

## Intradermal Vaccination against Influenza

**TO THE EDITOR:** I have been interested in the coverage by the media of the studies of intradermal influenza vaccination by Belshe et al.<sup>1</sup> and Kenney et al.<sup>2</sup> (Nov. 25 issue). We had quite similar findings — albeit without a control group — over 50 years ago.<sup>3</sup>

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1. Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. *N Engl J Med* 2004;351:2286-94.
2. 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.
3. Weller TH, Cheever FS, Enders JF. Immunologic reactions following the intradermal inoculation of influenza A and B vaccine. *Proc Soc Exp Biol Med* 1948;67:96-101.

**TO THE EDITOR:** In comparisons of intradermal and subcutaneous routes of inoculation, an important control is often omitted — namely, the comparison of equal doses of vaccine delivered by the two routes. This deficiency plagues the otherwise excellent studies of influenza vaccine by Belshe et al. and Kenney et al. An editorial in the same issue appears under the subtitle “Can Less Be More?”<sup>1</sup> Yes, it can — in a primed population. And in an immunologically “virgin” population (as in the pandemic of 1957) with a double-antigen change in the virus, it can at least be equal, as was shown by McCarroll and me in a report published in the *Journal* during that pandemic.<sup>2</sup>

Therefore, given the prospects of a pandemic or a vaccine shortage and the greater ease of subcutaneous injection of vaccine, future studies should compare apples with apples — without the assumption that either the booster or the priming effects of small doses of vaccine are dependent on the injection site, rather than the amount of vaccine given.

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1. La Montagne JR, Fauci AS. Intradermal influenza vaccination — can less be more? *N Engl J Med* 2004;351:2330-2.
2. McCarroll JR, Kilbourne ED. Immunization with Asian-strain influenza vaccine: equivalence of the subcutaneous and intradermal routes. *N Engl J Med* 1958;259:618-21.

**TO THE EDITOR:** As a hospital epidemiologist supporting mass immunization of health care workers against influenza, I welcome the recent studies in the *Journal* concluding that lower doses of intradermal influenza vaccine are equally immunogenic with the traditional intramuscular doses in younger, healthy adults. One cannot help but wonder, however, whether the findings of these studies were available to the Centers for Disease Control and Prevention (CDC) in early October 2004 (one month before the publication of the articles), when it advised against using partial doses of the recommended dosages of inactivated influenza vaccine<sup>1</sup> and instead recommended the use of live attenuated influenza vaccine (FluMist) in most health care workers. Unfortunately, data on the safety of the live attenuated vaccine in health care settings — with regard to transmission to susceptible patients — are lacking, the practice is not supported by the product label,<sup>2</sup> and such use is not approved by the Food and Drug Administration. Until safety data on the use of live attenuated influenza vaccine in health care settings become available, it would seem that the immunization of health care workers with reduced-dose injectable influenza vaccine would be preferable to the use of live attenuated vaccine during periods of vaccine shortage.

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1. Questions & answers: 2004-05 flu season. Atlanta: Centers for Disease Control and Prevention, January 18, 2005. (Accessed February 17, 2005, at <http://www.cdc.gov/flu/about/qa/0405season.htm>.)
2. Influenza virus vaccine live, intranasal, FluMist: 2004-2005 formula. Gaithersburg, Md.: Medimmune Vaccines, 2004.

**DR. BELSHE AND COLLEAGUES REPLY:** The study by Dr. Weller and his coworkers, conducted more than 50 years ago, foreshadowed many of the results of the recently published studies of intradermal influenza vaccine. Dr. Weller used a bivalent influenza A and B vaccine administered intradermally at 1/50th of the usual dose and observed serum antibody increases of 3.6-fold for influenza A and 2.9-fold for influenza B.<sup>1</sup> He also noted the local inflammatory responses that were seen in our more recent study.<sup>2</sup> Dr. Kilbourne correctly points out that low-dose

intramuscular vaccine in primed persons might have yielded responses equivalent to those observed after the administration of low-dose intradermal vaccine.<sup>3</sup> We agree that more definitive studies comparing the dose–response relationships of intradermally and intramuscularly administered influenza vaccine will be important to assess the potential benefits of intradermal immunization. These studies should include evaluation of the cell-mediated immune responses, as well as mucosal immune responses, in primed persons who receive intradermal vaccine.

Our study was preliminary, and the results should not be considered as definitive evidence that vaccination by the intradermal route will provide protection at the level currently provided by licensed influenza vaccines; larger studies to demonstrate the noninferiority of antibody responses after intradermal immunization, as compared with intramuscular immunization, and perhaps even vaccine-efficacy studies may be needed to elucidate the potential benefits of low-dose intradermal vaccination. We do not expect that recommending bodies such as the Advisory Committee on Immunization Practices (ACIP) would embrace this strategy without further data. In contrast, live attenuated vaccine has been studied extensively in adults and has been shown to be efficacious in this population. The ACIP recommendations preferentially recommending it for healthy persons such as health care workers in order to conserve trivalent influenza vaccine seemed quite reasonable in the face of a shortage of inactivated vaccine.

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1. Weller TH, Cheever FS, Enders JF. Immunologic reactions following the intradermal inoculation of influenza A and B vaccine. *Proc Soc Exp Biol Med* 1948;67:96-101.
2. Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. *N Engl J Med* 2004;351:2286-94.
3. Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. *Vaccine* 2002;20:1099-05.

**DRS. GLENN AND KENNEY REPLY:** Our report on intradermal influenza vaccination has brought to light some additional, older studies on the potential value of intradermal immunization.<sup>1,2</sup> Although they are informative, these early studies lacked relevant controls, were performed with monovalent vaccine, or used assays that were indicative but crude in comparison with those available today. The goal of our trial was not to compare doses, but rather to compare the responses — in a well-controlled study with the use of a highly reproducible immunoassay — to a modern trivalent influenza vaccine administered intradermally with as little as one fifth the normal dose of the available commercially licensed product.<sup>3</sup> We found a similar response with the two routes; statistically significant superiority was demonstrated for one strain as compared with the full intramuscular dose.

To move beyond these findings and make a general recommendation, a large, well-controlled, formal equivalence trial is needed to generate adequate data on safety and immunogenicity in several age groups. Although physicians may have elected to give influenza vaccine intradermally this year on the basis of the recent data, we recommend that this larger data set be generated quickly to support a public health recommendation for a dose-sparing strategy, particularly given the potential for pandemic influenza.

We disagree with Dr. Manian's contention that the CDC mishandled the information on dose-sparing vaccination this past fall, since it is this agency's duty to make sound policy recommendations, which must be based on larger efficacy and equivalence studies. In contrast, there is a tremendous amount of data on the safety of the live attenuated influenza vaccine. Although health care workers were asked to avoid severely immunocompromised patients after vaccination, in accordance with the package insert, the available safety data suggest that the CDC acted wisely in the midst of a supply crisis.

Dr. Kilbourne rightly points out that more should be learned about reduced-dose strategies. Treanor et al. recently studied half-dose intramuscular immunization against influenza and found reduced immune responses for all three strains, although they argue that these differences are not clinically significant.<sup>4</sup> Finally, we point out that the more permanent problem and principal unmet need in annual influenza immunization remains the vaccine's

relatively poor immunogenicity in elderly persons, leading to significant but substandard protection in the most susceptible population. The most lasting lesson from our recent data is the confirmation that the skin is a highly desirable immune environment for the delivery of vaccines. Targeting the skin may allow investigators to devise strategies for both dose sparing and improved immunogenicity in the elderly, as we have recently shown.<sup>5</sup>

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1. Weller TH, Cheever FS, Enders JF. Immunologic reactions following the intradermal inoculation of influenza A and B vaccine. *Proc Soc Exp Biol Med* 1948;67:96-101.
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## The U.S. Vaccine Supply

**TO THE EDITOR:** The National Vaccine Advisory Committee, of which I am a member, agrees with the Institute of Medicine (IOM) vaccine-financing committee<sup>1</sup> that legislative measures and additional funding are needed, but we differ with its recommendations for action, as described by Sloan et al. (Dec. 2 issue).<sup>2</sup> At the request of the IOM committee, the National Vaccine Advisory Committee convened stakeholder deliberations on vaccine-financing options and concluded that it is not advisable to replace the current system with an insurance mandate and a system of subsidies and vouchers, as the IOM recommends. We are skeptical that such a system would provide attractive incentives to manufacturers or would substantially improve immunization levels among children and adults.<sup>3</sup> We are concerned about undertaking a dramatic shift to an unproven, new model for which there is little detail and no estimate of costs. In addition, achieving the multiple simultaneous legislative changes that would be required at the national and state levels seems unlikely.

Instead of abandoning a system that has achieved record levels of immunization coverage, we recommend strengthening and expanding the two programs that currently supply approximately 57 percent of childhood vaccines (established under section 317 of the Public Health Service Act and the Vaccines for Children Program) and providing specific authorization and appropriations for programs to immunize adolescents and adults, including vaccine purchase.<sup>4</sup>

Harmonizing regulations between the United States and other countries and regions would facilitate the introduction of vaccines licensed in other countries that meet equivalent, although not identical, standards. Finally, since many practitioners currently lose money on immunizations,<sup>5,6</sup> we must ensure adequate reimbursement for the administration of vaccines to both children and adults.

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**TO THE EDITOR:** The Sounding Board article on the fragility of the U.S. vaccine supply by Sloan et al. makes a powerful case for a change in the way vaccines are produced and distributed in the United States. Unfortunately, the proposed reform favored