The Contribution of Residents Who Cooperate With Ring-Vaccination Measures Against Smallpox Epidemic

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ABSTRACT

Objectives: Establishing containment measures against the potential spread of the smallpox virus has become a major issue in the public health field since the 2001 anthrax attacks in the United States. The primary objective of the study was to investigate the relationship between the level of activity of public health agencies and the voluntary cooperation of residents with ring-vaccination measures against a smallpox epidemic.

Methods: A discrete-time, stochastic, individual-based model was used to simulate the spread of a smallpox epidemic that has become a more pressing topic due to 9/11 and to assess the effectiveness of and required resources for ring-vaccination measures in a closed community. In the simulation, we related sensitive tracing to the level of activity of the public health agency and strict isolation to the level of voluntary cooperation from residents.

Results: Our results suggest that early and intensive case detection and contact tracing by public health agencies can reduce the scale of an epidemic and use fewer total resources. In contrast, voluntary reporting by the traced contacts of symptom onset after vaccination had little impact on the scale of epidemic in our model. However, it reduced the total required resources, indicating that citizens' voluntary cooperation would contribute to reducing the burden on public health agencies.

Conclusions: We conclude that a combined effort on the part of public health agencies and residents in performing containment measures is essential to quickly ending a smallpox epidemic.

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Key Words: smallpox, bioterrorism, mathematical modeling

Establishing containment measures against the potential spread of the smallpox virus has come to be a major issue in the public health field after the 2001 anthrax attacks in the United States. Vaccination plays a key role in controlling the spread of smallpox because no other medical treatment has been proven to be effective at preventing infection or ameliorating the severity of the disease.[1] Three major types of vaccination policy can deal with the release of smallpox virus: mass vaccination, targeted vaccination, and ring vaccination.[2] A mass vaccination policy involves vaccinating susceptible individuals in an entire country. Although mass vaccination is effective in preventing the spread of a virus across extensive areas, a large number of medical personnel and a large stock of vaccines are needed. Furthermore, mass vaccination results in unnecessary vaccine-related adverse events.[2,3]

Targeted vaccination is similar to mass vaccination, but targets specific areas where smallpox cases exist. Targeted vaccination contains localized transmission effectively without involving the tracing of individuals who have come into contact with infectious cases. Some studies have assessed the effectiveness of targeted vaccination.[4-6] A ring vaccination policy requires tracing individuals who have come into contact with infectious cases and vaccinating them. Ring vaccination reduces total vaccine use and hence minimizes the incidence of vaccine-related adverse events.[2] Ring vaccination is more effective for the amount of resources required than mass vaccination and targeted vaccination.[7] Recent studies have recommended case isolation and ring vaccination instead of mass vaccination in the case of a small-scale epidemic.[8-11] Ring vaccination rather than targeted vaccination in the affected area would be optimal when transmissibility was low and the number of index cases was smaller.[5] In this study, we focus on the effectiveness of case isolation and ring vaccination against a smallpox outbreak.

In a ring-vaccination procedure, a public health agency identifies infectious cases and isolates them. Simultaneously, people who have come into close contact with identified cases are traced and vaccinated. Among the vaccinated contacts may be some already infected individuals who do not yet have overt symptoms because they are still in the noninfectious incubation period. If individuals are exposed more than three to four days before vaccination, they cannot obtain immunity to smallpox from the vaccination, and they will become infectious when they enter the rash period.[12-15] When they develop symptoms, identification and isolation are necessary, as with the other identified cases.

Monitoring of contacts after vaccination is required to immediately detect when symptoms develop. Monitoring can be mandatory or voluntary. Mandatory monitoring is conducted by the public health agency. Vaccinated people are mandatorily quarantined in a restricted area or in their homes and monitored. If any of them develop symptoms, they are rapidly and definitively identified. However, a large expenditure of human and material resources is required for a public health agency to quarantine and monitor vaccinated contacts in this way.

In contrast, voluntary monitoring is performed by the vaccinated contacts themselves. They remain in their homes after vaccination and voluntarily report to the public health agency if they develop symptoms. The smallpox response plan and guideline from the Centers for Disease Control and Prevention (CDC) recommends voluntary self-reporting by potentially infected individuals.[16] Voluntary monitoring by residents would conserve the resources of the public health agencies; however, effective self-reporting requires people to have a high level of conscience and cooperation with government and health officials. A previous study has suggested that the actions taken by nonprofessional individuals will have the greatest influence on the outcome of a bioterrorism event.[17] In addition to the level of activity of public health agencies, voluntary cooperation will be a determining factor in the effectiveness of containment measures.

In this study, we assessed the contributions of the level of activity of public health agencies and of residents' cooperation with ring-vaccination measures to the outcomes of a smallpox outbreak using a mathematical simulation.

METHODS

Target Population and Transmission Model

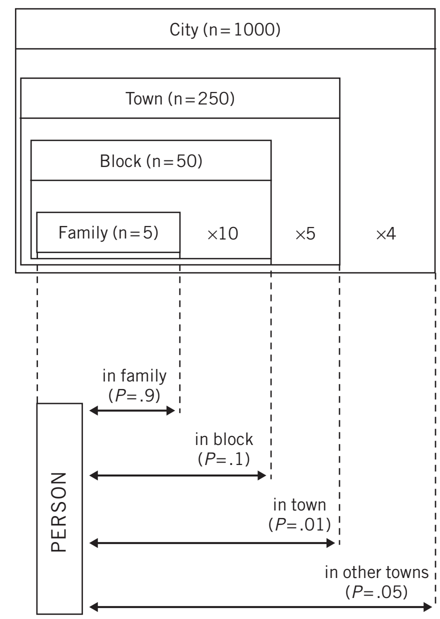
A discrete-time, stochastic, individual-based model was used to simulate the spread of smallpox virus and the effects of containment measures in a closed community. This type of simulation model has been employed in a similar previous study.[18] A community consisting of 1000 people was generated as a target population. The community was constructed using three nested structures corresponding to family, block, and town: five people forming a family (N = 5), 10 families forming a block (N = 50), five blocks forming a town (N = 250), and four neighborhoods forming a city of 1000 people (Figure 1).

Recent studies have suggested that contact patterns may influence the spread of epidemics.[19,20] It is more likely that people will have contact with family members or colleagues than with strangers living in other towns. We set the probability that a given individual had contact with another given individual in the course of a day according to the structural level of their relationship: whether they are in the same family ($P = .9$), the same block ($P = .1$), the same town ($P = .01$), or another town ($P = .005$). Using binomial distribution based on these contact probabilities, the other people with whom each susceptible person x had contact with on day i were specified. The number of infectious cases with whom a person x had contact with on day i was described as follows: the number in the same family, I_{fxi}; in the same block, I_{bxi}; in the same town, I_{txi}; and in other towns, I_{oxi}.

The probability that smallpox was transmitted to a susceptible person by the cases he or she came into contact within a day

FIGURE 1

Model of the Target Community With a 3-Layered Structure of Contact Patterns Between Individuals.



Contact patterns depend on the layered structure. The 4 contact patterns are contact within the same family, within the same block, within the same town, and with other towns. The daily-contact probability was determined for each contact pattern.

was estimated as follows. The mean household secondary attack rate (SAR) for susceptible people has historically been estimated to be 0.58 (the range varies from 0.44-0.88).[1] Based on the estimated household SAR and the duration of the infectious period, the daily transmission probability within a family, p_f, was described by the following equation:

$$SAR = 1 - (1 - p_f)^{\text{infectious period}}$$

The daily transmission probabilities within the same block, p_b; town, p_t, and other towns, p_o, were assumed to be 0.5, 0.25, and 0.1 times the estimated daily transmission probability within the family, p_f, respectively.

Using the number of infectious cases contacted in a day and the daily transmission probabilities, the probability that a susceptible person x was not infected by the cases he or she came into contact with on a given day i was calculated using the following equation:

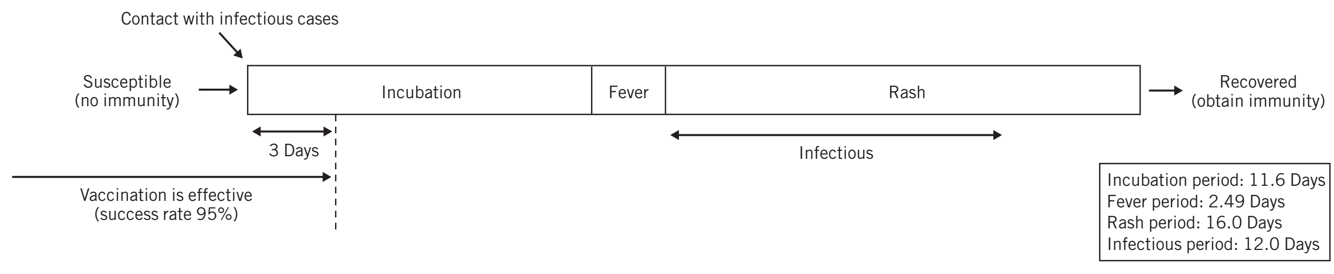
$$P_{xi}\ (\text{not infected}) = (1-p_f)^{I_{fxi}}\ (1-p_b)^{I_{bxi}}\ (1-p_t)^{I_{txi}}\ (1-p_o)^{I_{oxi}}$$

Thus, the probability that a susceptible person x became infected on day i was calculated as follows:

$$P_{xi}\ (\text{infected}) = 1 - P_{xi}\ (\text{not infected})$$
$$= (1-p_f)^{I_{fxi}}\ (1-p_b)^{I_{bxi}}\ (1-p_t)^{I_{txi}}\ (1-p_o)^{I_{oxi}}$$

FIGURE 2

The Natural History of Smallpox.



A susceptible person may become infected after coming into contact with an infectious case. After an incubation period, which lasts a mean of 11.6 days, the fever period starts. It lasts a mean of 2.49 days. Thereafter the rash period starts. It lasts a mean of 16.0 days. We assumed that the duration of the infectious period was 75% of the duration of the rash period.

Whether a susceptible person *x* was infected or not on day *i* was determined by a binomial random number generated using P_{xi} *(infected)*.

We simulated the spread of a smallpox epidemic and assessed the effectiveness of and required resources for ring-vaccination measures. It was assumed that none of the people in the community had immunity to smallpox. For the sake of simplicity, additional population characteristics such as gender or age distributions were not considered.

The Natural History of Smallpox and the Effects of Vaccination

Smallpox has three major phases, incubation, fever, and rash periods (Figure 2). The durations of these three phases were modeled using the mean values estimated by Eichner et al.[21] The authors calculated these parameters using historical data from an epidemic in 1967 in the town of Abakaliki, Nigeria. Infectivity was assumed to be negligible before the onset of the rash period, based on epidemiological evidence suggesting that transmission very rarely occurred before the first day that the rash appeared.[1] We assumed that cases were highly contagious from the day of onset of the rash until 75% of the way through the rash period.

Vaccination has been shown to have a 95% success rate in susceptible people.[12] Historical data have shown that vaccination within three to four days of exposure can protect individuals from smallpox, or at least reduce the severity of the infection.[12-15] Based on these data, vaccination within three days of exposure was assumed to result in immunity to smallpox. Successfully vaccinated individuals were assumed to obtain immunity immediately after vaccination. Vaccine-related adverse events were not considered.

Modeling Smallpox Spread and the Ring-Vaccination Measures

The following scenarios were modeled for the smallpox epidemic and the initiation of ring-vaccination measures. In all of the scenarios, an individual in the infectious period came into the community at day 0 and began to transmit the virus to other people. Some days later, the smallpox epidemic was detected, and the public health agency initiated the ring-vaccination measures.

A previous study has suggested that the effectiveness of ring vaccination would be increased by early intervention, sensitive tracing, and strict isolation.[8] In our simulation, these three factors were used to establish parameters for the measures taken. The first parameter, the starting date of intervention, was set to three values, 10, 30, and 50 days after the introduction of smallpox. We related sensitive tracing to the level of activity of the public health agency and strict isolation to the level of voluntary cooperation from residents. The level of activity of the public health agency was defined by the detection-probability parameter, ie, by how many cases and contacts they could detect. The level of voluntary cooperation was defined by the self-reporting-probability parameter, ie, by how many vaccinated contacts voluntarily reported to the public health agency at the onset of symptoms. The details of the latter two parameters are described in the following sections.

Detection Probability: Detection of Cases and Contacts by the Public Health Agency

When the epidemic was detected, the public health agency began to identify cases and contacts. Identified cases were immediately isolated and treated. At that point, they were no longer infectious. Identified contacts were vaccinated and then ordered to stay in their homes. The detection probability represented the percentage of cases and contacts that could be detected each day. A high-detection probability meant that the public health agency had enough resources for sensitive detection. The detection-probability parameter was set to three values, 50%, 75%, and 100%. Detection probabilities under 50% were not considered because almost all transmissions occurred between close contacts such as household members.[1,21] Implementing a fixed detection probability implicitly assumed that the public health agen-

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cies have the workforce to achieve that fixed level of detection probability, even at the peak of the epidemic.

Self-Reporting Probability: Vaccinated People Reporting Themselves

Individuals identified as contacts of infected cases were vaccinated and ordered to stay in their homes. Some of them developed symptoms because they had already been infected at the time of identification, and vaccination was unsuccessful. They should have reported to the public health agency at the onset of symptoms. If they did, the agency immediately isolated them, as with other identified cases. We defined the self-reporting probability as what percentage of the contacts identified as potential cases immediately reported to the public health agency when they developed overt symptoms.

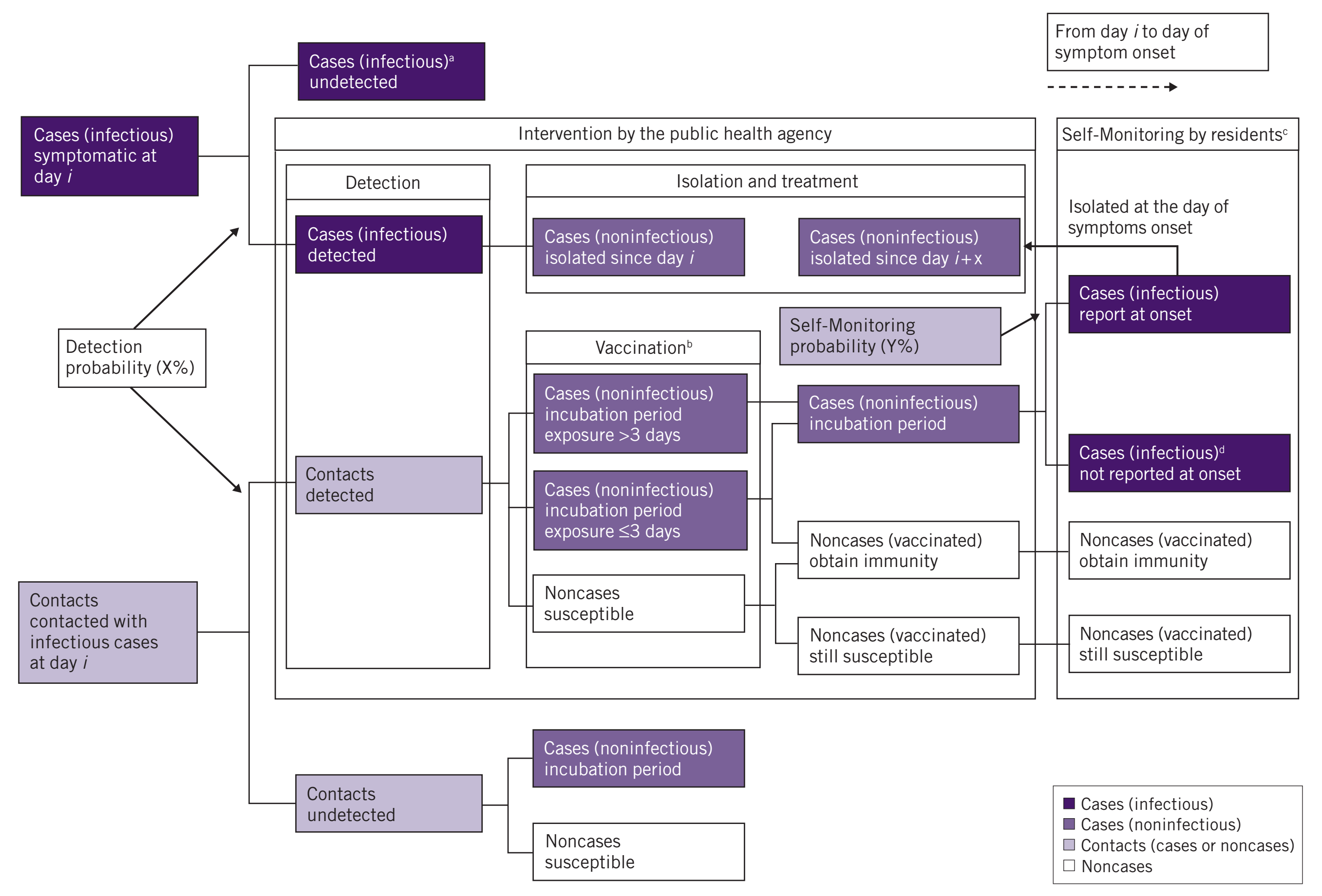
The self-reporting probability indicated the level of voluntary cooperation with ring-vaccination measures. A high self-reporting probability meant that residents were highly cooperative with the public health agency. The self-reporting probabilities were set to four values, 25%, 50%, 75%, and 100%.

Endpoints

The effectiveness of the containment measures modeled was evaluated using the cumulative number of infected cases within 200 days of the introduction of the smallpox virus. This number rep-

FIGURE 3

Procedures Involved in the Ring-Vaccination Measures at Day *i*.[a]



[a]Infectious cases that are as yet undetected at day *i* might be detected on or after day *n*+1 based on the detection probability, X%.
[b]Ninety-five percent of noncases and potential cases exposed within the past 3 days became immune to smallpox as a result of vaccination. The remainder did not obtain immunity (unsuccessful vaccination). As a result, 5% of individuals exposed within the 3 days before vaccination developed symptoms when they reached the potential fever period, and 5% of vaccinated noncases were still susceptible. All persons who were vaccinated more than 3 days after exposure developed symptoms when they reached the fever period.
[c]Self-reporting by vaccinated people began on the day of vaccination and lasted through the day of symptom onset. Y% of vaccinated cases reported themselves to the public health agency when they developed symptoms.
[d]Those who did not immediately report onset of symptoms themselves might be detected on other days.

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TABLE 1

Cumulative Numbers of Infected Cases at Day 200

Detection Probability, %		Intervention Starts at Day 10 Self-Reporting Probability, %				Intervention Starts at Day 30 Self-Reporting Probability, %				Intervention Starts at Day 50 Self-Reporting Probability, %			
		25	50	75	100	25	50	75	100	25	50	75	100
50	No. infected[a]	9.0	8.0	7.8	7.2	24.5	23.5	23.7	22.0	61.8	61.0	59.5	59.6
	Standardized ratio[b]	1.00	0.89	0.86	0.79	1.00	0.96	0.97	0.90	1.00	0.99	0.96	0.96
75	No. infected	4.8	4.7	4.7	4.4	18.1	17.6	17.2	17.0	52.2	51.9	51.3	51.2
	Standardized ratio	0.53	0.52	0.52	0.49	0.74	0.72	0.70	0.69	0.85	0.84	0.83	0.83
100	No. infected	3.6	3.6	3.5	3.3	15.3	15.1	15.1	14.8	48.0	47.7	47.4	47.3
	Standardized ratio	0.39	0.40	0.38	0.37	0.62	0.62	0.62	0.60	0.78	0.77	0.77	0.76

[a] Number infected: Cumulative number of infected cases on day 200 after the release of smallpox. Numbers were obtained by averaging the results of 200 simulations.
[b] Standardized ratio: Cumulative number of infected cases divided by the number of infected cases resulting from the worst self-reporting probability (25%) and the worst detection probability (50%) for the given intervention starting date.

resents the scale of the epidemic after implementation of ring-vaccination measures. Smaller numbers of infected cases mean more effective ring-vaccination measures. The simulation was continued until day 200 because the epidemic was over within 200 days after the introduction of smallpox in all of our scenarios.

Performing containment measures requires resources such as vaccine stockpiles, and limitations, such as the number of public health care workers, must also be taken into account. We estimated the amount of resources required for performing ring-vaccination measures by calculating the cumulative number of individuals who had been identified as cases or contacts by day 200. This number represented the scale of the ring-vaccination measures, indirectly indicating the burden on the public health agency in performing measures of that scale. The mean number and the maximum number of identified individuals per day within the intervention period were also calculated. We assumed that the intervention starts at the start date (day 10, day 30, or day 50) and ends at the day of the last detection of cases or contacts.

The trends in the numbers representing effectiveness and the level of resources required as a function of detection probability and self-reporting probability were described for each intervention starting date by a standardized ratio. The standardized ratios were calculated by dividing the cumulative number of infected cases (for effectiveness) and the cumulative number of identified cases and contacts (for required resources) resulting from each combination of parameters by the respective numbers resulting from the worst-case scenario (detection probability, 50%; self-reporting probability, 25%) for each intervention starting date. The cumulative numbers of infected cases and of identified cases and contacts at day 200 were obtained by averaging the results of 200 simulations. The procedures involved in the simulated ring-vaccination measures are depicted in Figure 3.

RESULTS

The effectiveness of the different combinations of measures, represented by the cumulative numbers of cases at day 200 under each scenario, is shown in Table 1. For each intervention's starting date, the maximum number of cases was observed for the lowest detection probability (50%) and self-reporting probability (25%). The minimum number of cases was observed with the highest detection probability (100%) and self-reporting probability (100%). Improving the detection probability decreased the cumulative number of infected cases.

When the detection probability was increased from 50% to 100% for scenarios in which the intervention began on day 10, the number of cases decreased by more than half. Even in scenarios in which the intervention began at day 50, the number of cases could be decreased by approximately 20% by increasing the detection probability from 50% to 100%. In contrast, the self-reporting probability did not affect the cumulative number of cases. Especially in comparing the scenarios with intensive detection, the standardized ratios were very similar between the four self-reporting levels. In the scenarios with the later intervention start dates, there was little reduction in the rate of cases when the self-reporting probability was increased.

Table 2 shows the resources required to perform ring-vaccination measures, represented by the cumulative number, daily mean number, and daily maximum number of identified cases and contacts within 200 days after the introduction of smallpox. For each intervention's starting date, the maximum numbers of cases and contacts identified were observed for the lowest detection probability (50%) and self-reporting probability (25%). The minimum numbers of cases and contacts identified were observed for the highest detection probability (100%) and self-reporting probability (100%). This trend was the same we observed with regard to the cumulative numbers of infected cases. The maximum number of people identified was 699.9 (of a population of 1000), in a scenario in which intervention began at day 50, the detection probability was 50%, and the self-reporting probability was 25%. Nearly 70% of the community had been in contact with the public health agency in the course of the 150 days between day 50 and day 200. Delaying the beginning of the intervention measures caused an increase in the cumulative number of cases and contacts identified.

TABLE 2

Numbers of Identified Cases and Contacts

Detection Probability, %		Intervention Starts at Day 10				Intervention Starts at Day 30				Intervention Starts at Day 50			
		Self-Reporting Probability, %				Self-Reporting Probability, %				Self-Reporting Probability, %			
		25	50	75	100	25	50	75	100	25	50	75	100
50	No. traced[a]	268.5	233.0	215.5	183.0	474.5	426.3	410.7	352.3	699.9	658.4	615.2	580.4
	Standardized ratio[b]	1.00	0.87	0.80	0.68	1.00	0.90	0.87	0.74	1.00	0.94	0.88	0.83
	No. detected per day[c]	3.9	3.9	3.7	3.6	6.0	5.9	5.9	5.8	9.1	9.1	9.4	9.2
	Max No. detected per day[d]	15.8	15.5	14.7	13.4	27.9	26.5	26.6	25.7	60.5	60.1	59.2	59.0
75	No. traced	207.8	184.9	171.5	145.8	426.9	382.5	348.3	318.6	674.8	640.6	596.7	556.8
	Standardized ratio	0.77	0.69	0.64	0.54	0.90	0.81	0.73	0.67	0.96	0.92	0.85	0.80
	No. detected per day	5.3	5.2	5.0	5.0	8.2	8.4	8.5	8.6	12.6	13.2	13.9	14.0
	Max No. detected per day	18.7	18.3	17.1	15.9	36.5	35.2	34.9	34.1	86.7	87.0	88.1	86.5
100	No. traced	183.3	169.9	152.3	130.5	389.5	365.1	332.5	295.7	677.1	641.0	596.6	544.6
	Standardized ratio	0.68	0.63	0.57	0.49	0.82	0.77	0.70	0.62	0.97	0.92	0.85	0.78
	No. detected per day	6.7	7.0	7.0	7.1	11.3	11.6	12.8	13.0	16.2	17.8	20.0	22.6
	Max No. detected per day		20.9	20.5	18.4	45.7	45.2	44.8	43.8	115.7	115.5	115.3	115.1

[a] Number traced: cumulative number of individuals identified as cases or contacts by the public health agency as of day 200. Numbers were obtained by averaging the results of 200 simulations.
[b] Standardized ratio: cumulative number of identified cases and contacts divided by the number of identified cases and contacts resulting from the worst self-reporting probability (25%) and the worst detection probability (50%) for the given intervention starting date.
[c] No. detected per day: mean number of individuals identified as cases or contacts per day.
[d] Maximum number detected per day: maximum number of individuals identified as cases or contacts per day.

For each value of the intervention's starting date and detection-probability parameters, the decrease in the number of people identified that resulted from increasing the self-reporting probability was greater than the corresponding decrease in the number of infected cases. When the intervention began at day 50 with the lowest detection probability (50%) and the self-reporting probability was increased to 100%, the number of infected cases decreased by only 4%. On the other hand, the total number of cases and contacts identified decreased by 17%, from 699.9 to 580.4. Intensive self-reporting did not affect the cumulative number of infected cases; however, it did reduce the cumulative number of cases and contacts identified.

DISCUSSION

We used a mathematical model to assess the contributions of the activity of public health agencies and of residents' voluntary cooperation with ring-vaccination measures. In comparing our simulations, we found that intensive procedures for identification of cases and their contacts reduced the scale of the epidemic and used fewer resources, especially when the intervention measures were initiated during the early phase of the epidemic. This finding suggests that public health agencies should enhance their use of routine surveillance systems for the early detection of smallpox epidemics and focus on detecting cases and their contacts to contain the spread of smallpox with fewer resources.

Self-reporting by identified contacts after vaccination did not affect the scale of the epidemic; however, it reduced the amount of resources required for intervention. This result can be explained as follows. A self-reporting case is quickly quarantined. Public health agencies require no further action for that person. In contrast, non-self-reporting cases will continue to come into contact with susceptible individuals. Most of these contacts would be detected and vaccinated within three days of exposure (vaccine-sensitive period). They are protected from smallpox using resources such as vaccines and public health workers. Consequently, self-reporting probability did not affect the cumulative number of cases, although it contributed to reduce the burden on public health agencies.

Voluntary cooperation in self-reporting would save human and material resources and reduce the burden on public health agencies; as a result, those agencies could focus their limited resources on detecting cases and tracing their contacts. Voluntary cooperation in self-reporting measures by residents themselves would contribute to the success of ring-vaccination measures in ending the epidemic quickly. In our simulation, self-reporting was especially effective when case- and contact-identification procedures were less intensive. This finding indicates that voluntary cooperation is likely to play a more important role when public health agencies have limited resources.

The CDC's smallpox response plan suggests that monitoring of individuals for the onset of symptoms could be conducted by the individuals themselves.[16] Our results confirmed that this policy is reasonable. Mandatory monitoring of vaccinated contacts by the public health agency would not necessarily be required for effectiveness because comprehensive (100%) monitoring did not significantly decrease the total number of cases. In addition, forced monitoring by public health agencies of all identified contacts after vaccination would be impractical because of the scope of resources required. In our model, even when detection and self-reporting began 10 days after the introduction of the smallpox

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virus and were both carried out at a rate of 100%, the public health agency had to identify 131.5 individuals, or 13.2% of the community, as cases or contacts.

Monitoring identified contacts for several days requires a large investment of human and material resources. We believe that it would be better to invest those resources in trying to achieve immediate detection of cases and contacts for early containment. Self-reporting would also be more plausible for social and ethical reasons. Potential cases and contacts taking an active part in intervention measures would prevent social panic and stigma against those individuals.[22] In addition, staying at home after vaccination would be more acceptable than being quarantined in a restricted area.

Residents' voluntary cooperation would not only contribute to monitoring contacts but also lead to a higher detection probability for cases and contacts. Meltzer et al have suggested that political will, public acceptance, and group discipline are all necessary for the successful enforcement of a quarantine.[10] Our results showed that the residents' voluntary cooperation with measures is still important even when monitoring of vaccinated contacts is not mandatory. Other recent studies have suggested that public awareness has a significant influence on the effectiveness of ring-vaccination measures accompanied by case isolation.[11,17,23]

Limitations

Our study had several limitations. First, the structure of the target community was simplified and does not fully represent a real social structure. For example, we specified that each household consisted of five people; however, in reality, family size is variable. Also, the chances of close contact at school or the workplace were not considered. Second, we made some assumptions regarding the probabilities of contact patterns. Third, other population characteristics, such as age and residual immunity, were not considered. However, we believe that the relationship reported here between the activity of public health agencies and residents' voluntary cooperation with containment measures would be consistent, regardless of these factors.

CONCLUSIONS

Public health agencies should concentrate on detecting cases and their contacts as soon as they become aware of a potential smallpox epidemic to achieve effective containment with fewer resources. Furthermore, residents' voluntary cooperation in self-reporting procedures would reduce the burden on public health agencies and consequently contribute to early containment of the epidemic. In our simulation, the combination of contributions by the public health agency and the community's residents to perform containment measures was essential in quickly ending the smallpox epidemic.

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