*Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.*



# Intradermal injection of reduced-dose influenza vaccine was highly immunogenic in persons ≤ 60 years of age but less so in persons > 60 years

Belshe RB, Newman FK, Cannon J, et al. **Serum antibody responses after intradermal vaccination against influenza.** N Engl J Med. 2004;351:2286-94.

## QUESTION

Is a reduced-dose intradermal injection of influenza vaccine as immunogenic as a standard-dose intramuscular injection?

## METHODS

**Design:** Randomized controlled trial.
**Allocation:** {Allocation concealed}†.*
**Blinding:** {Unblinded}†.*
**Follow-up period:** 21 to 28 days.
**Setting:** 2 clinical centers (St. Louis, Missouri, and Rochester, New York, USA).
**Patients:** 238 persons ≥ 18 years of age (130 persons 18 to 60 y [mean age 39 y, 63% women] and 108 persons > 60 y [mean age 62 y, 52% women]) who were free of obvious health problems. Exclusion criteria were receipt of immunosuppressants or other immune-modifying drugs in the previous 2 months, pregnancy, or lactation.
**Intervention:** Intradermal injection of 0.1 mL of trivalent inactivated influenza vaccine (GlaxoSmithKline) containing 6 μg of hemagglutinin antigen for each of 3 strains (A/New Caledonia/20/99 [H1N1], A/Panama/2007/99 [H3N2], and B/Johannesburg/5/99) (40% of the intramuscular dose) ($n$ = 119) or intramuscular injection of 0.5 mL of U.S.-licensed influenza vaccine (Fluzone, Aventis Pasteur) containing 15 μg of hemagglutinin antigen for each of 3 strains (A/New Caledonia, A/Panama, and B/Victoria/504/2000) ($n$ = 119).
**Outcomes:** Immunogenicity of the vaccines assessed with hemagglutination-inhibition (HAI) titers and determination of whether it met the guidelines of the European Committee for Proprietary Medicinal Products (CPMP) for annual relicensure of influenza vaccines (adults 18 to 60 y: seroconversion rate [percentage of persons with increase in HAI titers ≥ factor of 4 after vaccination] must be > 40%, seroconversion factor [fold increase in HAI titers after vaccination] must be > 2.5, and seroprotection rate [percentage of persons with HAI titer ≥ 1:40 after vaccination] must be > 70%; adults > 60 y: > 30%, > 2.0, and > 60%, respectively).
**Patient follow-up:** 95% for analysis of immunogenicity.

## MAIN RESULTS

In persons 18 to 60 years of age, the intradermal and intramuscular groups did not differ for immunogenicity—all persons had HAI titers ≥ 1:40 in response to each of the strains in the vaccines. HAI titers were lower for all strains in persons > 60 years of age than in younger persons. The intramuscular group had higher geometric mean HAI titers for A/Panama than did the intradermal group (Table). The seroconversion rate was < 30% in both intradermal and intramuscular groups except for A/Panama in the intramuscular group (39.1%). Local reactions were more common in the intradermal group for both age groups. Local pain was less common in the younger intradermal group.

## CONCLUSION

A reduced-dose intradermal injection of influenza vaccine prompted an antibody response similar to that of a standard-dose intramuscular injection in persons 18 to 60 years of age but was less immunogenic in persons > 60 years.

*Source of funding: GlaxoSmithKline.*

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*See Glossary.
†Information provided by author.

**Reduced-dose intradermal vs standard-dose intramuscular influenza vaccination in persons > 60 years of age‡**

| Strain | Geometric mean titer (95% CI) | | Ratio of geometric mean (CI) | *P* value |
|---|---|---|---|---|
| | Intradermal | Intramuscular | | |
| A/Panama | 136 (100 to 186) | 238 (168 to 338) | 1.8 (1.1 to 2.8) | 0.009 |

‡CI defined in Glossary.

## COMMENTARY

Influenza causes annual epidemics that are associated with excess morbidity and mortality in high-risk persons and excess antibiotic use, medical visits, and work days lost in healthy persons. Our main weapon against this predictable battle is immunization, which is offered each fall in targeted campaigns to persons at high risk for serious complications (e.g., underlying pulmonary disease) or their caregivers. In recent years, a few jurisdictions have embarked on universal influenza vaccine programs, but most public health programs target subpopulations and encourage, rather than recommend, influenza vaccine in healthy persons. The fragility of the influenza vaccine system became clear in the 2004 to 2005 season, with the withdrawal of 1 of the 2 suppliers of inactivated influenza vaccine to the U.S. market. This cut the national vaccine supply in half and precipitated heroic efforts by the public health community to ensure the most vulnerable persons received the available vaccine (1, 2).

The unexpected shortage this year is not the only reason that creative solutions are required to ensure an adequate, secure supply of efficacious influenza vaccines. Certain populations, particularly the elderly and the immunocompromised, do not mount vigorous immune responses to available vaccines. Protection from disease varies over time, depending on the match between circulating and vaccine strains, the host's experience with the virus, and the immunogenicity of the product. A need exists to prepare for the next pandemic of influenza in which ≥ 30% of the population could become ill. Consequently, many attempts have been made to improve influenza vaccines, such as different adjuvants to enhance immunogenicity, different formulations of vaccine (e.g., live attenuated and inactivated subunit), and different routes of antigen delivery (e.g., intranasal, intramuscular, and intradermal).

In the studies by Belshe and Kenney and their colleagues, low doses of inactivated influenza vaccines, licensed for intramuscular injection, were delivered to healthy participants by the intradermal route. This route of antigen delivery is known to engage the dendritic cell, a potent antigen-presenting cell located in peripheral tissues that links the innate arm of the immune system with the cellular and humoral arms (3). Dendritic-cell–based vaccination strategies have been explored for

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# Intradermal injection of reduced-dose influenza vaccine was immunogenic in young adults

Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. **Dose sparing with intradermal injection of influenza vaccine.** N Engl J Med. 2004;351:2295-301.

## QUESTION

Is an intradermal injection of one fifth the standard intramuscular dose of a commercial influenza vaccine as immunogenic as the standard-dose intramuscular injection in young adults?

## METHODS

**Design:** Randomized controlled trial.
**Allocation:** Unclear allocation concealment.*
**Blinding:** Unblinded.*
**Follow-up period:** 42 days.
**Setting:** A hospital in Antwerp, Belgium.
**Patients:** 100 persons 18 to 40 years of age (mean age 31 y, 66% women) who were free of clinically important abnormalities in their medical history or on physical examination, serum chemical analysis, hematolo-gic analysis, or urinalysis.
**Intervention:** Intradermal injection of 0.1 mL of trivalent influenza vaccine containing ≥ 3 µg of hemagglutinin antigen per strain ($n$ = 50), or intramuscular injection of 0.5 mL of vaccine containing ≥ 15 µg of hemagglutinin antigen per strain ($n$ = 50). The influenza virus strains were those recommended by the World Health Organization for the 2003 to 2004 season: A/New Caledonia/20/99 IVR-116, A/Panama/2007/99 Resvir-17, and B/Shangdong/7/97 (a B/Hong Kong/330/2001–like strain).
**Outcomes:** Immunogenicity of the vaccines assessed at 21 and 42 days with hemagglutination inhibition (HAI): The response for the A/New Caledonia, A/Panama, and B/Hong Kong strains was assessed by calculating geometric mean titers, fold increases in titer (geometric means of the ratio of the antibody titer after vaccination to the antibody titer on day 0), seroconversion rate (percentage of persons with increase in HAI titers ≥ factor of 4 after vaccination), and seroprotection rate (percentage of persons with HAI titer ≥ 1.40 after vaccination).
**Patient follow-up:** 100% (intention-to-treat analysis).

## MAIN RESULTS

The intradermal and intramuscular groups did not differ in HAI response or fold increase in titer for the A/New Caledonia or B/Hong Kong strains on day 21. The intramuscular group had a better response to the B/Hong Kong strain on day 42 (Table). The intradermal group had better response to the A/Panama strain on days 21 and 42 (Table). The intradermal and intramuscular groups did not differ for seroconversion rate (ranges at d 21, 78% to 82% vs 66% to 82%) or seroprotection rate (ranges at d 21, 84% to 100% vs 94% to 100%). Local reactions were more common in the intradermal group but were mild and transient.

## CONCLUSION

An intradermal injection of one fifth the standard intramuscular dose of a commercial influenza vaccine had a response similar to or better than that of a standard-dose intramuscular injection for 3 World Health Organization–recommended strains in young adults.

*Source of funding: National Institutes of Health.*

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*See Glossary.

**Reduced-dose intradermal vs standard-dose intramuscular influenza vaccination†**

| Strain | Day | Geometric mean titer (95% CI) | | CI for ratio of geometric mean | *P* value |
|---|---|---|---|---|---|
| | | Intradermal | Intramuscular | | |
| A/Panama | 21 | 431 (291 to 640) | 201 (143 to 282) | 28 to 79‡ | < 0.001 |
| | 42 | 373 (256 to 544) | 171 (123 to 238) | 28 to 76‡ | < 0.001 |
| B/Hong Kong | 42 | 147 (113 to 192) | 253 (181 to 353) | 112 to 264§ | < 0.04 |

†CI defined in Glossary.
‡Favors intradermal injection.
§Favors intramuscular injection.

## COMMENTARY *(continued from page 68)*

several infectious agents and have become an exciting new pathway for vaccine development and immune intervention.

Before large phase III efficacy trials are done, the candidate vaccines must succeed in phase I and II trials. The trials by Kenney and Belshe and colleagues evaluated immunogenicity rather than efficacy, and standard serologic correlates of vaccine protection were used as outcome measures. Both trials showed that intradermal administration of lower doses of inactivated vaccine compared favorably with standard doses of their intramuscular counterparts.

Much more must be learned about this new method of vaccine delivery before it enters clinical practice. We need to know more about the immunogenicity of intradermal vaccination in high-risk persons, particularly older adults, immunocompromised patients, and children. While the adverse events were confined to transient local injection site complaints, only larger trials would identify less common events and estimate their frequency with some precision. Devices that ensure intradermal administration of vaccine will need to be considered in future research. In both trials, a visible wheal was taken as confirmation that intradermal injection occurred; Belshe and colleagues used a disk that limited skin penetration, while Kenney and colleagues used a method similar to administration of a Mantoux test. These and other considerations will need to be included in the design of larger randomized controlled efficacy trials of intradermally administered influenza vaccines. These studies provide evidence that such studies are worth pursuing.

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