THE ROYAL SOCIETY
PUBLISHING

Optimal strategies to protect a sub-population at risk due to an established epidemic

Elliott H. Bussell and Nik J. Cunniffe

Department of Plant Sciences, University of Cambridge, Cambridge CB2 3EA, UK

NJC, 0000-0002-3533-8672

Epidemics can particularly threaten certain sub-populations. For example, for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the elderly are often preferentially protected. For diseases of plants and animals, certain sub-populations can drive mitigation because they are intrinsically more valuable for ecological, economic, socio-cultural or political reasons. Here, we use optimal control theory to identify strategies to optimally protect a 'high-value' sub-population when there is a limited budget and epidemiological uncertainty. We use protection of the Redwood National Park in California in the face of the large ongoing state-wide epidemic of sudden oak death (caused by *Phytophthora ramorum*) as a case study. We concentrate on whether control should be focused entirely within the National Park itself, or whether treatment of the growing epidemic in the surrounding 'buffer region' can instead be more profitable. We find that, depending on rates of infection and the size of the ongoing epidemic, focusing control on the high-value region is often optimal. However, priority should sometimes switch from the buffer region to the high-value region only as the local outbreak grows. We characterize how the timing of any switch depends on epidemiological and logistic parameters, and test robustness to systematic misspecification of these factors due to imperfect prior knowledge.

1. Introduction

Management of emerging infectious disease is most likely to be successful when it starts as soon as possible. Smaller epidemics are easier and less expensive to control than the larger epidemics which would result if management were to be delayed [1–4]. Sufficiently rapid intervention can even make eradication, or at least localized elimination, a realistic proposition [5,6]. Our recent experience with coronavirus disease 2019 (COVID-19) provides an object lesson. Governments of some countries in the Asia-Pacific region took early and decisive action to introduce non-pharmaceutical interventions [7,8]. Certain of these countries, perhaps most notably New Zealand, therefore appear to continue to be in a very good position to face the ongoing challenge of the global pandemic [9]. In particular, despite recent incursions [10], they seem better placed than any other nation to enact the 'zero COVID' strategy based on prompt responses to any incursion, with no tolerance for community transmission [11].

However, rapid responses are not always possible. Pathogens can become established in a host population without the diseases they cause being identified, particularly when effective surveillance systems are not in place [12–15] or if there is a long incubation period before symptoms [16,17]. Attempts to eliminate or eradicate are also not always successful [18]. If transmission is possible before—or perhaps even without—infected hosts showing symptoms, disease management is difficult [19–21]. Early in any outbreak, it might also

be unclear which controls or combinations of controls are likely to be most successful [22]. Particularly for plant and animal pathogens, there are often also economic constraints which mean that extensive and costly management is simply not justified [23].

Strategies to effectively mitigate well-established outbreaks are therefore very important. Plant disease epidemics provide a pressing example. The impacts of plant pathogens on food security [24] and ecosystem services [25] are well acknowledged. However, management of plant disease epidemics is very often a case of 'too little too late' [26]. For tree diseases, delays and/or deficiencies in detection have been implicated in high-profile failures of various large-scale control programmes, including for chestnut blight [27], white pine blister rust [28], Dutch elm disease [26] and citrus canker [29]. Indeed, elimination is often not even attempted. For example, following the first detection of ash dieback (a disease of ash trees caused by the fungus *Hymenoscyphus fraxineus*) into the UK in late 2012, a consensus was rapidly formed that country-wide management was unlikely to succeed because the pathogen was already so widely dispersed [30]. In Italy, control of olive quick decline syndrome (caused by the bacterial pathogen *Xylella fastidiosa*) is based entirely on slowing the spread, with management and detection focused on 'buffer' and 'containment' zones bordering an 'infected' zone within which the disease is, essentially, allowed to spread undetected and uncontrolled [31].

We take control of sudden oak death in coastal forests of central California to southwestern Oregon, caused by the oomycete *Phytophthora ramorum*, as an example of a well-established plant disease epidemic that still requires management. The generalist pathogen *P. ramorum* affects over 100 plant species, and broadly speaking causes two kinds of disease in the area in question: 'sudden oak death' on tanoaks and oaks (including coast live oak) and 'ramorum blight' on a large number of species of woody shrubs and forest understorey plants [32]. Sudden oak death causes large bleeding cankers to form on the main stem of affected trees, eventually leading to death [33]. However, some species affected by ramorum blight, in California most notably bay laurel, are not killed by the infection. They therefore act as 'spreader species' by supporting significant foliar sporulation over extended periods [34]. The pathogen spreads predominantly through short-distance rain splash dispersal of spores, but spores can be dispersed over longer distances by turbulent air currents, rivers and streams, or when carried by animals or human activity [35].

A very large sudden oak death epidemic has devastated coastal forests of central California to southwestern Oregon since its first detection in California in 1995, killing millions of oak (*Quercus* spp.) and tanoak (*Notholithocarpus densiflorus*) trees [36]. That epidemic is now very widespread, covering over 2000 km^2 in California alone [32,37] (figure 1*a*). Economic impacts are significant, with, for example, an estimated US \$135 million loss in property values attributed to the disease [39]. Recent large-scale modelling work has shown that successful control of sudden oak death in California is no longer possible, and indeed has been impossible for many years [40].

However, control of isolated outbreaks and localized management both remain firmly on the agenda. In 2001, a spatially distinct epidemic was identified in Curry County, Oregon, and since then over US\$20 million has been spent on identifying and treating that localized epidemic [32]. There are also other areas ahead of the main epidemic front

under active management, most notably a pair of relatively large outbreaks in Humboldt County, in California (figure 1*a*; the southern border of Humboldt County is at a latitude of around 40° N). Although further south than the outbreak in Oregon, the outbreaks in Humboldt county are some distance 'ahead' of the main bulk of the epidemic [41].

Disease management in Humboldt County exemplifies the challenges now posed by the control of sudden oak death. The goal is to design a management scheme that can effectively achieve a smaller, more local, objective than complete elimination or eradication. This could be, for example, slowing local rates of disease spread or protection of valuable resources [42]. This must be done when there is a limited budget available for control [40]. We focus here on strategies which reduce impacts of disease on a particular 'high-value' region, within which it is important to mitigate the effects of disease for ecological, economic, socio-cultural or political reasons.

For sudden oak death in California, any high-value region would most obviously be defined in terms of an area with particular ecological and/or socio-cultural value. The host species that is most affected—tanoak—is not grown for its timber. Disease impacts therefore predominantly include deleterious effects upon carbon sequestration, fuel dynamics and cultural resources. However, direct economic effects due to sudden oak death have been documented in California, most notably effects on property values [39]. Effects on timber production are also relevant in other areas. For example, emerging *P. ramorum* lineages in Oregon might also potentially threaten Douglas-fir silviculture. The epidemic caused by *P. ramorum* in the UK is most often known as 'sudden larch death', since the coniferous plantation species Japanese larch *Larix kaempferi* is predominantly affected in that context.

Although other controls such as chemical treatments have occasionally been promoted for *P. ramorum* [41], and despite targeted prophylactic removal of certain host species sometimes being recommended as a potentially highly effective strategy to reduce risks of sudden oak death epidemics [43], there is a consensus that effective disease management at medium to large spatial scales must be based upon removal of infected hosts [32,40]. The only outbreak of sudden oak death that is actively being controlled across large spatial scales in the USA, in Curry County, Oregon, is certainly being managed in this way [37]. We therefore concentrate exclusively on this type of control here.

The particular example we select to motivate our analysis is based upon the Redwood Creek outbreak (figure 1*b*). This outbreak was detected in May 2010 through stream monitoring, with the disease found to be present in a stream near Orick, at the mouth of Redwood Creek [44]. It was considered to be an outbreak of high significance owing to its proximity to Redwood National Park as well as the traditional and reservation lands of the Yurok and Hoopa tribes, respectively. Extensive detection efforts were carried out to identify the source of the infection, which was located in Redwood Valley in July 2010 [45]. Disease was also detected within the National Park within a few years of the initial incursion into Redwood Creek (figure 1*b*). Treatment aiming to prevent further damage to Redwood National Park is ongoing [46]. A pressing question is how limited control resources should be partitioned to protect the high-value region, i.e. the Redwood National Park. The most obvious, and pressing, question is whether management resources should be entirely focused on treating within the high-value region itself, or whether treatment of
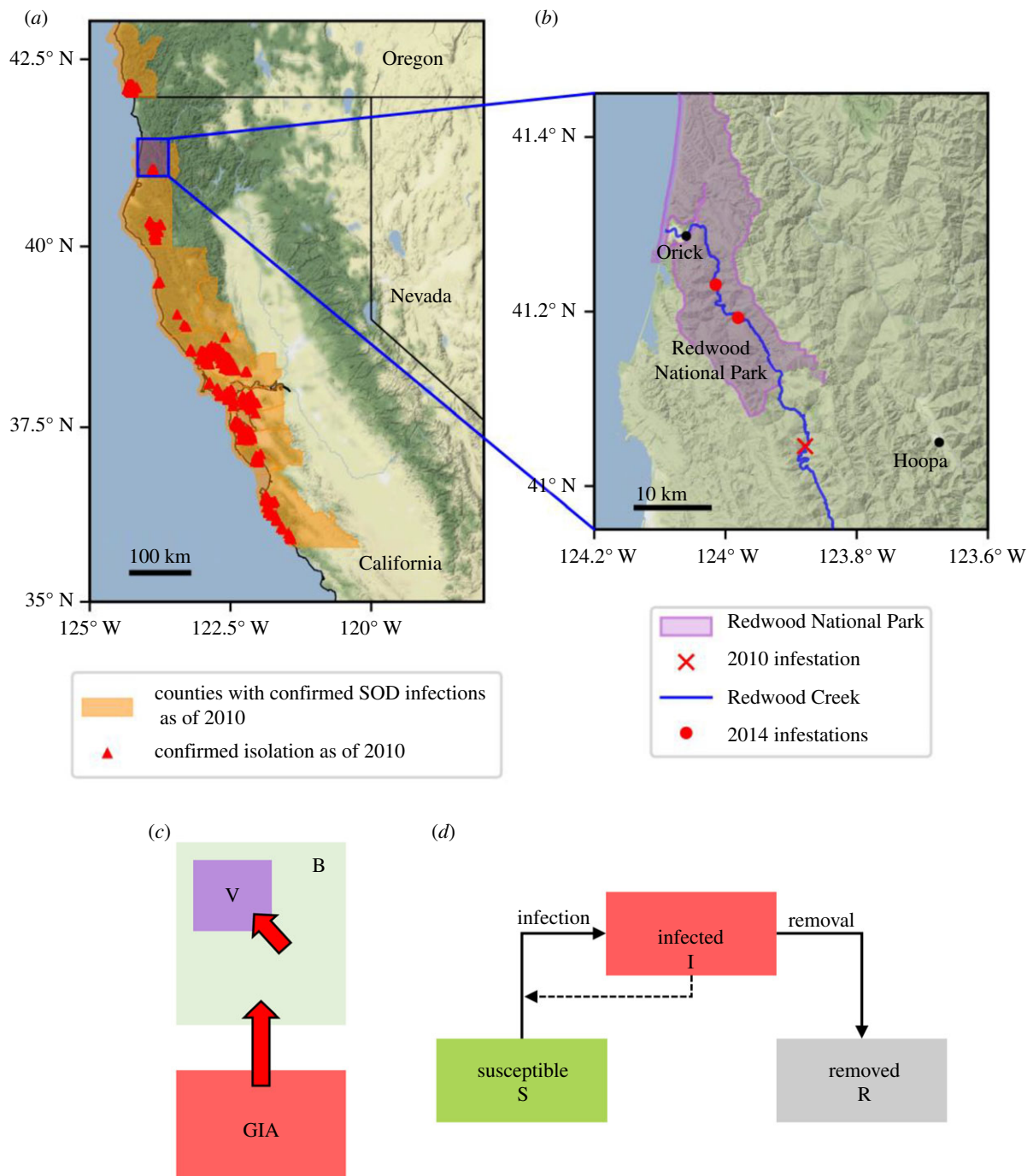
Figure 1. Maps showing areas with confirmed sudden oak death (SOD) infections, and schematics of our model's spatial structure and within-patch dynamics. (*a*) Confirmed sudden oak death infections in California in 2010 (infected counties as specified in [32], with locations of confirmed isolations taken from the SODmap project [38]). The bulk of the epidemic lies in a relatively contiguous and heavily infested area of coastal California centred roughly on latitude 37.5° N, near to the sites of first detection of the disease in Marin and Santa Cruz counties. More northerly outbreaks have thus far remained more spatially distinct. (*b*) Area near to Redwood National Park, showing the location of the initial incursion as well as the later detections of symptoms within the borders of the National Park itself (locations of infestations in 2010 and 2014 again taken from [38]). (*c*) The spatial structure of the system as modelled. A generally infested area (GIA, which here corresponds to the rest of California) provides a source of inoculum, generating a constant force of infection on a buffer region which is only very lightly infected (B, which here corresponds to Redwood Creek). The infection can then in turn invade the high-value region (V, which here corresponds to the Redwood Creek National Park). The goal of control is to protect the hosts in the high-value region. (*d*) Within each region the epidemic follows SIR dynamics, where hosts move from susceptible (S) to infected (I) and are removed by the disease or through control (R). The dashed line indicates that the number of infected hosts influences the infection rate; removal includes components corresponding to both disease-induced host mortality as well as roguing (i.e. removal of infectious hosts as a form of disease control).

the growing epidemic in the surrounding areas can better serve the goal of protecting the National Park.

We show in principle how control strategies to protect the high-value region can be designed and tested using a mathematical model. The role of modelling in optimizing decision making in disease control is now well established [47], including in plant health [19]. Models offer a rational

basis to decide where, when and how to control disease outbreaks [48]. However, the conventional approach for testing interventions via models—comparing a relatively small number of pre-specified intervention strategies—necessarily risks sub-optimal performance, since only a small subset of all possible strategies can ever be tested in depth [40]. Recent work has shown how the search space of possible

interventions can be unambiguously explored for plant diseases using optimal control theory [49–56].

We concentrate here upon how optimal control theory can be used to solve the problem of prioritizing different areas for disease management. Our analysis is a proof of concept, capturing the key features of the Redwood Creek outbreak of sudden oak death in a simple way. Indeed, while detailed models of this system are possible [40,50], here we instead concentrate on a rather general model, which in principle is applicable to many host–pathogen combinations. We test the performance of optimal control theory in optimizing management in this model, performing extensive scans over different values of epidemiological and logistical parameters, ensuring a wide range of scenarios are captured. Since we deliberately phrase our mathematical model to omit many system-specific details, our results therefore illustrate epidemiological principles important whenever a subset of host individuals must be protected in the face of a large, ongoing epidemic.

In particular, we use optimal control theory to understand how time-dependent disease management can be optimized in order to protect a high-value region at risk from a growing, spreading epidemic. We account for economic and logistical limitations in control by introducing a budgetary constraint such that only a finite number of infected hosts can be treated per unit time [52,56]. We then seek to understand how these finite resources for disease management should be partitioned, and whether and how the balance of control effort within *versus* outside the high-value region changes over time and with the state of the epidemic. Management strategies as derived using optimal control theory can often be rather complex [50,51]. We therefore focus here on how optimal strategies can be characterized in an intuitive and understandable fashion. This would be a precondition of implementation by local managers and other stakeholders. We also use our model to understand how optimal management strategies would be affected by alterations to, or imprecision in our knowledge of, epidemiological and/or logistic parameters, commonly the case in tackling an emerging epidemic [22].

2. Methods

2.1. Epidemiological model
We split the host landscape into three disjoint regions: a generally infested area in which the disease is already well established, a buffer region in which the disease might perhaps be present, but has not yet become established, and a high-value region that is currently entirely uninfected and that must be protected. In the context of Redwood Creek and sudden oak death, the generally infested area would correspond to the large epidemic across large parts of California [41], the buffer region would be the recently infected forests of the Redwood Creek watershed [45] and the high-value region would be the Redwood National Park [46] (figure 1*b*,*c*). To reduce the number of state variables and parameters in our model, we simplify the epidemic in the generally infested area such that it is represented as a source of external inoculum, generating a constant force of infection upon the buffer region (in general, the 'force of infection' is the *per capita* rate at which susceptible hosts become infected [57]; here we assume the component of this corresponding to the epidemic elsewhere remains constant over time). This simplification is valid when considering new, relatively isolated outbreaks of disease: a common situation for diseases such as sudden oak death that are spread over long distances through rare long-distance dispersal events [36]. As shown in electronic supplementary material, S1

text, the effects of even a growing rather than constant-sized external epidemic upon the dynamics within the region of interest can also often be subsumed into an appropriately time-averaged external force of infection. Since we scan over a range of values of the constant force of infection in the results we present, we consider the simplification we make to use only constant values of this parameter to therefore not be unduly restrictive.

The buffer and high-value regions are modelled as well-mixed patches, meaning that the only spatial component in our model is between-patch coupling. We use a (S)usceptible–(I)nfected–(R)emoved model for the epidemic dynamics in each patch [57], in which hosts can be susceptible to the disease (S), infected and infectious (I) or removed (R) (figure 1*d*). We assume that infection can potentially kill hosts, meaning that an infected host can be removed either by disease-induced death or via disease control. Guided by the epidemiology of sudden oak death, for which standing dead trees are not considered to be a significant source of inoculum (particularly in comparison with foliar hosts which are not killed by infection) we assume that removed hosts cannot cause other hosts to become infected [33]. We seek to optimize management of the epidemic by determining time-dependent allocations of control resource to the buffer and high-value regions, treating a time-varying proportion of the infected hosts in each region. This control, which for plant pathogens is often known as 'roguing' [58], is therefore the only form of disease management we allow for in our model.

Each patch has a particular fixed population size (N_B and N_V for the buffer and high-value regions, respectively), and the two patches are linked for transmission, symmetrically, by a coupling constant ϵ. Taking the within-patch transmission rate to be β, and assuming density-dependent transmission [57], we obtain the following system:

$$\frac{\mathrm{d}S_B}{\mathrm{d}t} = -\mathcal{F}S_B - \beta I_B S_B - \epsilon\beta I_V S_B, \tag{2.1a}$$

$$\frac{\mathrm{d}I_B}{\mathrm{d}t} = \mathcal{F}S_B + \beta I_B S_B + \epsilon\beta I_V S_B - \mu I_B - f_B(t)\eta I_B, \tag{2.1b}$$

$$\frac{\mathrm{d}S_V}{\mathrm{d}t} = -\beta I_V S_V - \epsilon\beta I_B S_V \tag{2.1c}$$

and $$\frac{\mathrm{d}I_V}{\mathrm{d}t} = \beta I_V S_V + \epsilon\beta I_B S_V - \mu I_V - f_V(t)\eta I_V, \tag{2.1d}$$

in which the subscripts B and V refer to the buffer and high-value regions, respectively. The (constant) external force of infection from the generally infested area is given by $\mathcal{F}$, and we assume that only the buffer region can be thus infected. The infectious period in the absence of control is assumed to be $1/\mu$. Infected hosts can also be removed by roguing at an additional rate η. The control inputs $f_B(t)$ and $f_V(t)$ are the time-dependent proportions of infected hosts that are being controlled at time t in the buffer and high-value regions, respectively. It is the functions $f_B(t)$ and $f_V(t)$ that we seek to identify in our optimal control problem.

2.2. Optimal control problem
The objective of control is to limit the pathogen's impacts on the high-value region. In particular, we aim to minimize the number of infected and removed hosts in the high-value region at some terminal time T. Since our model does not include host demography, this is equivalent to maximizing the number of susceptible hosts retained in the high-value region at this time.

We capture the economic and logistical limitations of disease management by restricting the total number of hosts that can be rogued per unit time (over both regions). The maximum expenditure rate, i.e. the largest number of hosts that can instantaneously be rogued, is assumed to be M. This gives the following optimal control problem:

$$\min_{f_i(t)} \quad J = N_V - S_V(T), \tag{2.2a}$$

$$\text{subject to} \quad f_B(t)I_B(t) + f_V(t)I_V(t) \leq M \;\forall t, \tag{2.2b}$$

$$0 \leq f_i(t) \leq 1, \tag{2.2c}$$

Table 1. Definitions of parameter and state variables, with biological meanings and default values.

symbol	meaning	default	sensitivity scans
N_B	number of hosts (buffer region)	500 hosts	
N_V	number of hosts (high-value region)	100 hosts	
S_B	number of susceptible hosts (buffer region)	n.a.	
S_V	number of susceptible hosts (high-value region)	n.a.	
I_B	number of infected hosts (buffer region)	n.a.	
I_V	number of infected hosts (high-value region)	n.a.	
$f_B(t)$	proportion rogued at time t (buffer region)	n.a.	
$f_V(t)$	proportion rogued at time t (high-value region)	n.a.	
J	objective function	equation (2.2a)	
M	maximum expenditure rate	10 hosts	figure 4a
β	infection rate	0.005 host^{-1} t^{-1}	figures 3–5
η	roguing rate	0.2 t^{-1}	figure 4b
$I_B(0)$	initial number of infected hosts (buffer region)	5 hosts	figure 5a
F	external force of infection	0.0 t^{-1}	figure 5b
$I_V(0)$	initial number of infected hosts (high-value region)	0 hosts	
T	time horizon of interest	12.5 t	
ϵ	coupling between regions	0.3	
μ	pathogen-induced death rate	1.0 t^{-1}	

in which the state dynamics are controlled by equation (2.1) and the index $i \in \{B, V\}$.

We solve the optimal control problem using a direct formulation [59]. In particular, we time-discretize values of the state and control variables, and treat these as optimization variables in a nonlinear programming (NLP) problem. State dynamics and initial conditions are included as constraints on the NLP variables, and the optimization is carried out to minimize the objective value.

We use the BOCOP package (v. 2.0.5) [60] to generate the NLP problem, coding the state dynamics (equation (2.1)) in C++. The package automates discretization of the system using a fourth-order Runge–Kutta method. The NLP problem that results is solved using the software Ipopt [61], which implements an interior point optimization method. The BOCOP software allows extraction of the Lagrange multipliers associated with the state dynamics, i.e. the co-state or adjoint dynamics of the optimal control problem. Using these the relative importance of control in each region can be derived since the higher the co-state, the more benefit to the objective there is from control in that region. This gives the control priority of each region over time, which characterizes the overall control policy in readily understandable terms.

2.3. Model parameterization

Although our modelling was motivated by the spread of sudden oak death in the vicinity of Redwood National Park, our focus here is not to develop detailed control recommendations for any particular application. Our numerical work instead concentrates upon characterizing the broad features of optimal controls, and how these features are conditioned on parameter values. We therefore identify a plausible, although arbitrary, parameterization of our model (table 1), and use it to drive our analysis.

We follow previous modelling work targeting the sudden oak death system [36,40,62] in using numbers of 'hosts' as a convenient shorthand for the appropriate modelling quantum, which almost always corresponds to a relatively large area of contiguous vegetation, and which accounts implicitly for species-specific differences in infectivity and susceptibility. The unit used to measure host abundance is scaled into the numerical values of the infection rate (β)

and maximum budget (M), anyway, and so the dimensions of these quantities do not affect our results. We scale time by the infectious period in the absence of control, allowing us to fix the disease-induced removal rate to be $\mu = 1$ in all numerical work.

2.4. Scenarios tested

In the absence of any budgetary constraint, it might be expected that control would be maximal at all times throughout the epidemic in both regions (i.e. $f_B(t) = f_V(t) = 1$ for all t). We verified this was indeed the case in our exploratory work by running our optimization procedure using our default parameterization, but with the maximum budget, M, set to be a very large value. We therefore reverted to a more limited budget for our remaining numerical work, and first concentrated on identifying broad classes of control strategy. As we describe below, these could conveniently be characterized in terms of which region was prioritized for control at which points of the epidemic. We then considered how the details of optimal management strategies were affected by the values of epidemiological and logistic parameters. Finally, we investigated the robustness of our results, by examining the performance of optimal controls as derived from a model in which the infection rate was systematically misspecified.

3. Results

3.1. Optimal strategies can be characterized in terms of which region(s) are prioritized for control

3.1.1. Prioritizing the high-value region for all time

For our default parameter set (table 1), the optimal strategy prioritizes control of infection in the high-value region throughout the entire epidemic (figure 2). However, since the cost of control within the high-value region at any given time depends on the number of infected hosts it then contains, often the high-value region can be treated at the
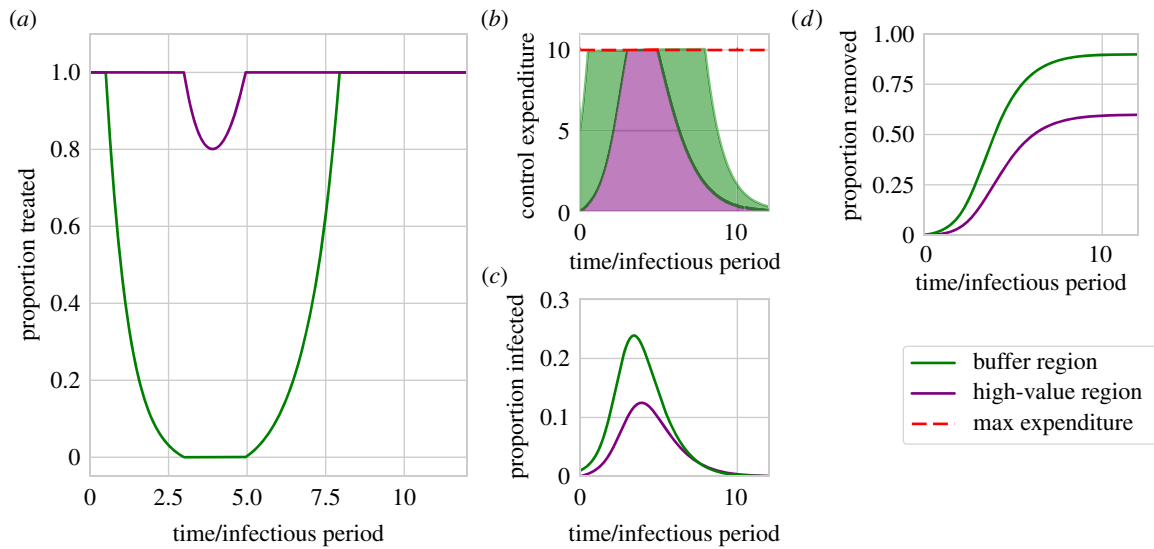
Figure 2. Optimal control can sometimes focus disease management upon the high-value region throughout the entire epidemic. The optimal strategy as found for the default model parameterization (table 1). (a) The proportion of hosts treated in each region over time. (b) The number of hosts being treated—which corresponds to the expenditure—in each region over time. The optimal strategy allocates as many resources as possible to the high-value region, before spending any remainder in the buffer region. Between around 3 and 5 time units the cost of maximally removing infected hosts in the high-value region would exceed the maximum permissible expenditure, M, and so a proportion of infected hosts go untreated even in the high-value region. (c) The time dependence in the proportion of hosts infected in both regions. (d) Proportions of hosts that are removed (either by disease-induced death or by control).

maximal rate (i.e. $f_V(t) = 1$), but some budget nevertheless remains unspent (i.e. $f_V(t)I_V(t) = I_V(t) < M$). During these periods the optimal strategy diverts any remaining resources to the buffer region (i.e. $f_B(t) > 0$ for these times).

However, for our default model parameterization, there is also a period in the vicinity of the epidemic peak during which there is insufficient resource to fully control all infected hosts in the high-value region (i.e. $I_V(t) > M$). Infected hosts within the high-value region then cannot be treated at the maximum rate (i.e. $f_V(t) < 1$), since it would be too expensive. For the default parameterization of our model, this occurs at around $3 < t < 5$ time units.

In general, for strategies which focus upon the high-value region throughout the epidemic, whether or not there is such a period within which the budget would be exceeded by fully controlling the epidemic in the high-value region depends on the interplay between the maximum budget and the dynamics of disease (see below).

3.1.2. Switching focus from the buffer to the high-value region

For other parameter sets, however, the optimal strategy switches focus between regions as the epidemic progresses (figure 3 shows results from a model parameterization for which this occurs). Early in the epidemic it is optimal to prioritize the buffer region, since doing so slows spread into the high-value region. However, later in the epidemic the high-value region is again prioritized (although for these parameters there is still some budget to partially treat the buffer region, even when the high-value region is treated as aggressively as possible, i.e. $f_V(t) = 1$).

A naive expectation might be that the switch is driven by the optimal strategy targeting whichever region generates the larger force of infection on the high-value region at any time. However, the switch time is not simply when the force of infection upon the high-value region from within itself becomes greater than that from outside. This is exemplified by figure 3e, which shows that, even for this

parameterization, the force of infection upon the high-value region from itself remains smaller than that from the buffer region throughout the epidemic, despite the switch in focus of the optimal control at $t \approx 6$ units of time.

Further switches, i.e. multiple changes in focus between the two regions, can occur while budgets are not limiting. In these cases, since the budget is not limiting, control can be maximal in both regions and so the switch has no effect on the control performed. For the range of parameters we considered here, we do not see strategies with multiple switches which impact the control performed.

3.2. The optimal strategy depends on epidemiological and logistic parameters

3.2.1. Switching focus between regions is often optimal at 'intermediate' transmission rates

The switching strategy exemplified by figure 3 is promoted by intermediate values of the infection rate, β, although the precise meaning of 'intermediate' is heavily conditioned upon the maximum budget, M (figure 4a).

Epidemics spreading slowly are relatively easy to manage, and so can be controlled simply by always treating in the high-value region. High infection rates give epidemics that spread rapidly, and so the more important high-value region must again always be prioritized to keep the epidemic under control there. At intermediate spread rates, however, disease spreads slowly enough to allow reduction of infectious pressure by initially treating in the buffer region, but sufficiently quickly that such a reduction of pressure from the buffer is necessary to ensure an optimal result.

The diagonal 'kink' in the shading in figure 4a corresponds to a change in optimal control regime. At high maximum budgets, the budget never limits the amount of control that can be carried out (above the diagonal kink). At very low maximum budgets, control resources are always limited and the optimal control must distribute the resource appropriately. There is
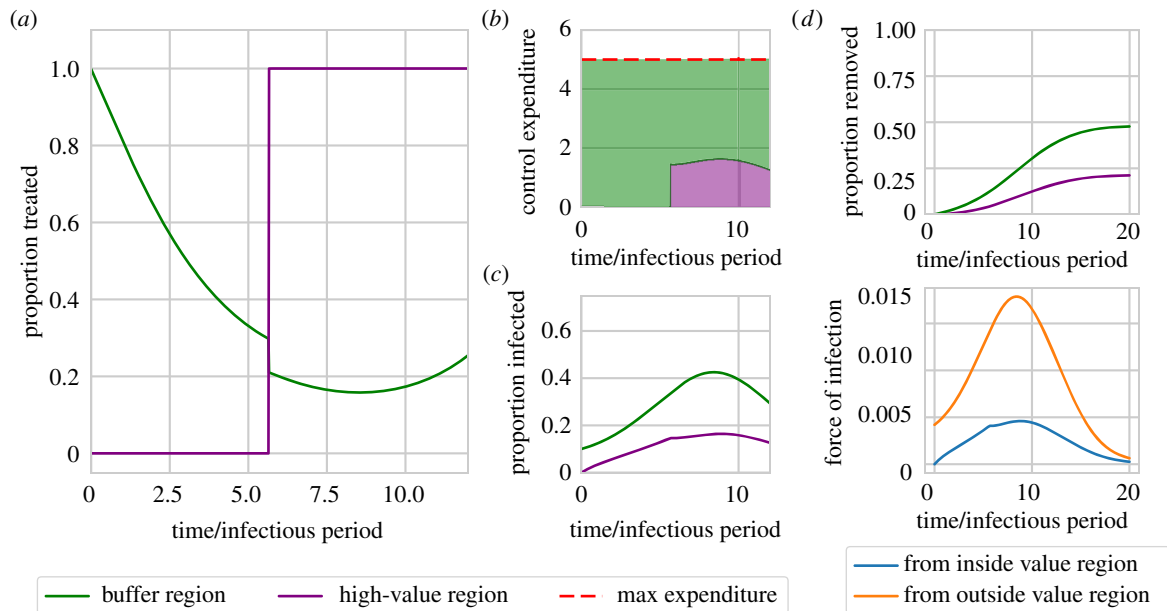
Figure 3. An alternative optimal strategy initially focuses management upon the buffer region, but switches to concentrate roguing within the high-value region as the epidemic takes hold. The optimal strategy as found for a model parameterization slightly altered from the default in table 1, with a smaller infection rate ($\beta = 0.0028$ host^{-1} t^{-1}) and smaller maximum budget ($M = 5$ hosts). Panels (a) and (b) show the proportion and number treated over time in both regions. For these parameters, for approximately the first 6 units of time, the buffer region is prioritized, before the optimal control strategy switches to prioritizing the high-value region thereafter. Disease progress curves are shown in (c) and (d). Panel (e) shows the force of infection in the high-value region from inside and outside the same region. Since the largest part of the infectious pressure on the high-value region comes from the buffer region throughout the entire epidemic, the identity of the region providing the dominant infectious pressure cannot be the sole driver of the switch.

an intermediate region where the optimal control transforms between the two regimes.

3.2.2. Effect of the maximum rate of control
The effect of the maximum control rate η is shown in figure 4b, revealing the value of this parameter also affects which values of the rate of infection (β) require a switch of focus in the optimal control strategy. As control becomes potentially more effective through faster maximum rates of treatment, the intermediate range over which a switching strategy is optimal shifts to faster spreading epidemics which have higher infection rates.

3.2.3. Effect of the initial level of infection and the external infectious pressure
Figure 5 shows the response of the switching time to the infection rate, β, the number of initially infected hosts in the buffer region, $I_B(0)$, and the external force of infection, F (recall in our model external inoculum can only infect the buffer region).

At low levels of initial infection in the buffer and/or external force of infection, the switching strategy is once again optimal at intermediate infection rates. However, as the rate of invasion of the buffer is increased, through either more initial infection or via a higher external force of infection, the range of infection rates over which a switching strategy is optimal decreases. For sufficiently high rates of invasion in the buffer region (i.e. moving up the y-axis in figure 5a,b) a switching strategy becomes sub-optimal, because the disease spreads faster in the buffer, and so control is less effective there than in the high-value region.

The particular shapes of the responses in figure 5a,b are affected by where the maximum expenditure rate becomes limiting, with the budget becoming more constraining towards the upper right corners. While we do not attempt to explain the

underlying drivers for the optimal control allocation for each parameterization, the pattern of optimal control does change when the budget no longer allows maximal control for the whole epidemic. Note that, for some values of the external force of infection, optimal strategies with additional switches are found; these are the grey regions in figure 5b. As described already, these switches occur while the budget is not limiting, and so have no effect on the control realized.

To illustrate the full range of possibilities for the optimal control strategy, we focus on three particular cases taken from figure 5b. Case A finds a switch but as the budget is not limiting, it has no effect. In case B, the budget is limiting so the switch has an effect. In case C, there is an additional switch early in the epidemic, but since the budget is not limiting at that point it has no effect.

3.3. Optimal strategies can be robust to model misspecification, but require some prior knowledge of transmission dynamics
Finally, we test how these optimal strategies perform when the parameters controlling the underlying model are not known accurately (figure 6). We do this by introducing a systematic error into the infection rate of the model used to optimize the control strategy, varying the value of β from 50% smaller to 50% larger than the 'true' value. The resulting optimal control specifies an expenditure over time ($f_i(t)I_i(t)$ for each region) which is applied to a model with the 'true' infection rate. Large errors in the infection rate lead to worse control of the epidemic. It is also important to note that, for large underestimates of the infection rate, the optimized control is worse than simply allocating the full budget to the high-value region, with no treatment in the buffer region. The optimized control strategies lead to
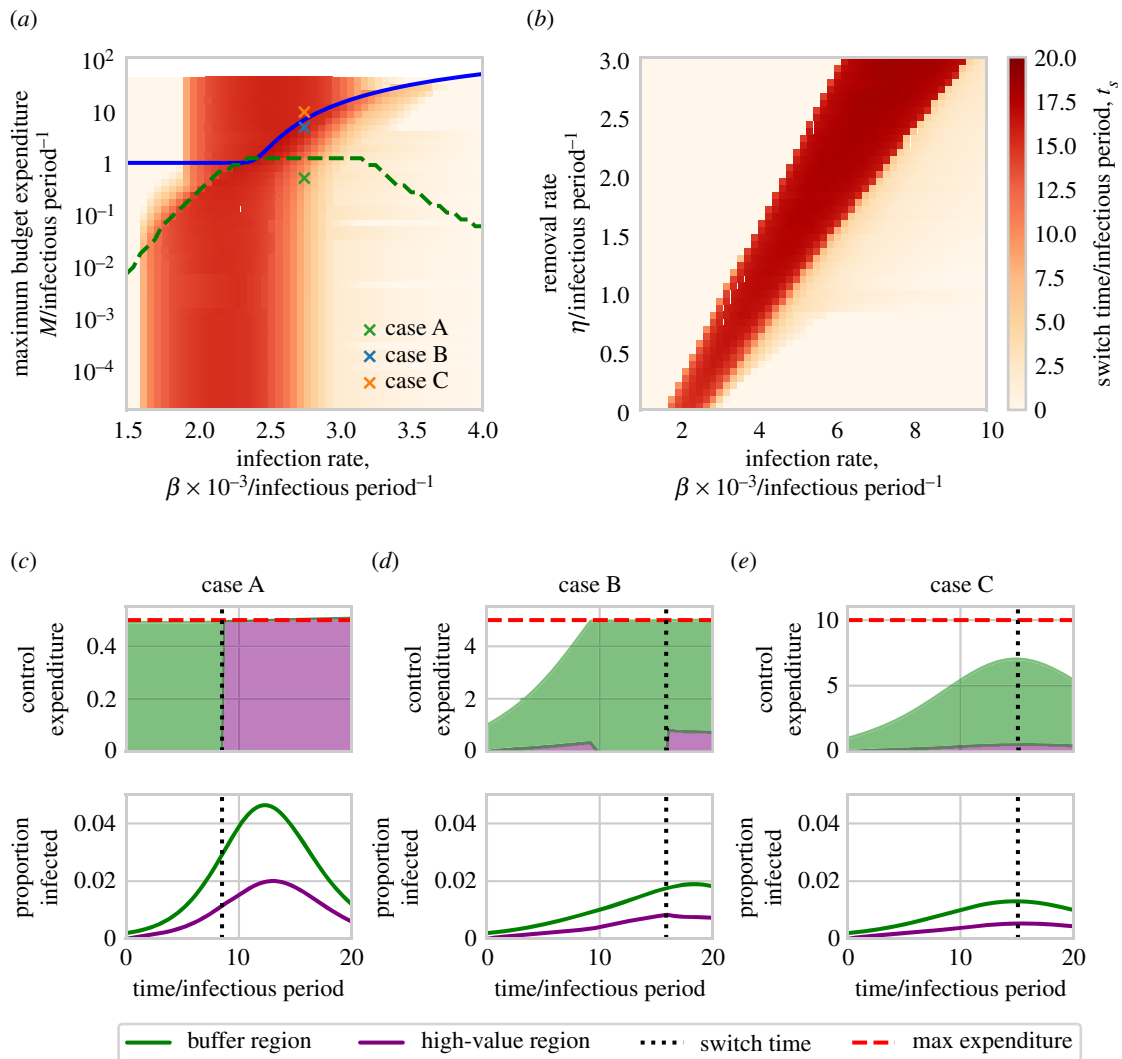
Figure 4. Effect of the infection rate, maximum budget and rate of control on the optimal switching time. Parameter scans were run relative to a baseline set by the default parameters in table 1, although with only a single initially infected host in the buffer region ($I_B(0) = 1$) and using a longer time scale of interest ($T = 20$) to allow patterns in switching times to be more clearly seen. Panels (a) and (b) show the effect of infection rate (β) combined with the maximum budget (M) and removal rate (η), respectively. In all cases, switching is optimal for intermediate values of the infection rate, β, although as control becomes more effective the range of infection rates over which a switch is optimal is shifted to higher values. The 'kink' in (a) is caused by whether or not the maximum budget is exceeded by fully treating the high-value region (see main text). The blue line indicates where the budget becomes limiting on control resources, i.e. below the blue line maximal control can be carried out in both regions for the full epidemic. The green dashed line indicates where the budget becomes limiting for the full simulation time, i.e. below this line there is never any resource to spare. Panels (c)–(e) show control expenditure and disease progress for parameter sets corresponding to points A, B and C (as marked on panel (a)), illustrating the range of behaviour that is possible as the maximum budget is changed. In all cases, the switching time is marked with a dotted vertical line. Note that the switch in priority in case C does not affect the control that is carried out, since the budget is not limiting at the time in question.

wasted resources that could be better allocated to the other region (figure 6b,c). These results suggest that if prior knowledge of parameters controlling transmission is imprecise, simpler control strategies might be better [63].

4. Discussion

Landscape-scale control of sudden oak death in California has not been possible for some years [40]. However, highly valuable sub-populations at risk due to the epidemic—such as areas important for tourism or cultural reasons, or for ecological reasons to conserve biodiversity—might yet be protected. Slowing spread to these regions is itself valuable [42]. An obvious question is then how this goal can best be achieved. This requires partitioning limited resources for

disease management between the population of particular interest and the growing epidemic elsewhere, and determining whether this partitioning should vary with time and with the current state of the epidemic [64]. This must be done in a situation in which different sets of stakeholders have different objectives [65], but must nevertheless work together [66].

We used the outbreak of sudden oak death in Humboldt County, California, to motivate our work. After developing a simple mathematical model representing disease within the 'high-value' region of the Redwood National Park and in a 'buffer' region surrounding it, we used optimal control theory to find the most effective time-varying allocation of a limited budget for disease management between these two regions. To minimize the final amount of infection in the National Park, we found it is very often better to prioritize exclusively that area for treatment (figure 2). However, while
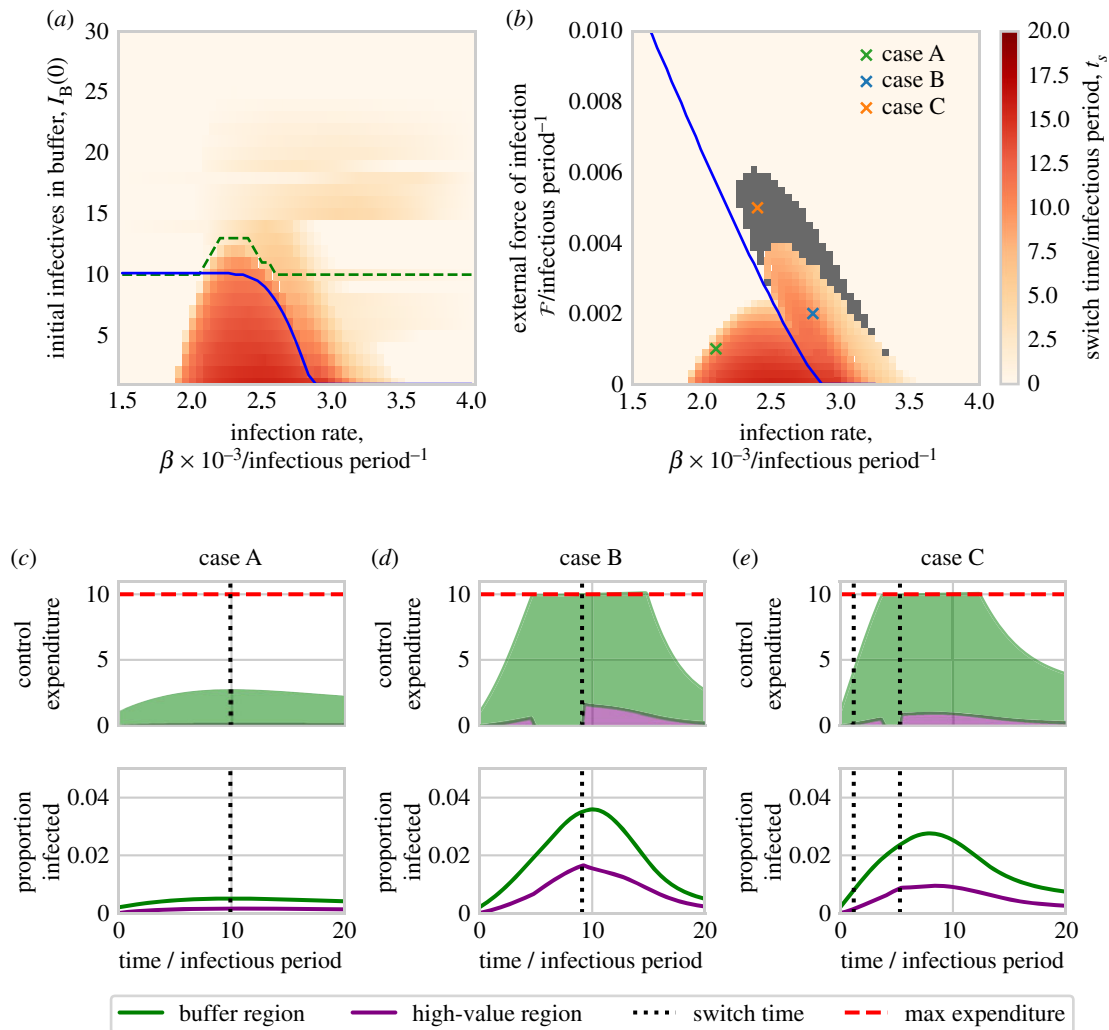
Figure 5. Effect of the initial level of infection within, and force of infection upon, the buffer region. Parameter scans were run relative to a baseline set by the default parameters in table 1, although using a longer time scale of interest ($T = 20$) to allow patterns in switching times to be more clearly seen. Panel (a) shows the switch time as a function of the infection rate, β, and the initial number of infected hosts in the buffer region, $I_B(0)$. The blue line indicates where the budget becomes limiting on control resources, i.e. below the blue line maximal control can be carried out in both regions for the full epidemic. The green dashed line indicates when the optimal control switch occurs while the budget is limiting, i.e. above this line when priority switches to the value region, the budget is still limiting. Panel (b) shows the effect of the infection rate, β, and the external force of infection on the buffer region, $\mathcal{F}$ (with a single initially infected host in the buffer region, $I_B(0) = 1$). The blue line has the same meaning as in (a). The grey region highlights sets of parameters for which multiple switches are identified. Panels (c–e) show control expenditure and disease progress for parameter sets corresponding to points A, B and C (as marked on (a)), illustrating the range of behaviour that is possible as the external force of infection is increased (see main text). In all cases, any switching time is marked with a dotted vertical line; note that for the single switch in case A, and the first of the two switches in case C, since the budget is not limiting at the time in question, the switch in priority does not affect the control that is carried out.

it is clearly very intuitive, we have identified that this strategy is not always optimal. It can instead be better to start by prioritizing disease control in the buffer region, and only to switch to prioritizing the high-value region later in the epidemic (figure 3). We have found that such a 'switching' strategy is most likely to be optimal for intermediate values of the infection rate (figure 3).

This type of policy involving switching attention from reducing a long-term threat to focusing on short-term gains has been identified before. For example, Hastings *et al.* [67] used a class-structured model to investigate control of *Spartina alterniflora* (an invasive species of deciduous grass) in Willapa Bay, Washington. The key prediction was that early control within each season should preferentially remove plants from the class with the highest reproductive value, only shifting later to remove plants that contribute most to the next season's population. Similar switching strategies

have also been found in other studies relating to management of invasive species [68].

Switching strategies have also been identified in other epidemiological models. For example, Ndeffo Mbah & Gilligan [56] found that disease management across sub-populations is most efficient when resources are first allocated to whichever group is more infected, and later switching to treat the less infected group. A similar strategy was even found in [55] for management of sudden oak death. Switching strategies have also been found for distribution of prophylactic vaccines in a spatially structured population [69], and switching between immunization and palliative care during an epidemic when resources are limited [70].

For the simple model we considered here, the optimal strategies could in fact probably have been identified by an exhaustive scan over switching times. However, for more complex models with more complex switching strategies this will
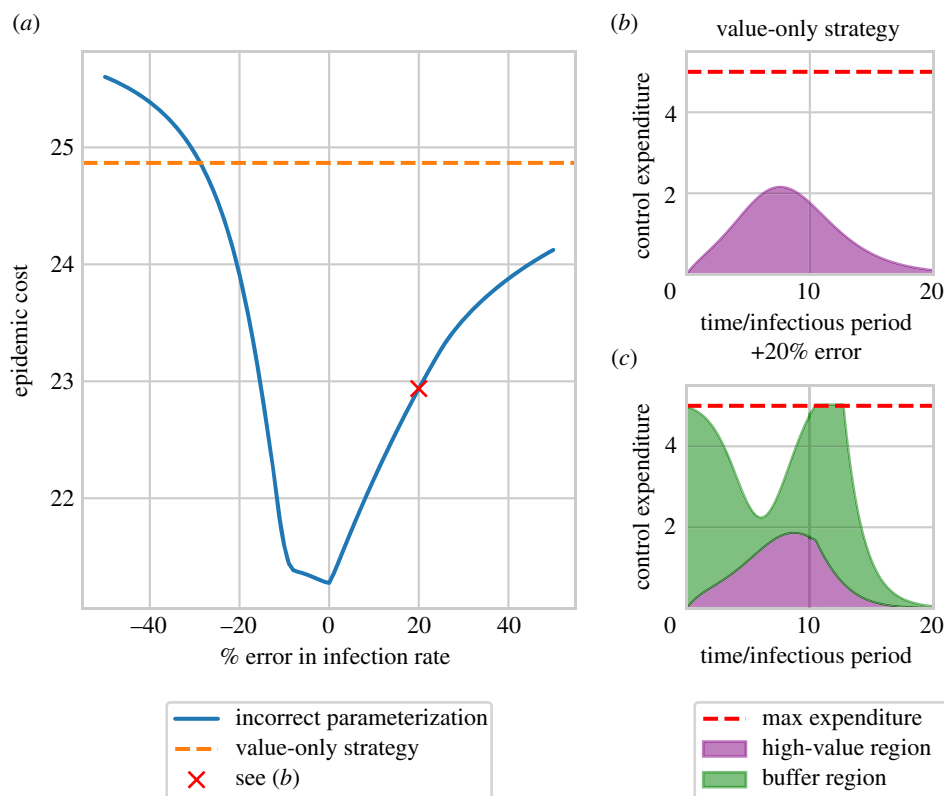
Figure 6. Effect of incorrect parameterization on the performance of optimal control strategies. Control is optimized using an incorrect infection rate, and the budget allocations applied to the correct model. The baseline parameters use the default values, with an infection rate of 0.0028 host^{-1} t^{-1} and a maximum expenditure rate of 5 hosts, the same values as used for the switching strategy in figure 3. Panel (a) shows the epidemic cost as the percentage error in the infection rate is varied. Larger errors lead to worse performance, and can be worse than the simple strategy of full allocation to the high-value region (shown in (b)). Panel (c) shows the wasted control resources using an infection rate overestimated by 20%. Here too much control is allocated to the high-value region that cannot be spent, and so is wasted. Similarly, not enough resources are allocated when the infection rate is underestimated, also leading to wasted control resources.

not generally be true. While the setting was highly simplified, we can already begin to see some of the potential limitations of these more complex strategies for practical use. Although not included in our analysis, there are additional costs associated with changing policy during an epidemic, i.e. switching region priorities, and these costs must be balanced with the benefit to epidemic control. These costs could be included in the objective function as optimized, for example, by adding a term penalizing rapidly changing controls [71].

Direct use of optimal control theory also facilitated the extensive scans over alternative parameterizations of our model (figures 3 and 5), allowing our relatively intuitive characterization of a number of outcomes based on which region is prioritized. Although some work in optimal control of plant disease does translate strategies for practical application, and consider the impact of parameters (e.g. [53]), more often results are presented for a single parameterization and tend not to focus on the practical implementability of the strategies that result [49,72–75].

We have also shown how imprecision in knowledge of parameters controlling disease spread can lead to less effective disease management (figure 6). Indeed, in such cases, it may even be better to use the simplest possible strategy rather than use optimal control theory at all. Consideration of parameter uncertainty when determining the optimal strategy is important [2]. The type of control strategy identified here, a bang–bang switching control, can be particularly sensitive to precise knowledge about the optimal switch time. Forster & Gilligan [76] showed that, when applying control optimized using

a mean-field model of an epidemic to a spatially explicit model, errors in the switch time can lead to performance that is worse than a simple constant strategy. A previous study [68] showed that, when controlling invasive species, the optimal strategy when parameters are known precisely is not always optimal when parameter uncertainty is introduced. This also echoes results from so-called 'risk-based' control strategies, which attempt to use additional epidemiological information to develop precise control strategies. When knowledge is limited simpler control strategies are very likely to be more appropriate [63].

While here we have focused on the particular example of sudden oak death, we note our model is sufficiently abstract that, at least in principle, it could apply in other settings. Control by artificially shortening hosts' infectious period could correspond to, for example, antibiotic treatment of agricultural animals, or encouraging individuals to self-isolate following symptoms of human respiratory diseases. Analogous problems in which a particular region or sub-population must be protected in the face of an ongoing epidemic also arise rather naturally for other pathosystems. For example, for COVID-19 in western Europe, an obvious focus before the effects of vaccination became apparent lay in reducing numbers of infections of elderly residents of care facilities, since older individuals tend to suffer much worse outcomes following infection [77].

We concentrated here upon only the relative amounts of one single control—i.e. removing infected hosts—in each of our two regions. For sudden oak death, a number of other management

strategies are sometimes recommended [43], and these were not included in our model. In particular, we did not consider preemptive removal of 'spreader' host species such as California bay laurel that drive local epidemics. Such 'thinning' is well acknowledged to reduce the risk of *P. ramorum* infection entering an individual stand, or the rate at which it spreads following invasion [50]. Our main motivation to only consider a single control strategy was simplicity: two distinct controls (i.e. reactive removal of infected hosts and preemptive removal of healthy hosts) would immediately double the complexity of the optimization problem (cf. equation (2.2)). It would also increase, perhaps significantly, the complexity of the optimal strategies that would need to be interpreted. We also note that preemptive removal of healthy hosts is somewhat specific to plant diseases in natural environments and so including it here would dilute the generic nature of our study. Finally, species-specific host removal rates would be difficult to represent in the type of model used here, in which all potentially infected species are amalgamated into a single category of 'hosts' [36,62]. However, we note preemptive removal of certain host species has been included in more detailed system-specific models of sudden oak death in particular, including our own [50], and (perhaps unsurprisingly) suggest the focus of control should switch from preemptive to reactive treatments as any local epidemic becomes larger.

This paper is intended to be an illustrative analysis, highlighting the epidemiological principles at play when protecting a valuable sub-population in the face of an otherwise unmitigated epidemic. We therefore deliberately simplified the wide range of management strategies available for sudden oak death, and instead concentrated in detail on a single type of management, i.e. removing infected hosts. However, this was sufficient for us to show that the obvious benefit of direct treatment of the most valuable region might be outweighed by the delayed benefit from treating elsewhere [64].

However, as illustrated by our analysis, the optimal strategy depends on the complex interplay between the epidemiological parameters, the level of precision with which these parameters are known, the budget available for control and the current state of the epidemic. For practical application, our model would need to be extended to more faithfully capture sudden oak death epidemiology, for which cryptic infection, long-distance dispersal, epidemiological differences between different host species, spatial structure, alternate control strategies and stochasticity are all likely to be important. Given that, at least under some circumstances, the cost of protecting the high-value region is felt by stakeholders elsewhere, accounting for stakeholder behaviour could also be an interesting extension to the modelling work presented here [78,79]. However, recent work has shown how insights derived via optimal control theory could nevertheless potentially be applied irrespective of any or all of these complexities [50,51]. By showing how non-intuitive control strategies might arise from such an exercise, the key contribution of this paper is to develop a framework for identifying broad categories of control strategy to further investigate in such a setting.

References

1. Althaus C, Low N, Musa EO, Shuaib F, Gsteiger S. 2015 Ebola virus disease outbreak in Nigeria: transmission dynamics and rapid control. *Epidemics* **11**, 80–84. (doi:10.1016/j.epidem.2015.03.001)

2. Epanchin-Niell RS, Hastings A. 2010 Controlling established invaders: integrating economics and spread dynamics to determine optimal management. *Ecol. Lett.* **13**, 528–541. (doi:10.1111/j.1461-0248.2010.01440.x)

3. Hoffman SJ, Silverberg SL. 2018 Delays in global disease outbreak responses: Lessons from H1N1, Ebola, and Zika. *Am. J. Public Health* **108**, 329–333. (doi:10.2105/AJPH.2017.304245)

4. Longini IMJ, Nizam A, Xu S, Ungchusak K, Hanshaoworakul W, Cummings DA, Halloran ME. 2015 Containing pandemic influenza at the source. *Science* **309**, 1083–1087. (doi:10.1126/science.1115717)

5. Dowdle WR. 1998 The principles of disease elimination and eradication. *Bull. World Health Organ.* **76**(Suppl 2), 22–25.

6. Klepac P, Funk S, Hollingsworth TD, Metcalf CJE, Hampson K. 2015 Six challenges in the eradication of infectious diseases. *Epidemics* **10**, 97–101. (doi:10.1016/j.epidem.2014.12.001)

7. Pearce N, Lawlor DA, Brickley EB. 2020 Comparisons between countries are essential for the control of COVID-19. *Int. J. Epidemiol.* **49**, 1059–1062. (doi:10.1093/ije/dyaa108)

8. Thompson RN *et al.* 2020 Key questions for modelling covid-19 exit strategies. *Proc. R. Soc. B* **287**, 20201405. (doi:10.1098/rspb.2020.1405)

9. Summers J, Cheng H-Y, Lin H-H, Barnard LT, Kvalsvig A, Wilson N, Baker MG. 2020 Potential lessons from the Taiwan and New Zealand health responses to the Covid-19 pandemic. *Lancet Reg. Health – Western Pacific* **4**, 100044. (doi:10.1016/j.lanwpc.2020.100044)

10. Dyer O. 2021 Covid-19: Australian outbreak surges as New Zealand sees first domestic cases in six months. *BMJ* **374**, n2050.

11. Baker MG, Kvalsvig A, Verrall AJ. 2020 New Zealand's COVID-19 elimination strategy. *Med. J. Aust.* **213**, 198–200. (doi:10.5694/mja2.50735)

12. Carvajal-Yepes M *et al.* 2019 A global surveillance system for crop diseases. *Science* **364**, 1237–1239. (doi:10.1126/science.aaw1572)

13. Grogan LF, Berger L, Rose K, Grillo V, Cashins SD, Skerratt LF. 2014 Surveillance for emerging biodiversity diseases of wildlife. *PLoS Pathog.* **10**, 1–4. (doi:10.1371/journal.ppat.1004015)

14. Mastin AJ, Gottwald TR, Cunniffe NJ, Parnell S. 2020 Optimising risk-based surveillance for early detection of invasive plant pathogens. *PLoS Biol.* **18**, e3000863. (doi:10.1371/journal.pbio.3000863)

15. Ristaino JB *et al.* 2021 The persistent threat of emerging plant disease pandemics to global food security. *Proc. Natl Acad. Sci. USA* **118**, e2022239118. (doi:10.1073/pnas.2022239118)

16. Khan R, Peak CM, Fernandez-Gracia J, Hill A, Jambaid A, Gandae L, Castrof MC, Buckee CO. 2020 Incubation periods impact the spatial predictability of cholera and Ebola outbreaks in Sierra Leone. *Proc. Natl Acad. Sci. USA* **117**, 5067–5073. (doi:10.1073/pnas.1922867117)

17. Thompson RN, Gilligan CA, Cunniffe NJ. 2016 Detecting presymptomatic infection is necessary to

forecast major epidemics in the earliest stages of infectious disease outbreaks. *PLoS Comput. Biol.* **12**, 1–18. (doi:10.1371/journal.pcbi.1004836)

18. Thompson RN, Gilligan CA, Cunniffe NJ. 2020 Will an outbreak exceed available resources for control? Estimating the risk from invading pathogens using practical definitions of a severe epidemic. *J. R. Soc. Interface* **17**, 20200690. (doi:10.1098/rsif.2020.0690)

19. Cunniffe NJ, Gilligan CA. 2020 Use of mathematical models to predict epidemics and to optimize disease detection and management. In *Emerging plant diseases and global food security* (eds JB Ristaino, A Records), ch. 12. St. Paul, MN: APS Press.

20. Cunniffe NJ, Stutt ROJH, DeSimone RE, Gottwald TR, Gilligan CA. 2015 Optimising and communicating options for the control of invasive plant disease when there is epidemiological uncertainty. *PLoS Comput. Biol.* **11**, e1004211. (doi:10.1371/journal.pcbi.1004211)

21. Fraser C, Riley S, Anderson RM, Ferguson NM. 2004 Factors that make an infectious disease outbreak controllable. *Proc. Natl Acad. Sci. USA* **101**, 6146–6151. (doi:10.1073/pnas.0307506101)

22. Thompson RN, Gilligan CA, Cunniffe NJ. 2018 Control fast or control smart: when should invading pathogens be controlled?. *PLoS Comput. Biol.* **14**, e1006014. (doi:10.1371/journal.pcbi.1006014)

23. Wilkinson K *et al.* 2011 Infectious diseases of animals and plants: an interdisciplinary approach. *Phil. Trans. R. Soc. B* **366**, 1933–1942. (doi:10.1098/rstb.2010.0415)

24. Strange RN, Scott PR. 2005 Plant disease: a threat to global food security. *Annu. Rev. Phytopathol.* **43**, 83–116. (doi:10.1146/annurev.phyto.43.113004.133839)

25. Boyd IL, Freer-Smith PH, Gilligan CA, Godfray HCJ. 2013 The consequence of tree pests and diseases for ecosystem services. *Science* **342**, 1235773.

26. Tomlinson I, Potter C. 2010 'Too little, too late'? Science, policy and Dutch elm disease in the UK. *J. Hist. Geogr.* **36**, 121–131. (doi:10.1016/j.jhg.2009.07.003)

27. Freinkel S. 1997 *American chestnut: the life, death, and rebirth of a perfect tree*. Oakland, CA: University of California Press.

28. Maloy O. 1997 White pine blister rust control in North America: a case history. *Annu. Rev. Phytopathol.* **35**, 87–109. (doi:10.1146/annurev.phyto.35.1.87)

29. Gottwald TR. 2007 Citrus canker and citrus huanglongbing, two exotic bacterial diseases threatening the citrus industries of the Western Hemisphere. *Outlooks Pest Manage.* **18**, 274–279. (doi:10.1564/18dec09)

30. Thomas PA. 2016 Biological flora of the british isles: Fraxinus excelsior. *J. Ecol.* **104**, 1158–1209. (doi:10.1111/1365-2745.12566)

31. EFSA Panel on Plant Health (PLH), Bragard C *et al.* 2019 Update of the scientific opinion on the risks to plant health posed by xylella fastidiosa in the eu territory. *EFSA J.* **17**, e05665.

32. Grünwald NJ, LeBoldus JM, Hamelin RC. 2019 Ecology and evolution of the sudden oak death pathogen *Phytophthora ramorum*. *Annu. Rev. Phytopathol.* **57**, 301–321. (doi:10.1146/annurev-phyto-082718-100117)

33. Rizzo D, Garbeletto M, Hansen EM. 2005 *Phytophthora ramorum*: integrative research and management of an emerging pathogen in California and Oregon forests. *Annu. Rev. Phytopathol.* **43**, 309–335. (doi:10.1146/annurev.phyto.42.040803.140418)

34. Grünwald NJ, Goss EM, Press CM. 2008 *Phytophthora ramorum*: a pathogen with a remarkably wide host range causing sudden oak death on oaks and ramorum blight on woody ornamentals. *Mol. Plant Pathol.* **9**, 729–740. (doi:10.1111/j.1364-3703.2008.00500.x)

35. Grünwald N, Garbeletto M, Goss EM, Heugnens K, Prospero S. 2012 Emergence of the sudden oak death pathogen *Phytophthora ramorum*. *Trends Microbiol.* **20**, 131–138. (doi:10.1016/j.tim.2011.12.006)

36. Meentemeyer RK, Cunniffe NJ, Cook AR, Filipe JAN, Hunter RD, Rizzo DM, Gilligan CA. 2011 Epidemiological modeling of invasion in heterogeneous landscapes: spread of sudden oak death in California (1990–2030). *Ecosphere* **2**, 17. (doi:10.1890/ES10-00192.1)

37. Peterson E, Hansen E, Kanaskie A. 2015 Temporal epidemiology of sudden oak death in Oregon. *Phytopathology* **105**, 937–946. (doi:10.1094/PHYTO-12-14-0348-FI)

38. Garbeletto M, Maddison E, Schmidt D. 2014 SODmap and SODmap Mobile: two tools to monitor the spread of sudden oak death. *Forest Phytophthoras* **4**. (doi:10.5399/osu/fp.4.1.3560)

39. Kovacs K, Vaclavik T, Haight R, Pang A, Cunniffe N, Gilligan C, Meentemeyer R. 2011 Predicting the economic costs and property value losses attributed to sudden oak death damage in California (2010-2020). *J. Environ. Manage.* **92**, 1292–1302. (doi:10.1016/j.jenvman.2010.12.018)

40. Cunniffe NJ, Cobb RC, Meentemeyer RK, Rizzo DM, Gilligan CA. 2016 Modeling when, where, and how to manage a forest epidemic, motivated by sudden oak death in California. *Proc. Natl Acad. Sci. USA* **113**, 5640–5645. (doi:10.1073/pnas.1602153113)

41. Alexander J, Lee CA. 2010 Lessons learned from a decade of sudden oak death in California: evaluating local management. *Environ. Manage.* **46**, 315–328. (doi:10.1007/s00267-010-9512-4)

42. Cobb R *et al.* 2013 Biodiversity conservation in the face of dramatic forest disease: an integrated conservation strategy for tanoak (*Notholithocarpus densiflorus*) threatened by sudden oak death. *Madrono* **60**, 151–164. (doi:10.3120/0024-9637-60.2.151)

43. Swiecki TJ, Bernhardt EA. 2013 A reference manual for managing sudden oak death in California. Technical Report PSW-GTR-242, U.S. Department of Agriculture, Forest Service, Pacific Southwest Research Station.

44. Valachovic Y, Quinn-Davidson L, Goldsworthy E, Cannon P. 2013 Novel approaches to SOD management in California wildlands: a case study of 'eradication' and collaboration in Redwood Valley. In *Proc. of the Sudden Oak Death Fifth Science Symp.*, pp. 99–107.

45. Stark D, Twieg B, Valachovic Y. 2014 Sudden oak death in the Redwood Creek watershed and potential drought impacts. In *Redwood Creek Symp. Proc.*, p. 10.

46. Croucher P, Mascheretti S, Garbelotto M. 2013 Combining field epidemiological information and genetic data to comprehensively reconstruct the invasion history and the microevolution of the sudden oak death agent *Phytophthora ramorum* (Stramenopila: Oomycetes) in California. *Biol. Invasions* **15**, 2281–2297. (doi:10.1007/s10530-013-0453-8)

47. Lofgren ET *et al.* 2014 Opinion: mathematical models: a key tool for outbreak response. *Proc. Natl Acad. Sci. USA* **111**, 18 095–18 096. (doi:10.1073/pnas.1421551111)

48. Cunniffe NJ, Koskella B, Parnell S, Gottwald TR, Gilligan CA. 2015 Thirteen challenges in modelling plant diseases. *Epidemics* **10**, 6–10. (doi:10.1016/j.epidem.2014.06.002)

49. Bokil VA, Allen LJS, Jeger MJ, Lenhart S. 2019 Optimal control of a vectored plant disease model for a crop with continuous replanting. *J. Biol. Dyn.* **13**, 325–353. (doi:10.1080/17513758.2019.1622808)

50. Bussell E, Cunniffe N. 2020 Applying optimal control theory to a spatial simulation model of sudden oak death: ongoing surveillance protects tanoak while conserving biodiversity. *J. R Soc. Interface* **17**, 20190671. (doi:10.1098/rsif.2019.0671)

51. Bussell E, Dangerfield C, Gilligan C, Cunniffe N. 2019 Applying optimal control theory to complex epidemiological models to inform real-world disease management. *Phil. Trans. R. Soc. B* **374**, 20180284. (doi:10.1098/rstb.2018.0284)

52. Dangerfield CE, Vyska M, Gilligan CA. 2019 Resource allocation for epidemic control across multiple sub-populations. *Bull. Math. Biol.* **81**, 1731–1759. (doi:10.1007/s11538-019-00584-2)

53. Hamelin FM, Bowen B, Bernhard P, Bokil VA. 2021 Optimal control of plant disease epidemics with clean seed usage. *Bull. Math. Biol.* **83**, 46. (doi:10.1007/s11538-021-00872-w)

54. Ndeffo Mbah ML, Gilligan CA. 2010 Balancing detection and eradication for control of epidemics: sudden oak death in mixed-species stands. *PLoS ONE* **5**, e12317. (doi:10.1371/journal.pone.0012317)

55. Ndeffo Mbah ML, Gilligan CA. 2010 Optimization of control strategies for epidemics in heterogeneous populations with symmetric and asymmetric transmission. *J. Theor. Biol.* **262**, 757–763. (doi:10.1016/j.jtbi.2009.11.001)

56. Ndeffo Mbah ML, Gilligan CA. 2011 Resource allocation for epidemic control in metapopulations. *PLoS ONE* **6**, e24577. (doi:10.1371/journal.pone.0024577)

57. Keeling MJ, Rohani P. 2008 *Modeling infectious diseases in humans and animals*. Princeton, NJ: Princeton University Press.

58. Cunniffe NJ, Laranjeira FF, Neri FM, DeSimone RE, Gilligan CA. 2014 Cost-effective control of plant disease when epidemiological knowledge is incomplete: modelling Bahia bark scaling of citrus. *PLoS Comput. Biol.* **10**, e1003753. (doi:10.1371/journal.pcbi.1003753)

59. Betts J. 2010 *Practical methods for optimal control and estimation using nonlinear programming*. Philidelphia, PA: SIAM.

60. Team Commands, Inria Saclay 2017. BOCOP: an open source toolbox for optimal control. See http://bocop.org.

61. Wächter A, Biegler LT. 2006 On the implementation of an interior-point filter line-search algorithm for large-scale nonlinear programming. *Math. Programming* **106**, 25–57. (doi:10.1007/s10107-004-0559-y)

62. Thompson RN, Cobb RC, Gilligan CA, Cunniffe NJ. 2016 Management of invading pathogens should be informed by epidemiology rather than administrative boundaries. *Ecol. Modell.* **324**, 28–32. (doi:10.1016/j.ecolmodel.2015.12.014)

63. Hyatt-Twynam SR, Parnell S, Stutt ROJH, Gottwald TR, Gilligan CA, Cunniffe NJ. 2017 Risk-based management of invading plant disease. *N. Phytol.* **214**, 1317–1329. (doi:10.1111/nph.14488)

64. Rowthorn RE, Laxminarayan R, Gilligan CA. 2009 Optimal control of epidemics in metapopulations. *J. R. Soc. Interface* **6**, 1135–1144. (doi:10.1098/rsif.2008.0402)

65. Craig AP, Cunniffe NJ, Parry M, Laranjeira FF, Gilligan CA. 2018 Grower and regulator conflict in management of the citrus disease huanglongbing in Brazil: a modelling study. *J. Appl. Ecol.* **55**, 1956–1965. (doi:10.1111/1365-2664.13122)

66. Laranjeira FF, Silva SXB, Murray-Watson RE, Soares ACF, Santos-Filho HP, Cunniffe NJ. 2020 Spatiotemporal dynamics and modelling support the case for area-wide management of citrus greasy spot in a Brazilian smallholder farming region. *Plant Pathol.* **69**, 467–483. (doi:10.1111/ppa.13146)

67. Hastings A, Hall RJ, Taylor CM. 2006 A simple approach to optimal control of invasive species. *Theor. Popul. Biol.* **70**, 431–435. (doi:10.1016/j.tpb.2006.05.003)

68. Carrasco LR, Baker R, MacLeod A, Knight JD, Mumford JD. 2009 Optimal and robust control of invasive alien species spreading in homogeneous landscapes. *J. R. Soc. Interface* **7**, 529–540. (doi:10.1098/rsif.2009.0266)

69. Keeling MJ, Shattock A. 2012 Optimal but unequitable prophylactic distribution of vaccine. *Epidemics* **4**, 78–85. (doi:10.1016/j.epidem.2012.03.001)

70. Klepac P, Bjørnstad ON, Metcalf CJE, Grenfell BT. 2012 Optimizing reactive responses to outbreaks of immunizing infections: balancing case management and vaccination. *PLoS ONE* **7**, e41428. (doi:10.1371/journal.pone.0041428)

71. Clarke J, White K, Turner K. 2013 Approximating optimal controls for networks when there are combinations of population-level and targeted measures available: chlamydia infection as a case-study. *Bull. Math. Biol.* **75**, 1747–1777. (doi:10.1007/s11538-013-9867-9)

72. Alemneh HT, Kassa AS, Godana AA. 2021 An optimal control model with cost effectiveness analysis of maize streak virus disease in maize plant. *Infect. Dis. Modell.* **6**, 169–182. (doi:10.1016/j.idm.2020.12.001)

73. Basir FA, Ray S. 2020 Impact of farming awareness based roguing, insecticide spraying and optimal control on the dynamics of mosaic disease. *Ricerche di Matematica* **69**, 393–412. (doi:10.1007/s11587-020-00522-8)

74. Basir FA, Roy P, Ray S. 2017 Impact of roguing and insecticide spraying on mosaic disease in *Jatropha curcas*. *Control Cybern.* **46**, 325–344.

75. Chen-Charpentier B, Jackson M. 2020 Optimal control of plant virus propagation. *Math. Methods Appl. Sci.* **43**, 8147–8157. (doi:10.1002/mma.6244)

76. Forster G, Gilligan CA. 2007 Optimizing the control of disease infestations at the landscape scale. *Proc. Natl Acad. Sci. USA* **104**, 4984–4989. (doi:10.1073/pnas.0607900104)

77. Palmer S, Cunniffe NJ, Donnelly R. 2021 Covid-19 hospitalization rates rise exponentially with age, inversely proportional to thymic T-cell production. *J. R. Soc. Interface* **18**, 20200982. (doi:10.1098/rsif.2020.0982)

78. Milne AE, Gottwald T, Parnell SR, Alonso Chavez V. 2020 What makes or breaks a campaign to stop an invading plant pathogen? *PLoS Comput. Biol.* **16**, e1007570. (doi:10.1371/journal.pcbi.1007570)

79. Murray-Watson RE, Hamelin FM, Cunniffe NJ. 2021 It ain't what you do, it's what drives why you do it: how the basis of growers' decision making affects the effectiveness of disease control. *BioRxiv*.