

Evaluating public health responses to re-introduced smallpox via dynamic, socially structured, and spatially distributed meta-population models

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ABSTRACT

The risk of smallpox re-introduction has motivated preparations in potential target countries. After reproducing the spatiotemporal pattern following the 1972 importation into Yugoslavia via coupled, biologically realistic systems of ordinary differential equations, we developed dynamic population models with current US age distributions and typical spatially-distributed social structures. Surveillance and containment (S&C) coupled with vaccination of 95% of hospital-based health-care workers (HCW) within 2 days of first diagnosis (estimated 18 days post-aerosol release) were modeled after simulated aerosol exposure of 10, 50 or 10,000 people in various settings. If 90% of patients are isolated within days of symptom onset and 75% of contacts are vaccinated and monitored, S&C reduces cases by 82-99%. Pre-emptive immunization of HCW, closing schools, and even vaccinating as many as 80% within one week have small marginal benefits. Preparations should emphasize stockpiling vaccine, training health workers, improving laboratory capacity, and fostering an understanding of S&C.

INTRODUCTION

Routine vaccination eliminated smallpox from the developed world, but was supplanted by surveillance and containment (S&C) in some less developed regions [1], completing eradication. In the surveillance-containment strategy, the only people vaccinated besides health-care workers (HCW) are those who have already been exposed or risk exposure because of proximity to smallpox patients. In the US, routine smallpox vaccination was discontinued in 1972 because the benefits were outweighed by the risks of severe adverse reactions [2]. However, concern about intentional re-introduction of smallpox via terrorist attack has led to discussion of the optimal contemporary vaccination policy.

Mathematical modeling can increase understanding, and assist in designing or evaluating, and possibly improving, control strategies. Policymakers concerned about extinct pathogens or acts of bio-terrorism must act on limited information, possibly quickly. Modelers can minimize the information required by grouping individuals by characteristics believed to affect disease transmission (e.g., age classes, immune states, social/spatial strata). Provided essential details are retained, simplification also expedites this process.

Evaluation of models increases understanding insofar as deficiencies responsible for failure to accurately reproduce natural phenomena are identified and remedied. Our biologically realistic smallpox model reproduces short-term consequences of importation into Stockholm in 1963, after smallpox had been eliminated from Europe. A seasonally-forced model also reproduces longer-term consequences of importation into Bangladesh in the aftermath of its civil war with Pakistan, before which no cases had been reported for many months. Here we use a spatially-stratified model to reproduce the last importation into Europe, Yugoslavia in 1972. Our

ability to replicate these disparate outbreaks is reassuring. Each experience helped us refine age- and socially-/spatially-stratified models that would be otherwise difficult to evaluate, but were necessary to model outbreaks following hypothetical reintroductions to the US.

During 2003, the Council on Public Health Preparedness, Department of Health and Human Services, asked several modeling groups if authorities could rely on the surveillance-containment strategy, which proved so effective in Africa and Asia 30-plus years ago, to meet the challenges of bio-terrorism today. Were smallpox intentionally re-introduced, public health objectives would be to limit cases and deaths while minimizing the adverse consequences of vaccination. In this article we present our model and evaluation of containment strategies.

METHODS

We describe our smallpox model, and use a spatial elaboration to reproduce consequences of the 1972 reintroduction to Yugoslavia. Then we describe how this experience assisted development of increasingly complex models required to evaluate the surveillance-containment strategy and various additional measures that policymakers might consider under hypothetical contemporary reintroduction scenarios.

Smallpox modeling. We partition host populations into the minimum number of states, represented by compartments and differential equations (Figure 1, Appendix), that faithfully describe smallpox infection, vaccination, and immunity. Individuals can move among states via processes represented by arrows in this diagram and mathematical functions in the corresponding equations, but are integer-valued only in discrete event-time simulations [3]. For clarity, we aggregate sub-states (e.g., during which effective contacts change, Figure 2) in our diagram and

equations, and omit mortality from our diagram, but the programs by which we simulate these models include those details.

Model individuals may remain susceptible, or be infected, vaccinated, or both.

Vaccination induces protective immunity among 97% of vaccinees within 8-10 days [4], averts disease among 90% if accomplished within four days of exposure [5], and mitigates symptoms among the remainder and 60% of those who are vaccinated within the next three days.

Artificially-induced immunity lasts 30 years on average, and acquired immunity a lifetime, although full protection is limited to 5 and 20 years, respectively. We distinguish intermediate stages, another 10 and 25 years, during which exposure or re-vaccination boosts immunity.

Exposure of individuals whose vaccine-induced or natural immunity has waned more than 15 or 45 years, respectively, results in modified-spectrum disease [6] unless they are re-vaccinated within six days, whereupon disease may be averted by virtue of their anamnestic response (with 90% efficacy). Without timely post-exposure vaccination, immunologically-naïve people develop a normal spectrum of disease. The latent period is about 14 days, and patients are infectious for about 10 days (Figure 2). We assume the course of immunity-modified disease is 2 days shorter and that patients with modified smallpox infect only 1/3 as many persons as ones with normal-spectrum disease.

Our models permit immediate isolation of contacts (i.e., people under observation by virtue of possible infection) who develop prodromal symptoms and others who develop the rash characteristic of smallpox. Ascertaining whom patients might have infected, and finding, vaccinating and observing them is the essence of S&C.

Historical observations. Smallpox was last re-introduced into Europe mid-winter of 1972 via a pilgrim who visited holy sites in Basra and Baghdad, where smallpox was reported, en

route home from Mecca. His own clinical course was unremarkable. No member of his large family became ill, despite several being unvaccinated. Epidemiologic evidence and serology suggests he initiated an outbreak involving 175 people in three generations, of whom 35 died. Smallpox spread within Kosovo and to Montenegro, Serbia and West Germany. Several cities in greater Serbia were involved, via hospitals to which a single patient was successively transferred, as was Voivodina via Belgrade [12].

We fit a spatially-stratified meta-population model to available data, estimating municipality-specific infection rates, β_i , and interconnections, $0 \leq m_{ij} \leq 1$, where both indices range over all sub-populations (details in Appendix). We calculated R_0 's, secondary infections caused by a newly-infectious person on introduction into a wholly-susceptible population, from these β_i via an expression derived in the appendix.

With few notable exceptions, clinical information is too fragmentary to allocate individuals to normal- or modified-spectrum disease. We estimated initial conditions from the 22-30% primary reactions upon vaccination in nearby municipalities [13]. Information about intervention timing, magnitude and effectiveness also is limited. Populating municipalities from the 1971 census [14], and allowing interventions to differ only in effectiveness, our meta-population model reproduces gross features of the resulting outbreak (Figure 3).

Hypothetical communities. We modeled hypothetical contemporary US communities of 6,000, 50,000, and 1.6 million people, hereafter called our village, town, and city. Our village comprises a commercial district, high school, hospital, and two neighborhoods, each with a lower/middle school. Our town comprises a hospital, three business districts and high schools, and six neighborhoods, each having its own lower/middle school, but pairs sharing high schools and commercial districts (Figure 4). Our city includes 18 neighborhoods, six lower/middle

schools, three high schools, six hospitals, and four business districts, with the central downtown district including cultural facilities and a stadium.

Age-appropriate activities determine connections, m_{ij} , between neighborhoods and schools or workplaces. We chose others to reproduce insofar as possible patterns evident in European re-introductions in the 20 years prior to Yugoslavia [15] (Table 2). During this period, 50% of cases were infected in hospital, 38% of whom were staff and 62% patients or visitors (i.e., connections involving hospitals are asymmetric). Among 29-33% infected at home or in their communities, 68% were in the same and 32% different neighborhoods (i.e., transmissions within were about twice as common as those among these larger social units). The remaining 17-21% of infections occurred at school or work. Ranges reflect unknown and unreported sources.

Other interconnections are more complex (Table 1, Figure 4). Children attend local schools, but social opportunities increase with community size (e.g., high schools have academic and athletic competitions, adults may work or shop in different business districts, with connections between neighborhoods and distant districts being half local ones in our town, and varying inversely with squares of intervening distance in our city). Some interconnections are dynamic. We multiply the m_{ij} between neighborhoods and other sub-populations by one minus proportions of residents who are infectious, weighting patients with modified- 1/3 those with normal-spectrum disease, to simulate ill people staying at home, and sever all connections involving schools to simulate closing them.

While we fabricated these hypothetical communities, the number and nature of constituent sub-populations, as well as their interconnections, could be estimated from observations. In our model of the 1972 reintroduction of smallpox into Yugoslavia, sub-populations represent municipalities among which non-zero m_{ij} range from 0.05 to 0.71 in

accordance with the observed spatiotemporal pattern. And we would use methods for reproducing larger-scale patterns, devised to model the spread of foot-and-mouth disease throughout Great Britain [16], to model real communities with more sub-populations.

Age-specific phenomena. Our model populations are dynamic by virtue of age-specific births and deaths at rates observed in the US during 2000 [17]. We project populations on an age-time grid via standard demographic methods (i.e., infants are sums of products of the reproductive age groups, proportions female and birth rates, all age groups are decremented via mortality, with interior ones also affected by aging). Mortality from normal or immunity-modified smallpox is 30% and 10%, respectively [18].

We distinguish infants, who can only be vaccinated post-exposure; pre- to middle- and high-school children, aged 1-14 and 15-19 years, respectively; and adults aged 20-29, 30-54, and 55+ years, distributing model populations among these classes according to the 2000 US census. Adults over 30 were born before cessation of smallpox vaccination, when proportions ever vaccinated ranged from 0.14 among infants to 0.94 among children aged 5-19 years [19]. If immunity decays exponentially, roughly 1/3 of durations exceed the mean, assumed to be 30 years. Accordingly, 10% of people over 30 years are fully, and 30% partially immune.

We based our sub-population-specific infection rates on estimated R_0 in Yugoslavian municipalities. Fitted $0.13 \leq \beta \leq 0.87$, with higher values in urban areas where transmission was largely nosocomial (e.g., Belgrade, Čačak) or rural ones where extended families reside together (e.g., Kosovo). These β 's correspond to $\sim 2 < R_0 < \sim 7$, with weighted average approximately six [20]. Smallpox is seasonal, with northern hemisphere maximal transmission during winter when this outbreak occurred [1]. Accordingly, we chose R_0 of 8, 6, 4, and 2 for our hospitals, schools,

neighborhoods and commercial districts, whose effective values also depend on their age distributions. Weighted average R_0 are approximately 4 in all model communities.

We were unable to find historical observations from which to estimate age-specific mixing or other parameters. We thus devised a general scheme based on our experience with other vaccine-preventable diseases. We use Hethcote's [21] method for combining preferential and proportionate mixing, with gamma-distributed activities and preference declining exponentially with age. Only three parameters are required to specify mixing within and among age classes (Figure 5). Our limited experience precludes specification of unique patterns for social/spatial sub-populations, but their age distributions and interconnections differ.

Scenarios and response. We explored consequences of hypothetical aerosol exposure of ten adults while dining in our village's commercial district, 500 people while viewing a movie in a neighborhood theatre in our town, and 10,000 while watching a game in our city's downtown stadium, the last two groups being cross-sections by age of their respective populations.

We simulated S&C, together with vaccination of 95% of hospital-based HCW within two days of the first smallpox diagnosis. We assumed that initially all normal- and 75% of modified-spectrum patients would be isolated when their vesicular rash appeared, typically 7 days after fever onset [1], which occurs about 11.5 days post-exposure [1]. The remaining 25% of modified-spectrum patients would be isolated by 10 days after onset of prodromal fever.

Thereafter, we assumed response teams would find and isolate 90% of patients, ascertaining those whom they might have exposed. We assume that 75% of these contacts ($90\% \times 0.75 = 67.5\%$ overall) would be found, vaccinated and observed. Responders would isolate febrile contacts, and patients when they developed papular rashes (i.e., fever plus 6 days). This would occur $0.675 \times 11.5 + 0.325 \times 17.5 \approx 13.45$ days post-exposure on average. We assume

that 95% of normal- and 50% of modified-spectrum patients would be isolated at home or in hospital by day 13, depending on severity of symptoms, with the remainder isolated by day 15.

Structural features of our model communities enable us to investigate pre-emptive immunization of 10% or 50% of hospital-based HCW, alone or together with closing schools for ten days and vaccinating 40% or 80% of the populace one year and older within a week of the initial diagnosis (estimated 18 days post-aerosol release). We modeled those features precisely to investigate the utility of supplemental measures.

RESULTS

We used our age- and socially-/spatially-structured smallpox model, some of whose characteristics were refined by fitting simpler models to historical observations, to evaluate the contributions of various interventions to outbreak control following hypothetical terrorist attacks (Table 2). Results are similar in our village, town, and city (Tables 3-5), so we limit our review to those from the intermediate community.

Baseline. Absent any response, smallpox would spread from the sub-population where aerosol was released throughout our village, town (Figure 6), and city, ultimately involving roughly half of their inhabitants (Table 3). Spread would be slowest in our village partly because only adults, rather than a cross-section by age of the populace, are exposed. All else equal, older people infect fewer than younger ones (Figure 5). Also, people over 30 years of age may have residual immunity, and develop modified-spectrum disease, further reducing the rates at which they infect others.

Primary intervention. S&C and protection of necessary personnel constitute the basic public health response. Together with vaccination of 95% of hospital-based HCW within 2 days of first diagnosis, S&C would reduce cases by 95% on average (Table 4), with a range from 82% to 99% depending on social/spatial sub-population (results not shown). Almost all reduction is attributable to isolation versus vaccination (compare scenarios 2 and 3, Table 4).

Other interventions. We assume health authorities would protect personnel needed to implement the surveillance-containment strategy and care for patients. Many have already been vaccinated. Consequently, we designed our experiments to determine effects of school closing and mass vaccination conditional on this primary response (Table 2).

The marginal impact of these control measures is limited. In our town, pre-emptive vaccination of 10% and 50% of hospital-based HCW reduces residual infections (i.e., the 1-18% not averted by the basic response) by as much as 4 and 17%, respectively, with these maxima in hospitals (results not shown). Closing schools for ten days and vaccinating 40% or 80% of the populace within a week reduces remaining cases by 57% and 70%, respectively, with the reduction due to closing schools alone being at most 37%. Reductions due to targeted interventions are greatest locally, but propagate to interconnected sub-populations.

We also estimate the impact of mass vaccination conditional on school closing and pre-emptive vaccination of hospital-based HCW. Mass vaccination reduces residual cases by as much as 34% and 53%, depending on coverage, and shortens epidemics by a week or more in our town (Table 4). But as relatively many doses are administered (Table 5), more adverse events would result.

DISCUSSION

Isolating cases, vaccinating contacts, and monitoring those vaccinated too late to ensure protection are so effective that pre-emptive vaccination of hospital-based HCW, closing of schools, and vaccination of intermediate and large proportions of the populace contribute little to overall outbreak control. Others using different modeling techniques, but similarly accurate information about smallpox, have reached the same conclusion [22, 23].

We combined viral isolations from the upper respiratory tract [8, 11], observations interpretable as probabilities of transmission on contact, with our observation that social interactions vary inversely with fever (Figure 2). By virtue of the distribution of infections, estimated as products of these probabilities and a surrogate for contact rates based on this clinical observation [7], patients are seriously ill for two days before they are likely to infect anyone. Subsequently, immunologically-naïve patients may be so incapacitated by illness that caretakers and visitors are their only contacts. This combination of laboratory and clinical observations is consistent with the epidemiological literature [6, 10] and an independent estimate [9].

Limiting vaccination to response teams and HCW who care for patients at suitable facilities minimizes adverse reactions. Common sense justifies vaccinating contacts and others for whom proximity to patients increases risk (i.e., family members, hospital-based HCW). Closing schools and making vaccinations available may be justified, if only to allay fears.

Limitations. Observations suitable for modeling are surprisingly scarce given the careful documentation of smallpox eradication [1]. Our models have been improved by efforts to reproduce historical outbreaks, but we have not found age- and socially/spatially-structured observations.

The nature and magnitude of indirect effects depend on social networks. These differ among our village, town and city because of the greater opportunities for interaction that larger communities afford. Bio-terrorism might disrupt interconnections and thus affect disease spread. We simulated confinement of ill people and schools closing via dynamic connections among appropriate sub-populations. Models designed to evaluate responses should include more information about social dynamics.

The surveillance-containment strategy exploits the biology of smallpox, particularly incapacitation while maximally infectious, which accounts for the predominance of transmission in European hospitals [15] and among those caring for or visiting patients at home [6, 10]. The index case and at least one super-spreader in Yugoslavia had mild illnesses, suggesting that increased social interaction may compensate for reduced infectiousness. If *Variola major* has indeed been bioengineered to thwart S&C [24], its altered characteristics should be modeled.

Our modeling approach minimizes the requisite information [25], permitting analytical and timely simulation results. A recent criticism of differential equations concerns the exponential distribution of their sojourns [26]. Gamma-distributed infection rates did not notably improve fits of unstructured models to the outbreaks following reintroduction to Stockholm and Bangladesh (results not shown), suggesting that available observations do not warrant this complexity. A more serious limitation is our inability to capture the chance nature of encounters close enough to transmit pathogens, an important feature of outbreaks involving small numbers of infections or limited opportunities for contact such as highly structured populations.

Because stochastic models have other virtues (e.g., results expressible as probabilities of various outcomes), we usually complement our analyses with discrete event-time simulations [3]. Other working group members modeled individuals and a hybrid of individuals and groups

stochastically, so we concentrated on identifying the biological essentials necessary to represent the surveillance-containment strategy faithfully, reproducing an informative historical reintroduction, and simulating hypothetical ones deterministically. The qualitative similarity of results from our model communities, and of our timely results with those ultimately obtained by other working group members, vindicates this choice.

Conclusions. Our modeling reaffirms the effectiveness of S&C, even in large outbreaks. Given the well recognized dangers of smallpox vaccine, rather than indiscriminate widespread vaccination in the absence of a definite threat, we suggest preparations for intentional reintroductions emphasize stockpiling of vaccine, training of health workers to recognize smallpox, improving laboratory capacity, and fostering an understanding of the surveillance-containment strategy.

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Table 1. Connections, m_{ij} , between (and, on the diagonal, among) sub-units of our hypothetical communities. Those between neighborhoods and nearby business districts are half those between them and distant ones in our town, and vary inversely with squares of intervening distances in the mosaic of contiguous hexagons representing our city.

	Commercial Districts	Neighborhoods	Lower/middle Schools	High Schools	Hospital
Commercial Districts	0.05	0.2	0	0	0.3
Neighborhoods	0.2	0.33	0.075	0.025	0.6
Lower/middle Schools	0	0.075	0	0	0.05
High Schools	0	0.025	0	0.005	0.1
Hospital	0.15	0.3	0.025	0.05	0.001

Note: Elements were adjusted so that marginal totals correspond insofar as possible with European re-introductions during the 20 years prior to Yugoslavia [15] (Table 2).

Table 2. Smallpox response scenarios modeled. Selected comparisons evaluate differences conditional on shared conditions (scenarios 1 and 3, e.g., evaluate S&C^a plus vaccination of hospital-based HCW^b, conditional on population immunity).

Key	Scenario
1	10% over 30 years of age wholly- and 30% partially-immune
2	#1 plus tracing, observing, and isolating contacts who become febrile
3	#2 plus vaccinating contacts and 95% of hospital-based HCW within 2 days of first diagnosis
4	#3 plus pre-emptive vaccination of 10% of hospital-based HCW
5	#3 plus pre-emptive vaccination of 50% of hospital-based HCW
6	#4 plus school closing for 7 days during which 40% of populace is vaccinated
7	#5 plus school closing for 7 days during which 40% of populace is vaccinated
8	#4 plus school closing for 7 days during which 80% of populace is vaccinated
9	#5 plus school closing for 7 days during which 80% of populace is vaccinated
10	#4 plus school closing

^a S&C = surveillance and containment

^b HCW = health-care workers

Table 3. Normal- and modified-spectrum cases, 30 and 10% of whom would die, respectively, during smallpox outbreaks following aerosol releases in hypothetical communities with residual immunity, but no intervention (i.e., scenario 1).

Spectrum	Village		Town		City	
	Normal	Modified	Normal	Modified	Normal	Modified
Neighborhoods	1,673	424	15,211	3,942	483,949	298,897
Low/Middle	239	2	2,029	43	60,901	496
Schools						
High Schools	92	2	688	7	22,165	185
Business	255	106	2,379	972	145,360	47,522
Districts						
Hospital	91	33	157	41	4,476	926
Total	2,350	567	20,464	5,005	716,851	348,026

Table 4. Characteristics of outbreaks in all scenarios and model communities. Normal- plus modified-spectrum cases and indices of outbreak duration, days until 95% of cases had occurred and days with at least one, respectively. Compare with scenario 1 (Figure 6).

Scenario	Village			Town			City		
	Cases	Days	Days	Cases	Days	Days	Cases	Days	Days
		until	with \geq		until	with \geq		until	with \geq
		95%	1 Case		95%	1 Case		95%	1 Case
1	2,917	230	276	25,471	132	271	1,064,876	125	303
2	6	41	23	1,546	76	139	23,089	68	179
3	6	40	23	1,347	67	121	18,049	57	146
4	6	40	23	1,347	67	121	18,049	57	146
5	6	40	23	1,347	67	121	18,049	57	146
6	6	40	23	1,205	59	104	15,725	51	120
7	6	40	23	1,205	59	104	15,725	51	120
8	6	40	23	1,089	53	90	13,975	48	104
9	6	40	23	1,089	53	90	13,975	48	104
10	6	40	23	1,345	67	121	18,022	57	146

Table 5. Vaccinations administered, coverage attained (among those wholly and partially susceptible), and effectiveness (i.e., cases averted per dose), by intervention scenario and model community.

Scenario	Village			Town			City		
	Doses	Coverage (percent)	Cases Averted per Dose	Doses	Coverage (percent)	Cases Averted per Dose	Doses	Coverage (percent)	Cases Averted per Dose
3	94	2	31	1,325	3	18	4,385	2	36
4	89	2	33	1,319	3	18	4,380	2	36
5	66	1	44	1,296	3	19	4,362	2	36
6	2,126	39	1.4	17,867	40	1.4	103,376	39	1.5
7	2,103	39	1.4	17,844	40	1.4	111,035	42	1.4
8	3,901	72	0.7	32,319	72	0.8	194,178	73	0.8
9	3,878	72	0.8	32,296	72	0.8	209,038	79	0.8
10	89	2	33	1,315	3	18	4,483	2	35

FIGURE LEGENDS

Figure 1. Disease and immune states, and processes by which individuals change state, compose our smallpox model. For clarity, we omit one process, all-cause and disease-induced mortality, and several sub-states over which we sum or average. For example, infections are not uniformly distributed during the course of illness (see Figure 2).

Figure 2. Distribution of infections. Infection rates are products of probabilities of transmission on contact and contact rates, both of which vary during illness. Absent information about contact rates, we assume social activity varies inversely with fever [7], and multiplied a linear index by laboratory results interpretable as probabilities of transmission on contact. Then we summed these products, divided each by their sum, and fitted a gamma distribution ($\alpha = 37.8$ and $\beta = 0.5$) to results represented by + symbols [8] via the method of moments. About 5% of this probability density precedes day 14 post-exposure, agreeing with an independent assessment [9] and epidemiological observations [6, 10]. Results represented by x symbols [11] attain 5% a day earlier.

Figure 3. Smallpox in Yugoslavia. Following the last reintroduction to Europe, in 1972, smallpox spread from Kosovo to Montenegro and greater Serbia, including Belgrade, from which it spread to Voivodina. Of seven sub-populations modeled simultaneously, only Kosovo (solid line, +'s), Belgrade (dashed line, triangles), Novi Pazar (dotted line, x's), and Čačak (line of alternating dashes and dots, diamonds) experienced multiple cases. We assume information available for any municipality (e.g., population immunity and intervention timing) applied

throughout the former Yugoslavia, allowed intervention efficiencies (i.e., coverage, isolation), infection rates, β_i , and interconnections, m_{ij} , to vary, and use estimates to inform hypothetical attack scenarios.

Figure 4. Schematic diagram of our model town, illustrating sub-populations (hexagons) and clusters of neighborhoods, schools and business districts (ovals). Our village comprises only two residential neighborhoods, each with its own lower/middle school, one business district, high school, and hospital. Our city comprises a downtown, six hospitals, three suburban business districts and high schools, six lower/middle schools, and 18 neighborhoods. Children attend local schools, but high schools have athletic and scholastic contests, businesses have commercial and people have social relations among as well as within districts and neighborhoods, respectively (Table 1). Among other interconnected sub-populations, m_{ij} decline with distance⁻².

Figure 5. Generalized 10-class mixing matrix whose diagonal is gamma-distributed ($\alpha = 3$, $\beta = 5$) and disposition to mix with others the same age declines exponentially ($\mu = 15$) with age. The elements thus are $\delta_{ij}\epsilon_i\gamma_i + (1-\epsilon_i)(\gamma_i\gamma_j)^{1/2}$, where δ_{ij} is the Kronecker delta (i.e., 1 when $i=j$ and 0 otherwise), ϵ and γ refer to the corresponding exponential and gamma probabilities, and subscripts refer to age classes. In this illustration, the maximum mixing occurs at 10-14 years and interval between successive isoclines is 0.05.

Figure 6. Outbreaks in our model town following aerosol release with residual immunity, but without intervention (scenario 1). Prevalence of normal spectrum disease in representative sub-populations (hospital, solid; high school, dashes; business district, dotted; school, alternating

dashes and dots; neighborhood, alternating dashes and double dots). Following detection of smallpox cases, timely intervention reduces cases and limits duration (Table 4) as well as curtails spread from the exposed sub-population.

APPENDIX

We describe our model of smallpox, a faithful representation of essential states and state-transition processes, generalize it to multiple sub-populations, and derive useful summary statistics. While our simulations are age- as well as socially-/spatially-structured, the only age-specific parameters are calculable from R_0 [27], given the mixing matrix described in the text (and legend to Figure 5). And we project the population independently.

Glossary. In our equations, upper case Roman and lower case Greek letters represent, respectively, immune states (Table A.1) and state-transition processes (Table A.2). The subscript N denotes normal-spectrum disease or naturally-acquired immunity, while M and A denote modified-spectrum disease and artificially-induced immunity.

Equations. Our unstructured model comprises 16 ordinary differential equations, one for each disease or immune state (boxes in Figure 1), and several identities that simplify these formulae. The differential equations describe temporal changes in the numbers in each by virtue of processes affecting their states (arrows in Figure 1).

$$\frac{dS}{dt} = \mu N + \kappa \{D_N + Q_N + \eta(D_M + Q_M)\} + \omega_1 R_N + \omega_2 R_A - [v_1 \varepsilon_1 + \lambda + \mu] S$$

$$\frac{dC_N}{dt} = \lambda S - [v_2 + \alpha_N + \mu] C_N$$

$$\frac{dC_M}{dt} = \lambda R - [v_6 \varepsilon_2 + \alpha_M + \mu] C_M$$

$$\frac{dE}{dt} = \alpha_N C_N - [v_3 \varepsilon_3 + \gamma + \mu] E$$

$$\frac{dH}{dt} = \gamma E - [\psi + \delta + \mu]H$$

$$\frac{dR_M}{dt} = \alpha_M C_M + \nu_2(1 - \varepsilon_2)C_N + \nu_3 \varepsilon_3 E - [\phi + \mu]R_M$$

$$\frac{dD_N}{dt} = \delta H - [\chi_N + \sigma_N + \kappa + \mu]D_N$$

$$\frac{dD_M}{dt} = \phi R_M - [\chi_M + \sigma_M + \eta \kappa + \mu]D_M$$

$$\frac{dQ_N}{dt} = \chi_N D_N + \psi H - [\theta + \kappa + \mu]Q_N$$

$$\frac{dQ_M}{dt} = \chi_M D_M - [\theta + \eta \kappa + \mu]Q_M$$

$$\frac{dR_A}{dt} = \omega_4 B_A - [\nu_5 \varepsilon_1 + \omega_2 + \lambda + \mu]R_A$$

$$\frac{dR_N}{dt} = \omega_3 B_N - [\nu_7 \varepsilon_1 + \omega_1 + \lambda + \mu]R_N$$

$$\frac{dB_A}{dt} = \omega_6 I_A - [\nu_4 \varepsilon_1 + \omega_4 + \lambda + \mu]B_A$$

$$\frac{dB_N}{dt} = \omega_5 I_N - [\nu_8 \varepsilon_1 + \omega_3 + \lambda + \mu]B_N$$

$$\frac{dI_A}{dt} = \nu_1 \varepsilon_1 S + \nu_4 \varepsilon_1 B_A + \nu_5 \varepsilon_1 R_A - [\omega_6 + \mu]I_A$$

$$\frac{dI_N}{dt} = \sigma_N D_N + \sigma_M D_M + \theta Q + \varepsilon_2 [v_2 C_N + v_6 C_M] + v_7 \varepsilon_1 R_N + v_8 \varepsilon_1 B_N + \lambda B - [\omega_5 + \mu] I_N$$

where $\lambda = \frac{\beta}{N} [D_N + \eta D_M + (1 - \rho_N) Q_N + (1 - \rho_M) \eta Q_M]$, and N is the total population.

Analyses. Population biologists define several interrelated quantities that facilitate comparing host-pathogen systems. Among them are R_0 , the average number of secondary infections induced by newly-infectious people on introduction to wholly-susceptible populations, S_c , the threshold number of susceptible people required for outbreaks, and p_c , the proportion of any population that must be immune to prevent an outbreak.

Neglecting the waning of immunity (whose temporal scale is much longer than other modeled phenomena) and all interventions (the quantities of interest are defined in their absence), we are left with the six equations representing disease in naïve populations. Omitting unnecessary terms, setting derivatives to zero, and solving the first, we obtain

$$D_N = \frac{N - S}{[\beta S / \mu N] - k}.$$

$D_N > 0$ implies that $N > S$ or $N/S > 1$. Solving the next four equations and substituting as needed to obtain an expression for S at equilibrium,

$$S^* = \frac{N(\alpha_N + \mu)(\gamma + \mu)(\delta + \mu)(\sigma_N + \kappa + \mu)}{\alpha_N \beta \gamma \delta}.$$

Substituting for S , we obtain an expression for the factor by which D_N would increase each generation in a wholly susceptible population,

$$R_0 = \frac{\alpha_N \beta \gamma \delta}{(\alpha_N + \mu)(\gamma + \mu)(\delta + \mu)(\sigma_N + \kappa + \mu)}.$$

The condition for control is $R(t) < 1$. When pre-exposure vaccination is the public health strategy, $R(t) = R_0[1 - p(t)]$, where $p(t)$ is population immunity. Defining p_c as the value of $p(t)$ at

which $R(t) = 1$ and rearranging, $p_c = 1 - (1/R_0)$. The surveillance-containment strategy involves post-exposure vaccination, by which disease may be averted or modified and infectiousness diminished, and the quarantine of dissemination-stage contacts, which permits prompt isolation of cases. Further analysis will appear separately (Feng et al. in preparation).

Generalizations. Our meta-population model has an additional parameter, m_{ij} , the extent to which susceptible members of sub-population i may be infected by infectious ones in sub-population j , where both indices range over all sub-populations. Thus,

$$\lambda_i = \sum_j m_{ij} \frac{\beta_j}{N_j} [D_N + \eta D_M + (1 - \rho_N) Q_N + (1 - \rho_M) \eta Q_M]_j, \text{ where } m_{ii} = 1 \text{ and } 0 \leq m_{ij} \leq 1.$$

Infection rates also vary with age, whose distribution differs among sub-populations, and time (Figure 2). The β_j are weighted by the relative rates at which individuals differing in age infect others, one margin of the generalized mixing matrix (Figure 5).

Initial conditions. Members of model communities are allocated among sub-populations of various sorts according to age-specific person-times working or in school, with the remainder at home or, in the city, downtown. Some adults work in hospitals, which also have patient populations. Within sub-populations, individuals are allocated among four or, if hospital staff, five states: $S = 0.6 * (1 - \text{proportion vaccinated preemptively}) * \text{population}$; $R_A = 0.3 * (1 - \text{proportion vaccinated preemptively}) * \text{population}$; $I_A = 0.1 * \text{proportion vaccinated preemptively} * \text{population}$; $C_N = 7$ people in the village, 350 in the town, and 7,000 in the city; and $C_M = 3$ people in the village, 150 in the town, and 3,000 in the city.

Parameters. Some rates are reciprocals of mean residence times in source states (e.g., disease progression, isolation). Others are calculable from proportions and periods via $dp/dt = r(1-p[t])$, where r is the rate corresponding to proportion p , given the appropriate period. Rearranging the solution, $r = -\ln(1-p)/\text{period}$.

The natural history parameters are reciprocals of mean residence times in source states: $\alpha_N=1/4$, $\alpha_M=1/6$, $\gamma=1/3$, $\phi=1/8$, $\delta=1/7$, $\sigma_N=1/10$, $\sigma_M=1/8$, $\theta=1/21$, $\omega_1=1/30$, $\omega_2=1/15$, $\omega_3=1/25$, $\omega_4=1/10$, $\omega_5=1/20$, and $\omega_6=1/5$ (with the omegas in years and other durations in days). Similarly, fertility and mortality, μ , are simply reciprocals of mean lifespan. But we calculate the incremental mortality caused by smallpox, κ , from 0.3 of normal spectrum cases succumbing during illness (via the expression in the preceding paragraph). The parameter $\eta=1/3$ describes the diminution in this probability resulting from residual immunity or vaccination soon enough post-exposure to ameliorate symptoms, but not avert disease. The remaining biological rate, β , may be calculated from some of the others given the expression for R_0 derived above.

Some interventions are constant. We assume some patients with modified-spectrum disease would stay home, for example, whereas all with normal-spectrum disease would be hospitalized, and that isolation at home is less effective than in hospital ($\rho_M=0.75$, $\rho_N=0.95$). Similarly, the release rate, θ , is the reciprocal of isolation, 3 weeks.

Other interventions vary with response strategy. We calculate the pre-exposure vaccination rates, v_1 , v_4 , v_5 , v_7 , v_8 , from 40 or 80% coverage attained during 7-day mass campaigns, for example. Similarly, we calculate the quarantine, ψ , isolation, χ_N and χ_M , and post-exposure vaccination rates, v_2 , v_3 , v_6 , from proportions of infected people under surveillance and isolated during their latent and infectious periods, respectively.

All vaccination rates are accompanied by efficacies of 0.97, 0.9/0.1, and 0.6 for, respectively, primary or re-vaccination, rescue/modification within 4 or 6 days of exposure, or modification within the next 3 days. The 4 and 6 days pertain to those without and with, respectively, residual immunity. The absence of primary failure among those vaccinated post-exposure seems unrealistic, but the discrepancy is small.

We calculate ψ , the rate at which 75% of the 90% of contacts that were found (i.e., 67.5%) are vaccinated and placed under observation (i.e., quarantined). They would be isolated immediately on their temperature spiking, as many as two days before the lesions in their throats ulcerated and they became infectious on day 13.45. In other words, traced contacts are isolated before becoming infectious.

Finally, we calculate χ_N and χ_M required for all and 0.75 of patients with normal- and modified-spectrum illness, respectively, to be isolated by day 18.5 (as the latent period is 14 days, this is 4.5 days after onset of infectiousness) and the remaining 0.25 modified-spectrum cases by day 21.5 (within 7.5 days of onset) in the first generation, and thereafter 0.9 of both within their 10 or 8 day infectious periods.

Table A.1. Immune or disease states.

Symbol	Description
S	Susceptible people
C_N, C_M	Immunologically-naïve or partially-immune people whose respiratory tracts have been colonized
E	Immunologically-naïve people within whose reticuloendothelial cells virus is replicating
H	Immunologically-naïve people who are experiencing the resultant viremia
R_M	People with residual immunity or post-exposure vaccination within whom virus is replicating or disseminating
D_N, D_M	People with normal or modified spectrum of disease
Q_N, Q_M	People with normal or modified spectrum of disease who are quarantined or isolated
I_N, I_A	People with naturally-acquired or artificially-induced immunity
B_N, B_A	People whose naturally-acquired or artificially-induced immunity is susceptible to immunologic boosting
R_N, R_A	People with residual naturally-acquired or artificially-induced immunity

Table A.2. State-transition processes (rates unless indicated).

Symbol	Description
v_3	Amelioration of symptoms by post-exposure vaccination
$\lambda, v_4, v_5, v_7, v_8$	Boosting of immunity by exposure or revaccination
λ	Infection
χ_N, χ_M	Isolation of patients with normal- and modified-spectrum disease
ρ_N, ρ_M	Proportions complying with infection-control procedures
α_N, α_M	Progression from colonization of epithelial cells to replication within reticuloendothelial cells
γ	Progression to viremic dissemination throughout hosts
φ, δ	Progression to clinical symptoms
v_1	Protection by vaccination
ψ	Quarantine of contacts
σ_N, σ_M	Recovery
μ, κ, η	Death via other causes, via smallpox, and reduction in immunity-modified relative to normal spectrum of disease
θ	Release from isolation
v_2, v_6	Rescue by vaccination
$\omega_1-\omega_6$	Waning of immunity
$\varepsilon_1, \varepsilon_2, \varepsilon_3$	Efficacy of primary or re-vaccination, rescue within 4 or 6 days of exposure, or modification within the next three days











