

ORIGINAL ARTICLE

## Dose Sparing with Intradermal Injection of Influenza Vaccine

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### ABSTRACT

#### BACKGROUND

The loss of half the U.S. supply of influenza vaccine due to contamination has created a critical shortage. Dose-sparing strategies that use intradermal delivery of vaccines may be one approach to consider.

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#### METHODS

We conducted a randomized, open-label trial outside the influenza season in 100 healthy adults 18 to 40 years of age to compare the immunogenicity and safety of intradermal immunization with influenza vaccine with standard intramuscular immunization. Subjects were randomly assigned to receive either a single intramuscular dose of 0.5 ml of trivalent influenza vaccine, containing at least 15  $\mu$ g of hemagglutinin per strain, by means of a prefilled syringe or a single intradermal dose of 0.1 ml, containing at least 3  $\mu$ g of hemagglutinin per strain, by means of a fine-gauge needle; both injections were in the deltoid region. Changes in the hemagglutination-inhibition (HAI) antibody titer were assessed by comparing geometric mean titers and fold increases relative to baseline values and by comparing changes in the seroconversion and seroprotection rates. Local and systemic adverse events were assessed after both types of vaccination.

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#### RESULTS

Subjects who received an intradermal injection with one fifth the standard dose of influenza vaccine had increases in the geometric mean HAI titer by a factor of 15.2 for the H1N1 strain in the vaccine, 19.0 for the H3N2 strain, and 12.4 for the B strain on day 21, as compared with respective increases by a factor of 14.9, 7.1, and 15.3 for the intramuscular injection of the standard dose. Seroconversion and seroprotection rates were similar in the two groups on day 21, ranging from 66 to 82 percent and 84 to 100 percent, respectively. Local reactions were significantly more frequent among recipients of intradermal injections than among recipients of intramuscular injections, but such reactions were mild and transient.

#### CONCLUSIONS

In this study of young adults, intradermal administration of one fifth the standard intramuscular dose of an influenza vaccine elicited immunogenicity that was similar to or better than that elicited by intramuscular injection. Intradermal administration could be used to expand the supplies of influenza vaccine, but further studies are needed before this strategy can be recommended for routine use.

VACCINATION AGAINST INFLUENZAVIRUS is an important public health measure to help protect against the annual morbidity and mortality associated with influenza. A major global supplier of influenza vaccine recently experienced manufacturing problems that led regulatory authorities to declare more than 48 million doses, almost half the U.S. supply of influenza vaccine, unfit for use.<sup>1</sup> This has created a public health crisis, with widespread shortages leaving many in the United States without vaccine coverage. Various emergency measures are being considered in an effort to expand the supply and consist either of reducing the intramuscular dose or importing doses from manufacturers that do not usually supply the United States. We studied a simple approach to vaccine administration that could ease the predicament faced by public health authorities.

The immune system in the skin has been recognized as a desirable target for vaccination, and there has been a surge in research on the delivery of vaccines into the skin.<sup>2</sup> The barrier function of the skin's immune system can be exploited for vaccination, since over 25 percent of the body-surface area is covered by dendritic cells, a form of antigen-presenting cell whose function is to recognize foreign microbes and initiate an effective immune response.<sup>3</sup> Delivery into the skin is effective for several vaccines — for example, bacille Calmette–Guérin vaccine is usually administered intradermally. The use of a different technique of skin delivery — scarification — for smallpox vaccine resulted in the worldwide elimination of this highly virulent disease, which is one of the great triumphs of modern public health.<sup>4</sup>

Intramuscular injection of vaccine bypasses the skin's immune system and delivers influenzavirus and other antigens into tissue that has no important resident population of antigen-presenting cells. Antigen delivered to muscle tissue is thought to be picked up by transient antigen-presenting cells or simply to circulate to the draining lymph node. By contrast, intradermal injection delivers antigen directly into the skin, an anatomical space that contains large numbers of antigen-presenting cells and thus has the potential for greater immunogenicity than intramuscular injection of a given amount of antigen. Studies involving intradermal injection of hepatitis B virus and rabies vaccines suggest the potential for improved immunogenicity,<sup>5-7</sup> but such studies are complicated by the fact that only small volumes of fluid can be injected, and thus direct

dose-for-dose comparisons are more difficult to conduct.

Intradermal injection of a fraction of the dose of commercial influenza vaccine would be a highly desirable dose-sparing strategy if it was found to be as immunogenic as a full-dose intramuscular injection, since it would allow a greater degree of responsiveness to public health emergencies and would have relevance for both annual influenza endemics and pandemic events. Intramuscular injection of a half dose of commercial influenza vaccine has been shown to result in smaller immune responses than intramuscular injection of a full dose.<sup>8</sup> We evaluated the immunogenicity of a simple intradermal injection of one fifth the intramuscular dose of commercial influenza vaccine with a tuberculin syringe.

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## METHODS

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### STUDY DESIGN

This open-label, randomized study was part of a larger study to evaluate influenza vaccination in healthy men and women 18 to 40 years of age that was conducted by SGS Life Sciences Services at the Stuienberg Hospital in Antwerp, Belgium. The objectives of this study were to compare the immune responses achieved by intramuscular and intradermal injections of influenza vaccine and to evaluate the safety of the different routes of administration. The final protocol and associated documents were approved by the local independent ethics committee (Commissie voor Medische Ethiek, Antwerp, Belgium). Recruitment occurred in May and June 2004, and vaccinations were given during June 2004.

### VACCINATION

One hundred subjects were recruited and provided written informed consent before enrollment. Subjects were considered ineligible if they had any clinically significant abnormalities in their medical history (including immunocompromising conditions) or on physical examination, serum chemical analysis, hematologic analysis, or urinalysis. A randomization list with a block size of four, generated by the sponsor, was used to assign study subjects to receive a single intramuscular dose of 0.5 ml of trivalent influenza vaccine, containing at least 15  $\mu$ g of hemagglutinin antigen per strain, or a single intradermal dose of 0.1 ml, containing at least 3  $\mu$ g of hemagglutinin antigen per strain, in the deltoid region. Group assignment was based on the time of

arrival at the clinic and was performed by the site study nurse. Simulated arms were used to train the clinical staff at the study site to perform intradermal and intramuscular vaccination.

Intradermal vaccination was performed as follows: a prefilled dose of influenza vaccine was gently shaken and then expelled into a transfer vial. Approximately 0.2 ml of vaccine solution was drawn from the transfer vial through a 27-gauge, 1/2-in. (1.3-cm) detachable needle (PrecisionGlide slip tip, with an intradermal bevel) into a 1-ml syringe (calibrated in hundredths) (Becton Dickinson). Excess liquid and bubbles were expelled until the plunger was at the 0.1-ml mark. The vaccination site on the deltoid was identified, and skin on either side of the vaccination area was stretched. The needle was inserted at a 15-degree angle to the skin, approximately 2 mm into the superficial layers. The vaccine was slowly injected until all material was expelled and a blanched bleb appeared. Intramuscular vaccination was performed according to the standard clinical protocol.

The influenza vaccine (Fluvirin, Evans Vaccines) contained purified surface antigen of the influenza virus strains recommended by the World Health Organization for the 2003–2004 season: A/New Caledonia/20/99 IVR-116, an A/New Caledonia/20/99 (H1N1)-like strain; A/Panama/2007/99 Resvir-17, an A/Moscow/10/99 (H3N2)-like strain; and B/Shangdong/7/97, a B/Hong Kong/330/2001-like strain. Each 0.5-ml dose contained at least 15 µg of hemagglutinin antigen from each strain.

Subjects were observed for 30 minutes after vaccination to identify any acute reactions. All subjects were given a diary card so that they could record local and systemic reactions that occurred after immunization. Solicited adverse events included the following local and systemic reactions: an induration, an area of redness, or an ecchymosis more than 5 mm in diameter; malaise; shivering; and fever (body temperature higher than 37.5°C). Subjects were evaluated on days 0, 3, 7, 21, 42, and 90 after vaccination.

#### SEROLOGIC STUDIES AND OUTCOME MEASURES

Serum samples from days 0, 21, and 42 were simultaneously tested for strain-specific hemagglutination inhibition (HAI) by Focus Technologies (Cypress, Calif.). Results were reported for the A/New Caledonia/20/99, A/Panama/2007/99, and B/Hong Kong/330/2001 strains. The humoral response to the three strains contained in the influenza vaccine

was assessed by calculating the following: geometric mean titers before and 21 and 42 days after vaccine administration; fold increases in the titer on days 21 and 42 after vaccination (i.e., geometric means of the ratio of the antibody titer after vaccination to the antibody titer on day 0); the seroconversion rate (the percentage of subjects with a four-fold increase in HAI-antibody titers 21 and 42 days after vaccination, as compared with baseline titers and a titer of at least 1:40); and the seroprotection rate (the percentage of subjects with a titer of at least 1:40) before vaccination, as well as 21 and 42 days after vaccination.

#### STATISTICAL ANALYSIS

All analyses were performed with the use of SAS statistical software (version 8.2) and StatXact (version 6). Safety data were analyzed for all subjects in the intention-to-treat population after the visit on day 42. Stopping rules were based on the occurrence of one or more severe or serious adverse events that could be related to the vaccination. Adverse events were tabulated according to severity (none, mild, moderate, or severe) with the use of the Medical Dictionary for Regulatory Activities (MedDRA) code and were compared between groups by means of Fisher's exact test and the Cochran–Mantel–Haenszel test with the use of StatXact software.

In this phase 1–2 study, group sizes of 50 were chosen on the basis of prior experience, since this approach was considered to be an appropriate compromise between safety risks and the ability to interpret the immunogenicity and safety findings, as well as to comply with the standard European recommendation for an annual evaluation of the influenza vaccine.<sup>9</sup> Statistical analyses of continuous titer and fold-increase outcomes were performed on a logarithmic (base 10) scale so that the distribution would be roughly Gaussian. This approach facilitates the use of regression models for the immunogenicity data and permits the comparison of adjusted mean log outcomes among the groups. Geometric mean titers and fold increases were compared with the use of Student's *t*-test as well as generalized linear models adjusted for age, sex, and (after day 0) baseline titer. The rates of seroconversion and seroprotection were compared between the groups with the use of Fisher's exact test and logistic regression with the same covariates.

The equivalence of the vaccination approaches was assessed post hoc by determining the 95 percent confidence interval for the ratio of geometric

mean titers (as a percentage) between the intramuscular and intradermal groups. Two vaccines are typically considered equivalent if this confidence interval is sufficiently narrow and lies within a range of 80 to 125 percent. With the fold increase defined relative to day 0, approximate standard deviations in the  $\log_{10}$  titer and  $\log_{10}$  fold increase were 0.55 and 0.65, respectively, with little variation during the follow-up period or according to strain. The sample size of 50 per group thus means that the study would have 80 percent statistical power to identify a difference between the intramuscular and intradermal routes (with the use of a two-sided test and a type I error rate of 5 percent) for a ratio of 2.05 in the geometric mean titer and a ratio of 2.33 in the fold increase. No adjustment was used for multiple comparisons.

## RESULTS

### SAFETY

Fifty subjects each were randomly assigned to receive either intramuscular or intradermal influenza vaccination. The demographic characteristics of the subjects are shown in Table 1. There were no substantial deviations from the protocol, although one subject turned 41 years of age on the day of randomization. All related adverse events reported during this trial were mild and transient. Local reactions were more frequent among recipients of an intradermal injection than among recipients of an intramuscular injection; among them were erythema (frequency, 96 percent in the intradermal group vs. 8 percent in the intramuscular group), pruritus (42 percent vs. 4 percent), swelling (84 percent vs. 10 percent), and induration (34 percent vs. 8 percent) ( $P < 0.05$  for each comparison). There were no significant differences between the groups in the reported frequencies of other local or systemic adverse events (e.g., pain, pyrexia, shivering, headache, diarrhea, and malaise). Four unrelated serious adverse events resulted in hospitalization during the study (gastroplasty for chronic obesity, abdominoplasty for cosmetic purposes, arthroscopy due to injury, and nephrolithiasis).

### IMMUNOGENICITY

The geometric mean titers, fold increases in titer, and rates of seroconversion and seroprotection in the two groups are shown in Table 2. The intramuscular and intradermal approaches both caused strong HAI responses to all three strains, which

**Table 1. Demographic Characteristics.**

Characteristic	Intramuscular Group (N=50)	Intradermal Group (N=50)
Age — yr		
Mean	31	31
Range	20–41	19–40
Male sex — no. (%)	15 (30)	29 (58)*
Race or ethnic group — no. (%)†		
White	49 (98)	50 (100)
Asian	1 (2)	0
Weight — kg		
Mean	75.3	78.1
Range	44.1–109.6	50.8–104.2
Height — cm		
Mean	170.6	173.3
Range	154.8–187.2	156.8–187.8
Influenza vaccination in past 3 yr — no.	11	2‡

\*  $P=0.003$  by Fisher's exact test.

† Race was determined during an initial interview.

‡  $P=0.006$  by Fisher's exact test.

were highest on day 21. There was no significant difference between the injection routes in the HAI response and the fold increase in titer for the A/New Caledonia (H1N1) or B/Hong Kong strain on day 21, although the response to B/Hong Kong was better in the intramuscular group than in the intradermal group by day 42. On the other hand, the response to the A/Panama (H3N2) strain was significantly greater after intradermal injection than after intramuscular injection with respect to both the geometric mean titer and the fold increase on both day 21 and day 42.

Seroconversion rates on day 21 ranged from 66 percent to 82 percent for the intramuscular route, as compared with 78 percent to 82 percent for the intradermal route, with no significant difference between the routes for any strain on the basis of logistic regression. It is generally thought that an HAI response of at least 1:40 leads to protection against strain-matched disease in more than 50 percent of vaccine recipients. After vaccination, the seroprotection rates (defined by an HAI response of at least 1:40) achieved by both approaches on day 21 were high and similar (84 to 100 percent). The absolute changes in the rates of seroprotection from day 0 to day 21 were also similar in the two groups

**Table 2. Strain-Specific Hemagglutination Inhibition.\***

Variable	A/New Caledonia (H1N1)				A/Panama (H3N2)				B/Hong Kong			
	Day 0	Day 21	Day 42	Day 0	Day 21	Day 42	Day 0	Day 21	Day 42	Day 0	Day 21	Day 42
<b>Geometric mean titer Value (95% CI)</b>												
Intramuscular group	10 (8 to 14)	153 (106 to 221)	131 (91 to 188)	28 (19 to 43)	201 (143 to 282)	171 (123 to 238)	19 (14 to 27)	297 (215 to 409)	253 (181 to 353)			
Intradermal group	8 (7 to 10)	126 (85 to 189)	112 (73 to 170)	23 (15 to 33)	431 (291 to 640)†	373 (256 to 544)†	14 (10 to 19)	175 (130 to 236)	147 (113 to 192)‡			
95% CI for ratio of geometric mean — %	85 to 180	70 to 210	67 to 205	71 to 221	28 to 79	28 to 76	86 to 217	109 to 264	112 to 264			
<b>Fold increase in geometric mean titer Value (95% CI)</b>												
Intramuscular group		14.9 (9.5 to 23.5)	12.7 (8.2 to 19.8)		7.1 (4.8 to 10.3)	6.0 (4.3 to 8.5)		15.3 (10.0 to 23.5)	13.1 (8.5 to 20.2)			
Intradermal group		15.2 (10.3 to 22.5)	13.4 (9.0 to 20.1)		19.0 (11.4 to 31.8)†	16.4 (10.1 to 26.7)†		12.4 (8.2 to 18.6)	10.4 (7.2 to 15.1)‡			
95% CI for ratio of fold increase — %		53 to 179	52 to 173		19 to 71	20 to 67		68 to 225	70 to 224			
<b>Seroconversion rate (%)</b>												
Intramuscular group		78	74		66	60		82	78			
Intradermal group		82	84		78	78		82	72			
Difference between groups (95% CI)		-4 (-20 to 12)	-10 (-26 to 7)		-12 (-30 to 7)	-18 (-36 to 1)		0 (-16 to 16)	6 (-11 to 23)			
<b>Seroprotection rate (%)</b>												
Intramuscular group	24	94	90	50	98	94	38	100	100			
Intradermal group	10	84	86	42	96	96	28	100	92			
Difference between groups (95% CI)		14 (-1 to 30)	4 (-10 to 18)	8 (-12 to 28)	2 (-7 to 12)	2 (-13 to 8)	10 (-9 to 26)	0	8 (0 to 19)			

\* CI denotes confidence interval.

† P&lt;0.001 for the comparison with the intramuscular group with the use of a generalized linear model.

‡ P&lt;0.04 for the comparison with the intramuscular group with the use of a generalized linear model.

(70 percent for A/New Caledonia (H1N1), 48 percent for A/Panama (H3N2), and 62 percent for B/Hong Kong in the intramuscular group, as compared with respective values of 74 percent, 54 percent, and 72 percent in the intradermal group).

To compare quantitative HAI outcomes between the intramuscular and intradermal routes, we estimated the ratios of the geometric mean titers and the fold increases and their 95 percent confidence intervals. As might be expected, given the available sample size, formal vaccine equivalence was not demonstrated for the A/New Caledonia (H1N1) and B/Hong Kong strains. However, the 95 percent confidence interval for the A/Panama (H3N2) strain was wholly below the accepted range of equivalence (geometric mean titer, 28 to 71 percent; fold increase, 19 to 71 percent), suggesting the intradermal approach was superior in this case, in agreement with the results of the t-test comparison. Similarly, all the 95 percent confidence intervals for the differences between the intramuscular and intradermal routes in the rates of seroconversion and seroprotection included 0, indicating that differences between the groups in these binary outcomes were not significant.

#### DISCUSSION

We evaluated the relative immunogenicity and safety of intramuscular and intradermal injection of influenza vaccine, and our results support the use of a dose-sparing strategy for influenza vaccination. The data clearly show that intradermal injection of one fifth the standard dose of commercial influenza vaccine elicits immune responses that are similar or superior to those elicited by a full dose of vaccine given intramuscularly to healthy young adults. This strategy is particularly appealing, because standard tuberculin syringes and needles can be used with multidose vials of influenza to increase the supply of influenza vaccine by a factor of about five. The correlates for protection against influenza are not without controversy, but it is generally accepted that antibodies confer protection and that the HAI response represents a fair surrogate marker.<sup>10-12</sup> Thus, our data show that using one fifth the dose of commercial vaccine can achieve HAI-antibody titers that differ little from those induced by the standard dose of influenza vaccine and suggest that the change to an intradermal approach may be expected to elicit protective immune responses.

The dose of influenza vaccine was standardized

in the early 1980s after the development of consistent methods of potency testing and the realization that most of the annual variation in response could be minimized with the use of a 15- $\mu$ g dose of hemagglutinin per strain. Although the response can be enhanced by increasing the dose, going beyond a dose of 15  $\mu$ g appears to have diminishing returns.<sup>13,14</sup> Cutting the intramuscular dose in half decreased the response to all three antigens, but the differences were small enough that this was thought to be a reasonable approach if vaccine happened to be in short supply.<sup>8</sup>

Intradermal administration is generally studied with the same concentration of product as intramuscular administration but involves injection of a smaller volume. Several studies conducted in the 1970s used monovalent or bivalent influenza preparations that were less standardized than more recent commercial vaccines and suggested that the response to intradermal injection is similar to the response to intramuscular or subcutaneous administration,<sup>15-18</sup> but to our knowledge, no subsequent reports have been published. A more recent study using two different jet-injection devices delivering 0.2 to 0.5 ml of a modern, split-virus influenza vaccine induced responses similar to those evoked by a 0.5-ml intramuscular dose.<sup>19</sup> However, because older versions of jet injectors resulted in transmission of hepatitis B virus from patient to patient, newer devices are being redesigned and tested for safety,<sup>20</sup> and they are not yet available for widespread use. In the current study, we elicited similar or better responses with intradermal injection using a standard needle and tuberculin syringe.

It is possible that results similar to ours would not be seen in other populations, such as elderly persons, young children, or those with underlying medical conditions. In addition, vaccines from other manufacturers may behave differently. Our study was limited to healthy young adults, was conducted in central Europe, and used one supplier's vaccine from a single year. Although the percentage of men and the number of subjects with a history of influenza vaccination in the preceding three years differed significantly between the two groups, correction for age, sex, and baseline HAI titers enabled us to make a statistical comparison. Further work is needed to demonstrate the wide-ranging relevance of reduced-dose intradermal injection of influenza vaccine before this approach can be recommended for routine use. Such studies are urgently needed to provide options for expanding the use of annual

influenza supplies as well as to prepare for pandemic influenza.

The relative immune responsiveness of the skin's immune system has been a topic of great interest to vaccine researchers. The dense population of first-line immune cells (dendritic cells) suggests that the skin is an ideal target for the delivery of vaccine antigen. Strategies to target the skin with patches, injectors, and other devices are being developed and hold promise. Our data reinforce the assertion that the immune system of the skin is a feasible and practical target and suggest that the relative immunogenicity of intradermal administration of influenza vaccine should at least equal that of intramuscular injection. This finding points to the viability of a dose-sparing strategy involving intradermal

injection with a fraction of the intramuscular dose, a technique that is used worldwide for bacille Calmette-Guérin vaccination<sup>21</sup> and in the United States for tuberculin testing. We believe skilled health care workers can be trained to administer vaccines by intradermal injection. Within the limitations of our study, we recommend that policymakers carefully consider the use of dose-sparing intradermal injection of influenza vaccine in select groups as a solution to future shortages of influenza vaccine.

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Iomai is developing patches for transcutaneous delivery of vaccines, none of which were used in the study.

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