IMA Journal of Mathematics Applied in Medicine and Biology (2002) **19**, 235–255

Dynamic resource allocation for epidemic control in multiple populations

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[Received on 11 July 2001; revised on 22 February 2002 and 8 June 2002; accepted on 5 November 2002]

We develop a dynamic resource allocation model in which a limited budget for epidemic control is allocated over multiple time periods to interventions that affect multiple populations. For certain special cases with two time periods, multiple independent populations, and a linear relationship between investment in a prevention programme and the resulting change in risky behaviour, we demonstrate that the optimal solution involves investing in each period as much as possible in some of the populations and nothing in all the other populations. We present heuristic algorithms for solving the general problem, and present numerical results. Our computational analyses suggest that good allocations can be made based on some fairly simple heuristics. Our analyses also suggest that allowing for some reallocation of resources over the time horizon of the problem, rather than allocating resources just once at the beginning of the time horizon, can lead to significant increases in health benefits. Allowing for reallocation of funds may generate more health benefits than use of a sophisticated model for one-time allocation of resources.

Keywords: epidemic control; resource allocation; optimization; health planning.

1. Introduction

To control epidemics, policy makers must allocate limited budgets among competing prevention and treatment programs. Often, budgets may be only available for limited time horizons, such as for the next fiscal year. However, for endemic diseases such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), malaria or tuberculosis, it is unlikely that the disease will be eradicated through a short-term control effort. For example, smallpox eradication occurred due to long-term efforts of the World Health Organization from 1967 to 1980 (World Health Organization, 1998b). Similar efforts are currently underway for polio and leprosy (World Health Organization, 1998a). When policy makers have a budget to allocate to epidemic control efforts over multiple

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time periods, they can incorporate information about future allocation decisions into the resource allocation decision of the current period, and thus allocate resources more effectively.

A number of researchers have considered the one-time allocation of resources for epidemic control at the beginning of a time horizon. Some researchers have proposed mixed integer–linear programming models (Chen & Bush, 1976; Stinnett & Paltiel, 1996; Weinstein & Zeckhauser, 1973). These models typically assume that interventions are independent and that all interventions are divisible (if investment is made) with constant returns to scale. Other approaches include numerical simulation to choose the best allocation from among a limited set of alternatives (Bernstein *et al.*, 1998; Hethcote, 1982; Kahn, 1996; Robinson *et al.*, 1995), other numerical procedures (Longini *et al.*, 1978; Richter *et al.*, 1999; ReVelle *et al.*, 1969) and equilibrium analysis to optimize some function of the equilibrium state of an epidemic, when it exists (Hethcote & Van Ark, 1987; May & Anderson, 1984).

Richter (1996), Richter *et al.* (1999) and Brandeau *et al.* (in press) considered the problem of allocating resources at the beginning of a T-year time horizon to minimize the number of new infections that occur in multiple independent populations. The epidemic in each population was modelled by a susceptible–infected (SI) epidemic model with replacement. For each population, one intervention that reduces sufficient contact rates in that population was assumed to be available. The relationship between investment in each intervention and the reduction in the sufficient contact rate was assumed to be described by a non-increasing ‘production function’ of arbitrary shape. Zaric & Brandeau (2001a,b) extended the work of (Richter, 1996) and Brandeau *et al.* (in press) to more general epidemic models with interacting populations and interventions that affect more than one population. They considered as objectives maximizing the number of quality-adjusted life years (QALYs) gained or minimizing the number of new infections that occur over a T-year time horizon.

Many researchers have considered the problem of allocating epidemic control resources to a single population over multiple time periods. Control theory techniques have been used to determine the timing and intensity of interventions to optimize a function related to the spread of an epidemic (Sethi, 1974, 1978; Greenhalgh, 1986, 1988; Muller, 1998; Sethi & Staats, 1978; Blount *et al.*, 1997; Wickwire, 1977). A typical analysis (Blount *et al.*, 1997) uses a simple epidemic model and finds an optimal control sequence to minimize the sum over T periods of the cost of an epidemic (the cost associated with new infections plus the cost of treating those already infected) subject to a budget constraint that limits the number of periods in which the control can be applied. Control theory approaches are summarized by Wickwire (1977).

In this paper we develop a dynamic resource allocation model in which a limited budget for epidemic control is allocated over multiple time periods to interventions that affect multiple populations. For certain special cases with two time periods, multiple independent populations, and a linear relationship between investment in a prevention programme and the resulting change in risky behaviour, we demonstrate that the optimal solution involves investing in each period as much as possible in some of the populations and nothing in all the other populations. We present heuristic algorithms for solving the general problem, and present numerical results. Our computational analyses suggest that good allocations can be made based on some fairly simple heuristics. Our analyses also suggest that allowing for some reallocation of resources over the time horizon of the problem, rather than allocating resources just once at the beginning of the time horizon, can lead to significant increases in health benefits. In fact, allowing for reallocation of funds may generate more health benefits than use of a sophisticated model for one-time allocation of resources.

2. Dynamic resource allocation model

We extend the model of Zaric & Brandeau (2001b) to problems in which resource allocation decisions are made in τ different time periods. All notation is summarized in Table 1. Let $T_1 = 0$, let $T_2, T_3, \dots, T_\tau$ be the starting times of periods $1, \dots, \tau$, and let $T_{\tau+1}$ be the ending time of period τ. Thus, period k is defined as $[T_k, T_{k+1})$, $k = 1, \dots, \tau$. We assume that the decision maker may allocate resources to n different interventions in each period. A resource allocation decision is made at the beginning of period k $(k = 1, \dots, \tau)$ and cannot be changed until the beginning of period $k + 1$. We consider two possible objectives: maximizing the number of QALYs gained and maximizing the number of infections averted. QALYs gained is the recommended measure of benefit for cost effectiveness analysis in health and medicine (Gold *et al.*, 1996). We also consider infections averted because it is frequently used in evaluations of epidemic control programs (e.g. Richter *et al.*, 1999; Kaplan & Pollack, 1998; Zaric & Brandeau, 2001b).

We assume that the epidemic is modelled by a compartmental epidemic model, a common assumption for models of infectious diseases (e.g. Capasso, 1993; Bailey, 1975; Hethcote, 1976; Zaric *et al.*, 1998, 2000). The population is divided into m compartments. A set of p parameters (e.g. sufficient contact rates, death rates, replacement rates, migration rates, etc.) describes the epidemic.

Let v_h^k be the amount of money invested in intervention $h (h = 1, \dots, n)$ in period $k (k = 1, \dots, \tau)$. The investment v_h^k is made at time $t = T_k$. Let $\mathbf{v}^k = (v_1^k, v_2^k, \dots, v_n^k)$ be the vector of investment decisions in period k, and let $\mathbf{v} = (\mathbf{v}^1, \mathbf{v}^2, \dots, \mathbf{v}^\tau)$. Let $\mathbf{V}^k = (V_1^k, V_2^k, \dots, V_n^k)$ be the vector of upper bounds on investment in period k. We assume that $0 \leqslant v_h^k \leqslant V_h^k$ for all h, k. The decision maker's budget in period k is denoted by B^k. We assume that the budget for each time period is known at time $t = 0$. We assume that $V_i^k \leqslant B^k$ for all i, k. This is not a restrictive assumption: if $V_i^k > B^k$, we can replace V_i^k with $V_i^{k'} = B^k$.

Let $w_g^k(\mathbf{v}^k)$ be the value of parameter $g (g = 1, \dots, p)$ associated with investment decision $\mathbf{v}^k$ in period $k (k = 1, \dots, \tau)$. The function $w_g^k(\cdot)$ is a 'production function' that describes the relationship between the amount invested in interventions in period k and the value of parameter g in the epidemic model during period k. We assume that allocations take effect instantaneously at the beginning of each period, and that the effects expire instantaneously at the end of each period if no additional funds are invested. Thus, $w_g^1(\mathbf{0}) = w_g^2(\mathbf{0}) = \dots = w_g^\tau(\mathbf{0})$, $g = 1, \dots, p$.

Let $y_i(t, \mathbf{v})$ denote the number of individuals in compartment $i (i = 1, \dots, m)$ at time $t (0 \leqslant t \leqslant T_{\tau+1})$, given investment vector $\mathbf{v}$. We assume that the values of $y_i(0, \mathbf{0})$ are known for all i. Let $0 \leqslant q_i \leqslant 1$ be the quality adjustment for years of life lived in compartment $i (i = 1, \dots, m)$ and let r be the discount rate $(r \geqslant 0)$. The (discounted)

TABLE 1 *Summary of notation*

Indices	
k	index over time periods, $k = 1, \ldots, \tau$
g	index over epidemic model parameters, $g = 1, \ldots, p$
i	index over epidemic model compartments, $i = 1, \ldots, m$
h	index over interventions, $h = 1, \ldots, n$
t	time index, $0 \leqslant t \leqslant T_{\tau+1}$
Decision variables	
v_h^k	amount invested in intervention h at the beginning of period $k, h = 1, \ldots, n, k = 1, \ldots, \tau$
$\mathbf{v}^k$	vector of investments in period $k = (v_1^k, v_2^k, \ldots, v_n^k)$, $k = 1, \ldots, \tau$
$\mathbf{v}$	vector of investment decisions $= (\mathbf{v}^1, \mathbf{v}^2, \ldots, \mathbf{v}^\tau)$
Parameters	
τ	number of time periods
p	number of parameters in epidemic model
m	number of epidemic model compartments
n	number of interventions
T_k	starting time of period k, $k = 1, \ldots, \tau$
$T_{\tau+1}$	ending time of period τ
$\mathbf{V}^k$	vector of upper bounds on investment in period $k = (V_1^k, V_2^k, \ldots, V_n^k)$, $k = 1, \ldots, \tau$
B^k	budget in period k, $k = 1, \ldots, \tau$
q_i	quality adjustment for years of life lived in compartment i, $i = 1, \ldots, m$
r	discount rate
T	length of each time period in the model RA$'$-τ-n
N_i	number of individuals in population i, $i = 1, \ldots, n$, in the model RA$'$-τ-n
δ_i	replacement rate in population i, $i = 1, \ldots, n$, in the model RA$'$-τ-n
Calculated quantities	
$w_g^k(\mathbf{v}^k)$	value of parameter g given investment decision $\mathbf{v}^k$ in period k, $g = 1, \ldots, p, k = 1, \ldots, \tau$
$\lambda_{ij}(t, \mathbf{v})$	rate of contacts sufficient to cause disease transmission between an individual in compartment i and an individual in compartment j at time t given investment $\mathbf{v}$, $i, j = 1, \ldots, m, 0 \leqslant t \leqslant T_{\tau+1}$
$y_i(t, \mathbf{v})$	number of individuals in compartment i at time t given investment $\mathbf{v}$, $i = 1, \ldots, m, 0 \leqslant t \leqslant T_{\tau+1}$
$x_i(t, \mathbf{v})$	fraction of individuals in population i who are uninfected at time t in the model RA$'$-τ-n given investment $\mathbf{v}$, $i = 1, \ldots, n, 0 \leqslant t \leqslant T_{\tau+1}$
$x_{i+n}(t, \mathbf{v})$	fraction of individuals in population i who are infected at time t in the model RA$'$-τ-n given investment $\mathbf{v}$, $i = 1, \ldots, n, 0 \leqslant t \leqslant T_{\tau+1}$
QALY($\mathbf{v}$)	total number of QALYs experienced over τ time periods given investment $\mathbf{v}$
INF($\mathbf{v}$)	total number of new infections that occur over τ time periods given investment $\mathbf{v}$

total number of QALYs experienced over τ periods given investment $\mathbf{v}$ is

$$\mathrm{QALY}(\mathbf{v}) = \mathrm{QALY}(\mathbf{v}^1, \ldots, \mathbf{v}^\tau) = \sum_{k=1}^{\tau} \int_{T_k}^{T_{k+1}} \sum_{i=1}^{m} q_i y_i(t, \mathbf{v}) \mathrm{e}^{-rt} \, \mathrm{d}t. \tag{1}$$

The number of QALYs gained as a result of allocation $\mathbf{v}$ equals $\mathrm{QALY}(\mathbf{v}) - \mathrm{QALY}(\mathbf{0})$. Since $\mathrm{QALY}(\mathbf{0})$ is constant, we use $\mathrm{QALY}(\mathbf{v})$ as the objective function. When $q_i = 1$ for all i, $\mathrm{QALY}(\mathbf{v})$ represents (discounted) life years gained.

Let $\lambda_{ij}(t, \mathbf{v})$ be the rate of contacts sufficient to cause disease transmission between an individual in compartment i and an individual in compartment $j\,(i, j = 1, \ldots, m)$ at time $t\,(0 \leqslant t \leqslant T_{\tau+1})$ given investment $\mathbf{v}$. The (discounted) total number of new infections that occur over τ periods given investment $\mathbf{v}$ is

$$\mathrm{INF}(\mathbf{v}) = \mathrm{INF}(\mathbf{v}^1, \ldots, \mathbf{v}^\tau) = \sum_{k=1}^{\tau} \int_{T_k}^{T_{k+1}} \left[\sum_{i=1}^{m} y_i(t, \mathbf{v}) \sum_{j=1}^{m} \lambda_{ij}(t, \mathbf{v}) y_j(t, \mathbf{v}) \right] \mathrm{e}^{-rt} \, \mathrm{d}t. \tag{2}$$

The number of infections averted as a result of investment $\mathbf{v}$ is $\mathrm{INF}(\mathbf{0})$-$\mathrm{INF}(\mathbf{v})$. Since $\mathrm{INF}(\mathbf{0})$ is a constant, maximizing the number of infections averted is equivalent to minimizing $\mathrm{INF}(\mathbf{v})$.

The multi-period resource allocation problem is

$$\text{RA-}\tau\text{: maximize } \mathrm{QALY}(\mathbf{v}) \text{ or minimize } \mathrm{INF}(\mathbf{v}) \tag{3}$$

$$\text{s.t.} \quad \sum_{h=1}^{n} v_h^k \leqslant B^k \qquad k = 1, \ldots, \tau \tag{4}$$

$$0 \leqslant v_h^k \leqslant V_h^k \qquad k = 1, \ldots, \tau; \; h = 1, \ldots, n. \tag{5}$$

3. Analysis of RA-τ

Solving RA-τ presents several challenges. Closed-form solutions for the compartment size functions are not known for many epidemic models, so it is often not possible to derive an analytic expression for the objective function. In instances where closed-form solutions for the compartment size functions are known (for example, for the SI model and closely related variants Bailey, 1975), the objective function of RA-τ may be neither convex nor concave (Brandeau *et al.*, in press), allowing for little theoretical insight. When the populations do not interact (i.e. no migration or cross-infection occurs), and each intervention affects only a single population, and the epidemic in each population is modelled by an SI model, then RA-1 is a knapsack problem (Hillier & Lieberman, 1993) that can be solved numerically to any degree of accuracy using dynamic programming (Kaplan, 1998; Zaric & Brandeau, 2001b).

For $\tau > 1$, the problem RA-τ does not have a knapsack structure even when the populations are independent and each intervention only affects a single population. Allocation decisions in period k determine the initial conditions in period $(k+1)$, and these new initial conditions are non-linear functions of allocations in previous periods (because of the non-linear nature of the infection transmission process). The objective functions of

RA-τ contain terms made up of the product of variables from multiple time periods, so the objective functions are in general not separable across time periods. Thus, dynamic programming cannot always be used to solve RA-τ.

We now consider a restricted version of RA-τ which we denote by RA$'$-τ-n: we assume τ time periods, each of length T, and n non-interacting populations, each modelled by an SI model with replacement and approximated by first-order approximations (Zaric & Brandeau, 2001b). To simplify notation we drop the argument $\mathbf{v}$ from $y_i(t, \mathbf{v})$ unless we wish to emphasize the dependence on the investment decisions.

Let N_i be the (constant) size of population i, $i = 1, \ldots, n$. Let $x_i(t) = y_i(t)/N_i$ and $x_{i+n}(t) = y_{i+n}(t)/N_i$ be the proportion of individuals in population $i (i = 1, \ldots, n)$ who are uninfected and infected, respectively, at time $t (0 \leqslant t \leqslant T_{\tau+1})$. Let δ_i, $0 < \delta_i < 1$, be the (constant) replacement rate in population $i (i = 1, \ldots, n)$. We assume that $T < 1/\delta_i$ for all i. Using the notation introduced in the previous section, the sufficient contact rate in population i is $\lambda_{i,i+n}(t, \mathbf{v})$; for simplicity we write this as $\lambda_i(t, \mathbf{v})$, and we exclude the arguments t and $\mathbf{v}$ unless we wish to emphasize the dependence on t and $\mathbf{v}$. The equations of the SI model in population $i (i = 1, \ldots, n)$ are

$$x_i'(t) = \delta_i - \delta_i x_i(t) - \lambda_i x_i(t) x_{i+n}(t) \tag{6}$$

$$x_{i+n}'(t) = \lambda_i x_i(t) x_{i+n}(t) - \delta_i x_{i+n}(t) \tag{7}$$

$$x_i(t) + x_{i+n}(t) = 1. \tag{8}$$

We assume that n interventions are available, one to reduce the rate of sufficient contacts in each population. We assume that investment in the intervention targeted to a given population has no effect on the rate of sufficient contacts in the other populations, and that the production function for each intervention i has the same form in all periods. Thus, we write the production function for intervention $i (i = 1, \ldots, n)$ as $w_i(v_i^k)$. We assume linear production functions of the following form:

$$w_i(v_i^k) = \lambda_i(t, v_i^k) = a_i - b_i v_i^k \quad i = 1, \ldots, n;\ k = 1, \ldots, \tau;\ T_k < t < T_{k+1}. \tag{9}$$

We assume that sufficient contact rates are always non-negative (i.e. $a_i - b_i V_i^k \geqslant 0, i = 1, \ldots, n$). We also assume that infection reduces quality of life; thus, $q_i > q_{i+n}$, $i = 1, \ldots, n$.

We approximate the compartment size functions using the following first-order approximation (Zaric & Brandeau, 2001b):

$$x_i(t) \approx x_i(T_k) + x_i'(T_k)(t - T_k) \qquad i = 1, \ldots, n;\ t \in [T_k, T_{k+1}). \tag{10}$$

We use (10) in (1) and (2) to create the objective functions of RA$'$-τ-n, which we denote by QALY$'(\mathbf{v})$ and INF$'(\mathbf{v})$. The above first-order approximation has been shown to be accurate for time horizons up to ten years (Zaric & Brandeau, 2001b); thus, as long as the length (T) of each of the τ time periods in RA$'$-τ-n is ten years or less, (10) will provide a good approximation of the compartment size functions and objective functions in each of the time periods.

We now develop some analytical results characterizing the optimal solution to certain instances of RA$'$-τ-n. We use an asterisk to denote optimal values. All proofs are in the appendix. We first consider the case of two populations and two time periods:

RA′-2-2: max QALY′(**v**) or min INF′(**v**)

$$\text{s.t.} \quad v_1^1 + v_2^1 \leqslant B^1$$
$$v_1^2 + v_2^2 \leqslant B^2$$
$$0 \leqslant v_i^k \leqslant V_i^k \qquad i = 1, 2;\ k = 1, 2.$$

PROPOSITION 1 For RA′-2-2 with the QALYs objective function, the optimal solution is

$$(v_1^{1^*}, v_2^{1^*}) = (V_1^1, B^1 - V_1^1) \text{ or } (B^1 - V_2^1, V_2^1)$$
$$(v_1^{2^*}, v_2^{2^*}) = (V_1^2, B^2 - V_1^2) \text{ or } (B^2 - V_2^2, V_2^2).$$

The optimal solution to RA′-2-2 is to allocate as much as possible to one population in each period. The allocation in the second period is made by comparing the product of the number of infections averted and the number of QALYs gained per infection averted for each population given the proportion infected at the start of the period; the population for which this quantity is largest is allocated as much of the resource as possible. The proportion infected at the start of the second period is determined by the decision made in the first period. Thus, the optimal decision in the first period is made on the basis of the number of QALYs gained in the first period and the potential number of QALYs gained in the second period as a result of the first-period decision. While the form of the solution is the same as if the corresponding single-period problem had been solved in each period, the first-period decision in the two-period problem may not be the same as the single-period knapsack solution.

In the optimal solution to RA′-2-2 with the QALYs objective, the majority of resources are not necessarily allocated to the high-risk population nor to the same population in both periods. To illustrate, we constructed four examples, shown in Table 2. In these examples, resources are allocated between a low-risk population ($i = 1$) and a smaller, high-risk population ($i = 2$). We assumed that there is a quality-of-life reduction associated with infection and a quality-of-life reduction associated with being in the high-risk group. We assumed $\lambda_i(0, 0) > \delta_i$ for $i = 1, 2$ in each example. There are two interventions that reduce the sufficient contact rate in each population, respectively. We assumed that $B^k = 1000$ and $V_i^k = 0{\cdot}8B^k$ for $i = 1, 2$, and $k = 1, 2$. For the production functions (9) we set $a_i = \lambda_i(0, 0)$ and $b_i = [(0{\cdot}5)(\lambda_i(0, 0) - \delta_i)/1000]$. Thus, investment of the entire budget in either population reduces risk by 50% of the difference between the initial sufficient contact rate in that population in the absence of investment and the replacement rate in that population (i.e. $\lambda_i(t, 1000) = \lambda_i(0, 0) - (0{\cdot}5)(\lambda_i(0, 0) - \delta_i)$) for $0 \leqslant t \leqslant T$. Table 2 shows that all four extreme point allocations are possible, depending on problem parameters. Thus, simple rules that advocate always targeting resources (e.g. based on relative risk, population size, or infection status of individuals (Kahn, 1996; King-Spooner, 1999)) may lead to sub-optimal allocations.

We now consider RA′-2-2 with the infections-averted objective function.

PROPOSITION 2 For RA′-2-2 with the infections-averted objective function, the objective function may be strictly convex, strictly concave, or neither.

If the goal in allocating resources over two time periods and between two populations is to maximize QALYs, an extreme point solution is always optimal, as established by

TABLE 2 *Examples of RA′-2-2 with the QALYs objective function showing different optimal allocation patterns*

Example	Parameters Describing Low-Risk Population*	Parameters Describing High-Risk Population*	Population receiving maximum investment in period 1	Population receiving maximum investment in period 2
1	$N_1 = 1\,000\,000$ $x_3(0) = 0{\cdot}09246$ $\delta_1 = 0{\cdot}04987$ $\lambda_1 = 0{\cdot}07061$ $q_1 = 1, q_3 = 0{\cdot}81$	$N_2 = 376\,424$ $x_4(0) = 0{\cdot}12643$ $\delta_2 = 0{\cdot}12258$ $\lambda_2 = 0{\cdot}13510$ $q_2 = 0{\cdot}62, q_4 = 0{\cdot}50$	Low risk	Low risk
2	$N_1 = 1\,000\,000$ $x_3(0) = 0{\cdot}02529$ $\delta_1 = 0{\cdot}04879$ $\lambda_1 = 0{\cdot}06283$ $q_1 = 1, q_3 = 0{\cdot}96$	$N_2 = 255\,705$ $x_4(0) = 0{\cdot}05041$ $\delta_2 = 0{\cdot}11011$ $\lambda_2 = 0{\cdot}14797$ $q_2 = 0{\cdot}74, q_4 = 0{\cdot}71$	Low risk	High risk
3	$N_1 = 1\,000\,000$ $x_3(0) = 0{\cdot}01476$ $\delta_1 = 0{\cdot}05944$ $\lambda_1 = 0{\cdot}0669$ $q_1 = 1, q_3 = 0{\cdot}57$	$N_2 = 879\,459$ $x_4(0) = 0{\cdot}08688$ $\delta_2 = 0{\cdot}10947$ $\lambda_2 = 0{\cdot}12582$ $q_2 = 0{\cdot}88, q_4 = 0{\cdot}50$	High risk	High risk
4	$N_1 = 1\,000\,000$ $x_3(0) = 0{\cdot}03933$ $\delta_1 = 0{\cdot}06112$ $\lambda_1 = 0{\cdot}07577$ $q_1 = 1, q_3 = 0{\cdot}61$	$N_2 = 631\,474$ $x_4(0) = 0{\cdot}29544$ $\delta_2 = 0{\cdot}22817$ $\lambda_2 = 0{\cdot}23402$ $q_2 = 0{\cdot}76, q_4 = 0{\cdot}46$	High risk	Low risk

* $x_1(0) = 1 - x_3(0);\ x_2(0) = 1 - x_4(0)$.

Proposition 1. If the goal is to minimize the number of new infections, an extreme point solution is not always optimal.

We now consider the case of more than two populations.

PROPOSITION 3 For RA′-2-*n* with the QALYs objective function, the optimal solution in each time period is an extreme point of the feasible region.

Thus, for RA′-2-*n* with the QALYs objective function it is optimal to allocate in each period as much of the resource as possible to certain of the populations, and nothing to other populations. In the optimal solution, for each time period k there will be at most one population i' with an allocation $0 < v_{i'}^{k^*} < V_{i'}^k$; for all other populations i $\neq i'$, $v_i^{k^*} = 0$ or V_i^k.

Although we can characterize the form of the optimal solution to RA′-2-*n* with the QALYs objective function, solving the problem may be very challenging. The number of possible solutions in the second period may grow exponentially in the number of decision variables. Hence the number of solutions to evaluate in the first period may grow exponentially, since the optimal first-period decision is determined by comparing the optimal solution for each of the possible solutions for the second period. Additionally, the functions that must be maximized in the first period are convex, and thus the problem is NP-hard (Horst & Tuy, 1996). In the two-population case, the feasible region has only four extreme points, so it is relatively easy to state the solution. For more than two populations it may not be practical to enumerate all extreme points of the feasible region. For RA′-2-n with the infections-averted objective function, the objective function may be convex or concave in certain cases, but will not be so in general.

For RA′-τ-2 with the QALYs objective function, we can derive expressions for $x_i(T_2,\mathbf{v})$, $x_i(T_3, \mathbf{v}), \ldots, x_i(T_\tau, \mathbf{v})$ similar to the expressions for $x_i(T_2, \mathbf{v})$ developed in (A.1)–(A.4). We showed in the proof of Proposition 1 that the first-period objective function for RA′-2-2 is a quadratic function of v_1^1. By substituting values of $x_i(T_{k-1}, \mathbf{v})$ into the formulae for $x_i(T_k, \mathbf{v})$ in the τ-period problem, it is easily seen that the first-period problem is a $2^{(\tau-1)}$-degree polynomial in $\mathbf{v}_1$, which will not, in general, be convex or concave over the entire feasible region. Similarly, for RA′-τ-2 with the infections-averted objective function, it is easy to construct examples in which the objective function is not necessarily convex nor concave. Thus, for $\tau > 2$ an extreme point solution to RA′-τ-2 is not guaranteed to be optimal.

4. Numerical Analysis of RA

For more general instances of RA-τ than those considered in Propositions 1–3, such as those based on an epidemic model other than the SI model, or those with non-linear production functions or second- or higher-order compartment size approximations, the optimization problem in each stage of the dynamic programme may be neither convex nor concave, and in general may be much harder to solve than simple enumeration of extreme points of the feasible region. Thus, we developed four heuristics for solving RA-τ.

- HDE: *Exhaustive search over discretized feasible region*. Consider $N + 1$ values for each variable $v_h^k : 0, 1/N \times V_h^k, 2/N \times V_h^k, \ldots, (N-1)/N \times V_h^k, V_h^k$. For all feasible combinations of the v_h^ks' (those that do not violate the budget constraint), evaluate the objective function by dividing the time horizon T into S_D equal time steps and simulating the discrete-time version of the system of differential equations (e.g. Zaric *et al.*, 1998). Select the best solution found.
- HLP: *Single-period linear programming (LP) solution in each period*. Approximate the production functions $w_g^k(\mathbf{v}^k)$ with linear functions for all g, k. Construct first-order compartment size approximations. Starting with the first time period, substitute in the coefficients from the linearized production functions, sort the resulting objective function coefficients, and determine the (greedy) solution to the resulting linear program (Zaric & Brandeau, 2001b). Use that solution to forecast the population sizes at the beginning of the next time period. Repeat the solution process for all remaining time periods.
- HPF: *Penalty function heuristic*. In each period, search over variables $v_1^k, v_2^k, \ldots, v_{n-1}^k$. Let $v_n^k = B^k - (v_1^k + v_2^k + \cdots + v_{n-1}^k)$. Randomly choose M feasible initial starting points. Then follow a penalty function approach for each starting point: choose a search direction; find the optimal step size; evaluate the objective function using second-order approximations and quadratic penalty functions; iterate over several search directions;

gradually increase the penalty coefficient; select the best solution from the M solutions found.

- HSD: *Steepest descent heuristic*. Select a random starting point. Approximate the gradient of the objective function at the starting point using a secant method. The partial derivative in direction i is estimated as $\{F(x_1, x_2, \ldots, x_i + M, \ldots, x_n) - F(x_1, x_2, \ldots, x_i, \ldots, x_n)\}/M$, where F is the objective function and M is a large number (such as the total budget B). Determine the maximum distance that the solution can be changed in each direction without violating either the upper bounds or the budget constraint, then find the optimal step size in the direction of the gradient. At each step, update the current solution accordingly. Repeat the process until a limit on the number of iterations has been reached.

Heuristic HDE exhaustively searches over the feasible region. Results obtained by HDE can be made arbitrarily accurate by increasing N and S_D. The computation time of HDE grows linearly with S_D, polynomially with N, and exponentially with the number of time periods and interventions. We used HDE as a reference for evaluating the other heuristics. We used $N = 20$ and $S_D = 10$ in our computational tests.

HLP solves the LP knapsack problem that results in any single time period when linear production functions and first-order approximations for the compartment size functions are used, and when a first-order approximation is used for the new-infections function if the objective is infections averted. Details of the resulting LP formulation and its solution can be found in Zaric & Brandeau (2001b); details of the LP knapsack problem can be found in Hillier & Lieberman (1993). The LP in each period has a ‘greedy’ solution that depends only on the ordering of the objective function coefficients (for each time period, funds are allocated sequentially to the interventions according to decreasing order of objective function coefficients, until all the funds are allocated). Thus, HLP can be applied without knowledge of optimization theory. The proof of Proposition 1 established some conditions under which HLP will yield an optimal solution.

HPF is a standard penalty search procedure. Details of such a procedure used to solve the single-period resource allocation problem can be found in Zaric & Brandeau (2001b). HSD is a straightforward steepest descent heuristic. In our computational tests, we applied HPF and HSD with second-order approximations for the compartment size functions.

We first considered a problem with two populations, each with two disease stages, that allows for migration and cross-infection, as illustrated in Fig. 1. We considered the QALYs objective, and time horizons of 2, 6, 10 and 12 years. We assumed that two interventions were available. Intervention 1 (Intervention 2) reduces λ_{13} and λ_{14}(λ_{23} and λ_{24}) according to exponential production functions. A multiplier approach was used for the production functions: we set $\lambda_{ij}(t, \mathbf{v}) = \lambda_{ij}(t, 0) \times \xi(v_i^k)$ for $i = 1, 2$, and $j = 3, 4$, where the function $\xi(v_i^k)$ is an exponential function of the form $\xi(v_i^k) = a_i + b_i \mathrm{e}^{c_i v_i^k}$. The function $\xi(v_i^k)$ was set so that $\xi(0) = 1$ (i.e. no change), $\xi(0{\cdot}5B) = 0{\cdot}6$, and $\xi(\infty) = 0{\cdot}5$. For HLP, $\xi(v_i^k)$ was linearized by fitting a line between $\xi(0)$ and $\xi(B)$.

For each computational test we randomly generated 100 problem instances. For the initial sufficient contact rates, we assumed $\lambda_{ij}(0, 0) \sim U(0{\cdot}04, 0{\cdot}13)$ for $i = 1, 2$ and $j = 3, 4$; $\lambda_{ij}(0, 0) = 0$ otherwise. The entry and exit rates were chosen as $\rho_i \sim U(0, 0{\cdot}04)$ and $\delta_i \sim U(0, 0{\cdot}1)$ for $i = 1, \ldots, 4$. We set the inter-population transition rates ϕ_{12}, ϕ_{21},

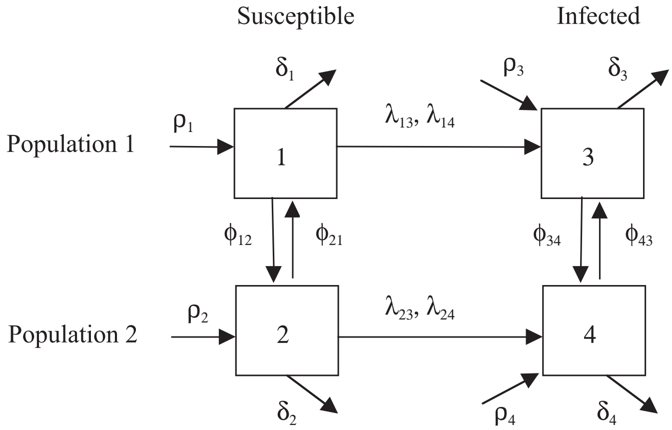

FIG. 1. Four-compartment model used in numerical examples.

ϕ_{34}, and ϕ_{43} as $\phi_{ij} \sim U(0{\cdot}01, 0{\cdot}03)$. For the quality multipliers we assumed q_1, $q_2 \sim U(0{\cdot}6, 1)$, $QI \sim U(0{\cdot}6, 1)$, $q_3 = q_1 \times QI$, and $q_4 = q_2 \times QI$. For initial compartment sizes, we set $y_i(0) \sim U(1000, 100\,000)$, $i = 1, \ldots, 4$. The sizes of the two populations for each problem instance at any time t are found by adding the appropriate values of $y_i(t)$: thus, $N_1(t) = y_1(t) + y_3(t)$, and $N_2(t) = y_2(t) + y_4(t)$ for $0 \leqslant t \leqslant T_{\tau+1}$.

Table 3 shows the average and maximum percentage difference in the objective function value for the solutions obtained by the heuristics HLP, HPF and HSD compared to the solution found by exhaustive search (HDE). In all cases we assumed that the time horizon (2, 6, 10 or 12 years) was divided into two time periods ($\tau = 2$); thus, investment was made at the beginning of the time horizon and halfway through the time horizon. All three heuristics found good solutions compared to the solution obtained by exhaustive search (HDE). The heuristics performed worse on average as the time horizon increased, although the differences were modest even at 12 years. The solutions obtained by HSD were furthest from those found by HDE, but even for a 12-year time horizon the average difference in solution value between HSD and HDE was only about 1%.

Table 4 shows the effect of considering different numbers of times at which the portfolio can be adjusted during the time horizon; this is represented by the value τ in the resource allocation model. We applied the heuristics assuming that investment could be made two, three or four times ($\tau = 2, 3$ or 4) during the time horizon (6 or 12 years). Table 4 shows that, even when investment was made only twice during the time horizon, the heuristics HLP, HPF and HSD all provided good solutions compared to those obtained by exhaustive search, with the average percentage difference being less than 1·1% in all cases. Increasing the number of time periods (τ) to three or four slightly improved the solutions relative to the solution obtained using exhaustive search. The quality of solutions found by all three heuristics became slightly worse as the time horizon increased, given a fixed number of time periods. The solutions found by HSD were slightly worse than those found by HLP and HPF.

TABLE 3 *Average and maximum differences between heuristic solutions versus HDE for a 4-compartment model (illustrated in Fig. 1) with the QALYs objective; each result is based on 100 randomly generated problem instances*

		Heuristic compared to HDE: percentage difference in objective function value					
Length of time horizon (years)	Number of periods (τ)	HLP		HPF		HSD	
		Avg	Max.	Avg	Max.	Avg	Max.
2	2	−0·01%	−0·03%	−0·00%	−0·00%	−0·16%	−0·26%
6	2	−0·03%	−0·12%	−0·00%	−0·06%	−0·50%	−1·17%
10	2	−0·06%	−0·35%	−0·02%	−0·38%	−0·76%	−3·71%
12	2	−0·08%	−0·35%	−0·04%	−0·39%	−1·07%	−4·17%

TABLE 4 *Average difference between heuristic solutions versus HDE for a 4-compartment model (illustrated in Fig. 1) with the QALYs objective for different values of τ; each result is based on 100 randomly generated problem instances*

		Heuristic compared to HDE: average percentage difference in objective function value.		
	Length of time	Number of periods (τ)		
Heuristic	horizon (years)	2‡	3	4
HLP	6	−0·03%	−0·03%	−0·02%
	12	−0·08%	−0·09%	−0·08%
HPF	6	−0·00%	−0·00%	−0·00%
	12	−0·04%	−0·03%	−0·03%
HSD	6	−0·50%	−0·41%	−0·31%
	12	−1·07%	−0·88%	−0·80%

‡ For $\tau = 2$, the data used were the same as for the problems used to generate Table 3.

The required computation time for HSD and HLP was minimal. HPF required significantly more computation time. For a problem with $\tau = 4$, for example, HSD and HLP required less than one CPU second, whereas HPF required 30 CPU seconds. For the same problem, HDE required 4 CPU seconds; however, the computation time for HDE increases exponentially with τ, making it impractical to use for larger numbers of time periods.

We next considered a larger, more realistic problem with four populations and three disease stages, illustrated in Fig. 2. This epidemic model allows for migration between populations, cross-infection, and disease progression. We considered the QALYs objective, and we assumed a 12-year time horizon. For each computational test we randomly generated 100 problem instances. For initial compartment sizes, we set $y_i(0) + y_{i+4}(0) + y_{i+8}(0) \sim U(10\,000, 100\,000)$, $i = 1, \ldots, 4$. We set initial prevalence in each population as $\text{prev}_i \sim U(0{\cdot}01, 0{\cdot}1)$, $i = 1, 2, 3$; $\text{prev}_4 \sim U(0{\cdot}1, 0{\cdot}3)$, and we set

$$\frac{y_{i+4}(0) + y_{i+8}(0)}{y_i(0) + y_{i+4}(0) + y_{i+8}(0)} = \text{prev}_i,\ i = 1, 2, 3.$$

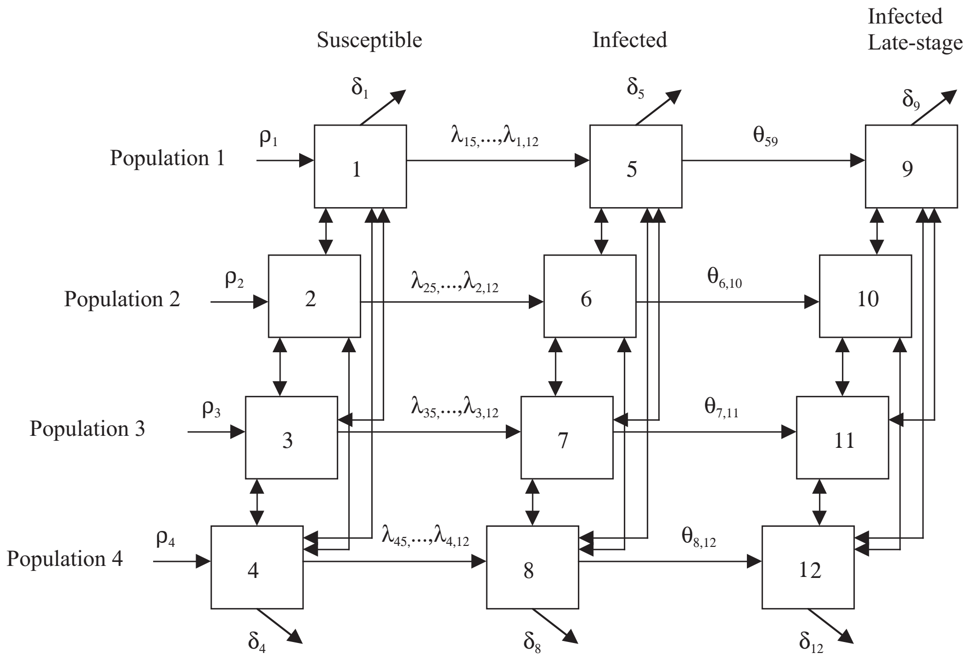

FIG. 2. Twelve-compartment model used in numerical examples. The interclass (vertical) transition rate from compartment i to compartment j is given by ϕ_{ij}.

We assumed that the division of individuals between early and late-stage infection was given by $\text{split}_i \sim U(0{\cdot}5, 1)$, $i = 1, \ldots, 4$, and we set

$$\frac{y_{i+4}(0)}{y_{i+4}(0) + y_{i+8}(0)} = \text{split}_i, i = 1, \ldots, 4.$$

Entry rates were $\rho_i \sim U(0{\cdot}01, 0{\cdot}1)$ for $i = 1, \ldots, 4$. We assumed that incremental death rates associated with infection were $\alpha_i = 0$ for $i = 1, \ldots, 4, \alpha_i \sim U(0{\cdot}05, 0{\cdot}2)$ for $i = 5, \ldots, 8$, and $\alpha_i \sim \alpha_{i-4} + U(0{\cdot}05, 0{\cdot}2)$ for $i = 9, \ldots, 12$. Exit rates were set as $\delta_i \sim U(0{\cdot}0001, 0{\cdot}01) + \alpha_i$ for $i = 1, \ldots, 12$. Inter-population transition rates were set at $\phi_{ij} \sim U(0{\cdot}01, 0{\cdot}1)$ for i, j in the same disease stage, and 0 otherwise. We set the disease progression rates θ_{59}, $\theta_{6,10}$, $\theta_{7,11}$, and $\theta_{8,12}$ as $\theta_{ij} \sim U(0{\cdot}05, 0{\cdot}3)$. We calculated the initial sufficient contact rates as follows: For each population ($i = 1, \ldots, 4$) we set $\text{risk}_i \sim U(1, (3 + i)/4)$. Then for each $i = 1, \ldots, 4$ we set $\lambda_{ij}(0, 0) = \gamma_j \times \text{risk}_i$, where $\gamma_j \sim U(0{\cdot}05, 0{\cdot}15)$ for $j = 5, \ldots, 12$. Quality multipliers were set as $q_i \sim U(0{\cdot}8, 1)$ for $i = 1, \ldots, 4$; $q_i = q_{i-4} \times QI$ for $i = 5, \ldots, 8$, where $QI \sim U(0{\cdot}8, 1)$; and $q_i = q_{i-8} \times QI \times QI2$ for $i = 9, \ldots, 12$, where $QI2 \sim U(0{\cdot}8, 1)$.

We assumed that four interventions were available, one to reduce the sufficient contact rates in each of the four populations. Thus, intervention $i (i = 1, \ldots, 4)$ reduced the sufficient contact rates $\lambda_{i5}, \ldots, \lambda_{i,12}$. Similar to the four-compartment example, we assumed production functions of the form $\lambda_{ij}(t, \mathbf{v}) = \lambda_{ij}(t, 0) \times \xi(v_i^k)$ for $i = 1, \ldots, 4$ and $j = 5, \ldots, 12$, where the function $\xi(v_i^k)$ is an exponential function of the form

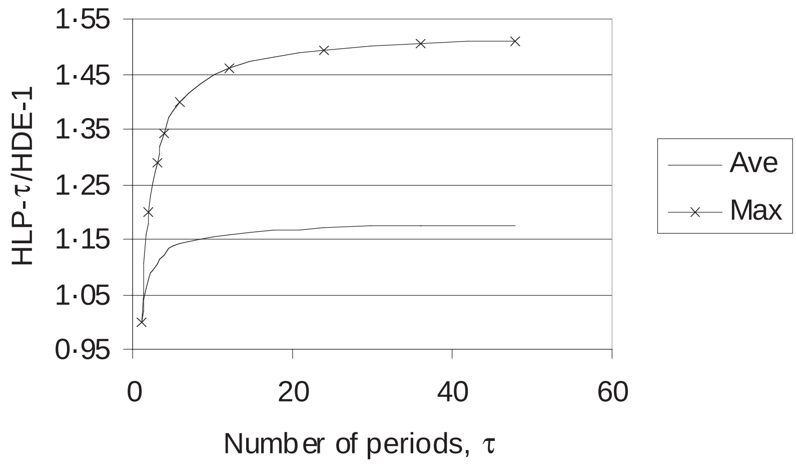

FIG. 3. Comparison of HLP with τ time periods versus HDE with $\tau = 1$ for 12-compartment model (illustrated in Fig. 2) with a 12-year time horizon. The same 100 randomly generated problems were used for all values of τ.

$\xi(v_i^k) = a_i + b_i e^{c_i v_i^k}$. The function $\xi(v_i^k)$ was set so that $\xi(0) = 1, \xi(0{\cdot}5B) = 0{\cdot}6$, and $\xi(\infty) = 0{\cdot}5$. For HLP, $\xi(v_i^k)$ was linearized by fitting a line between $\xi(0)$ and $\xi(B)$.

For this problem we compared HLP and HSD with different values of τ to HDE with $\tau = 1$; HPF required too much computation time, so we did not apply it. Table 5 shows results for $\tau = 1$, 2, 3, 4, 6 and 12, and Fig. 3 shows results for $\tau = 1, \ldots, 50$. As shown in Table 5, when HLP and HSD were applied with $\tau = 1$, the solutions they found were only slightly worse on average than those found by HDE with $\tau = 1$. As the value of τ increased, the solutions obtained by HLP and HSD became increasingly better than the solution found using exhaustive search and a single time period. For example, when 12 time periods were considered, HLP and HSD both found solutions with average value 15% higher (i.e. 15% more QALYs gained) than the solution found using HDE with $\tau = 1$. In some cases, the gains from reallocation were substantial, as indicated by the 'Maximum' (improvement) line in Fig. 3: for example, in one case the solution value found using HLP with $\tau = 12$ was 45% higher than the solution found using HDE with $\tau = 1$. HLP and HSD each required less than 2 CPU seconds to solve these problems, even when 12 time periods were considered. For each value of τ, the average value of solutions found by HLP was about the same as the average value of solutions found by HSD.

For 100 instances of the 12-compartment problem, we compared the solution obtained by HLP with $\tau = 1$ (i.e. no reallocation of funds allowed over the time horizon) to the solution obtained by HLP with $\tau = 12$ (which allows for reallocation of funds in each year of the time horizon). For all 100 problems, the first-period allocations generated by HLP were the same whether or not reallocation was allowed. However, when reallocation was allowed (the case $\tau = 12$), it occurred in 85 of the problems. In half of the instances, reallocation involved dropping an intervention and adding a new intervention to the

TABLE 5 *Average difference between HLP and HSD for different values of τ versus HDE with $\tau = 1$ for a 12-compartment model (illustrated in Fig. 2) with the QALYs objective; each result is based on a common set of 100 randomly generated problem instances*

Length of time horizon (years)	Number of periods (τ)	Heuristic compared to HDE with $\tau = 1$: average percentage difference in objective function value — HLP	HSD
12	1	−0·04%	−0·02%
12	2	7·05%	7·07%
12	3	9·99%	10·01%
12	4	11·59%	11·61%
12	6	13·30%	13·45%
12	12	15·11%	15·14%

investment portfolio. In one-third of the instances, reallocation involved funding the same set of interventions that was funded in the previous period but changing the relative levels of funding. When reallocation occurred, it occurred one to four times over the 12-year time horizon.

As shown in Table 5, allowing for the possibility of reallocation once each year ($\tau = 12$) improved the average solution by 15%. Allowing for just one reallocation ($\tau = 2$) improved the average solution by 7%. The results in Fig. 3 and Table 5 suggest that significant improvement in the solution to the resource allocation problem can be achieved by allowing at least one or two times at which resources can be reallocated over the time horizon of the problem (i.e. by allowing $\tau = 2$ or 3). As shown in Fig. 3, increases in τ eventually led to little improvement in the solution.

5. Discussion

We have formulated a model of resource allocation for epidemic control in multiple populations over multiple time periods. Our computational analyses suggest that good allocations can be made based on some fairly simple heuristics. For example, using linear production functions (or linear approximations for the production functions) and first-order approximations for the compartment size functions, and applying the heuristic HLP—which requires no knowledge of optimization—yielded good solutions for the problems we tested.

Our analyses also suggest that allowing for some reallocation of resources over the time horizon of the problem, rather than allocating resources just once at the beginning of the time horizon, can lead to significant increases in health benefits. This occurs because the best allocation of resources at one point in an epidemic may not be the best allocation later in the epidemic. Paltiel (1994) made a similar observation about HIV prevention programs: via simulation of a simple epidemic model, he showed that early in an epidemic the greatest number of new infections is averted by targeting prevention programs to infected individuals, whereas later in an epidemic the greatest number of new infections is averted by targeting both infected and susceptible individuals.

We considered the objectives of maximizing QALYs or minimizing new infections. The QALYs objective includes life years gained as a special case. Other objective functions are possible, including objectives based on cost or value to society. Details on how to modify the single-period model to include such concepts can be found in Zaric & Brandeau (2001b). For the modified multi-period model one could construct new approximations for the objective function and constraints using methodology similar to that used in this paper, and then solve the problem using the methodology we have presented.

Our analysis has several limitations. We considered a deterministic model. However, the size of future budgets may not be known at the time of the initial allocation decision. Moreover, the effects of allocation decisions on parameter values may be stochastic. Future work on the dynamic resource allocation problem could include uncertainty in the model. We assumed that allocations take effect instantaneously at the beginning of each time period and their effects expire instantaneously at the end of each period if no additional funds are invested. In reality, interventions may not take effect instantaneously, and benefits (e.g. reduced risk behaviour) may persist when funds are no longer being invested. Future work could relax these assumptions about the timing of benefits.

In our computational tests, the use of the heuristic HLP with a limited number of reallocations yielded solutions that were as good as those obtained using much more computationally intense procedures such as HDE. Given the high quality of solutions generated by this simple heuristic, we conclude that allowing for reallocation of funds in a multi-year resource allocation problem may be more important than developing a sophisticated model for one-time allocation of resources. An important next step is to work with policy makers to help improve resource allocation for prevention of endemic diseases, such as HIV/AIDS, other sexually transmitted diseases, and tuberculosis. Such work might involve the establishment of longer-term budgets for control of endemic diseases, consideration of future resource allocation decisions when making the current allocation decision, and regular review of and possible reallocation of epidemic control resources over time.

Acknowledgements

Drs Brandeau and Zaric were supported by the Societal Institute of the Mathematical Sciences (SIMS) through grants from the National Institutes of Health (NIH) (Grant # R-01-DA09531 and R01-DA15612). GSZ is the M.B.A. ’80 Faculty Fellow at the Ivey School of Business.

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Appendix

For simplicity in the following proofs we let x_i^k denote the size of compartment i at the start of period k given any investment $\mathbf{v}$ (i.e. $x_i^k \equiv x_i(T_k, \mathbf{v})$) and we let λ_i^k denote the value of the sufficient contact rate in compartment i during period k given any investment $\mathbf{v}$ (i.e. $\lambda_i^k \equiv \lambda_i(t, \mathbf{v})$ for all $t \in [T_k, T_{k+1})$). To distinguish exponents from superscripts we adopt the following convention: superscripts will be written beside the variable or parameter, and any term raised to an exponent will be enclosed in parentheses. For example, x_i^2 represents $x_i(T_2, \mathbf{v})$, and $(x_i^2)^2$ represents $x_i(T_2, \mathbf{v})$ squared. Additionally, we introduce the following notation for discounted polynomials of t over a time period of length T:

$$D(j) = \int_{t=0}^{T} t^j \mathrm{e}^{-rt}\, \mathrm{d}t.$$

Proof of Proposition 1. Substituting (9) and (10) in (6)–(8) yields

$$x_1^2 = x_1^1 + \delta_1 x_3^1 T - (a_1 - b_1 v_1^1) x_1^1 x_3^1 T \tag{A.1}$$

$$x_2^2 = x_2^1 + \delta_2 x_4^1 T - (a_2 - b_2 v_2^1) x_2^1 x_4^1 T \tag{A.2}$$

$$x_3^2 = x_3^1 - \delta_1 x_3^1 T + (a_1 - b_1 v_1^1) x_1^1 x_3^1 T \tag{A.3}$$

$$x_4^2 = x_4^1 - \delta_2 x_4^1 T + (a_2 - b_2 v_2^1) x_2^1 x_4^1 T. \tag{A.4}$$

We calculate the objective function using these approximations. The QALYs objective function is the sum of the total QALYs experienced in periods 1 and 2. The total QALYs experienced in period 1 is

$$\begin{aligned}
&\int_0^T \{N_1[q_1x_1(t) + q_3x_3(t)] + N_2[q_2x_2(t) + q_4x_4(t)]\}\mathrm{e}^{-rt}\,\mathrm{d}t \\
&= \int_0^T \{N_1[q_1\{x_1(0) + x_1'(0)t\} + q_3\{x_3(0) + x_3'(0)t\}] \\
&+N_2[q_2\{x_2(0) + x_2'(0)t\} + q_4\{x_4(0) + x_4'(0)t\}]\}\mathrm{e}^{-rt}\,\mathrm{d}t \\
&= D(0)[N_1(q_1x_1^1 + q_3x_3^1) + N_2(q_2x_2^1 + q_4x_4^1)] \\
&+D(1)\{N_1(q_1 - q_3)[\delta_1x_3^1 - \lambda_1x_1^1x_3^1] + N_2(q_2 - q_4)[\delta_2x_4^1 - \lambda_2x_2^1x_4^1]\}. \qquad \text{(A.5)}
\end{aligned}$$

The total QALYs in period 2 are calculated similarly, substituting x_i^2 for x_i^1, $D(0)\mathrm{e}^{-rT}$ for $D(0)$, and $D(1)\mathrm{e}^{-rT}$ for $D(1)$ everywhere. The resulting objective function is

$$\begin{aligned}
\mathrm{QALY}(v) = c_0 + N_1c_1(a_1 - b_1v_1^1) + N_2c_2(a_2 - b_2v_2^1) + \mathrm{e}^{-rT}\{\, N_1 f_1(\mathbf{v}^1) \\
+N_2 f_2(\mathbf{v}^1) + N_1g_1(\mathbf{v}^1)(a_1 - b_1v_1^2) + N_2g_2(\mathbf{v}^1)(a_2 - b_2v_2^2)\}. \qquad \text{(A.6)}
\end{aligned}$$

The terms c_0 , c_1, and c_2 are constants, with

$$\begin{aligned}
c_0 \equiv D(0)[N_1(q_1x_1^1 + q_3x_3^1) + N_2(q_2x_2^1 + q_4x_4^1)] \\
+D(1)\{N_1(q_1 - q_3)\delta_1x_3^1 + N_2(q_2 - q_4)\delta_2x_4^1\}. \qquad \text{(A.7)}
\end{aligned}$$

We substitute $x_1^1 = 1 - x_3^1$ and $x_2^1 = 1 - x_4^1$ in the first term of c_0. This yields

$$\begin{aligned}
c_0 &= D(0)[q_1N_1(1 - x_3^1) + q_2N_2(1 - x_4^1) + q_3N_1x_3^1 + q_4N_2x_4^1] \\
&\quad +D(1)\{N_1(q_1 - q_3)\delta_1x_3^1 + N_2(q_2 - q_4)\delta_2x_4^1\} \\
&= D(0)[q_1N_1 + q_2N_2] \\
&\quad +(q_3 - q_1)N_1[D(0) - D(1)\delta_1]x_3^1 + (q_4 - q_2)N_2[D(0) - D(1)\delta_2]x_4^1.
\end{aligned}$$

The terms c_1 and c_2 are defined as

$$c_1 \equiv (q_3 - q_1)x_1^1x_3^1D(1) \qquad \text{(A.8)}$$

$$c_2 \equiv (q_4 - q_2)x_2^1x_4^1D(1). \qquad \text{(A.9)}$$

The terms $f_1(\mathbf{v}^1)$, $f_2(\mathbf{v}^1)$, $g_1(\mathbf{v}^1)$, and $g_2(\mathbf{v}^1)$ in (A.6) are functions of the resource allocation decision made in the first period and are defined as

$$f_1(\mathbf{v}^1) \equiv q_1D(0) + (q_3 - q_1)(D(0) - \delta_1D(1))x_3^2 \qquad \text{(A.10)}$$

$$f_2(\mathbf{v}^1) \equiv q_2D(0) + (q_4 - q_2)(D(0) - \delta_2D(1))x_4^2 \qquad \text{(A.11)}$$

$$g_1(\mathbf{v}^1) \equiv (q_3 - q_1)x_1^2x_3^2D(1) \qquad \text{(A.12)}$$

$$g_2(\mathbf{v}^1) \equiv (q_4 - q_2)x_2^2x_4^2D(1). \qquad \text{(A.13)}$$

We solve RA′-2-2 using dynamic programming, with the time periods being the stages. The sufficient contact rates are strictly decreasing functions of the amount invested, so

QALY(**v**) is a strictly increasing function of amounts invested, and the budget constraints will be binding in each time period. We express the first-period variables as $v_2^1 = B^1 - v_1^1$; then the first-period problem becomes a single-variable optimization problem. We express $g_i(\mathbf{v}^1)$ as $g_i(v_1^1)$, and $f_i(\mathbf{v}^1)$ as $f_i(v_1^1)$. In stage two we determine v_1^2 and v_2^2. From (A.6), we see that the problem in stage two is an LP knapsack problem (see Hillier & Lieberman, 1993) with the following solution:

$$(v_1^2, v_2^2) = \begin{cases} (V_1^2, B^2 - V_1^2) & \text{if} \quad -b_1 N_1 g_1(v_1^1) > -b_2 N_2 g_2(v_1^1) \\ (B^2 - V_2^2, V_2^2) & \text{if} \quad -b_1 N_1 g_1(v_1^1) < -b_2 N_2 g_2(v_1^1). \end{cases} \tag{A.14}$$

Since b_i and N_i are constants, the solution in stage two depends on the values of $g_1(v_1^1)$ and $g_2(v_1^1)$. However, the solution in the second period involves allocating as much of the resource as possible to one of the populations, regardless of the allocation in the first period.

Define R_1 and R_2 as

$$R_1 \equiv \{v_1^1 | -b_1 N_1 g_1(v_1^1) > -b_2 N_2 g_2(v_1^1)\} \tag{A.15}$$

$$R_2 \equiv \{v_1^1 | -b_1 N_1 g_1(v_1^1) \leqslant -b_2 N_2 g_2(v_1^1)\}. \tag{A.16}$$

Clearly $R_1 \cup R_2 = [-\infty, \infty]$. We determine v_1^1 by maximizing the following function:

$$G(v_1^1) = \begin{cases} G_1(v_1^1) & v_1^1 \in R_1 \\ G_2(v_1^1) & v_1^1 \in R_2 \end{cases} \tag{A.17}$$

subject to $0 \leqslant v_1^1 \leqslant B^1$. $G_1(v_1^1)$ and $G_2(v_1^1)$ are defined by substituting the two possible second-period solutions in (A.14) into (A.6). Thus,

$$\begin{aligned} G_1(v_1^1) = {} & c_0 + N_1 c_1(a_1 - b_1 v_1^1) + N_2 c_2(a_2 - b_2 B^1 + b_2 v_1^1) + \mathrm{e}^{-rT}\{N_1 f_1(v_1^1) \\ & + N_2 f_2(v_1^1) + N_1 g_1(v_1^1)(a_1 - b_1 V_1^2) + N_2 g_2(v_1^1)(a_2 - b_2 B^2 + b_2 V_1^2)\} \end{aligned} \tag{A.18}$$

$$\begin{aligned} G_2(v_1^1) = {} & c_0 + N_1 c_1(a_1 - b_1 v_1^1) + N_2 c_2(a_2 - b_2 B^1 + b_2 v_1^1) + \mathrm{e}^{-rT}\{N_1 f_1(v_1^1) \\ & + N_2 f_2(v_1^1) + N_1 g_1(v_1^1)(a_1 - b_1 B^2 + b_1 V_2^2) + N_2 g_2(v_1^1)(a_2 - b_2 V_2^2)\}. \end{aligned} \tag{A.19}$$

We maximize $G(v_1^1)$ by maximizing $G_1(v_1^1)$ and $G_2(v_1^1)$, and taking the maximum of these:

$$\max_{v_1^1} G(v_1^1) = \max\left\{ \max_{v_1^1 \in R_1} G_1(v_1^1), \max_{v_1^1 \in R_2} G_2(v_1^1) \right\}. \tag{A.20}$$

By substituting (A.1)–(A.4) into (A.12) and (A.13) we see that both (A.18) and (A.19) are quadratic in v_1^1. Convexity properties of $G_1(v_1^1)$ and $G_2(v_1^1)$ are determined by the coefficients of $(v_1^1)^2$. The coefficient of $(v_1^1)^2$ in $G_i(v_1^1)$ depends on the sum of the coefficients of $(v_1^1)^2$ in $g_1(v_1^1)$ and $g_2(v_1^1)$. The coefficient of $(v_1^1)^2$ in $g_1(v_1^1)$ is given by

$$k_1 = -(q_3 - q_1)[b_1 x_1^1 x_3^1 T]^2 D(1). \tag{A.21}$$

Similarly, the coefficient of $(v_1^1)^2$ in $g_2(v_1^1)$ is given by

$$k_2 = -(q_4 - q_2)[b_2 x_2^1 x_4^1 T]^2 D(1). \tag{A.22}$$

Since $q_i > q_{i+2}$, we have $k_1, k_2 > 0$. Thus, $G_1(v_1^1)$ and $G_2(v_1^1)$ are convex. The maximum of a convex function over a convex feasible region is an extreme point of the feasible region (Luenberger, 1984). In this case, the solution is either $v_1^1 = V_1^1$ or $v_1^1 = B^1 - V_2^1$. Since $G = \max\{G_1, G_2\}$, the allocation that maximizes G is of the same form as the one that maximizes G_1 and G_2. □

Proof of Proposition 2. Proof by example. Let $N_1 = N_2$, $\delta_i = 0{\cdot}05$, $\lambda_1(0, 0) = 0{\cdot}1$ and $\lambda_2(0, 0) = 0{\cdot}2$. For the production functions (9), let $a_i = \lambda_i(0, 0)$, $b_1 = 2{\cdot}5 \times 10^{-8}$ and $b_2 = 5 \times 10^{-8}$. Let $T = 1$, $r = 0{\cdot}03$, and $B^k = \$1\,000\,000$ for $k = 1, 2$. Let $V_i^k = B^k$ for $i, k = 1, 2$. By the assumptions of the model, $x_{i+2}(0, \mathbf{0}) = 1 - x_i(0, \mathbf{0})$, $i = 1, 2$. When $x_1(0, \mathbf{0}) = 0{\cdot}478$ and $x_2(0, \mathbf{0}) = 0{\cdot}071$, then the infections-averted objective function is concave for all feasible $\mathbf{v}$. When $x_1(0, \mathbf{0}) = 0{\cdot}383$ and $x_2(0, \mathbf{0}) = 0{\cdot}585$, then the infections-averted objective function is convex for all feasible $\mathbf{v}$. When $x_1(0, \mathbf{0}) = 0{\cdot}333$ and $x_2(0, \mathbf{0}) = 0{\cdot}429$, then the infections-averted objective function is neither convex nor concave for all feasible $\mathbf{v}$. □

Proof of Proposition 3. We extend the proof of Proposition 1. In the second period we have a knapsack LP for which a greedy solution is known to be optimal (for each time period, funds are allocated sequentially to the interventions according to decreasing order of objective function coefficients, until all the funds are allocated). In the first period the problem is to determine $\mathbf{v}^1 = (v_1^1, v_2^1, \ldots, v_n^1)$. This is done by maximizing

$$G(v_1^1, \ldots, v_n^1) = \begin{cases} G_1(v_1^1, \ldots, v_n^1) & (v_1^1, \ldots, v_n^1) \in R_1 \\ G_2(v_1^1, \ldots, v_n^1) & (v_1^1, \ldots, v_n^1) \in R_2 \\ \quad\vdots & \\ G_N(v_1^1, \ldots, v_n^1) & (v_1^1, \ldots, v_n^1) \in R_N \end{cases} \tag{A.23}$$

where $R_1, \ldots, R_N$ are different regions corresponding to different optimal second-period solutions (as a function of the first-period allocation). As in the two-population case, each function $G_i(\mathbf{v}^1)$ is quadratic in $\mathbf{v}^1$. Following an argument similar to that used in the proof of Proposition 1, it is straightforward to show that each $G_i(\mathbf{v}^1)$ is convex. Thus, the optimal solution is an extreme point of the feasible region. □