Stochastic Simulation of Bioterrorist Smallpox

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Executive Summary

Based on our baseline epidemiological parameter setting agreed upon by the working group, we come to the following general conclusions:

1. Surveillance and containment alone is sufficient to effectively contain even a large intentional smallpox release.

2. Given that surveillance and containment measures are taking place, there is relatively small marginal benefit in prevaccination of hospital workers or mass vaccination of the population after an outbreak begins.

3. In the absence of any interventions, the strongest controlling factor is simply people withdrawing to the home when they become ill.

4. The size of the epidemic is extremely sensitive to when cases withdraw to the home and go to the hospital. A two day further delay in this variable results in a 46-fold increase in the number of cases. This increase could also be interpreted as the effect of individuals being more infectious before pox symptoms appear

5. The number of smallpox deaths is sensitive to the proportion of cases that are hemorrhagic. If the proportion of cases that are hemorrhagic increases from 5% to 50%, the number of deaths has a five-fold increase.

1 Introduction

This report gives the results of modeling the control of intentional bioterrorist smallpox attacks according to parameters and scenarios determined by the Smallpox Modeling Working

Group, Secretary's Advisory Council on Public Health Preparedness. We model two attack scenarios:

1. 10 initial adult cases from separate households due to an aerosol release in a restaurant, population of 6,000 people.

2. 500 mixed (adult and children) initial cases from separate households due to an aerosol release in a movie-theater, in a population of 48,000 people.

Many of the parameters and modeling decisions made by the working group were based on the group's collective knowledge of smallpox epidemiology and on the information found in the comprehensive book by Fenner, *et al.* [1]. The simulation model we developed is a direct extension of our previous model [2].

2 Natural history, behavior and control measures

We have described the natural history in terms of three time lines: 1. disease symptoms and recognition, 2. infectiousness, and 3. behavior of infected people. We divide the appearance of cases into waves. The first wave involves the initial cases before at least one is recognized in the hospital as a smallpox case. The second wave is defined as those cases after smallpox has been recognized in the hospital.

2.1 Forms of smallpox

For those who have never been vaccinated, we assume that 95% would develop ordinary smallpox if infected, and the remaining 5% would develop hemorrhagic smallpox if infected

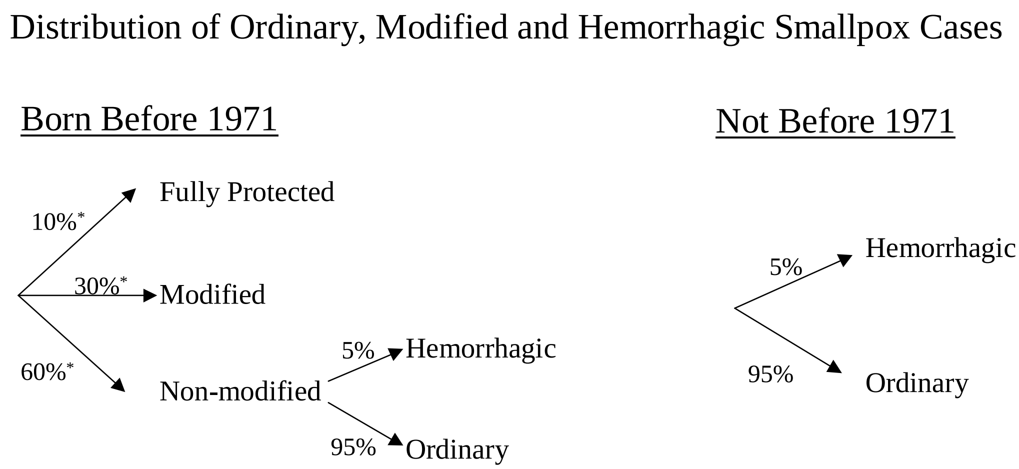

Figure 1: *Branching diagram for different forms of smallpox.*

(see Figure 1). For those people over 30 years old who were vaccinated before 1972, we assume that 10% would be fully protected against smallpox infection, 30% would develop a less-severe modified case of smallpox, and the remaining 60% would develop non-modified smallpox. Among that 60%, 95% of the cases would be ordinary smallpox and 5% hemorrhagic smallpox.

2.2 Ordinary smallpox

Figure 2 shows the distribution of the infectious period, symptomatic events, infectiousness and behavior of infected people with ordinary smallpox. The incubation period distribution varies from 7 to 17 days with a mean of 11.48 days. The incubation period ends with the onset of fever, followed by a macular rash on the 4th day of fever. This is followed by the onset of papules and then vesicles as shown in Figure 2. During the first wave, smallpox cases are not recognized until the onset of vesicles, seven days after the onset of fever. During subsequent waves, smallpox cases are recognized at the onset of papules, six days after the onset of fever. Thirty percent of the cases die 7 - 14 days after the onset of fever.

People have varying degrees of infectiousness over the course of their infectious period as shown in Figure 2. The basic per contact transmission probability x, is set for the first day of fever, it is increased to 2x, for the second day of fever, 4x at the onset of rash, *etc.*, with an upper limit of 1. In terms of behavior, Figure 2 shows that 47.5% of the cases withdraw to the home at the end of the first day of fever, and 47.5% go to the hospital at that time. The remaining 5% continue to circulate but go to the hospital at the end of the third day of fever. We assume that 30% of unvaccinated people with ordinary smallpox will die.

2.3 Modified smallpox

Figure 3 shows the distribution of the infectious period, symptomatic events, infectiousness and behavior of infected people with modified smallpox. The incubation period distribution varies from 7 to 17 days with a mean of 11.48 days. Infected people are assumed not to have symptoms during the incubation period. The incubation period ends with the onset

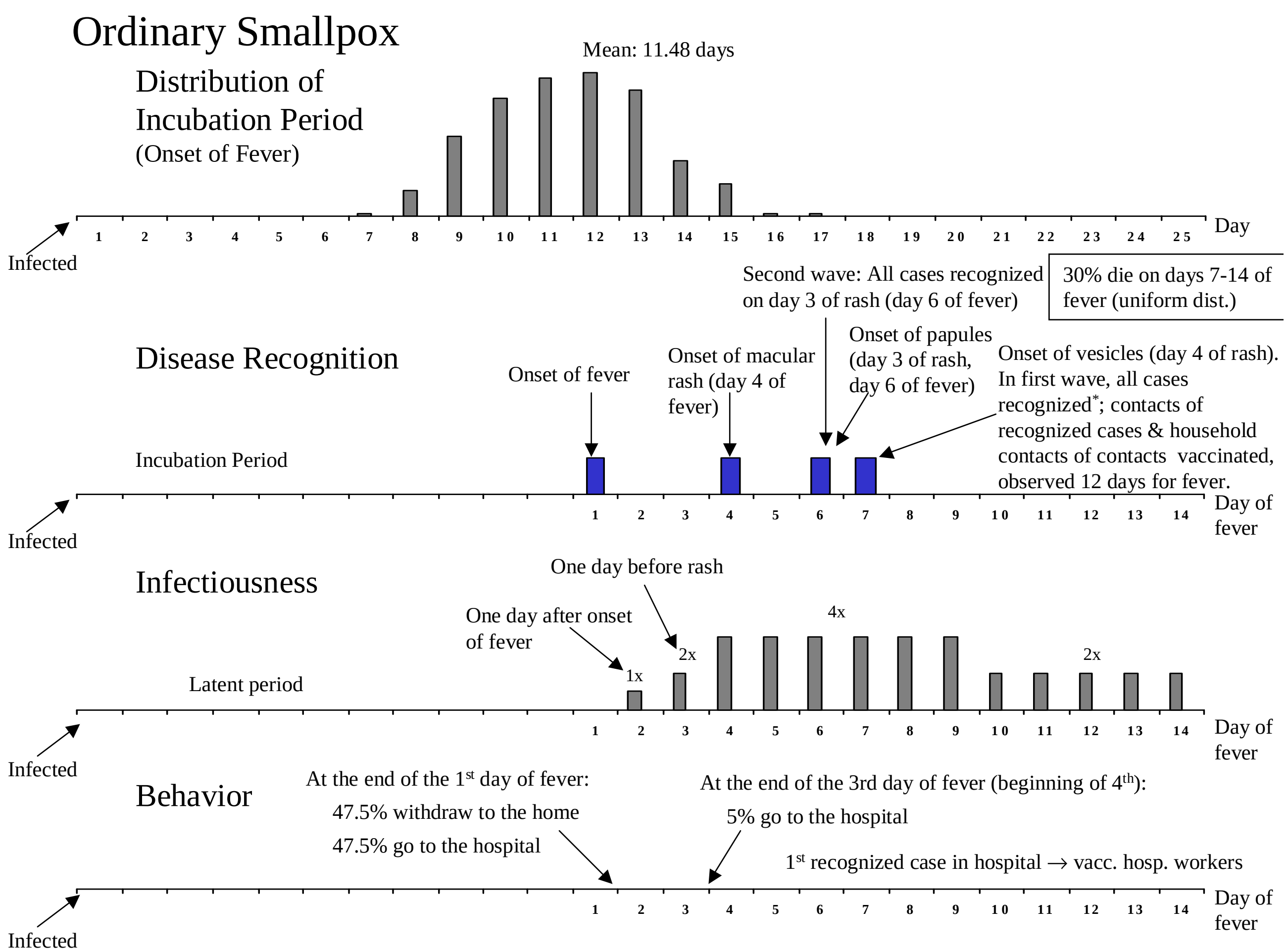

Figure 2: *Natural history of ordinary smallpox.*

of fever, followed by a macular rash on the 4th day of fever. This is followed by the onset of papules and then vesicles as shown in Figure 3. During the first wave, smallpox cases are not recognized until the onset of vesicles, seven days after the onset of fever. During subsequent waves, smallpox cases are recognized at the onset of papules, six days after the onset of fever. Thirty percent of the cases die 7 - 14 days after the onset of fever.

The infectiousness of people with modified smallpox is 33% of that for people with ordinary smallpox as shown in Figure 3. In terms of behavior, Figure 3 shows that 47.5% of the cases withdraw to the home at the end of the first day of fever, and 47.5% go to the hospital at that time. The remaining 5% continue to circulate but go to the hospital at the end of the third day of fever. We assume that 10% of unvaccinated people with modified smallpox will die.

2.4 Hemorrhagic smallpox

Figure 4 shows the distribution of the infectious period, symptomatic events, infectiousness and behavior of infected people with hemorrhagic smallpox. The incubation period distribution varies from 7 to 15 days with a mean of 10.24 days. Infected people begin internal bleeding four days after the onset of fever, and die on the seventh day after the onset of bleeding. During the first wave of cases, 50% of hemorrhagic smallpox cases are not recognized and 50% are recognized on the fifth day of fever. During the second wave of cases, all hemorrhagic cases are recognized in the hospital on the fourth day of fever.

People with hemorrhagic smallpox are more infectious than are those with ordinary smallpox, as shown in Figure 4. The transmission probability is set to 5x, for the first day of fever,

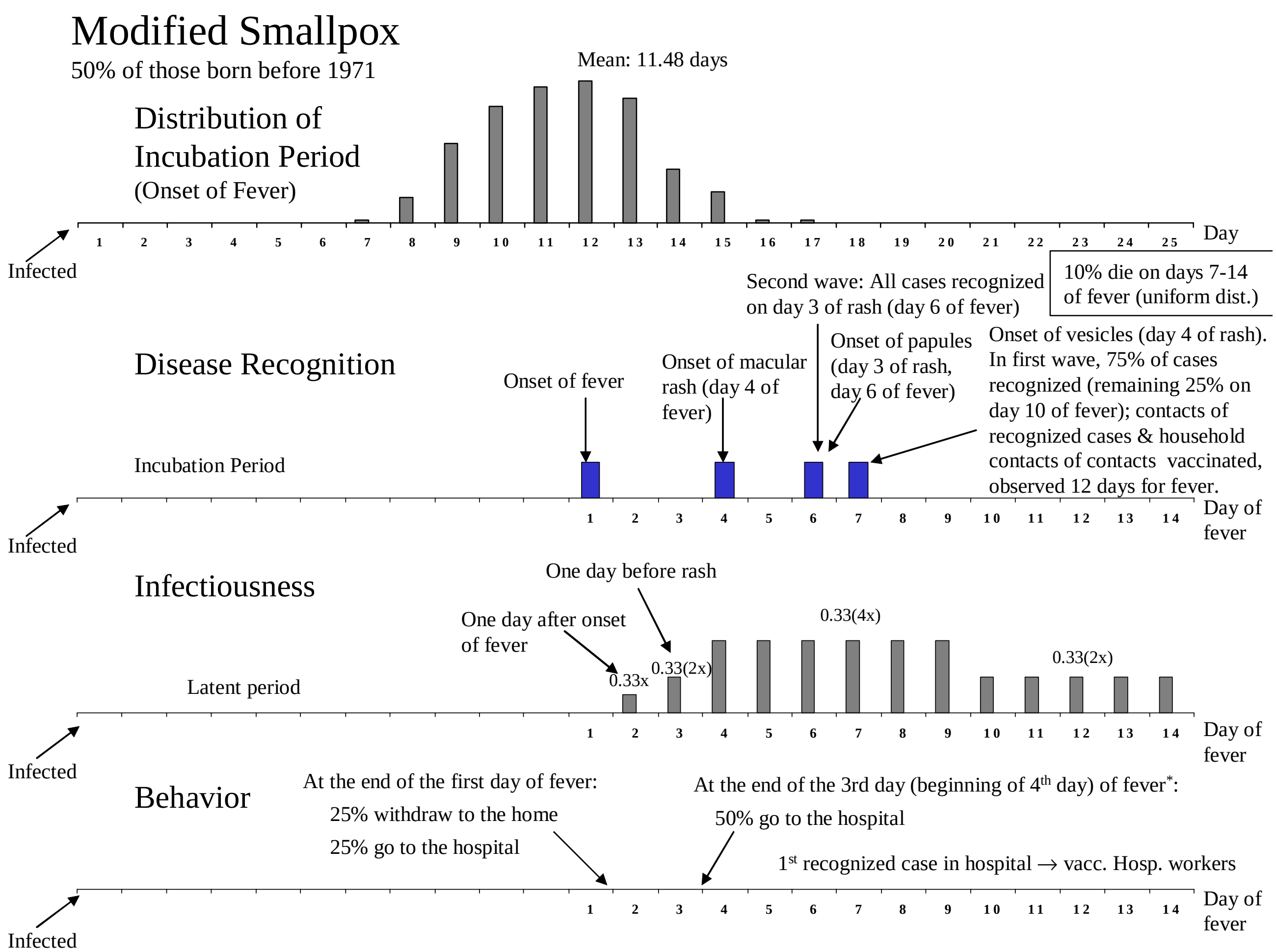

Figure 3: *Natural history of modified smallpox.*

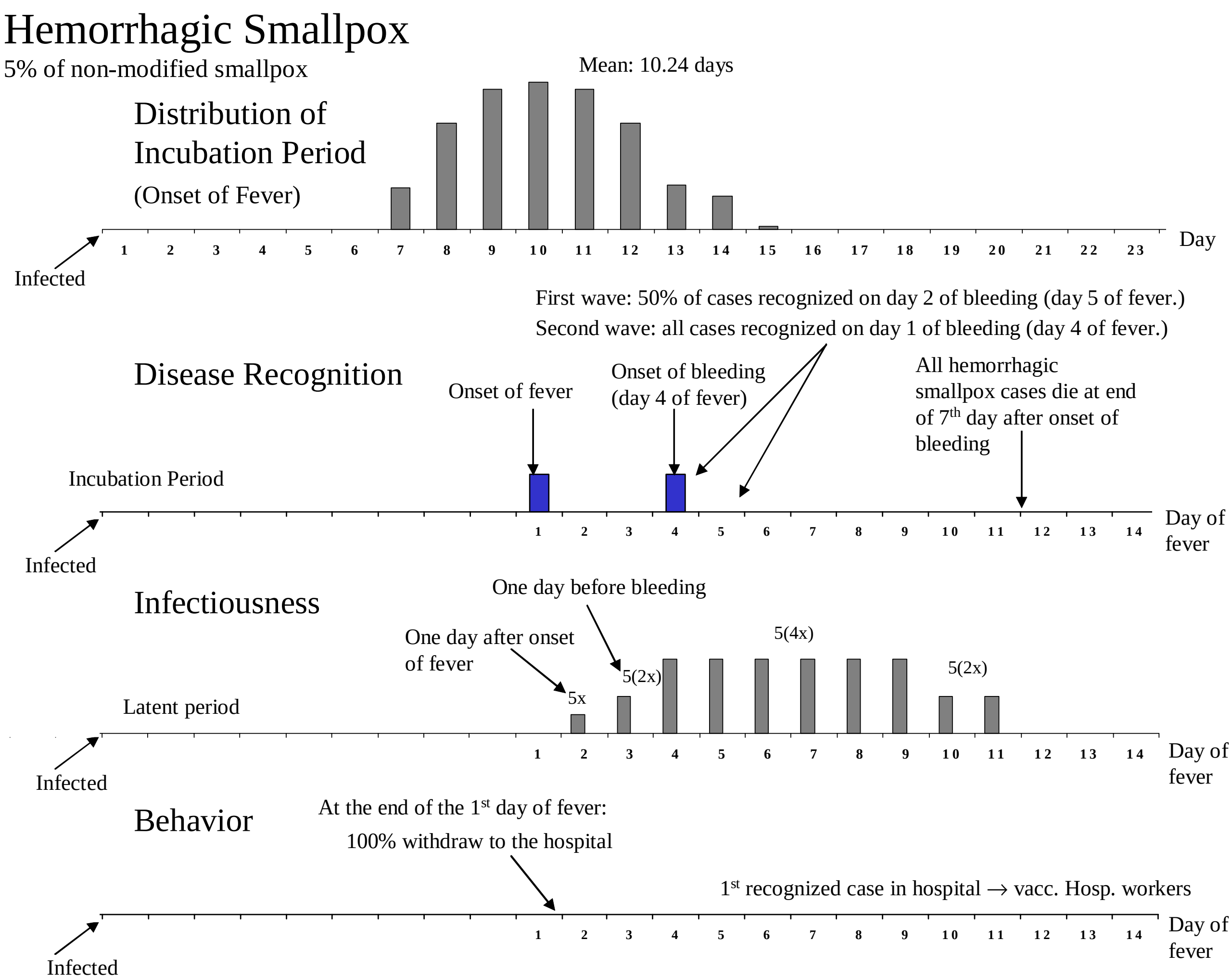

Figure 4: *Natural history of hemorrhagic smallpox.*

it is increased to $10x$, for the second day of fever, $20x$ at the onset bleeding, *etc.*, with an upper bound of 1. We assume that 100% of unvaccinated people with hemorrhagic smallpox will die.

3 Population Structure

The model population is based on a network of structured subpopulations of 2,000 people mixing in households, neighborhood clusters of households, neighborhoods, preschool groups, schools and community at large. The subpopulations are connected through adult workplaces, children through high schools, and the whole population through hospitals. The hospital has a total of 686 workers, 133 of which can make close contact with smallpox cases. Each person in the population may visit the hospital with probability 0.001 each day. They mix with all infected people in the hospital before smallpox is recognized, but only with unisolated circulating cases after smallpox is recognized. Figure 5 shows a schematic of the configuration of a subpopulation of 2,000 people. Figure 6 shows how the three subpopulations are connected through workplaces and a hospital to form the 6,000 person population. Figure 7 shows how a population of 48,000 is formed by connecting the eight populations of size 6,000. The basic person-to-person daily transmission probabilities (see the definition of x in *Section* 2) are highest in households, lower in neighborhood clusters, and still lower in the other mixing groups. The mixing groups sizes and transmission probabilities used are given in Tables 1-4. For example, from Table 1, if an unvaccinated child is infected with ordinary smallpox, the probability that this child would infect an unvaccinated adult in the household, one day after the onset of fever would be 0.0124. On the second day of fever, this

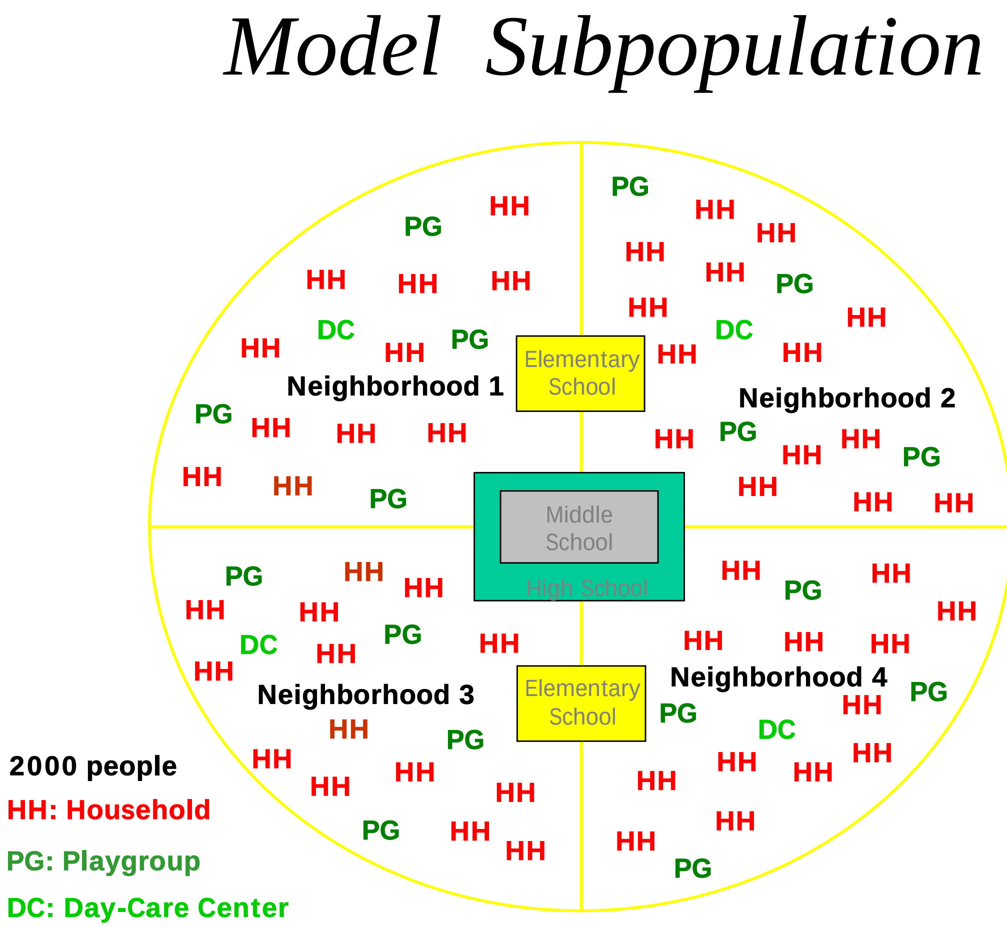

Figure 5: *Model subpopulation of 2,000 people distributed into households, neighorhoods, playgroups, day-care centers and schools. Groups of four households form neighborhood clusters.*

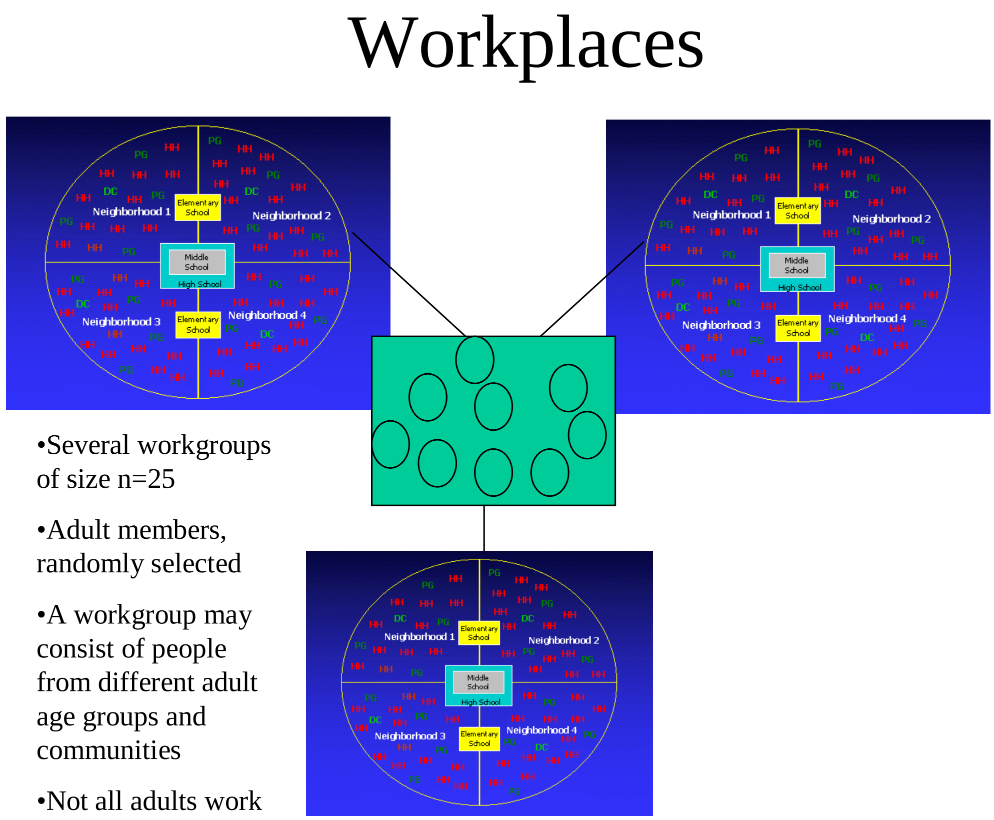

Figure 6: *Network created by workplaces. All 6,000 people are also connected through a single hospital. The high schools connect some of the children among the three subpopulations.*

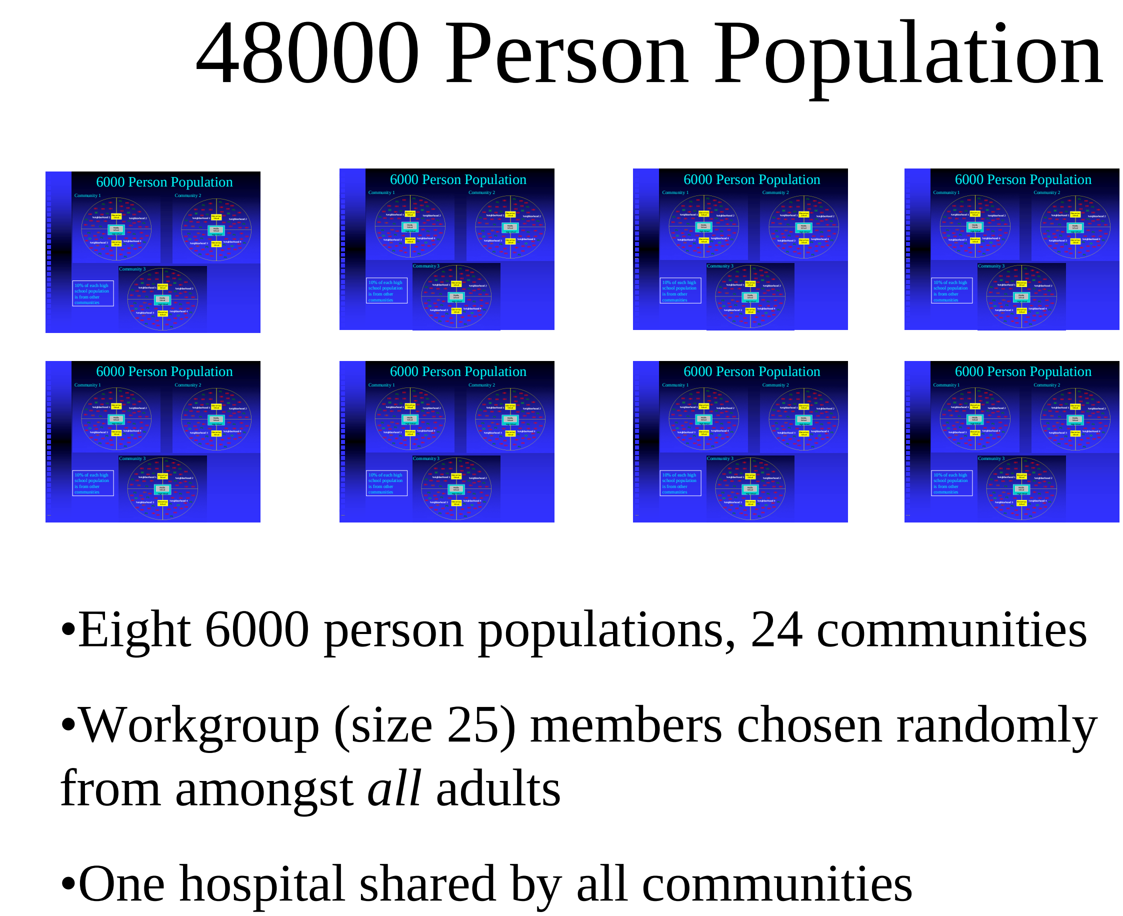

Figure 7: *Large population connected through workplaces and a hospital.*

probability would increase to 0.0248, and it would be 0.0372 for days three through eight.

Table 1: Transmission probabilities, *x*: Families and Household Clusters

Group	Aver. Size	Child-child	Adult-child	Child-adult	Adult-adult
Family	2.5	0.0352	0.0124	0.0124	0.0151
House cluster	10.1	0.03	0.01	0.01	0.01

Table 2: Transmission Probabilities, *x*: neighborhoods and Communities

Group	Size	Preschool	School	Adult
Neigh.	500	0.000041	0.000046	0.000135
Com.	2000	0.000010	0.000011	0.000033

Table 3: Transmission Probabilities: Preschools, Schools and Workplaces

Group	Size	x
Play Groups	3.4	0.030
Daycare	15.8	0.020
School		
Elementary	77.8	0.010
Middle	145.3	0.008
High	113.7	0.008
Workplace	25.0	0.010

Table 4: Transmission Probabilities: Hospital

Section	Size	x, Worker to worker	x, patient to others
Smallpox patients	133	0.002	0.0001
No smallpox patients	553	0.0005	-

Each day, for each susceptible, the probability of becoming infected is calculated based on his vaccination status, who is infectious in his contact groups and their vaccination status, as well as the group-specific transmission probabilities. As an example, consider the simplest case that no one is vaccinated. An elementary school child is exposed to the number of child and adult infectives in his household, I_{hc} and I_{ha}, his household cluster, I_{ncc} and I_{nca} his school I_{es}, his neighborhood I_n, and the community I_c with corresponding transmission probabilities for each contact of p_{hcc} (child to child), p_{hac} (adult to child), p_{es}, p_{ns}, and p_{cs}, respectively. The probability P for that child to become infected on that day is

$$P = 1 - (1 - p_{hc})^{I_{hc}}(1 - p_{ha})^{I_{ha}}(1 - p_{ncc})^{I_{ncc}}(1 - p_{nca})^{I_{nca}}(1 - p_{es})^{I_{es}}(1 - p_n)^{I_n}(1 - p_c)^{I_c}.$$

This equation is evaluated term-by-term in order to identify the source of infection if an infection occurs. Once infected, a person passes through the natural history of the infection process (see Figures 1 - 4) according to stochastic simulation based on pre specified probability distributions. Determinants of the infected person's behavior such as if and when he withdraws to the home or goes to the hospital are also simulated stochastically according to pre specified probability distributions.

Calibration of the model was based on historical data available on smallpox, including household secondary attack rates [1], relative age-specific attack rates being higher in children [3], and numbers of secondary cases produced by an introductory case [1][4].

4 Control measures

4.1 Surveillance and containment

When the first case of smallpox is recognized, all the hospital workers who deal with smallpox cases are immediately vaccinated. Recognized cases of smallpox are placed in hospital-based isolation and their close contacts are vaccinated, under the vaccination scenario. Close contacts are considered to be all those people in the case's household and when appropriate in the case's household cluster, daycare center, school or workplace. Contacts in the neighborhood or the community at large are not considered to be close contacts and are not traced. We also consider various levels of prevaccination of the hospital workers who deal with smallpox cases.

4.2 Vaccination

For those people who receive a fresh smallpox vaccination before they are infected, we assume the vaccine efficacy is 0.97, and that response to vaccination is all-or-none [5]. For those who receive a fresh vaccination within four days of infection, we assume that 90% will not develop disease and 10% will develop modified smallpox. For those vaccinated between 5-7 days of infection, 60% will develop modified smallpox, 38% ordinary smallpox, and 2% hemorrhagic smallpox. Vaccination reduces the death rate of breakthrough infections to a very low level. (Details will be given later.)

4.2.1 Mass Vaccination

We assume that if a decision to mass vaccinate is made, that it will occur twenty days after the first case is infected. We further assume that it would take ten days to mass vaccinate at a particular level. The schools, which serve as vaccination centers, would be closed for that ten day period.

4.2.2 Prevaccination of health care workers

We allow for various fractions of health care workers who could come into contact with smallpox cases to be vaccinated prior to the introduction of smallpox.

5 Results

5.1 No intervention

We first run the simulation with no background immunity, no hospitalization and with nobody withdrawing to the home when ill. This is the absolute worst case scenario where people ill with smallpox continue to circulate in the population until they recover or die. In this case, for the population with 6,000 people, an average of 5,649.7 are infected, nearly the entire population. (All reported case totals exclude the initial cases.) For the population with 48,000 people, an average of 44,788.5 are infected. Figure 8 shows a single stochastic realization of the number of cases over time. The epidemic has a large second wave and then a huge third wave that consumes most of the remaining susceptible population. If people do not go to the hospital, but withdraw to the home according to distributions described

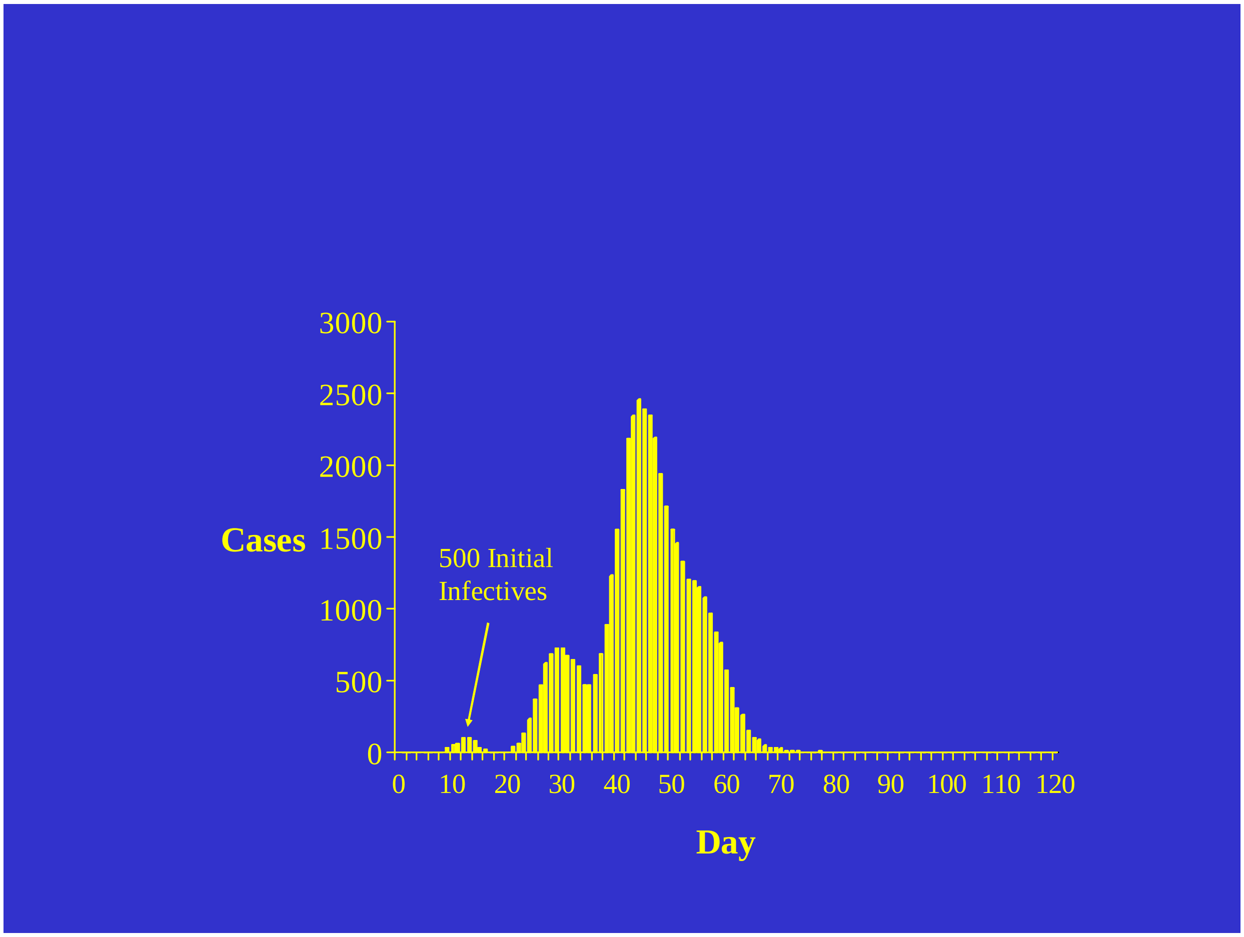

Figure 8: *A single stochastic realization of the baseline cases over time in the 48,000 person population, 500 initial infectives, with no vaccination, no hospitalization, and no withdrawal to household.*

above, the average total number infected drops to an average of 18.1 in the 6,000 person population and an average of 1,246.0 in the 48,000 person population. Thus, the simple act of ill people withdrawing to the home makes a large difference in the number of cases.

5.2 6,000 person population with interventions

Table 5 shows the results when surveillance and containment is instituted in the 6,000 person population both with and without vaccination of the identified close contacts. We see a dramatic drop in the total number of cases that averages 4.1 cases with vaccination of close contacts and 5.1 cases with no vaccination of close contacts (standard deviations are in parentheses). Table 5 also shows the sources of the infections. We see that most of the cases come from hospital contacts.

Table 5: Average Number of Infections with Surveillance and Containment

6000 Person Population, 10 Adult Initial Infectives, No Pre-vaccination

Sources of Infection	Vaccination of All Close Contacts	No Vaccination of Close Contacts
Hospital	2.5 (2.3)	3.8 (2.9)
Family	0.5 (0.7)	0.8 (1.0)
Household Cluster	0.2 (0.4)	0.3 (0.6)
Daycare/Playgroup	0.0 (0.0)	0.0 (0.0)
School	0.1 (0.3)	0.1 (0.5)
Workgroup	0.5 (0.8)	0.6 (0.9)
Neighborhood	0.2 (0.5)	0.2 (0.4)
Community	0.1 (0.4)	0.2 (0.5)
Total	4.1 (3.1)	5.8 (4.1)

We consider surveillance and containment with prevaccination of 10% and 50% of the hospital workers. The results are summarized in Table 6. Prevaccination of hospital workers has little additional effect. Because the number of cases where already so low after surveillance and containment measures were instituted, we did not consider mass vaccination in the 6,000 person population.

Table 6: Summary of Average Number of Infected People, N=6000, 10 adult initial infectives

Population	Vaccination of All Contacts	No Vaccination of Contacts
Baseline (no withdrawals)	-	5649.7
Baseline (no hospitalization)	-	18.1
With Surveillance and Containment		
No pre-vaccination	4.1	5.8
10% Hospital pre-vaccination	4.0	5.5
50% Hospital pre-vaccination	3.9	4.6

5.3 48,000 person population with interventions

Table 7 shows the results when surveillance and containment is instituted in the 48,000 person population both with and without vaccination of the identified close contacts. Again, we see a dramatic drop in the total number of cases that averages 218.6 cases with vaccination of close contacts and 279.2 cases with no vaccination of close contacts. Figure 9 shows a single stochastic realization of the number of cases over time when surveillance and containment is used with vaccination. The epidemic is quickly contained with a small second wave and even smaller third wave. Table 8 shows the percentage of infections that occurred in each setting. We note that 54% were from the hospital, 21% were from the family or other close contact, 19% were from daycare centers, schools or the workplace, and 7% were from the neighborhood and community at large. This latter 7% of infectious contacts would be untraceable. These percentages are quite close to those observed for European smallpox outbreaks for 1958-1973 [4].

Table 7: Average Number of Infections with Surveillance and Containment

48000 Person Population, 500 Initial Infectives, No Pre-vaccination

Sources of Infection	Vaccination of All Contacts	No Vaccination of Contacts
Hospital	118.5 (11.2)	160.0 (15.8)
Family	33.2 (8.1)	44.8 (7.6)
Household Cluster	13.0 (4.2)	15.7 (4.9)
Daycare/Playgroup	1.2 (1.1)	1.1 (1.1)
School	21.3 (9.6)	22.9 (9.3)
Workgroup	16.6 (5.7)	19.9 (6.3)
Neighborhood	7.8 (3.4)	7.9 (2.5)
Community	7.3 (3.4)	7.3 (3.1)
Total	218.6 (18.7)	279.2 (26.2)

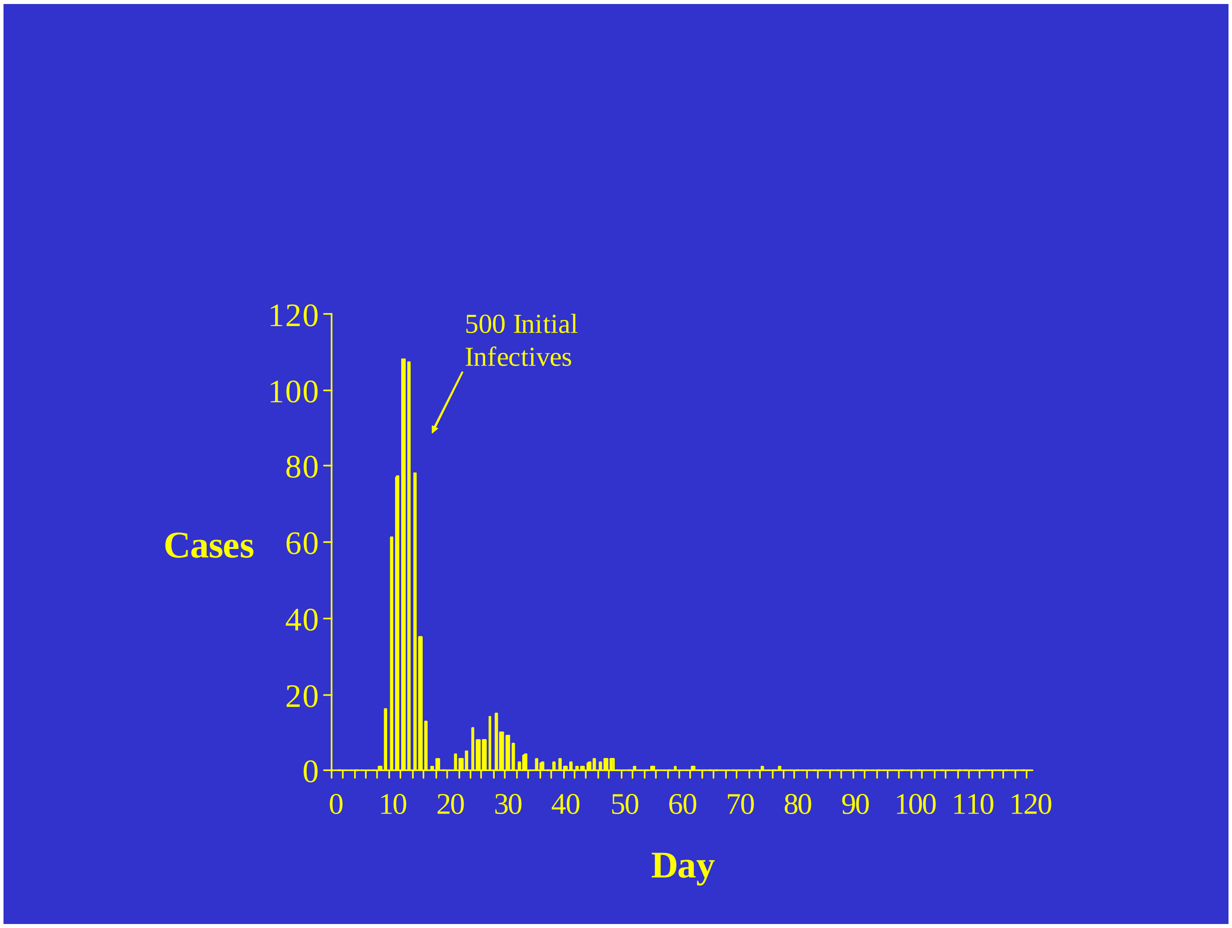

Figure 9: *A single stochastic realization of the baseline cases over time in the 48,000 person population, 500 initial infectives, when surveillance and containment is carried out with vaccination.*

Table 8: Percent of Infections From Each Source

48000 Person Population, 500 Initial Infectives,
No Pre-vaccination

Sources of Infection	Vaccination of All Close Contacts	No Vaccination of Close Contacts
Hospital	54%	57%
Family	15%	16%
Household Cluster	6%	6%
Daycare/Playgroup	1%	0%
School	10%	8%
Workgroup	8%	7%
Neighborhood	4%	3%
Community	3%	3%

We also considered prevaccination of hospital works and mass vaccination (see *Section* 4.2.1) as shown in Table 9. When considered with surveillance and containment, the various vaccination strategies lead to modest decreases in the number of smallpox cases.

Table 9: Summary of Average Number of Infected People, N=48000, 500 initial infectives

Population	Number infected
Baseline (no withdraw)	44788.5
Baseline (withdraw to home only)	1246.0
Surveillance and containment with vaccination	
No pre-vaccination	218.6
10% Hospital pre-vaccination	216.3
50% Hospital pre-vaccination	210.0
40% Mass vaccination	199.7
80% Mass vaccination	191.0

Table 10 shows the average number of deaths and the case fatality ratio that would be expected under each of the different scenarios in the 48,000 population. If people just withdraw to the home, the number of deaths is dramatically reduced. Also, fresh vaccination that comes with surveillance and containment cuts the case fatality ratio in half.

Table 10: Summary of Average Number of Deaths, N=48000, 500 initial infectives

Population	Number deaths	Case fatality ratio
Baseline (no withdraw)	13169.0	0.29
Baseline (withdraw to the home only)	350.0	0.28
Surveillance and containment with vaccination		
No pre-vaccination	30.9	0.14
10% Hospital pre-vaccination	29.9	0.14
50% Hospital pre-vaccination	27.8	0.13
40% Mass Vaccination	23.2	0.12
80% Mass Vaccination	19.5	0.10

5.4 Sensitivity analyses

We carried out sensitivity analyses on the larger population of 48,000 people. In all cases, surveillance and containment with vaccination of close contacts was carried out. We varied the following factors:

1. Delay in withdraw to home or hospital
2. Proportion of cases that are hemorrhagic.
3. Percent cases recognized in the hospital during the first wave.

5.4.1 Delay in withdraw to home or hospital

In order to see how delays in individual withdraw to the home and hospital affected the size of an outbreak, we extended these delays by one and two days. This means that infected people will continue to circulate in the community as they become increasingly infectious. In the case of one day, for example, a 47.5% of ordinary smallpox cases would withdraw to the home and 47.5% would go to he hospital on the 2nd of fever, and the remaining 5% would go to the hospital at the end of the 4th day of fever (see figure 2). Table 11 shows the results for the sensitivity analyses. We see that the process is extremely sensitive to this delay. With one additional day delay, the average number of cases jumps from 218.6 to 850.6, and further jumps to 10,139.5 with two further days delay.

Table 11: Sensitivity Analyses

48000 Person Population, 500 initial infectives
100% Close Contact Vaccination

Population	Average Cases	Average Deaths
Standard Natural History	218.6	30.9
Sensitivity Analyses:		
Withdrawal delayed 1 day	850.6	116.0
Withdrawal delayed 2 days	10139.5	1166.0
10% Hemorrhagic	257.1	73.0
20% Hemorrhagic	282.0	96.2
50% Hemorrhagic	342.2	164.9
20% Reduction in recognized cases	262.7	67.7
40% Reduction in recognized cases	274.3	71.0

5.4.2 Proportion of cases that are hemorrhagic

Also, shown in Table 11 are the results with an increasing proportion of cases being hemorrhagic, which is 5% for the baseline case. We see that the average number of smallpox cases in only mildly sensitive to increases in the proportion of cases that are hemorrhagic, but the number of deaths is quite sensitive to this variable.

5.4.3 Percent cases recognized in the hospital during the first wave

Finally, Table 11 shows what happens when we reduce the proportion of cases recognized the first wave, which is 100% for the baseline case. We see that the system is only moderately sensitive to this variable.

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