamics of the system around 0 *are totally determined by a and b.*

(i) *$a > 0, b > 0$. When $\phi < 0$ with $\mid \phi \mid \ll 1, 0$ is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1, 0$ is unstable and there exists a negative and locally asymptotically stable equilibrium;*

(ii) *$a < 0, b < 0$. When $\phi < 0$ with $\mid \phi \mid \ll 1, 0$ is unstable, when $0 < \phi \ll 1, 0$ is locally asymptotically stable, and there exists a positive unstable equilibrium;*

(iii) $a > 0, b < 0$. *When* $\phi < 0$ *with* $\mid \phi \mid \ll 1, 0$ *is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1, 0$ *is stable, and a positive unstable equilibrium appears;*

(iv) $a < 0, b > 0$. *When* ϕ *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ *and* $b > 0$*, then a backward bifurcation occurs at* $\phi = 0$.

Appendix B
Probability Distributions for Two BTV Serotypes in Two Patches

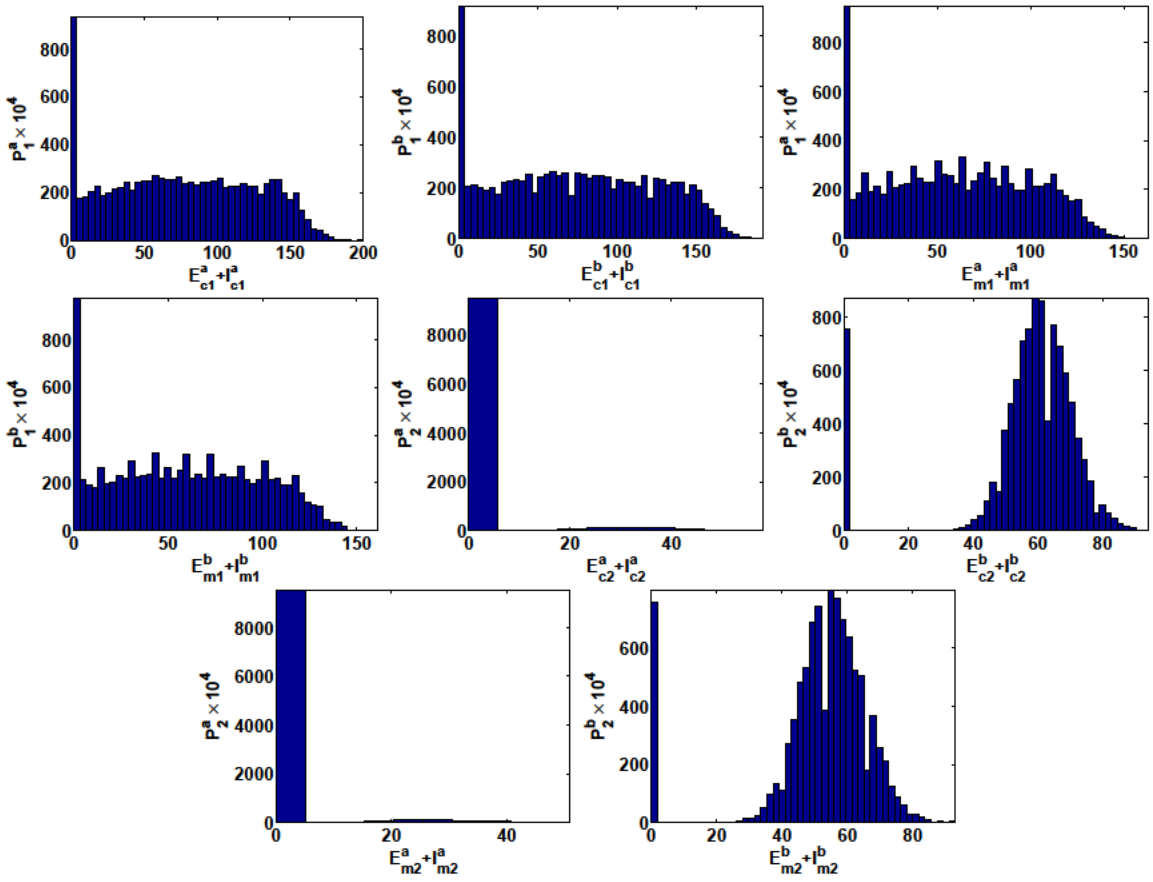

Figure B.1: Approximate probability distributions for serotypes *a* and *b* in two patches for the CTMC model at t=2000 days with no cattle and/or midge movement (case (i) in Table 4.3) indicating coexistence in the high-risk patch and competitive exclusion in the low-risk patch. Parameter values and initial conditions are the same as in Figure 4.1. Computations are based on 10,000 sample paths.

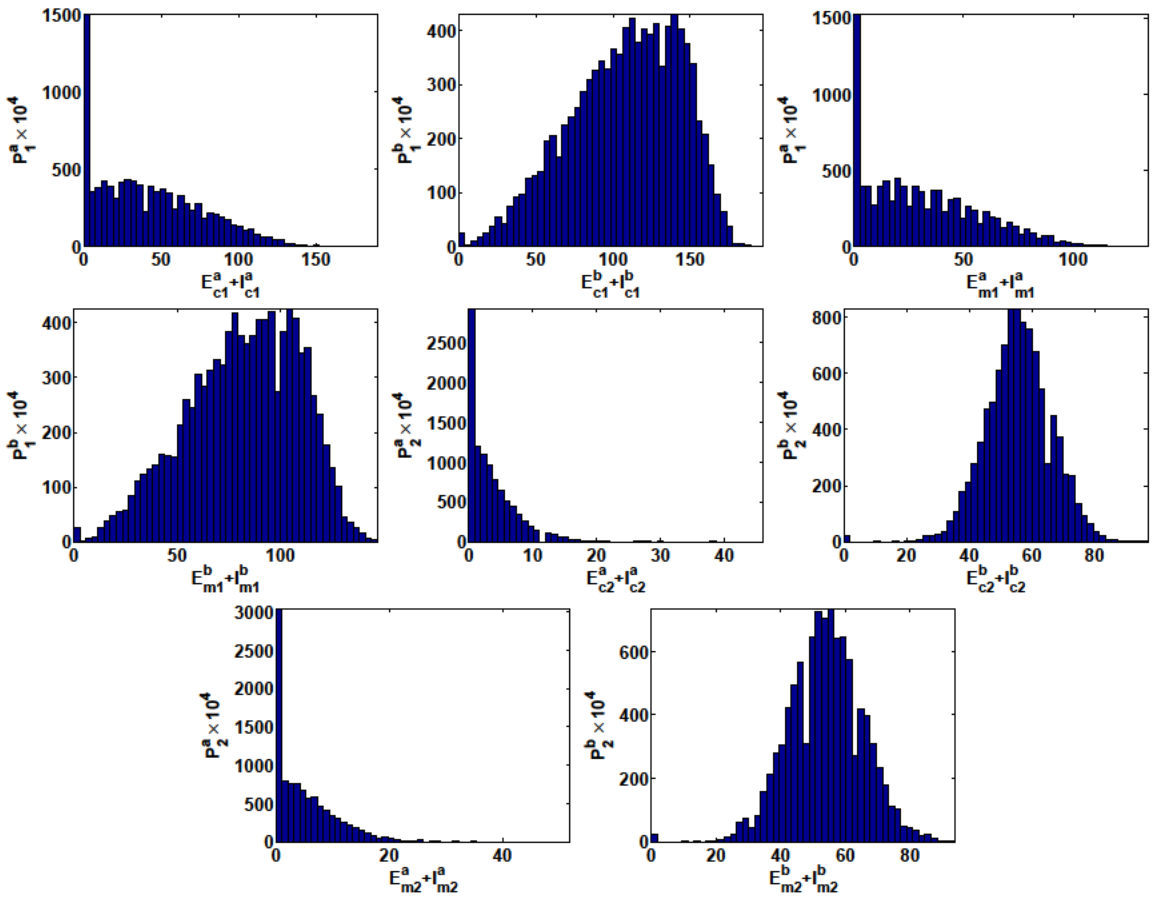

Figure B.2: Approximate probability distributions for serotypes a and b in two patches for the CTMC model at t=2000 days with equal midge movement and no cattle movement (case (ii) in Table 4.3) indicating coexistence in both patches. Parameter values and initial conditions are the same as in Figure 4.1, except for $m_{12} = m_{21} = 0.002$. Computations are based on 10,000 sample paths.

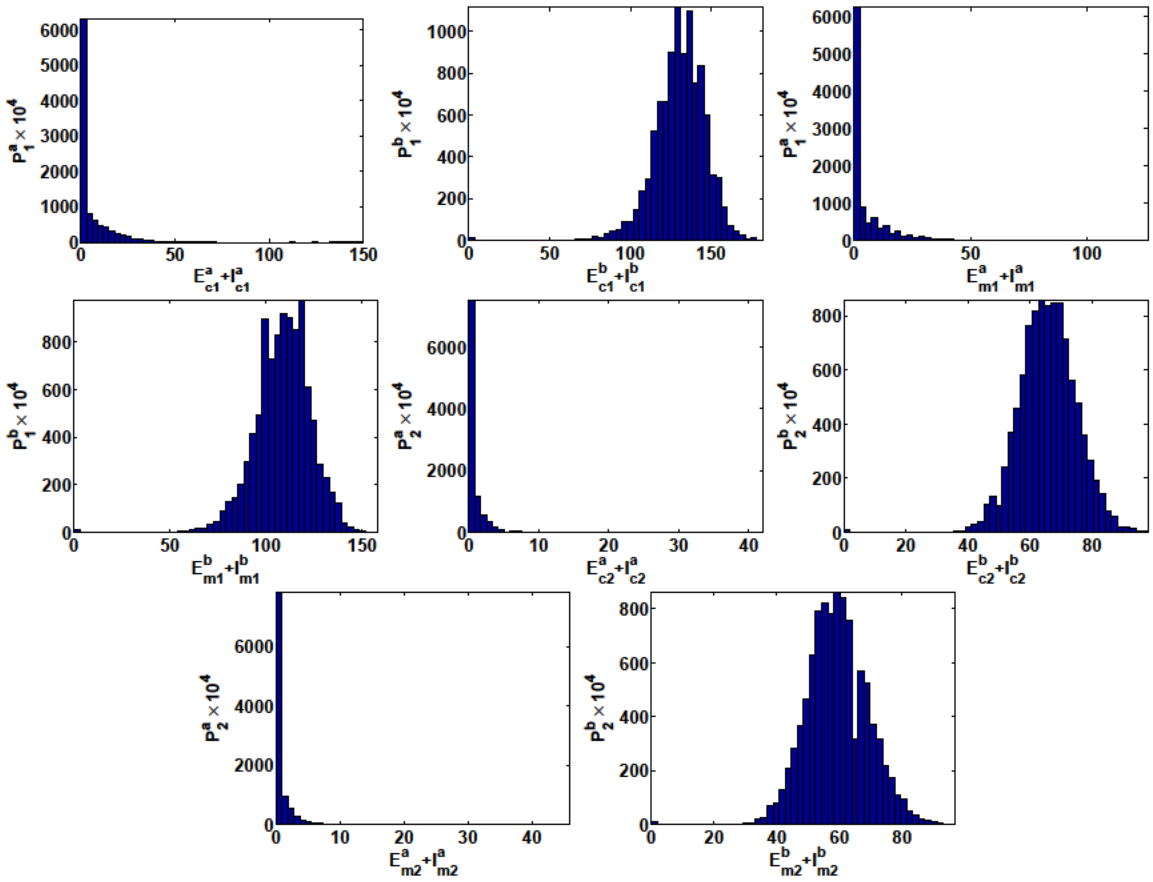

Figure B.3: Approximate probability distributions for serotypes a and b in two patches for the CTMC model at t=2000 days with equal cattle movement and no midge movement (case (ii) in Table 4.4) indicating competitive exclusion in both patches. Parameter values and initial conditions are the same as in Figure 4.1, except for $c_{12} = c_{21} = 0.002$. Computations are based on 10,000 sample paths.