SPECIAL ARTICLE

A Model for a Smallpox-Vaccination Policy

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ABSTRACT

BACKGROUND

The new reality of biologic terrorism and warfare has ignited a debate about whether to reintroduce smallpox vaccination.

METHODS

We developed scenarios of smallpox attacks and built a stochastic model of outcomes under various control policies. We conducted a systematic literature review and estimated model parameters on the basis of European and North American outbreaks since World War II. We assessed the trade-offs between vaccine-related harms and benefits.

RESULTS

Nations or terrorists possessing a smallpox weapon could feasibly mount attacks that vary with respect to tactical complexity and target size, and patterns of spread can be expected to vary according to whether index patients are hospitalized early. For acceptable results, vaccination of contacts must be accompanied by effective isolation. Vaccination of contacts plus isolation is expected to result in 7 deaths (from vaccine or smallpox) in a scenario involving the release of variola virus from a laboratory, 19 deaths in a human-vector scenario, 300 deaths in a building-attack scenario, 2735 deaths in a scenario involving a low-impact airport attack, and 54,728 deaths in a scenario involving a high-impact airport attack. Immediate vaccination of the public in an attacked region would provide little additional benefit. Prior vaccination of health care workers, who would be disproportionately affected, would save lives in large local or national attacks but would cause 25 deaths nationally. Prior vaccination of health care workers and the public would save lives in a national attack but would cause 482 deaths nationally. The expected net benefits of vaccination depend on the assessed probability of an attack. Prior vaccination of health care workers would be expected to save lives if the probability of a building attack exceeded 0.22 or if the probability of a high-impact airport attack exceeded 0.002. The probability would have to be much higher to make vaccination of the public life-saving.

CONCLUSIONS

The analysis favors prior vaccination of health care workers unless the likelihood of any attack is very low, but it favors vaccination of the public only if the likelihood of a national attack or of multiple attacks is high.

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THE NEW REALITY OF BIOTERRORISM has led nations to reconsider smallpox vaccination, which has not been generally recommended since the elimination of the natural disease.[1,2] The current policy may be appropriate, since the risk of natural infection is negligible, the complications of vaccination can be severe, and measures instituted after an outbreak have been effective in controlling the spread of disease. Also, the risk of a smallpox attack is probably low. The known supplies of variola virus are limited, rogue states with the virus would probably fear "boomerang" effects or devastating retaliation, and terrorists are unlikely to be capable of successfully handling a lethal mammalian virus.[3] However, variola stocks could be hidden, coordinated lethal terrorist attacks have occurred, the taboo on biologic weapons has been broken, and a government facing military defeat might feel unconstrained in using a smallpox weapon.

To inform the debate over a smallpox-vaccination policy for the United States, we developed scenarios reflecting a range of threats and built a mathematical model that realistically describes policy effects on the basis of parameters that can be reliably estimated. We then analyzed the predicted outcomes, identifying the probability of attack at which the expected benefits of prior vaccination (i.e., vaccination before an attack has occurred) exceed the harms.

METHODS

SCENARIOS AND CONTROL STRATEGIES

We used public sources of data and expert opinion to develop detailed, realistic, and feasible scenarios for smallpox attacks, given access to variola, historical tendencies and methods of terrorists, and known domestic vulnerabilities.

We considered several control strategies, including vaccination of contacts of infected persons (household members, health care workers, and others) and isolation of patients, as well as pre- or post-attack vaccination of 60 percent of 290 million U.S. residents, 90 percent of 10.1 million health care workers, or both. We obtained the estimate for the number of health care workers by eliminating those in certain occupations (e.g., dispensing opticians) but not others (e.g., food-service workers and paramedics) from industry-specific employment estimates.[4] For vaccination of contacts, we assumed that 98 percent of health care worker contacts, 80 percent of other close contacts, and 50 percent of distant contacts would be identified.

LITERATURE REVIEW

We used multiple sources (the National Library of Medicine's LOCATORplus, Medline, EMBASE, BIOSIS, the Cochrane Collaboration, and the Defense Technical Information Center) to identify literature on smallpox vaccination, the natural history of smallpox, and the spread of outbreaks after World War II in Europe and North America. We chose this period because the social structure of Western countries and the health status of their populations were similar to those of the United States today, although persons were less mobile and were less likely to be immunocompromised. Population immunity may have been similar as well — vaccination was often refused and, except in the case of health care workers, not renewed.[5,6]

We identified 25 smaller and 20 larger outbreaks of smallpox after World War II; details were available for 7[7-10] and 18[7,10-16] of these outbreaks, respectively. Two of us independently abstracted the numbers of cases and deaths for each generation of cases; the distribution of cases among hospital, household, and distant contacts; the presentation and vaccination status of the index patient; the timing of recognition of disease; missed cases; and the use of control measures. Discrepancies were resolved by consensus.

We explored key relations between the reproductive rate (the average number of next-generation cases of smallpox arising from the current generation of cases) and the circumstances of each outbreak, using semiquantitative and qualitative analyses because the outbreaks were few and heterogeneous. The primary approach was repeated examination of tabular data, after relevant variables had been sorted.

We identified three patterns of spread: hospital, community, and mixed. We noted the distribution of reproductive rates before and after the institution of control measures (R_u and R_c, respectively). We used the median reproductive rate for the first generation from the 25 post–World War II outbreaks reported in detail to estimate the typical R_u for each type of outbreak, after adjusting for the underrepresentation of smaller outbreaks (to avoid overestimates) and for the low vaccination rate in the current health care workforce. We calculated initial estimates of R_c and the time required to control the outbreak from the observed rates of decline in numbers of cases in each generation in previ-

ous outbreaks. To estimate the effect of adding isolation as a control measure to the vaccination of contacts, which is never actually used alone, we compared the rates of decline in hospital outbreaks, where isolation is very effective, to rates that could theoretically be achieved from vaccination alone.[10,11,17-20]

We also derived key assumptions about the natural history of smallpox from the literature. We assumed that the mean times for the stages of smallpox would be as follows: incubation, 12.0 days; fever, 3.0 days; rash, 8.5 days; scab formation, 8.5 days; and recovery. We assumed that the death rate would be 0.225 among unvaccinated persons, 0.085 among persons vaccinated in the remote past, and 0.043 among the small number of persons infected after recent vaccination.[5,10,20-24] We assumed that vaccine would be protective in 80 percent of those immunized once, as would occur with vaccination of contacts, and that protection would be achieved in 95 percent of persons repeatedly vaccinated. We assumed the following rates of serious complications of the vaccine: vaccinia necrosum, 1.5 cases per 1 million doses of vaccine; eczema vaccinatum, 38.0 cases per 1 million; and encephalopathy, 12.5 cases per 1 million. We assumed that the mortality due to these complications, with the use of vaccinia immune globulin when indicated, would be 33 percent, 1 percent, and 15 percent, respectively.[5,25-34]

MATHEMATICAL MODELING

We constructed a stochastic event-driven model to predict the evolution of smallpox outbreaks in populations of interest (e.g., health care workers) under alternative control measures (see Supplementary Appendix 1, available with the full text of this article at http://www.nejm.org). In the model, the number of initially infected persons ranges from 2 to 100,000 according to the scenario and population immunity. Each person passes through the stages of smallpox, with the duration of each stage, the rate of death, and the rate of transmission determined probabilistically. The number and timing of new cases were simulated by multiplying a randomly selected value for infectiousness for each person by a second value chosen to reflect the daily rate of new infections, as determined by the relevant specified value for the reproductive rate. New cases were apportioned between health care workers and others according to historical patterns. Implementation of control measures a certain number of days (T) after the initial infection (usually 26) changed R_u to R_c, thereby altering the subsequent rates of infection. Prior vaccination also reduced the number of index cases by reducing the susceptibility of exposed persons.

We adjusted the model parameters R_u, R_c, and T to reproduce the historical hospital, mixed, and community outbreaks. We ran the model 10,000 times for each type of outbreak and achieved a close fit between the modeled and observed R_u. The values for R_u were then set at 15.4, 3.4, and 1.8 for the hospital, mixed, and community outbreaks, respectively. Prior vaccination of health care workers reduced the values to 7.23, 1.88, and 1.34, respectively; the addition of prior vaccination of the public reduced them to 3.85, 0.95, and 0.62. The values for R_c were set at 0.1, 0.1, and 0.1 with the use of contact vaccination and isolation but not prior vaccination to control hospital, mixed, and community outbreaks, respectively; at 0.065, 0.093, and 0.098 with the addition of prior vaccination of health care workers; and at 0.038, 0.044, and 0.045 with the addition of prior vaccination of the public.

To simulate outbreaks, we chose values for the parameters according to the appropriate response to the scenario and ran the model for a specified number of days or until the outbreak died out. We repeated this procedure 100 to 10,000 times for each response. For one sensitivity analysis, the interventions applied only to a metropolitan area of 4 million people (to reflect a local perspective); all other runs reflected a national perspective. In another analysis, we used values for R_u ranging from 1.1 to 30.0, values for R_c ranging from less than 0.1 to more than 0.9, and values for the time from the time of the first exposure to the recognition of the outbreak ranging from 14 to 48 days.

POLICY THRESHOLDS

A good decision about whether to institute a policy of prior vaccination is expected to yield more gains than losses — that is,

> Probability (outbreak) × (lives saved given an outbreak) > Probability (no outbreak) × (lives lost given no outbreak).

By rearrangement, the threshold for prior vaccination is as follows:

> Probability (outbreak) > (lives lost given no outbreak) ÷ [(lives lost given no outbreak) + (lives saved given an outbreak)].

The results of all analyses refer to the next five years, before immunizations would have to be renewed.

RESULTS

SCENARIOS

Given the availability of variola virus, smallpox attacks that vary in complexity, tactics, and target size are plausible. Since outbreaks and issues surrounding them will vary according to the circumstances, we developed six hypothetical scenarios. The scenarios incorporate the tendencies of terrorists to be members of loosely affiliated organizations but to work alone or, less commonly, in coordination and to target clinics, government offices, and airplanes or airports. The scenarios are a hoax (mailed monkeypox, which is not transmitted from person to person), laboratory release (a contaminated laboratory worker who infects his children), an attack involving human vectors (suicide attackers using mass transit), a building attack (virus sprayed into a vent), and airport attacks with a low or high impact (successful or very successful aerosolization of variola in terminals) (Table 1).

HISTORICAL OUTBREAKS

The post–World War II outbreaks of smallpox in Europe and North America were usually started by a single, atypical index case, but the pattern of spread varied. The highest initial transmission rates were in hospitals, where there was a median of 18 second-generation cases. However, these hospital outbreaks were limited to one or two generations because of the effectiveness of vaccination and in-hospital isolation. Community outbreaks were initially smaller, with fewer than two second-generation cases, but lasted for three to six generations, with longer outbreaks characterized by missed and distant cases. A number of outbreaks were of a mixed type. We classified the outbreaks in the attack scenarios as follows: no outbreak in the hoax scenario, a hospital outbreak in the laboratory-release scenario (with the affected children treated early in the hospital), a mixed outbreak in the building-attack scenario (with employees in the building, but not visitors, treated early in the hospital), and a community outbreak in the human-vector and airport-attack scenarios (with many persons unaware of their exposure).

Table 1. Scenarios of a Smallpox Attack.

Attack	Description
Hoax	An activist obtains monkeypox under false pretenses from a laboratory-supply company and mails it with a threatening letter to a clinic in a city of 500,000 people. The nation is alarmed when field tests are positive for poxvirus, and health officials elect to vaccinate 25 health care workers and patients at the clinic. Luckily, no infections occur.
Laboratory release	A Biosafety Level 4 hood malfunctions, probably because of sabotage, in a metropolitan area of 4 million people. A previously vaccinated laboratory technician contracts a mild case of modified smallpox, but his two children become quite ill and infect others.
Human vectors	Three persons residing in a U.S. border city of 4 million people infect themselves with variola smuggled into a neighboring country by separatist radicals from their homeland and then return to the United States. They become only moderately ill, since they were vaccinated in the 1970s. As in the 1947 outbreak in New York City, they use the mass transit system while ill, coming into contact with many persons, and each infects five other persons.
Building attack	A rogue nation produces variola major virus from samples stealthily acquired during the worldwide eradication campaign and makes a preparation available to terrorists for "testing." A U.S. resident, who obtained the agent during training abroad, aerosolizes the liquid and sprays it into the ventilation system of a federal office building in a city of about 6 million people. Hundreds of workers and visitors are heavily exposed; some 350 are infected.
Low- and high-impact airport attacks	In response to military actions threatening their regime, a nation's leaders activate 40 "sleeper" agents and instruct them to retrieve variola virus previously sent to the United States in a container ship. These agents go to the 10 largest U.S. airports during busy periods and distribute virus throughout the domestic terminals, using portable nebulizers. Up to 200,000 people are in the terminals during those times. In the low-impact case, they infect 5000 persons; in the high-impact case, they infect 100,000 persons.

MODEL OUTCOMES

In our model, a strategy of vaccinating and isolating contacts to control the outbreaks in the hoax, laboratory-release, human-vector, building-attack, and low- and high-impact airport attacks resulted in 0, 7, 19, 300, 2735, and 54,729 deaths, respectively (Table 2). These are net values — the result of disease and approximately 25, 1700, 4600, 75,000, 680,000, and 14 million vaccinations, respectively (Table 3). In all the scenarios, prior vaccination of the public caused approximately 500 deaths. Vaccination of the public in affected areas immediately after the outbreak provided little additional benefit, except in the largest attacks. Prior vaccination of health care workers provided a net benefit in the building and airport attacks, but prior vaccination of the public provided a benefit only in the airport attacks and greatly increased the number of deaths from vaccination.

Two additional results provide important insights. First, in the modeled scenarios, health care workers accounted for 19 percent of all infected persons in the airport attacks and for 57 percent of those infected in the laboratory-release scenario. Prior vaccination of health care workers greatly reduced the number of smallpox cases in this group (a median reduction of 85 percent as compared with contact vaccination and isolation of contacts alone), whereas adding vaccination of health care workers immediately after the outbreak to contact vaccination provided little additional benefit. Second, contact vaccination without isolation was less effective than the combination and failed to control an outbreak due to laboratory release of vaccinia or a building attack (data not shown).

TRADE-OFFS

In making decisions about prior vaccination, policymakers must balance the potential for saving lives against the likelihood of losing lives from complications of vaccination. For the laboratory-release and human-vector scenarios, the expected number of deaths from vaccination exceeds the number of lives saved, even if an attack is certain (Fig. 1). For the building and low- and high-impact airport attacks, prior vaccination of health care workers is

Table 2. Expected Deaths Due to Smallpox and Vaccination, According to the Attack Scenario and Control Strategy.

Control Strategy and Cause of Death*	Hoax	Laboratory Release	Human Vectors	Building Attack	Airport Attack	
					Low Impact	High Impact
			number of deaths			
Contact vaccination and isolation alone	0	7	19	300	2735	54,728
Smallpox	0	7	19	300	2733	54,691
Vaccination	0	0	0	0	2	37
Post-attack vaccination of health care workers	0	7	19	299	2757	54,698
Smallpox	0	7	18	298	2731	54,643
Vaccination	0	0	1	1	26	55
Post-attack vaccination of health care workers and public	0	13	26	296	3113	53,037
Smallpox	0	6	18	286	2631	52,541
Vaccination	0	7	8	10	482	496
Prior vaccination of health care workers	25	28	37	213	2218	43,901
Smallpox	0	3	12	188	2192	43,852
Vaccination	25	25	25	25	26	49
Prior vaccination of health care workers and post-attack vaccination of public	25	34	44	215	2596	42,813
Smallpox	0	3	11	181	2114	42,320
Vaccination	25	31	33	34	482	493
Prior vaccination of health care workers and public	482	484	484	535	1123	13,342
Smallpox	0	2	2	53	641	12,857
Vaccination	482	482	482	482	482	485

* Contact vaccination and isolation are part of all control strategies.

Table 3. Approximate Number of Vaccinations According to the Attack Scenario and Control Strategy.

Control Strategy*	Hoax	Laboratory Release	Human Vectors	Building Attack	Airport Attack	
					Low Impact	High Impact
	number of vaccinations (thousands)					
Contact vaccination and isolation alone	0	1.7	4.6	75	680	14,000
Post-attack vaccination of health care workers	0	130	160	250	9,700	20,000
Post-attack vaccination of health care workers and public	0	2,400	3,100	3,700	177,000	182,000
Prior vaccination of health care workers	9,100	9,100	9,100	9,200	9,600	18,000
Prior vaccination of health care workers and post-attack vaccination of public	9,100	11,000	12,000	13,000	177,000	181,000
Prior vaccination of health care workers and public	177,000	177,000	177,000	177,000	177,000	178,000

* Contact vaccination and isolation are part of all control strategies.

expected to save lives if the probabilities of attack are above 0.22, 0.05, and 0.002, respectively, and prior vaccination of the public is expected to save lives at probabilities above 0.47, 0.23, and 0.01, respectively.

SENSITIVITY ANALYSIS

Federal decision makers must balance the risks and benefits of prior vaccination for the nation as a whole, whereas local officials must balance the local benefits and risks. Because the expected number of vaccine complications within a given region is small, the thresholds for local policymakers are lower than those for national policymakers (Fig. 1B). Variations in model assumptions also affect the thresholds, which are most sensitive to the time that it takes to recognize the outbreak and the initial reproductive rate. For example, in the event of a building attack, early recognition makes prior vaccination unnecessary, but late recognition decreases the threshold for prior vaccination of health care workers to a 0.04 probability of an attack. High infectivity decreases this threshold to a similar level, whereas low initial infectivity increases it to 0.80. Changes in assumptions have smaller effects on thresholds for prior vaccination of the public.

MULTIPLE OUTBREAKS

Simultaneous consideration of multiple outbreaks lowers the threshold for prior vaccination, because the complications of vaccination occur only once. For example, the threshold for prior vaccination to provide protection against a low-impact airport attack decreases as the probability of a building attack increases (Fig. 2).

All five scenarios can be considered simultaneously with the use of the following equations:

$$D_R = 6.8P_L + 18.5P_P + 300.2P_B + 2735.1P_{AL} + 54729.5P_{AH} + 0,$$

$$D_H = 3.2P_L + 11.7P_P + 187.9P_B + 2192.8P_{AL} + 43875.9P_{AH} + 24.8, \text{ and}$$

$$D_P = 1.8P_L + 2.4P_P + 53.3P_B + 641.4P_{AL} + 12860.2P_{AH} + 481.6,$$

where D_R is the number of deaths expected with contact vaccination and isolation, D_H the number with prior vaccination of health care workers, and D_P the number with prior vaccination of health care workers and the public; P_L is the probability of a laboratory-release attack, P_V that of a human-vector attack, P_B that of a building attack, P_{AL} that of a low-impact airport attack, and P_{AH} that of a high-impact airport attack. For example, if the probability of the three local attacks is each 0.01 and the probability of the two national attacks is each 0.005, the expected number of deaths is 291 with contact vaccination and isolation, 257 with the addition of

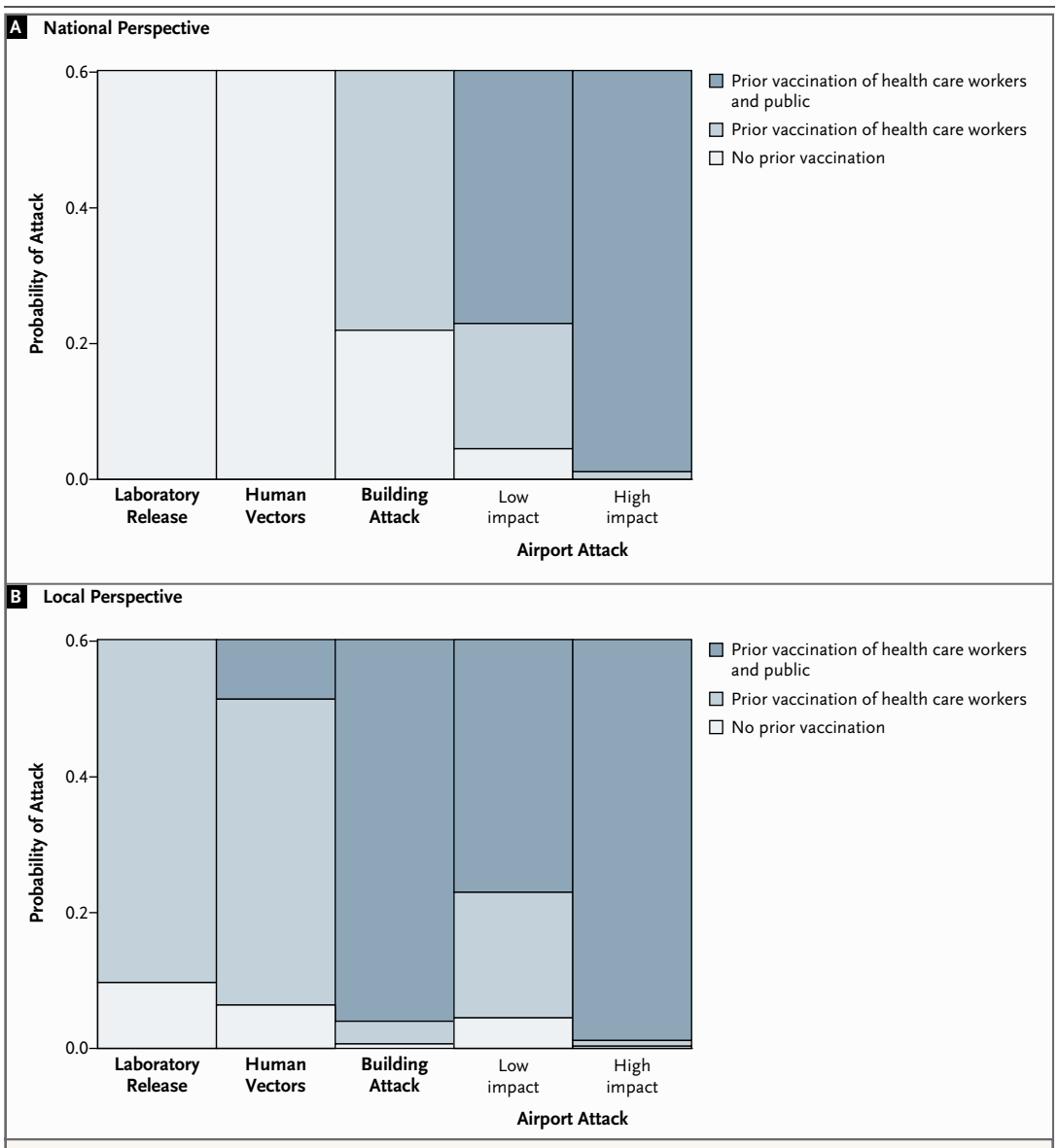

Figure 1. Instituting a Policy of Threshold for Prior Vaccination, According to the Probability of an Attack.

The policy goal is to minimize the number of deaths. The policies considered are no prior vaccination (i.e., vaccination before an attack has occurred), prior vaccination of health care workers only, and prior vaccination of health care workers and the public. The optimal policy for each attack scenario at each judged probability of attack is shown. For example, if federal policymakers consider the chance of a building attack to be about 10 percent, they should choose a policy of no prior vaccination, whereas if they consider the chance to be about 30 percent, they should choose a policy of prior vaccination of health care workers; prior vaccination of both health care workers and the public is never the optimal policy for protection from such an attack (Panel A). Local policymakers face a lower number of complications and have lower thresholds for prior vaccination. This is because, from a national perspective, vaccinating health care workers means vaccinating 3.5 percent of the entire U.S. population or about 10 million persons, whereas from a local perspective, it means vaccinating 3.5 percent of the local population, or about 140,000 persons in a city of 4 million (Panel B).

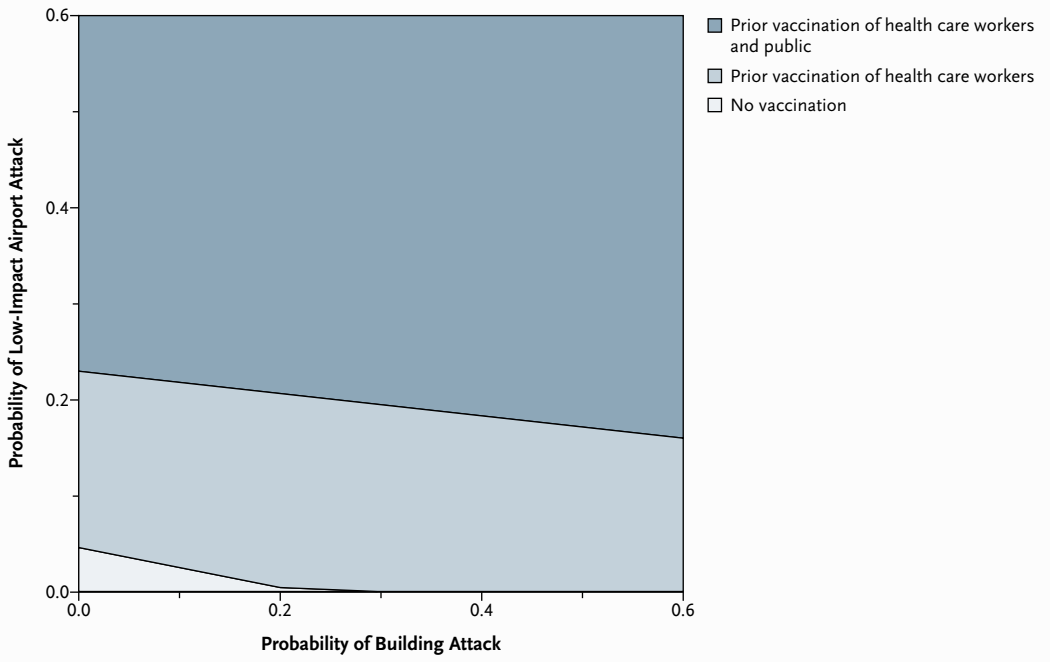

Figure 2. Threshold for Instituting a Policy of Prior Vaccination, According to the Probability of a Low-Impact Airport Attack or a Building Attack.

The policy goal is to minimize the number of deaths. The optimal policy for each attack scenario at each judged probability of attack is shown. The downward slope of each threshold for instituting a policy of prior vaccination indicates that the threshold decreases with joint consideration of multiple threats.

prior vaccination of health care workers, and 550 with the addition of prior vaccination of the public. Thus, prior vaccination of health care workers results in the fewest deaths and is the favored strategy.

DISCUSSION

We built a multipart policy model that considered a range of threats, predicted the numbers of deaths with the use of various measures to control the spread of disease, and illuminated the implications of various policies. The model supports increased preparedness and planning, since our analysis shows that early recognition, efficient delivery of vaccine, and effective isolation substantially decrease the burden of an attack. These measures pose operational challenges: an early response requires investment in education, surveillance, and operations, and effective isolation requires nearly complete case finding and denial of civil liberties.

Our analysis shows that the addition of mass vaccination to vaccination plus isolation of contacts after an outbreak provides little additional benefit. Others have directly compared these strategies. One analysis favors mass vaccination over vaccination of contacts for containment, but this result seems to arise in part from underestimation of the value of isolating symptomatic contacts and conflicts with the success of contact vaccination and isolation in controlling past outbreaks.[35] A model of a community of 2000 indicates that mass vaccination is more effective but less efficient than targeted vaccination and that increasing preexisting immunity with prior vaccination closes the efficacy gap.[36] However, neither model explicitly considers policymaking at a scale at which many deaths from vaccination are expected.

In our national policy model, prior vaccination of the public is expected to save lives on a net basis when the chance of a low- or high-impact airport attack exceeds 0.22 and 0.01, respectively. However, at the "break-even" thresholds, the policy implications of vaccination are not equivalent to the policy implications of forgoing vaccination. For example,

if the probability of a low-impact airport attack is at the threshold of 0.22, the expected number of deaths is about 600, with or without prior vaccination of the public. However, forgoing prior vaccination means risking higher losses in an attack for a 0.78 probability that there will be no attack and no deaths. In contrast, instituting prior vaccination ensures that losses will be lower, should an attack occur, but requires acceptance of the certainty of many vaccine-related deaths.

Prior vaccination of health care workers is expected to save lives at lower threshold probabilities of an attack and is expected to cause relatively few deaths, which will be concentrated among workers whose professional ethic includes acceptance of a risk of personal harm for the public good. In addition, prior vaccination sharply reduces the disproportionate burden of disease among health care workers in the event of an attack and, by eliminating a major route of exposure, helps protect their families — effects that should help maintain staffing levels at health care facilities. First responders who are not classified as health care workers but who are likely to come into contact with persons who have undiagnosed smallpox could be included in a vaccination program, or alternatively, a somewhat smaller population of health care workers considered to be at high risk might be identified. However, a policy of vaccinating a much larger group of workers will cause unnecessary deaths; vaccinating a much smaller group will be less effective in containing outbreaks, since patients will transmit disease before being referred to vaccinated providers.

Ultimately, the smallpox-vaccination policy must be based on judgments about the probability of an attack and on the recognition that the probability may be increased by military engagements abroad or decreased by preparedness at home. For this reason, we structured our analysis to identify thresholds above which prior immunization is justified. Our model suggests that prior vaccination of health care workers can be expected to save lives unless the risk of an attack is low. Encouraging vaccination of the public can be expected to save lives in coordinated multisite attacks but will cause substantial harm under most other circumstances.

In our judgment, the probability of a release of variola virus may exceed the thresholds for prior vaccination of health care workers. We endorse a policy of vaccinating all eligible health care workers and first responders before an attack. Local officials should welcome such a program, which should include appropriate monitoring and evaluation. In contrast, we cannot endorse a public vaccination campaign at this time, because the certainty of harm outweighs the small chance of a net benefit. Nonetheless, we acknowledge the distinction between this position and the argument for allowing access to vaccination on demand.

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