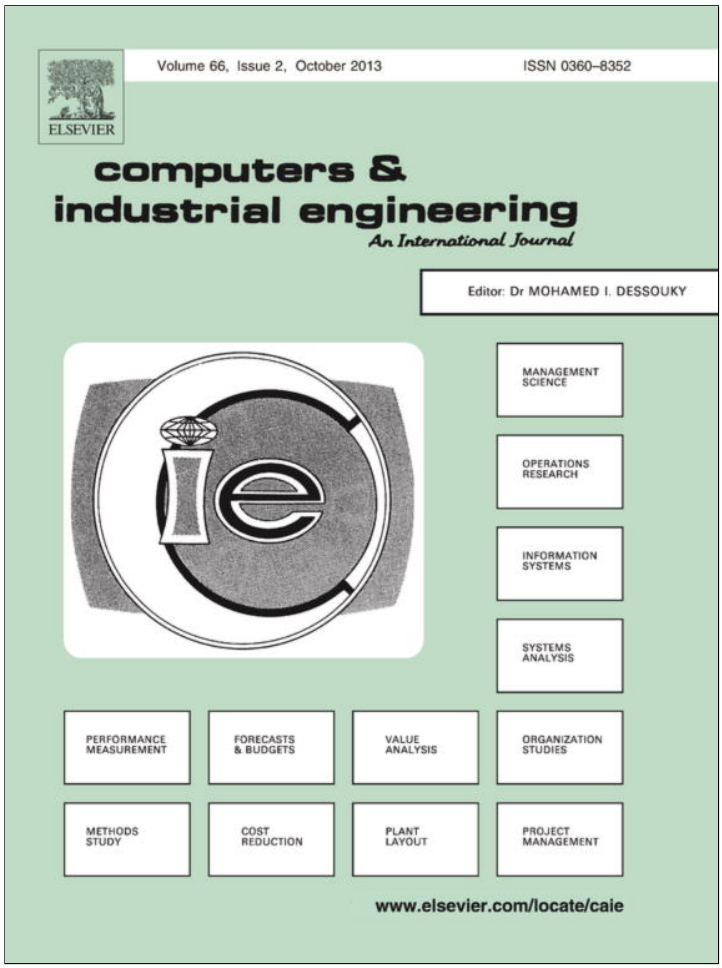

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Optimal resource allocation response to a smallpox outbreak

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ABSTRACT

Infectious disease outbreaks, caused by nature or bioterrorism, are unfortunately very real threats to the general population. Planning an effective response to an infectious disease outbreak requires a coordinated effort in multiple locations to best allocate the limited resources. This decision problem is further complicated by the non-linear nature of disease propagation and the fact that outbreaks can jump urban, even national, boundaries. In this work we present a multi-city resource allocation model to distribute a limited amount of vaccine in order to minimize the total number of fatalities due to a smallpox outbreak.

The model decides the amount of limited supplies to deliver and which infection control measure (isolation, ring, or mass vaccination) to use in each location in order to decrease the number of fatalities. The proposed model approximates the disease propagation dynamics in order to represent the problem as a mixed integer programming problem. Furthermore we develop an efficient heuristic to solve the resulting large scale mixed integer programming problem. Our results analyze the quality of the approximate disease propagation model and the efficiency of the heuristic algorithm. We also conduct a case study applying the multi-city model in planning an emergency response to a hypothetical national smallpox outbreak, which shows the possibility of saving a significant number of lives compared with a prorated allocation policy.

1. Introduction

Infectious disease outbreaks caused by nature or bioterrorism are unfortunately very real threats to the general population. A recent example of an epidemic outbreak is the swine flu (H1N1) that spread quickly around the world in 2009. Other examples include SARS during 2002–2003 and the appearance of avian flu events since 2004. The SARS outbreak highlighted the massive impact of such emergencies on society. The disease caused 8096 known infected cases and 774 fatalities (a case-fatality rate of 9.6%) (World Health Organization, 2004). These examples show that massive infectious disease outbreaks can indeed occur naturally. An example of infectious disease outbreak due to a deliberate exposure because of terrorism was the 2001 anthrax attacks in the United States. In the past, terrorists have shown their willingness to select transportation networks such as buses, trains, and airplanes as targets. These networksare a target, not only because it is possible to harm a large number of people, but in the case of an infectious disease attack, the transportation network itself can help distribute the infection further.

A notable bioterrorism agent is the smallpox virus. It poses a serious threat because people are no longer routinely vaccinated for smallpox since its global eradication about 30 years ago. Thus, at least half of the population is now susceptible to the disease. Smallpox can be transmitted person-to-person and is highly lethal with a case-fatality rate of 20%, and on average the infected person shows no symptoms for the first 2 weeks (Bozzette et al., 2003). Currently, there is no effective treatment for smallpox. This could lead to large numbers of fatalities if smallpox were used in a bioterrorist attack to a highly populated site. For example, a covert smallpox attack at an airport could spread to many cities or even the entire nation due to the time it would take to correctly diagnose patients. Bozzette et al. (2003) described two airport attack scenarios that could infect 5000–100,000 individuals nationwide.

The objective of this paper is to propose and analyze a mathematical model to plan an efficient response to a nationwide smallpox outbreak. This model should determine the best strategy to distribute the limited resources among the different locations in order to reduce the total number of fatalities. The effect of different medical strategies (control measures) in controlling the outbreak and the possibility of cross-city infections should also be taken into account.

In particular we note that resources available to respond to a disease outbreak emergency could be limited due to a lack of supplies, or a limited delivery capacity caused by inadequate personnel or equipment, as was observed during SARS outbreak (Cheng & Lu, 2003; US Government Accounting Office, 2004). Furthermore,

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possible response strategies to a smallpox outbreak include: (1) isolation strategy alone, which is isolation of known cases and known contacts; (2) ring strategy (vaccination of known contacts plus isolation); and (3) mass vaccination, which is a vaccination of a percentage of the population plus ring strategy for susceptible individuals. The smallpox vaccine has an estimated fatality rate of 2.72 per million by summing up fatalities due to all complications (Bozzette et al., 2003). The model should also take into account that each location can have different transmission rates due to differing demographics and initial number of cases. This can lead to different optimal control policies for different locations. Furthermore, the decisions at one city will influence the disease propagation in neighboring cities due to cross-city infections.

Even in a single city, the optimal decision of how to control an outbreak is complicated by the disease propagation dynamics. For example, if the number of infected individuals or the transmission rate is sufficiently low, then it might be preferable to isolate identified cases and contacts rather than vaccinate the entire population. These dynamics, typically represented by differential equations, are difficult to incorporate precisely in large integer optimization problems. Thus, it is fundamental to have a simple but accurate representation of these disease dynamics to build a multi-city resource allocation model.

The main contributions of this work are:

- We develop a constant rate approximate disease propagation model with an analysis of the conditions where it approximates well the total number of fatalities. Our results show that updating the constant rate every 4 periods (corresponding to 2 months) estimates the total fatalities well. The average deviation from the fatality estimate of a micro-simulation model is less than 2% (a maximum of 11%).
- Based on the approximate disease propagation model, a mixed integer mathematical programming formulation is developed to decide the optimal resource allocation to mitigate a disease outbreak. Since past vaccination strategies modify the transmission rates for subsequent stages, the proposed model includes integer variables to represent disjunctive constraints characterizing the different possible future transmission rate scenarios.
- We develop a heuristic algorithm to efficiently solve this large-scale multi-city resource allocation model. Due to the size of the problem to represent a nationwide outbreak, the computation time to obtain exact solutions (an average of 1.2 h.) can make it difficult to use this model in practice. We developed a heuristic solution method, based on ideas from heuristics for the knapsack problem. Our computational experiments show that the heuristic was able to obtain solutions within 0.5% of the optimal solution in less than 1 s. It provides valuable insights on how to prioritize the affected cities when allocating resources. In addition, it could help a lot when we solve a two-stage stochastic programming problem because we need to consider a large number of scenarios, and the time to solve the second stage sub-problem is very important.

We point out that although the approximate disease propagation model presented here is based on specifics of smallpox, the modeling and optimization methodology used is generic and applicable to other infectious diseases. In particular, the approach presented here would directly apply for diseases which have an incubation period and an infectious period of roughly the same length. The key step is developing a simple approximate disease propagation model and making sure it is used only when it provides good estimation of how the disease outbreak evolves.

The structure of the paper is as follows: we provide a review of relevant literature in Section 2. In Section 3, we analyze disease propagation models and present the constant rate approximation model used in the optimal resource allocation models. In Section 4, we present a single city disease propagation model and introduce a model for different control measures under limited resources. In Section 5, we extend the single city model to a multi-city model with cross-city infection and a constraint on total resources and provide a heuristic for its solution. In Section 6, we present computational results that study the fitness of the disease propagation model, present a solution to an illustrative multi-city scenario with sensitivity analysis, and show the efficiency of the proposed heuristic. We conclude the paper and provide directions for future work in Section 7.

2. Literature review

2.1. Single-city model for smallpox control policy

Traditional epidemiological models characterize the rate at which susceptible individuals become infected, the rate at which infected individuals recover or die, the length of the infection, birth rate and death rate, etc. (see Bailey, 1975; Frauenthal, 1980). For example, the Susceptible, Infected, Recovered (SIR) model and its variations have been widely used to model the spread of epidemics and to study immunization strategies (Anderson & May, 1992). Ferguson et al. (2003) reviewed the use of models in smallpox planning within the broader epidemiological context set by recent outbreaks of both novel and re-emerging pathogens. Previous decision models for smallpox outbreaks involve stochastic simulation models (Bozzette et al., 2003; Eichner, 2003; Eubank et al., 2004; Kretzschmar, Hof, Wallinga, & van Wijngaarden, 2004; Legrand, Viboud, Boelle, Valleron, & Flahault, 2004; Longini et al., 2007; Meltzer, Damon, LeDunc, & Millar, 2001) and differential equations (Kaplan, Craft, & Wein, 2002, 2003).

Detailed stochastic simulation models have been used to evaluate the performance of different control measures. Meltzer et al. (2001) found that a combined contact vaccination and isolation campaign is more effective in containing the disease than implementing either one alone. Eichner demonstrated that contact vaccination with surveillance and case isolation could extinguish smallpox outbreaks in highly susceptible populations within half a year (Eichner, 2003). Legrand et al. (2004) and Kretzschmar et al. (2004) showed that a smallpox outbreak can be controlled by ring vaccination and case isolation. A ring strategy was also shown to be successful if infectious cases are rapidly diagnosed. However, because of the inherent stochastic nature of epidemic outbreaks, both the size and duration of contained outbreaks were highly variable. Eubank et al. (2004) explored the use of dynamic bipartite graphs to model the physical contact patterns that result from movements of individuals between specific locations. Their simulation results suggested that outbreaks could be contained by a strategy of traced vaccination combined with early detection without resorting to mass vaccination of a population.

The above simulation models did not consider pre-attack control measures, e.g., pre-attack vaccination of health care workers. In Bozzette et al. (2003) the authors developed scenarios of smallpox attacks and built a stochastic model to simulate the outcomes under various control policies: contact vaccination and isolation, pre- or post-attack vaccination of 60% of the population and 90% of the health care workers, or both. Their analysis favored prior vaccination of health care workers unless the likelihood of a smallpox attack is sufficiently small. Vaccination of the public would only be recommended when the likelihood of a national attack or of multiple attacks is high. Longini et al. (2007) found that ring strategy would be sufficient to effectively contain a large intentional smallpox release. Given a ring strategy, a preemptive vaccination of hospital workers would further reduce the number of

smallpox cases and fatalities but would require large numbers of pre-vaccinations. Post-attack mass vaccination would further reduce smallpox cases and fatalities, but requires an even larger number of vaccinations.

Deterministic differential equation models are relatively easy to parameterize, rapid to use, and can accurately represent the average epidemic behavior. Kaplan et al. (2002) compared a traced vaccination and mass vaccination strategies in a smallpox attack, and found that mass vaccination would result in both far fewer fatalities and much faster epidemic eradication over a wide range of disease and infection control policy parameters. Mass vaccination could also outperform the existing Center for Disease Control and Prevention (CDC) policy of starting with traced vaccination and switching to mass vaccination only if deemed necessary by federal authorities (Centers for Disease Control, 2001). Kaplan et al. (2003) provided approximate closed form estimates for the total number of fatalities and the maximum vaccination queue length by approximately solving a system of ordinary differential equations (ODEs). This work explicitly incorporated a tracing/vaccination queue. A survey of previous models with age structure, heterogeneity, and spatial structure appears in Hethcote (2000). The author obtained expressions for the initial rate of transmission for some variants of SIR endemic models with either continuous age or age groups, and the minimum immune fractions for herd immunity for smallpox and other infectious diseases.

We notice that these previous works make different recommendations. This is due to different assumptions. For example, the initial number of infected individuals, the rate of transmission, and the time to detect the outbreak are all different. They could be all valid, because we find out that one policy does not fit for all situations. With different parameters' values, different control policy should be implemented to minimize the number of fatalities.

2.2. Resource allocation in an infectious disease outbreak

Large-scale emergencies are faced with substantial uncertainties. For instance, the number of cases, rates of transmission, and number of contacts in different cities are quite uncertain and usually difficult to estimate (Gani & Leach, 2001; Henderson et al., 1999; Kretzschmar et al., 2004; Rao, 1972). In Tanner, Sattenspiel, and Ntaimo (2008), a stochastic programming framework was used to find the optimal vaccination policy for controlling infectious disease epidemics under parameter uncertainty. The objective was to minimize total cost of the control policy to reduce the basic reproductive number to below one. A numerical example showed that including uncertain parameters could improve the robustness of the optimal strategy at the cost of higher coverage of the population. Tanner and Ntaimo (2010) then developed an irreducibly infeasible subsystems branch-and-cut algorithm to find the optimal vaccine allocation for joint chance-constrained stochastic programs. Our approach differs from their work because we consider an objective that minimizes the number of fatalities, and we also consider a mass vaccination strategy.

Dynamic resource allocation for epidemic control in multiple populations was studied in Zaric and Brandeau (2002). However, they considered multiple independent populations, and a linear relationship between investment and benefit. In our model we consider cross-city infection between different populations and the benefit/cost ratio is not linear, which is more realistic.

2.3. Research gap

Generally speaking the previous work has concentrated on the spread of the disease in a single city with unlimited resources. However, as seen with the spread of the 2009 H1N1 flu, an infectious disease today could spread through several cities or even across several countries. This could easily make existing resources to fight the epidemic scarce, and make a multi-city model necessary to allocate resources efficiently. Furthermore, most prior work proposes stochastic simulation models or differential equations which are difficult to include in an optimization model with integer decisions. Recent work on stochastic optimization models (Tanner & Ntaimo, 2010; Tanner et al., 2008) focus on making the basic reproductive number less than one, which might not be possible with limited resources. In addition they do not consider mass vaccination strategies.

Our work addresses this gap by investigating whether an optimization based model is appropriate to help decide how to distribute scarce resources. A central question is whether a tractable optimization framework can produce an accurate enough disease propagation model. In particular, we aim to develop optimization models that include the effect of limited resources, and the different characteristics of locations that contain the infection and susceptible population. Our approach is based on developing approximate representations of disease propagation that are reasonable in known parameter ranges. These representations are then used to build tractable optimization problems that represent the large scale multi-city problem.

A central goal of these models is to help give practical recommendations on how to distribute limited resources. Due to differing assumptions, previous work can make conflicting recommendations. Our work gives decision rules on when to execute each of the different control measures and compares it to previous results. In addition we study whether there is any benefit to allocate the resources optimally over an equitable distribution of resources in proportion to a city's population.

3. Approximate disease propagation models

Key in the development of good decision support models is the ability to accurately represent the evolution of the disease outbreak. In this section we present the classic disease propagation differential equation model (the Susceptible, Infected, Recovered SIR model), and discuss how it can be approximated to obtain closed form estimates of the total number of infected individuals. We also present the constant infection rate approximate model that will be used in this paper.

These models will concentrate on approximating the spread of smallpox. The exposure to smallpox first leads to an incubation period, which lasts approximately 12 days. The incubation period is followed by 2–4 days of fever (the prodromal stage), and a severe rash stage of about 9 days. Finally there is a scab stage which lasts about 9 days before causing death or recovery (Centers for Disease Control, 2004; Fenner, Henderson, Arita, Jezek, & Ladnyi, 1988; Mack, 1972). Smallpox is most contagious during the first 7–10 days following rash onset (Centers for Disease Control & Prevention, 2004). Once the infected individuals begin to manifest symptoms of infection, people might be misdiagnosed as having other similar diseases for 2–3 days, further delaying initiation of disease control measures.

3.1. The Susceptible, Infected, Recovered (SIR) model

The SIR model described below is based on the work by Kermack and McKendrick (1927) and Getz and Lloyd-Smith (2006). This model classifies the total population Q into three groups: susceptible (S), infected (I), recovered (R). It represents the evolution of a disease with the following set of differential equations:

$$\frac{dS}{dt} = -\beta SI \quad \frac{dI}{dt} = (\beta S - k)I \quad \frac{dR}{dt} = kI. \tag{1}$$

Following Kermack and McKendrick (1927), let β represent the average number of infections per patient, per unit time, and per person in the population. The parameter k is the fraction of the infected people that cease to be infected per unit time. Depending on the mortality rate of the disease, a certain percentage of the recovered persons are fatalities. The basic reproduction number, ρ, is defined as the expected number of secondary cases of a typical single infected case in a completely susceptible population. A single case in that situation would infect on average βQ people per unit time, and remain on average $1/k$ in the infectious stage. Therefore, we can express ρ as $\rho = \beta Q/k$ (Bailey, 1975; Nunn & Altizer, 2006). A numerical solution to this system can be obtained by the Euler's method of finite differences.

Let S_t, I_t, and R_t (or $s_t = S_t/Q$, $i_t = I_t/Q$, and $r_t = R_t/Q$) represent the total number (percentage) of susceptible, infected and recovered individuals in a population at time t. The system of differential equations in (1) can be used to provide a global estimate on the total percentage of individuals that were infected by a disease outbreak, which is defined as $\lim_{t\to\infty}\frac{R_t}{Q} = \lim_{t\to\infty} r_t = r_\infty$. Combining the first two equations in (1) we have $\frac{dI}{dt} = \left(\frac{k}{\beta S} - 1\right)\frac{dS}{dt}$, which by integration implies

$$I_t - I_0 = \frac{k}{\beta}\ln(S_t/S_0) - (S_t - S_0).$$

Since $\lim_{t\to\infty} I_t = 0$ and $S_0 = Q - I_0$ this last equation implies $(S_\infty - Q) - \frac{k}{\beta}\ln(S_\infty/S_0) = 0$. Dividing by Q we obtain the equivalent expression in terms of percentages of population $\rho(s_\infty - 1) = \ln(s_\infty) - \ln(s_0)$, where $\rho = \beta Q/k$. Finally, the change of variable $r_\infty = 1 - s_\infty$, gives

$$r_\infty = 1 - s_0 e^{-\rho r_\infty}. \tag{2}$$

This equation has no closed form solution but can be solved numerically. We can approximate r_∞ by replacing the function $f(\rho) = s_0 e^{-\rho r_\infty}$ by its second order Taylor expansion and solving the quadratic equation for r_∞. Below we present approximations considering Taylor expansions around $\rho = 0$ and $\rho = 1/r_\infty$. For large values of ρ we have that r_∞ will be close to 1, and therefore we can approximate Eq. (2) by $r_\infty = 1 - s_0 e^{-\rho r_\infty} \approx 1 - s_0 e^{-\rho}$. The following table summarizes these approximations. The ranges for ρ indicate when each approximation can obtain the best absolute relative error, based on $s_0 = 0.9999$.

In Fig. 1 we present the exact solution of (2) and the approximations described above for different values of ρ.

3.2. Constant transmission rate approximation of SIR model

We now present a constant transmission rate approximation of an SIR model for smallpox. The quality of this approximate model will be explored computationally by comparing its total infection estimates to what is obtained from the SIR model in Section 6.

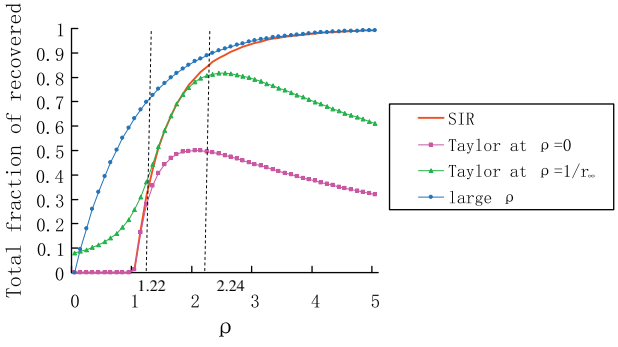

Fig. 1. Comparison of exact and approximate r_∞ solutions.

This proposed model is specific to smallpox as it takes into account the unique characteristics of how smallpox spreads. We simplify the progression of the disease representing it with two major periods. Period one is a 15-day non-infectious phase that corresponds to the incubation and prodromal stages, and period two is a 15-day infectious stage, corresponding roughly to the rash and scab stages of smallpox. Although this second phase takes on average around 18 days, smallpox is most contagious within the first 7–10 days following rash onset (Centers for Disease Control & Prevention, 2004). Therefore this simplification is reasonable. Similar assumptions were made by Meltzer et al. (2001) and Kaplan et al., 2002.

The constant transmission rate model considers fixed time periods ($\Delta T = 15$ days), a constant transmission rate ρ, a fatality rate α, and assumes all infections occur at the beginning of the period. In other words, at the start of period t, every newly infectious patient infects ρ individuals who will become infectious at the beginning of period $t+1$. This is a reasonable approximation as a study of 60 smallpox patients indicated that 70% of infections would have occurred by day 4 of the rash stage (Rao, 1972). The newly infectious patients of period t will recover (in SIR parlance) from the disease during period t, with a fraction α of them dying. With these assumptions we can track the total number of infected, susceptible and recovered individuals in every time period. Given an initial number of infected cases, I_0, at the start of period 1 (period t goes from $(t-1)\Delta T$ to $t\Delta T$), at the start of period 2 there are I_0 newly infectious cases. At the start of period 3 there are ρI_0, and so on. In general, at the start of period $t \geqslant 2$ there are $\rho^{t-2} I_0$ newly infectious cases. Including the non-infectious patients, the total number of infected patients is

$$I = \rho^{t-2} I_0 + \rho^{t-1} I_0.$$

The number of recovered patients at the start of period t is

$$R = \sum_{i=2}^{t-1} \rho^{i-2} I_0 = I_0 \frac{1-\rho^{t-2}}{1-\rho}.$$

The number of susceptible individuals can be obtained from $S = Q - I - R$. As α of the recovered patients have died, the number of fatalities at the start of period t is

$$\alpha I_0 \frac{1-\rho^{t-2}}{1-\rho}. \tag{3}$$

The constant transmission rate model is a bad approximation when the transmission rate ρ is larger than one. In that case, the number of newly infectious people increases from period to period and the total number of infected people at the start of period t is $I_0(1-\rho^{t-1})/(1-\rho)$, which diverges with t. Going back to Fig. 1, a line representing the total recovered of a constant transmission rate model would be close to the SIR curve for values of $\rho < 1$ but would have a vertical asymptote at $\rho = 1$. This is unreasonable as the total number of people that could be infected is bounded by the population Q. In practice, when the number of infected people is small relative to Q the disease propagates at close to constant rate until a significant portion of the population is affected, which reduces the actual transmission rate due to the lack of susceptible individuals. This process eventually controls the propagation of the disease. This is a fundamental limitation of the constant transmission rate model. It remains possible that for a few periods (while the amount of susceptible individuals is still large with respect to the infected and recovered) the estimation is reasonable. Our computational comparisons in Section 6 explore the suitability of a constant rate model as we vary ρ and the number of periods.

4. Control measures for a disease outbreak in a city

In this section we present in detail the different control measures that are possible to address a smallpox outbreak in a single city. We use "city" to represent a contiguous urban area that may contain multiple cities that are highly connected and where the disease can easily spread. Before the disease is detected and control measures are executed, the uncontrolled disease evolves with a constant transmission rate of ρ_u. Therefore if the control measures are implemented at the start of period t_0, then the number of fatalities up to that moment is given by Eq. (3).

We follow closely the assumptions of Bozzette et al. (2003) for the control measures and attack scenarios. The control measures will reduce the transmission rate, but can also cause a small number of fatalities due to vaccination and change the number of susceptible people. We denote the disease transmission rates after isolation, ring strategy vaccination, and mass vaccination by ρ_l, ρ_r, and ρ_m respectively. In addition we let a be the efficacy of isolation, p the probability of identifying a contact, e the efficacy of vaccination, and q the percentage of the population that is vaccinated in a mass vaccination. Note that not all people are willing to be vaccinated (Bozzette et al., 2003). In terms of the relationship among ρ_l, ρ_r, ρ_m, according to (Bozzette et al., 2003), the ring strategy includes the isolation strategy, and the mass vaccination strategy includes both the ring and isolation strategies. Therefore we have

$$\rho_l = \rho_u(1-a),$$
$$\rho_r = \rho_l(1-pe) = \rho_u(1-a)(1-pe),$$
$$\rho_m = \rho_r(1-qe) = \rho_u(1-a)(1-pe)(1-qe).$$

The expressions mean that the number of infected cases is reduced by a factor of a due to isolation alone and is further reduced by a factor of pe due to contact vaccination in ring strategy. After mass vaccination is implemented, the rate of transmission is further reduced by a factor of qe, because qe of the population becomes immunized. This model implies that $\rho_l > \rho_r > \rho_m$.

We denote τ the period where the first intervention is executed. Thus $I_\tau = \rho^{\tau-2} I_0$ is the number of newly infectious cases at the start of period τ. For simplicity, we assume that any intervention will be executed instantaneously at the start of a period. The disease propagation model considered is illustrated in Fig. 2. In this figure we assume that $\tau = 4$ and ρ_x is the transmission rate when a control measure is implemented.

The decision problem for a policy maker is choosing a strategy (isolation alone, ring strategy, or mass vaccination) to minimize the total number of fatalities from the disease and the vaccination. To quantify the fatalities due to vaccination we need to take into account that every case involves v contacts for ring strategy and γ is the fatality rate due to vaccination.

Below we quantify the total number of fatalities when each of the control measures is implemented. In the discussion below we assume that $\rho_l < 1$, which means that $\rho_r < 1$ and $\rho_m < 1$. This will allow us to obtain closed form solutions for the total number of fatalities. The expressions when transmission rates are greater than one are more cumbersome and therefore not insightful, as they depend on the number of periods and are only valid if the total population affected by the disease is small relative to Q.

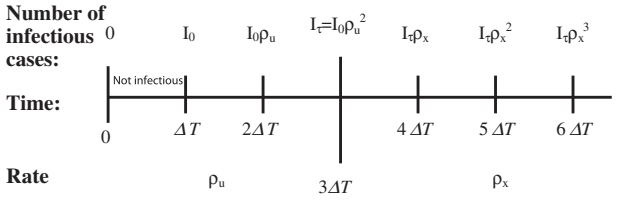

Fig. 2. The disease propagation model.

4.1. Total fatalities estimates for different control measures

If there are an initial I_0 cases and a control measure x is implemented at the start of period τ, then the total fatalities have the form $\alpha I_0 \frac{1-\rho_u^{\tau-2}}{1-\rho_u} + D_x + V_x$, where D_x represents the fatalities due to the disease and V_x are the fatalities due to vaccination. Taking into consideration the transmission rate after intervention and fatality rates, the total fatalities are:

- *Isolation strategy*: $\alpha I_0 \frac{1-\rho_u^{\tau-2}}{1-\rho_u} + \alpha I_0 \frac{\rho_u^{\tau-2}}{1-\rho_l}$.
- *Ring strategy*: $\alpha I_0 \frac{1-\rho_u^{\tau-2}}{1-\rho_u} + \alpha I_0 \frac{\rho_u^{\tau-2}}{1-\rho_r} + vp\gamma I_0 \frac{\rho_u^{\tau-2}}{1-\rho_r}$.
- *Mass vaccination*: $\alpha I_0 \frac{1-\rho_u^{\tau-2}}{1-\rho_u} + \alpha I_0 \frac{\rho_u^{\tau-2}}{1-\rho_m} + Qq\gamma + vp(1-qe)\gamma I_0 \frac{\rho_u^{\tau-2}}{1-\rho_m}$.

We note that the number of fatalities after intervention have to consider $I_\tau = I_0\rho_u^{\tau-2}$ as the initial number of infected individuals. The fatalities due to vaccination consider that p of the v contacts of every patient are vaccinated. In the case of mass vaccination the fatalities due to vaccination are separated into the one-time vaccination of a fraction q of the whole population Q and implementing a ring strategy on remaining susceptible individuals (Bozzette et al., 2003). Given that the vaccine has an efficacy of e, the fraction of contacts v that would be vaccinated in a ring strategy after mass vaccination is $vp(1-qe)$.

Comparing these total fatality expressions we can identify when each control strategy is preferable, defining threshold bounds, which we refer to as BND_{rl}, BND_{mr} and BND_{ml}, respectively. In particular ring strategy is more favorable than the isolation strategy when

$$BND_{rl} := \rho_l - (1-\rho_l)\frac{vp\gamma}{\alpha} > \rho_r. \tag{4}$$

Mass vaccination has less total fatalities than a ring strategy when

$$BND_{mr} := Qq\gamma\rho_u^{2-\tau}\left(\frac{\alpha + vp\gamma}{1-\rho_r} - \frac{\alpha + vp\gamma(1-qe)}{1-\rho_m}\right)^{-1} < I_0. \tag{5}$$

Mass vaccination has less total fatalities than an isolation strategy when:

$$BND_{ml} := Qq\gamma\rho_u^{2-\tau}\left(\frac{\alpha}{1-\rho_l} - \frac{\alpha + vp\gamma(1-qe)}{1-\rho_m}\right)^{-1} < I_0. \tag{6}$$

Condition (4) states that for the ring strategy to be preferable, the transmission rate has to be smaller than ρ_l by at least $(1-\rho_l)$-$vp\gamma/\alpha$. Note that this decision is independent on the initial number of infections I_0 or the time to the intervention τ. Conditions (5) and (6) characterize a threshold for I_0 to justify mass vaccination. Note that the threshold for I_0 increases with γ, which means that riskier vaccines require a higher initial infection to justify mass vaccination.

4.2. Relations between different control measures

A key question is, given that there are three possible control measures to contain the spread of the disease, when should we use each strategy? We now show that, based on the pairwise conditions (4)–(6), we can identify the best strategy as a function of the problem parameters. We then consider the implications of multiple periods and limited resources in the decision of selecting the best strategy.

Proposition 1. *Each strategy leads to fewer fatalities, and therefore is preferred, in the following cases*:

- *Isolation – when condition (4) and condition (6) do not hold.*
- *Ring – when condition (4) holds, condition (5) does not hold.*
- *Mass – when condition (4) and condition (5) hold or condition (4) does not hold, condition (6) holds.*

Proof. If condition (4) holds, then a ring strategy is better than an isolation strategy and $\frac{\alpha}{1-\rho_l} > \frac{\alpha+\nu p\gamma}{1-\rho_r}$. We have that $BND_{ml} < BND_{mr}$ from the expressions of conditions (5) and (6). If $I_0 > BND_{mr}$ (condition (5) holds), then a mass vaccination strategy is preferred over a ring strategy and should be implemented; If $I_0 \leqslant BND_{mr}$, then a ring strategy is better than mass vaccination and thus a ring strategy should be implemented.

Similarly, if condition (4) is not satisfied, then an isolation strategy is better than a ring strategy and $\frac{\alpha}{1-\rho_l} \leqslant \frac{\alpha+\nu p\gamma}{1-\rho_r}$. In this case, $BND_{mr} \leqslant BND_{ml}$. If $I_0 > BND_{ml}$ (condition (6) holds), then a mass vaccination strategy should be implemented; if $I_0 \leqslant BND_{ml}$, then an isolation strategy should be implemented. □

Since the problem in practice involves multiple periods, we can make decisions on which control measure to adopt in each period. In Proposition 2 we investigate whether delaying the implementation of mass vaccination would be beneficial. Here we compare the ring strategy and mass vaccination, although a similar argument applies in comparing isolation and mass vaccination.

Proposition 2. *When there are enough resources, if mass vaccination is implemented, then mass vaccination should be implemented in period* 1.

Proof. The number of fatalities from a mass vaccination is $Qq\gamma$ whether the mass vaccination is implemented in period 1 or t ($t \geqslant 2$). If we implement the mass vaccination earlier, the rate of transmission decreases from ρ_r to ρ_m earlier, thus the number of cases and the amount of vaccine used for a ring strategy (after the mass vaccination) are both smaller. Therefore we should implement the mass vaccination in period 1. □

4.3. Control measures with limited resources

Up to now we have assumed that there are sufficient resources to implement the selected strategy at every time period. However, this may not be possible in practice due to lack of supply or lack of delivery capacity. For example, there may not be enough personnel to perform a certain control measure or to deliver enough resources to all the people in one time period. In this situation, the resulting transmission rate will be higher.

Consider for example the problem of implementing a ring strategy on multiple periods with limited resources, where we denote the amount of vaccine used on the ring strategy in period t by x_t. If we assume that no mass vaccination has been previously executed, we can determine the effect on the transmission rate of this possibly limited ring strategy. Let I_t be the number of newly infectious cases in period t. If there is enough vaccine, i.e. $x_t \geqslant I_t\nu p$, then all identified contacts can be vaccinated using $I_t\nu p$ doses of vaccine. As a result, we get a full ring strategy implementation, and the rate is $\rho_r = \rho_l(1-pe)$. However, if $0 \leqslant x_t \leqslant I_t\nu p$ then only a fraction $x_t/(I_t\nu p)$ of the contacts can be vaccinated, and we get $\rho_r = \rho_l(1 - pex_t/(I_t\nu p)) = \rho_l - \rho_l ex_t/(I_t\nu)$. Letting $b = \rho_l e/\nu$ we can express the transmission rate of the ring strategy as

$$\rho_r = \rho_l - bx_t/I_t \quad 0 \leqslant x_t \leqslant I_t\nu p. \tag{7}$$

Note that using more than $I_t\nu p$ resources does not further decrease ρ_r (since there are no more identified contacts) and when $x_t = 0$ an isolation strategy is actually implemented, i.e. $\rho_r = \rho_l$. The following result characterizes how limited resources should be distributed to implement a ring strategy over a finite planning horizon.

Proposition 3. *Given B doses of vaccine to implement ring strategy over T periods to address an outbreak that starts with I_1 newly infectious patients in period* 1. *Then the optimal use of resources is to set* $x_t = \begin{cases} 0 & \phi(t) \leqslant \gamma \\ \zeta_t & \phi(t) > \gamma \end{cases}$ *until B is exhausted (the last one can be fractional), where* $\phi(t) = \alpha b\frac{1-\rho_l^{T-t}}{1-\rho_l}$ *and starting from* $t = 1$, $\zeta_t = I_t\nu p$.

Proof. Using expression (7) repeatedly we have that the number of cases in period t is $I_t = I_{t-1}\rho_l^{t-1} - b\sum_{k=1}^{t-1}\rho_l^{t-k-1}x_k$, which implies that the total number of newly infectious cases is

$$\begin{aligned}\sum_{t=1}^{T} I_t &= I_1\frac{1-\rho_l^T}{1-\rho_l} - b\frac{1-\rho_l^{T-1}}{1-\rho_l}x_1 - b\frac{1-\rho_l^{T-2}}{1-\rho_l}x_2 - \cdots - bx_{T-1} \\ &= I_1\frac{1-\rho_l^T}{1-\rho_l} - b\sum_{t=1}^{T-1}\frac{1-\rho_l^{T-t}}{1-\rho_l}x_t.\end{aligned}$$

Thus, the total number of fatalities is

$$\begin{aligned}&\alpha\left(I_1\frac{1-\rho_l^T}{1-\rho_l} - b\sum_{t=1}^{T-1}\frac{1-\rho_l^{T-t}}{1-\rho_l}x_t\right) + \gamma\sum_{t=1}^{T-1}x_t \\ &= \alpha I_1\frac{1-\rho_l^T}{1-\rho_l} - \sum_{t=1}^{T-1}\left(\alpha b\frac{1-\rho_l^{T-t}}{1-\rho_l} - \gamma\right)x_t.\end{aligned}$$

The coefficient multiplying x_t in this previous sum is $\phi(t) - \gamma$, therefore the total number of fatalities is reduced if we set $x_t = 0$ when $\phi(t) \leqslant \gamma$ and set x_t as large as possible when $\phi(t) > \gamma$. Since $\phi(t)$ is decreasing in t, and x_t is bounded by $I_t\nu p$, we obtain the characterization of the optimal solution. □

We previously showed, in the case of unlimited resources, if condition (4) holds then a ring strategy is preferable to an isolation strategy. It turns out that condition (4) is equivalent to $\frac{\alpha b}{1-\rho_l} - \gamma > 0$, and is therefore implied by Proposition 3, since $\frac{\alpha b}{1-\rho_l} > \alpha b\frac{1-\rho_l^{T-t}}{1-\rho_l}$. A similar analysis is possible when mass vaccination is already implemented. In this case the transmission rate ρ_m equals $\rho_l(1-pe)(1-qe)$ if there are enough resources to do a ring strategy on the remaining susceptible individuals (which are $I_t\nu p(1-qe)$ of them). In this case the resource dependent transmission rate is

$$\rho_m = \rho_l(1-qe) - bx_t/I_t \quad 0 \leqslant x_t \leqslant I_t\nu p(1-qe). \tag{8}$$

This expression can then be used to characterize the optimal decisions of how to assign limited resources for ring strategies after a mass vaccination similar to Proposition 3 above.

5. The multi-city model

5.1. Formulation of the multi-city model

Suppose terrorists launch a smallpox attack and n cities are infected by the disease. We reset time 0 as the intervention start time, thus $[0, \Delta t]$ is period 1, $[\Delta t, 2\Delta t]$ is period 2, and so on. City i has I_{i1} infectious cases at time period 1. At time period t, the replenishment of the vaccine is H_t. The decision for the government is to allocate the vaccine to the n cities for every time period to minimize the total number of fatalities in T time periods.

To model the disease propagation between different cities, it is reasonable to assume a fraction of newly infected cases in one city appear in another city. We let f_{ij} represent the percentage of the

newly infected cases of city i that "flow" to city j. This parameter depends on the traffic flow F_{ij} between the two cities. In particular, we can use a gravity model. For populations Q_i and Q_j and distance d_{ij} we can take F_{ij} to be

$$F_{ij} = k_0 Q_i^{k_1} Q_j^{k_2} / d_{ij}^{k_3},$$

where k_0, k_1, k_2 and k_3 are parameters. Then we set $f_{ij} = F_{ij}/Q_i$. The gravity model is commonly used in transportation theory to estimate traffic flows between origin and destination pairs (Erlander & Stewart, 1990; Ortúzar & Willumsen, 2001). Balcan et al. (2009) also used a gravity model to predict commuting flows for the spread of an infectious disease, and the gravity model reproduced well the real-world commuting flows.

We stress two key assumptions needed to simplify the model:

(1) The shipment of resources can be done instantly. This assumption is reasonable since shipping takes only a few days, which is small compared with a 15-day ΔT for smallpox.
(2) Mass vaccination can be done instantly at the start of a period. After deploying resources mass vaccination could be implemented in 3–4 days, which is also small relative to ΔT.

We let decision variables x_{it} and m_{it} be the amount of vaccine allocated for a ring strategy and a mass vaccination for city i at period t, respectively. The number of infectious cases of city i at time t is denoted I_{it} for $t \in \{2,\ldots,T\}$, note that I_{i1} is a parameter. Variable B_t denotes the total amount of vaccine available at time period t, and $B_1 = H_1$.

The binary variable z_{it} equals 1 if mass vaccination strategy is selected in city i at period t, and 0 otherwise. The binary variable y_{it} indicates whether mass vaccination has been implemented in city i by period t. Clearly $y_{it} = \sum_{k=1}^{t} z_{ik}$.

We introduce an auxiliary variable J_{it}, which represents the number of infectious cases of city i at period t before considering cross-city infection. In addition, we let ρ_{it} be the transmission rate of city i at time period t. According to (7), $\rho_{it} = \rho_{li} - b_i x_{it}/I_{it}$ if mass vaccination has not been implemented (i.e., $y_{it} = 0$). Using $J_{it} = I_{i,t-1}\rho_{i,t-1}$, we have

$$J_{it} = \rho_{li} I_{i,t-1} - b_i x_{i,t-1} \quad 0 \leqslant x_{it} \leqslant I_{it} v_i p_i. \tag{9}$$

Because x_{it} is non-negative, we can rewrite the above expression as two constraints:

$$J_{it} = \rho_{li} I_{i,t-1} - b_i x_{i,t-1} \quad \forall i \in \{1,\ldots,n\},\ t \in \{2,\ldots,T\}, \tag{10}$$

$$x_{it} \leqslant I_{it} v_i p_i \quad \forall i \in \{1,\ldots,n\},\ t \in \{1,\ldots,T\}. \tag{11}$$

If a mass vaccination is already implemented in city i, similarly from (8), we get:

$$J_{it} = \rho_{li}(1-qe) I_{i,t-1} - b_i x_{i,t-1} \quad \forall i \in \{1,\ldots,n\},\ t \in \{2,\ldots,T\}, \tag{12}$$

$$x_{it} \leqslant I_{it} v_i (1-qe) p_i \quad \forall i \in \{1,\ldots,n\},\ t \in \{1,\ldots,T\}. \tag{13}$$

Note that after the mass vaccination although b_i does not change, x_{it} has a smaller upper bound. This ensures that the effect of a ring strategy is not the same as before the mass vaccination. We summarize the parameters and decision variables for the multi-city model in Table 2. Note that ρ_{li} and b_i are expressions used to simplify the model.

The objective is to minimize the total number of fatalities, which is the sum of the fatalities from the disease and the vaccination after the control measures are taken. We formulate the problem as a mixed-integer program (MIP):

$$\text{Minimize} \quad \sum_{i=1}^{n}\sum_{t=1}^{T}(\alpha I_{it} + \gamma(x_{it} + m_{it})), \tag{14.1}$$

$$\text{Subject to :} \quad y_{it} = \sum_{k=1}^{t} z_{ik} \quad \forall i \in \{1,\ldots,n\},\ t \in \{1,\ldots,T\},$$

$$J_{it} \geqslant \rho_{li} I_{i,t-1} - b_i x_{i,t-1} - M y_{i,t-1} \quad \forall i \in \{1,\ldots,n\},\ t \in \{2,\ldots,T\}, \tag{14.2}$$

$$x_{it} \leqslant I_{it} v_i p_i + M y_{it} \quad \forall i \in \{1,\ldots,n\},\ t \in \{1,\ldots,T\}, \tag{14.3}$$

$$J_{it} \geqslant \rho_{li}(1-qe) I_{i,t-1} - b_i x_{i,t-1} - M(1-y_{i,t-1}) \quad \forall i \in \{1,\ldots,n\},\ t \in \{2,\ldots,T\}, \tag{14.4}$$

$$x_{it} \leqslant I_{it} v_i (1-qe) p_i + M(1-y_{it}) \quad \forall i \in \{1,\ldots,n\},\ t \in \{1,\ldots,T\}, \tag{14.5}$$

$$I_{it} = \sum_{j=1}^{n} f_{ji} J_{jt} \quad \forall i \in \{1,\ldots,n\},\ t \in \{2,\ldots,T\}, \tag{14.6}$$

$$m_{it} \geqslant Q_i q z_{it} \quad \forall i \in \{1,\ldots,n\},\ t \in \{1,\ldots,T\}, \tag{14.7}$$

$$\sum_{i=1}^{n}(x_{it} + m_{it}) \leqslant B_t \quad \forall t \in \{1,\ldots,T\}, \tag{14.8}$$

$$B_1 = H_1, \tag{14.9}$$

$$B_t = B_{t-1} - \sum_{i=1}^{n}(x_{i,t-1} + m_{i,t-1}) + H_t \quad \forall t \in \{2,\ldots,T\}. \tag{14.10}$$

Constraints (14.1) determine the value of y_{it}. Constraints (14.2)–(14.5) update J_{it} depending on $x_{i,t-1}$ and $y_{i,t-1}$. Here the binary variables y_{it} and a large constant M are used to formulate disjunctive constraints that characterize the disease transmission rates with or without mass vaccination in location i by time t from expressions (10)–(13). If $y_{it} = 0$, (14.2) and (14.3) are active; if $y_{it} = 1$, (14.4) and (14.5) are active. Constraints (14.6) model the cross-city infection between different cities. Constraints (14.7) enforce $m_{it} = Q_i q$ if mass vaccination is implemented. Constraints (14.8) are total resource constraints. Constraints (14.9) set B_1 to H_1, and constraints (14.10) update the amount of vaccine for periods 2 to T. Note that we do not need to assume transmission rates are less than one since the MIP considers a finite time horizon.

5.2. Heuristic solution for the multi-city model

When there are multiple cities, limited resources, and no cross-city infections the decision of where to assign the resources is akin to a knapsack problem. For example, a full implementation of a ring strategy in a city provides a benefit in the number of lives saved while consuming a certain amount of vaccines. The capacity here would be the total available vaccine. Similar to the knapsack problem, we want to determine whether or not to implement a ring strategy in each city looking to maximize the number of lives saved, under a total resource constraint.

We build a heuristic based on pairwise comparisons of control measures that can be stated as 0–1 knapsacks. Using these pairwise decisions we aim to obtain decision rules for deciding at each period which strategy to implement (similar to Proposition 1). Note the following analysis assumes $\rho_l < 1$, which implies that

Table 1
Different types of approximate solutions to Eq. (2).

Type	Approximate Eq. (2) and solution	Range/relative error	
		ρ Range	r_∞ Error (%)
2nd order	$r_\infty \approx 1 - s_0(1 - \rho r_\infty + (\rho r_\infty)^2/2)$	0	0
Taylor at $\rho = 0$	$r_\infty = \frac{(s_0\rho-1)+\sqrt{(s_0\rho-1)^2-2s_0\rho^2(s_0-1)}}{s_0\rho^2}$	1.22	−12.42
		Avg. error	−1.27
2nd order	$r_\infty \approx 1 - s_0e^{-1}(1 + (-r_\infty\rho + 1) + (-r_\infty\rho + 1)^2/2)$	1.22	10.95
Taylor at $\rho = 1/r_\infty$	$r_\infty = \frac{(2\rho s_0e^{-1}-1)+\sqrt{(2\rho s_0e^{-1}-1)^2-s_0e^{-1}\rho^2(5s_0e^{-1}-2)}}{s_0e^{-1}\rho^2}$	2.24	−4.92
		Avg. error	−0.29
Large ρ $r_\infty \approx 1$	$r_\infty = 1 - s_0e^{-\rho r_\infty} \approx 1 - s_0e^{-\rho}$	2.24	4.72
		+∞	0
		Avg. error	0.85

$\rho_r < 1$ and $\rho_m < 1$. Therefore the heuristic we propose below helps to decide the use of resources among cities that have $\rho_l < 1$. If a certain city has a $\rho_l > 1$, then that city would have priority in receiving resources. It means we first allocate resources to these cities, as much as possible.

We first decide which strategy to use between isolation and full ring strategies, assuming that the implemented strategy is maintained thereafter. This is a knapsack problem, where for each city the benefit/capacity ratio is given in Proposition 4.

Proposition 4. *The benefit/capacity ratio of doing a full ring strategy over an isolation strategy is* $\frac{\alpha\rho_l e}{v(1-\rho_l)} - \gamma$.

Proof. If we implement a ring strategy, then compared with an isolation strategy, we use $\frac{I_1 vp}{1-\rho_r}$ additional resources. The number of lives saved from the disease is $\alpha I_1(\frac{1}{1-\rho_l} - \frac{1}{1-\rho_r})$, and the number of additional fatalities caused by the vaccination is $\gamma\frac{I_1 vp}{1-\rho_r}$. Therefore, the benefit/capacity ratio is: $\left(\alpha I_1\left(\frac{1}{1-\rho_l} - \frac{1}{1-\rho_r}\right) - \gamma\frac{I_1 vp}{1-\rho_r}\right)\left(\frac{I_1 vp}{1-\rho_r}\right)^{-1} = \frac{\alpha\rho_l e}{v(1-\rho_l)} - \gamma$. □

From Proposition 4, we can see that if $\frac{\alpha\rho_l e}{v(1-\rho_l)} \leqslant \gamma$, then an isolation strategy should be implemented because a ring strategy can only increase the number of fatalities. If $\frac{\alpha\rho_l e}{v(1-\rho_l)} > \gamma$, then a ring strategy should be implemented if there are resources available. This condition is actually equivalent with condition (4). Thus, full ring strategies should be carried out in the cities that satisfy $\frac{\alpha\rho_l e}{v(1-\rho_l)} > \gamma$, and the cities with a higher value of $\frac{\alpha\rho_l e}{v(1-\rho_l)} - \gamma$ are the ones that would experience a greater benefit of implementing a ring strategy. For this knapsack problem, according to Dantzig's greedy heuristic (Dantzig, 1957), resources should be allocated to the cities that satisfy $\frac{\alpha\rho_l e}{v(1-\rho_l)} > \gamma$ in decreasing order of this ratio until resources are exhausted.

We can obtain analogous results characterizing the benefit/capacity ratio of deciding whether to implement full mass vaccination over isolation strategy (Proposition 5) and deciding whether to do full mass vaccination over a full ring strategy (Proposition 6). Here full mass vaccination strategy means allocating enough resources to vaccinate the general population and do full ring strategy for remaining susceptible people for all periods. These results assume that the decision made in a city is maintained thereafter and are obtained by comparing the number of lives saved over the resources consumed. We omit these poofs given the similarity to Proposition 4.

Proposition 5. *The benefit/capacity ratio of doing mass vaccination over an isolation strategy is* $\frac{\alpha I_1(\rho_l-\rho_m)}{Qq(1-\rho_l)(1-\rho_m)+I_1 vp(1-\rho_l)(1-qe)} - \gamma$.

Proposition 6. *The benefit/capacity ratio of doing a mass vaccination over a full ring strategy is* $\frac{\alpha I_1\rho_r e}{Q(1-\rho_r)(1-\rho_m)-I_1 vpe} - \gamma$.

Similar to Proposition 4, these last two results imply that a knapsack heuristic would allocate resources to do a mass vaccination instead of maintaining an isolation strategy (or a ring strategy) if $\frac{\alpha I_1(\rho_l-\rho_m)}{Qq(1-\rho_l)(1-\rho_m)+I_1 vp(1-\rho_l)(1-qe)} > \gamma$ $\left(\text{or } \frac{\alpha I_t\rho_r e}{Q(1-\rho_r)(1-\rho_m)-I_t vpe} > \gamma\right)$ in decreasing order of the ratio until resources are exhausted.

We propose a heuristic for the resource allocation problem based on the decision rules suggested by the benefit/capacity ratios from Propositions 4–6. This heuristic allows a fractional implementation of ring strategy before and after a mass vaccination. In each period t, we define the ratios $l_{it} = \frac{\alpha\rho_{li}e}{v_i(1-\rho_{li})}$, $c_{it} = \frac{\alpha I_{it}(\rho_{li}-\rho_{mi})}{Q_iq(1-\rho_{li})(1-\rho_{mi})+I_{it}v_ip(1-\rho_{li})(1-qe)}$, and $s_{it} = \frac{\alpha I_{it}\rho_r e}{Q_i(1-\rho_{ri})(1-\rho_{mi})-I_{it}v_ip_ie}$. These ratios are used to prioritize the cities and the strategies. The heuristic is composed of two iterations over all cities each period to decide whether to do mass vaccination over doing a full ring strategy. We evaluate the performance of this heuristic in Section 6.

Pseudocode Multi-city Model Heuristic

Input: n, T, I_{i1}, H_t, ρ_{ui}, p_i, v_i, Q_i, q, B_t=H_t
Set all cities to isolation strategy
for *t=1 to T−1* ***do***
  for *city i=1 to n* ***do***:
    let h_{it} = max(l_{it}, c_{it}) ***if*** *i does isolation*; h_{it} = s_{it} ***if*** *i does ring strategy*; *and* h_{it} =-1 ***otherwise***
  end for
  Rank h_{it} *in decreasing order*
  repeat once (*to decide ring strategy and then mass vaccination*)
    for *i=1 to n* ***do***
      if $B_t > 0$ ***and*** $\alpha h_{it} - \gamma > 0$, ***then***
        if *city i does isolation* ***and*** $l_{it} \geqslant c_{it}$, ***then***
          Do ring strategy in city i, x_{it} = min($I_{it}v_ip_i$, B_t)
        else if (*city i does isolation* ***and*** $c_{it} > l_{it}$ ***and*** $B_t \geqslant Q_iq$)
          or (*city i does ring strategy* ***and*** $B_t \geqslant Q_iq$), ***then***
          Do mass vaccination in city i, z_{it} = 1, $m_{it} = Q_iq$
          x_{it} = min($I_{it}v_ip_i(1 - qe)$, $B_t - Q_iq$)
        end if
      else *Keep same strategy for city i and set* x_{it}, m_{it} *accordingly*
      end if
    end for
    $B_t = B_t - x_{it} - m_{it}$
  end repeat
  if y_{it} = 0, ***then*** $J_{i,t+1} = \rho_{li}I_{it}$ - b_ix_{it} ***else*** $J_{i,t+1} = \rho_{li}I_{it}(1 - qe) - b_ix_{it}$ ***end if***
  $I_{it} = \sum_{j=1}^{n} J_{jt}f_{ji}$, $B_t = B_t + H_t$
end for
Return: x_{it}, m_{it}, z_{it}

6. Computational results

6.1. Computational results for the single city model

We use smallpox as an example to validate our model. We compare our results with the results from the simulation model of Bozzette et al. (2003) for five scenarios: laboratory release, human

Table 2
Parameters and variables for the multi-city model.

(1) Parameters	
N	Number of cities
T	Number of time periods
f_{ij}	Percentage of the newly infected cases of city i that is in city j
H_t	Replenishment of vaccine in every period t, $t \in \{1,\ldots,T\}$
I_{i1}	Initial number of infected cases of city i in period 1
ρ_{li}	$\rho_{li} = \rho_{ui}(1-a_i)$, $i \in \{1,\ldots,n\}$
b_i	$b_i = \rho_{ui}(1-a_i)\frac{e}{v_i}$, $i \in \{1,\ldots,n\}$
(2) Continuous decision variables	
I_{it}	Number of infected cases of city i in period t, $t \in \{2,\ldots,T\}$, $I_{it} \geqslant 0$
J_{it}	Initial number of infected cases of city i at time period t before considering cross-city infection, $t \in \{2,\ldots,T\}$, $J_{it} \geqslant 0$
B_t	Total amount of vaccine available in period t, $B_1 = H_1$
x_{it}	Amount of vaccine allocated to city i for ring strategy in period t, $x_{it} \geqslant 0$
m_{it}	Amount of vaccine allocated to city i for mass vaccination in period t, $m_{it} \geqslant 0$
(3) Binary decision variables	
z_{it}	1 if mass vaccination is chosen in city i in period t, and 0 otherwise
y_{it}	Whether mass vaccination has been implemented in i by period t, $y_{it} = \sum_{k=1}^{t} z_{ik}$

vectors, building attack, low- and high-impact airport attack. For the first three scenarios, a single city is considered. The last two scenarios consider the whole population of the United States. Table 3 shows the parameters and their sources. In (Bozzette et al. (2003) different percentages of healthcare workers and the public are vaccinated, we let q be the weighted average of the two. The probability p is also the weighted average of identification probabilities for different types of contacts.

Table 4 shows the comparison of our results and the results reported in Bozzette et al. (2003). The columns "Ref" refer to the value reported in the reference, and the columns "AM" refer to the results from our approximation model. We only compare the results of a ring strategy and a mass vaccination because a pure isolation strategy is not considered in the reference. We report the fatalities from smallpox and vaccination, and the total of the two. We note that both models provide similar trends with (Bozzette et al., 2003) providing slightly higher predicted deaths except in the Human Vectors scenario. This difference does not increase significantly with the size of the emergency, which makes the relative accuracy increase when I_0 increases. A possible reason for this is that for large I_0, the stochastic simulation used in Bozzette et al. (2003) behaves closer to an expected outcome, which is used for the AM analysis.

We present in Table 5 the threshold values of ρ_r and I_0 for the same five scenarios based on conditions (4)–(6). We can make decisions according to Proposition 1. For the high-impact airport attack, since condition (4) is satisfied and $I_0 > BND_{ml}$, mass vaccination should be implemented. For other cases, since condition (4) is satisfied and $I_0 < BND_{ml}$, ring strategy should be implemented. Our decision is the same as in Bozzette et al. (2003) if we choose the strategy with a smaller number of fatalities. Note that in the building attack scenario, BND_{mr} is very close to I_0, meaning that the choice is indifferent. In this case, we choose a less involved strategy to reduce costs on all kinds of resources such as personnel and vaccine.

Table 3
The value of the parameters for the five smallpox scenarios.

Parameter	Units	Laboratory release	Human vectors	building attack	Low impact airpt. attack	High impact airpt. attack	Source
Q	People	4×10^6	4×10^6	6×10^6	290×10^6	290×10^6	Bozzette et al. (2003)
I_0	People	2	15	350	5,000	100,000	Bozzette et al. (2003)
$(\tau-1)\Delta T$	Days	26	48	26	26	26	Bozzette et al. (2003)
ΔT	Days	15	15	15	15	15	Meltzer et al. (2001)
T	Periods	2.73	4.20	2.73	2.73	2.73	Bozzette et al. (2003)
ρ_u		15.4	1.8	3.4	1.8	1.8	Bozzette et al. (2003)
ρ_l		0.370	0.212	0.235	0.212	0.212	Derived from Bozzette et al. (2003)
ρ_r		0.1	0.1	0.1	0.1	0.1	Bozzette et al. (2003)
ρ_m		0.053	0.053	0.053	0.053	0.053	$\rho_m = \rho_r(1-qe)$
q		0.61	0.61	0.61	0.61	0.61	Derived from Bozzette et al. (2003)
e		0.764	0.764	0.764	0.764	0.764	Dick (1966), Dixon (1962), Bauer (1974)
v	People	50	50	50	50	50	Bozzette et al. (2003)
p		0.97	0.80	0.88	0.80	0.80	Derived from Bozzette et al. (2003)
α		0.20	0.20	0.20	0.20	0.20	Bozzette et al. (2003)
γ		2.72×10^{-6}	2.72×10^{-6}	2.72×10^{-6}	2.72×10^{-6}	2.72×10^{-6}	Bozzette et al. (2003)

Table 4
Predicted fatalities (AM) with those reported in Bozzette et al. (2003) (Ref).

Fatality		Scenario									
		Laboratory release		Human vectors		Building attack		Low impact airport attack		High impact airport attack	
		Ref	AM	Ref	AM	Ref	AM	Ref	AM	Ref	AM
Ring strategy	Disease	7	4	19	30	300	261	2733	2710	54,691	54,197
	Vaccination	0	0	0	0	0	0	2	1	37	19
	Total	7	4	19	30	300	261	2735	2711	54,728	54,216
Mass vaccination	Disease	6	4	18	27	298	251	2631	2626	52,541	52,512
	Vaccination	7	7	8	7	10	10	482	482	496	491
	Total	13	11	26	34	308	261	3113	3108	53,037	53,003

Table 5
The threshold of ρ_l and I_0 for the five scenarios.

Scenario	Laboratory release	Human vectors	Building attack	Low impact airport attack	High impact airport attack
BND_{rl}	0.37	0.21	0.23	0.21	0.21
BND_{mr}	81	166	369	28,425	28,425
BND_{ml}	8	43	81	7367	7367

Table 6
Comparison of the current model with an SIR model.

			Period 4	Period 8	Total		
			CRAM/SIR	CRAM/SIR	CRAM/SIR	AM4/SIR	CFAM/SIR
$\rho_u = 1.8$	Iso.	$\rho_l = 0.36$	1.000	1.000	1.000	1.000	1.000
$a = 0.8$	Ring	$\rho_r = 0.14$	1.000	1.000	1.000	1.000	1.000
	Mass	$\rho_m = 0.08$	1.000	1.000	1.000	1.000	1.000
$\rho_u = 1.8$	Iso.	$\rho_l = 0.63$	1.000	1.001	1.001	1.001	1.000
$a = 0.65$	Ring	$\rho_r = 0.25$	1.000	1.001	1.001	1.001	1.001
	Mass	$\rho_m = 0.13$	1.000	1.000	1.000	1.000	1.000
$\rho_u = 3$	Iso.	$\rho_l = 0.60$	1.000	1.001	1.001	1.001	1.000
$a = 0.8$	Ring	$\rho_r = 0.23$	1.001	1.001	1.001	1.001	1.000
	Mass	$\rho_m = 0.13$	1.000	1.000	1.000	1.000	1.000
$\rho_u = 3$	Iso.	$\rho_l = 1.05$	1.001	1.003	$+\infty$	1.028	0.961
$a = 0.65$	Ring	$\rho_r = 0.41$	1.001	1.003	1.003	1.003	1.003
	Mass	$\rho_m = 0.22$	1.001	1.001	1.001	1.001	1.001
$\rho_u = 6$	Iso.	$\rho_l = 1.20$	1.001	1.009	$+\infty$	1.067	0.861
$a = 0.8$	Ring	$\rho_r = 0.47$	1.003	1.010	1.011	1.008	1.011
	Mass	$\rho_m = 0.25$	1.001	1.002	1.002	1.002	1.001
$\rho_u = 6$	Iso.	$\rho_l = 2.10$	1.002	1.059	$+\infty$	1.112	0.886
$a = 0.65$	Ring	$\rho_r = 0.82$	1.006	1.058	1.189	1.043	1.177
	Mass	$\rho_m = 0.44$	1.003	1.008	1.008	1.008	1.007

We compare the prediction of our model with the model of Legrand et al. (2004), which studied the implementation of a ring strategy. Using the parameters' values in Legrand et al. (2004) ($I_0 = 100$, $\rho_u = 3$, $(\tau - 1)\Delta T = 25$), we estimate the number of infected cases as 650, while (Legrand et al., 2004) found 730. The difference is 10%. If $(\tau - 1)\Delta t = 45$, our prediction is 2807, and theirs is 2800, yielding a difference of 0.3%. Eichner (2003) considered a case of $\rho_u = 5$ and $I_0 = 100$, and only isolation and contact tracing were implemented. The total estimated number of infections is 506 while our approximate model predicts 487. The difference is 3.7%. Although (Eichner, 2003) has a higher ρ_u, the number of infected cases is smaller than in Legrand et al. (2004) mainly because τ is smaller.

We also compare the results from our model with those from two other references. Our recommendation for high impact case are consistent with Kaplan et al. (2002) that mass vaccination results in both far fewer fatalities and much faster epidemic eradication than ring strategy when I_0 is large. This is consistent with condition (4). Our model is also consistent with (Meltzer et al., 2001) which found that ring strategy is more effective than isolation alone or contact vaccination alone. We can see from condition (4) that this is due to the small value for γ. The above shows that the proposed disease propagation model approximates existing results, especially for large I_0.

To see the applicable range of our constant rate approximation model, we compare it with an SIR model for realistic values of ρ_u and a. When there is a control measure, we adjust the basic SIR model introduced in Section 3.1 to take into account the individuals who get immunity or die from vaccination. We consider a city with a population of 10 million and 1000 initial cases. The results are shown in Table 6. We report the ratio between the number of fatalities of the two models at periods 4 and 8. We can see that the difference is less than 1% in all cases for 4 periods. Therefore we can re-estimate ρ_u after every 4 periods. The column "Total" reports the ratios in the total number of fatalities between three models and the SIR model. The three models are the constant rate approximate model (CRAM), an approximation model with ρ_u updated every 4 periods (AM4), and the closed-form approximation model (CFAM) in Table 1. For the CRAM model, when the resulting ρ is above one, the error is infinite. A good fix is the AM4 model, where the largest difference in total fatalities is 11.2% when ρ_l is 2.1. The precision of AM4 is comparable to the CFAM model, and if the resulting ρ is at the intersection of the segments of CFAM, AM4 is better than CFAM. The CRAM model compares more favorably to the SIR model than to the first three cases of Bozzette et al. (2003) because I_0 here is larger.

6.2. Computational results for the multi-city model

6.2.1. A hypothetical problem

We consider a worst-case smallpox attack in which terrorists discharge the variola virus during busy periods throughout the domestic terminals in a large airport. Exposed people would scatter across the country and infect 50 largest cities in the United States. The scenario is similar to the high-impact airport attack described in Bozzette et al. (2003), and we fix the reference values accordingly at $\rho_u = 1.8$, $\alpha = 0.2$, $\gamma = 0.00000272$, $e = 0.764$, $q = 0.61$, $p = 0.8$, $a = 0.8$, $v = 50$, $\Delta T = 15$, and $(\tau - 1)\Delta T = 26$. Due to a lack of estimates for the parameters' values in each city, we build an instance based on literature following some generic principles as we outline below. In a real outbreak, the parameters' values can be replaced by real data or expert estimates.

Demographics such as population size, density and socioeconomic factors influence the rate of transmission (Kiang & Krathwohl, 2003). Historical data suggests that high population densities are required to sustain transmission (Belongia & Naleway, 2003), and that lower population density contributed to the elimination of transmission in many regions (Anderson & May,

Table 7
The base case (H_t = 50,000,000; γ = 0.00000272; I_0 = 10,000; ρ_u = 1.8).

Period	Iso.	Ring	Mass	RingVac	MassVac	NumCase	Fatal.
1	0	28	22	906,366	49,068,676	21,353	4406
2	0	50	0	165,743	0	3666	733
3	0	50	0	32,857	0	689	137
4	0	50	0	6976	0	140	28
5	0	50	0	909	0	30	6
6	0	6	0	98	0	3	0
7	0	1	0	11	0	0	0
8	0	0	0	0	0	0	0
Total	0	235	22	1,112,960	49,068,676	25,881	5310

Table 8
The parameters' values for the sensitivity analysis.

Level	H_t	γ	I_0	ρ_u
Low	1,000,000	0.000001	1000	0.9
Medium	50,000,000	0.00000272	10,000	1.8
High	100,000,000	0.000005	100,000	3.6

1992). Therefore we assume the rate of transmission ρ_{ui} of city i is proportional to its population density E_i, and the reference value corresponds to the average density of US urban areas (denoted by $\bar{E}$). Accordingly, we set $\rho_{ui} = 1.8E_i/\bar{E}$. The values of Q_i, E_i, and $\bar{E}$ of the top 50 US urban areas are obtained from the US Census Bureau (2000). Let I_0 be the total number of initial infected individuals of all infected cities. We assume I_{0i} is proportional to the population of the city, i.e., $I_{0i} = I_0 Q_i / \sum_i Q_i$. It is reasonable to assume that the p decreases with population density. For each city we adjust the reference value by setting $p_i = p - 0.02(E_i/\bar{E} - 1)$, where 0.02 is chosen such that $p_i \leqslant 1$. The efficacy of isolation a_i should also decrease with population density. For each city we also adjust it by setting $a_i = a - 0.02(E_i/\bar{E} - 1)$. We assume that v_i is proportional to the density, i.e., $v_i = vE_i/\bar{E}$. We consider making decisions for 8 periods, i.e., $T = 8$. The initial number of cases at each city at the time of intervention is obtained using I_{0i}, ρ_{ui}, and constraint (14.6) for each period before the intervention. We set I_0 = 10,000, and H_t = 50,000,000, $t = 1 \cdots T$. To estimate f_{ij} we use air traffic data between two cities in Appendix 3 of Puentes and Tomer (2009) as training data to estimate the parameters of the gravity model. The mean absolute percentage error on the training data is less than 5%.

6.2.2. The solution of the base case

The MIP model is solved by ILOG CPLEX 9.0. All the computations are performed on a Dell Precision 670 computer with a 3.2 GHz Intel Xeon Processor and 2 GB RAM. The solution of the base case is summarized in Table 7. The columns "Iso.", "Ring" and "Mass" are the number of cities that implement the corresponding strategy in each period. "RingVac" and "MassVac" are the total amount of vaccine used for the ring strategy (i.e. $\sum_{i=1}^{n} x_{it}$) and the mass vaccination strategy (i.e. $\sum_{i=1}^{n} m_{it}$) for each period, respectively. By definition, the total amount of vaccine used for isolation strategy is 0 for each period. "NumCase" is the total number of cases at the beginning of each period, i.e. $\sum_{i=1}^{n} I_{it}$. The last column "Fatal." is the total number of fatalities of each period. The last row reports the sum of every item for all T periods. Note that we update ρ_u every 4 periods by multiplying it by the new percentage of the susceptible people in the total population. It means we solve two MIP models, one for periods 1–4 and another for periods 5–8 with an updated ρ_u. This introduces some sub optimality, but it is not significant because the fatalities of the first 4 periods dominate that of the last 4 periods.

The base case considers limited resources. The total number of fatalities is 5310. The disease is contained at the end of period 7. 22 cities implement mass vaccination and all other cities implement the ring strategy in period 1. From then on, all cities implement the ring strategy until the disease dies out. The isolation alone strategy is not implemented, which can be explained by Propositions 4–6. Because γ is small, the ratios are positive, so either the ring strategy or the mass vaccination strategy is implemented when there are resources available.

6.2.3. Sensitivity analysis

We did sensitivity analysis on four parameters: H_t, γ, I_0, and ρ_u. Each parameter has three values: low, medium and high, as shown in Table 8. The base case takes medium values. When doing sensitivity analysis for one parameter, we only change the value of that parameter; all other parameters take the base value. Note that a low γ of 0.000001 is commonly used in the literature (Fenner et al., 1988). The medium and high values of γ are due to (Bozzette et al., 2003).

The sensitivity analysis of the resource level is shown in Table 9. We can see that the number of fatalities decreases with H_t, which is intuitive. For the high H_t case, the isolation alone strategy is not implemented as in the base case. When mass vaccination is implemented, it is implemented in period 1, which means the earlier the better. This is consistent with Proposition 2. Compared with the base case, more cities implement mass vaccination because more vaccine is available. The disease is under control, and the number of fatalities is decreasing faster than the base case. For the low H_t case, the disease is still under control. In period 1, the ring strategy is only implemented in 8 cities, and the isolation alone strategy is implemented in all other cities because of resource limitation. The mass vaccination strategy is implemented in one city in period 4 when there is enough vaccine.

The sensitivity of the solution to the fatality rate of vaccination is also shown in Table 9. We can see that the number of fatalities increases with γ. In both cases, the isolation alone strategy is not implemented. As γ increases, the mass vaccination strategy is implemented in fewer cities, and the ring strategy is more

Table 9
Solution sensitivity to resource level (H_t) and fatality rate of vaccination (γ).

Period	High H_t (100,000,000)				Low H_t (1,000,000)				Low γ (0.000001)				High γ (0.000005)			
	Iso.	Ring	Mass	Fatal.	Iso.	Ring	Mass	Fatal.	Iso.	Ring	Mass	Fatal.	Iso.	Ring	Mass	Fatal.
1	0	8	42	4467	0	9	0	4273	0	29	21	4320	0	31	19	4500
2	0	50	0	666	0	50	0	1779	0	47	3	735	0	50	0	748
3	0	50	0	120	0	50	0	519	0	50	0	136	0	50	0	141
4	0	50	0	24	0	49	1	185	0	50	0	27	0	50	0	28
5	0	39	0	5	0	50	0	67	0	50	0	6	0	50	0	6
6	0	3	0	0	0	50	0	26	0	4	0	0	0	8	0	0
7	0	1	0	0	0	46	0	11	0	1	0	0	0	1	0	0
8	0	1	0	0	0	21	0	4	0	1	0	0	0	1	0	0
Total	0	202	42	5282	0	325	1	6864	0	232	24	5224	0	31	19	5423

Table 10
Solution sensitivity to initial number of infections (I_0) and initial transmission rate (ρ_u).

Period	Low I_0 (1000)				High I_0 (100,000)				Low ρ_u (0.9)				High ρ_u (3.6)			
	Iso.	Ring	Mass	Fatal.	Iso.	Ring	Mass	Fatal.	Iso.	Ring	Mass	Fatal.	Iso.	Ring	Mass	Fatal.
1	0	47	3	449	0	34	16	42,892	0	43	7	2637	0	29	21	7240
2	0	50	0	102	0	18	32	7780	0	50	0	257	0	44	6	2469
3	0	50	0	26	0	50	0	1300	0	50	0	26	0	50	0	898
4	0	50	0	7	0	50	0	255	0	40	0	2	0	50	0	362
5	0	44	0	2	0	50	0	55	0	8	0	0	0	50	0	157
6	0	11	0	0	0	8	0	2	0	2	0	0	0	50	0	38
7	0	4	0	0	0	2	0	0	0	0	0	0	0	50	0	9
8	0	1	0	0	0	0	0	0	0	0	0	0	0	36	0	2
Total	0	257	3	586	0	212	48	52,284	0	193	7	2922	0	359	27	11,175

Table 11
Comparison of the solution of the multi-city model and a pro-rata allocation.

Problem case	Pro-rata allocation	Multi-city model	Number of lives saved	Difference (%)
High H_t (100,000,000)	5287	5282	5	0.09
Medium H_t (50,000,000)	6186	5310	876	14.16
Low H_t (1,000,000)	9065	6864	2201	24.28

Table 12
Comparison of the heuristic and CPLEX solver solutions.

Problem case	CPLEX		Solver time (s)	Heuristic	Heuristic time (s)	Difference in objective (%)
Base case	5310		7208.0	5313	1.0	0.06
Low H_t	6864		12.0	6874	0.2	0.15
High H_t	5282		690.0	5286	0.1	0.07
Low γ	5224		7209.0	5968	0.2	0.06
High γ	5423		7211.0	12,091	0.1	0.07
Low I_0	586		543.0	587	0.1	0.25
High I_0[a]	52,284	0.52%	7217.0	52,300	0.2	0.03
Low ρ_u	2922		24.0	2925	1.0	0.12
High ρ_u[a]	11,175	2.02%	9296.0	11,127	0.2	−0.43

[a] Optimal with a relative MIP gap; the second value is the gap in percentage.

favorable and implemented in more cities. This can be explained by condition (5) because BND_{mr} increases with γ.

The sensitivity of the solution to I_0 and ρ_u is shown in Table 10. We can see that the number of fatalities increases with I_0. Consistent with condition (5), the mass vaccination strategy is implemented in more cities as I_0 increases. For a high I_0, the mass vaccination strategy is implemented in period 2 in some cities due to vaccine limitation in period 1. For this case, the best solution the solver can get has a relative MIP gap of 0.52% due to memory limitation. The effect of ρ_u is similar as I_0. The number of cities that implement the mass vaccination strategy increases with ρ_u. For a high ρ_u, the best solution the solver can get has a relative MIP gap of 2.02% due to memory limitation.

6.2.4. The benefit of allowing different policies for different cities

One way to deal with the multi-city resource allocation is to treat the total population of the 50 cities as a "super city" and assume a uniform $\bar{\rho}_u$ for all cities. Under this assumption, it is reasonable to allocate vaccine in proportion to the population of a city for fairness. We compare the number of fatalities of our model with a pro-rata allocation strategy for three cases: high H_t, medium H_t, and low H_t. The results are shown in Table 11. It can be seen that the number of lives saved increases when the resource level decreases. For a high H_t, the number of lives saved is not significant. However, when the resource level is medium, the number of lives saved is significant. When the resource level is low, thousands of lives can be saved using our model. Note I_{0i} is proportional to the population in current parameter setting. For an uneven distribution of I_0, the saving in lives could be larger.

6.2.5. Validation of the heuristic

We compare the performance of the heuristic with the solution from the CPLEX solver for all sensitivity analysis instances. The results are shown in Table 12. We can see that the solutions of the heuristic are very close to the solutions from the solver. In the last case, the solution of the heuristic is better than the solution from the solver. For other cases, the largest difference is 0.25%. This validates Propositions 4–6 indirectly. The heuristic can obtain a good solution quickly. In two instances, CPLEX was not able to solve the problems to optimality after more than 2 h and using up to 2 GB of memory. It takes at most one second to get comparable solutions using the heuristic. For larger problems such as 100 cities and 16 periods, it may be impossible to get an optimal solution by the solver. In addition, the heuristic is intuitive and provides insights on how to allocate resources intelligently.

7. Conclusion and discussion

In this paper, we propose an optimization based model to determine efficient distribution strategies of limited resources over multiple locations to address a smallpox outbreak. In particular we consider the effects of limited resources on transmission rates when conditions in each city are different and there is cross-city infection. The approach is based on introducing approximate

representations of disease propagation that are reasonable within parameter ranges. These representations are then used to build a tractable optimization problem that represents the large scale multi-city problem. In building the multi-city model we obtain a series of intermediate results: (1) we give a closed form approximation to the number of total infected of an SIR model; (2) we present a constant rate disease propagation model that can include limited resources and approximates an SIR model when the number of periods is small; (3) from pair-wise comparisons we obtain threshold conditions to trigger more intense control measures; and (4) these threshold conditions are the basis of a heuristic to solve large multi-city resource allocation problems in seconds, yielding solutions within a fraction of a percent of the optimal one.

Our computational results help identify the parameter ranges where the approximate disease propagation models are reasonable and analyze the sensitivity of the distribution strategy on a multi-city example to key problem parameters (such as the total resources, base transmission rate, and vaccine death rate). Not surprisingly we observe that larger initial infection and transmission rate makes mass vaccination more preferable and that a higher vaccination fatality rate makes an isolation strategy preferable. Finally, we show that for a multi-city outbreak, the proposed assignment of resources saves more lives than allocating medicine proportional to population. The number of lives saved can be significant when resources are limited.

The proposed model contributes to the literature by presenting an optimization model that considers new realistic aspects of a multi-city disease outbreak, such as different parameters in each city, cross city infection, effect of limited resources on transmission rate, and a vaccination fatality rate. The model nevertheless makes some important assumptions, such as: the transmission rate ρ_u is constant, population in a city is homogeneous, contacts of each infectious individual are independent, all infections occur at the start of a period, etc. We believe that developing more realistic models, capable of relaxing these assumptions, is an interesting topic for further research. Of these assumptions, it is particularly severe to consider a constant transmission rate ρ_u. To address this limitation in a finite horizon optimization problem, we update ρ_u every 4 periods, using the constant rate in each part of the model. We believe that a model that considers the effect of both the number of susceptible individuals and having limited resources on the transmission rate is challenging, as this would lead to a non-linear representation of the transmission rate. Considering the uncertainty present in such emergency situations is another challenging area for future research. This work gives an efficient heuristic solution for simple deterministic disease propagation models that could be used as the basis for a solution method for a multi-city disease propagation model with uncertainty.

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