

lion recipients were reported; the next day, after noting that only 200,000 additional persons had received vaccine, the total swelled to 4.4 million (9).

These data reflect the difficulties intrinsic to managing such a massive program. The discrepancy may simply be a case of not adding columns of numbers in a systematic way; however, the fuzzy numbers do have a certain appeal to the modern, more cynical reader.

Whatever occurred, understanding the specifics of “the great vaccination miracle” of 1947 is important for maintaining equilibrium during our current smallpox vaccination program and any future programs directed at now-unanticipated infections. Not just New York City’s, but the entire country’s sense of confidence that it can handle a major rapid vaccination or pill distribution campaign leans very heavily on the apocryphal vaccine campaign of April 1947. Yet, as described above, there may be much less to the miracle than meets the eye.

Kent A. Sepkowitz*

*Infectious Disease Service, New York, New York, USA

References

1. Smallpox in city, inoculation urged. *The New York Times*. 1947 Apr 5. p. 21.
2. Curb of smallpox a ‘miracle,’ says city health commissioner. *The New York Times*. 1947 Apr 26. p. 15.
3. Second smallpox death spurs vaccination. *The New York Times*. 1947 Apr 13. p. 1.
4. One more smallpox case found; lone source of infection traced. *The New York Times*. 1947 Apr 15. p. 1.
5. Vaccinations stop; drug supply gone. *The New York Times*. 1947 Apr 16. p. 1.
6. Smallpox scare soon dissipated. *The New York Times*. 1947 Apr 17. p. 1.
7. Physicians chided on smallpox aid. *The New York Times*. 1947 Apr 24. p. 21.
8. Half million were vaccinated in day. *The New York Times*. 1947 Apr 18. p. 21.
9. Physicians explain vaccination reaction, Weinstein urges all to be immunized. *The New York Times*. 1947 Apr 22. p. 21.

Address for correspondence: Kent A. Sepkowitz, Infectious Disease Service Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA; fax: 212-717-3021; email: sepkowitz@mskcc.org

Smallpox Vaccination and Adverse Cardiac Events

To the Editor: The incidence of adverse cardiac events related to smallpox vaccinations administered during the National Smallpox Vaccination Program (NSVP) in 2003 has received widespread attention. From January 24 through August 8, 2003, suspected or probable myo- or pericarditis was reported in 22 of 38,257 civilian vaccinees (1); as of November 4, 2003, suspected or probable myo- or pericarditis was reported in 63 of 515,000 military vaccinees (2). Additionally, cases of coronary artery disease, including myocardial infarction and cardiac death, were reported in the weeks after vaccination although no causal link has been established.

An October 3, 2003, MMWR article, “Cardiac deaths after a mass smallpox vaccination campaign—New York City, 1947” states that the NYC experience suggests “. . . that cardiac deaths observed in 2003 might have been unrelated to smallpox vaccination.” While the causes of these cardiac or coronary deaths have not been established, the 1947 data lack the power to address whether there is a relationship to the vaccine.

Cardiac or coronary deaths after vaccination in 2003 were rare, with a total of 3 of 488,550 military and civilian vaccinees (6 per 1 million vaccinees), approximately the same as might be expected in a generally healthy population. The total number

of cardiac or coronary deaths in 1947 during the 2-week estimated risk period after vaccination was 1,545. While the denominator (number vaccinated in the previous 4–17 days) was not reported, a total of 6.4 million persons were vaccinated during the 4 weeks of the vaccination program. The 4-week vaccination period would result in a 6-week period of susceptibility for cardiac death according to the 4–17 day latency period. Thus, we extrapolate that the denominator for the 2-week observation period is approximately 2.1 to 6.4 million vaccinees at risk during the study period. This would mean that approximately 240 to 720 cardiac deaths occurred per million vaccinees.

Suppose that the 1947 smallpox vaccine indeed caused serious cardiac disease, including myopericarditis and myocardial infarctions, with 10 fatal cases per million. Viewed in perspective, this would approximate the historic rate of vaccine-induced encephalitis and would be well in excess of the historic rate of progressive vaccinia. In this scenario, at a hypothetical incidence of 10 per million, from 21 to 64 of the 1,545 cardiac deaths (1.4% to 4.1%, respectively) would have been caused by the vaccine. This magnitude of effect would have been very difficult to detect in this study. Thus, the results of such investigations must be considered in the context of power limitations. Further, studying death rates sheds no light on cardiac illness such as myo- or pericarditis.

The proper interpretation of these data is important given the national policy impact that resulted from the observation of cardiac and coronary illness and death after vaccination in 2003. At this time, adverse cardiac events associated with the vaccine, particularly myo- or pericarditis, are still of concern. Whether coronary or cardiac deaths can be attributed to the vaccine remains an open question.

Mark J. Upfal,* and Sandro Cinti†

*Detroit Medical Center, Detroit, Michigan, USA; and †University of Michigan, Ann Arbor, Michigan, USA

References

- Centers for Disease Control and Prevention. Update: adverse events following civilian smallpox vaccination—United States, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:819–20.
- U.S. Army. Smallpox vaccine—cardiac related reactions. 2003 Nov [Accessed Mar 9, 2004]. Available from: <http://www.smallpox.army.mil/media/pdf/spQAshort.pdf>
- Centers for Disease Control and Prevention. Cardiac deaths after a mass smallpox vaccination campaign—New York City, 1947. *MMWR Morb Mortal Wkly Rep* 2003;52:933–6.

Address for correspondence: Mark Upfal, Corporate Medical Director, Detroit Medical Center, Occupational Health Services, 4201 St. Antoine, UHC-4G-3, Detroit, 48201, USA; fax 313-745-3263; email: mupfal@dmc.org

In Reply: We have reviewed the letter submitted by Upfal and his colleagues (1), and we applaud their careful examination of our previously published data (2). Their aim was to assess whether the study was adequately powered to detect a small but potentially relevant effect in cardiac death rates. This question is important, and their message regarding the difficulty of measuring small effects is certainly true. We address these problems in the discussion section of

our article published in this edition of *Emerging Infectious Diseases*; however, we would also like to clarify some points that were misleading in their letter.

While the methods Upfal et al. employ to assess statistical power are generally correct, they base their argument on estimates derived from 2003 deaths in both the civilian and military population. We remind readers that the military is a unique group, more physically fit and potentially younger than the general population, today and in 1947. A more appropriate estimate of potential risk for the general population (i.e., what we would have seen in 1947 if a vaccine-associated risk for cardiac death existed) would be to use risk estimates derived from deaths among civilians. If observed civilian deaths in 2003 were indeed vaccine-associated, our study certainly had the power to detect such an effect in 1947.

Also, when calculating the rate of cardiac deaths among 2003 vaccinees, Upfal et al. refer to additional 2003 vaccinations in the military that have occurred since the time our article was published. Since no additional deaths occurred, these additional vaccinations further dilute the risk. However, this larger number of vaccinees modestly affects the estimated risk size. In the Table below, we show that our study had sufficient power to detect effects of a relevant size.

We agree with Upfal's basic premise that our study lacks the statistical power to detect very small risks (such as 1% increases), but most studies struggle with the same limitation. Our study does provide useful and convincing evidence that neither moderate nor large increases in cardiac mortality occurred in 1947 as a result of smallpox vaccination.

Lorna E. Thorpe,*†

Farzad Mostashari,*

Adam M. Karpati,*

Steven P. Schwartz,*

Susan E. Manning,*†

Melissa A. Marx,*†

and Thomas R. Frieden*

*New York City Department of Health and Mental Hygiene, New York, New York, USA; and †Centers for Disease Control and Prevention, Atlanta, Georgia, USA

References

- Upfal MJ, Cinti S. Smallpox vaccination and adverse cardiac events. *Emerg Infect Dis* 2004;10:971–2.
- Centers for Disease Control and Prevention. Cardiac deaths after a mass smallpox vaccination campaign—New York City, 1947. *MMWR Morb Mortal Wkly Rep* 2003;52:933–6.

Address for correspondence: Lorna E. Thorpe, NYC DOHMH, 125 Worth St. Rm. 315 (CN6), New York, NY 10013, USA; fax: 212-788-4473; email: lthorpe@health.nyc.gov

Table. Smallpox vaccination and estimated risk for cardiac death

	All cardiac deaths ^a	Atherosclerotic deaths ^{a,b}	All cardiac deaths, civilians only ^c
Estimated vaccine-associated death risk (deaths/vaccinees) based on 2003 experience ^d	6.1 per million (3/488,550)	6.1 per million (3/488,550)	52.3 per million (2/38,257)
1947 rate of cardiac deaths in 2-week risk period (deaths/vaccinees)	241 per million (1,545/6.4 million)	44 per million (280/6.4 million)	44 per million (280/6.4 million)
Percent of 1947 deaths that would have been due to vaccination, given estimated vaccine-associated risk	2.5%	14.0%	100%
Sufficient power to detect?	Possibly	Definitely	Definitely

^aFor these estimates, we used the total number of vaccinees as of November 2003, per Upfal's letter. Our original article estimated risk based on 394,584 vaccinees as of April 2003; the resulting effect size would be even larger and more easily detectable.

^bAll cardiac deaths in 2003 were atherosclerotic.

^cFor this calculation, we used the total number of civilian vaccinees as of August 2003, per Upfal's letter. Our original article estimated risk based on 29,584 civilian vaccinees as of April 2003; the resulting effect size would be even larger and more easily detectable.

^dEstimated risk for death caused by vaccine, if one assumes that all 2003 cardiac deaths were vaccine-related.