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Authors Robert E. Rowthorn[1], Ramanan Laxminaryan[2] and Christopher A. Gilligan[3]

[1] Dept. of Economics, University of Cambridge, Sidgwick Avenue, Cambridge, CB3 9DD, U.K.

[2] Resources for the Future, 1616 P Street, NW Washington, DC 20036, U.S.A.

[3]Epidemiology and Modelling Group, Dept. of Plant Sciences, University of Cambridge, Downing Street, Cambridge, CB2 3EA, U.K.

Corresponding author C.A. Gilligan Telephone +44 1223 333900 email – cag1@cam.ac.uk

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Table 1	15	1800
120 space above figs		960
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Optimal control of epidemics in metapopulations

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Abstract

Little is known about how best to deploy scarce resources for disease control when epidemics occur in different but inter-connected regions. We use a combination of optimal control methods and epidemiological theory for metapopulations to address this problem. We consider what strategy should be used if the objective is to minimise the discounted number of infected individuals during the course of an epidemic. We show, for a system with two inter-connected regions and an epidemic in which infected individuals recover and can be reinfected, that equalising infection in the two regions is the worst possible strategy in minimising the total level of infection. Indeed we show analytically that this is the worst possible strategy. Treatment should instead be preferentially directed at the region with the lower level of infection, treating the other sub-population only when there is resource left over. The same strategy holds with preferential treatments of regions with lower levels of infection when quarantine is introduced.

Key words: epidemiological modelling, economic modelling, quarantine, spatio-temporal epidemics.

Many epidemics outstrip the resources available to treat all infected individuals (1), especially when disease occurs simultaneously in different but interconnected regions (2-4). Seeking to control in more than one region, poses a dilemma for epidemiologists and health administrators of how best to deploy limited resources amongst different regions: should preference be given to treating infected individuals in regions with high or with low levels of infection, or to equalising levels of infection in different regions as fast as possible? Choosing between these options requires a combination of epidemiological and economic insight that hitherto have tended to remain separate: epidemiological models take little account of economic constraints, while economic models mostly ignore the spatial and temporal dynamics of disease (5, 6).

The influence of the spatial structure of susceptible populations on the invasion and persistence of human, animal and plant pathogens is now well established (2-4, 7). Much contemporary epidemiological theory is focused on the dynamics of disease in so-called 'structured-metapopulations' (8-11), in which epidemics occur in loosely-coupled sub-populations. These sub-populations correspond with natural aggregations of susceptibles, such as hospitals, towns, cities or countries. Infecteds and susceptibles mix more or less freely within sub-populations, with a smaller movement of infecteds or inoculum amongst sub-populations. The system of loose coupling leads to spatially-distributed epidemics with local fade-out but global persistence (12), as infection is transmitted between infected and healthy sub-populations. It follows that local deployment of control in one region may benefit other regions by reducing the number of infecteds capable of transmitting infection between sub-populations but the regional benefits of control may also be countermanded by reinvasion from neighbouring populations. Using a combination of optimal control methods from economic theory (5, 13-15) with a metapopulation model from epidemiological theory (16-19), we show, however, that it is possible to optimise the deployment of control. By formalising the problem as one of control of a dynamic, spatially-structured system

subject to economic constraints, it becomes apparent that one plausible intuition to give preference to the most highly infected regions when resources are limited may be the worst possible strategy in limiting the amount of infection suffered by the entire population.

The models We first consider two coupled sub-populations of susceptible individuals, in which an epidemic is described by a simple *SIS* (Susceptible-Infected-Susceptible) compartmental model. An *SIS* model is characteristic of a sexually-transmitted disease, such as gonorrhea, in which infecteds (*I*) recover naturally or after treatment (20, 21). Infected individuals do not gain immunity to the disease, rejoining the susceptible class (*S*) and so may be reinfected. This relatively simple model of an epidemic allows a rigorous analysis of strategies for optimal control of disease. Here we consider a simple control strategy in which a certain drug is administered to some or all of the infected individuals in two regions, each with populations of the same size *N*. The model is inspired by the analysis of Goldman and Lightwood (13) for optimal drug use in a single region. We envisage regions as encompassing local districts, counties, provinces or countries. The dynamics of infection for the *SIS* model in the two regions I_i are given by,

$$\frac{\mathrm{d}I_1}{\mathrm{d}t} = (N - I_1)(\beta I_1 + \gamma I_2) - \mu I_1 - \alpha F_1 , \qquad (1)$$

$$\frac{\mathrm{d}I_2}{\mathrm{d}t} = (N - I_2)(\beta I_2 + \gamma I_1) - \mu I_2 - \alpha F_2 , \qquad (2)$$

in which β and γ are the transmission rates within and between sub-populations, respectively; μ^{-1} is the infectious period and α is a measure of the rate at which infecteds are cured by the drug. The number receiving treatment in region *i* is equal to F_i. We assume that the drug is not used as a prophylactic so that only infected individuals receive it, hence $F_i \leq I_i$.

Optimal control Suppose that expenditure on drugs is subject to a budget constraint $c(F_1+F_2) \leq M$. We assume that finance is not transferable through time, so that money which is not spent immediately cannot be saved for the future purchase of drugs. If there are sufficient resources,

every infected individual will be treated. Otherwise, drugs are allocated so as to minimise the discounted sum of total infection in the two regions. Hence we choose F_1 and F_2 so as to minimise the following integral,

$$V = \int_0^\infty e^{-rt}(I_1 + I_2)\, dt\,. \qquad (3)$$

This is done by optimising the current value Hamiltonian (22, 23) for the propagation equations (1, 2) subject to the constraints of the epidemiological and economic system (See Methods and Supplementary Information for details). The objective function in eqn (3) is concerned only with minimizing total infection across both sub-populations. We also briefly consider objective functions of the form $V = \int_0^\infty e^{-rt}\left(I_1^\theta + I_2^\theta\right) dt$. If $\theta > 1$ such an objective function will give extra weight to the area with the higher level of infection. The discount rate is included to allow for long-term changes, so giving greater emphasis to control in the short rather than the long term (5).

Results

Preferential treatment of region with higher prevalence First we consider preferential treatment of the region with higher prevalence. So long as $(I_1 + I_2) \le M/c$ all infected individuals are treated and the epidemic is either eliminated in each sub-population, if $R_0 = \frac{N(\beta+\gamma)}{\alpha+\mu} \le 1$, or brought to some non-negative equilibrium density in each sub-population if $R_0 > 1$. When, however, (I_1+ I_2) > *M/c*, some infecteds remain untreated and a decision must be made as to how to allocate the drug between regions so as to minimise the discounted numbers of infected individuals. One obvious strategy is to equalise the levels of infection within the two regions as fast as possible. Many people would regard this as the socially equitable strategy (24). Formally it involves deflection of the two sub-populations onto a singular solution in which the levels of infection within each region are held constant (See Methods and *Supplementary Information (SI), Appendix A*). Such a strategy would be

achieved by preferential treatment of infecteds in the region with the *higher* prevalence of infecteds. The policy is called the MRAP since it involves the most rapid approach path to the singular solution, in which infection is equalised in both sub-populations (Fig. 1). However, as we show analytically (see methods and *SI*), the MRAP is the *worst* possible strategy within the constraints of the system. Rather than minimising the discounted amount of infection over time (eqn (3)) it maximises that quantity (Fig. 1: see methods).

Finding the optimal strategy To find the best (i.e. optimal) path, we chose to give preference to the region with the *lower* level of infection (and, by corollary, the higher level of susceptibles), treating the other as a residual claimant (See methods and SI, Appendix B). Individuals in the latter region only receive treatment when there are resources left over after treating all the infecteds in the target region (Fig. 1). Although it is not possible to prove analytically that this is the optimal path, extensive numerical simulations using a variety of parameters support the hypothesis. This alternative policy is known as the ANTIMRAP since it goes away from the singular solution as fast as possible (Fig. 1c). By concentrating scarce resources on the least infected region, where there are the most susceptibles, we maximise the social benefit associated with the prevention of disease.

<Figs 1 & 2 and Table 1 near here>

The difference between the best and worst paths depends upon the amount of initial infection in each population when the treatment is first introduced and can be separated into three regimes in infection space (Figs 1,2, Table 1). In zone A, the best and worst scenarios each bring the epidemic under control. The difference between the two is relatively small. In zone B, the worst path fails to bring the epidemic under control while the best path does (Fig. 1) and the error of choosing the wrong strategy is large (Table 1). We refer to this zone as an 'instability zone' to indicate the fact that the outcome is highly sensitive to the choice of policy. Neither policy is capable of bringing the epidemic under control in zone C but preferential treatment of the less infected sub-population is

substantially more successful in reducing the discounted amount of infection (Fig. 1, Table 1). The same is also true in the case of the objective function involving shown in Table 1. Thus, even if some weight is assigned to equalizing levels of infection in the two regions, our results show that it is still better to give priority to the region with the lower level of infection. For completeness, we also show consistency in the results for an objective function involving $\left(I_1^{2/3}+I_2^{2/3}\right)$, in which the exponents are less than unity (Table 1), implying some penalty for control effort as the level of infection increases.

Effects of relative transmission parameters on best and worst solutions The size of the instability zone B, in which the best and worst paths diverge, depends upon the relative magnitudes of transmission within (β) and between (γ) sub-populations (Fig. 2). Increasing the value of γ has two effects. It shifts the instability zone inwards reflecting the fact that it has become more difficult to control infection. At the same time the size of the instability zone shrinks (Fig. 2). Both the average and maximum values of the error ratio for the difference between the best and worst paths decline as (γ/β) gets larger (Fig. 2). Thus, as the rate of transmission between sub-populations, increases the outcome becomes less sensitive to the choice of policy. Moreover, at a certain point there is a sharp decline in the maximum error ratio. This occurs when γ/β becomes so large that, irrespective of the starting point, it is impossible to contain infection. Under these conditions, zones A and B disappear and zone C covers the entire infection space.

Quarantine control Suppose that the parameter γ can be altered by imposing quarantine controls that restrict the reciprocal rate of cross-infection between the two regions. Such controls may be costly to administer and may also impose indirect costs arising from restrictions on free circulation. Let Q be the total amount of direct and indirect costs involved in the quarantine policy. We shall assume that γ and Q are functionally related as follows,

$$\gamma = \gamma_0\, h(Q)\,, \qquad (4)$$

where $Q \in [0, Q_{\max}]$, $h(0) = 1$, $h(Q_{\max}) = 0$, $dh/dQ < 0$ and $d^2h/dQ^2 > 0$. Thus, when there are no restrictions the cross infection parameter γ is equal to γ_0. When a total ban is imposed γ = 0 and the cost of restrictions is equal to Q_{max}. We also assume that the budgets for medical treatment and for quarantine restrictions are separate, so that funds cannot be transferred between uses. The optimal strategy is now to choose F_1, F_2 and Q so as to minimise the following integral,

$$V_Q = \int_0^\infty e^{-rt}(I_1 + I_2 + Q/p)\, dt\,, \qquad (5)$$

subject to the same constraints as before (see methods) plus the additional constraint $Q \in [0, Q_{\max}]$ and $\gamma = \gamma_0\, h(Q)$. In this integral Q/p measures the cost of restrictions expressed in terms of infection equivalents. Using the standard procedure (see methods and SI) we derive an optimal value for $\hat{Q}$ from which it is possible to calculate the corresponding value for quarantine (from eqn 4). Extensive numerical analysis again shows that the optimal strategy is the ANTIMRAP, giving preference to the population with the lower prevalence of infection while also imposing quarantine to restrict transmission between the two sub-populations (Fig. 3a). For the example shown in Fig. 3, a severe quarantine, with γ close to zero (Fig. 3b), is initially imposed to isolate the high infection region 2. The limited medical resources available are mostly used to saturate the low infection region 1 leaving only a small residual for use in region 2. As infection falls in region 1, more medical resources become available for use in region 2 and infection is eventually brought down there as well. At a certain point, infection is sufficiently low in both regions that it is optimal to lift the quarantine and allow γ to return rapidly to its unrestricted value of 0.03. This is done quite rapidly. Without imposing a temporary quarantine, it is impossible to bring infection down from the starting point shown. With γ fixed at 0.03 total infection increases no matter what treatment policy is followed (cf Fig. 1d). Thus, the possibility of quarantine may radically alter the time paths of

infection in the two regions. Table 1 compares the integrals for the discounted cost of infection with and without quarantine costs.

<Fig 3 near here >

Conclusions and discussion

Epidemics of the *SIS* form, in which infected individuals recover and can be reinfected, apply to a small but important class of epidemics. With just two classes and a fixed population size, our *SIS* formulation allows a rigorous analysis to show that equalising infection in each sub-population is the worst possible strategy when resources are limited for control. It also shows that treatment should be focused on sub-populations with the lower level of infected individuals. This is equivalent to allocating treatment preferentially to sub-populations with the higher proportions of susceptible individuals. Will the strategy hold for other classes of epidemics? We have explored this numerically for epidemics in which treated individuals become immune (*SIR*) or rejoin the susceptible class (*SIRS*). Rigorous analysis is extremely difficult for these types of epidemics because of the increased number of state and co-state variables involved, and we were not able to obtain unequivocal results. By means of simulation, we were able to establish that for certain initial conditions it is more efficient to follow the ANTIMRAP strategy of giving priority to the infected area with the lower level of infection than it is to equalise infection as fast as possible (see *SI,* Fig 4 Appendix C). However, this is not always the case. The simulations also indicate that the optimal solution is more complex in the case of SIR and SIRS infections than in the SIS case.

The methods introduced here provide new insights into optimal disease control. The results overturn a simple intuition that preference should be given to strategies designed to equalise infection in different sub-populations. We have shown this rigorously for *SIS* models and conditionally for some *SIR* models (SI, Appendix B). The social context of the optimal

(ANTIMRAP) analyses implies that equal weighting be given to the health of all individuals i.e. for the collective social good of the entire metapopulation. Deviation from the optimal strategy necessarily changes this criterion, with greater weight being placed upon the health of some individuals compared with others. That is, preferential treatment of the sub-population with higher levels of infection and fewer susceptibles necessarily places a greater weighting on the health of individuals in that sub-population. Such considerations require further debate and greater integration of epidemiological models with insight from social sciences.

Methods

Optimisation The objective is to minimise the discounted level of infection (Eqn (3)) subject to the propagation equations (1, 2) (23) and subject to the following epidemiological and economic constraints: $I_i(0) = I_{i0}$; $0 \le F_i \le I_i$, $F_1 + F_2 = \min(I_1 + I_2, M/c)$. Let $A = \{I_1, I_2 : I_1 + I_2 \le M/c\}$ be the region where there are sufficient resources to treat all infecteds. Within this region the propagation equations are:

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = (N - I_i)(\beta I_i + \gamma I_j) - (\alpha + \mu) I_i \qquad i, j = 1, 2; \quad j \ne i . \tag{6}$$

These equations have one stable equilibrium which is given by

$$\hat{I}_1 = \hat{I}_2 = \max\left[0, N - (\alpha + \mu)/(\beta + \gamma)\right]. \tag{7}$$

We assume that $N - (\alpha + \mu)/(\beta + \gamma) < 0.5M/c$. This ensures that $(\hat{I}_1, \hat{I}_2) \in A$. It also ensures that any allowable path that enters the region A will remain permanently within this region and eventually converge to the stable equilibrium point.

When there are more infecteds than can be treated, $c(I_1 + I_2) > M$ and hence $F_1 + F_2 = M/c$. The relevant Hamiltonian in this case is

$$\begin{aligned} H = & -e^{-rt}\left(I_1 + I_2\right) \\ & + m_1\left[\left(N - I_1\right)\left(\beta I_1 + \gamma I_2\right) - \mu I_1 - \alpha F_1\right] \\ & + m_2\left[\left(N - I_2\right)\left(\beta I_2 + \gamma I_1\right) - \mu I_2 - \alpha F_2\right], \end{aligned} \tag{8}$$

where m_i are costate variables. Since $F_2 = M/c - F_1$ we can eliminate F_2 to obtain

$$\begin{aligned} H = & -e^{-rt}\left(I_1 + I_2\right) \\ & + m_1\left[\left(N - I_1\right)\left(\beta I_1 + \gamma I_2\right) - \mu I_1\right] \\ & + m_2\left[\left(N - I_2\right)\left(\beta I_2 + \gamma I_1\right) - \mu I_2\right] \\ & - m_2\alpha M / c + \alpha\left(m_2 - m_1\right)F_1 \ . \end{aligned} \tag{9}$$

When $c(I_1 + I_2) > M$ the control variable F_1 is subject to the following inequalities

$$\begin{aligned} & F_1 \geq 0, \\ & I_1 - F_1 \geq 0, \\ & F_2 \geq M / c - F, \\ & I_2 - F_2 = I_2 + F_1 - M / c \geq 0 \ . \end{aligned} \tag{10}$$

Some of these are 'mixed' constraints which include both state and costate variables. In this case the standard procedure is to include *all* constraints in a Lagrangean known as the 'augmented' Hamiltonian, which is given as follows (22),

$$L = H + x_1F_1 + x_2(M / c - F_1) + y_1(I_1 - F_1) + y_2(I_2 + F_1 - M / c) \ , \tag{11}$$

where the x's and y's are multipliers which satisfy the complementary slack conditions

$$\begin{aligned} & x_1 \geq 0, \quad F_1 \geq 0, \quad x_1F_1 = 0 \ , \\ & y_1 \geq 0, \quad I_1 - F_1 \geq 0, \quad y_1(I_1 - F) = 0 \ , \\ & x_2 \geq 0, \quad M / c - F_1 \geq 0, \quad x_2(M / c - F) = 0 \ , \\ & y_2 \geq 0, \quad I_2 + F_1 - M / c \geq 0, \quad y_2(I_2 + F_1 - M / c) = 0 \ . \end{aligned} \tag{12}$$

The first order conditions for an optimum require that

$$\frac{\partial L}{\partial F_1} = \alpha(m_2 - m_1) + x_1 - y_1 - x_2 + y_2 = 0 \tag{13}$$

and that F_1 (and hence F_2) is chosen so as to maximise the Hamiltonian. This yields the following result:

$$\begin{aligned} &\text{If } m_2 - m_1 > 0 \text{ then } F_1 = \min(I_1, \frac{M}{c}) \text{ and } F_2 = \frac{M}{c} - F_1 , \\ &\text{If } m_2 - m_1 < 0 \text{ then } F_2 = \min(I_2, \frac{M}{c}) \text{ and } F_1 = \frac{M}{c} - F_2 . \end{aligned} \tag{14}$$

It must also be the case that

$$\dot{m}_i = -\frac{\partial L}{\partial I_i} = -\frac{\partial H}{\partial I_i} - y_i \qquad i = 1,2 . \tag{15}$$

Finally, there are the transversality conditions. Allowable paths fall into two groups: those that never enter the region $A = \{I_1, I_2 : M/c \geq I_1 + I_2\}$, and those that enter this region and never leave it again. In the former case, there are alternative transversality conditions. Define the function W as follows

$$W(Z_1, Z_2) = \int_0^t e^{-rt} \left(I_1 + I_2\right) \mathrm{d}t \tag{16}$$

where the integral is evaluated along the path defined by the "treat all" propagation equations (1) and starting from the point $I_1(0) = Z_1, I_2(0) = Z_2$. The transversality conditions for a path that enters this set are as follows:

$$\begin{aligned} m_2 - m_1 &= -\left(\frac{\partial W_2}{\partial t} - \frac{\partial W_1}{\partial t} \right) \\ rW = H &= -(I_1 + I_2) + m_1 \dot{I}_1 + m_2 \dot{I}_2 \end{aligned} \tag{17}$$

The singular solution Suppose that the control variables are chosen from the interior of their domains so that $0 < F_i < I_i$. This implies that $x_i = y_i = 0$ for *i=1,2* and hence from (8) it follows that $m_2 = m_1$. Suppose also that the latter equality holds throughout an open interval of time. Then $\dot{m}_2 = \dot{m}_1$ from which it is simple to show that $I_1 = I_2$, whence $\dot{I}_2 = \dot{I}_1$ and $F_2 = F_1 = M/2c$. This yields the "singular" solution which is given by,

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = (N - I_i)(\beta I_i + \gamma I_j) - \alpha I_i - \frac{\alpha M}{2c}, \qquad i = 1,2; \quad j = 2,1. \tag{18}$$

The most rapid approach path The most rapid approach path (MRAP) involves reaching the singular solution as fast as possible and remaining on this solution thereafter. This means giving preferential treatment to the sub-population with the higher prevalence of disease until disease in the two populations is equalized, and then treating these populations equally. This strategy implies that,

$$\begin{aligned} &\text{If } I_i > I_j \text{ then } F_i = \min(I_i, M/c) \text{ and } F_j = M/c - F_i\,, \\ &\text{If } I_i = I_j \text{ then } F_i = F_j = M/2c\,. \end{aligned} \tag{19}$$

To confirm that this strategy is the *worst* case we show that this path *maximises* the discounted level of infection (eqn (3)). The Hamiltonian is identical to eqn (9) save that the first term $-e^{-rt}(I_1 + I_2)$ is replaced by $+e^{-rt}(I_1 + I_2)$ for maximisation rather than minimisation of the integral V. Hence the conditions on F_1 for maximisation are identical to eqn (10) only this time the costate variables are positive. Mangasarian's sufficiency conditions for a maximum require that the Hamiltonian be a concave function of I_1, I_2 and F_1 (22). These conditions require that the following matrix is negative semi-definite,

$$\begin{bmatrix} \dfrac{\partial^2 H}{\partial I_1^2} & \dfrac{\partial^2 H}{\partial I_2 \partial I_1} & \dfrac{\partial^2 H}{\partial F_1 \partial I_1} \\ \dfrac{\partial^2 H}{\partial I_1 \partial I_2} & \dfrac{\partial^2 H}{\partial I_2^2} & \dfrac{\partial^2 H}{\partial F_1 \partial I_2} \\ \dfrac{\partial^2 H}{\partial I_1 \partial F_1} & \dfrac{\partial^2 H}{\partial I_2 \partial F_1} & \dfrac{\partial^2 H}{\partial F_1^2} \end{bmatrix} = \begin{bmatrix} -2\beta m_1 & -\gamma(m_1 + m_2) & 0 \\ -\gamma(m_1 + m_2) & -2\beta m_2 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tag{20}$$

which will be the case if $m_1 \geq 0$ and

$$4\beta^2 m_1 m_2 - \gamma^2 (m_1 + m_2)^2 \geq 0\,. \tag{21}$$

Provided $\beta > \gamma$ the above inequality is always strictly satisfied on the singular solution where $m_1 = m_2$. By continuity it must also be weakly satisfied on the MRAP for points close to the singular solution. Our simulations indicate that strictly positive costate variables can be found that satisfy the augmented Hamiltonian conditions along the whole length of the MRAP. Moreover, for the

parameter values we consider, the inequality given in eqn (21) is also satisfied along the whole length of the trajectory to the singular solution. This condition establishes that the Hamiltonian is concave. For paths that remain permanently outside of the region $A = \{I_1, I_2 : I_1 + I_2 \le M/c\}$ the transversality conditions $\lim_{t\to\infty} m_i(t) = 0$ for *i=1,2* are satisfied. For paths that enter this region the transversality condition $m_1 = m_2$ at the point where they enter is satisfied. For paths of this type an additional concavity condition is required (22). Simulations indicate that $W(Z_1, Z_2)$ is concave. Under these conditions, the MRAP maximises the integral V and is therefore as bad as, or worse than, any other path that satisfies the constraints of the problem (22).

Finding the optimal path We propose an alternative candidate for the optimal path when (I_1+ I_2) > M/c. The path is determined by the following decision rules,

$$\begin{aligned} &\text{If } I_i < I_j \text{ then } F_i = \min(I_i, M/c) \text{ and } F_j = M/c - F_i\,, \\ &\text{If } I_i = I_j \text{ then } F_i = \min(I_i, M/c) \text{ and } F_j = M/c - F_i\,, \\ &\quad \text{or } \textit{vice-versa}\,. \end{aligned} \qquad (22)$$

This path is the ANTIMRAP in which preference is given to treating the sub-population with *lower* prevalence of infection. Standard sufficiency theorems cannot be used to prove analytically that this is the optimal path since $m_1 < 0$ and the Hamiltonian is not concave. However, simulations indicate that the ANTIMRAP is in fact optimal (*SI*, Appendix B).

Using a 100 times 100 grid of starting points we compared the following three paths. Path 1 which always gives priority to region 1, Path 2 which always gives priority to region 2, and the MRAP which equalises infection levels in the two regions as fast as possible and then splits the drug equally between them. Starting from an initial point with $I_1 < I_2$, the smallest integral was obtained with Path 1, the next smallest with Path 2, and the strictly largest integral with the MRAP. From an initial point with $I_2 < I_1$, the smallest integral was obtained with Path 2 and the strictly largest integral with the MRAP. With $I_1 = I_2$ initially, the MRAP always gave the strictly largest integral,

but Path 1 and Path 2 gave identical integrals. We were also able to show that the three paths just described were the only paths which entered the treat-all set (given a suitable starting point) and satisfied both the Hamiltonian and transversality conditions. This suggests that the AntiMRAP strategy of favouring the least infected area is best. We were not able to rule out the possibility that there are other paths which yield an even lower integral than the AntiMRAP, but we were not able to locate such a path from any starting point.

Quarantine The Hamiltonian for the case with quarantine is the same as in eqn (9) except that γ is replaced by $\gamma_0 h(Q)$ as in eqn (4) and the objective function by eqn (5) The decision rules are identical to eqn (22) with the additional constraint that the quarantine variable Q is selected from the set $[0, Q_{\max}]$ so as to maximise the Hamiltonian, taking all other variables as given. The optimal value of Q is thus equal to,

$$\hat{Q} = Q \operatorname{argmax}\left(-\frac{e^{-rt}Q}{p} + [m_1(N - I_1)I_2 + m_2(N - I_2)I_1]\, h(Q) \right). \qquad (23)$$

Error of worst relative to best path The error ratio for the worst compared with the best paths is computed by $(V_{\text{worst}} - V_{\text{best}})/ V_{\text{best}}$ in which V_{worst} and V_{best} are the values of the discounted infection along the best and worst paths, respectively. We distinguish between the maximum and the average value (computed as the average error over all starting points in infection space for which $(I_1 + I_2) > M/c$ for given ratios of transmission between and within sub-populations. The instability region in which the best path leads to disease control and the worst to explosive spread shown in Fig. 2 were computed for each of 21 x 21 starting points laid out on a uniform grid on the infection space. When $\gamma = \beta$ the two regions are effectively a single region and all allowable treatment policies lead to exactly the same trajectory for total infection and hence to the same value for the integral V (eqn 3).

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Table 1. Differences and errors associated with best and worst strategies* to control disease in a metapopulation when resources are limited. Alternative objective functions are shown for the *SIS* model without quarantine.

Zone	Path	$I_1(0)$	$I_2(0)$	$I_1(\infty)$	$I_2(\infty)$	$\int_0^\infty e^{-rt}\left(I_1+I_2\right)\mathrm{d}t$ (% Error)†	$\int_0^\infty e^{-rt}\left(I_1^{2/3}+I_2^{2/3}\right)\mathrm{d}t$ (% Error)†	$\int_0^\infty e^{-rt}\left(I_1^{3/2}+I_2^{3/2}\right)\mathrm{d}t$ (% Error)†
	SIS model without quarantine							
A	Worst	0.090	0.165	0	0	2.27 (5.09)	4.66 (4.59)	0.78 (3.77)
	Best	0.090	0.165	0	0	2.16	4.45	0.75
B	Worst	0.085	0.180	0.69	0.69	3.38 (30.05)	5.99 (19.07)	1.51 (52.04)
	Best	0.085	0.180	0	0	2.59	5.03	0.99
C	Worst	0.100	0.250	0.69	0.69	6.14 (18.76)	8.89 (14.05)	3.68 (19.81)
	Best	0.100	0.250	0.19	0.80	5.17	7.73	3.07
	SIS model with quarantine							
C	Best	0.100	0.250	0	0	3.83		

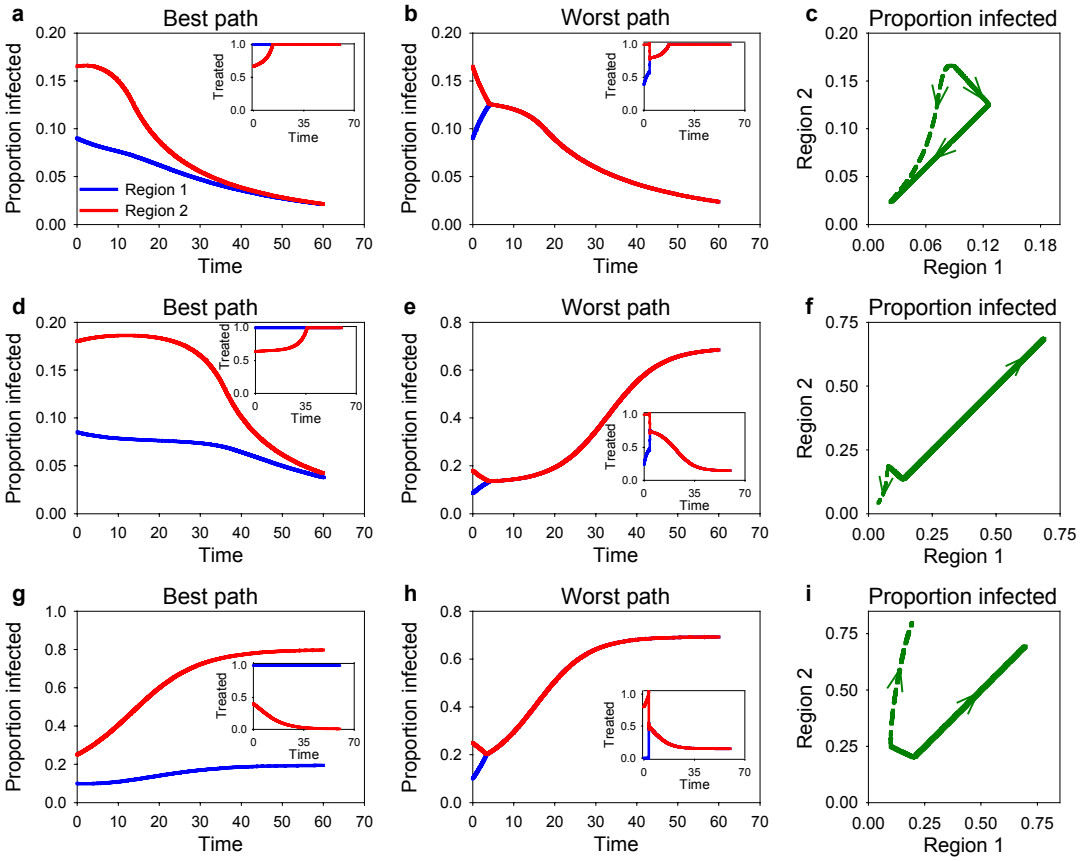
*Parameter values as for Fig. 1. †Computed by $(V_{worst} - V_{best})/ V_{best}$ in which V_{worst} and V_{best} are the values of the discounted infection along the worst and best paths, respectively.

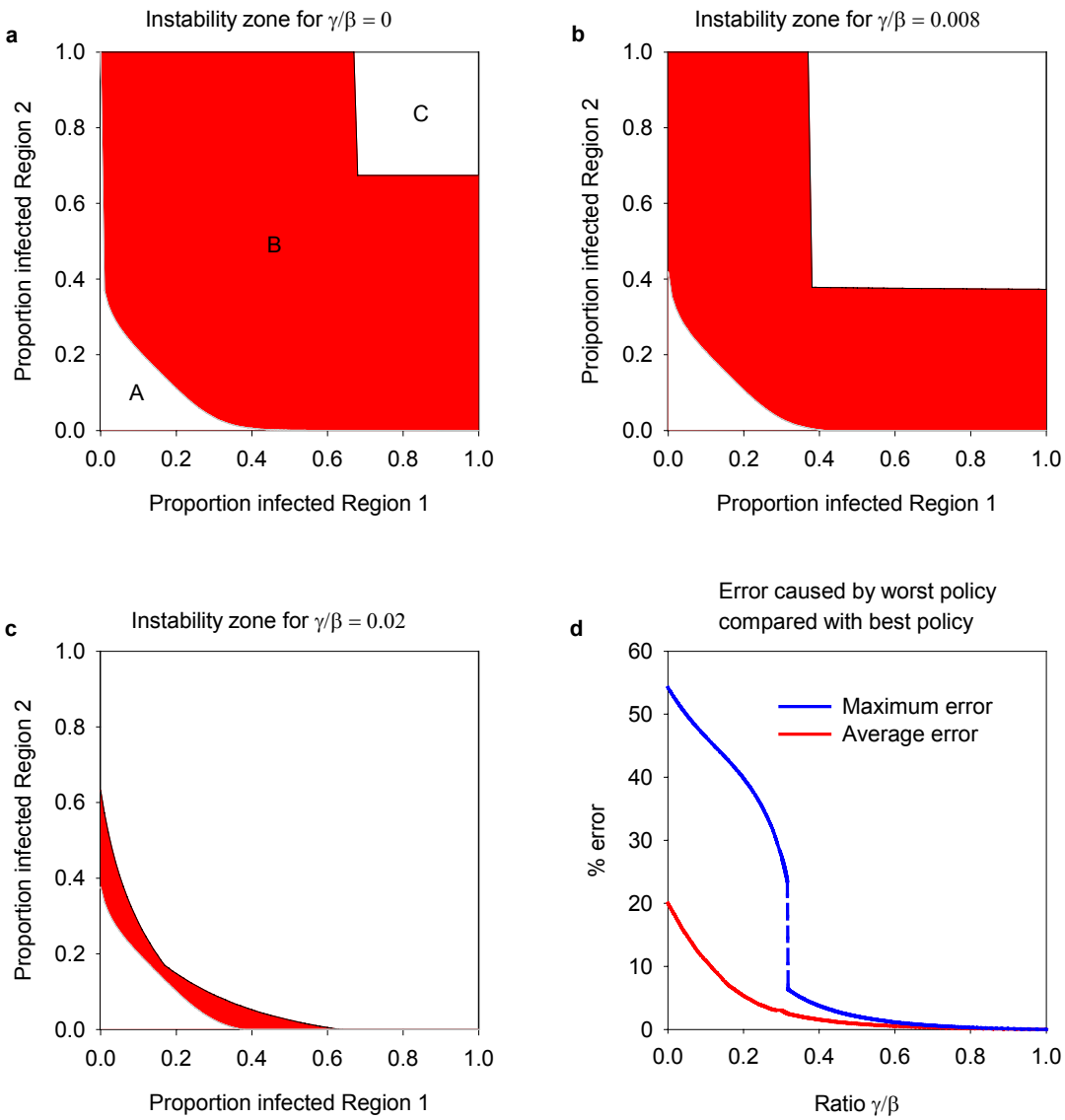
Figure Legends

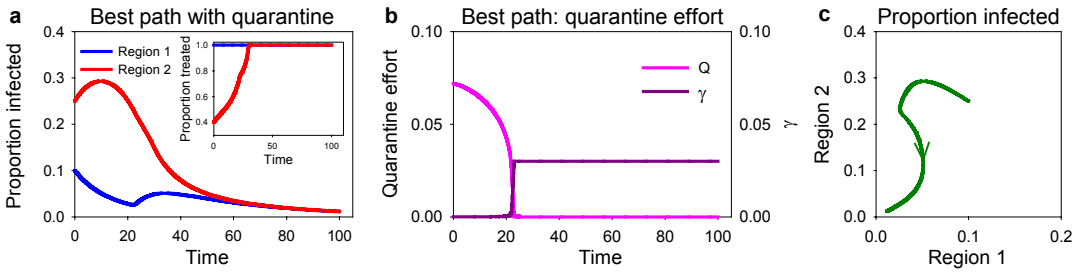
Fig. 1 Comparison of disease progress curves for best and worst policies. **(A-C**) Progress of disease in two inter-connected regions 1 and 2, with treatment dynamics in insets, showing small differences between best and worst paths when initial infection occurs in Zone A (Table 1). (**D-F**) Best and worst paths diverge markedly when initial infection occurs in the instability zone B (Table 1). (**G-I**) Disease continues to increase but markedly less steeply in the region with the lower infestation (region 1) when infection occurs in Zone C (Table 1). Default parameters are $\alpha = 0.25$ (efficiency of control), $\beta = 0.25$ (within-region transmission rate), $\gamma = 0.03$ (between-region transmission rate), $r = 0.1$ (discount rate), $\mu = 0.05$ (recovery rate), $M = 0.2$ (fixed costs) with $N = 1$.

Fig. 2 Transmission between regions and the error between best and worst policies. (**A-C**) Effect of the between-region transmission rate, γ, (scaled by β) on the magnitude of the instability zone B (shown in red) in which the best and worst paths lead to marked differences in epidemic behaviour with one controlling the epidemic and the other leading to 'explosive' infection towards high levels of infection (see Fig. 1). (**D**) Effect of changing the ratio of γ/β on the maximum error (red line) and average error (blue line) between best and worst policies.

Fig. 3 The role of quarantine. (**A**) Disease progress curves in the two regions with treatment allocation shown in inset, together with quarantine. (**B**) Quarantine effort and corresponding value for γ: note the sudden change in quarantine policy. (**C**) Phase portrait showing how a potentially explosive epidemic (*cf* Fig. 1j and Table 1) can be brought under control by optimising quarantine together with preferential treatment of the region with the lower prevalence of infection. Default parameters as in Fig. 1, except that $p = 1$, b=100, $Q_{\max} = 5$ $\gamma = \gamma_0 h(Q)$ where $\gamma_0 = 0.03$ and $h(Q) = (e^{-bQ} - e^{-bQ_{\max}})/(1 - e^{-bQ_{\max}})$.


a
Best path
Proportion infected
Time
Region 1
Region 2
Treated
b
Worst path
c
Proportion infected
Region 2
Region 1
d
e
f
g
h
i


a
Instability zone for γ/β = 0
Proportion infected Region 2
Proportion infected Region 1
A
B
C
b
Instability zone for γ/β = 0.008
Proiportion infected Region 2
Proportion infected Region 1
c
Instability zone for γ/β = 0.02
Proportion infected Region 2
Proportion infected Region 1
d
Error caused by worst policy
compared with best policy
Maximum error
Average error
% error
Ratio γ/β
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
40
50
60


a
Best path with quarantine
Proportion infected
Region 1
Region 2
Proportion treated
Time
b
Best path: quarantine effort
Quarantine effort
Q
γ
Time
c
Proportion infected
Region 2
Region 1