A Statistical Model of Smallpox Vaccine Dilution

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Introduction and Summary

There is a small but disturbing chance that some terrorist group or rogue nation may have access to smallpox virus and be both ruthless and reckless enough to use it (Henderson et al. 1999, CDC 2001b). A recent Associated Press poll found that in the wake of the September and October 2001 attacks, three-fifths of Americans would like to be vaccinated against smallpox immediately (Lester 2001), yet the U.S. Center for Disease Control (CDC) has only 15.4 million doses of old vaccine in stock. The U.S. government has an additional 263 million doses on order (Stolberg and Petersen 2001), but these will not be available, barring the inevitable unforeseen delays, until the end of 2002, which would be much too late to be of help against an attack this winter.

A recent study by Drs. Robert B. Belshe and Sharon Frey at the St. Louis University School of Medicine has found, using a small sample of 60 subjects, that the existing stocks of smallpox vaccine have a 95% "take" rate when administered at the standard concentration, 70% when diluted 10:1, and 15% when diluted 100:1 (Harding 2001). These figures imply that a standard dose can produce 0.95 successful takes at full strength, 7.0 successful takes at 10:1, and 15 successful takes at 100:1. The last figure would allow the existing U.S. stocks to vaccinate the approximately 170 million Americans who want immediate vaccination, with 60 million to spare, but only with an unmanageable average of 6.7 vaccination attempts per take.

The present note investigates three statistical models to infer the number of successful takes per standard dose that would occur at unobserved dilutions. The best fitting model predicts that as many as 16.7 takes per dose could be obtained at a dilution

of 58.2:1. The model predicts that the 15 takes per dose that were found at 100:1 could also be obtained at 33.7:1, with only about a third as many vaccination attempts.

These results could undoubtedly be refined with the forthcoming results of the larger dilution study employing over 600 subjects that is currently in progress, but meanwhile they do suggest that dilutions on the order of 20:1, 30:1, or 40:1 could give up to double the number of takes per dose obtained at 10:1, without the excessive number of attempts required at 100:1, and hence are well worth considering and investigating with further trials.

Concluding remarks argue for the immediate vaccination, using diluted existing vaccine, of all willing Americans who are not at high risk of complications, giving first priority to medical and emergency workers, and then to those who have never been vaccinated.

The Model

Smallpox vaccination requires injecting a drop of reconstituted vaccine into the skin with k repeated pricks of a special bifurcated needle, where k is normally taken to be 15 (CDC 2001a). We assume that the multiple pricks are required because each prick injects only a small, random amount v_i of vaccine, which by itself would have only a small probability of being adequate to induce the desired local infection. Together the multiple pricks introduce a larger and more predictable effective quantity V of vaccine into the skin, which may be thought of either as the sum of the individual v_i or as their maximum. At dilution D relative to the standard concentration, i.e. at concentration $1/D$ relative to the standard, a random number of immunization units $U = V/D$ will be

introduced. It is assumed that if this random number is greater than some deterministic threshold, T, the vaccination will be successful. If the cumulative probability distribution function of V itself is $F(x)$, i..e. if

$$\text{Prob}(V \le x) = F(x),$$

then the probability of failure with dilution D is

$$\text{Prob}(U = V/D \le T) = \text{Prob}(V \le TD) = F(TD),$$

and the probability of success is

$$\text{Prob}(U = V/D > T) = \text{Prob}(V > TD) = 1 - F(TD).$$

We consider first the case in which V arises as the sum of k independently and identically distributed (i.i.d.) individual v_i's:

$$V = \sum_{i=1}^{k} v_i \ .$$

If k is sufficiently large, the Central Limit Theorem implies that V has an approximately *Gaussian* (or *normal*) *distribution*. Since T has the same arbitrary units as V and must be estimated, we may without loss of generality set the standard deviation of V equal to unity, so that

$$F(x) = \frac{1}{\sqrt{2p}} \int_{-\infty}^{x} \exp(-\frac{1}{2}(z-m)^2)dz \ ,$$

where the mean m is an unknown parameter to be estimated along with T (Casella and Berger 2002, p. 102). Despite its great familiarity and appealing Central Limit Theorem property, the Gaussian distribution does have the disadvantage that it implies some positive probability that V will be less than 0, despite the fact that V is necessarily nonnegative. However, if k is large enough to justify the Gaussian approximation to the

true distribution, the estimated mean will turn out to be sufficiently large, relative to the unitary standard deviation, that this probability will be negligible.

A *gamma distribution* of order $a > 0$ may also arise from the sum of k i.i.d. random variables, each of which is gamma of order a/k. As α approaches infinity, the gamma distribution becomes Gaussian in shape, but for small to moderate α, it may be highly skewed to the right, and it has the advantage over the Gaussian that it always has positive support. The gamma cumulative probability distribution with unit scale (also known as the incomplete gamma function) is

$$F(x) = \frac{1}{\Gamma(a)} \int_0^x z^{a-1} e^{-z} dz, \quad x \geq 0,$$

where

$$\Gamma(a) = \int_0^\infty z^{a-1} e^{-z} dz$$

is the (complete) gamma function (Casella and Berger 2002, p. 99). As in the Gaussian case, we may without loss of generality set the scale equal to unity, if T is to be estimated along with a.

If, on the other hand, X arises as the maximum of a large number of i.i.d. random variables, rather than as their sum, one of the three *Greatest Extreme Value distributions*, the *Weibull*, *Gumbel*, or *Fréchet*, would be suggested. Of these, only the *Fréchet distribution* has the required positive support. Again, we may without loss of generality set the scale equal to unity, in which case the standard Fréchet cumulative distribution function with shape parameter $a > 0$, to be estimated along with T, is

$$F(x) = \exp(-x^{-a}), \quad x \geq 0$$

(Leadbetter et al., 1983).

Estimation results

Let the three dilution levels tested be $D_1 = 1$, $D_2 = 10$, and $D_3 = 100$, let N_j be the number of trials at each of the three dilutions, and let M_j be the number of successes at each dilution level. In the St. Louis University experiment, $N_1 = N_2 = N_3 = 20$, $M_1 = 19$, $M_2 = 14$, and $M_3 = 3$ (inferred from Harding 2001 in conjunction with McCanse 2000). The log likelihood of the unknown parameters given the data is then

$$\log L = \sum_{j=1}^{3} \left(M_j \ln(1 - F(D_j T)) + (N_j - M_j) \ln F(D_j T) \right)$$

This expression was numerically maximized over T and m, a, or a, respectively, for the three distributions considered, by means of the Nelder-Mead polytope (or simplex) algorithm (Press et al., 1992). The restrictions $T > 0$, $a > 0$, and $a > 0$ were indirectly imposed by replacing these variables with their respective logarithms.

Table 1 shows the likelihood-maximizing parameters for each of the three distributions considered, along with the maximized log likelihood, the dilution D_{max} that maximizes the expected number of takes per dose, and the maximized number of takes per dose. The latter were found by computing the takes per dose for each value of D from 0 to 110 in steps of 0.1. Because the Fréchet's estimated shape parameter a turns out to be less than unity, it unrealistically predicts that the number of takes per dose could be increased without bound by increasing the dilution to infinity.

Table 1

Estimation results

Distribution	Parameters	Log L	D_{max}	Maximized Takes per dose
Gaussian	m = 1.086 T = 0.0216	-26.23	54.2	25.2
Gamma	a = 0.674 T = 0.0139	-24.70	58.2	16.7
Fréchet	a = 0.580 T = 0.1144	-25.44	∞	∞
Unrestricted		-24.64		

Figures 1-3 show the estimated number of takes per dose as a function of dilution for the three distributions. The three data points are shown as dots. Note that the vertical scales are somewhat different, and that discrepancies in fit at high values of D are magnified in proportion to D.

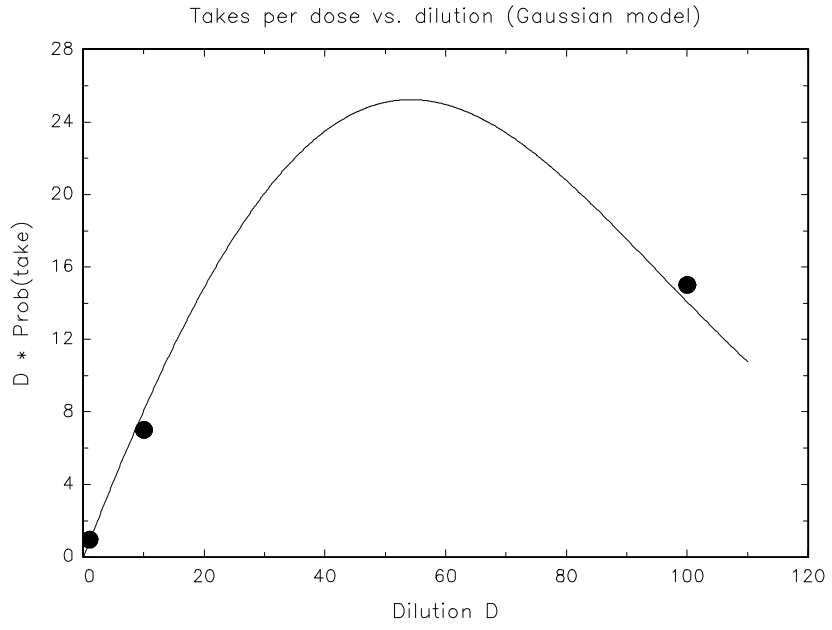

Figure 1

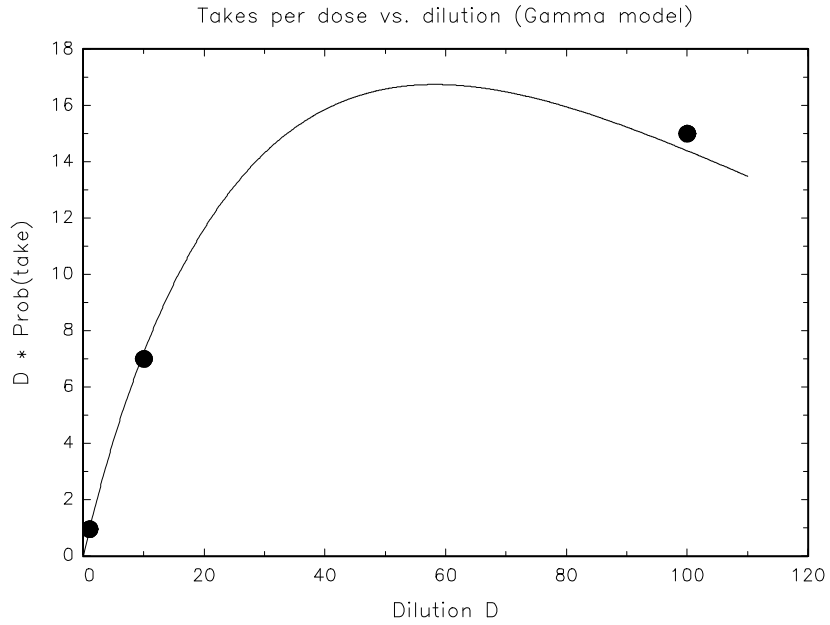

Figure 2

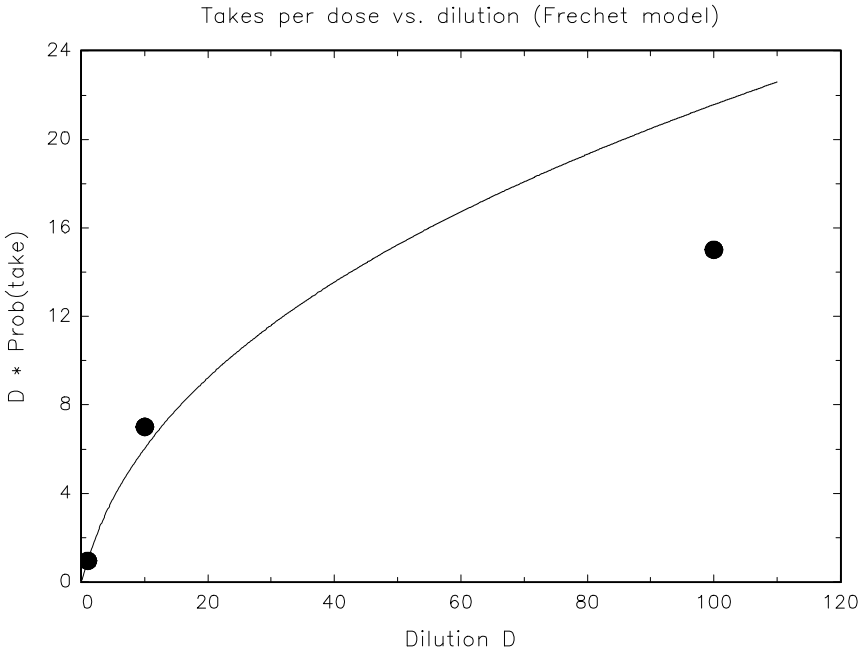

Figure 3

The last line of Table 1 indicates that the unrestricted log likelihood, computed by estimating the probability of a take at the three dilutions independently, without the restriction of a functional form, is –24.64. Each of the three models estimates two parameters, and therefore imposes a single restriction on the probabilities at the three observed dilutions, and some loss in log likelihood relative to the unrestricted model. If the model in question is valid and the total sample size is sufficiently large, twice the loss in log likelihood is distributed χ^2 with 1 degree of freedom (because of the single restriction), so that if the loss in log likelihood is less than 3.84/2 = 1.92, the model in question cannot be rejected at the .05 level.

It may be seen from the third column of Table 1 that the maximized log likelihood is highest, i.e. the best fit is obtained, for the gamma distribution. The gamma model imposes a log likelihood loss of only 0.06, so the gamma distribution is far from being rejectable. The Fréchet distribution comes in second, with a log *L* loss of 0.80, and the Gaussian third, with a log *L* loss of 1.59. Due to the small sample size, neither of these is rejectable at the .05 critical value, but the gamma distribution performs distinctly better than either of these, and is therefore to be preferred. A further reason for preferring the gamma model over the Fréchet is that the latter unrealistically predicts that the number of takes per dose could be increased without bound by increasing the dilution to infinity, as noted above. Although the Gaussian distribution fits well at $D = 100$, this comes at the expense of the fit at $D = 1$ (where the predicted probability of a take is 85.6% rather than the observed 95%) and at $D = 10$ (where the predicted probability of a take is 80.8%

rather than the observed 70%). The Gaussian model also unrealistically predicts a 13.9% probability that *V* will be negative.

The preferred gamma model predicts a very flat peak around *D* = 58.2, so that the dilution could be cut considerably below this value with only negligible loss in expected number of takes per dose. Table 2 shows that the same 15 takes per dose observed at *D* = 100 is predicted for *D* = 33.7, which implies a take rate of 44.5%, or almost three times that observed at *D* = 100. Dilutions of 20, 30, and 40 are predicted to yield substantially higher takes per dose than *D* = 10. The model also predicts that the dilution of 5:1, which is being studied in the forthcoming larger dilution study, will yield an 82.2% take rate, for 4.11 takes per standard dose.

Table 2

Predicted dependence of takes per dose upon dilution (gamma model)

D	**Takes per Dose**
1	0.938
5	4.11
10	7.23
20	11.6
30	14.3
33.7	15.0
40	15.9
50	16.6
58.2	16.7
100	14.4

Concluding remarks

Even though the United States has now undergone grievous terrorist attacks, including even attacks with biological weapons, the CDC, which controls all existing stocks of smallpox vaccine in the country, plans to wait for a smallpox attack to occur, and then to restrict vaccination to the immediate and secondary contacts of infected persons (CDC 2001b). Spokespersons assure us that vaccine could be made available, as needed, anywhere in the country, within "hours" (Rotz 2001).

Such "ring vaccination" after the fact may have worked well 30 to 40 years ago against natural outbreaks in Third World countries where mobility was limited and considerable immunity from prior infection or vaccination was already present, but will be far less successful against a deliberate attack on our highly mobile and completely susceptible society. Suppose, for example, that a small group surreptitiously released smallpox virus in aerosol form at a few crowded airports. Two weeks later, thousands of cases would simultaneously appear without warning in dozens of cities and a handful of foreign countries. If, as is not unlikely, the airports and highways are closed and entire cities are quarantined, it will be next to impossible to distribute vaccine to where it is needed, particularly if a few well-timed anthrax letters close down the postal system and parcel services, and if other calculated disturbances also add to the pandemonium. Just finding the requisite bifurcated needles would be a feat in itself (Landers 2001). O'Toole (1999) projects that existing vaccine stocks could quickly be exhausted, even in a scenario in which there are far fewer initial cases, and in which the response is ideally prompt.

After one has been exposed or when one is about to be exposed in the line of duty, a take probability of even 95%, which is equivalent to 20-cylinder Russian Roulette, will be unacceptably low. Freshly vaccinated medical and emergency workers could therefore reasonably be expected to refuse to examine potentially infected persons or to move them to quarantine centers during the first week, until after their own vaccinations prove positive. One hundred CDC immunologists, who will be expected to collect and analyze fluid samples from the first victims, have prudently had themselves pre-vaccinated (Connolly 2001), even though the CDC dictates that all other health and emergency workers must wait until after an outbreak is confirmed. After an attack occurs, no one will be satisfied with any but the highest probability of a take, and stretching existing stocks with dilution will become a moot issue.

Before an attack occurs, however, we have plenty of time to vaccinate, and revaccinate as necessary with dilute vaccine, all Americans who want to be protected. First priority should be given to medical and emergency workers, and then to those born after 1972 who have never been vaccinated, but the present study suggests that at a dilution rate of 30:1, or so, there may be adequate vaccine in stock for all who want it.

Pre-vaccinating millions of Americans will greatly reduce the rate of spread of any infection, and will create a cadre of persons who can keep the country running in the face of otherwise crippling quarantines. Getting a vaccination program underway before an attack would vastly mitigate its effects, since vaccine would already be in the hands of clinics in every city, personnel would already have the necessary training and equipment, and health and emergency workers would be among the first to be vaccinated. Just knowing that the vaccine is available nearby and flowing on a rational basis, and not

locked away in a vault in a distant city, to be released at the discretion of timid bureaucrats and squabbling politicians, will enormously reduce the sense of panic that would follow any outbreak. And best of all, simply reducing America's vulnerability to smallpox by launching such a campaign is likely to discourage anyone from using it as a weapon against us in the first place.

The CDC (2001b) has expressed concern that the high risk of complications in a few individuals with certain conditions would lead to numerous deaths if all Americans were "indiscriminately" vaccinated. These complications could lead to about one death per million vaccinations using 1960s experience, and to even more with today's higher incidence of organ transplant recipients, cancer survivors, and HIV carriers. However, there is no reason to allow this elevated risk in a few readily identifiable individuals to delay the *discriminate* and voluntary vaccination of the 90% or so of Americans who are *not* at high risk (McCulloch 2001, Millar 2002).

Many of the complications of smallpox vaccination can be mitigated or even prevented by the administration of Vaccine Immune Globulin (VIG), a product made from the blood serum of recently vaccinated individuals (CDC 2001a). The Catch-22 is that the CDC is down to only about 600 doses of VIG (Rotz 2001) and virtually no one has been recently vaccinated. Pre-vaccinating millions of healthy Americans will create a pool of potential donors to replenish these stocks, and thereby provide a measure of protection even for those who are at high risk of complications.

REFERENCES

Casella, George, and Roger L. Berger. *Statistical Inference*, Second edition, Duxbury, 2002.

Center for Disease Control Advisory Committee on Immunization Practices [CDC 2001a]. "Vaccinia (Smallpox) Vaccine," *Morbidity and Mortality Weekly Report* **50**, No. RR-10 (June 22, 2001). Online at <http://www.cdc.gov/nip/smallox/News.htm#ACIP>.

Center for Disease Control [CDC 2001b]. "Interim Smallpox Response Plan and Guidelines," Draft 2.0, 11/21/01. Online via <http://www.cdc.gov/nip/smallpox/>.

Connolly, Ceci. "HHS Set to Order Smallpox Vaccine for All Americans," *The Washington Post* Nov. 7, 2001. Online at <http://www.washingtonpost.com/wp-dyn/articles/A51468-2001Nov6.html>.

Harding, Anne. "Old Smallpox Shots Work, but Jury Out on Dilution," Reuters news story, Dec. 18, 2001. (Report on Poster Presentation by Dr. Robert Belshe at 41st ICAAC conference in Chicago) Online at <http://www.nlm.nih.gov/medlineplus/news/fullstory_5304.html>.

Henderson, Donald A., T.V. Inglesby, J.G. Bartlett, M.S. Ascher, E. Eitzen, P.B. Jahrling, J. Hauer, M. Layton, J. McDade, M.T. Osterholm, T. O'Toole, G. Parker, T. Perl, P.K. Russell, and K. Tonat, for the Working Group on Civilian Biodefense. "Smallpox as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 281, No. 22 (June 9, 1999): 2127-2137.

Landers, Susan J. "Smallpox Vaccine: Balancing the Benefits and the Risks," *AMNews* Nov. 12, 2001. Online at <http://www.ama-assn.org/sci-pubs/amnews/pick_01/hlsb1112.htm>.

Leadbetter, M.R., Georg Lindgren, and Holger Rootzén. *Extremes and Related Properties of Random Sequences and Processes*. Springer Verlag 1983.

Lester, Will. "Poll Backs Smallpox Vaccinations," Associated Press story, Sunday, Nov. 18, 2001. Online at <http://icrsurvey.com/icr/AP_Bioterror.htm>.

McCanse, Cindy. "Vaccinate against smallpox? Preposterous! But will a vaccine be there if you need it? *FPReport* **6**, No. 5 (May 2000). Online at <http://www.aafp.org/fpr/20000500/03.html>.

McCulloch, J. Huston. "Vaccinating Now Could Curb Outbreak," Letter to Editor of *Wall St. Journal*, Nov. 6, 2001.

Millar, J. Donald. "Free to Choose the Smallpox Vaccine," excerpt from an article to appear in the Winter 2002 issue of *Regulation, the Cato Institute Review of Business and Government*. Online at <http://www.cato.org/dailys/01-04-02.html>.

O'Toole, Tara. "Smallpox: An Attack Scenario," *Emerging Infectious Diseases* **5** (July-August 1999): 540-546.

Press, William H., Saul A. Teukolsky, William T. Vetterling, and Brian P. Flannery. *Numerical Recipes in FORTRAN: The Art of Scientific Computing*, Second edition, Cambridge Univ. Press, 1992.

Rotz, Lisa, in "CDC-Interim Smallpox Response Plan and Guidelines Conference Call," CDC Office of Communication, Nov. 26, 2001. Online at <http://www.cdc.gov/od/oc/media/transcripts/t011126.htm>.

Stolberg, Sheryl Gay, and Melody Petersen. "U.S. Orders Vast Supply of Vaccine for Smallpox," *New York Times* Nov. 29, 2001.