Optimal Control Strategies in Epidemic Models: Analysis of Community and Traveler Isolation Strategies Under Resource Constraints

by

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Abstract

In some regions, health authorities may implement an elimination strategy involving public health measures that apply to travelers and community members to control infectious disease spread. Optimal control theory consists of mathematical results that apply to epidemiological models and describe control strategies that maximize or minimize an epidemiologically-relevant quantity given constraints. The previous work of Hansen and Day (2011) has characterized optimal controls involving community isolation and vaccination with the objective of minimizing outbreak size. We build on this previous work by considering epidemiological dynamics involving infection importation, traveler isolation as a control measure, and by characterizing the optimal controls in the terminology of public health. We discuss a related theorem from Hansen and Day (2011) in the context of our extensions of their modelling. We numerically implement control measures and characterize the resulting epidemiology and resource use as an elimination, mitigation, or circuit breaker strategy. We find that which public health strategy the implemented control is characterized as depends on parameter values that can be interpreted as corresponding to regional conditions. When resources are not limited, the implemented strategy corresponds to: an elimination strategy, when the maximum daily isolation rate is high and the importation rate is low; and a mitigation strategy, when the maximum daily isolation rate is low and the importation rate is high. When resources are limited, the implemented strategy corresponds to a circuit breaker strategy. No previous studies have provided a general framework whereby elimination, mitigation, or circuit breaker strategies can arise as solutions to optimal control problems for different epidemiological and resource use-related parameters, and such results show that different infectious disease control strategies can be optimal in different regions.

I dedicate this thesis to my family for their constant support and whose inspiration and vision continue to guide me.

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SIR	Susceptible-Infected-Recovered
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
PMP	Pontryagin's Maximum Principle
ODEs	Ordinary Differential Equations
IVP	Initial-Value Problem
SARS	Severe Acute Respiratory Syndrome

Chapter 1

Introduction

Optimal control theory is a mathematical framework for determining the application of control measures to a dynamical system to achieve the best possible outcome. It is an effective tool for decision-making in complex biological situations [47]. Optimal control theory has been applied to epidemiology to identify the best strategies to control and mitigate infectious diseases [1, 3, 10, 24, 32, 42, 47, 50, 57]. To the best of our knowledge, optimal control theory has yet to be applied to problems involving infection importation, where infection importation refers to infected travelers that arrive at a destination from another region.

The arrival of an infected traveler into a susceptible destination population can trigger the onset of a local outbreak if the local conditions (population density, public health infrastructure, etc.) favour the spread of the disease [38]. Various approaches to modelling importation have been developed [12, 67, 6, 46, 31, 9, 4]. Some previous work has found that imported infections are likely to contribute little to local epidemics [64, 36, 30, 5, 15, 72]. As part of the control measures available to public health authorities, some specifically aim to reduce the risk of importations, i.e., travel restrictions or bans, self-isolation upon arrival and so forth. Since the effect of these measures varies, it is important to understand the importation process to evaluate the relative effectiveness of control measures that aim to reduce the importation rate [4].

Our analysis bridges the mathematical framework of optimal control theory with terminology used in public health to describe different types of infectious disease control strategies. Elimination is a strategy which aims to bring the incidence of the disease down to zero [8, 55, 35, 74]. The elimination strategy, together with its challenges, has been studied in the context of vaccine-preventable diseases such as measles and polio [25, 7, 56, 21]. Mitigation strategies aim to slow the spread of an infectious disease to avoid overwhelming healthcare capacities [41, 74]. Research has demonstrated the usefulness of mitigation strategies during flu pandemics, highlighting the role of targeted measures such as antiviral distribution, prioritization of high-risk groups, and public health communications [54]. A circuit breaker strategy involves the implementation of public health measures for a fixed, short period to reduce community transmission of a disease [44, 11] with intermittent breaks from public health measures to minimize the adverse impacts associated with extended restrictions [16]. The theoretical underpinnings of a circuit breaker strategy can be found in studies of disease dynamics, which highlight the non-linear benefits of temporarily halting transmission [43]. During the COVID-19 pandemic, short-term lockdowns implemented in numerous countries, including the United Kingdom, demonstrated that circuit breakers could effectively reduce transmission rates and provide a crucial respite for drained healthcare systems [17].

Significant progress has been made by proposing mathematical models, which offer valuable information for decision-making in global health [32, 71, 75, 70, 76, 14, 61, 2, 65, 69]. One common aim when modelling resource constraints is to describe how changes in intervention measures will affect the characteristics of the infection dynamics and consequently affect disease control. Hansen and Day (2011) provided optimal control policies for an isolation-only model, a vaccination-only model and a combined isolation–vaccination model, with analytic solutions for the controls that minimize the infectious burden under the assumption that there are limited control resources [32]. Our research builds upon the framework and analysis developed by Hansen and Day [32].

In this thesis, we extend the framework of Hansen and Day [32] by considering an epidemic model with infection of community members due to importations. We aim to determine the optimal control when the control measures are: community isolation only; post-arrival isolation of infected travelers only; and the combination of both community isolation and post-arrival isolation of infected travelers. We characterize the optimal control as an elimination, mitigation, or circuit breaker strategy, and quantify the outbreak size and duration for the optimal controls corresponding to each strategy. Our work explores infectious disease control strategies using optimal control theory to consider resource limitations and minimize the number of cases in an outbreak. We answer the question of "when" and "how" control measures can be implemented within resource constraints.

Chapter 2

Basic fundamental properties of ODEs and the PMP

This chapter considers the theoretical foundations for understanding and applying differential equations and optimal control theory to infectious disease modelling [67]. We establish the existence of solutions for a particular type of optimization problem. This problem involves an objective function, which is an integral of variables that are described by a system of ordinary differential equations ODEs (see Section 2.2, equations (2.5)-(2.6)). To establish the existence of the optimal control(s), we first establish the existence and uniqueness of solutions to ODEs, with a particular focus on Gronwall's Inequality Theorem. This theorem ensures that the mathematical models we employ in Chapter 3 are well-defined. We describe the Pontryagin Maximum Principle (PMP), a cornerstone of optimal control theory, and a theorem which is applied in Chapter 3. Finally, we examine the existence of optimal controls. In this section, the Fillipov Existence Theorem is presented to describe the conditions under which optimal solutions exist.

A reason for using ODEs for our modelling is their ability to capture the continuous change in population compartments, which correspond to the disease states and other variables [18]. This is achieved through rate equations that combine various processes, including transmission rates, recovery rates, and death rates. The resulting systems of ODEs can be studied analytically and numerically to determine disease trajectories and evaluate the potential impact of health policies [34].

The mathematical properties of the existence and uniqueness of solutions ensure that, for a given set of initial conditions and parameters, there is a well-defined and unique trajectory that the model will follow [19, 63]. With the notion of admissibility of control functions, we set a framework that ensures the system's responses remain within feasible bounds [47]. Verifying the solutions' existence and uniqueness, which we will consider in the upcoming section, is a step that ensures the model's predictive consistency and application to infectious disease modelling [58].

We state some essential characteristics of the solutions to ordinary differential equations, including existence, uniqueness, continuous dependence on initial conditions, and continuous dependence on parameters. Consider the nonlinear dynamical control system

$$\dot{x}(t) = f(t, x(t), u(t)); \quad x(t_0) = x_0, \tag{2.1}$$

where $x(t) = (x_1(t), \cdots, x_n(t)) \in \mathbb{R}^n, u(t) = (u_1(t), \cdots, u_m(t)) \in \mathbb{R}^m$. For the mathematical model to predict the system's future state from its current state, the Initial-Value Problem (IVP) (2.1) must have a unique solution. A trajectory of the system (2.1) corresponding to a control $u(t)$ is a continuous curve $x(t)$ solving equation (2.1) for almost all t, which means that the differential equation (2.1) is satisfied for all (t) in a given set, ensuring that the property holds throughout the entire interval of interest, except for finitely many points (an insignificant subset). We also refer to $x(t) \in \mathbb{R}^n$ as the state. An admissible control $u(t)$ will be a piecewise-continuous vector-valued function such that $u : [0, T] \to K$ for some compact K. We address the question of existence and uniqueness in the next section.

2.1 Existence and uniqueness of solutions to ODEs

The first goal of this section is to establish the local existence and uniqueness of solutions. Thus, we are interested in solutions to the differential equations (2.1) that appear to take a more general form. Let $\mathbb{I} \subset \mathbb{R}^n$ an interval of time, $U \subset \mathbb{R}^n$ and $\Theta \subset \mathbb{R}^m$ be open sets and let $f : \mathbb{I} \times U \times \Theta \to \mathbb{R}^n$ be a continuous function. We focus on solutions to the initial value problem

$$\dot{x} = f(t, x, \theta), \quad x(t_0) = x_0, \tag{2.2}$$

that is, the existence of a solution $x : \mathbb{I} \to U$ such that $t_0 \in \mathbb{I}$, $\theta \in \Theta$ and $x(t_0) = x_0$.

It is known from the theory of ordinary differential equations [33, 63] that under certain regularity assumptions (i.e. $f(t, x, \theta)$ satisfies a global Lipschitz condition), a (nonlinear) differential equation (2.2) has a unique solution passing through x_0 at $t = t_0$.

Definition 2.1.1. *Consider metric spaces (X, d_X) and (Y, d_Y). A function $f : X \to Y$ is Lipschitz if there exists a real constant $K \geq 0$ such that, for all $x_1, x_2 \in X$*

$$d_Y(f(x_1), f(x_2) \leq K d_X(x_1, x_2)$$

The smallest K satisfying this inequality is denoted by $Lip(f) := K$ and is called the

Lipschitz constant of f.

The corresponding existence and uniqueness theorem is as follows. The proofs can be found in [37, 51, 66].

Theorem 2.1.2. *Let $\mathbb{I} \subset \mathbb{R}$, $U \subset \mathbb{R}^n$ and $\Theta \subset \mathbb{R}^m$ be open sets, and assume $f : \mathbb{I} \times U \times \Theta \to \mathbb{R}^n$ is a Lipschitz function. If $(t_0, x_0, \theta_0) \in \mathbb{I} \times U \times \Theta$, then there exists an open neighbourhood of the form $\mathbb{I}_0 \times U_0 \times \Theta_0$ of (t_0, x_0, θ_0) and a Lipschitz continuous function $\varphi : \mathbb{I}_0 \times U_0 \times \Theta_0 \to \mathbb{R}^n$ such that for every $(t, x, \theta) \in \mathbb{I}_0 \times U_0 \times \Theta_0$*

$$\varphi(t_0, x_0, \theta_0) : \mathbb{I}_0 \to \mathbb{R}^n$$

is a solution to the initial value problem

$$\dot{x} = f(t, x, \theta_0), \quad x(t_0) = x_0. \tag{2.3}$$

Furthermore, if $\psi(., t_0, x_0, \theta_0)$ is another solution to the initial value problem (2.3), then $\psi(t) = \varphi(t)$ on the intersection of their domains of definition.

By solving the relevant differential equation (2.3), we can use Gronwall's inequality (Theorem 2.1.3) to constrain a function known to satisfy integral inequalities [29] by bounding the difference between two solutions and demonstrating this difference is zero under the same initial conditions (i.e. the two solutions converge from the same initial condition and remain identical). Gronwall's inequality offers a comparison theorem, which can be utilized to demonstrate the uniqueness of a solution to the initial value problem (2.3).

Theorem 2.1.3. ***(Gronwall's Inequality)*** *Let $\alpha, \beta : (a, b) \to [0, \infty)$ be continuous* *functions. Assume*

$$\alpha(t) \leq C + \left| \int_{t_0}^{t} \alpha(s)\beta(s)ds \right|, \quad t_0, t \in (a, b)$$

for some constant $C \geq 0$*. Then,*

$$\alpha(t) \leq C \exp\left(\left| \int_{t_0}^{t} \beta(s)ds \right| \right)$$

Applying Gronwall's inequality to our initial value problem (2.3), with $\alpha(t) := \|\varphi(., x_0) - \psi(., y_0)\|$, $C = \|x_0 - y_0\|$ and $\beta(t) = K$, we obtain the proposition below.

Proposition 2.1.4. *Let* $U \subset \mathbb{R}^n$ *be an open set and assume* $f : U \to \mathbb{R}^n$ *is a Lipschitz continuous function with* $Lip(f) = K$*. If* $\varphi(., x_0) : \mathbb{I}_{x_0} \to \mathbb{R}^n$ *and* $\psi(., y_0) : \mathbb{I}_{y_0} \to \mathbb{R}^n$ *are solutions to the initial value problem* (2.3) *with* $x(t_0) = x_0$ *and* $x(t_0) = y_0$*, respectively, then*

$$\|\varphi(t, x_0, \theta_0) - \psi(t, y_0, \theta_0)\| \leq \|x_0 - y_0\| e^{K|t-t_0|} \tag{2.4}$$

for all $t \in \mathbb{I}_{x_0} \cap \mathbb{I}_{y_0}$*.*

Remark 2.1.5. *Proposition 2.1.4 guarantees the existence and uniqueness of solutions. To show that two solutions to the same initial value problem* (2.3) *agree on the intersection of their domains of definition, we let* $\varphi : \mathbb{I}_0 \to \mathbb{R}^n$ *and* $\psi : \mathbb{I}_1 \to \mathbb{R}^n$ *denote two solutions to the initial value problem* (2.3)*. Given that* $x(t_0) = x_0 = y_0$*, from equation* (2.4) *for all* $t \in \mathbb{I}_0 \cap \mathbb{I}_1$*,*

$$\|\varphi(t) - \psi(t)\| = 0,$$

which establishes the uniqueness of the solution to the initial value problem (2.3)*.*

2.2 Pontryagin Maximum Principle (PMP)

An optimal control problem for ordinary differential equations consists of finding a control $u(t)$ and the associated state variable $x(t)$ to maximize the given objective functional below [20]:

$$J := \int_{t_0}^{T} L(t, x(t), u(t))\, dt \tag{2.5}$$

$$\text{subject to } \; \dot{x} = f(t, x(t), u(t)), \quad x(t_0) = x_0. \tag{2.6}$$

where equation (2.6) models the system dynamics, and the term $L(t, x(t), u(t))$ is referred to as the integral cost. The function $L(t, x(t), u(t))$ is assumed to be non-negative and continuous in all arguments for $t \in [t_0, T]$ [48]. To solve the optimal control problem (2.5)-(2.6), we define the Hamiltonian as

$$H(t, x(t), u(t), \lambda(t)) = \lambda_0 L(t, x(t), u(t)) + \lambda(t) f(t, x(t), u(t)) \tag{2.7}$$

where $\lambda(t)$ is the adjoint variable and λ_0 a constant.

Remark 2.2.1. $\lambda_0 = -1$ *if* $u(t)$ *is feasible and the objective functional* (2.5) *is to be minimized.* $\lambda_0 = +1$ *if* $u(t)$ *is feasible and the objective functional* (2.5) *is to be maximized.* $\lambda_0 = 0$ *if* $u(t)$ *is unfeasible.*

The set of admissible controls is given by

$$\begin{aligned} U_{ad} = \{ & u = (u_1, u_2, \cdots, u_m) \text{ such that } (u_1, u_2, \cdots, u_m) \text{ measurable}; (u_1(t), u_2(t), \cdots), \\ & u_m(t) \in [0, n], \text{where } n \in \mathbb{R}\} \end{aligned} \tag{2.8}$$

being a compact convex subset of $\mathbb{R}^m$ and the controls are bounded and Lebesgue measurable [48]. Thus, all possible sets u must be contained in the set of admissible controls U_{ad}.

Further, let $u_1, u_2 \in U_{ad}$, then it follows that

$$bu_1 + (1-b)u_2 \in [0, \infty)$$

for all $b \in [0,1]$. Consequently $bu_1 + (1-b)u_2 \in U_{ad}$, implying the convexity of U_{ad}.

The Pontryagin Maximum Principle provides necessary conditions that an optimal control (2.5) and corresponding state trajectory (2.6) must satisfy [59, 68].

The Pontryagin Maximum Principle is widely used to analyze and solve optimal control problems, where the goal is to find the best control strategy for the optimal control problem defined in Chapter 3 [59].

Theorem 2.2.2. *(PMP) If $u^*(t)$ and $x^*(t)$ are the optimal solution of the control problem, then there exist piecewise differentiable adjoint variables $\lambda(t)$ such that*

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)) \tag{2.9}$$

for all controls u at each time t, where H is the Hamiltonian and

$$\dot{\lambda}(t) = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \tag{2.10}$$

$$\lambda(T) = 0 \tag{2.11}$$

are the costate and transversality conditions, respectively.

We focus on the application of the PMP theorem, excluding detailed proof. We refer to [3, 59] for the proof.

Definition 2.2.3. *A triple* (x^*, u^*, λ) *is called extremal if* (x^*, u^*) *is admissible and the equations* $\dot{x} = H_\lambda$ *and* $\dot{\lambda} = -H_x$ *hold along* (x^*, u^*).

Theorem 2.2.4. *Suppose that* $f(t, x, u)$ *is a continuously differentiable function in its three arguments and concave in* u. *Suppose* u^* *is an optimal control with associated state* x^*, *and* λ *a piecewise differentiable function with* $\lambda(t) \geq 0 \ \forall \ t$. *Suppose for all* $t_0 \leq t \leq T$

$$0 = H_u(t, x^*(t), u^*(t), \lambda(t)) \ \ (\textit{optimality condition}). \tag{2.12}$$

Then for all controls u *and each* $t_0 \leq t \leq T$, *we have*

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)). \tag{2.13}$$

The same essential conditions are derived through similar reasoning when the problem involves minimizing rather than maximizing. In a minimization problem, we minimize the Hamiltonian pointwise and the inequality in equation (2.2.4) is reversed [47]. Indeed, for a minimization problem with f being convex in u, we can derive

$$H(t, x^*(t), u(t), \lambda(t)) \geq H(t, x^*(t), u^*(t), \lambda(t)) \tag{2.14}$$

by the same argument as in Theorem 2.2.4.

2.2.1 Existence of optimal controls

The PMP only provides necessary conditions for optimality (2.9)-(2.12), and the fulfilment of these conditions alone does not guarantee optimality [45]. For an optimal control to exist, we want to have compactness of feasible solution sets [13]. We provide a result stating the existence of at least one optimal solution to the optimal control problem (2.5)-(2.6) under some appropriate compactness and convexity assumptions. Precisely, we follow the standard Filippov's approach [24]. Filippov's existence theorem is a result of the theory of differential inclusions; which are generalizations of ordinary differential equations that allow for multiple possible trajectories at a single point in the state space. Filippov's existence theorem addresses the existence of solutions for differential inclusions [23, 24].

Theorem 2.2.5. ***(Filippov's existence theorem)*** *Consider an optimal control problem defined by a differential inclusion $\dot{x} \in f(t, x, u)$, where $f : [t_0, T] \times \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ is a set-valued mapping representing the dynamics, t is time, x is the state variable and u is the control input. Assume that the set-valued map f is upper semi-continuous in x and continuous in u for each fixed t. If the optimal control problem has nonempty, compact, and convex solution sets for all t, then an optimal control exists for almost every initial point in $\mathbb{R}^n$.*

To establish the existence of the optimal control, we rely on findings presented in [26] and [62]. Initially, we address the boundedness of the state variables in the system (2.5)-(2.6). In other words, the state variables of the system should be bounded. The assurance of the existence of an optimal control solution is ensured by satisfying the following conditions:

(a) The set of control variables and corresponding state variables are not empty.

(b) The admissible control set U_{ad} is compact and bounded.

(c) The vector function $f(t, x, u)$ is continuous.

Chapter 3

Mathematical Model

Our modelling builds on that of Hansen and Day [32]. They considered an optimal control problem involving the spread of an infectious disease, where public health officials can isolate a fixed number of infected individuals. The aim of the optimal control problem is to minimize the number of infections in the outbreak. In Hansen and Day's formulation, the outbreak is defined as over when infection prevalence decreases to below a small value.

One of the situations that they considered is where the only public health measure available is to isolate infected individuals. For this problem (isolation only), they proved that the optimal control depends on whether isolation resources are sufficient to last until the outbreak is over or not (see Theorem 1 in [32]). In the case when resources are sufficient, it was showed that the optimal control is to isolate infected individuals at the maximum rate until the end of the outbreak. In the case when resources are limiting, the optimal control is to use all available resources, and to isolate infected individuals at the maximum rate, or not at all; but that the timing of the implementation of the control measures does not matter as long as all of the isolation resources are used [32].

Our work builds on Hansen and Day, but only in so much as to motivate extensions of the modelling framework (Problems 2-4 in this Chapter), and to numerically study and interpret the results of the models in this Chapter in terms of public health terminology (Chapter 4). In this Chapter, we discuss four problems. Problem 1 is identical to the isolation only scenario that is presented in [32], and we describe some components of the proof of the nature of the optimal control as part of our discussion of Problem 1. Problems 2-4 are extensions of the modelling framework from Hansen and Day, and in addition to developing these models, we also describe the likely features of the structure of the optimal controls for these problems, based on the proof from the reference, and based on numerical exploration concerning the structure of the optimal control.

The extension that we consider is to formulate an epidemiological model that includes imported infections as a process that can produce infections in community members and to consider post-arrival travel measures as a control. The isolation only scenario from Hansen and Day is a special case of this more general model that we developed. The motivation for this extension modelling is due to the importance of understanding when travel measures are appropriate to control infectious disease outbreaks.

3.1 Problem description and assumptions

The model that we consider is,

$$\frac{dS}{dt} = -\beta S(I_1 + cI_2), \tag{3.1}$$

$$\frac{dI_1}{dt} = \beta S(I_1 + cI_2) - (\mu + u_1(t))I_1, \tag{3.2}$$

$$\frac{dI_2}{dt} = \theta - (\gamma + u_2(t))I_2, \tag{3.3}$$

with $S(0) > 0, I_1(0) > I_{\min}$ (see Section 3.2 for an explanation), $I_2(0) \geq 0,\ \beta, \mu, \theta, \gamma, c > 0$ where S is the number of susceptible community members. The extension from Hansen and Day is to partition infections as infection prevalence in community members, I_1, and infection prevalence in travelers, I_2. The force of infection term considers that susceptible community members are either infected by community members at rate β (per infected community member) or at rate $c\beta$ (per infected traveler), where c is a constant that measures the relative transmissibility of infected travelers as compared to infected community members. The rate that infected travelers arrive in the community is $\theta > 0$, and the rate that travelers become uninfectious, relative to their arrival date at the community is γ. We consider post-arrival travel measures that isolate infectious travelers from the community at a rate $u_2(t)$. The rate that infected travelers become uninfectious is γ, with γ greater than μ, because community members were in the community from their first day of infectiousness, while travelers may have spent some time away from the community, while infectious before arriving, or they may leave before their infectious period is over. The rate at which infectious community members are isolated is $u_1(t)$.

There are several different ways that importations might be included in an epidemic model. Our formulation assumes that travelers are a source of infection for susceptible members of the community, but does not explicitly consider the origin of the infected travelers or any infectious disease dynamics at the origin. Further, our formulation assumes that the community members themselves do not become travelers. This model formulation was chosen because we can examine the risk of infection from a non-community source without adding so much model complexity to the dynamics of the number of susceptible community members that the optimal control analysis becomes not possible. Further, we do not consider births and background mortality of community members. Vaccination, as a control variable, was considered in the analysis of Hansen and Day [32]; in this present work, vaccination is not considered.

3.2 Defining an outbreak end point

Hansen and Day [32] observed that after a control measure successfully lowers infection prevalence to a very low level, releasing that control might lead to a second wave of infection. This resurgence could be triggered by just a small fraction of individuals and is not biologically plausible. This second wave of infection, which can be caused by a 'nano-individual' [27], is an artifact of the ordinary differential equation model formulation which necessarily describes infection prevalence as a continuous variable. A discrete state model formulation, such as a branching process model, would not have this limitation, however, optimal control for problems described as branching processes are substantially more challenging to analyze [52]. We recognize the need to prevent artificial waves of infection for our problem of interest as such waves could lead to the incorrect conclusion that elimination is not the optimal strategy [53]. This is necessary because we consider elimination strategies in Chapter 4.

To avoid this artificial second wave of infection, we use the approach of Hansen and Day and define an outbreak as over at $t = T$ if infection prevalence is less than some small value. Specifically, T is the smallest t such that $I_1(t) \leq I_{\min}$ where $I_{\min} \leq 1$, so as to prevent artificial second waves attributable to a fraction of an individual, and $I_1(0)$ needs to be chosen as bigger than $I_{\min}$.

3.3 Resource constraints (Optimal control problem)

The control variables in equations (3.1)-(3.3) are $u_1(t)$ and $u_2(t)$, which are the daily isolation rates per infected community member and per infected traveler, and $(u_1(t), u_2(t)) \in [0, u_{1\max}] \times [0, u_{2\max}]$, where 0 corresponds to no control and $u_{1\max}$ and $u_{2\max}$ corresponds to the maximum daily rate of community member isolation and traveler isolation, respectively.

Let

$$U_{1[u_1,u_2]}(T) = \int_0^T u_1(t) I_{1[u_1,u_2]}\, dt, \tag{3.4}$$

and

$$U_{2[u_1,u_2]}(T) = \int_0^T u_2(t) I_{2[u_1,u_2]}\, dt, \tag{3.5}$$

denote the total number of community residents and travelers that have been isolated up until time T respectively, where the square brackets represent the dependence of this quantity on the controls, $u_1(t)$ and $u_2(t)$. This dependence occurs directly due to the total resources used, and indirectly as the controls being implemented impact infection prevalence. A quantity that appears in our subsequent analysis is $U_{1[u_{1\max},u_{2\max}]}(T)$ which is the total number of community members that are isolated if the isolation rate for community members and travelers is maximal for all time until the outbreak ends, and where $U_{2[u_{1\max},u_{2\max}]}(T)$ is defined similarly.

The control problem is constrained as $U_{1\max}$ and $U_{2\max}$ are defined as the total resources available for community isolation and traveler isolation, respectively. Examples of such resources are funding to pay the staff employed in testing, tracing, and isolating infected community members, as well as the resources, such as testing facilities to complete these activities; and funding to pay the staff involved in developing, implementing, and enforcing post-arrival travel measures, as well as the necessary resources, such as isolation facilities or testing equipment to complete these activities.

In keeping with [32], we assume that these resources are limited, such that,

$$U_{1[u_1,u_2]}(T) \leq U_{1\max}, \tag{3.6}$$

and

$$U_{2[u_1,u_2]}(T) \leq U_{2\max}. \tag{3.7}$$

The aim of public health measures is to minimize the number of infections in the outbreak,

$$J = \int_0^T \beta S_{[u_1,u_2]}(I_{1[u_1,u_2]} + cI_{2[u_1,u_2]})\ dt, \tag{3.8}$$

subject to the resource constraints (3.6)-(3.7).

To apply the PMP, we define the Hamiltonian as

$$H = \lambda_0 \beta S(I_1 + cI_2) + \lambda_{I_1}\frac{dI_1}{dt} + \lambda_{I_2}\frac{dI_2}{dt} + \lambda_{U_1}\frac{dU_1}{dt} + \lambda_{U_2}\frac{dU_2}{dt}. \tag{3.9}$$

3.4 Bang-bang optimal controls

Equations (3.1)-(3.8) are a linear optimization problem, which is a class of optimal control problems where the control function appears only linearly [28]. In these cases, optimal solutions often incorporate discontinuities in the control variables [47]. Notice that equations (3.1)-(3.3) and the integrand in (3.8) are both linear functions of the controls $u_1(t)$ and $u_2(t)$. Thus, the Hamiltonian (3.9) is also a linear function of the controls; hence, the optimality condition (2.12) contains no information on the controls [47]. The PMP (Section 2.2), when applied to bounded control problems that are linear in the control variable defines the bang-bang control.

Remark 3.4.1. *Hansen and Day [32] show that the optimal control for our model (i.e., see Problem 1 in Section 3.6) is bang-bang, where a bang-bang control is characterized by switching between two extreme values. Specifically, for our model* (3.1)-(3.8)*, the Hamiltonian is given as:*

$$H = \lambda_0 \beta S(I_1 + cI_2) - \lambda_S \beta S(I_1 + cI_2) + \lambda_{I_1}(\mu + u_1)I_1 + \lambda_{I_2}\theta - \lambda_{I_2}(\gamma + u_2)I_2 + \lambda_{U_1} u_1 I_1 + \lambda_{U_2} u_2 I_2. \tag{3.10}$$

From equation (2.12)*, the optimality conditions are:*

$$\frac{\partial H}{\partial u_1} = (\lambda_{U_1} - \lambda_{I_1})I_1 = 0 \tag{3.11}$$

$$\frac{\partial H}{\partial u_2} = (\lambda_{U_2} - \lambda_{I_2})I_2 = 0 \tag{3.12}$$

Let $\psi_1(t) = \lambda_{U_1}(t) - \lambda_{I_1}(t)$ and $\psi_2(t) = \lambda_{U_2}(t) - \lambda_{I_2}(t)$ where $\psi_1(t)$ and $\psi_2(t)$ are called the switching functions, and the controls $u_1(t)$ and $u_2(t)$ switches between the upper and lower bounds of the controls range (i.e. $(u_1(t), u_2(t)) \in [0, u_{1max}] \times [0, u_{2max}]$). The *times at which these switches occur are determined by the switching functions [47].*

We use the notation $\equiv$ to indicate that a function is equal to the same value for all time, $t \in [0, T]$. For example, $u_1^*(t) \equiv u_{1max}$ means that the optimal control is to isolate infected community members at the maximum rate for the entire outbreak.

Hence the controls are characterized as:

$$u_1^*(t) = \begin{cases} u_{1max}, & \textit{if } \lambda_{U_1}(t) < \lambda_{I_1}(t) \quad \textit{maximum rate of community isolation,} \\ 0, & \textit{if } \lambda_{U_1}(t) > \lambda_{I_1}(t) \quad \textit{no community isolation,} \end{cases} \tag{3.13}$$

and

$$u_2^*(t) = \begin{cases} u_{2max}, & \textit{if } \lambda_{U_2}(t) < \lambda_{I_2}(t) \quad \textit{maximum rate of traveler isolation,} \\ 0, & \textit{if } \lambda_{U_2}(t) > \lambda_{I_2}(t) \quad \textit{no traveler isolation.} \end{cases} \tag{3.14}$$

3.5 Problem classification

We classify our general problem (equations (3.1)-(3.8)) into the following four parts as described in Table 3.1.

Table 3.1: The four problems that we analyze

Problem	**Description**	**Special values of parameters**
1	Community member isolation only, no importations.	$I_2(0) = 0, \theta = 0$, and $U_{2\max} = 0$.
2	Community member isolation, with importations.	$U_{2\max} = 0$.
3	Post-traveler isolation measures only.	$U_{1\max} = 0$.
4	Both community member isolation and travel measures.	None.

3.6 Problem 1: Community Isolation Only (no case importation)

Considering community isolation as the only control, and with no importations, our model (3.1)-(3.3) with resource limitation now becomes,

$$\frac{dS}{dt} = -\beta S I_1, \tag{3.15}$$

$$\frac{dI_1}{dt} = \beta S I_1 - (\mu + u_1(t)) I_1, \tag{3.16}$$

$$U_{1[u_1]}(T) = \int_0^T u_1(t) I_{1[u_1]} \; dt \leq U_{1\max}. \tag{3.17}$$

Our objective function is,

$$J = \int_0^T \beta S_{[u_1]} I_{1[u_1]} \; dt, \tag{3.18}$$

subject to equations (3.15)-(3.17), $T = \inf\{t \mid I_{1[u_1]}(t) = I_{\min}\}, u_1(t) \in [0, u_{1\max}]$ for all $t \in [0, T]$.

Note that $S_{[u_1]} = S,\ I_{1[u_1]} = I_1$ are the number of susceptibles and community infections for a given $u_1(t)$ respectively, where the change in notation is to explicitly denote the dependence of these variables on the control being considered. This completes the statement of Hansen and Day's isolation only problem, which is equivalent to our Problem 1.

The main result of the community isolation only problem is stated in the theorem below.

Theorem 3.6.1. *[32]* ***(Optimal Community Isolation Strategy)*** *For Problem 1, if $U_{1[u_{1max}]}(T) \leq U_{1max}$, then the optimal community isolation strategy is $u_1^*(t) \equiv$*

u_{1max}. *If* $U_{1[u_{1max}]}(T) > U_{1max}$, *then the optimal control* $u_1^*(t)$ *is any bang-bang control such that* $U_{1[u_1^*]}(T) = U_{1max}$.

The optimal isolation policy, as outlined in Theorem 3.6.1, is to implement maximal isolation efforts throughout the epidemic, provided that sufficient resources are available. Without adequate resources, the optimal policy is any bang-bang control that utilizes all available resources.

When resources are allocated in a manner that the optimal policy leads to a reduction in infections (Theorem 3.6.1), the result is that a greater number of individuals remain susceptible, as demonstrated in the claim below.

Claim 3.6.2. *[32] Minimizing the total number of new infections,* J, *is equivalent to maximizing the number of susceptible individuals* $S(T)$ *at the end of the outbreak.*

***Proof* (Claim 3.6.2)**: From equation (3.15), we have

$$dS = -\beta S I_1 \, dt. \tag{3.19}$$

Integrating both sides of (3.19), we get

$$\int_0^T dS = -\int_0^T \beta S I_1 \, dt, \tag{3.20}$$

$$S(T) - S(0) = -\int_0^T \beta S I_1 \, dt, \tag{3.21}$$

$$S(0) - S(T) = \int_0^T \beta S I_1 \, dt. \tag{3.22}$$

Rearranging equation (3.15), we get

$$\frac{1}{S} \, dS = -\beta I_1 \, dt. \tag{3.23}$$

Taking the integral on both sides of (3.23), we have

$$\int_0^T \frac{1}{S}\, dS = -\beta \int_0^T I_1\, dt, \tag{3.24}$$

$$-\frac{1}{\beta}\ln\left(\frac{S(T)}{S(0)}\right) = \int_0^T I_1\, dt. \tag{3.25}$$

From equations (3.18) and (3.22), we get

$$S(0) - S(T) = J. \tag{3.26}$$

We observe that the terms on the right-hand side of equations (3.25) and (3.26) are both minimized by maximizing $S(T)$ since $S(0)$ is a fixed quantity.

Again, from equation (3.15), we can write $-\dot{S} = \beta S I_1$ and $I_1 = -\frac{\dot{S}}{\beta S}$. Substituting these two expressions into equation (3.16) gives

$$\dot{I}_1 = -\dot{S} + \frac{\mu}{\beta}\frac{\dot{S}}{S} - u_1 I_1. \tag{3.27}$$

Rearranging equation (3.27) and integrating from 0 to T, the total number of community members isolated during the outbreak for any $u_1(t)$ is,

$$U_{1[u_1]}(T) = \int_0^T u_1 I_{1[u_1]}\, dt = S(0) - S_{[u_1]}(T) + I_1(0) - I_{\min} + \frac{\mu}{\beta}\ln\left(\frac{S_{[u_1]}(T)}{S(0)}\right), \tag{3.28}$$

where we note that to satisfy the constraint $U_{1[u_1]}(T)$ must be less than or equal to $U_{1\max}$.

The objective function (3.18) can be rewritten as

$$\int_0^T \beta I_{1[u_1]} S_{[u_1]} \, dt = S(0) - S_{[u_1]}(T), \tag{3.29}$$

and, therefore, minimizing the objective function is equivalent to maximizing $S_{[u_1]}(T)$. This completes the proof of Claim 3.6.2 as proved in Hansen and Day [32].

Equation (3.28) is illustrated in Figure 3.1. For $S_{[u_1]}(T) > \mu/\beta$, resources are not limiting. When $S_{[u_1]}(T) < \mu/\beta$ resources are limiting ($U_{1[u_1]}(T) < U_{1[u_{1\max}]}(T)$), and then $U_{1[u_1]}(T)$ and $S_{[u_1]}(T)$ are positively related (equation (3.28); Figure 3.1), such that increasing $U_{1[u_1]}(T)$, increases $S_{[u_1]}(T)$. Therefore, any bang-bang control $u_1^*(t)$ that uses all available resources (see Remark 3.4.1), $U_{1[u_1]}(T) = U_{1\max}$, minimizes equation (3.29) (see the proof of Theorem 1 on page 432 of Hansen and Day [32]).

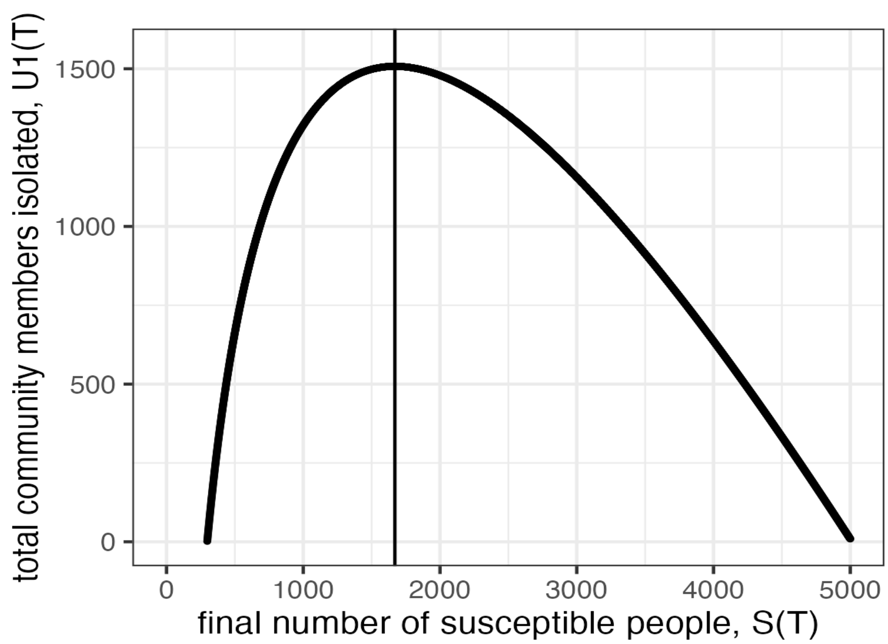

Figure 3.1: Equation (3.28) (black curve) describes the total community members isolated, $U_{1[u_1]}(T)$, as a function of the final number of susceptible people, $S_{[u_1]}(T)$. Resources are limiting when $S_{[u_1]}(T) < \mu/\beta$ (left of the vertical line at μ/β), and here $S_{[u_1]}(T)$ and $U_{1[u_1]}(T)$ are positively related such that any $u_1(t)$ that uses all the resources is optimal. See Table 3.2 for parameter values.

Table 3.2: Parameter values used for the figures in this chapter

Figure	**Parameter values**
Figure 3.1	$\beta = 0.0002$ person^{-1} day^{-1}, $\mu = 0.334$ day^{-1}, $S(0) = 5000$ people, $I_1(0) = 10$ people.
Figure 3.2	As for Figure 3.1 but with $u_{1\,\max} = 1$ day^{-1} and $\theta = 1$ people day^{-1}. No constraint is implemented. For the values of $c = 0.4, 0.5$ and 1, T is 466, 614, and 925 days.
Figure 3.3	$\theta = 2$ people day^{-1}, $U_{1\max} = 1500$ people, $I_{\min} = 1$ person, $I_2(0) = \frac{\theta}{\gamma + u_{2max}}$ people, and all other parameters are the same as Figure 3.1. For the successively increasing values of $c = 0, 0.05, 0.1, 0.2, 0.5,$ and 1, the outbreak ends at $T = 16, 36, 377, 717, 1044$ and 1057 days.
Figure 3.4	$c = 1$, (a-b): $\beta = 0.0002$ person^{-1} day^{-1}, $U_{2\max} = 50$ people, (c-d): $\beta = 0.00005$ person^{-1} day^{-1}, $U_{2\max} = 500$ people, and all other parameters and initial conditions are as Figure 3.1 and Figure 3.3. For the increasing values of $u_{2\max}$ that are shown in the upper panels ($u_{2\max} =$ 0, 0.5, 1, 2, and 5), the outbreak end times are $T = 42.8, 41.1, 40.7, 42.9$ and 43.4 days (a-b). For the increasing values of $u_{2\max}$ that are shown in the lower panels ($u_{2\max}$ = 0, 0.5, 1, 2, and 4.5) the outbreak end times are $T > 2000$ days for $u_{2\max} = 0, 0.5, 1$ and 3 day^{-1}, and $T = 284$ and 119 days for $u_{2\max} = 4.75$ and 5 day^{-1} (c-d).
Figure 3.5	$\theta = 1$ person day^{-1}, $u_{1\max} = 0.6$ $u_{2\max} = 1.3$ day^{-1}, $U_{1\max} =$ 500 , $U_{2\max} = 100$ people (a-c), $U_{1\max} = 2500$, $U_{2\max} = 200$ people, $u_{2\max} = 1.3$ day^{-1} (d-f).

3.7 Problem 2: Community isolation only (with imported infections)

For Problem 2, we assume that there are imported infections and the only control measure is community isolation. The epidemiological dynamics are

$$\frac{dS}{dt} = -\beta S(I_1 + cI_2), \tag{3.30}$$
$$\frac{dI_1}{dt} = \beta S(I_1 + cI_2) - (\mu + u_1(t))I_1, \tag{3.31}$$
$$\frac{dI_2}{dt} = \theta - \gamma I_2, \tag{3.32}$$
$$\frac{dU_1}{dt} = u_1(t)I_1. \tag{3.33}$$

Problem 2 still describes a linear optimization problem such that the control is bang-bang as described by Remark 3.4.1. For Problem 2, the problem is to find the $u_1(t)$ that minimizes the number of community members that are infected,

$$J = \int_0^T \beta S(I_1 + cI_2) \ dt, \tag{3.34}$$

where susceptible community members (S) can be infected by either an infectious community member (I_1) or an infectious traveler (I_2) and subject to the terminal condition $I_1(T) = I_{\min}$, and the constraint $U_1(T) \leq U_{1\max}$.

Remark 3.7.1. *As for Problem 1, for Problem 2 minimizing the total number of infected people is equivalent to maximizing the number of susceptible community members at the end of the outbreak.*

This is shown by integrating equation (3.30)

$$S(T) - S(0) = -\int_0^T \beta S(I_1 + cI_2)\, dt = -J. \tag{3.35}$$

Next, we observe that from equation (3.30), we can write $-\dot{S} = \beta S(I_1 + cI_2)$ and making I_1 the subject, we get $I_1 = -\frac{\dot{S}}{\beta S} - cI_2$. Substituting these two expressions into equation (3.31) gives,

$$\dot{I}_1 = -\dot{S} + \frac{\mu}{\beta}(1 + c\beta I_2) - u_1 I_1. \tag{3.36}$$

If we let $I_2(0) = \theta/\gamma$, then $I_2 \equiv \theta/\gamma$ is constant, rearranging equation (3.36) and integrating from 0 to T, we obtain the total number of isolated infected community members,

$$\begin{aligned} U_{1[u_1]}(T) &= \int_0^T u_1 I_{1[u_1]}\, dt, \\ &= S(0) - S_{[u_1]}(T) + I_1(0) - I_{\min} + \frac{\mu}{\beta} \ln\left(\frac{S_{[u_1]}(T)}{S(0)}\right) + \frac{\theta}{\gamma}\mu c T_{[u_1]}. \end{aligned} \tag{3.37}$$

Equation (3.37) is identical to (3.28) except for the $+\frac{\theta}{\gamma}\mu c T_{[u_1]}$ term, where $T_{[u_1]}$ is the duration of the outbreak and the subscript $[u_1]$ has been added to emphasize that this duration depends on the control, $u_1(t)$. This new term is positive, and so the impact of importations is to move the $U_{1[u_1]}(T)$ curve (as shown in Figure 3.2) upwards, although this upwards shift is not the same for all $S_{[u_1]}(T)$ due to the co-dependence of $S_{[u_1]}(T)$ and $T_{[u_1]}$ on the control strategy, $u_1(t)$. We do not know how this additional term affects the optimal control.

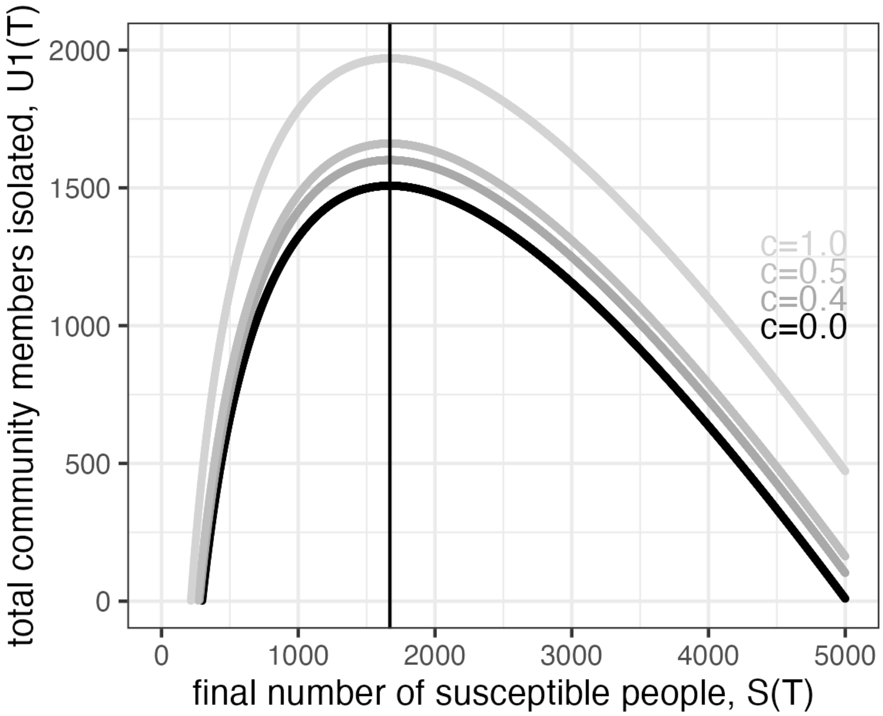

Figure 3.2: Equation (3.37) describes the total community members isolated, $U_{1[u_1]}(T)$, as a function of the final number of susceptible people, $S_{[u_1]}(T)$, for different c. The black lines are identical to Figure 3.1 and parameter values are provided in Table 3.2.

This concludes our analysis of Remark 3.7.1.

3.7.1 Numerical methods

In Figure 3.3, we present some numerical results that show the precautionary strategy and the resulting epidemiological dynamics. The precautionary strategy is,

$$u_1^{**}(t) = \begin{cases} u_{1\max}, & \text{if} \quad 0 \leq t \leq t_{1\max} \quad \text{and} \\ 0, & \text{if} \quad t > t_{1\max}, \end{cases} \tag{3.38}$$

which is to use all resources at the maximum rate until they are used up at $t = t_{1\max}$. For Theorem 3.6.1 (i.e., Theorem 1 in [32]), which applies to Problem 1, the precautionary principle is always optimal although it is not uniquely optimal when resources are limiting. Problems 1 and 2 are closely related, and identical when $c = 0$, so we numerically evaluate the epidemiological dynamics (Figure 3.3a) and resource use (Figure 3.3b) given that the precautionary strategy is implemented. When $c = 0$, we know that the precautionary strategy is an optimal control. We do not know this for $c > 0$, but we present the epidemiological dynamics and resource use to build our understanding of what the optimal control might be in this situation.

We produce numerical results by numerically integrating equations 3.30 to 3.33 using the R package `deSolve` to implement the implicit Runge-Kutta method RADAU. To implement the outbreak endpoint when $I_1(t) = I_{\min}$, we use the `events` and `rootfun` options for the function `ode()` in the `deSolve` package. The event is `terminalroot = 1` and `rootfun` is $I_{\min} - I_1(t)$. To implement the resource constraint, we evaluate an `if()` clause for $U_1(t) < U_{1\,\max}$ where $U_1(t)$ is evaluated by numerically solving equation (3.33). To implement the constraint, and the precautionary strategy, the `if()` clause evaluates as false, then $u_1(t)$ is set to 0.

The simulation codes for all the figures in this thesis can be found here `https://github.com/King-Jorge/Thesis_Codes`. Numerical methods for other figures in the thesis also build on the numerical methods described in this subsection, with any other relevant details described in the relevant subsequent sections.

3.7.2 Numerical results

Figure 3.3a shows that the impact that infected travelers spreading infections to community members ($c > 0$) can have on the optimal control is that more community infections occur, and this may mean that community isolation resources are not sufficient (Figure 3.3b, $c = 0.5$ and 1). In this case, when resources are exhausted and

$u_1(t) = 0$ occurs, community infection prevalence can rebound (Figure 3.3b, $c = 0.5$ and 1). Further, when infected travelers spread infections to community members more readily, the outbreak can last substantially longer (up to $T = 1057$ days for $c = 1$, as compared to $T = 16$ when there is no infection spread from travelers). However, these substantial effects of infection spread from travelers occur when the community outbreak initially declines. When the community outbreak initially increases, infection spread from travelers can have a negligible effect as will be discussed in the next section.

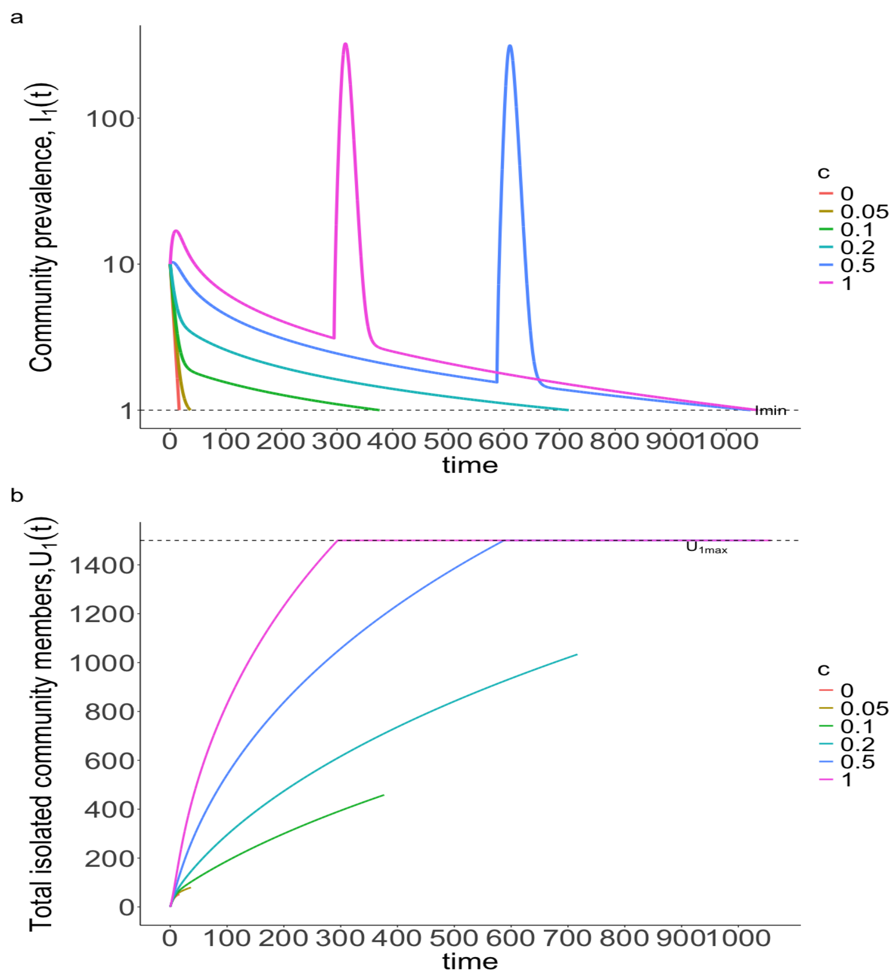

Figure 3.3: The effect of the relative transmissibility of infected travelers, c, on community infection prevalence when the precautionary strategy (equation 3.38) is implemented. All parameter values are in Table 3.2.

3.8 Problem 3: Post-Arrival Traveler isolation Only

In Problem 3, we consider post-arrival isolation of infected travelers as the only public health measure used to control infection prevalence in the community. Our model now becomes

$$\frac{dS}{dt} = -\beta S(I_1 + cI_2), \tag{3.39}$$
$$\frac{dI_1}{dt} = \beta S(I_1 + cI_2) - \mu I_1, \tag{3.40}$$
$$\frac{dI_2}{dt} = \theta - (u_2(t) + \gamma)I_2, \tag{3.41}$$
$$\frac{dU_2}{dt} = u_2(t)I_2. \tag{3.42}$$

The objective function is,

$$J = \int_0^T \beta S_{[u_2]}(I_{1[u_2]} + cI_{2[u_2]})\ dt, \tag{3.43}$$

subject to equations (3.39)-(3.42), $T = \inf\{t \mid I_{1[u_2]}(t) = I_{\min}\}, u_2(t) \in [0, u_{2\max}]$ for all $t \in [0, T]$ and subject to the resource constraint,

$$U_{2[u_2]}(T) = \int_0^T u_2 I_2\ dt \leq U_{2\max}. \tag{3.44}$$

As for Problems 1 and 2, it is possible to show that min J is equivalent to maximizing $S_{[u_1]}(T)$, and Problem 3 is still a linear optimization problem such that $u_2^*(t)$ is a bang-bang control as described by Remark 3.4.1. For $u_2(t) \equiv u_{2\max}$ and $I_2(0) = \theta/(\gamma + u_{2\max})$, integrating equation (3.41) gives,

$$U_{2[u_{2\max}]}(T) = \frac{u_{2\max}\ \theta\ T_{[u_{2\max}]}}{u_{2\max} + \gamma}, \tag{3.45}$$

and this expression can be evaluated to determine if resources are limiting.

3.8.1 Numerical results

The numerical methods are similar to as described in Section 3.7.1 for Problem 2. As for Problem 2, we consider the precautionary strategy, which in this case is,

$$u_2^{**}(t) = \begin{cases} u_{2\max}, & \text{if} \quad 0 \leq t \leq t_{2\max} \text{ and} \\ 0, & \text{if} \quad t > t_{2\max}, \end{cases} \tag{3.46}$$

where $t_{2\max}$ is the time when traveler isolation resources are used up, and evaluate the epidemiological dynamics (Figure 3.4a,c) and resource use (Figure 3.4b,d) for this precautionary strategy. The scenarios considered are when community infections initially increase (Figure 3.4, upper panels) or decrease (Figure 3.4, lower panels).

The effect of post-arrival isolation of travelers is negligible for a community outbreak where cases initially increase (Figure 3.4a), but can be substantial for outbreaks where community cases initially decrease (Figure 3.4c). Figure 3.4a-b, where the transmission rate is $\beta = 0.0002$ person^{-1} such that community cases initially increase, shows epidemiological dynamics that are very similar irrespective of the maximum rate that travelers are isolated ($u_{2\max}$ ranging from 0 to 5 day^{-1}) and irrespective of whether resources are limiting ($u_{2\max} = 2, 3$ or 5) or not ($u_{2\max} = 0, 0.5$ and 1; Figure 3.4b).

However, for Figure 3.4c-d, where the transmission rate is $\beta = 0.00005$ person^{-1} such that community cases initially decrease, the outbreak can be substantially prolonged when the maximum rate that travelers are isolated, $u_{2\,\max}$, is low. When the post-arrival traveler isolation rate is high (i.e., $u_{2\max} = 5$ day^{-1}) the outbreak ends quickly (i.e., in 284 days or less, Figure 3.4c) and resources are sufficient to implement $u_2(t) \equiv u_{2\max}$ for the entire outbreak (Figure 3.4d). However, when the post-arrival traveler isolation ratis low (i.e., $u_{2\max} = 0, 1$ or 4.5) then the community outbreak decreases more slowly and does not reach the terminal condition, $I_1(t) = I_{\min}$ before all the resources for traveler isolation are used (Figure 3.4d). Community infection prevalence, $I_1(t)$ then rebounds (Figure 3.4c) and the outbreak takes a very long time to terminate. In Figure 3.4c, for $u_{2\max} = 0, 1$ and 4.5, the outbreak has still not concluded after 2000 days. However, the outbreak will eventually terminate because $S(t)$ is always decreasing, and dI_1/dt will be negative when $S(t)$ becomes small enough.

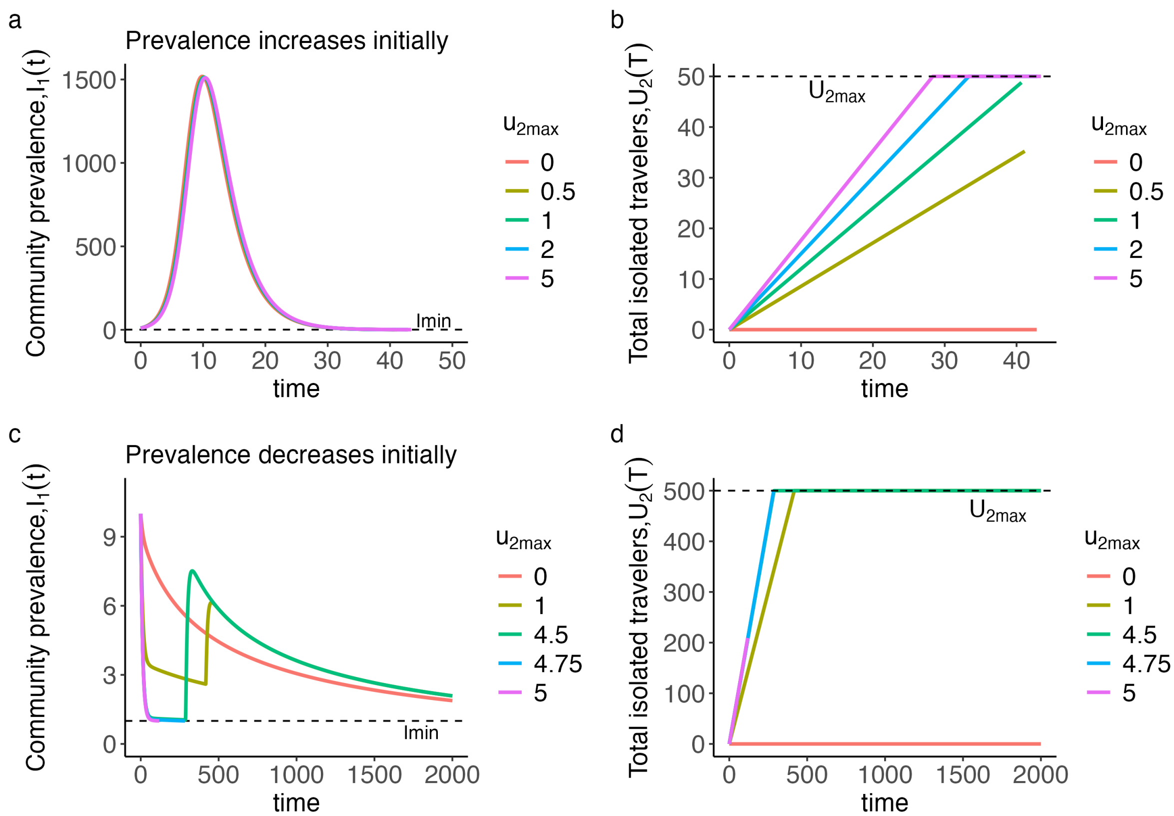

Figure 3.4: The effect of the post-arrival traveler isolation rate ($u_{2\max}$) on community infection prevalence, $I_1(t)$, when the precautionary strategy (equation 3.46) is implemented, and the transmission rate is such that community infections increase initially (a-b; $\beta = 0.0002$ person^{-1} day^{-1}) or decrease initially (c-d; $\beta = 0.00005$ person^{-1} day^{-1}). All parameter values are in Table 3.2.

3.9 Problem 4: Combined Strategies

The model for the combined strategies: isolation of infected community members, $u_1(t)$, and post-arrival isolation of infected travelers, $u_2(t)$, is described by the system of ordinary differential equations:

$$\frac{dS}{dt} = -\beta S(I_1 + cI_2), \tag{3.47}$$

$$\frac{dI_1}{dt} = \beta S(I_1 + cI_2) - (\mu + u_1(t))I_1, \tag{3.48}$$

$$\frac{dI_2}{dt} = \theta - (\gamma + u_2)I_2, \tag{3.49}$$

$$\frac{dU_1}{dt} = u_1(t)I_1, \tag{3.50}$$

$$\frac{dU_2}{dt} = u_2(t)I_2. \tag{3.51}$$

Let the precautionary combined strategy be defined as,

$$u_1^{**}(t) = \begin{cases} u_{1\max}, & \text{if} \quad 0 \le t \le t_{1\max} \quad \text{and} \\ 0, & \text{if} \quad t > t_{1\max}, \end{cases} \tag{3.52}$$

and,

$$u_2^{**}(t) = \begin{cases} u_{2\max}, & \text{if} \quad 0 \le t \le t_{2\max} \quad \text{and} \\ 0, & \text{if} \quad t > t_{2\max}, \end{cases} \tag{3.53}$$

where $t_{1\max}$ and $t_{2\max}$ are the times when all resources are used if the controls are implemented from $t = 0$ onwards. If resources are not limiting for $[u_1^{**}, u_2^{**}]$ then set $t_{1\max} = t_{2\max} = T^{**}$, which is the duration of the outbreak when $[u_1^{**}, u_2^{**}]$ is implemented.

Consider the resources used when $u_1(t) = u_1^{**}(t)$ and $u_2(t) = u_2^{**}(t)$ are implemented. These are

$$U_{1[u_1^{**},u_2^{**}]}(T^{**}) = \int_0^{t_{1\max}} u_1^{**} I_1 \; dt \leq U_{1\max}, \tag{3.54}$$

and

$$U_{2[u_1^{**},u_2^{**}]}(T^{**}) = \int_0^{t_{2\max}} u_2^{**} I_2 \; dt \leq U_{2\max}. \tag{3.55}$$

We also consider alternative strategies, which are bang-bang controls and are different from a precautionary strategy. These alternative strategies necessarily have a break in the implementation measures that correspond to a control for which resources are limiting. Our discussion of the optimal combined controls will consider four cases, which are the four possible combinations of limiting and non-limiting resources for the community isolation and the traveler isolation resources.

Definition 3.9.1. ***Optimal preferred strategy.*** *If only one resource is limiting, we note that a strategy that uses less of the non-limiting resource should be preferred if all else is equal. We define an optimal preferred strategy, as satisfying the requirements of an optimal control, but where this strategy is preferred because it uses the least amount of the non-limiting resource.*

Case 1: Both resources are not limited. We conjecture that the optimal combined strategy is to use both resources at the maximum rate until the end of the outbreak. Specifically, that the precautionary combined strategy when both resources are not limiting is $[u_1^{**}(t), u_2^{**}(t)] \equiv [u_{1\max}, u_{2\max}]$.

Case 2: Community resources (limited); traveler resources (not limited). We conjecture that the optimal combined strategy is to use all of the limited community isolation resources, and to use the non-limiting traveler isolation resources at the maximum rate until the end of the outbreak. Specifically, we conjecture the optimal combined strategy is $[u_1(t), u_2(t)] = [u_1^*(t), u_{2\max}]$ where $u_1^*(t)$ denotes a strategy that uses all the available resources for community isolation, and where $u_2(t) \equiv u_{2\max}$ means that traveler isolation resources are implemented at the maximum rate for the duration of the outbreak.

We further explore the potential structure of the optimal combined strategy for this case by numerical evaluation of the objective function. Consider two strategies that might meet the requirements for $u_1^*(t)$: the precautionary strategy, $u_1^{**}(t)$, and $\tilde{u}_1(t)$, where the latter is different from $u_1^{**}(t)$ and uses all the available resources for community isolation. Let $\tilde{T}$ be the duration of the outbreak when $[\tilde{u}_1(t), u_{2\max}]$ is implemented and let $U_{2[\tilde{u}_1, u_{2\max}]}(\tilde{T})$ be the amount of traveler isolation resources used.

Consider whether the total number of community infections, J (see equation 3.34) is smaller for $[u_1^{**}(t), u_{2\max}]$ or $[\tilde{u}_1(t), u_{2\max}]$. In general, we cannot determine this, but we consider a numerical example where the alternative strategy is to have a precautionary break where no community isolation measures are implemented from time 5 to 15. The numerical example (Figure 3.5a) shows that J (dashed horizontal line) is the same for the precautionary combined strategy, $[u_1^{**}(t), u_{2\max}]$ (red line), and the alternative strategy $[\tilde{u}_1(t), u_{2\max}]$ (blue line).

While both of these strategies satisfy the constraints and have the same value of the objective function, $[\tilde{u}_1(t), u_{2\max}]$ is preferred. This is because less of the non-limiting traveler isolation resource is used for $[\tilde{u}_1(t), u_{2\max}]$ (Figure 3.5c, blue line). Less of the traveler isolation resource is used for $[\tilde{u}_1(t), u_{2\max}]$ because the outbreak ends more quickly ($\tilde{T}$=51 days, while T^{**}=82 days for the precautionary strategy of implementing community isolation resources.

This may be surprising because it may seem that the strategy with the earliest implementation of community isolation measures ($t = 0$ for $[u_1^{**}(t), u_{2\max}]$) would end first, however, this is not the case, likely because community infection prevalence is low initially, so few community members are isolated at this time. The delayed implementation of community isolation measures for $\tilde{u}_1(t)$ is timed to correspond with high infection prevalence and results in an outbreak that ends more quickly.

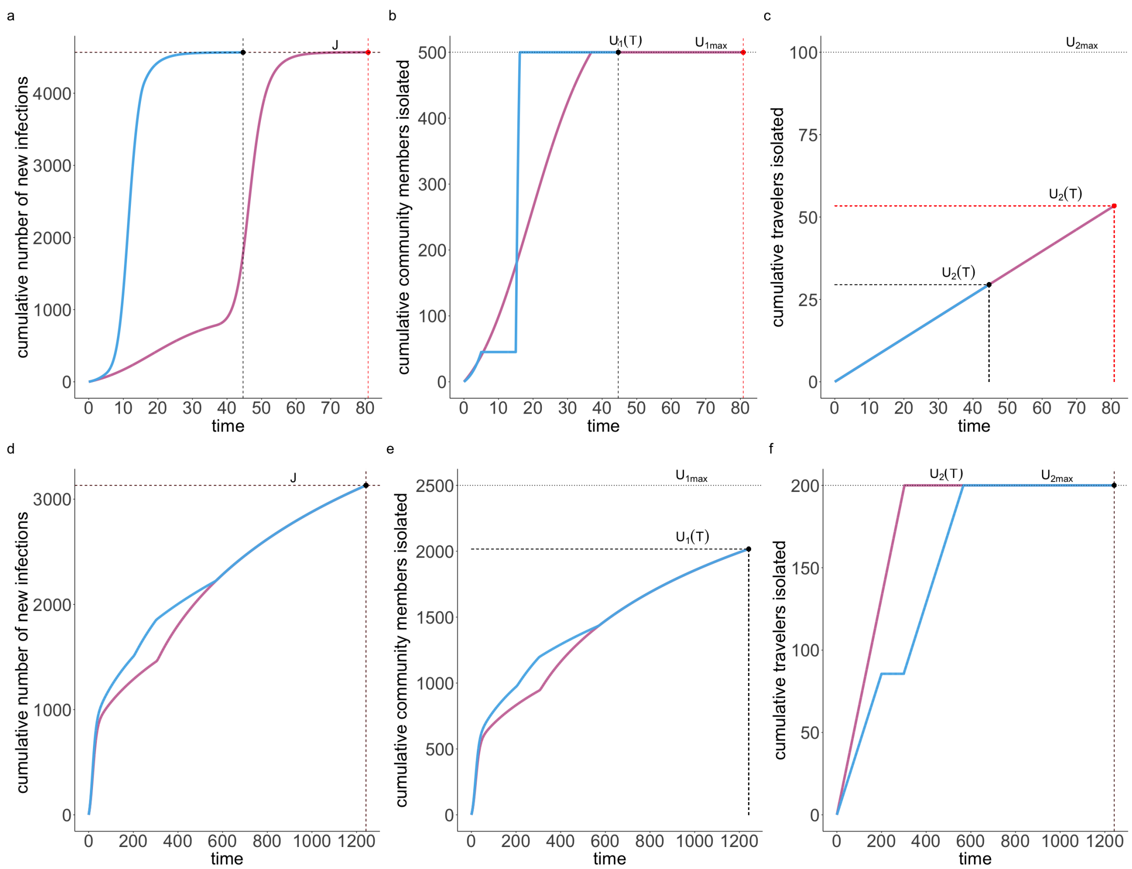

Figure 3.5: Comparison of the precautionary combined strategy (red) and an alternative strategy (blue) when one resource is limiting: traveler isolation resources are limiting (a-c; Case 2); and community isolation resources are limiting (d-f; Case 3). Parameter values are listed in Table 3.2.

Case 3: Community resources (not limited); traveler resources (limited). We conjecture that the optimal combined strategy is to use the non-limiting community isolation resource at the maximum rate for the duration of the outbreak, and to use all of the limited traveler isolation resources. Specifically, we conjecture the optimal combined strategy is $[u_1(t), u_2(t)] = [u_{1\max}, u_2^*(t)]$ where $u_1(t) \equiv u_{1\max}$ means that community isolation resources are implemented at the maximum rate for the duration of the outbreak, and $u_2^*(t)$ denotes a strategy for that uses all the available resources for traveler isolation.

As for Case 2, we further explore the potential structure of the combined optimal control by numerical evaluation of the objective function. The two strategies that might meet the requirements for $u_2^*(t)$, are the precautionary strategy, $u_2^{**}(t)$, and the alternative strategy, $\tilde{u}_2(t)$ where the latter is different from $u_2^{**}(t)$, and uses all the available resources for traveler isolation. Let $\tilde{T}$ be the duration of the outbreak when $[u_{1\max}, \tilde{u}_2(t)]$ is implemented and let $U_{1[u_{1\max}],\tilde{u}_2}(\tilde{T})$ be the amount of community isolation resources used. For the numerical example, the specific form of the alternative strategy is to have a precautionary break where no traveler isolation measures are implemented from time 200 to 300.

It is notable for Case 3, that traveler isolation measures do not noticeably impact community prevalence, and so both strategies, $[u_{1\max}, u_2^{**}]$ (red line) and $[u_{1\max}, \tilde{u}_2]$ (blue line) end at a similar time ($T^{**} = \tilde{T} = 1143$ days; Figure 3.5d-f) and require the same amount of the non-limiting resource ($U_{2[u_{1\max},\tilde{u}_2]}(\tilde{T}) = U_{2[u_{1\max},u_2^{**}]}(T^{**})$, Figure 3.5e).

Case 4: Both resources are limited. We cannot determine the structure of the optimal control in this case.

Chapter 4

Optimal controls and public health strategies

4.1 Definitions of public health strategies

In this section, we provide mathematical definitions of the public health strategies so that the results of Chapter 3 can be discussed using public health terminology. These definitions are provided for community isolation measures (Table 4.1 and Figure 4.1) and traveler isolation measures (Table 4.3 and Figure 4.2). The requirement that the elimination strategy decreases infection prevalence shortly after the control is implemented is because elimination strategies should involve control measures that are sufficiently strong to decrease infection prevalence.

Table 4.1: Definition of public health strategies for community isolation $u_1(t)$.

Public Health Strategy	**Description**	**Definition**
Elimination	Infection prevalence is reduced to zero locally, but not in all regions, such that there remains a risk of disease importation [8, 55].	(a) The outbreak is eliminated by public health measures, i.e., $U_{1[u_{1\max}]}(T) \leq U_{1\max}$. (b) $\frac{dI_1}{dt} < 0$ shortly after $u_1^*(t)$ is implemented.
Mitigation	Mitigation aims to slow the spread of an infectious disease to avoid overwhelming healthcare capacities and to reduce overall morbidity and mortality [41, 74].	(a) Public health measures are implemented throughout the entire outbreak, i.e., $U_{1[u_{1\max}]}(T) \leq U_{1\max}$. (b) $\frac{dI_1}{dt} \geq 0$ shortly after $u_1(t)$ is implemented.
Circuit Breaker	Public health measures are intermittent with breaks in between.	The control involves at least two switches between public health measures of different intensities.

Another public health strategy not listed in Table 4.1 is suppression. Suppression strategies aim to reverse epidemic growth [22] and bring the number of cases down to a low-level [35, 41] noting that community transmission may still take place [74, 8, 35]. From a mathematical perspective, it is difficult to distinguish between suppression and mitigation. The cited definitions imply that the difference is whether infection prevalence is eventually low (suppression), or reduced so as to not overwhelm healthcare capacity (mitigation). These definitions imply that low infection prevalence cannot overwhelm healthcare capacity (which may not always be the case), and we opted to use the terminology of mitigation rather than suppression because some of our subsequent results (i.e. Figures 4.1b and 4.2b-c) show infection prevalences that can not reasonably be referred to as low.

Given these definitions (Table 4.1), Theorem (3.6.1; i.e., Theorem 1 in [32]) can be restated as:

(a) If resources for community isolation are not limited, then optimal control for Problem 1 is: elimination, if community infections decrease initially; or mitigation, if community infections do not decrease initially.

(b) If resources for community isolation are limited, then an optimal control for Problem 1 is any circuit breaker strategy that uses all of the available resources. In this case, the circuit breaker strategy that uses all available resources is equivalent to a non-circuit breaker strategy that uses all available resources (for example, the precautionary strategy, i.e. equation 3.38).

Figure 4.1a-d shows the dynamics of community infection prevalence, $I_1(t)$, for Problem 1 given the definitions of the public health strategies (Table 4.1). Note that for the elimination strategy, the outbreak is over more quickly (Figure 4.1a, less than 17 days) than any other public health strategy (Figure 4.1b-d, more than 45 days). Figure 4.1e confirms numerically that any strategy that uses all available resources is equivalent, in terms of J (equation 3.18), when resources are limiting, i.e., circuit breakers 1 and 2 are two optimal controls that have the same number of cases in the outbreak. Note that at any point during the outbreak, the cumulative number of cases may be different for circuit breakers 1 and 2, but when the outbreak ends, this total number of cases is the same.

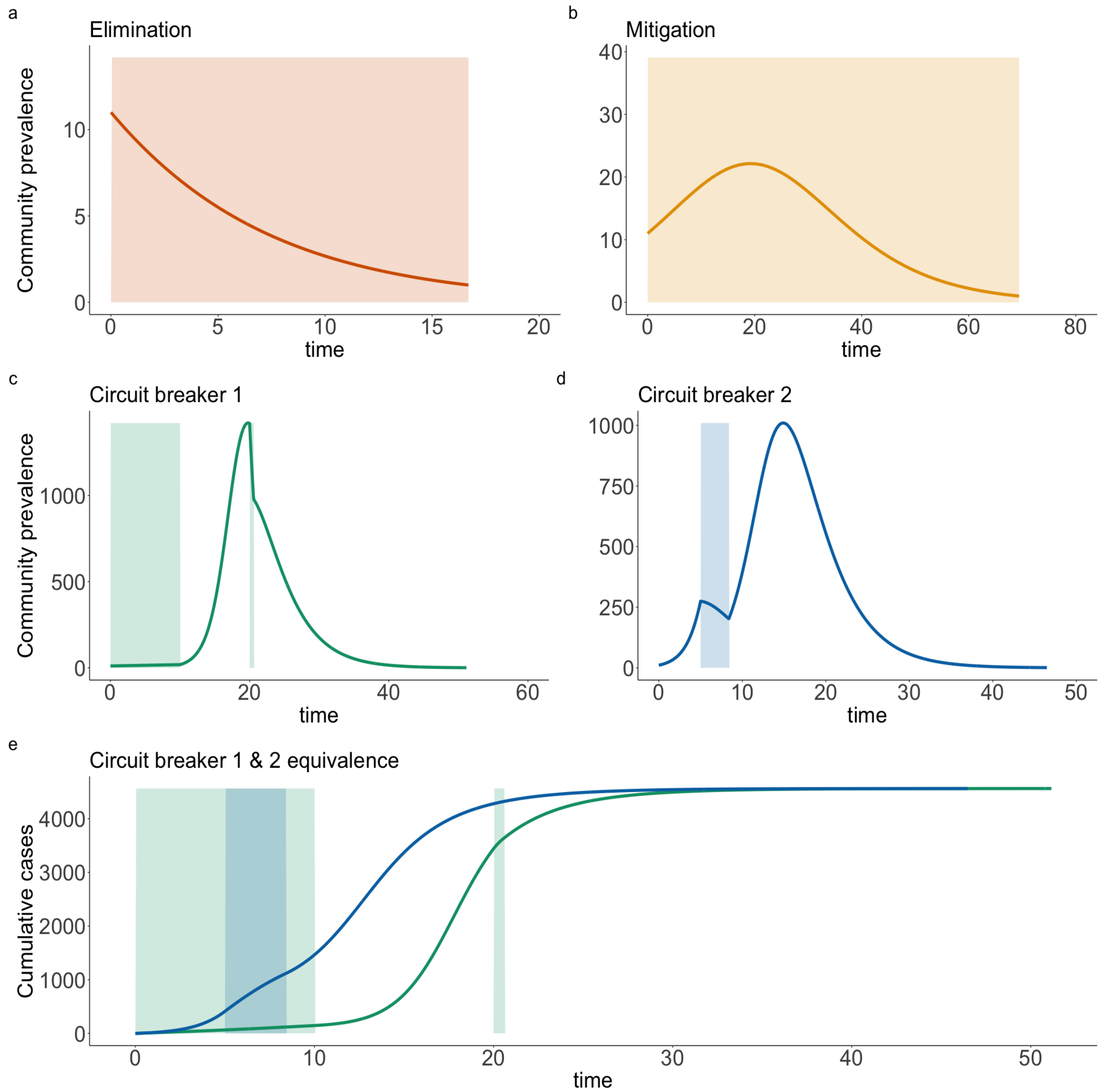

Figure 4.1: Visualization of the definitions of the different public health strategies. The shaded regions correspond to $u_1(t) = u_{1\max}$ and the unshaded regions correspond to $u_1(t) = 0$ for the optimal controls for Problem 1, where different public health strategies are optimal in each panel due to different parameter values (see Table 4.2 for parameter values).

For traveler isolation, the control strategies are categorized as either continuous or circuit breaker (Table 4.3). This is because the definitions of elimination and mitigation are defined in terms of community prevalence.

Table 4.2: Parameter values used for the figures in this chapter

Figure	Parameter values
Figure 4.1	$u_{1\max} = 0.7$ day^{-1} (a) or 0.6 day^{-1} (b-e), $U_{1\max} = 1500$ people (a-b) or 500 people (c-d), $\beta = 0.0002$ person^{-1} day^{-1}, $\mu = 0.334$ person^{-1} day^{-1}, $\theta = 2$ people day^{-1}, $S(0) = 5000$ people, $I_1(0) = 10$ people, $I_{\min} = 1$ person, $I_2(0) = \frac{\theta}{\gamma + u_{2max}}$
Figure 4.2	$u_{1\max} = 0.2$ day^{-1}, $u_{2\max} = 1.3$ day^{-1} for (a-b), $u_{1\max} = 0.2$ day^{-1}, $u_{2\max} = 1.8$ day^{-1} for (c-d), $u_{1\max} = 0.7$ day^{-1}, $u_{2\max} = 1.3$ day^{-1} for (e-f), $u_{1\max} = 0.7$ day^{-1}, $u_{2\max} = 1.8$ day^{-1} for (g-h), and all other parameters and initial conditions are the same as Figure 4.1.
Figure 4.3	$U_{2\max} = 50$ people, and all other parameters and initial conditions are the same as Figure 4.1.
Figures 4.4, 4.5, and 4.6	Low importation (a) has $\theta = 1$ and the high importation has $\theta = 2$. All other parameters and initial conditions are the same as in Figure 4.1.

Table 4.3: Definition of public health strategies for traveler isolation $u_2(t)$.

Public Health Strategy	Description	Definition
Continuous	Public health measures are implemented throughout the outbreak to slow the spread of the disease, and to avoid overwhelming healthcare capacities.	Public health measures are implemented throughout the entire outbreak, i.e., $U_{2[u_{2\max}]}(T) \leq U_{2\max}$, and $u_2^*(t) \neq 0$ at any point in time.
Circuit Breaker	Public health measures are intermittent with breaks in between.	An optimal control involves at least two switches between public health measures of different intensities.

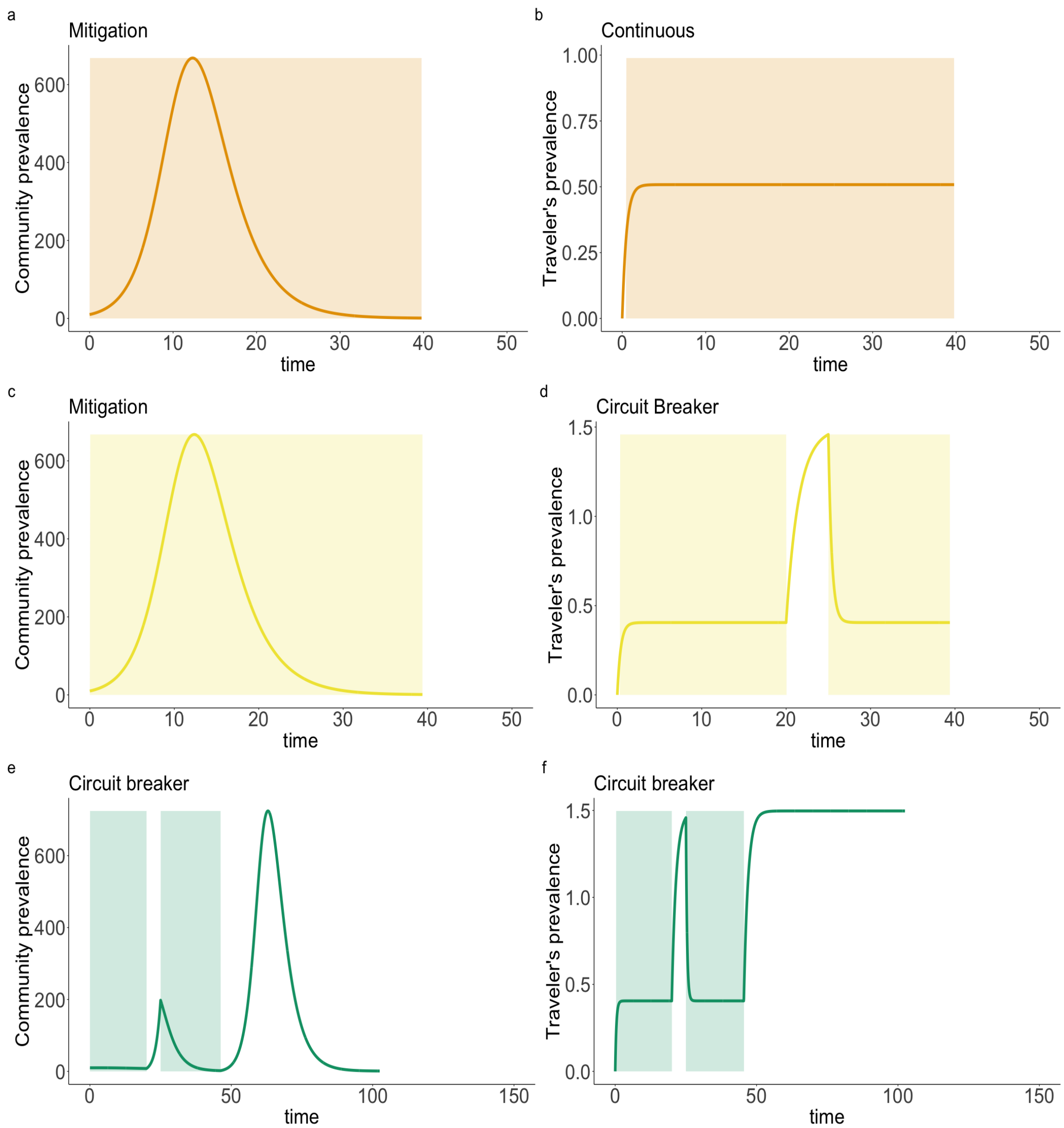

Figure 4.2: Illustration of three of the six possible combined strategies. The shading overlayed on $I_1(t)$ shows where $u_1(t) = u_{1\,\max}$ and the unshaded regions show where $u_1(t) = 0$ (left columns), and the shading overlayed on $I_2(t)$ shows where $u_2(t) = u_{2\,\max}$ with the unshaded regions corresponding to $u_2(t) = 0$. Parameter values are provided in Table 4.2.

The definitions from Table 4.1 are applicable to Problems 1 and 2 (Sections 3.6 and 3.7), and the definitions from Table 4.3 are applicable to Problem 3. For Problem 4, we need to specify whether the strategy corresponds to the community isolation control, or the traveler isolation control, and this is indicated with the notation, $[\mathrm{mit}, \mathrm{circ}]$ for example, to indicate that the precautionary combined strategy involves community measures implemented as a mitigation strategy, and the travel measures implemented as a circuit breaker strategy that uses all of the available resources. The possible combined controls are: $[\mathrm{elim}, \mathrm{cont}]$, $[\mathrm{elim}, \mathrm{circ}]$, $[\mathrm{mit}, \mathrm{cont}]$, $[\mathrm{mit}, \mathrm{circ}]$, $[\mathrm{circ}, \mathrm{cont}]$, and $[\mathrm{circ}, \mathrm{circ}]$.

4.2 Effect of the parameter values on the characterization of the controls

In this section, we will numerically investigate how the characterization of the controls, as a type of public health strategy, changes for different values of the parameters. These different parameter values might correspond to the situation in different regions, and so in this respect, we are showing that the best public health response to an infectious disease outbreak can depend on regional factors.

The results shown in this section are limited by having not been able to characterize the optimal control for Problems 2-4 in the previous Chapter. Ideally, in this Chapter, we would characterize the optimal control as a particular type of public health strategy. As we do not know the optimal control for Problem 4, what we do instead is implement the combined precautionary strategy (equations 3.52 and 3.53). Assuming the combined precautionary strategy, the system of equations 3.47-3.51 is numerically solved. Then the definitions, as described in Tables 4.1 and 4.3, are applied to the resulting $I_1(t)$, $U_1(T)$ and $U_2(T)$ to characterize the resulting public health strategy.

4.2.1 Resources are not limiting

We consider the case when resources are not limiting, such that the public health strategy that the precautionary strategy implementation results in, is either an elimination or mitigation strategy depending on whether infection prevalence decreases initially or not. Figure 4.3 shows that the precautionary strategy results in elimination if both $u_{1\,\max}$ and $u_{2\,\max}$ are sufficiently large. Furthermore, Figure 4.3 shows that an incremental increase in $u_{1\,\max}$ results in a bigger decrease in the slope, $\frac{dI_1}{dt}|_{t=0}$, than an incremental change in $u_{2\,\max}$, such that increasing $u_{1\,\max}$ by a fixed amount is a more impactful action that can be taken such that the resulting public health strategy changes from mitigation to elimination as indicated in the heatmap Figure 4.3d.

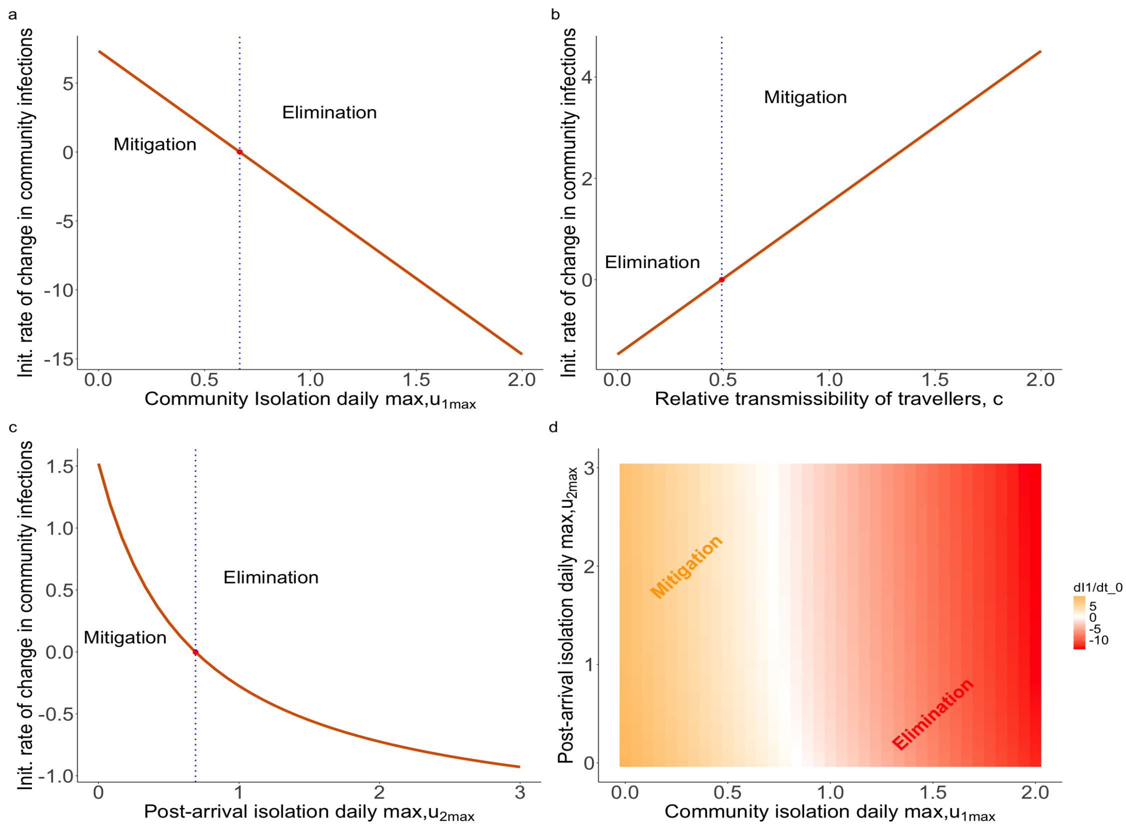

Figure 4.3: The effect of $u_{1\,\max}$ and $u_{2\,\max}$ on the initial change in the number of community infections. Parameter values are described in Table 4.2.

4.2.2 Without requiring that resources are not limiting

In Figure 4.3, we set the resource constraints, $U_{1\,\max}$ and $U_{2\,\max}$ to be large, such that resources were never limiting. In this subsection, parameter values, and the resulting epidemiological and resource consumption dynamics determine whether the community isolation strategy is categorized as an elimination, mitigation, or circuit breaker strategy (Table 4.1), and whether the traveler isolation strategy is categorized as continuous or circuit breaker (Table 4.3). The strategy that is implemented is the combined precautionary strategy (equations 3.52 and 3.53).

As described in Tables 4.1 and 4.3, the control implementation is categorized as circuit breaker if $U_1(T) = U_{1\,\max}$ for the community isolation control and $U_2(T) = U_{2\,\max}$ for the traveler isolation control. The values of $U_1(T)$ and $U_2(T)$ are determined by solving equations 3.50 and 3.51. In the case where $U_2(T) < U_{2\,\max}$ then the traveler isolation strategy is categorized as continuous. In the case where $U_I(T) < U_{1\,\max}$ the condition for elimination $\frac{dI_1}{dt}|_{t=0}$ is evaluated numerically as requiring that $I_1(t) \leq I_1(0)$ for all time, and otherwise the community isolation control is categorized as mitigation.

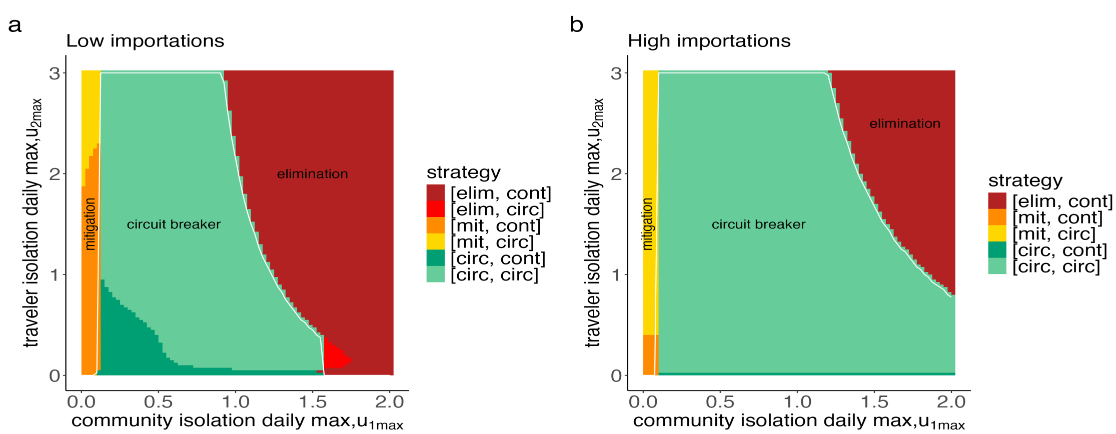

Figure 4.4: The effect of the maximum daily isolation rate of community members, $u_{1\max}$, and travelers, $u_{2\max}$ on the precautionary combined control described in terms of public health strategies, where the labels "elimination", "mitigation", and "circuit breaker" refer to the community isolation component of the control. Parameter values are shown in Table 4.2

When both community measures and travel measures can be used in combination to control the outbreak, if the maximum daily isolation rates for both community members, $u_{1\max}$, and travelers, $u_{2\max}$, is high, then the precautionary combined control corresponds to the [elim, cont] strategy, whereby community isolation measures are implemented continuously and achieve elimination, and traveler isolation is implemented continuously (Figure 4.4a-b; red region). This elimination strategy is achieved because the control measures are highly effective in decreasing community prevalence and quickly ending the outbreak (Figure 4.5a-b; see the region labeled as [elim, cont]).

When the importation rate is high (Figure 4.4b), larger maximum daily isolation rates are needed for the precautionary combined control to correspond to elimination (i.e., the red region is smaller in panel b of Figure 4.4). The regions corresponding to a continuous strategy for travel measures (Figure 4.4, light green and yellow) become smaller with higher importation rates.

When both of the daily maximum isolation rates, $u_{1\max}$ and $u_{2\max}$ are low, the precautionary combined strategy corresponds to a mitigation and continuous strategy for community and traveler isolation measures respectively (Figure 4.4a-b; orange region). For these parameter values, the control measures have only a very small effect on the outbreak, with only a few people isolated, so that the total resources available are not used up.

Our categorization of the precautionary combined controls into different types of public health strategies corresponds to substantial changes in the duration and number of cases in the outbreak. If resources are not limited, and the control measures can stay in place until the outbreak ends (i.e., an elimination, mitigation or continuous strategy) then the outbreak is shorter (Figure 4.5). This is perhaps surprising in the case of the mitigation strategy, however in this case the outbreak progresses rapidly due to lack of control because the maximum community isolation rates are low.

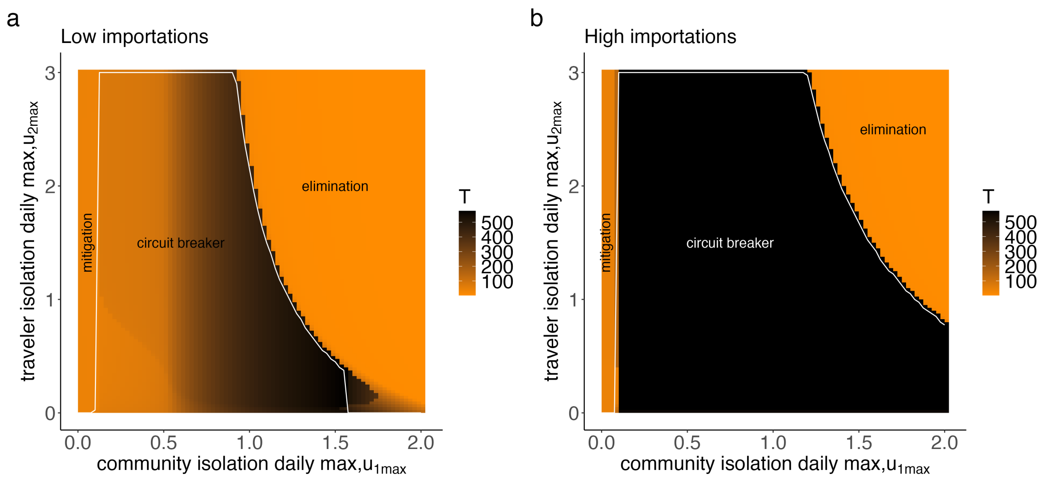

Figure 4.5: The duration of the outbreak, T, when the precautionary combined control is implemented. All parameters are the same as 4.4, and for reference, the regions where the community isolation strategy corresponds to "elimination", "mitigation", and "circuit breaker" strategy are provided.

The longest duration outbreaks occur when resources are limited and a circuit breaker strategy is needed, alternating between moderate intensity maximum community isolation rates and no measures. In these situations, the outbreak is prolonged, especially when the importation rate is high. This high importation rate slows down the decline in community infection prevalence, such that it takes longer for infection prevalence to reach the level needed to declare the outbreak over. Long outbreaks also occur when the maximum daily infection rates are slightly below the threshold necessary for elimination.

When the parameter values are such that the categorization of the precautionary combined strategy is an elimination-continuous strategy (labeled as [elim, cont]) the outbreak will be short (Figure 4.6) and consist of relatively few cases (Figure 4.6). When the conditions are such that the community isolation strategy is categorized as a mitigation strategy (labeled as [mit, cont] and [mit, circ]) the outbreak will be short (Figure 4.5) and consist of many cases (Figure 4.6). When the conditions are such that the optimal strategy for community isolation is a circuit breaker strategy (labeled as [circ, cont] and [circ, circ]) the outbreak will be long (Figure 4.5) and consist of many cases (Figure 4.6).

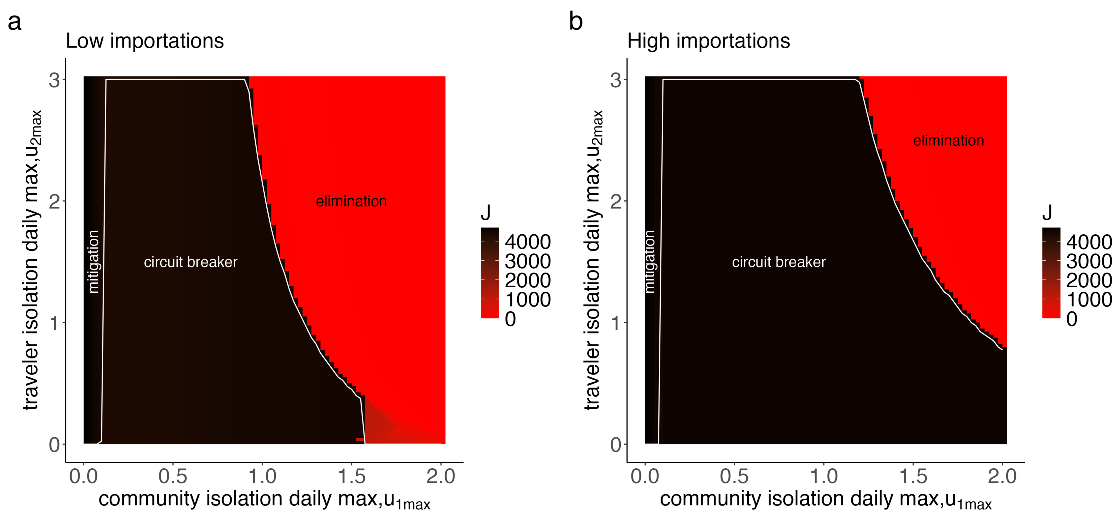

Figure 4.6: The number of cases in the outbreak, J, when the precautionary combined control is implemented. All parameters are the same as 4.4, and for reference, the regions where the community isolation strategy corresponds to “elimination”, “mitigation”, and “circuit breaker” strategy are provided.

Finally, our results suggest that the maximum community isolation rate, $u_{1\,\max}$ is more important for determining the type of public health strategy that results from implementing the precautionary combined strategy than the maximum traveler isolation rate, $u_{2\,\max}$. This is evident because the slope of the boundary between [circ, circ] and [elim, circ] is bigger than 1 in absolute value. This is not surprising as it has often been stated that importations make a negligible contribution to outbreaks when community spread is occurring [64, 36, 30, 5, 15, 72]. The boundary between the community isolation strategies of mitigation and the circuit breaker is seemingly vertical, which means that the traveler isolation rate has a negligible impact on the boundary between these regions. However, our results do not show that the importation rate, and traveler isolation measures are universally inconsequential. Rather, we find that both the importation rate and the maximum rate that travelers are isolated are impactful in determining whether elimination is possible, although we note that the maximum community isolation rate also matters.

Chapter 5

Conclusion

We expanded on the work of Hansen and Day [32] by considering infection spread to community members from travelers, and implementing post-arrival traveler isolation as a control measure. Hansen and Day [32] had previously found that when isolation resources are limited, any strategy that uses all available resources is optimal. This thesis describes how the modelling framework of Hansen and Day [32] can be built upon to consider importations and post-arrival travel measures. Furthermore, this thesis explains how the results of this modelling can be framed in the terminology of public health strategies. This contribution is valuable as we show how to formulate a general modelling framework where different public health strategies might potentially be optimal for different parameter values that might correspond to regional factors. This dependence of best public health strategies on regional factors is consistent with the World Health Organization's *'Technical considerations for implementing a risk-based approach to international travel in the context of COVID-19: Interim guidance, 2 July 2021'* [73] that describes regional factors as necessary considerations for the recommended implementation of travel measures.

We interpret the results of Hansen and Day ([32]; Theorem 1, which applies to our Problem 1): that any strategy that uses all the available resources is optimal, as support for a circuit breaker strategy. The circuit breaker strategy involves precautionary breaks from public health restrictions [44]. Following Hansen and Day ([32]; Theorem 1), such a strategy is optimal as long as the delays to implementing public health measures are not so long as to have the outbreak be nearly over by the time measures are implemented. When lengthy delays to implementing measures occur, too few individuals remain to potentially be infected and all of the isolation resources cannot be used, which is not optimal.

While the precautionary strategy is always optimal for Problem 1 (as proved in [32]), we do not know this to be the case for Problem 4, which involves implementing both controls, although numerical exploration of two alternative combined strategies finds that both are optimal (Figure 3.5) in terms of the objective function, J, which is the total number of community cases in the outbreak. Nonetheless, we note some differences between the precautionary and the alternative strategy that are not considered in the objective function. Particularly, we note a difference with regard to defining a preferred strategy, which is one that uses less of a non-limiting resource. Often this preferred strategy ends the outbreak more quickly while achieving the same number of cases. We proceeded with a numerical exploration of the characterization of the combined precautionary strategy in terms of different public health strategies for Problem 4, but we do not know whether this is an optimal control as we did for Problem 1 (although Figure 3.5 suggests that the precautionary combined control may also always be optimal for Problem 4).

Our numerical exploration of public health strategies that result from implementing the precautionary combined control strategy found that a circuit breaker strategy results when resources are limited, and a mitigation strategy results when the maximum isolation rates is low and/or the importation rate is high, but community isolation resources are not limited. However, in the situations where an elimination strategy is the characterization of the public health strategy that is implemented, the elimination strategy performs substantially better than any other strategy, both in terms of shorter (Figure 4.5) and smaller (Figure 4.6) outbreaks. While not captured in our objective function, there is a significant benefit to short duration outbreaks as this means that public health interventions need to be in place for a shorter duration.

When the elimination strategy is possible, this strategy performs very well, suggesting that future work might consider optimization problems where the control variables may allow the situation to become favourable for elimination. For example, the maximum isolation rates are fixed values in our optimization problems, but future work could consider the maximum isolation rate as a control variable. Similarly, in our formulation the resource constraints are fixed, however, in some situations, all the resources are used just before the outbreak is about to end. In this situation, releasing the public health measures results in a second wave of infection (see Figure 3.3a) that would have been avoided if more resources could have been made available, such that the public health measures could have remained in place for just a short time longer, and a second wave prevented, if just a few more resources could have been made available.

A simple recommendation from our results, and that follows mostly from Theorem 1 as was proved is Hansen and Day [32], is that initiating maximum isolation efforts as soon as the outbreak is detected, i.e., 'don't wait, re-escalate' [39], is likely always a very good action that can be justified by a formal optimal control framework. Following from Theorem 1 in Hansen and Day [32], if the outbreak ends before resources are exhausted, then this precautionary 'don't wait' strategy is *the* best action when the only available control is community isolation. If resources are exhausted before the outbreak ends, then the 'don't wait' strategy results in the same number of infections in the outbreak as a circuit breaker strategy that uses all of the available resources. However, even in this latter case, the 'don't wait' strategy was still one of many equivalent, and optimal, strategies. Further support for the 'don't wait' strategy comes from the precautionary principle, which states that even when information is lacking, actions should be taken to prevent catastrophes [40]. In the context of our problem, when the outbreak begins, it is likely not known if resources will be sufficient to remain in place for the entire outbreak, the precautionary principle would then suggest the early, precautionary, implementation of public health measures, and our results further suggest that this approach would, at worst, perform the same as a different strategy.

5.1 Study limitations and future directions

The formalizations of the optimization problems that we consider follow closely from Hansen and Day [32], and are advantageous as the framework leads to clear descriptions of the qualitative characteristics of the optimal controls that are likely applicable in many general settings. However, some aspects of the problem formulation are likely responsible for the results.

The model formulation does not consider a cost associated with resource use and considers only a binary distinction between resources being limited or not limited. In reality, less resource use is likely to cost less and be preferred. Further, it is likely possible to increase the total resources available, although perhaps at some high cost. The conclusion that any strategy utilizing all available resources is optimal under limited resources might stem from the assumption of a fixed constraint on these resources (i.e., equations 3.6 and 3.7). Furthermore, the objective function does not consider the duration of the outbreak, and shorter outbreaks may be more desirable as public health measures do not need to remain in place for an extended period.

Our study uses a terminal condition which defines the outbreak as over when community infection prevalence reaches some low value, $I_{\min}$, which was necessary to prevent artificial second waves of infection when measures are released, and which occurs due to the formulation of the epidemiological dynamics modelled as ordinary differential equations. For the reasons stated, this type of formulation is necessary, however considering the problem on a fixed interval of time may have been more instructive since it is arguably not appropriate to compare the number of cases that occur for outbreaks that occur for different lengths of time, and especially when it is possible that another outbreak may occur after the end of a short outbreak.

The recent work of [53] contains important ideas on how to reconcile this challenge. Fully stochastic models can be difficult to analyze and questions considering elimination strategies can still be assessed if community outbreaks are modelled using deterministic Susceptible-Infected-Recovered-type models that are 'pieced together' over some fixed time, with zero incidence in the between-outbreak periods, with individual outbreak termination conditions as defined Hansen and Day [32], and with importations represented as discrete events that introduce infections and initiate the community outbreak. We refer to this as the 'community spread switch model' because the community spread model is turned on when an importation occurs and turned off when the terminal condition is met, and this occurs repeatedly across the fixed period being considered.

Our study has not considered any mechanisms, other than infection, whereby the number of susceptible individuals could change. Such mechanisms could be births, waning immunity, vaccination, human behaviour, and the evolution of the pathogen. Note that our optimal strategies require that if resources are limited, all available resources need to be used. Therefore, if susceptible individuals are removed by a mechanism other other infection, it is necessary to implement public health measures earlier, to ensure that resources do not remain after the outbreak ends, which is not optimal. This is similar to strategies implemented by some jurisdictions, i.e., Newfoundland and Labrador, during the COVID-19 pandemic, where relatively strict public health measures were implemented until the local community obtained substantial immunity through vaccination and the 'Together. Again' a plan to relax these measures was proposed [60].

If the pathogen evolves new epidemiological characteristics, as the SARS-CoV-2 virus did during the pandemic, it remains an open problem to determine the optimal timing of public health measures, such as the isolation of infected community members. 'Pandemic fatigue' [49] is a necessary consideration as compliance is likely to be lower after already prolonged periods of restrictions. Further, the pathogen may evolve, to be uncontrollable, for example evolving short generation times that make contact tracing difficult, and this would be an evolutionary reason why measures are less effective when timed later. Finally, public health measures are a component of the selection pressure that acts on the pathogen, and so the characteristics that pathogens evolve depend also on the public health strategy.

Our primary contributions have been to show that the model formulation of Hansen and Day [32] generalizes to problems that consider infection of community members from travelers. The framework of Hansen and Day [32] is amenable to novel insights, and we recommend that future work continues to expand on this problem set-up. In this thesis, we also worked to unite the terminology used in public health with the results of optimal control problems. The value of the optimal control problem formulation is to tangibly describe the situations in which each public health strategy is best. While the problem set-up involves the assumptions typically associated with ordinary differential equation model formulations, the results are qualitative, i.e., elimination, mitigation or circuit breaker strategies result from the implementation of a precautionary strategy. The specific details of any specific application might change quantitative nuances of the best public health strategies, but the general principles that we describe are likely applicable in many settings and contribute insights into important public health problems.

References

[1] A. Abakuks. Optimal Immunisation Policies for Epidemics. *Advances in Applied Probability*, 6(3):494–511, 1974.

[2] A. Abdelrazec, J. Bélair, C. Shan, and H. Zhu. Modeling the spread and control of dengue with limited public health resources. *Mathematical Biosciences*, 271:136–145, 2016.

[3] A. A. Agrachev and Y. L. Sachkov. *Control Theory from the Geometric Viewpoint*, volume 87 of *Encyclopaedia of Mathematical Sciences.* Springer Berlin Heidelberg, Berlin, Heidelberg, 2004.

[4] J. Arino, N. Bajeux, S. Portet, and J. Watmough. Quarantine and the risk of COVID-19 importation. *Epidemiology and Infection*, 148(298), 2020.

[5] J. Arino, P.-Y. Boëlle, E. Milliken, and S. Portet. Risk of COVID-19 variant importation – How useful are travel control measures? *Infectious Disease Modelling*, 6:875–897, 2021.

[6] J. Arino, J. R. Davis, D. Hartley, R. Jordan, J. M. Miller, and P. Van Den Driessche. A multi-species epidemic model with spatial dynamics. *Mathematical Medicine and Biology*, 22(2):129–142, 2005.

[7] R. Aylward and A. Alwan. Polio in Syria. *Lancet*, 383(9916):489–491, 2014.

[8] M. Baker, N. Wilson, and T. Blakely. Elimination could be the optimal response strategy for COVID-19 and other emerging pandemic diseases. *BMJ*, 371:4907, 2020.

[9] D. Balcan, V. Colizza, B. Goncalves, H. Hu, J. J. Ramasco, and A. Vespignani. Multiscale mobility networks and the spatial spreading of infectious diseases. *Proceedings of the National Academy of Sciences*, 106(51):28484–21489, 2009.

[10] H. Behncke. Optimal control of deterministic epidemics. *Optimal Control Applications and Methods*, 21(6):269–285, 2000.

[11] M. B. Bonsall, C. Huntingford, and T. Rawson. Optimal time to return to normality: parallel use of COVID-19 vaccines and circuit breakers, 2021.

[12] D. Brockmann and D. Helbing. The Hidden Geometry of Complex, Network-Driven Contagion Phenomena. *Science*, 342(6164):1337–1342, 2013.

[13] R. S. Burachik, C. Y. Kaya, and W. M. Moursi. Infeasible and Critically Feasible Optimal Control. *Journal of Optimization Theory and Applications*, 203(2):1219–1245, 2024.

[14] L. Böttcher, O. Woolley-Meza, N. a. M. Araújo, H. J. Herrmann, and D. Helbing. Disease-induced resource constraints can trigger explosive epidemics. *Scientific Reports*, 5(1):16571, 2015.

[15] M. Chinazzi, J. T. Davis, M. Ajelli, C. Gioannini, M. Litvinova, S. Merler, A. Pastore y Piontti, K. Mu, L. Rossi, K. Sun, C. Viboud, X. Xiong, H. Yu, M. E. Halloran, I. M. Longini, and A. Vespignani. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science*, 368(6489):395–400, 2020.

[16] A. Cox. 'Circuit-breaker' could help reduce COVID transmission, but not right away. *CBC News*, 2021.

[17] N. G. Davies, A. J. Kucharski, R. M. Eggo, A. Gimma, W. J. Edmunds, T. Jombart, K. O'Reilly, A. Endo, J. Hellewell, E. S. Nightingale, B. J. Quilty, C. I. Jarvis, T. W. Russell, P. Klepac, N. I. Bosse, S. Funk, S. Abbott, G. F. Medley, H. Gibbs, C. A. B. Pearson, S. Flasche, M. Jit, S. Clifford, K. Prem, C. Diamond, J. Emery, A. K. Deol, S. R. Procter, K. van Zandvoort, Y. F. Sun, J. D. Munday, A. Rosello, M. Auzenbergs, G. Knight, R. M. G. J. Houben, and Y. Liu. Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. *The Lancet Public Health*, 5(7):375–385, 2020.

[18] O. Diekmann, J. Heesterbeek, and T. Britton. Mathematical Tools for Understanding Infectious Disease Dynamics. *Mathematical Tools for Understanding Infectious Disease Dynamics*, 2013.

[19] L. C. Evans. *Partial Differential Equations*. American Mathematical Society, Providence, R.I, 2nd edition, 2010.

[20] L. C. Evans. *An Introduction to Mathematical Optimal Control Theory*. Lecture notes, 2013.

[21] A. S. Fauci and D. M. Morens. The Perpetual Challenge of Infectious Diseases. *New England Journal of Medicine*, 366(5):454–461, 2012.

[22] N. Ferguson, D. Laydon, G. Nedjati Gilani, N. Imai, K. Ainslie, M. Baguelin, S. Bhatia, A. Boonyasiri, Z. Cucunuba Perez, G. Cuomo-Dannenburg, A. Dighe, I. Dorigatti, H. Fu, K. Gaythorpe, W. Green, A. Hamlet, W. Hinsley, L. Okell, S. Van Elsland, H. Thompson, R. Verity, E. Volz, H. Wang, Y. Wang, P. Walker,

P. Winskill, C. Whittaker, C. Donnelly, S. Riley, and A. Ghani. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Technical report, Imperial College London, 2020.

[23] A. F. Filippov. On Certain Questions in the Theory of Optimal Control. *Journal of the Society for Industrial and Applied Mathematics Series A Control*, 1(1):76–84, 1962.

[24] A. F. Filippov. *Differential Equations with Discontinuous Righthand Sides: Control Systems*. Springer Science & Business Media, 1988.

[25] P. E. Fine and J. A. Clarkson. The recurrence of whooping cough: possible implications for assessment of vaccine efficacy. *Lancet (London, England)*, 1(8273):666–669, 1982.

[26] W. Fleming and R. Rishel. Existence and Continuity Properties of Optimal Controls. In W. Fleming and R. Rishel, editors, *Deterministic and Stochastic Optimal Control*, Applications of Mathematics. Springer, New York, NY, 1975.

[27] A. C. Fowler. Atto-Foxes and Other Minutiae. *Bulletin of Mathematical Biology*, 83(10):104, 2021.

[28] J. Gibson and C. Johnson. Singular Solutions in Problems of Optimal Control. *Department of Electrical and Computer Engineering Technical Reports*, 1963.

[29] T. H. Gronwall. Note on the Derivatives with Respect to a Parameter of the Solutions of a System of Differential Equations. *Annals of Mathematics*, 20(4):292–296, 1919.

[30] A. B. Gumel, S. Ruan, T. Day, J. Watmough, F. Brauer, P. van den Driessche,

D. Gabrielson, C. Bowman, M. E. Alexander, S. Ardal, J. Wu, and B. M. Sahai. Modelling strategies for controlling SARS outbreaks. *Proceedings. Biological Sciences*, 271(1554):2223–2232, 2004.

[31] X. W. S. Gwee, P. E. Y. Chua, and J. Pang. Global dengue importation: a systematic review. *BMC Infectious Diseases*, 21(1):1078, 2021.

[32] E. Hansen and T. Day. Optimal control of epidemics with limited resources. *Journal of Mathematical Biology*, 62(3):423–451, 2011.

[33] P. Hartman. *Ordinary differential equations.* Secaucus, New Jersey, U.S.A.: Birkhauser, 2nd edition, 1982.

[34] H. W. Hethcote. The Mathematics of Infectious Diseases. *SIAM Review*, 42(4):599–653, 2000.

[35] A. Heywood and C. R. MacIntyre. Eradication, elimination, suppression: let's understand what they mean before debating Australia's course, 2020.

[36] T. D. Hollingsworth, N. M. Ferguson, and R. M. Anderson. Will travel restrictions control the international spread of pandemic influenza? *Nature Medicine*, 12(5):497–499, 2006.

[37] R. Howard. The Gronwall Inequality, 1998.

[38] A. Hurford, M. Martignoni, J. Loredo-Osti, F. Anokye, J. Arino, B. Husain, B. Gaas, and J. Watmough. Pandemic modelling for regions implementing an elimination strategy. *Journal of Theoretical Biology*, 561:111378, 2022.

[39] A. Hurford and J. Watmough. Don't Wait, Re-escalate: Delayed Action Results in Longer Duration of COVID-19 Restrictions. In *Mathematics of Public*

Health: Proceedings of the Seminar on the Mathematical Modelling of COVID-19. Springer International Publishing, Cham, 2022.

[40] W. Jackson. *Protecting Public Health and the Environment: Implementing The Precautionary Principle*. Island Press, Washington, D.C, 1999.

[41] A. James, S. C. Hendy, M. J. Plank, and N. Steyn. Suppression and Mitigation Strategies for Control of COVID-19 in New Zealand, 2020.

[42] H. R. Joshi. Optimal control of an HIV immunology model. *Optimal Control Applications and Methods*, 23(4):199–213, 2002.

[43] M. Keeling and P. Rohani. *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press, 2007.

[44] M. J. Keeling, G. Guyver-Fletcher, L. Dyson, M. J. Tildesley, E. M. Hill, and G. F. Medley. Precautionary breaks: Planned, limited duration circuit breaks to control the prevalence of SARS-CoV-2 and the burden of COVID-19 disease. *Epidemics*, 37:100526, 2021.

[45] N. Khalil. *Optimality conditions for optimal control problems and applications*. PhD thesis, 2018.

[46] M. U. G. Kraemer, C.-H. Yang, B. Gutierrez, C.-H. Wu, B. Klein, D. M. Pigott, Open COVID-19 Data Working Group, L. du Plessis, N. R. Faria, R. Li, W. P. Hanage, J. S. Brownstein, M. Layan, A. Vespignani, H. Tian, C. Dye, O. G. Pybus, and S. V. Scarpino. The effect of human mobility and control measures on the COVID-19 epidemic in China. *Science (New York, N.Y.)*, 368(6490):493–497, 2020.

[47] S. Lenhart and J. T. Workman. *Optimal Control Applied to Biological Models*. Chapman and Hall/CRC, New York, 2007.

[48] A. Li and J. J. Ye. Necessary Optimality Conditions for Optimal Control Problems with Nonsmooth Mixed State and Control Constraints. *Set-Valued and Variational Analysis*, 24(3):449–470, 2016.

[49] L. Lilleholt, I. Zettler, C. Betsch, and R. Böhm. Development and validation of the pandemic fatigue scale. *Nature Communications*, 14(1):6352, 2023.

[50] K. Liu. Optimal Control Policy on COVID-19: An Empirical Study on Lockdown and Travel Restriction Measures using Reinforcement Learning. *International Journal of High School Research*, 4(3):60–68, 2022.

[51] M. Gameiro, J.P. Lessard, J. Mireles James, and K. Mischaikow. Gronwall Inequality - an overview | ScienceDirect Topics.

[52] S. Mannor and K. Xu. Go Viral, or Not: Rate-Optimal Control for Resource-Constrained Branching Processes, 2013.

[53] M. M. Martignoni, J. Arino, and A. Hurford. Is SARS-CoV-2 elimination or mitigation best? Regional and disease characteristics determine the recommended strategy. *Royal Society Open Science*, 11(6):240186, 2024.

[54] M. Meltzer, N. Cox, and K. Fukuda. The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention. *Emerging infectious diseases*, 5:659–71, 1999.

[55] C. J. E. Metcalf, S. F. Andriamandimby, R. E. Baker, E. E. Glennon, K. Hampson, T. D. Hollingsworth, P. Klepac, and A. Wesolowski. Challenges in evaluating

risks and policy options around endemic establishment or elimination of novel pathogens. *Epidemics*, 37:100507, 2021.

[56] W. Orenstein and S. M. Ahmed. Simply put: Vaccination saves lives. *Proceedings of the National Academy of Sciences*, 114:201704507, 2017.

[57] M. J. Penn and C. A. Donnelly. Asymptotic Analysis of Optimal Vaccination Policies. *Bulletin of Mathematical Biology*, 85(3):15, 2023.

[58] L. Perko. *Differential Equations and Dynamical Systems*, volume 7 of *Texts in Applied Mathematics*. Springer, New York, NY, 2001.

[59] L. S. Pontryagin. *L.S. Pontryagin selected works / Volume 4, The mathematical theory of optimal processes*. L.S. Pontryagin selected works. Gordon and Breach, New York, 1986.

[60] Public Health Emergency Committee. Report to the House of Assembly on the COVID-19 Public Health Emergency. Technical report, Feb. 2021.

[61] W. Qin, S. Tang, C. Xiang, and Y. Yang. Effects of limited medical resource on a Filippov infectious disease model induced by selection pressure. *Applied Mathematics and Computation*, 283:339–354, 2016.

[62] E. Roxin. Differential Equations: Classical to Controlled By Dahlard L. Lukes. *The American Mathematical Monthly, Taylor & Francis*, 1985.

[63] W. Rudin. *Principles of Mathematical Analysis*. McGraw-Hill, 1976.

[64] T. W. Russell, J. T. Wu, S. Clifford, W. J. Edmunds, A. J. Kucharski, and M. Jit. Effect of internationally imported cases on internal spread of COVID-19: a mathematical modelling study. *The Lancet Public Health*, 6(1):12–20, 2021.

[65] C. Shan, Y. Yi, and H. Zhu. Nilpotent singularities and dynamics in an SIR type of compartmental model with hospital resources. *Journal of Differential Equations*, 260(5):4339–4365, 2016.

[66] G. Teschl. *Ordinary Differential Equations and Dynamical Systems*. American Mathematical Society, 2012.

[67] H. E. Tillett. Infectious Diseases of Humans: Dynamics and Control. *Epidemiology & Infection*, 108(1):211–211, 1992.

[68] R. B. Vinter. Optimal Control and Pontryagin's Maximum Principle. In *Encyclopedia of Systems and Control*. Springer, London, 2013.

[69] A. Wang, Y. Xiao, and R. A. Cheke. Global dynamics of a piece-wise epidemic model with switching vaccination strategy. *Discrete and Continuous Dynamical Systems - B*, 19(9):2915–2940, 2014.

[70] W. Wang. Backward bifurcation of an epidemic model with treatment. *Mathematical Biosciences*, 201(1):58–71, May 2006.

[71] W. Wang and S. Ruan. Bifurcations in an epidemic model with constant removal rate of the infectives. *Journal of Mathematical Analysis and Applications*, 291(2):775–793, 2004.

[72] C. R. Wells, P. Sah, S. M. Moghadas, A. Pandey, A. Shoukat, Y. Wang, Z. Wang, L. A. Meyers, B. H. Singer, and A. P. Galvani. Impact of international travel and border control measures on the global spread of the novel 2019 coronavirus outbreak. *Proceedings of the National Academy of Sciences of the United States of America*, 117(13):7504–7509, 2020.

[73] WHO. Technical considerations for implementing a risk-based approach to international travel in the context of COVID-19: Interim guidance, 2 July 2021.

[74] S. Wu, R. Neill, C. D. Foo, A. Q. Chua, A.-S. Jung, V. Haldane, S. M. Abdalla, W.-j. Guan, S. Singh, A. Nordström, and H. Legido-Quigley. Aggressive containment, suppression, and mitigation of COVID-19: lessons learnt from eight countries. *BMJ*, 375:067508, 2021.

[75] X. Zhang and X. Liu. Backward bifurcation of an epidemic model with saturated treatment function. *Journal of Mathematical Analysis and Applications*, 348(1):433–443, 2008.

[76] L. Zhou and M. Fan. Dynamics of an SIR epidemic model with limited medical resources revisited. *Nonlinear Analysis: Real World Applications*, 13:312–324, 2012.