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Forecasting the geographical spread of smallpox cases by air travel

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SUMMARY

Instituting air travel restrictions to slow the geographical spread of smallpox cases would have significant consequences and present serious logistical concerns. Public health decision makers must weigh the potential benefits of such restrictions against their negative impact. The goal of this research is to provide a basic analytical framework to explore some of the issues surrounding the use of air travel restrictions as a part of an overall containment strategy. We report preliminary results of a compartmental model for the inter-city spread of smallpox cases resulting from US domestic air travel. Although air traffic can be halted within hours as was shown following the terrorist attacks of 11 September 2001, these results suggest that the consequences of halting domestic air travel may not be outweighed by public health benefits.

INTRODUCTION

As a biological weapon, smallpox poses one of the greatest risks. Many experts now believe that supplies of smallpox virus may exist outside the official confines of CDC (Atlanta, Georgia) and Vector (Koltsovo, Novosibirsk) [1]. Although the probability of an intentional release of smallpox may be small, if it were to occur the public health consequences would be considerable.

Recent analyses intended to improve our understanding of the impacts of an epidemic and alternative control strategies have not directly addressed the effects of air travel on the dissemination of smallpox cases [2–4]. The long incubation period, combined with over one million travellers boarding planes daily in the US alone raises the possibility of cases of smallpox being geographically dispersed before cases were detected and control measures, such as case isolation and ring vaccinations, implemented [1, 5, 6]. The potential geographical dispersion of cases has important implications for resource allocation. Knowledge of where potential cases are likely to appear following case detection in a single city may provide additional information concerning where to target control measures (e.g. vaccination).

Instituting air travel restrictions to retard the spread of smallpox would have significant consequences and present serious logistical concerns. Public health decision makers must weigh the potential benefits of such restrictions against their negative impact. This research explores the possible geographical spread of smallpox cases resulting from air travel within the US after an initial release in an urban area. We do not examine smallpox transmission on the airplane itself but examine movements of susceptible and latent individuals by air travel. The goal of this research is to provide a basic framework to explore questions such as: (1) Under what conditions, if any, would air travel restrictions (either as policy or self-imposed) decrease the forecast epidemic magnitude? (2) How rapidly

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would air travel restrictions have to be put in place to slow the spread of the epidemic? and (3) What impact does the initial city of pathogen release have on the magnitude and pattern of spread of the epidemic?

METHODS

To simulate the spread of smallpox via air travel, we modified a model based on the research of Rvachev and Longini [7]. Rvachev and Longini used a compartmental model coupled with transportation data to recreate the temporal and spatial spread of the 1968–1969 influenza pandemic. Although there are obvious and significant differences between the infectiousness, expression and epidemiological characteristics of smallpox and influenza, both are spread by aerosol. The validated success of the Rvachev and Longini model and the similar transmission characteristics of smallpox and influenza suggest the model can be modified to explore the potential dispersion of smallpox cases. For detailed model formulation and discussion of validation see reference [7]. The following is a brief overview of the model formulation.

The definitions of state variables and parameters are provided in Table 1. The population of city $i(P_i)$ is divided into four mutually exclusive disease states: susceptible $S_i(t)$ (those able to contract smallpox), latent $E_i(\tau, t)$ (those who have been infected but are not yet infectious), infectious $I_i(\tau, t)$ (those capable of transmitting the disease), and removed $R_i(t)$ (those unable to acquire or transmit infection). Two time indices are employed: calendar time (t) and a shifted time index (τ) used to describe the progress of infection within individuals once they have been infected ($\tau=0$). Individuals are latent for a minimum period (τ_1) until they become infectious (τ_2) and remain infectious for a minimum period (τ_3). The maximum length of infection (τ_4) is the sum of the latency period and infectious period.

Contact $\lambda(t)$ between susceptible and infectious individuals sufficient for infection determines whether an individual may become infected. Newly infected individuals are calculated by the standard mass action formulation as the product of the number of susceptibles, number of infectious persons and the contact rate at time t in city i. Once infected, individuals remain latent for an uncertain upper-bounded period $f(\tau)$ and progress to the infectious state for uncertain upper-bounded period $g(\tau)$ until they enter the removed state $h(\tau)$.

Table 1. *State variable and parameter definitions*

$S_i(t)$	Number of susceptible individuals on day t in city i
$E_i(\tau, t)$	Number of latent individuals on day t who were infected on day $t-\tau$
$I_i(\tau, t)$	Number of infectious individuals on day t who were infected on day $t-\tau$ in city i
τ_1	The minimum length of the latency period
τ_2	The first day of the infectious period
τ_3	The minimum length of the infectious period
τ_4	The maximum length of infection
P_i	Size of the population of city i
$f(\tau)$	Probability an individual is latent at time τ
$g(\tau)$	Probability an individual is infectious at time τ
$h(\tau)$	Probability an individual is removed at time τ
$\gamma(\tau)$	The probability that an individual becomes infectious at time $\tau+1$ given that the individual has been latent for time τ
$\delta(\tau)$	The probability that an infectious individual recovers on day $\tau+1$ given that the individual was still infectious at time τ
$\lambda(t)$	Rate of contact between susceptibles and infectives sufficient for transmission
α	Fraction of the population susceptible
σ_{ij}	Average daily number of persons travelling between city i and city j

The probabilities of transition from the latent to infectious state $\gamma(\tau)$ and from the infectious to the removed states $\delta(\tau)$ are computed from the probabilities that prescribe the length of time an individual spends in the latent and infectious states. The probability of an individual becoming infectious at time $\tau+1$ given that the individual is latent at time τ is given by

$$\gamma(\tau)=\frac{f(\tau)-f(\tau+1)}{f(\tau)}, \quad f(\tau)>0, \ \tau=0, \ldots, \tau_2-1 \qquad (1)$$

The probability that an infectious individual transitions to the removed state on day $\tau+1$ given that the individual was infectious at time τ is calculated by the following equation:

$$\delta(\tau)=\frac{h(\tau+1)-h(\tau)}{g(\tau)}, \quad g(\tau)>0, \quad \tau=\tau_2, \ \ldots, \ \tau_4 \qquad (2)$$

Travel between cities

Cities are directly and/or indirectly connected through a symmetrical air travel transportation matrix. The elements of the matrix (σ_{ij}) are defined as the daily passenger flow from city i to j (i.e. the average number of individuals that travel from city i to city j in 24 h). The probability of travel is calculated

by dividing the average daily number of travellers from city i to j by the population of city $i(\sigma_{ij}/P_i)$. Similarly, the probability of travel from city j to city i is calculated by dividing the average daily number of travellers from city j to i by the population of city j. We assume that susceptible and well latent individuals travel. Individuals in the prodromal period (ill but before onset of rash) and infectious (onset of rash) individuals do not travel. Susceptible and latent individuals are assumed to travel in proportion to their representation in each city at time t. A transportation operator (Ω) is applied to the susceptible and latent state equations (equations 4 and 5) to account for travel between cities. Epidemics within each city can occur and individuals travelling through the transportation network can create inter-city epidemics.

Because we use a unique value for both city population and average daily travellers, these probabilities are constant. In addition, arriving and departing passengers have the same probability of remaining in a city as they do of leaving it. This means that once travellers have arrived at their destination, they are considered inhabitants and have the same probability as other residents of travelling back to their origin. In reality, this probability is clearly much higher. Further, the average trip length by air within the US is shorter than the minimum latency period. The majority of travellers would complete their trips and return to their origin before exhibiting symptoms of smallpox. As a result, we chose to include only travelling latent individuals who are expected to enter the prodromal period at their destination. We assume that only latent individuals between the minimum latency period (τ_1) and the prodromal period (τ_2-4 to τ_2-1) travel. The prodromal period was taken to be 3 days [8] where day τ_2 represents the first day of the infectious period. Additional issues associated with probabilities of travel are discussed in the forthcoming limitations and data sections.

Computational algorithm

The model consists of a separate but identical set of difference equations defining the disease states for each city. The initial conditions for susceptible and latent individuals are pre-specified. The initial number of susceptible individuals is assumed to be a fraction (α) of the city population. The initial number of latent individuals is pre-specified for the initial city of release and is zero for all other cities. There are assumed to be no initial infectious individuals in any city.

The daily incidence in city i is calculated by stepping through the following equations for all cities and all time:

$$E_i(0,\ t) = S_i(t)\frac{\lambda(t)}{P_i}\sum_{\tau=\tau_2}^{\tau_4} I_i(\tau,\ t) \tag{3}$$

$$\Omega[S_i(t)] = S_i(t) + \sum_{j=1}^{N}\left[S_j(t)\frac{\sigma_{ji}}{P_j} - S_i(t)\frac{\sigma_{ij}}{P_i}\right], \quad i = 1,\ 2,\ \ldots,\ N \tag{4}$$

$$\Omega[E_i(\tau,\ t)] = E_i(\tau,\ t) + \sum_{j=1}^{N}\left[E_j(\tau,\ t)\frac{\sigma_{ji}}{P_j} - E_i(\tau,\ t)\frac{\sigma_{ij}}{P_i}\right], \quad i = 1,\ 2,\ \ldots,\ N,\quad \tau = \tau_1,\ \ldots,\ \tau_2 - 1 - 3 \tag{5}$$

$$S_i(t+1) = \Omega[S_i(t)] - E_i(0,\ t) \tag{6}$$

$$E_i(\tau+1,\ t+1) = [1-\gamma(\tau)]\Omega[E_i(\tau,\ t)], \quad \tau = 0,\ 1,\ \ldots,\ \tau_2 - 1 \tag{7}$$

$$I_i(\tau+1,\ t+1) = \begin{cases} \gamma(\tau)\Omega[E_i(\tau,\ t)] + [1-\delta(\tau)]I_i(\tau,\ t), & \tau = 0,\ 1,\ \ldots,\ \tau_2 \\ [1-\delta(\tau)]I_i(\tau,\ t), & \tau = \tau_2+1,\ \tau_2+2,\ \ldots,\ \tau_4 - 1 \end{cases} \tag{8}$$

To address the questions of how and when air travel restrictions would have to be instituted to slow the geographical spread of the epidemic, we performed a series of simulations. When air travel restrictions are implemented in city i, the average daily number of travellers in and out of city i is set to zero ($\sigma_{ij} = \sigma_{ji} = 0$) as soon as a given number of cases are forecast. We compared implementing no travel restrictions to implementing restrictions at 500, 250, 100, 50, and 10, 5 and 1 case. Air travel restrictions are implemented in any city after a given number of cumulative cases are forecast.

Key model limitations and assumptions

The transmission of smallpox from an infected individual to a susceptible individual is a complex process dependent upon a variety of factors. Forecasting the spatial and temporal spread is similarly complex. The following paragraphs discuss some of the key model limitations and simplifying assumptions.

In this formulation, we assume complete instantaneous mixing within a city. Individuals have the

same probability of contacting any other individual. This population density dependent mixing has been shown to be sufficient for large populations and relatively short time periods [9, 10]. To examine the spread of smallpox within cities, heterogeneities such as age structure and social networks are necessary to account for the dynamic nature of human contacts [8, 10]. Examining the potential geographical spread of cases by air travel on a smaller scale also necessitates incorporation of different contact rates between travellers and non-travellers. We would expect the contact rate among travellers to be higher than the contact rate between travellers and non-travellers. This is a clear area for model refinement and extension.

A constant and closed population is assumed meaning that although the number of individuals in each disease state changes over time, the sum of all states is always equal to the population size. Vital dynamics (i.e. births and deaths) are not considered. In historical epidemics of smallpox, the case fatality rate has been shown to be as high as 30% in unvaccinated populations [8]. The population of a particular city may decrease as individuals die from the disease. We estimated the error of neglecting deaths by removing 30% of persons in the infectious state from the city population. There was a negligible difference (<1 case) between cumulative forecast cases accounting for deaths and cumulative forecast cases excluding them. As a result, we chose not to include vital dynamics in the analyses. Inclusion of birth and death processes would be required when examining longer time periods and exploring the possible persistence of disease in populations.

Probabilities of travel are assumed constant throughout the time horizon and for all individuals. Although an approach incorporating the complex dynamics of domestic air travel would improve the model, we were limited by available data. Air transportation data available to us significantly underestimates the number of travellers per day within the US. Also, air travel is the only mechanism by which individuals are assumed to leave a city and cities are treated as having defined boundaries. This means that the results of the model are best suited to examining cities where the predominant means of travel between them is via air (e.g. New York and Los Angeles). Analyses of the geographical dispersion of smallpox between city clusters or corridors (e.g. Baltimore, Washington, DC and Philadelphia) would need to incorporate other modes of transportation and dynamics of spread.

Fig. 1. Location of cities included in analyses.

In essence, because the model is deterministic it is best conceptualized as an approximation of large-scale temporal and spatial trends. Deterministic models describe disease spread under the assumption of mass action, relying on the law of large numbers. Applied to large susceptible populations, deterministic models are an adequate approximation of the dynamics of disease dispersion [10, 11]. As the scope and scale of interest decreases, stochastic effects become increasingly important. In the event of the release of smallpox in a US city, spread of smallpox by air travel to other cities is a chance event. There is always a probability of spread as long as air transportation connections exist. Deterministic models such as this cannot account for underlying stochastic processes. Subsequent research aims to incorporate these processes by developing the stochastic counterpart to the model.

Data sources

The elements of the air travel transportation matrix were obtained from the Department of Transportation's (DOT) Domestic Airline Fares Consumer Report for the year 2000 [12]. The report gives average daily number of passengers per quarter travelling between 116 cities in the continental US (Fig. 1). Although all 116 cities were used in the analyses, we present the results for select cities for ease and clarity of presentation. A sample of the matrix is given in Table 2. There are several key limitations to this data. First, individuals who transit an intermediate city (do not leave the airport) between their origin and destination are not distinguished from persons who travel directly. Passenger counts between a city pair represent the origin and final destination of travellers (leave the airport). For example, an individual flying

Table 2. *Select city populations and average daily passengers travelling between select cities (2000 first quarter)**

	Atl.	Bos.	Chi.	Den.	Hous.	LA	Mia	NYC	Phoe.	San Fr.	WDC
Atlanta	0	1969	3143	1310	1432	1330	1543	5762	671	1094	3160
Boston		0	1385	868	520	1146	877	6611	469	1545	3289
Chicago			0	2367	1608	3004	1306	6108	3403	2131	2128
Denver				0	977	1930	450	2033	1839	1714	1127
Houston					0	1173	417	1973	746	798	779
LA						0	808	5827	3300	3855	1587
Miami							0	4393	192	120	1232
NYC								0	1602	4641	5786
Phoenix									0	1695	387
San Fr.										0	1208
WDC											0

* US Department of Transportation Domestic Airline Fares Consumer Report: First Quarter 2000 Passenger and Fare Information. In cities with multiple airports the average daily passengers includes both airports.

from Miami to New York connecting in Atlanta is represented as a Miami–New York passenger. The only passengers that appear as Miami–Atlanta passengers are those travelling to Atlanta as their ultimate destination, even if they got off the plane to board another one. Passengers who depart and return to their origin city within 24 h are counted twice in the data. This type of travel represents a small fraction of air travellers [12].

Second, commuter traffic on airplanes smaller than 60 seats (i.e. regional jets, turboprops, business aviation) are not included in the passenger counts. Regional airlines operate short and medium-haul scheduled airline service connecting smaller communities with larger ones and connecting hubs. Regional jet traffic alone comprises 12·5% of domestic passengers enplaned and 30% of the US commercial airline fleet [13]. The DOT estimates that scheduled commercial air travel (non-commuter) accounts for approximately 70% of domestic 48-state US travel [12]. Third, characteristics of individual travellers are not included in the analysis. We do not differentiate between business and leisure travellers. Approximately 48% of domestic travel is for business with an average trip length of 3 days [14]. The average business traveller takes 5·4 trips per year. Frequent fliers (10+ trips per year) comprise 14% of business travellers but account for 40% of trips [14]. The potential inflation of geographical spread due to lack of differentiation between business and leisure travellers is of concern. This concern may be somewhat counterbalanced by the significant underestimation of daily passenger air travel. More refined transportation data and the inclusion of passenger demographics are an obvious direction for future research.

Metropolitan Statistical Area (MSA) population estimates from the 2000 Census were used for city populations [15]. We estimated the fraction of the population susceptible, transmission potential and infection distributions from the published literature on the natural history of smallpox. The portion of the US population susceptible to smallpox is unknown. CDC estimates that currently no more that 50% of the US population has been vaccinated [16]. Henderson estimates that only 10–15% of the US population has residual smallpox immunity [17]. We chose an initial value of 75% population susceptibility as a conservative estimate and varied susceptibility during sensitivity analyses.

The average incubation period was taken to be 12 days (range 7–17 days) [6]. Individuals were assumed to be infectious for a minimum of 1 week with infectivity declining thereafter to a maximum total length of infection of 30 days [6, 8, 18]. The average infectious period was taken to be 12 days (range 7–20 days) [8]. The probabilities of being in the latent, infectious and removed states are given in Figure 2.

Estimates of the infectiousness of smallpox, defined as the average number of secondary infections produced by one infected individual within an entirely susceptible population (i.e. $\alpha = 1$) range from 2 to greater than 20 [2]. This number is typically referred to as the reproductive rate $R_{1-\alpha}$ [10]. There is considerable debate concerning the actual range of $R_{1-\alpha}$ for smallpox [22]. We chose a range of $R_{1-\alpha}$ between 1·8 and 4·5 based on an assessment of the available literature [2, 3, 6, 8, 17–19].

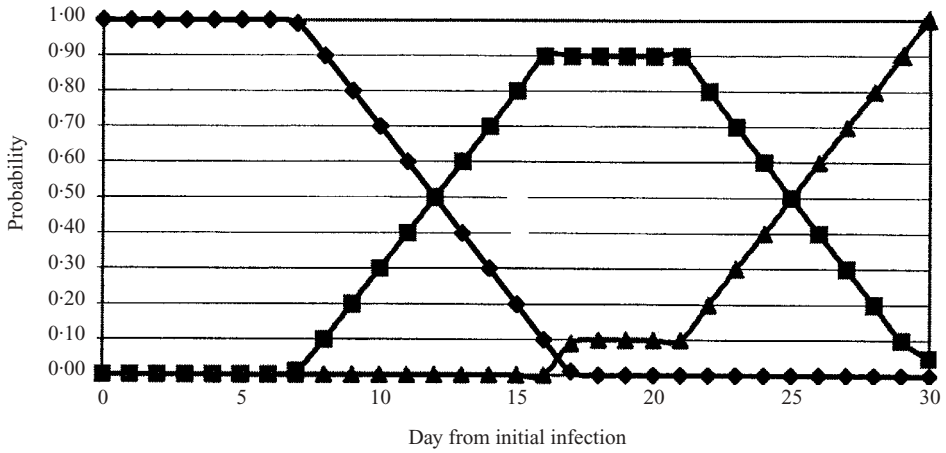

Fig. 2. Probabilities of individual remaining in the latent (–◆–), infectious (–■–) and removed (–▲–) states.

In this formulation, we define $R_{1-\alpha}$ as the product of the contact rate between susceptibles and infectives $\lambda(t)$, the fraction of the population susceptible α and the average length of infection. We chose a starting value of 2·7 for $R_{1-\alpha}$. This value was calculated by assuming population susceptibility of 75%, a contact rate of 0·30 and an average infectious period of 12 days. A value of 0·30 was chosen for the contact rate based on estimates of the proportion of susceptibles who became infectious in historical outbreaks of smallpox [8, 19]. During sensitivity analyses, we varied the contact parameter and susceptible fraction for $R_{1-\alpha}=1{\cdot}8, 2{\cdot}7, 3{\cdot}6$ and 4·5. The contact parameter was varied (0·2, 0·3, 0·4 and 0·5) while holding the susceptible fraction and average length of infection constant. The susceptible fraction was also varied (0·50, 0·75 and 1) while holding the contact parameter and average length of infection constant.

As an initial scenario, we assumed the virus was released in Washington, DC involving transmission to 100 individuals. We chose 100 individuals based on a possible scenario suggested by Henderson [1, 6]. We also performed simulations with 10 and 50 initial latents. The time horizon for all simulations was 365 days beginning 1 January 2000. Unless otherwise noted, the contact parameter was set at 0·3 and the susceptible fraction at 0·75 corresponding to an $R_{1-\alpha}=2{\cdot}7$.

RESULTS

The first set of simulations explores the cumulative forecast cases at increasing $R_{1-\alpha}$ by varying the contact parameter. Across all cities, there is an average increase of 30% cumulative cases when comparing an increase in the contact parameter from 0·2 ($R_{1-\alpha}=1{\cdot}8$) to 0·3 ($R_{1-\alpha}=2{\cdot}7$). This large difference is not evident at higher values of $R_{1-\alpha}$. Comparing an increase of 0·3 ($R_{1-\alpha}=2{\cdot}7$) to 0·4 ($R_{1-\alpha}=3{\cdot}6$) there is an average increase of 7% and of 0·4 ($R_{1-\alpha}=3{\cdot}6$) to 0·5 ($R_{1-\alpha}=4{\cdot}5$) an average of 5% in cumulative cases across all cities.

When the susceptible fraction is varied and contact parameter held constant, there is an average increase of 20% when comparing a susceptible fraction of 0·5 ($R_{1-\alpha}=1{\cdot}8$) to 0·75 ($R_{1-\alpha}=2{\cdot}7$). When 100% of population is assumed susceptible ($R_{1-\alpha}=3{\cdot}6$), there is an average increase of 38% across all cities compared to $R_{1-\alpha}=2{\cdot}7$.

The influence of the contact rate and susceptible fraction is examined by comparing simulations with the same $R_{1-\alpha}$ but with different parameter combinations. Averaging across cities, when $R_{1-\alpha}$ is held constant at 1·8, there is a 66% increase in cumulative cases when the susceptible fraction is 0·75 and contact parameter is 0·2, compared to a susceptible fraction of 0·5 and contact parameter of 0·3. However, for $R_{1-\alpha}=3{\cdot}6$, there is an average increase of 76% comparing 100% population susceptibility and a contact parameter of 0·3, to 75% susceptibility and a contact parameter of 0·4. At the same values of $R_{1-\alpha}$, higher values of the susceptible fraction forecast greater increases in cumulative cases than higher values for the contact parameter.

When the initial number of latents is varied (10, 50 and 100), there is an average increase of 11% across all cities comparing 10 initial latents to 50, and of 15% comparing 50 initial latents to 100.

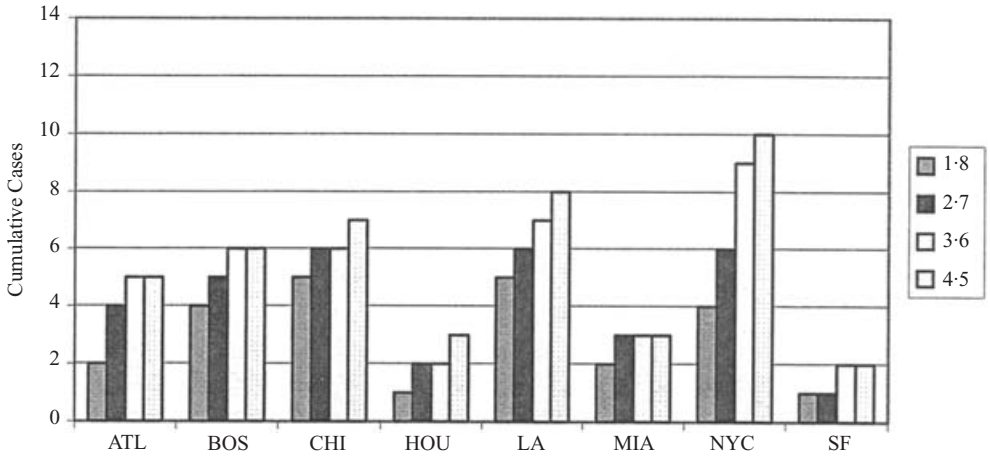

Fig. 3. Cumulative cases at increasing values of $R_{1-\alpha}$ (restrictions instituted at 250 cases, Washington, DC initial city).

Air travel

Large reductions in cumulative cases are forecast when travel is suspended at 500 cases compared to no restrictions, with cases forecast to occur in only 8 of the 116 cities. When restrictions are instituted at 250 cases compared to 500 cases, an average decrease of 64% is forecast; comparing restrictions at 100–250 cases the average reduction is 38%. Only New York is forecast to have cases when restrictions are instituted at 50 cases. When restrictions are implemented at 10, or 5 or 1 case, no cases are forecast to be introduced by air travel into other cities in the network.

To evaluate the impact of air travel restrictions under different assumptions of transmissibility, we performed the same analyses ranging $R_{1-\alpha}$ between 1·8 and 4·5. As expected, the impact of air travel restrictions depends strongly on $R_{1-\alpha}$. When air travel is suspended at 500 cases, reduction in cumulative cases is greatest at increasing $R_{1-\alpha}$. Comparing increasing $R_{1-\alpha}=1{\cdot}8$ to 2·7 an average reduction of 22% is forecast. Comparing 2·7 to 3·6, the average reduction is 53%, and 78% comparing 3·6 to 4·5. Where restrictions are implemented at 250 cases (Fig. 3), there is an exponential relationship between forecast cumulative cases and increasing values of $R_{1-\alpha}$. Similar trends were exhibited for suspending travel at 100 and 50 cases. At low $R_{1-\alpha}$, Atlanta, Boston, Chicago, Los Angeles and New York are forecast to have at least one case when restrictions are implemented at 100 or 50 cases, whereas restrictions implemented at 10, 5 or 1 case, smallpox is not forecast to be introduced by air travel into other cities for $R_{1-\alpha}=1{\cdot}8$–$3{\cdot}6$. When $R_{1-\alpha}=4{\cdot}5$, cases are forecast to appear in New York.

Table 3. *Number of days from epidemic start when select travel restrictions would be implemented at increasing values of R*

	$R_{1-\alpha}=1{\cdot}8$	$R_{1-\alpha}=2{\cdot}7$	$R_{1-\alpha}=3{\cdot}6$	$R_{1-\alpha}=4{\cdot}5$
500	12	9	8	7
250	9	8	5	3
100	5	5	3	2
50	3	2	2	1
10, 5, 1	1	1	1	1

Although a reduction in total cases occurs when travel restrictions are implemented, the time frame for implementation is short. Table 3 gives the day from epidemic start (one forecast case in Washington, DC) when travel restrictions would need to be implemented under different transmissibility assumptions. If air travel restrictions are instituted at 10, 5 or 1 cases the restrictions would need to be implemented as soon as the first cases are recognized. A 50 case detection trigger affords several additional days when $R_{1-\alpha}$ is below 3·6.

City of initial release

We chose nine cities geographically spread across the continental US (Atlanta, Boston, Chicago, Houston, Los Angeles, Miami, New York City, San Francisco and Washington, DC) and performed simulations with these cities as the initial city of release. $R_{1-\alpha}$ was taken to be 2·7 with 100 persons initially infected.

Regardless of the city of initial release, the cumulative forecast cases in Chicago, Atlanta and New York varied by an average of 5% regardless of the

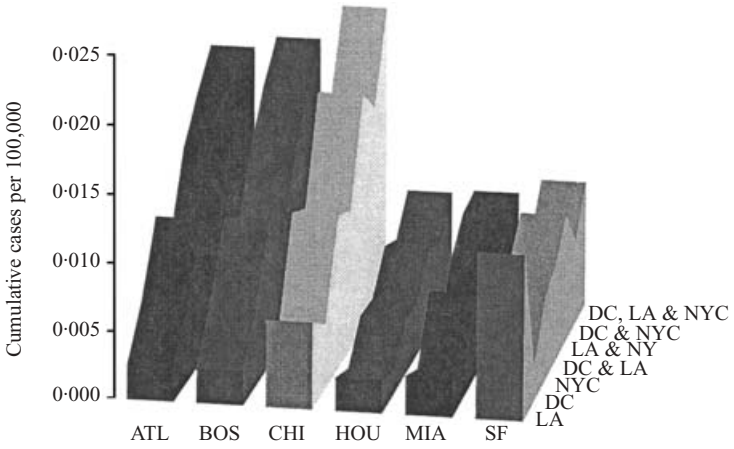

Fig. 4. Cumulative cases per 100 000 for simultaneous release in multiple cities ($R_{1-\alpha}=2{\cdot}7$) no air travel restrictions.

initial city of release. In 2000, Atlanta Hartsfield, Chicago O'Hare airport had the first and second largest domestic passenger volumes with New York's JFK and LaGuardia airports combined falling within the top five [20]. In cities with relatively lower passenger volumes, the initial city of release had a larger impact of the spread of disease.

The final set of simulations explored the spatial and temporal spread when simultaneous releases occur in multiple cities. We compared release in New York, Los Angeles and Washington, DC only, to simultaneous release in two of the cities and to release in all three (Fig. 4). The impact of forecast cumulative cases varied across cities. For release in a single city, New York produced the greatest number of cases in all cities with the exception of San Francisco, whilst Los Angeles produced the greatest cumulative magnitude. When examining simultaneous release in two cities, magnitude depended on air traffic connections. Cumulative cases were greatest in San Francisco and Houston when release occurred in New York and Los Angeles. Cumulative cases were greatest for all other cities when release occurred in New York and Washington, DC. As expected, cumulative case magnitude was greatest with release in all three cities.

DISCUSSION

The results of these simulations suggest that air travel restrictions instituted as soon as the first cases are recognized may still result in epidemic seeding in other cities but may reduce epidemic magnitude. These analyses also highlight the importance of instituting air travel restrictions quickly if they are used as a part of a containment strategy. Delays of a few days result in increases in cumulative forecast cases and in potential geographical spread. Knowledge of where cases are likely in the event of a release may provide information for public health decision makers to aid in prioritization of resources in the event of a mass vaccination campaign. Further, although commercial air traffic can be halted within a matter of hours as was shown following the terrorist attacks of 11 September 2001 these results suggest that the consequences of halting air travel within the entire country may not be outweighed by public health benefits.

Disease containment plans may also need to consider different resource needs based on city of initial release. Air travel connections between urban centres may be of central concern in addition to geographical proximity to the city or cities of initial release. Cities such as New York may require the same degree of intervention as larger urban areas regardless of city of initial release.

In addition to the limitations discussed previously, there are several important issues regarding conclusions that can be drawn from these results. We do not consider any interventions, such as case isolation and ring vaccination, that would be instituted once cases are recognized. In the event of a release, the rate and pattern of transmission would change as the result of interventions and changes in travel behaviour and societal interactions. Individuals may self-limit travel to infected areas and residents of infected areas may flee infected areas by other modes of transportation. It is important to emphasize that these analyses address the potential spread of cases by air travel only after an initial release in an urban area and there are a myriad of other means by which smallpox could potentially spread throughout the US.

These analyses also assume low infectiousness and that cases are detected as soon as they are forecast to occur. It has been suggested that there may be a considerable delay recognizing the first cases and in the implementation of public health interventions [8, 21]. The infectiousness of smallpox is also the subject of significant debate [22]. We did not assume an $R_{1-\alpha}$ above 4·5, which some experts believe may be a significant underestimate [21]. During a recent simulation of a covert smallpox attack on the US entitled 'Dark Winter', participating policy makers mentioned the need for knowledge of the worst-case scenario to assess adequately the risks and benefits of policy options [21].

These simulations begin to quantify and examine some of the policy issues surrounding a release of smallpox. While the results of this research help provide insight, these analyses are only suggestive of potential trends in the spatial and temporal spread of smallpox cases within the US. Because our assumptions concerning the degree to which smallpox cases would spread govern control and containment policy decisions, these analyses also serve to emphasize the importance of refining information on the infectiousness of smallpox in a modern setting.

The primary contribution of this research is to provide a starting point for discussion of some of the public health policy issues surrounding release of an infectious bio-weapon. Future research aims to incorporate more complex transmission and population dynamics. Modelling approaches, such as agent-based models, and those that incorporate the stochastic nature of disease spread within cities is an obvious direction for future research. Additional areas for future research include examination of the dynamics of spread within a city incorporating other modes of transportation and socio-demographic differences between travellers and residents.

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