A Comparison of the Intradermal and Subcutaneous Routes of Influenza Vaccination with A/New Jersey/76 (Swine Flu) and A/Victoria/75: Report of a Study and Review of the Literature

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Abstract: A trial of influenza vaccination, with use of bivalent split virus vaccine (A/New Jersey/76 and A/Victoria/75), was conducted to compare the immunogenicity and reactions when vaccine was given by the subcutaneous and intradermal routes. Volunteers 18 to 24 years old were randomized into equal groups, one group receiving 0.1 ml of vaccine intradermally and the other receiving 0.5 ml subcutaneously. For the A/Victoria vaccine, the immunogenicity of the intradermal route seemed superior; for A/New Jersey vaccine, the routes were equivalent. Adverse reactions were minimal and equivalent for both groups. In times of vaccine shortage, the intradermal route is considered to stretch vaccine supplies. Field trials of new influenza vaccines should include evaluation of the immunogenicity of and adverse reactions caused by the same vaccine given by different routes in varied dosages. (*Am J Public Health* 69:1247-1250, 1979.)

Introduction

The controversy concerning preferred route of immunization dates to 1930, when Tuft[1-3] demonstrated that a small dose of typhoid vaccine given intradermally (id) was as immunogenic and produced fewer systemic reactions than a larger dose given subcutaneously (sc). When experimental influenza vaccine was first administered to humans by Francis[4] in 1936, both the id and sc routes were utilized, and no substantial difference in immunogenicity was observed. Subsequent changes in antigenic constitution of influenza vaccines have prompted reexamination of the immunogenicity and reactions associated with alternative routes of immunization.

Studies that are often cited come from the 1940s, when a less-refined combined Type A and Type B vaccine was employed. Van Gelder[5] evaluated the responses in a total of 1,953 naval personnel to one 0.1 ml dose given id, two 0.1-ml doses given id at an interval of two weeks, and one 1-ml dose given sc. The group mean titers reached were highest for persons receiving one id inoculation, next for those receiving two id inoculations, and least for those receiving the sc inoculation, with the id groups having a greater incidence of mild local reactions and the sc group having more severe local and systemic reactions. Bruyn[6] demonstrated greater mean titer rises for adults receiving 0.1 ml of vaccine id compared with 1 ml sc, both for PR8 and Lee strains. A similar result was observed in children given 0.2 ml, either sc or id. In addition, Bruyn[7] demonstrated the highest rate of titer rise and seroconversion in children given two 0.1 ml doses

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id, compared with one 0.5-ml dose sc or a single 0.1-ml dose id.

Substantial experience was gained from trials with Asian (A/Japan/305) vaccine strain in the late 1950s. Hilleman,[8] in the face of a new epidemic strain and inadequate vaccine production, gave an essentially immunologically virginal adult population 0.1 ml of vaccine id and 1 ml sc. Equivalent immunogenicity was found with both routes. In a similar trial, Sanger[9] vaccinated 366 adults 20–70 years old with either 20 CCA units id or 200 units sc. Forty-one per cent of the id group and 45 per cent of the sc group responded with a fourfold or greater rise in antibody. Sigel[10] evaluated the efficacy of immunization by alternate routes in a mixed-age population with a variety of dosages and antigen masses. In response to a single immunization, three lots of vaccine resulted in rates of fourfold conversions of 78 per cent, 88 per cent and 77 per cent by the sc route, compared with 45 per cent, 74 per cent, and 62 per cent by the id route.

Only one study contradicts the trials that showed no difference in efficacy between sc and id routes of immunization. Boger,[11] in an elderly population, found that 22 of 28 individuals receiving 500 CCA units of Asian (Japan/305) vaccine sc developed antibody, compared with eight of 22 persons receiving 50 CCA units by the id route.

In a variation in the usual research design, Klein[12] questioned if the route rather than route-dose combination was playing a role in the different rates of efficacy. He vaccinated children two months to five years of age, sc or id, with the same small doses of Asian vaccine. Neither the percentage responding serologically nor the geometric mean titers differed significantly between groups. In another variation, McCarroll[13] evaluated whether small doses administered to adults by repeated sc injections were as effective as those given by repeated id injections. Substantial differences were not found regardless of the route or sequence of immunization. Clark[14] also observed no difference between combined influenza A and B vaccines when given by needle and syringe (1 ml twice sc and 0.1 ml twice id), but found superior results when the larger dose was given by injector gun. Stille,[15] in an attempt to understand the contradictory results available, immunized multiple groups with varied doses of vaccine by the sc or id route. He demonstrated that, in the id groups, the log mean titer rose linearly with doses but that, with the sc route, the titer rose exponentially. For small antigen mass, the id route was superior, but as antigen mass increased a critical point was reached beyond which the sc route was more immunogenic. Kirkham[16] reported a study that may best reflect the realities of the times. The influenza attack rates in Mason City, Iowa, in 1957, in populations given 200 CCA units sc and those given 40 units id when vaccine ran short, were compared with the rate for the unvaccinated population. Both vaccinated groups suffered attack rates of 10 per cent, compared with 33 per cent for the unvaccinated group. The vaccine efficiency for either route was 75 per cent.

Saslaw,[17, 18] in a series of trials between 1960 and 1963 with an institutionalized, incapacitated elderly population who had been vaccinated previously with Asian and polyvalent influenza vaccine, evaluated the efficacy of sc and id routes for initial, booster and yearly vaccinations. After initial vaccination, 60–78 per cent (depending on the type of antibody evaluated) of subjects in the sc group had fourfold seroconversion, as compared with 39–56 per cent for the id group, who received one-tenth the dose. However, three months later no significant difference was observed in rate of seroconversion after a booster dose was given by the same route. Subsequently, the populations received yearly inoculations with 1 ml of polyvalent vaccine given sc. Then, in 1963, this population was administered 1.0, 0.5, or 0.25 ml of polyvalent vaccine sc or 0.1 ml id. For the most part, no significant differences were observed. The 0.25-ml sc dose proved inadequate. Saslaw surmised that although both routes produced substantial rates of seroconversion, a higher dose by the sc route was superior for first immunization, but that for booster or yearly immunization in an experienced population sc and id routes were essentially equivalent.

Philip[19] administered A2/IACHI/2/68 vaccine to female nursing students in 1968: 400 chick cell agglutinating (CCA) units by the sc route, 80 CCA units by the id route, or 400 CCA by nasal drop. The rates of fourfold or greater seroconversion, 89, 79 and 73 per cent, respectively, were not significantly different from each other. However, geometric mean titers of 46.7, 26.7, and 18.8, respectively, did vary significantly. Marks[20] also used A2/IACHI/2/68 vaccine to inoculate 24 adults with 160 CCA units id and a non-comparable group of 98 institutionalized retarded children with 400 CCA units sc. Eighty-six per cent of each group with initially undetectable antibody had fourfold or greater seroconversions; the geometric mean titer reached 63 for the id and 56 for the sc groups.

Payler,[21] in 1973, administered A/England/42/72, B/VIC/98926/70, and B/Hong Kong/8/73 combined vaccine, either 1 ml sc or 0.15 ml id, by injector gun to schoolchildren. The result achieved by the sc route was superior but did not reach statistical significance.

Prior to this report, only one study evaluating the preferred route of immunization with the combined A/Victoria, A/New Jersey vaccine had been reported. Hutchinson[22] administered 0.1 ml of combined vaccine id to 38 adult health workers. Eleven of 17 had seroconversions to A/Victoria and 22 of 26 to A/New Jersey. These results suggest the efficacy of the id route for this vaccine, but since the study was uncontrolled, no judgment relative to other routes of administration can be made.

The route of influenza vaccination has been of interest to public health workers and clinicians for 40 years. If smaller doses of antigen administered by the id route are as effective as larger doses given by the sc or im route, then limited supplies of vaccine could be offered to more people. In addition, if the smaller id dose is associated with a lower rate of adverse reactions, immunization could be offered to more people at greater risk of serious consequences of influenza. For these reasons, in 1976, with the discovery of influenza A/Hsw_1/N_1 (swine flu) virus in recruits at Fort Dix, New Jersey,[23] and the potential for a shortage of vaccine if the National Influenza Immunization Program were to come near its stated goals of immunizing the entire population, we

TABLE 1—Cross-Table Comparison of Pre- and Post-Immunization Titers of Antibody to A/Victoria Influenza Virus in Persons Receiving Vaccine Subcutaneously

Pre-immunization Titer	Post-immunization Titer						
	<10	10	20	40	80	160	TOTAL
<10	3(9.1)*	4(12.1)	15(45.4)	11(33.3)			33
10		1(16.7)		3(50.0)	2(33.3)		6
20			3(23.1)	6(46.1)	1(7.7)	3(23.1)	13
40					4(66.7)	2(33.3)	6
80					2(66.7)	1(33.3)	3
TOTAL	3(4.9)	5(8.2)	18(29.5)	20(32.8)	9(14.8)	6(9.8)	61

*Number with titer (percentage of total).

launched a trial of influenza vaccine comparing the immunogenicity and adverse reactions of a small id dose of vaccine with those of a larger sc dose.

Methods

In the fall of 1976, a group of 18 to 24-year-olds were recruited from the staff of St. Barnabas Medical Center and the surrounding community to participate in the study. After informed consents were obtained, the volunteers were divided by alternate randomization into groups to receive sc (sc group) and id (id group) vaccinations.

The original design called for a prevaccination serologic analysis and vaccination on the first visit, a serologic analysis and a second vaccination one month later, and a third serologic analysis after an additional month. Midway in the study, cancellation of the National Immunization Program on December 16, 1976 prevented completion of our vaccination program and limited the data to titers of prevaccination serum specimens and one postvaccination specimen. For the same reason, a promise to vaccinate the participants by the alternate route, if the prior two vaccinations had not resulted in seroconversion, could not be kept. Each participant was supplied an oral thermometer and instructed to record temperatures for each three days after vaccination. Participants were also given a questionnaire about specific symptoms for the same days and a list of physicians' phone numbers for emergency advice.

Serologic Techniques: Serum was collected and stored frozen until tested. Immunization routes were not revealed to the serologist. Paired sera were analyzed at the same time. Standard techniques[24] were used for the hemagglutination inhibition test. Antigens used were influenza A/New Jersey/8/76 and A/Victoria/75. The A/Victoria antigen was grown by the New Jersey State Department of Health from an A/Victoria virus isolated in New Jersey in 1976.

Vaccine: One lot of bivalent "split-virus" influenza vaccine was used for all participants.* For id injection, we used 0.1 ml of vaccine containing 40 CCA units of influenza A/New Jersey/76 (Hsw_1 N_1) virus and 40 CCA units of influenza A/Victoria/75 (H_2 N_2) virus. For sc injection, we used 0.5 ml of vaccine containing 200 CCA units of each vaccine. Two allergists with long experience in giving id injections administered all vaccine by needle and syringe.

Statistical Methodology: Significant differences were tested with Fishers exact t-test and the chi-square test (with Yates correction for continuity applied when appropriate). In computing geometric mean values, we omitted titers less than 10.

Results

Initially, 145 persons participated in the study: 72 in the sc group and 73 in the id group. Sixty-one of the sc group and 64 of the id group had a second serologic analysis (X^2 = 0.265, not significant [NS]). The interval from influenza immunization to second serologic study for the sc group ranged from 20 to 77 days (mean, 30.3 days), and for the id group from 20 days to 67 days (mean, 30.4 days).

A/Victoria

Tables 1 and 2 show the hemagglutination inhibition titers before and after immunization against A/Victoria antigen for individuals receiving sc and id inoculations.

On pre-immunization screen, there was no significant difference in the per cent range of each group with detectable antibody. Twenty-eight of 61 (45.9 per cent) of the sc group and 31 of 64 (48.4 per cent) of the id group had pre-immunization titers of ≥10 (X^2 = 0.081, ns). The geometric mean titer of detectable antibody was 23.2 for the sc group and 20.91 for the id group (T_{57} = 0.610, NS).

In the post-immunization serologic analysis, antibody was detectable (≥10) in 58 (95.1 per cent) of the sc group and in 62 (96.8 per cent) of the id group. A significantly smaller fraction of the sc group (36.1 per cent X^2 = 4.366, $p < 0.05$) had a fourfold rise in antibody titer compared with the id group (54.7 per cent). The geometric mean titer of detectable antibody was 40.97 in the sc group and 55.32 in the id group (T_{118} = 1.882, NS).

*Parke-Davis Influenza Virus Vaccine Bivalent, Type A., Lot #913340A.

TABLE 2—Cross-Table Comparison of Pre- and Post-Immunization Titers of Antibody to Type A/Victoria Influenza Virus in Persons Receiving Vaccine Intradermally

Pre-immunization Titer	Post-immunization Titer								
	<10	10	20	40	80	160	320	640	TOTAL
<10	2(6.1)*	2(6.1)	11(33.3)	18(54.5)					33
10		1(11.1)			3(33.3)	3(33.3)	1(11.1)	1(11.1)	9
20				7(46.7)	6(40)	2(13.3)			15
40				3(60.0)	1(20)	1(20)			5
80					1(100)				1
160						1(100)			1
TOTAL	2(3.1)	3(4.7)	11(17.2)	28(43.7)	11(17.2)	7(10.9)	1(1.6)	1(1.6)	64

*Number with titer (percentage of total).

Considering only those participants with pre-immunization titers of <10, titer rises to ≥40 in post-immunization sera occurred in 11 of 33 (33.33 per cent) in the sc group and 18 of 33 (54.5 per cent) of the id group ($X^2 = 3.014$, NS). The geometric mean titer of detectable antibody in post-immunization serologies in the sc group was 28.94 compared with 39.12 in the id group ($T_{59} = 1.401$, NS). The distribution of post-immunization titers into the categories <10, 10, 20, and 40+ did not vary significantly between groups ($X^2_3 = 3.1717$, NS).

Among the participants with pre-immunization titers of ≥10, fourfold rises in titer in post-immunization serum occurred in 11 of 28 (39.2 per cent) in the sc group, and 17 of 31 (54.8 per cent) in the id group ($X^2 = 1.427$, NS). The geometric mean titer of detectable antibody in post-immunization serum was 59.44 for the sc group and 78.23 for the id group ($T_{57} = 1.373$, NS).

Swine Flu

Sixty of 61 volunteers in the sc group had undetectable titers of antibody to swine flu antigens as did all those in the id group. One participant was excluded from subsequent analysis because she had detectable antibody. Her initial titer was 20 and rose to 80 in a post-immunization serum specimen drawn at 29 days. No significant difference was found between the sc and id groups in the distribution of post-immunization titers (Table 3). In addition, there was no significant difference in percentage with titers of ≥10, (39 of 60, or 65 per cent, of the sc group and 38 of 64, or 59.4 per cent of the id group), of ≥20 (33 of 60, or 55 per cent of the sc group, and 29 of 64, or 45.3 per cent of the id group, $X^2 = 1.479$, NS), nor of ≥40 (12 of 60, or 20 per cent of the sc group and 13 of 64, or 20.3 per cent of id group, $X^2 = 0.002$, NS). The mean titer of detectable post-immunization antibody for the sc groups was 25.19, which is not significantly different from the 22.71 in the id group ($T_{75} = 0.697$, NS).

Adverse Reactions

No significant difference was found between the sc and id groups in either the percentage returning the adverse reaction questionnaire, having an oral temperature above 100° F, or experiencing any systemic symptoms. The rate of local reaction bordered on significance with the id group, exceeding the rate for the sc group (Table 4).

Discussion

Our own study supports the equivalent efficacy of the id and sc routes of vaccination. For the A/Victoria component, the id route was significantly superior. Trends toward superiority, although not significant, were evident for the subgroups with and without detectable preimmunization antibodies. Had our study been larger, these differences might have proved significant. For the A/New Jersey component, no significant difference in efficacy between routes was evident. The paltry seroconversion rates for A/New Jersey are consistent with results of field trials that tested the im route.[25] The injections in our study were given by two allergists with long experience with the id route. The results may not be comparable in the hands of those less proficient with id injection.

The systemic reaction rates for both routes in our study are comparable and consistent with rates for split-virus vaccine observed in the national field trials.[25] Two previous studies of modern, zonal, ultracentrifuged vaccine, administered by alternate routes, have also failed to demonstrate a difference in reaction rates.[19, 20] If these findings are repro-

TABLE 3—Distribution of Post-Immunization Titers of Antibody to Type A Swine Flu in Subcutaneous and Intradermal Groups

Titer	Subcutaneous		Intradermal	
	No.	(%)	No.	(%)
<10	21	(35)	26	(41)
10	6	(10)	9	(14)
20	21	(35)	16	(25)
40+	12	(20)	13	(20)
TOTAL	60	(100)	64	(100)

$X^2 = 1.7203$, N.S.

TABLE 4—Adverse Reactions to Vaccination Against Influenza by the Subcutaneous and Intradermal Routes

Reaction	Subcutaneous Route		Intradermal Route		
	No.	Percentage	No.	Percentage	Statistic
Temperature greater than 100° F	2	3.6	1	1.8	F.E.P. = 0.613 N.S.
Local reaction	13	23.2	23	41.1	$X^2 = 0.210$ N.S.
Any one or more of following symptoms	33	58.9	32	50.0	$X^2 = 0.210$ N.S.
Muscle ache	14	25.2	22	39.3	
Feverish	15	26.8	9	16.1	
Chills	10	17.9	11	19.6	
Vomiting	2	3.6	1	1.8	
Headache	25	44.6	17	30.4	
Diarrhea	4	4.1	8	14.3	
TOTAL	56		56		

ducible in field trials using different age groups with varied immunologic experience, there will be little justification for the assumption that the id route minimizes systemic reactions. The rationale for this choice has been based, apparently, on the diminished reaction rates seen with the id route when older, less-refined vaccine was available.

In times of shortage of vaccine and predicted pandemic or epidemic influenza, questions of "significant" superiority or inferiority of route of immunization are spurious. In a large vaccine efficacy trial, a small difference in seroconversion rate, or mean titer reached, can be significant statistically. However, if the goal is to maximize benefit for the population rather than the individual, a route that requires substantially less antigen mass, even if slightly less efficacious, may be chosen. This situation is not totally hypothetical; it did occur in 1957 when, at times, the id route was used to conserve vaccine. Thus, evaluation of influenza vaccine, especially of a new antigenic strain, should routinely include a trial to evaluate the efficacy of using a smaller dose by the id route.

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