

Preventing Second-Generation Infections in a Smallpox Bioterror Attack

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Abstract: This article presents a new probabilistic model for the prevention of second-generation infections by different vaccination strategies in the event of a smallpox bioterror attack. The main results are independent of the reproductive number R_0 (the number of secondary infections transmitted per index infected individual) and population mixing patterns. General expressions are derived for the fraction of second-generation infections that can be prevented through vaccination, whereas specific results are obtained for traced and mass vaccination, respectively. Expressions for total outbreak size in controlled epidemics are also presented. The analysis highlights the importance of vaccination logistics in addition to beliefs and assumptions regarding smallpox epidemiology in evaluating alternative responses to a smallpox bioterror attack.

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In the event of a smallpox bioterror attack, barring preattack vaccination, the first infections that can be prevented are those transmitted from the initial attack victims to their contacts. Clearly, such second-generation infections are only a lower bound on the total number that would result from an attack; particularly if many people are infected at the outset (thus essentially ensuring that an epidemic will follow), second-generation infections could prove decisive in scaling the ultimate size of an outbreak under many vaccination schemes, and policies that allow the fewest second-generation infections are thus likely (although not guaranteed) to allow the fewest total infections as well. The number of preventable second-generation infections follows rather gen-

erally from the intersection of the epidemiology of smallpox progression and transmission with vaccination logistics. Of particular methodologic interest, using probability modeling, it is possible to derive results that are independent of the underlying reproductive rate of infection or R_0 (which is the number of secondary infections transmitted per index initially infected in an attack), as well as population mixing patterns. Results of such generality are of great importance, because in the event of a deliberate bioterror attack with weaponized smallpox, it is simply impossible to know what the ensuing R_0 value would equal or what the mixing pattern would be in the population attacked. Such an investigation is the subject of this report.

MODELING SMALLPOX DISEASE PROGRESSION AND TRANSMISSION

Historically, on infection with variola, individuals were observed to progress through a noninfectious incubation period and a prodrome of limited infectiousness relative to the period of high infectiousness that followed.¹ A 2-stage model, whereby someone infected at time 0 remains noninfectious for X units of time, and is then highly infectious for Y units of time, is therefore sufficient to capture the dynamics of smallpox incubation and contagion.

Let X be the sum of the incubation and prodromal periods, with probability density $f_X(x)$ derived from the estimates of Eichner and Dietz² (Fig. 1); henceforth, X will be referred to as the incubation time to simplify the presentation. Because symptomatic smallpox cases would be isolated once detected and diagnosed, under any reasonable response to a smallpox outbreak, the effective infectious period will be determined by the time required to recognize and isolate symptomatic cases, as opposed to the actual duration of infectiousness. The infectious period Y is therefore modeled as an exponential random variable with mean r^{-1} reflecting a constant detection and isolation rate per unit time^{3,4} (Fig. 2).

Assume that the number of persons initially infected in the attack comprises a negligible fraction of the total population, that those who are infected constitute a random sample from the population, and that infections directly transmitted by a randomly selected person infected in the attack occur at

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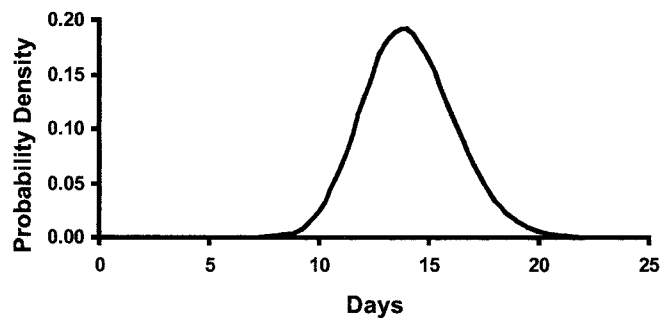


FIGURE 1. Incubation time density based on the sum of the incubation and prodromal periods, as estimated by Eichner and Dietz.²

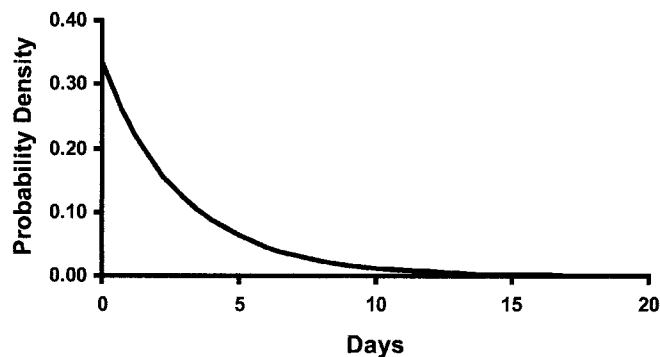


FIGURE 2. Infectious time density based on the assumption that index cases remain infectious until they are isolated, and that the detection and isolation of symptomatic cases occurs at a constant rate with a mean of 3 days, as assumed by Kaplan, Craft and Wein.^{3,4}

a constant rate during the infectious period.³⁻⁵ With these assumptions, the expected number of infections transmitted by an infected person from the time (s)he becomes infectious until (s)he is detected and isolated, R_0 , can be expressed as

$$R_0 = kE(Y) \tag{1}$$

where E denotes mathematical expectation and k is the transmission rate. Note that because those initially infected are assumed to constitute a negligible random sample of the total population, equation 1 is independent of population mixing patterns.

THE IMPACT OF CONTACT VACCINATION ON THE EFFECTIVE DURATION OF INDEX INFECTIOUS PERIODS

Suppose that a smallpox bioterror attack occurs at time 0. At some point the attack is detected by whatever means (earliest symptomatic cases, syndromic surveillance, or perhaps biosensors in the event of an aerosol attack), and members of the population will be vaccinated in accord with

some strategy. Focus on the contacts of those initially infected in the attack, and let V denote the time from the attack until a randomly selected contact is successfully vaccinated (with probability density $f_V(v)$). Different vaccination plans can be represented by different probability laws for V . Note that the density $f_V(v)$ need not be proper (that is, need not integrate to unity), because not all contact vaccination attempts will be successful (eg, the vaccine fails to confer protection, a contact cannot be located, or a contact refuses vaccination).

Now suppose that a contact is vaccinated before the end of his or her index's incubation time. From the contact's viewpoint, the effect is equivalent to erasing the index's entire infectious period (assuming that vaccination provides immediate protection against infection). Similarly, if contact vaccination occurs after the index has completed the incubation period but before the entire infectious period has passed, the effect on transmission is equivalent to shortening the index's infectious period to end at the time the contact is vaccinated. Contact vaccination after the index has completed both the incubation and infectious periods is too late to prevent second-generation infections.

Thus, assuming that effective vaccination provides immediate protection against infection for those successfully vaccinated, the effect of such vaccination from a contact's perspective is equivalent to reducing the duration of infectiousness for an index infected in the attack from Y to Y^* where

$$Y^* = \begin{cases} 0 & 0 < V \leq X \\ V - X & X < V \leq X + Y \\ Y & X + Y < V \end{cases} \tag{2}$$

The number of secondary infections transmitted per index thus declines from R_0 to $R_0^* = kE(Y^*)$ where

$$E(Y^*) = \int_{x=0}^{\infty} f_X(x) \int_{y=0}^{\infty} f_Y(y) \left\{ \int_{v=x}^{x+y} (v-x)f_V(v)dv + \int_{v=x+y}^{\infty} yf_V(v)dv \right\} dy dx \tag{3}$$

and as a consequence, the fraction of second-generation infections that can be prevented among the contacts, π , is given by

$$\pi = \frac{R_0 - R_0^*}{R_0} = 1 - \frac{E(Y^*)}{E(Y)} \tag{4}$$

Note that if contacts are quarantined for a sufficient period of time instead of vaccinated, the same effect would be

achieved with respect to preventing second-generation infections.

INCORPORATING A POSTEXPOSURE VACCINE-SENSITIVE WINDOW PERIOD

Thus far, the model represents vaccination as protective only if received successfully before exposure to smallpox, but many experts believe that postexposure vaccination is also protective if received within a few days after infection.^{1,6} To incorporate the impact of postexposure vaccination, define W as the duration of the vaccine sensitive window. From the perspective of a contact vaccinated at time V , the effect of the window is identical to shifting the physical time of vaccination W time units earlier in a model with no window. Thus, a contact successfully vaccinated at time V is effectively protected from time $V-W$ onward. Letting V^* be the effective time of vaccination on account of the window, we see that

$$V^* = \max(V - W, 0). \quad (5)$$

Denoting the probability density of the vaccine sensitive window by $f_W(w)$, the effective vaccination time V^* will equal 0 with probability

$$\Pr\{V^* = 0\} = \Pr\{V \leq W\} = \int_{w=0}^{\infty} \Pr\{V \leq w\} f_W(w) dw, \quad (6)$$

whereas the probability density for $V^* > 0$, $f_{V^*}(v^*)$, is given by

$$f_{V^*}(v^*) = \int_{w=0}^{\infty} f_V(v^* + w) f_W(w) dw. \quad (7)$$

The effect of the window period W on the mean effective duration of infectiousness $E(Y^*)$ is then captured by substituting $f_{V^*}(v^*)$ for $f_V(v)$ in equation 3. Consistent with past data and modeling,^{1,3,4,7} two models for the window period W will be considered: that W is exponentially distributed with mean μ^{-1} , or that W is a constant. In both cases, the mean duration of the window is set to 3 days in the examples here. Note that with the introduction of the window period, quarantine no longer achieves the same effect as vaccination in preventing second-generation infections, because there is no effective shifting of quarantine to an earlier point in time.

TRACED VACCINATION

Consider two different vaccination policies that have been discussed with respect to smallpox—traced (or “ring”) vaccination and mass vaccination.^{1–6} With traced vaccination, vaccination only occurs after those initially infected in the attack are recognized, isolated, and questioned to ascertain their contacts, and the contacts are traced and located. Let T denote the time required from the isolation of an index case

until the location and vaccination of a randomly selected contact (which might be never, because some contacts might not be found, but could also happen almost immediately, like in the case of household contacts). Then the time V at which a contact is vaccinated can be written as

$$V = X + Y + T \quad (8)$$

and thus the effective time of contact vaccination, V^* , follows from equation 5 as

$$V^* = \max(X + Y + T - W, 0). \quad (9)$$

Substituting directly into equation 2 yields

$$Y^* = \begin{cases} 0 & Y + T < W \\ Y + T - W & T < W \leq Y + T \\ Y & 0 < W \leq T \end{cases} \quad (10)$$

We assume that a fraction ϕ of contacts are both found and vaccinated,^{3–5} and that the time to locate a randomly chosen contact who is found is given by an exponentially distributed random variable L with mean ℓ^{-1} (reflecting a constant contact discovery rate), thus the (defective) density for T is given by

$$f_T(t) = \phi \ell e^{-\ell t} \text{ for } t > 0. \quad (11)$$

With these assumptions, the fraction of second-generation infections that can be prevented through traced vaccination when the window period W is exponentially distributed with mean μ^{-1} is equal to

$$\pi = 1 - \frac{E(Y^*)}{E(Y)} = \phi \frac{\ell}{\ell + \mu} \frac{r}{r + \mu}. \quad (12)$$

If instead the window period W is constant and equal to μ^{-1} , then the fraction of second-generation infections that can be prevented through traced vaccination is given by

$$\pi = \phi \frac{r(1 - e^{-\ell/\mu}) - \ell(1 - e^{-r/\mu})}{r - \ell}. \quad (13)$$

Note that if those contacts that are located are found instantaneously (that is, $\ell \rightarrow \infty$), then equations 12–13 are equivalent to the probability of winning the race to trace,^{3,4} that is, the probability of finding a contact within the window period after infection. Equations 12–13 also highlight the importance of the window period. Clearly, with traced vaccination, no second-generation infections can be prevented in the absence of a window, because physical vaccination of contacts can only begin at the end of the index’s infectious period. Letting $\mu \rightarrow \infty$ drives the window period to zero, and

equations 12–13 imply that no second generations are prevented as expected.

Figure 3 reports the percentage of second-generation infections that can be prevented through traced vaccination assuming an exponentially distributed window period (solid lines) or constant window (filled squares) with mean $\mu^{-1} = 3$ days, an effective infectious period (ie, time to recognize and isolate smallpox cases) exponentially distributed with mean $r^{-1} = 3$ days, and probability of locating contacts (ϕ) and mean time required to locate those found (ℓ^{-1}) as shown. Note that these results are independent of the value of the transmission rate k (and hence the value of R_0) and the specific mixing pattern involved (because the reduction from $E(Y)$ to $E(Y^*)$ applies to all contacts). The results for exponential versus constant window periods are quite similar if the mean time required to locate contacts equals or exceeds the mean window of 3 days. However, if contacts are located rapidly, a greater percentage of second-generation infections will be prevented if the window period is constant rather than exponentially distributed.

MASS VACCINATION

Mass vaccination works differently. Rather than waiting for each index to be identified before that index's contacts can be pursued, mass vaccination of the population ensues once the attack has been detected and clinic operations can begin. Even in the absence of biosensors or other early detection systems, mass vaccination would be triggered at the time the first cases are detected. Again, assuming recognition shortly after the incubation period has passed, if n persons were initially infected in the attack, mass vaccination could start shortly after $\min_{1 \leq i \leq n} \{X_i\}$ time units have passed

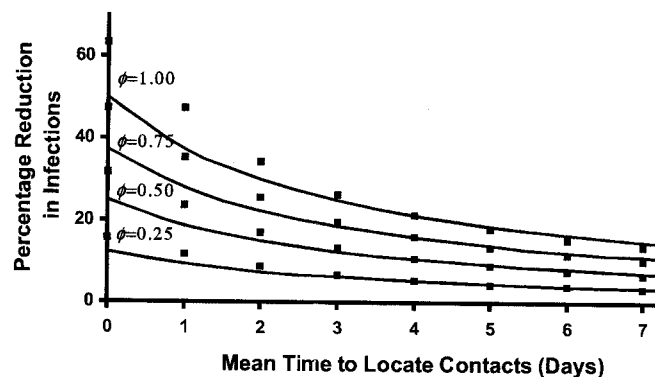


FIGURE 3. Percentage of second-generation infections prevented by traced vaccination, assuming the incubation and infectious period densities of Figures 1 and 2, postexposure vaccine-sensitive window period with mean 3 days (exponentially distributed shown as solid line; constant shown as filled squares), and vaccination of a fraction ϕ of contacts on average ℓ^{-1} days after index case isolation (equations 12 and 13).

(where X_i is the incubation time for the i^{th} person infected in the attack) if public health authorities are prepared for such an event. To allow for shorter delay (eg, detection through biosensors or syndromic surveillance) versus longer delay (eg, time to prepare clinics and “vaccinate the vaccinators”), assume that mass vaccination begins at some time τ postattack. Also, assume that the duration of time required to vaccinate the population (which depends on the number of available vaccinators, the speed with which they work, and the size of the population that must be vaccinated) is given by δ . Under these assumptions, a randomly selected member of the population who actually receives the vaccine is equally likely to be vaccinated at any time between τ and $\tau + \delta$. However, some people would not effectively receive the vaccine (as a result of screening for contraindications, refusal to participate in mass vaccination, or because they are vaccinated but the vaccine does not work and hence offers no protection), so assume that only a fraction ϕ of the population is actually vaccinated and protected from smallpox. Together these assumptions lead to a (defective) uniform distribution for V under mass vaccination, that is

$$f_V(v) = \begin{cases} \frac{\phi}{\delta} & \tau \leq v \leq \tau + \delta \\ 0 & \text{all other } v \end{cases} \quad (14)$$

This probability density is shown in Figure 4 for complete coverage ($\phi = 1$). Incorporating an exponentially distributed window period W leads, by equation 7, to the probability density for the effective vaccination time V^* shown in Figure 5 (assuming $\tau = \delta = 10$ days, and $\mu^{-1} = 3$ days). Figure 5 again demonstrates the importance of the

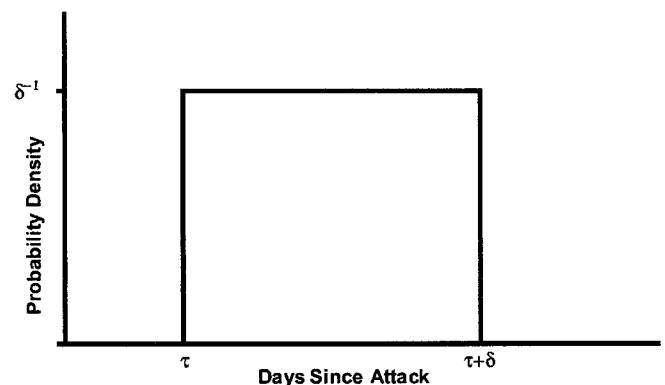


FIGURE 4. Probability density for the time of vaccination under a mass vaccination response that begins τ days after the attack, requires δ days to complete, and reaches 100% of the population.

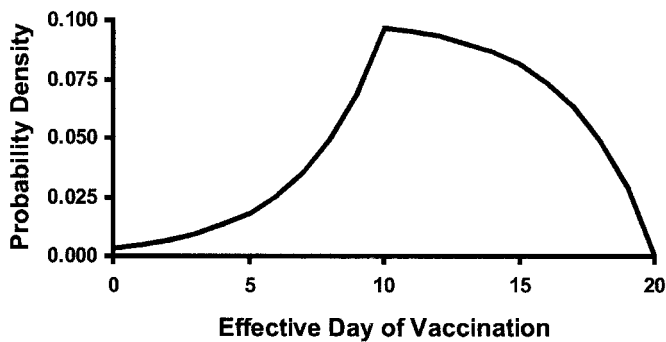


FIGURE 5. Probability density for the effective time of vaccination under the assumptions of Figure 4, coupled with the existence of an exponentially distributed postexposure vaccine-sensitive window period with a mean of 3 days.

window period, because the effective time of vaccination can occur much earlier than the physical time of vaccination. Indeed, for a constant window period of duration μ^{-1} , the density of the effective vaccination time V^* is found simply by shifting the uniform density of Figure 4 μ^{-1} time units to the left.

Substituting the density for V^* into equation 3 and using equation 4 enables computation of the fraction of second-generation infections that would be prevented by mass vaccination. Results are shown in Figure 6 for different mass vaccination start times τ and durations δ , assuming that 100% of the population is vaccinated ($\phi = 1$) and using the probability densities for the incubation and effective infectious periods shown in Figures 1 and 2. Examples using both exponential (solid lines) and constant (filled squares) window periods are displayed. As might be expected, the specific probability distribution assumed for the window period has

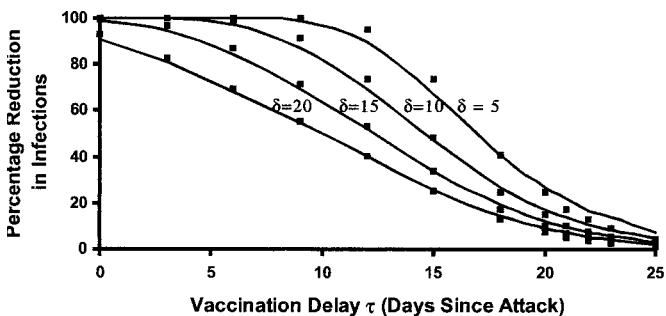


FIGURE 6. Percentage of second-generation infections prevented by mass vaccination assuming the incubation and infectious period densities of Figures 1 and 2 and effective vaccination time densities corresponding to exponential (solid line) or constant (filled squares) window periods for mass vaccination campaigns that begin τ days after the attack and require δ days to complete (for τ and δ values as shown) and reach 100% of the population (equation 4).

almost negligible impact on the results of mass vaccination. Note again that these results are independent of the underlying reproductive number R_0 and population mixing pattern. Also, although the results presented here apply only to the prevention of second-generation infections, it seems clear that providing mass vaccination achieves sufficient coverage and occurs rapidly relative to the smallpox intergeneration time, the great majority of infections in an outbreak controlled by mass vaccination would occur among initial attack victims or their second-generation contacts.^{3,4}

COMPARING TRACED AND MASS VACCINATION

Comparing the ability of traced versus mass vaccination to prevent second-generation infections, consider the following observation. Assume that all those infected in the attack pass through a noninfectious period with distribution shown in Figure 1, that they remain infectious until detected and isolated for a period with distribution shown in Figure 2, and that the vaccine-sensitive window period follows an exponential distribution with a mean of 3 days. It follows that traced vaccination can prevent at most 50% of those infections that would otherwise have been transmitted from those infected in the attack to their contacts (Fig. 3). This would be the situation if all contacts were found and vaccinated ($\phi = 1$) immediately ($\ell \rightarrow \infty$) after the isolation of the index case. Under the same epidemiologic assumptions, a mass vaccination of the entire population that begins on day $\tau = 15$ after the attack and lasts for $\delta = 10$ days would also prevent approximately 50% of all second-generation infections (Fig. 6). Starting from this rough equivalence, one can explore the conditions under which one policy or the other results in fewer second-generation infections.

Mass vaccination holds one obvious advantage over traced vaccination, which is the ability to vaccinate contacts before the end of their index's infectious period. To exploit this advantage, however, requires rapid recognition of an attack, and rapid and relatively complete vaccination of the population. As is clear from Figure 6, increasing either τ or δ reduces the effectiveness of mass vaccination even with complete coverage. Because the first cases observed in an attack will be those with the shortest incubation times, in the event of a large attack, those infected but not yet symptomatic at the time the first cases are seen will shortly enter an infectious state. Failure to act quickly once the first symptomatic smallpox cases have been observed thus allows such hidden attack victims to progress to contagion and infect others. The ability to respond rapidly depends on the government's state of readiness for such an attack. For example, if numerous first-responders must first be vaccinated themselves before clinics can begin operations, the time required to do so equates to inserting delay at the very time that asymptomatic infected attack victims are becoming infectious

and starting to infect their contacts. Vaccination coverage is also critical in a mass vaccination response. As vaccination coverage falls below 100%, second-generation infections prevented fall in proportion. For example, if only 50% of the population was vaccinated, a 10-day campaign starting on day 15 would prevent only 25% of second-generation infections.

The downside of mass vaccination is that so many persons must be vaccinated. Especially in the event of a small attack, many people would see such an overwhelming response as unnecessary, whereas some would fear that morbidity and mortality from vaccination could compete with or exceed that from smallpox,⁸ although the recent U.S. military experience somewhat mitigates this concern.⁹ Although tracing surely results in fewer persons receiving vaccine, with exponential windows, only half of all contacts can be vaccinated within the window period thought to protect against infection if contact tracing is both accurate ($\phi \rightarrow 1$) and efficient ($\ell \rightarrow \infty$). If the constant window provides a better model, the fraction of contacts that can be vaccinated in time improves to 63%. However, it should be clear that the ability of traced vaccination to prevent any second-generation infections depends crucially on the vaccine-sensitive window period, the existence of which has been questioned.¹⁰

SCALING EPIDEMICS BEYOND SECOND GENERATION INFECTIONS IN CONTROLLED OUTBREAKS

Second-generation infections scale the total size of an epidemic under the models considered here provided that the vaccination strategy adopted can ultimately control an outbreak. For example, if traced vaccination is successful in reducing the adjusted reproductive number R_0^* below unity, then the expected total number of infections that result would equal the sum of a geometric series,⁴ that is,

$$E_{TV} [\text{Total Infections}] = \frac{I_0}{1 - R_0^*} \quad (15)$$

where I_0 is the initial attack size. As detailed in section 4 of Kaplan et al.,⁴ for R_0^* to be reduced below unity, the original R_0 in the absence of vaccination (but with the isolation of symptomatic cases) must satisfy the threshold

$$R_0 < \frac{1}{1 - \pi} \quad (16)$$

Thus, for example, if under traced vaccination one could locate only 80% of all contacts ($\phi = .8$), the average time to locate those found contacts was 1 day ($\ell^{-1} = 1$), the average time to detect, diagnose, and isolate symptomatic cases was 3 days ($r^{-1} = 3$), and the window period was

constant with a mean of 3 days ($\mu^{-1} = 3$), then, through equation 13, an outbreak could be controlled through traced vaccination only if $R_0 < 1.6$. Under the conditions of this example, one should only feel confident in using traced vaccination if one were extremely certain that in fact R_0 would fall beneath 1.6 in the event of a bioterror attack.

Under rapid mass vaccination with complete coverage, the total number of infections will essentially equal the sum of the attack size and second-generation infections,⁴ that is

$$E_{MV} [\text{Total Infections}] = I_0(1 + R_0^*) \quad (17)$$

although this is clearly a lower bound when vaccination coverage is less than 100%. In the case of essentially complete vaccination coverage under both traced and mass vaccination (that is, $\phi \approx 1$), mass vaccination would clearly lead to fewer total cases if it also leads to fewer second-generation infections. The converse is not true, however; if traced vaccination leads to fewer second-generation infections, it could result in either a smaller or larger total number of infections when compared with mass vaccination, depending on the specific values of R_0^* that result for each policy.

BELIEFS AND ASSUMPTIONS IN SMALLPOX BIOTERROR PREPAREDNESS

The analysis and discussion here highlight the importance of beliefs regarding the nature of a bioterror attack and response logistics, in addition to smallpox epidemiology, in arguments surrounding appropriate smallpox response policies. Would an attack be small and controllable through traced vaccination or large enough to require mass vaccination? Would an attack be overt, in which case it could prove possible to respond immediately in a highly targeted fashion and obtain much better results, or covert and detected only from symptomatic cases as assumed in this article? If traced vaccination was used in response to an attack, would tracing prove accurate and efficient (as documented for a highly unusual natural outbreak that occurred in a Nigerian town)² or inaccurate (as suggested by a simulated large attack in a metropolitan area with population 10 million)?³ Could a rapid mass vaccination campaign be mounted soon enough after an attack occurs and with sufficiently high population coverage to avert most of the second-generation infections, but with care to avoid vaccine complications among those with contraindications? Having never faced a deliberate smallpox attack, there are no empiric answers to questions such as these. In particular, it is an *assumption* to pretend that parameters such as R_0 are known, even if estimated on the basis of past outbreaks, because such outbreaks could bear no resemblance to what could occur in a bioterror attack. Models

remain a valuable approach to helping us think about bioterror preparedness and response.

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