American Journal of Epidemiology
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Vol. 158, No. 2
Printed in U.S.A.
DOI: 10.1093/aje/kwg103

SPECIAL ARTICLES

Transmission Potential of Smallpox: Estimates Based on Detailed Data from an Outbreak

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Received for publication August 7, 2002; accepted for publication January 23, 2003.

Recent discussions on the use of variola virus by bioterrorists have rekindled interest in the parameters that govern the transmissibility of smallpox. Here, the authors estimate by maximum likelihood the parameters of the spread of smallpox from historical data on an epidemic in 1967 in the town of Abakaliki, Nigeria, afflicting a religious group that refused vaccination. According to the authors' estimates, 79.9% (95% confidence interval (CI): 63.6, 87.9) of the infectious contacts occurred within the compounds of the cases and 93.3% (95% CI: 80.6, 98.8) among compound members and other close contacts. Each case had 0.164 (95% CI: 0, 1.31) sufficiently close contacts on average during the fever period that preceded the rash and 6.87 (95% CI: 4.52, 10.1) sufficiently close contacts during the whole course of infectivity. These results support the widely held belief that smallpox spreads slowly, mainly among close contacts, and that infectivity before the onset of rash was negligible.

disease outbreaks; infection; inference; models, statistical; smallpox; variola virus

Abbreviations: CI, confidence interval; FTC, Faith Tabernacle Church.

Recent discussions on possible bioterrorist attacks using variola virus have rekindled interest in the parameters governing the spread of smallpox (1). Publications on smallpox attack scenarios are based on the assumption that each case can produce up to dozens of secondary cases (2–4), which led to the prediction of devastating epidemics. Other scientists, however, assume that the infectivity of smallpox is considerably less (5–7). Gani and Leach (8, 9) have recently evaluated historical smallpox data and estimated values of 3.5–6 for the basic reproduction number R_0 of smallpox (after discounting for hospital-associated cases). This means that each case would infect 3.5–6 other people on average if the population were completely susceptible.

Another issue that urgently needs clarification is the question of when people become infectious and spread the disease. In their definitive book on smallpox, Fenner et al. summarize laboratory studies showing that huge titers of virus particles can be found in the throats of infected people during the earliest days of fever that usually precede the onset of rash by 2–3 days, yet they conclude, "it was difficult to obtain evidence of the infectivity of patients during the latter part of the incubation period or during the pre-eruptive fever …. Epidemiological experience suggested that transmission very rarely occurred before the first day of rash" (6, p. 189). Contrary to these conclusions, Kaplan et al. (10) assume in their recently published model that practically all infections occur during the 3-day period that precedes the onset of rash. In spite of their assumption that overtly sick cases (i.e., people who have developed the typical smallpox rash) are immediately isolated, they predict tremendous epidemics, because they assume that only 50 percent of each case's contacts are traced and subsequently vaccinated. Likewise, Halloran et al. (11) assume in their individual-based stochastic model that smallpox is highly contagious during the prodromal period, but they conclude that, under all scenarios, targeted vaccination prevented more cases per dose of vaccine than did mass vaccination when their model incorporated the residual immunity of those vaccinated

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TABLE 1. Information on the smallpox cases that occurred during an epidemic in Abakaliki, Nigeria, in 1967*

Case no.	Onset of rash	Compound	Confession	Vaccination	
i	t_i	c_i	f_i	Scar	Year(s)
0	0	1	FTC	–	No vaccination
1	13	1	FTC	–	No vaccination
2	20	1	FTC	–	No vaccination
3	22	1	FTC	–	No vaccination
4	25	1	FTC	–	No vaccination
5	25	1	FTC	–	No vaccination
6	25	1	FTC	–	No vaccination
7	26	2	FTC	–	1966
8	30	2	FTC	+	1963
9	35	1	FTC	–	No vaccination
10	38	4	FTC	–	No vaccination
11	40	5	FTC	–	No vaccination
12	40	1	FTC	–	No vaccination
13	42	1	FTC	–	No vaccination
14	42	1	FTC	–	No vaccination
15	47	1	FTC	–	No vaccination
16	50	5	FTC	–	No vaccination
17	51	2	FTC	–	No vaccination
18	55	1	FTC	–	No vaccination
19	55	2	FTC	–	No vaccination
20	56	6	Other	–	1963, 1967
21	56	5	FTC	+	1958
22	57	2	FTC	–	1948
23	58	7	FTC	–	No vaccination
24	60	4	FTC	–	No vaccination
25	60	2	FTC	–	No vaccination
26	61	2	FTC	–	No vaccination
27	63	8	Other	–	1956
28	66	3	FTC	–	No vaccination
29	66	9	FTC	–	No vaccination
30	71	5	FTC	–	No vaccination
31	76	2	FTC	+	1963

* Time $t_i = 0$ corresponds to April 5, 1967. Thirty of the 32 cases occurred among members of the Faith Tabernacle Church (FTC). Note that cases 7 and 8 moved from compound 1 to compound 2 on day 25.

before 1972. Bozzette et al. (12, 13) assume in their model that cases become infective halfway between the onset of fever and the onset of rash (12), but they do not consider an elevated level of infectivity during the fever period.

In this paper, we evaluate historical data on an epidemic that occurred in 1967 in Nigeria to estimate how smallpox spread to members of the same compound, to other close contacts, and to remote contacts. We also examine to what degree smallpox was transmitted during the fever period that preceded the rash.

MATERIALS AND METHODS

Description of the epidemic

Between April and June of 1967, a smallpox outbreak with 32 cases occurred in Abakaliki, an important trading town with approximately 31,200 inhabitants (1963 census) located in southeastern Nigeria (14). The outbreak attracted considerable attention from the World Health Organization as Abakaliki was the center site of a pilot project of the Smallpox Eradication and Measles Control Programme where at least 88.5 percent of the population had success-

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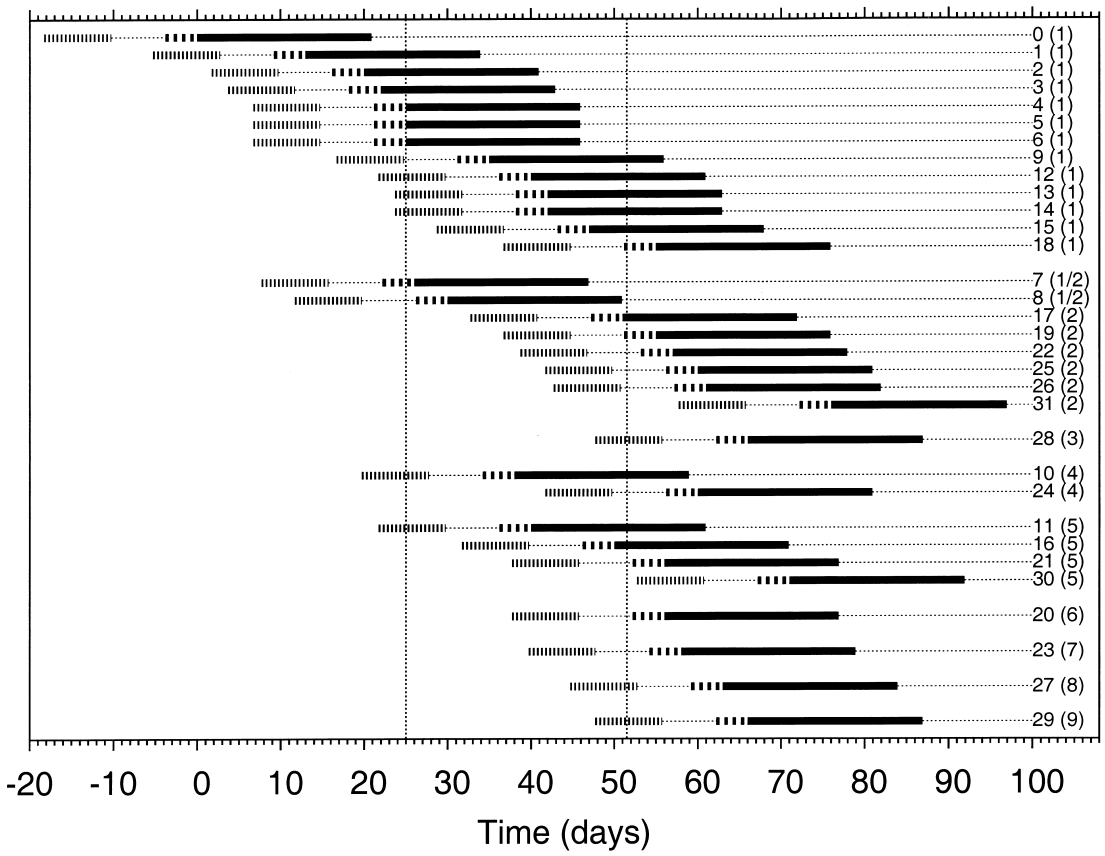

FIGURE 1. Course of the smallpox outbreak in Abakaliki, Nigeria, 1967. Day 0 corresponds to April 5, 1967, the day when the first case developed smallpox rash. Each case is represented by a horizontal line. The thinly striped sections represent the intervals within which the cases acquired infection (95% intervals, back-calculated from the onset of disease). The starting points of the thickly striped sections denote the 95th percentile of the onset of fever (back-calculated from the onset of rash) (figures 2 and 3; table 3). The starting points of the full sections denote the onset of rash, and their ending points represent the 95th percentile of the period with overt symptoms (calculated from the onset of rash) (table 1). Case identifiers and compound identifiers, respectively, are given at the end of each line. Note that cases 7 and 8 moved from compound 1 to compound 2 on day 25 (shown as vertical line). The second vertical line at day 51.5 shows the estimated onset of interventions.

fully been vaccinated a few months before the outbreak (6). The first case was an unvaccinated girl 10 years of age who had moved on April 2, 1967, from the town Effium (where a smallpox epidemic occurred at that time) to live with her stepfather in Abakaliki. The girl was febrile on the day she arrived and continued to have fever, headache, and backache until April 5 ("day 0") when she developed a macular rash. In the following weeks, the infection continually spread to people who lived in the same compound (table 1; figure 1). On day 25, a family seemingly free of smallpox moved from the index case's house ("compound 1") to another building ("compound 2"), where on day 26 the family's daughter aged 8 years and on day 30 their son aged 12 years developed clinical signs of smallpox. In spite of the obvious spread of the infection, cases were not reported before the last week of May. The last case occurred on June 20, 76 days after the beginning of the outbreak. Table 2 summarizes the composition of the nine compounds that were afflicted by the outbreak (unfortunately, we could not determine the exact composition with respect to vaccination status and membership in the Faith Tabernacle Church of each of them, so that all five possible compositions had to be used to calculate the likelihood; see the Appendix for details).

Thirty of the 32 cases belonged to the Faith Tabernacle Church (FTC), a religious group that refuses vaccination and medical treatment. FTC members were closely related, they regularly visited each other, and they met at church up to four times a week but remained somewhat isolated from the rest of the community. When the first case appeared, the minister of the church instructed his parishioners not to visit houses of families with smallpox, but he admits that his admonitions went unheeded. After the health authorities discovered the first case (case 11), all those who were still ill or who subsequently became ill with smallpox were isolated at the Infectious Disease Hospital. This was the only concession that FTC members made to the health authorities; they steadfastly refused to be vaccinated.

The only two non-FTC members among the cases were a woman (case 20) who sold plantains in a booth at the market that was opposite to the booth of case 1 and a man (case 27)

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TABLE 2. Information on the composition of the nine compounds that were afflicted in a smallpox epidemic in Abakaliki, Nigeria, in 1967*

Compound c	FTC			Non-FTC		
	Vaccinated (no.)	Nonvaccinated (no.)	$n_{c,\mathrm{FTC}}$	Vaccinated (no.)	Nonvaccinated (no.)	$n_{c,\mathrm{non}}$
1	18	15	33	0	0	0
2	9	5	14	1	0	1
3	2	8	10	0	0	0
4	$2 - i_4$	$2 + i_4$	4	$28 + i_4$	$1 - i_4$	29
5	$4 - i_5$	$3 + i_5$	7	$13 + i_5$	$2 - i_5$	15
6	0	0	0	40	3	43
7	$4 - i_7$	$1 + i_7$	5	$12 + i_7$	$3 - i_7$	15
8	0	0	0	37	5	42
9	0	1	1	26	6	32
Sum 1–9	35	39	74	161	16	177
Other	$46 \times 35/74$	$46 \times 39/74$	46	$30{,}903 \times 161/177$	$30{,}903 \times 16/177$	30,903
Total			120			31,080

* As complete information was not available for all compounds, we have to choose three numbers ($i_4 \in \{0, 1\}$, $i_5 \in \{0, 1, 2\}$, and $i_7 \in \{1, 2, 3\}$) such that $i_4 + i_5 + i_7 = 4$, which can be done in five different ways (the log-likelihood is calculated for each of these five possibilities of arranging the table; the value presented in table 4 is the arithmetic mean of these five log-likelihoods). Note that three vaccinated Faith Tabernacle Church (FTC) members and one nonvaccinated FTC member moved from compound 1 to compound 2 on day 25 (the given numbers show the composition of the population after moving). Vaccination status was given only for the 74 FTC members and the 177 nonmembers living in compounds 1–9. We assume that the vaccination coverage of the remaining FTC members and nonmembers was identical to the observed fractions 35/74 and 161/177, respectively.

who washed clothes for people in compound 1. Seven cases reported having been vaccinated, but visible vaccination scars were present in only three of them (table 1).

Model description

We assume that the periods from infection to onset of fever, from onset of fever to onset of rash, and from onset of rash to recovery, respectively, are gamma distributed with the parameters given in table 3. The distributions for the incubation and prodromal fever period were estimated from data where the exact date of infection was known (figures 2 and 3). As the duration of rash that lasts for about 16 days (6) does not necessarily correspond to the period of contagiousness, alternative assumptions about the duration of infectivity will be discussed. We consider the possibility that cases were infectious during the fever period that precedes the onset of rash. To estimate the relative infectivity during the fever period, we multiply all contact rates by a factor b before the rash. To describe the spread of infection, we assume 1) that each case had a daily number κ_h of contacts with people who lived in the same house and shared the same confession (the latter constraint was necessary because FTC members disassociated with others to such an extent that the infection never spread from FTC members to nonmembers who lived in the same compound), 2) that each FTC member had an additional daily number κ_f of contacts with other FTC members (including his or her household members), and 3) that each FTC member had an additional daily number κ_a of contacts with anybody in the population. Because no infor-

TABLE 3. Durations of the period from infection to onset of fever, from onset of fever to onset of rash, and from onset of rash to recovery, respectively, Abakaliki, Nigeria, 1967

	Mean (days)	Standard deviation (days)	Percentile		Coefficient of variation (%)
			5%	95%	
Period before fever	$\mu_I = 11.6$	$\sigma_I = 1.90$	8.62	14.9	16.4
Period from fever to rash	$\mu_F = 2.49$	$\sigma_F = 0.88$	1.32	3.8	35.3
Period with rash	$\mu_R = 16.0$	$\sigma_R = 2.83$	11.70	20.9	17.7
Duration until isolation	$\mu_Q = 2.0$	$\sigma_Q = 2.00$	0.10	6.0	100.0

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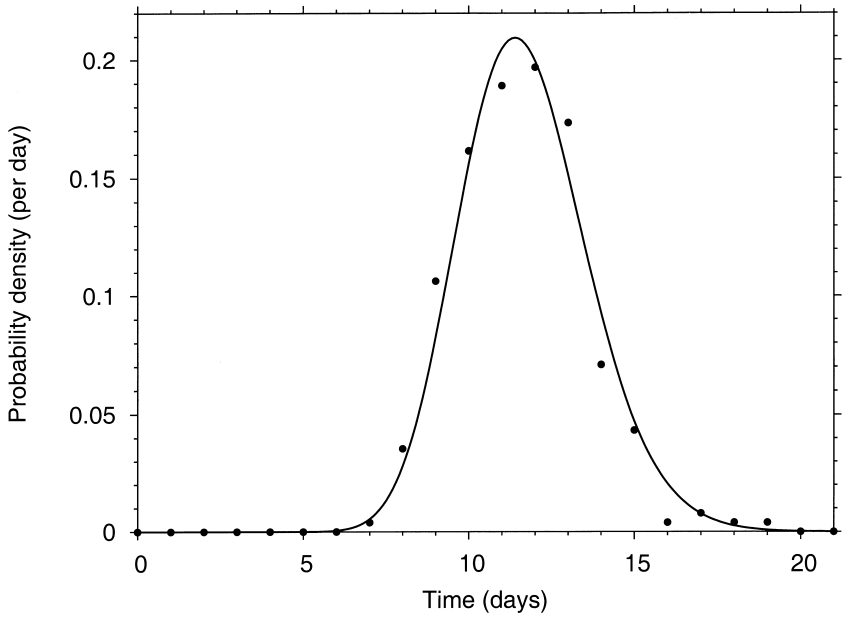

FIGURE 2. Estimated distribution of the duration of the period between infection and onset of fever. A gamma distribution was fitted to the observations with maximum likelihood. (For parameter estimates, see table 3). The dots show relative frequencies of 254 observations with known duration (6).

mation on close contacts of non-FTC members was available, we assume that each of them had a daily number $\kappa_f + \kappa_a$ of contacts with anybody in the population. A fraction v of vaccinated individuals is assumed to be protected, whereas the remaining fraction $1 - v$ is completely susceptible to infection and disease. Each infected person passes through a gamma-distributed incubation period before developing fever and through a gamma-distributed prodromal period

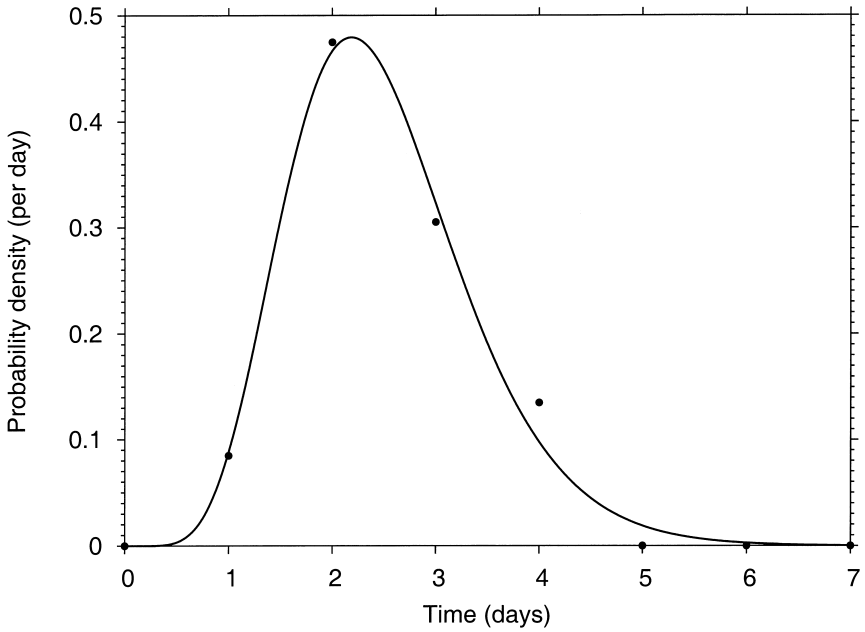

FIGURE 3. Estimated distribution of the duration of the prodromal fever period. A gamma distribution was fitted (by maximum likelihood) to the 40 observations described previously (15) and to the 19 observations from the epidemic in Meschede, Germany (16). (For parameter estimates, see table 3). Analysis of a subset of 35 cases with known incubation and prodromal period (see figure 2) showed no correlation between these durations (Spearman's rank correlation coefficient $r_s = -0.055$, $p = 0.75$).

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TABLE 4. Parameter estimates and 95% confidence intervals (based on the profile likelihood with $\ln(L_{max}) = -332.08$) for a smallpox epidemic in Abakaliki, Nigeria, in 1967

		Estimate	95% confidence interval
Vaccine efficacy	v	0.816	0.644, 0.922
Contacts in compound (per day)	κ_h	0.335	0.192, 0.527
Contacts in Faith Tabernacle Church (per day)	κ_f	0.0562	0.0187, 0.127
Contacts in total population (per day)	κ_a	0.0281	0.00447, 0.101
Factor for early infectivity	b	0.157	0, 1.89
Onset of isolation measures (days)	t_Q	51.5	44.7, 59.6
Basic reproduction number	$R_0 = (\mu_R + b\mu_F)(\kappa_h + \kappa_f + \kappa_a)$	6.87	4.52, 10.1
Reproduction number before rash	$R_F = b\mu_F(\kappa_h + \kappa_f + \kappa_a)$	0.164	0, 1.31
Fraction of compound contacts	$H = \kappa_h/(\kappa_h + \kappa_f + \kappa_a)$	0.799	0.636, 0.879
Fraction of close contacts	$C = (\kappa_h + \kappa_f)/(\kappa_h + \kappa_f + \kappa_a)$	0.933	0.806, 0.988

before developing the typical rash (table 3; figures 2 and 3). The contact rates κ_h, κ_f, and κ_a, the vaccine efficacy v, and the factor for early infectivity b are estimated from the data by maximum likelihood. As we lack the exact date when cases were isolated, we also had to estimate the time t_Q when isolation measures started (we assume that it took 2 days on average between the onset of rash and the isolation of the patient; table 3). For each parameter, we calculate 95 percent confidence intervals using the profile likelihood. For details of the model and the estimation procedure, see the Appendix.

RESULTS

Results of the parameter estimates and their 95 percent confidence intervals are given in table 4. The basic reproduction number, R_0, was 6.87 (95 percent confidence interval (CI): 4.52, 10.1) for the whole course of infectivity, and R_F = 0.164 (95 percent CI: 0, 1.31) for the fever period that preceded the rash. This means that, in a completely susceptible population, infected persons caused 0.164 secondary cases before the onset of rash. A fraction of 79.9 percent (95 percent CI: 63.6, 87.9) of the contacts occurred within the household of cases, and 93.3 percent (95 percent CI: 80.6, 98.8) of the contacts occurred among household members and other close contacts. Apart from using an infectious duration of μ_R = 16 days, we have also run the estimation procedure for the values used by Meltzer et al. (1) and by Gani and Leach (8), respectively, which led to similar parameter estimates but to significantly inferior likelihood values. (Meltzer et al. use the value μ_R = 12.5 days (1), which leads to an estimate of H = 0.78, C = 0.93, R_F = 0.35, and R_0 = 5.8 with $\ln(L_{max}) = -335.0$; Gani and Leach use μ_R = 8.6 days (8), which leads to H = 0.74, C = 0.93, R_F = 0.80, and R_0 = 4.7 with $\ln(L_{max}) = -339.7$. Compare these values with those given in table 4 of this paper).

DISCUSSION

Four of the seven vaccinated cases had received their vaccination more than 9 years before they were infected. Loss of immune protection may have contributed to the relatively low effective vaccine efficacy of 81.6 percent, but primary vaccination failure must also have occurred, as three of the vaccinated cases did not show any vaccination scars (table 1).

Our estimate of a basic reproduction number of R_0 = 6.87 is higher than the maximum of the estimates obtained by Gani and Leach (8, 9) after discounting hospital-associated cases. This can partly be explained by the fact that FTC members preferred home care to medical treatment. Our R_0 value may also be slightly overestimated because we were not able to consider close contacts other than household members for the two non-FTC members. Recent methodological considerations used the Abakaliki data for illustration (17–19). As they assume that all 120 FTC members initially were susceptible and that they were homogeneously mixing, these papers highly underestimate the basic reproduction number ($R_0 \approx 1.1$).

Our finding of a reproduction number R_F before the onset of rash of only 0.164 contrasts strikingly with the assumption of Kaplan et al. (10) and Halloran et al. (11) who use a value of approximately 3 for R_F in their models. Our result, that 93.3 percent of contacts occurred among close contacts who could easily be traced in an outbreak, also shows that a fraction of only 50 percent of traceable contacts, as used by Kaplan et al. (10), is much too small. Similar observations were made by Henderson and Yekpe who examined a smallpox outbreak in Dahomey and concluded, "the transmission of smallpox appeared to stop when the supply of susceptibles in the village who were in casual contact with cases was still abundant, but when the supply of susceptibles in prolonged and intimate contact with cases was virtually exhausted" (20, p. 427). Considering the possible consequence that a mass vaccination as recommended by Kaplan et al. (10) would itself cause numerous cases of severe sickness and hundreds of deaths (21), the case for a combination of a targeted vaccination strategy and isolation measures should be reexamined (7). By using a stochastic transmission model that considers the spread of smallpox among close and remote contacts and that allows

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for some days until cases can be isolated, we found that smallpox could even be controlled by isolation alone (22).

Summarizing our results, we agree with Fenner et al. who already discussed a possible bioterrorist attack with variola virus in 1988 and concluded, "the risk of any such act leading to the re-establishment of endemic smallpox should not be exaggerated. As has already been mentioned, smallpox spreads comparatively slowly, by face-to-face contact. Unless the public health services had completely broken down, the existence of reserve stocks of vaccine ... would ensure the containment of any outbreak that followed a deliberate release of variola virus" (6, p. 1341).

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APPENDIX

We assume that the period from infection to onset of fever is gamma distributed with mean μ_I and variance σ_I^2 (figure 2). The probability density $g(t_I)$ that it takes t_I days from infection to the appearance of fever is given by

$$g(t_I) = \frac{e^{-\beta_I t_I} t_I^{\alpha_I - 1} \beta_I^{\alpha_I}}{\Gamma(\alpha_I)} \text{ for } t_I > 0 \qquad \text{(A1)}$$

and 0 otherwise; $\Gamma(\alpha_I)$ is the gamma function with $\alpha_I = \mu_I^2/\sigma_I^2$ and $\beta_I = \mu_I/\sigma_I^2$ (table 3).

The period from onset of fever to onset of disease is also gamma distributed with a mean μ_F and a variance σ_F^2 (figure 3). The probability density $f(t_F)$ that it takes t_F days from the appearance of fever to the appearance of the rash is given by

$$f(t_F) = \frac{e^{-\beta_F t_F} t_F^{\alpha_F - 1} \beta_F^{\alpha_F}}{\Gamma(\alpha_F)} \text{ for } t_F > 0 \qquad \text{(A2)}$$

and 0 otherwise; $\Gamma(\alpha_F)$ is the gamma function with $\alpha_F = \mu_F^2/\sigma_F^2$ and $\beta_F = \mu_F/\sigma_F^2$.

If case j developed the rash at time t_j, the probability that he or she had fever at time t is given by

$$F(t_j, t) = 1 - \int_t^{t_j} f(t_j - \tau)\, d\tau \text{ for } t \le t_j \qquad \text{(A3)}$$

and 0 otherwise.

The probability density $l(t_j, t)$ that case j who developed the rash at time t_j was infected at time t (i.e., that it took $t_j - t$ days from infection to the onset of rash) can, therefore, be obtained from the convolution of $g(t)$ and $f(t)$:

$$l(t_j, t) = \int_0^{t_j - t} g((t_j - t) - \tau) f(\tau)\, d\tau \text{ for } t < t_j \qquad \text{(A4)}$$

and 0 otherwise.

As we assume that the period of rash is gamma distributed with a mean μ_R and a variance σ_R^2, the probability that an individual with onset of rash at time t_j is still overtly sick and not isolated at time t is

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$$R(t_j, t) = \begin{cases} \dfrac{\Gamma(\alpha_R, (t - t_j)\beta_R)}{\Gamma(\alpha_R)} & \text{for } t_j \le t \text{ and } t < t_Q \\ \dfrac{\Gamma(\alpha_R, (t - t_j)\beta_R)}{\Gamma(\alpha_R)} e^{-\alpha_Q(t - \max(t_j, t_Q))} & \text{for } t_j \le t \text{ and } t \ge t_Q \end{cases} \tag{A5}$$

and 0 otherwise. $\Gamma(\alpha_R)$ is the gamma function with $\alpha_R = \mu_R^2/\sigma_R^2$, $\Gamma(\alpha_R, x) = \int_x^\infty \tau^{\alpha_R - 1} e^{-\tau} d\tau$, and $\beta_R = \mu_R/\sigma_R^2$. After day t_Q, overt cases are isolated at rate $\alpha_Q = 1/\mu_Q$ (i.e., we assume that the delay between the onset of rash and the isolation of a case is exponentially distributed with a mean μ_Q).

The force of infection λ to which any person k is exposed depends on time t, the compound c_k where the person lives, and his or her confession f_k. It is

$$\lambda(t, c_k, f_k) = \sum_{j=0}^{31} (b F(t_j, t) + R(t_j, t)) \times \begin{cases} \left(\dfrac{\kappa_a}{N-1} + \dfrac{\kappa_f \delta_f(j,k)}{n-1} + \dfrac{\kappa_h \delta_c(j,k)}{n_{c,f_j} - 1}\right) & \text{if } f_j = \text{FTC} \\ \left(\dfrac{\kappa_a + \kappa_f}{N-1} + \dfrac{\kappa_h \delta_c(j,k)}{n_{c,f_j} - 1}\right) & \text{otherwise} \end{cases} \tag{A6}$$

where $\delta_f(j, k)$ is equal to 1 if both individuals j and k belong to FTC and 0 otherwise; $\delta_c(j, k)$ is equal to 1 if both individuals j and k live in the same compound *and* are of the same confession and 0 otherwise. $N = 31{,}200$ is the total population size, $n = 120$ is the number of FTC members, and n_{c,f_j} is the number of people who live in the same compound as case j and have the same confession as j (compare with table 2). Note that on day 25, four FTC members (two cases and two noncases) moved from compound 1 to compound 2, so that the compound of these persons and the denominators in compounds 1 and 2 had to be changed on day 25. With these assumptions, the likelihood of a case with onset of disease t_k who lives in compound c_k, who belongs to religion f_k, and who has vaccination status s_k is

$$L_{\text{case}}(t_k, c_k, f_k, s_k) = (1 - v)^{\delta_s(k)} \int_{-\infty}^{t_k} \lambda(t, c_k, f_k) e^{-\int_{-\infty}^{t} \lambda(\tau, c_k, f_k) d\tau} l(t_k, t) dt \tag{A7}$$

where $\delta_s(k)$ is equal to 1 if person k has been vaccinated and 0 otherwise. Accordingly, the likelihood of a noncase is given by

$$L_{\text{non}}(c_k, f_k, s_k) = \begin{cases} v + (1 - v) e^{-\int_{-\infty}^{+\infty} \lambda(\tau, c_k, f_k) d\tau} & \text{if vaccinated} \\ e^{-\int_{-\infty}^{+\infty} \lambda(\tau, c_k, f_k) d\tau} & \text{if unvaccinated.} \end{cases} \tag{A8}$$

The combined likelihood of all observations is

$$L = \left(\prod_{k=1}^{31} L_{\text{case}}(t_k, c_k, f_k, s_k)\right)\left(\prod_{k=32}^{N} L_{\text{non}}(c_k, f_k, s_k)\right) \tag{A9}$$

To consider all possible compositions of the nine afflicted compounds, we calculated the likelihood for the five possibilities described in table 2 and then calculated the arithmetic mean of the five resulting log-likelihoods; 95 percent confidence intervals for the parameters were determined by using the profile likelihood. That is, the minimum and maximum values of each parameter were determined from the set of all parameter constellations that led to a log-likelihood $\ln(L) \ge \ln(L_{\max}) - \chi^2_{1,\,0.95}/2$. In an analogous manner, confidence intervals for R_0 and for other terms that depend on more than one parameter were calculated by using the profile likelihood.

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