TAKE RATES BY DOUBLE VERSUS SINGLE INSERTIONS OF SMALLPOX VACCINE IN REVACCINEES

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PRIMARY SMALLPOX vaccination does not confer lifelong immunity against smallpox. Data from recent epidemics in Western Europe indicate that effective immunity may persist as long as 7 years after a successful vaccination (*1*). In these outbreaks, cases were very rare in persons vaccinated within 3 years of exposure and uncommon in those vaccinated within 7 years.

The World Health Organization and the Public Health Service currently recommend that vaccination be repeated at 3-year intervals for optimal protection. In the United States, more than half the vaccinations performed each year are revaccinations (*2*).

The vaccination take rate among revaccinees is variable and often disappointingly low. Many factors influence the take rate, especially the length of time since the previous vaccination, vaccine potency, and vaccination technique (*3–8*). Take rates generally increase as the time since previous vaccination increases. In very recent revaccinees, take rates are low, and in many persons only the 48- to 72-hour reaction, formerly called the reaction of immunity, occurs. This reaction was shown by Benenson to result from ineffective vaccination as well as from vaccination of fully immune persons (*9*). The reaction of immunity is now called an equivocal reaction (*10*).

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Comparisons of freeze-dried, high-titered vaccines in varying dilutions with a variety of fresh or glycerinated lymphs have shown that vaccine must have a titer of at least 10^6 pock-forming units per ml. in order to induce acceptable take rates (*7*). Evidence indicates that good multiple-pressure technique effects more takes than the scratch method (*4*), and jet injection of vaccine through an intradermal head may be superior to multiple pressure (*11*). The revaccination take rates found in recent literature vary from 27 to 93 percent, with most investigators reporting rates of approximately 85 percent (*4–8, 12, 13*).

Current international travel regulations do not require documentation of a take in revaccinees, but rather only of an attempt to revaccinate. The alarm caused by importation of smallpox into Western Europe—many of the patients had valid international certificates of (re) vaccination (*1*)—has led to proposals to try to increase the probability of a major reaction in revaccinees, or to insist on documentation of the take by reading the vaccination on the seventh postvaccinal day (*14, 15*), or both.

Simultaneous multiple vaccinations have been proposed to increase the take rate in revaccinees (*14*). A double insertion theoretically would increase the chance of success by doubling the viral inoculum used, by halving the risk of failure due to human errors by the vaccinator, or both. The study reported in this paper was undertaken to test this hypothesis.

Materials and Methods

Male prisoners between the ages of 18 and 51 at the Georgia State Prison volunteered for vaccination. Volunteers were screened to eliminate those with contraindications to vaccination and

Table 1. Major and equivocal reactions of single and double vaccinees, by interval since last vaccination

Years since last vaccination	Reactions of single vaccinees			Reactions of double vaccinees			
	Major	Equivocal	Total	2 major	2 equivocal	1 equivocal	Total
1–6	26	1	27	22	3	2	27
7–9	36	1	37	32	1	2	35
10–19	51	1	52	48	3	7	58
20 or more	23	1	24	26	0	4	30
Unknown	19	2	21	18	0	5	23
Total	155	6	161	146	7	20	173

to include only men with definite vaccination scars. The remaining 334 volunteers were asked for their age, race, and date of last vaccination. The men were matched for race and time since previous vaccination, and each was assigned to either the single vaccination or the double vaccination group. Prevaccination blood samples were drawn from all the men in the study, and postvaccination serums were obtained on the 28th postvaccinal day.

All vaccinations were performed during one 3-hour period by a single vaccinator using the multiple-pressure technique with 30 needle pressures per insertion. Vaccinations were all done approximately 5 cm. from the old scar. All vaccinations were done with the same batch of freeze-dried vaccine which was reconstituted immediately before the vaccinations began. The remaining reconstituted vaccine was frozen for later titration and proved to have a titer of $10^{8.9}$ $TCID_{50}$ per ml. in primary cultures of rhesus monkey kidney monolayer tissue.

Table 2. Number of reactors and kind of reactions among single and double vaccinees, by race

Race and vaccinations given	Persons with reactions			Percent equivocal
	Major	Equivocal	Total	
White	172	3	175	1.7
Single	84	1	85	1.2
Double	88	[1] 2	90	2.2
Negro	149	10	159	6.3
Single	71	5	76	6.6
Double	78	[1] 5	83	6.0

[1] Includes only those with 2 equivocal reactions.

Measurements of erythematous areas and vesicle size of the resulting vaccination lesions were made to the nearest half centimeter on the 4th, 7th, and 14th postvaccinal days. The lesions were photographed on the same days. Three persons did the readings. Each patient whose vaccination was thought to be "equivocal" was seen by all three readers, and a consensus was reached.

The readings of the vaccinations were tabulated in accordance with the World Health Organization's criteria for a successful revaccination (*10*).

A successful revaccination is one which, on examination one week (six to eight days) later, shows a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion, which may be a scab or an ulcer.

Results

Vaccinations were given to 334 men; 161 were given a single vaccination, and 173 were given simultaneous double vaccinations. The composition of the two groups by race and time since last vaccination was similar.

Results of the vaccination readings are presented in table 1. Take rates between the two study groups were not markedly different. It appeared that more severe reactions occurred in the group vaccinated more than 20 years previously than in the group vaccinated within the preceding 10 years. Among those receiving double insertions, 20 men had only one major reaction. These 20 men are considered among those with major reactions in the following analysis and discussion. When the single reactions among men with double insertions are counted

as major reactions, there are still more equivocal reactions among the group who received double insertions than among those receiving single insertions.

The take rates in the subgroups in the study population are shown in tables 2 and 3. There is a slight, statistically insignificant higher take rate in the men who received a single vaccination. The only significant difference between the various subgroups is that observed between the entire group of Negroes and the entire white group. This difference, 1.7 percent equivocal reactions among the white group as compared with 6.3 percent among the Negroes, may result from the difficulty of detecting minimal erythema in dark skin.

The results of the determination of neutralizing antibodies in a sample of 65 paired serums are presented in table 4. Paired serums were randomly selected and titered to a dilution of 1:1,024 using a modification of the tissue culture method of Cutchins and co-workers (*15*). Since all of the men were revaccinees, many prevaccination titers were too high to enable documentation of a fourfold rise in titer in the postvaccination serum because dilutions were not carried beyond 1:1,024. For this reason, titers of vaccinees who had fourfold titer rises are tabulated separately from those who had high prevaccination titers. There is no difference between the groups in the proportions in each serologic category. When vaccinees with fourfold serologic titer rises were added to those with high prevaccinal titers, the resulting number was about 90 percent for each group.

Table 3. Number of reactors and kind of reactions among single and double vaccinees, by interval since last vaccination

Interval and vaccinations given	Persons with reactions			Percent equivocal
	Major	Equivocal	Total	
10 years or less	120	6	126	4.8
Single	62	2	64	3.1
Double	58	[1] 4	62	6.5
More than 10 years	159	5	164	3.0
Single	74	2	76	2.6
Double	85	[1] 3	88	3.4

[1] Includes only those with 2 equivocal reactions.

Table 4. Serologic findings for 30 single and 35 double vaccinees before or after vaccination

Titer	Single		Double	
	Number	Percent	Number	Percent
Before vaccination:				
1:256 or more	5	16.7	7	20.0
1:1,024 or more	4	13.3	5	14.3
Change after vaccination:				
4-fold rise	18	60.0	21	60.0
Not significant	[1] 3	10.0	[2] 2	5.7
Total pairs	30	100.0	35	100.0

[1] 1:151 to 1:209, 1:162 to 1:50, and 1:8 to 1:7.
[2] 1:256 to 1:490 and 1:256 to 1:457.

Discussion

This study demonstrates that under optimal conditions there is little gained by an additional insertion of vaccinia. If the amount of virus introduced is a factor influencing the take rate in revaccinees, then use of a fully potent vaccine (one with at least 10^8 PFU per ml.), more potent than many vaccines currently in use in some smallpox endemic areas, will increase the number of active virus particles inserted much more than increasing the number of insertions. As high-titered, freeze-dried vaccines are relatively easy to produce, vaccine potency is a factor more readily amenable to change than the method of vaccination. The human errors in vaccination are best minimized by careful instruction in technique.

This investigation demonstrated a higher revaccination take rate than is generally found in the literature, although at least three recent studies of large numbers of revaccinations have shown take rates of more than 90 percent (*8–10*). The observed lack of difference between reaction rates in the two main study groups is best explained by the use of optimal materials and methods. The vaccine used was similar to vaccines available commercially, and the vaccinator, while trained, was not exceptional in his experience or methods. If the take rate in routine revaccinations can generally approach this high rate, there is little need to require revaccinations to be read. Such a requirement would raise major administrative problems for travelers, physicians, and public health workers.

Summary

Testing the hypothesis that a double insertion would increase the probability of a successful smallpox revaccination by doubling the viral inoculum used, we vaccinated 334 men 18 to 51 years old at the Georgia State Prison. All volunteers who had been vaccinated previously, the men were matched for race and time since previous vaccination. Single vaccinations were given to 85 white and 76 Negro inmates; simultaneous double vaccinations to 90 white and 83 Negro inmates. All vaccinations were done by a single vaccinator using the multiple-pressure technique with 30 needle pressures per insertion.

Readings of the skin responses on the 4th, 7th, and 14th postvaccinal days showed no superiority of double insertions. Six single vaccinees had equivocal reactions, and 155 had major reactions. Seven double vaccinees had two equivocal reactions, 20 had one equivocal reaction, and 146 had two major reactions.

Of the white single vaccinees, 84 had a major reaction and one had an equivocal reaction. Of the Negro single vaccinees, 71 had a major reaction and five had an equivocal reaction. Eighty-eight white and 78 Negro double vaccinees had a major reaction.

Among the single vaccinees who had been vaccinated less than 10 years previously were 62 with major reactions and two with equivocal reactions. Seventy-four single vaccinees with major reactions had been vaccinated more than 10 years previously as had two with equivocal reactions.

Fifty-eight double vaccinees who manifested major reactions had been vaccinated within 10 years, and four others with equivocal reactions had been vaccinated within the same period. Among double vaccinees who had been vaccinated more than 10 years previously were three men with equivocal reactions and 85 with major reactions.

Serologic examination of a subsample confirmed the results of the skin examinations. Prevaccination titers of serums from 30 men selected for single insertion and 35 selected for double insertions showed five prospective single vaccinees and seven prospective double vaccinees with titers of at least 1:256. Four candidates for a single insertion and five for double insertions had titers of 1:1,024 or more.

Eighteen single vaccinees and 21 double vaccinees had a fourfold rise in titer after vaccination. Five men had no significant change in titer. Of these, three were single vaccinees and two were double vaccinees.

Good technique and full potency of vaccine are the most important factors affecting revaccination takes. These factors are also the most readily amenable to improvement.

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Tearsheet Requests

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New Tool to Fight Cancer

A potentially powerful new tool in the fight against cancer is being developed by a team of researchers at the University of Wisconsin Medical Center. The research, funded by a recent grant from the National Institutes of Health, may well enable the cure of many cancers previously untreatable by standard X- or gamma radiation.

Dr. Max L. M. Boone, head of the radiotherapy department, and Dr. Charles A. Kelsey, associate professor of radiology, and a group of Wisconsin physicists, are developing a low-cost, compact machine to deliver high-energy neutron beams for treatment of cancer.

The possibility of neutron treatment has long been considered by cancer researchers. Many cancers contain clumps of cells which live without oxygen. These cells, resistant to X- and gamma rays, may survive such radiation treatment and cause regrowth of the tumor. These anoxic cells, however, are not as resistant to neutrons, and a beam of the highly energized particles can destroy the entire tumor.

Dr. Boone was among the pioneers in neutron cancer treatment in 1967 at Hammersmith, London. The patients treated there were those whose cancers were deemed unmanageable by any other therapy. Neutron beams, however, proved effective in many of the tumors, and cured some of even the most hopeless cases.

The machine at Hammersmith, a cyclotron, was both unwieldy and expensive. Dr. Boone and his associates felt this potentially powerful tool of neutron therapy must be provided in a more flexible and inexpensive way. Dr. Boone and Dr. Kelsey began work on their new concept in neutron treatment in 1969. Instead of a cyclotron, they hoped to produce high-energy neutron beams by fusion of tritium and deuterium.

With expert advice from nuclear physicists Henry H. Barschall and Willy Haeberli, the scientists, along with Ednor Rowe and William Winter of the university's physical sciences laboratory research complex, began building a prototype. They are using a high-energy plasma generator to accelerate deuterium (H^2) onto a gaseous tritium (H^3) target. The resulting nuclear fusion produced neutron beams at 14 million electron volts, a high enough energy for cancer treatment. The machine is unique in that the gas target is not contained by barriers. Such barriers would lower the energy of the plasma beam before it could reach the target to cause fusion.

A machine voltage which is quite low can be used. Because of the great energy production of the fusion reaction, only 200,000 volts put into the machine results in a 14-million volt neutron beam. Collimation, or shaping, of the beam is accomplished using steel and other neutron-blocking materials to prevent escape of neutrons except in a narrow beam emerging from the fusion chamber.

The main difficulties at present are perfecting the plasma optics to shoot sufficient beam into the gas target and engineering a reliable pumping system to handle the gas volumes necessary for the machine.

If the neutron therapy project proves as effective as indicated now, the scientists believe it will be possible to produce an inexpensive, usable machine for hospitals in about 2 years.