PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Immunogenicity and Safety of Intradermal Influenza Immunization at a Reduced Dose in Healthy Children

Susan S. Chiu, J.S. Malik Peiris, Kwok H. Chan, Wilfred Hing Sang Wong and Yu Lung Lau

Pediatrics 2007;119;1076-1082
DOI: 10.1542/peds.2006-3176

ARTICLE

Immunogenicity and Safety of Intradermal Influenza Immunization at a Reduced Dose in Healthy Children

Susan S. Chiu, MD, FAAP[a], J. S. Malik Peiris, DPhil, FRCPath, FRS[b,c], Kwok H. Chan, PhD[b], Wilfred Hing Sang Wong, MMedSc[a], Yu Lung Lau, MD[a]

Departments of [a]Pediatrics and Adolescent Medicine and [b]Microbiology, University of Hong Kong, Hong Kong, China; [c]Pasteur Research Centre, Hong Kong University, Hong Kong, China

Financial Disclosure: Dr Lau has conducted clinical trials for Wyeth, GlaxoSmithKline, Medimmune, and Merck Sharp and Dohme (Asia) Limited and is a member of the Steering Committee for Prevention and Control of Infectious Diseases in Asia for GlaxoSmithKline. The other authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVES. We conducted this study to test the hypothesis that intradermal influenza vaccination at one fifth of a standard dose elicits comparable immunogenicity to full-dose intramuscular vaccination in children.

PATIENTS AND METHODS. We conducted a randomized, open-label study in 112 healthy children aged 3 to <18 years to compare the immunogenicity and safety of intradermal vaccination at one fifth of a dose with standard intramuscular vaccination. Analyses of hemagglutination inhibition antibody titers to each antigen in each group included geometric mean titers before and 21 days after vaccination, fold increase in geometric mean titers after vaccination, seroprotection rate, and seroconversion rate.

RESULTS. The mean age of the subjects was 10.11 ± 4.04 years in the intradermal vaccination group and 10.57 ± 3.91 years in the intramuscular group. Intradermal vaccination was safe. Induration and mild erythema at the injection site were reported at 25% and 57%, respectively, in the intradermal group. Fold increase of geometric mean titers against influenza A/Caledonia was robust in both groups (11.1-fold and 12.9-fold increase in the intramuscular and intradermal groups, respectively), whereas that for B/Shandong was more modest (4.3–4.4). Both approaches elicited very high geometric mean titers against influenza A/Panama: 1360.5 and 893.9 for the intramuscular and intradermal groups, respectively, but because the prevaccination antibody titers were high, the fold increase of geometric mean titers was only 4.5 and 2.6, respectively.

CONCLUSION. The immunogenicity of one fifth of a dose of influenza vaccine delivered by the intradermal route is comparable to the standard-dose intramuscular vaccination in children as young as 3 years of age.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-3176

doi:10.1542/peds.2006-3176

Key Words
influenza vaccine, children, intradermal, reduced dosage

Abbreviations
H1N1—A/New Caledonia/20/99
H3N2— A/California/7/2004
HAI— hemagglutination inhibition
RDE—receptor-destroying enzyme
GMT— geometric mean titer

Accepted for publication Jan 30, 2007

Address correspondence to Susan S. Chiu, MD, FAAP, Department of Pediatrics and Adolescent Medicine, Queen Mary Hospital, Pokfulam, Hong Kong Special Administrative Region, China. E-mail: ssschiu@hkucc.hku.hk

SEASONAL INTERPANDEMIC INFLUENZA infection has serious health impacts worldwide, and vaccination is an important public health intervention.[1–5] Vaccination is also a key intervention in containing an influenza pandemic.[6,7] Even with well-established vaccine production for interpandemic influenza, shortage of supply sometimes occurs. Therefore, there is justified concern that when large populations need to be vaccinated within a short period of time, demand may exceed production capacity.

Intradermal vaccination exploits the abundance of antigen-presenting cells (macrophages and dendritic cells) that allow a robust immune response to be elicited with a small dose of antigen delivered directly to the skin, which may be a solution to vaccine shortage. Intradermal vaccination is not new. Bacille Calmette-Guerin vaccination, which is widely practiced in many parts of the world, is routinely performed by the intradermal route. Studies exploring intradermal vaccination were conducted with hepatitis B, rabies, and in influenza vaccines as early as the 1940s.[10–16] However, these early studies either had no control group or had control groups using the subcutaneous method of administration, were conducted with monovalent or bivalent vaccines with antigen dosages not directly comparable to those available now, lack a clear definition of response in at least 1 study, or used assays that were crude when compared with what is available today. Two recent articles reported on the effectiveness of intradermal influenza vaccination at a reduced dose in adults.[17–18] It is important to investigate the possibility of influenza vaccination using the intradermal approach in children.

METHODS

Study Design

This was an open-label, randomized study to compare the safety and immune responses of intramuscular administration of an inactivated influenza vaccine with intradermal administration of the same vaccine at one fifth of a dose in healthy children 3 to <18 years of age. The hypothesis was that intradermal vaccination with one fifth of a standard dose of influenza vaccine elicited comparable immunogenicity as full dose of intramuscular vaccination of the same vaccine. The study protocol was approved by the joint institutional review board of the University of Hong Kong and Queen Mary Hospital (Hong Kong) and was in accordance with the Helsinki Declaration of 1975, as revised in 1983. Subjects were patients who were admitted to the hospital for an acute illness or followed in our outpatient clinic. Written informed consent was obtained from parents and the older children before enrollment. Subjects were considered ineligible if they had an underlying condition that rendered them at risk for influenza complications or a need for regular medication. For children between 3 and <9 years of age, only those who had previous influenza vaccination were recruited to avoid the need for a second dose of immunization. Subjects were matched by age, and a computer-generated randomization list with a block size of 4 was used to assign study subjects to receive an intramuscular dose of 0.5 mL of inactivated trivalent influenza vaccine, or an intradermal dose of 0.1 mL of the same vaccine. Randomization was performed by study personnel immediately before vaccination. The randomization assignment was blinded to the laboratory investigators. All subjects had height and weight measured and the history of influenza vaccination in the previous year elicited. The children were vaccinated in October and November 2005, before the influenza season in Hong Kong that usually peaked in January or February.

Vaccination

The influenza vaccine (Fluarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) we used contained purified surface antigen equivalent to the influenza types and subtypes recommended by the World Health Organization for the 2005–2006 season: A/New Caledonia/20/99 (H1N1)-like strain; A/California/7/2004 (H3N2)-like strain, and B/Shanghai/361/2002-like strain. Each 0.5-mL dose contains at least 15 μg of hemagglutinin antigen per recommended strain.

Intramuscular injection was performed in the deltoid area according to standard procedure. Intradermal injection was performed using a 1-mL syringe calibrated in hundredths (Becton Dickinson, Franklin Lakes, NJ). One research nurse performed all the injections at each subject's deltoid area (Fig 1). The needle was inserted at a 15° angle to the skin according to standard intradermal injection techniques.[18] The resulting wheal was graded by the research nurse as 0 (no wheal), 1 (wheal size of 1–2 mm in diameter), 2 (3–5 mm in diameter), or 3 (>5 mm in diameter).

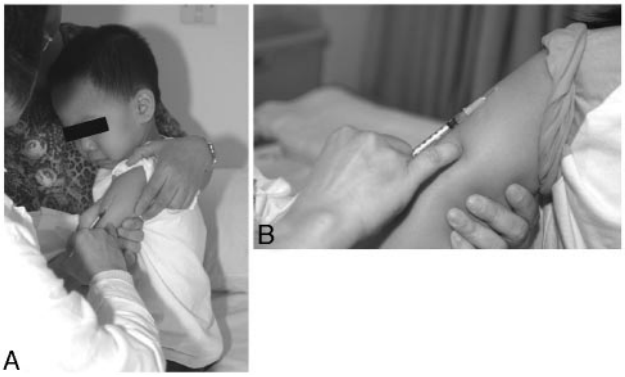

FIGURE 1
A, Intradermal vaccination using the 1-hand technique with the help of a caretaker in a 3-year-old boy during the study. B, Intradermal vaccination using the 1-hand technique.

Safety

Subjects were observed for 15 to 30 minutes after vaccination for acute reactions. Caretakers were given a diary card for recording of reactions for 3 days. Solicited reactions were fever, malaise, shivering, erythema, induration, and bruising of the injection site of >5 mm in diameter. Adverse effects were graded according to severity. A mild adverse event was one in which that the symptoms were easily tolerated, a moderate reaction caused interference with usual activities, and a serious one resulted in inability to perform usual activities. Research personnel retrieved the adverse events information on day 4 by telephone. Parents were asked to bring back the diary card for cross-checking when the subjects returned for the postvaccination blood draw.

Serologic Studies and Outcome Measures

Serum samples were drawn on day 0 (before vaccination) and day 21 from each subject. The paired samples were tested together by hemagglutination inhibition (HAI) using reference antigens provided as part of the World Health Organization kit provided by the World Health Organization Influenza Collaborating Centre, Centers for Disease Control and Prevention (Atlanta, GA). The sera were treated with receptor-destroying enzyme (RDE) (1:3) at 37°C overnight to remove nonspecific inhibitors, and residual RDE was destroyed by heat inactivation at 56°C for 30 minutes. Serial twofold dilutions of RDE-treated serum (1 in 10) were titrated in a 96-well microtiter plate against 4 hemagglutinin units of reference antigens (H1N1, H3N1, and B/Shanghai/361/2002-like) using 0.25% turkey erythrocytes.[19]

The following analyses were conducted on the antibody titers to each antigen obtained in the 2 groups of patients: geometric mean titers (GMTs) before and at 21 days after vaccination; fold increase in GMT (calculated as the mean of the ratio of titer before and 21 days after vaccination); the seroprotection rate (defined as the percentage of patients with antibody titers ≥40); and the seroconversion rate (calculated as the percentage of subjects with a prevaccination antibody titer of <40 who developed a fourfold rise or a titer of ≥40 after vaccination).[20] Those with a fourfold increase in antibody titer were determined for the intramuscular and intradermal vaccine groups overall, with subset analyses for those whose prevaccine antibody titer was <40 and for those ≥40.

Statistical Analysis

The 2 methods of vaccine administration are considered equivalent if the 95% confidence interval (CI) for the ratio of geometric mean titers (as a percentage) is sufficiently narrow and lies within a range of 80% to 120%. A sample size of 50 subjects per group would have 80% statistical power to identify a difference between the 2 methods using a 2-sided test and a type 1 error rate of 5%, to detect a significant difference of a minimum difference of a ratio of 2.05 in the geometric mean titer and a ratio of 2.33 in the fold increase between the 2 groups. Fifty-six subjects were recruited for each group to take into account an attrition rate of 12%. For the intention-to-treat analysis, missing values of convalescent serology would be assigned the mean value of the group. Pearson correlation was used to detect correlation between individual titers in the intradermal group with age, induration size and BMI. Adverse events for the 2 groups were compared by means of the χ^2 test.

RESULTS

Fifty-six subjects each were assigned randomly to receive either intramuscular or intradermal influenza vaccination. Two children in the intramuscular group failed to return for convalescent blood taking. The demographics of the subjects are shown in Table 1. They were comparable in age, male to female ratio, BMI, and history of influenza vaccine in the previous year. When using the 1-hand injection technique, the intradermal vaccination did not pose significant problems, even in young children. Median score of the intradermal lesions was 2 (3- to 5-mm wheal), with a range of 1 to 3.

Reactogenicity

Complete reactogenicity data were available from all subjects. Both methods of influenza vaccination were well tolerated (Table 2). Not surprisingly, induration was reported more in the intradermal group, but disappeared by the next day in the majority. Mild erythema was reported in 57.1% of the intradermal group, significantly more frequent than in the intramuscular group (3.6%). There was no other significant difference of either local or systemic adverse effects in both groups.

Immunogenicity

Of the 112 subjects recruited and vaccinated, 110 returned for convalescent blood draw. Two subjects in the intramuscular group, aged 9.4 and 10.1 years, failed to

TABLE 1 **Demographics of Children Randomly Assigned to Receive Either 0.1 mL of Influenza Vaccine by Intradermal Injection or 0.5 mL of Influenza Vaccine by Intramuscular Injection**

Characteristics	Intradermal Group ($n = 56$)	Intramuscular Group ($n = 56$)	*P*
Mean age, y	10.11 ± 4.04	10.57 ± 3.91	.546
Age range, y	3.2–17.4	3.1–17.2	1
Male/female ratio	30:26	30:26	.442
Mean BMI	18.3 ± 3.3	17.8 ± 4	.472
Range of BMI	13.7–30.2	12.8–30.9	
Influenza vaccine in past year, yes, %	17 (30.4)	13 (23.2)	.393
Age, *n*/*N* (%)			
<9 y	12/16 (75)	6/15 (40)	.467
≥9 y	5/40 (12.5)	7/41 (17)	.849

TABLE 2 **Adverse Effects in Vaccinated Children During the First 3 Days After Vaccination**

Symptoms	Intramuscular Group ($n = 56$), %	Intradermal Group ($n = 56$), %	*P*
Induration (mild)	5.4	25	.007
Erythema (mild)	3.6	57.1	<.0001
Ecchymosis >0.5 cm	0	5.4	NS
Itchiness around injection site	0	5.4	NS
Pain around injection site	5.4	1.8	NS
Malaise (overall)	23.2	26.8	NS
Mild	16.1	17.9	NS
Moderate	1.8	7.1	NS
Severe	5.4	1.8	NS
Shivering/chills	5.4	3.6	NS
Fever >38°C	7.1	5.4	NS
Headache	1.8	3.6	NS
Cough	3.6	3.6	NS
Hoarseness of voice	1.8	0	NS
Muscle pain	0	1.8	NS

NS indicates not significant.

return for convalescent serology and were assigned the mean serology titers of the group. Convalescent blood was drawn at a mean of 23.7 ± 3.1 day and 24.4 ± 5.9 days after vaccination in the intradermal and intramuscular group, respectively (P = not significant). All blood was drawn before the onset of influenza season in January 2006.

There was no statistically significant difference in seroconversion rate and seroprotection rate after vaccination between subjects in the 2 groups against any of the 3 antigens (Table 3). High postvaccination GMT were elicited in both groups against all 3 antigens, especially for the 2 influenza A antigens. There was no correlation of all individual antibody titers with age, BMI, or history of influenza vaccine in the previous year. There was also no correlation between antibody titers and induration size in the intradermal group (data not shown). There was no significant difference between the intramuscular and intradermal groups in the fold increase in GMT antibody titer for H1N1, at 11.1- and 12.9-fold increase respective, or B/Shandong, at 4.4- and 4.3-fold increase, respectively. However, there was a significant difference in fold increase of GMT against H3N2, with a fold rise of 4.5 in the intramuscular group compared with that of 2.6 in the intradermal group (P = .005). Despite this difference, both approaches elicited very high GMT: 1360.5 and 893.9 for the intramuscular and intradermal groups, respectively. For all those with prevaccination antibody titer of <40 to any of the 3 antigens (n = 68), there was no difference in fold-rise in GMT for all antigens combined: 12.5-fold in the intramuscular group and 17.9-fold in the intradermal group, suggesting that the response in seronegative subjects using either method of vaccine administration was equally robust.

A significant proportion of subjects in both groups had at least a fourfold increase in titers against the 3 antigens. There was, again, a significant difference in the proportion of children with at least a fourfold rise in GMT against H3N2 between the intramuscular group (66%) and the intradermal group (43%). Those with a lower prevaccination titer were more likely to respond with at least a fourfold rise of titer. A higher percentage of subjects in either group with prevaccination titers of <40 against any of the 3 antigens had at least fourfold increase in GMT when compared with those who had prevaccination titers of ≥40 (Table 3). More subjects with high prevaccination titers had a modest or no increase in titer after vaccination in the intradermal group. Twenty-seven subjects (55%) in the intradermal group with prevaccination titers against H3N2 ≥1: 160 had less than a fourfold rise in titer, as compared with 16 such subjects (33.3%) in the intramuscular group (P = .04).

To validate the power calculation of our sample size, we calculated, with the fold increase defined relative to day 0, the standard deviations of GMT and the mean log10 ratio of GMT to be 0.66 and 0.764, respectively, with little variation according to strain. The sample size of 56 in each group, therefore, had 80% statistical power to identify a difference between the 2 methods using a 2-sided test and a type 1 error rate of 5%, for a ratio of 2.07 in GMT and a ratio of 2.52 in the fold increase.

DISCUSSION

Intradermal administration of influenza vaccine in children was safe and immunogenic. Local reaction was more common in subjects who received the intradermal injection. This finding is similar to that reported in a study of intradermal rabies vaccine in children.[15] We did not find any difference in systemic reactions between the 2 groups.

Very high HAI GMTs against all 3 antigens of the influenza vaccine were elicited by the intradermal route by using one fifth of the standard dose. These titers were much higher than those reported in similar adult studies.[17,18] Without direct comparison, it is not known whether intradermal influenza vaccination in children is in fact more immunogenic than in adults. However, available data show that young skin is superior to old skin in resting Langerhans cell numbers and migration response after intradermal injection.[21] Because H3N2 has been in circulation worldwide since 1968 and H1N1 since 1977, and young children with previous influenza vaccination were recruited by design, it is not surprising that the majority of children with a mean age of 10 years in this study already had HAI titers of ≥1:40 against both antigens. The protective and high prevaccination GMT supports the notion that children in Hong Kong are heavily influenza experienced. It was suggested that in a partially seropositive population like that in the current study, fold increase in titers tends to underestimate vaccine immunogenicity.[22] This, rather than the route of administration, may partly explain the statistical signif-

TABLE 3 **Strain-Specific HAI Result for the 3 Antigenic Components of the Trivalent Influenza Vaccine**

	Intramuscular Group	Intradermal Group	*P*
Geometric mean (95% CI)			
H1N1			
Day 0	72.6 (50.6–103.9)	49.9 (34.7–71.9)	NS
Day 21	803.7 (560.8–1152.1)	647.9 (435.2–964.8)	NS
H2N2			
Day 0	302.8 (219.6–417.5)	340.4 (249.9–463.8)	NS
Day 21	1360.5 (1041.5–1777.3)	893.9 (685.9–1165.1)	
B/Shanghai			
Day 0	90.9 (65.1–126.8)	88.3 (62.9–123.9)	NS
Day 21	400 (272.4–587.5)	385.3 (255.6–580.8)	NS
Seroprotection rate, *n/N* (%)			
H1N1			
Day 0	41/56 (73)	34/56 (61)	NS
Day 21	55/56 (98)	55/56 (98)	NS
H3N2			
Day 0	53/56 (95)	52/56 (93)	NS
Day 21	56/56 (100)	56/56 (100)	NS
B/Shanghai			
Day 0	43/56 (77)	45/56 (80)	NS
Day 21	52/56 (93)	54/56 (96)	NS
Seroconversion rate, *n/N* (%)			
H1N1	14/15 (93)	21/22 (95)	NS
H3N2	15/15 (100)	22/22 (100)	NS
B/Shanghai	9/13 (69)	9/11 (82)	NS
Fold increase in geometric mean titer (95% CI)			
H1N1	11.1 (7.2–17.1)	12.9 (7.9–21.4)	NS
H3N2	4.5 (3.4–5.9)	2.6 (2.1–3.4)	.005[a]
B/Shanghai	4.4 (3.3–5.8)	4.3 (3.2–5.8)	NS
Fourfold increase (overall), *n/N* (%)			
H1N1	42/56 (75)	42/56 (75)	NS
H3N2	37/56 (66)[a]	24/56 (43)	.023[b]
B/Shanghai	19/56 (34)	29/56 (52)	NS
Fourfold increase in subjects with prevaccination <40, *n/N* (%)			
H1N1	14/15 (93)	21/22 (95)	NS
H3N2	3/3 (100)	3/3 (100)	NS
B/Shanghai	10/20 (50)	20/27 (74)	NS
Fourfold increase in subjects with prevaccination ≥40, *n/N* (%)			
H1N1	28/41 (68.3)	21/34 (61.8)	NS
H3N2	34/53 (64.2)[a]	21/53 (39.6)[a]	.02[b]
B/Shanghai	9/36 (25)	9/29 (31)	NS

CI indicates confidence interval; NS, not significant.

[a] Using unpaired *t* test.

[b] Using χ^2 test.

icant difference in GMT fold increase against H3N2 observed. This hypothesis is supported by (1) the comparable fold rises against H1N1 and influenza B/Shandong, against which subjects from both groups had a lower prevaccination GMT and were less likely to have an antibody level ≥1:40, (2) a higher percentage of at least fourfold rise in titer in both groups in those with seronegative prevaccination titers, and (3) a robust and equivalent fold increase for seronegative prevaccination titers against all 3 antigens in both groups. In rabies vaccination of children, there has been concern that antibodies elicited by intradermal vaccination were of lower titer, and may not be as durable.[15]With very high postvaccination GMT, it is unlikely that the difference in postvaccination GMT against H3N2 between the 2 groups would be clinically significant. Moreover, with influenza vaccine being given annually, the long-term durability of antibodies is less relevant.

The skin has been the target of immunization for many years, and there is recent renewal of interest in exploiting this immune organ. Studies performed in animals and humans have had promising results.[23–25] Epidermal vaccination that includes transcutaneous immunization or needle-free jet injectors targets the epidermis that is abundant in Langerhans cells, and epidermal and dermal vaccination that uses gene gun or electroporation technology targets both layers of the skin that contains Langerhans cells as well as dendritic cells.[26] These methods of vaccination require special preparations and devices. Intradermal vaccination targets the dermis that is abundant in dendritic cells and can be performed by a simple needle and syringe using existing vaccine prepa-

ration. However, in general, intradermal injection requires more skill than intramuscular injection. Performing intradermal vaccination in struggling young children is more challenging than in obliging small infants. The current study has demonstrated that intradermal injection can be performed safely and effectively even in children as young as 3 years of age using the 1-hand injection technique, which can be easily mastered using standard tuberculin syringes and can also be performed effectively in overweight children with more subcutaneous fat. This has important implication for use in resource poor countries, because sophisticated devices are likely to mean increased costs.

There are limitations in our study. Our subjects were heavily influenza experienced. Although this situation reflects reality, where a proportion of the population is likely to be seropositive to the strains in the vaccine, this will not hold true regarding the pandemic strain. All the intradermal injections were administered by 1 experienced person. A larger variation of results may be expected when many persons give the vaccine. We designed the experiment to obtain the convalescent blood samples 21 days after vaccination. Ideally, another sampling on day 42 postvaccination would have provided additional information on antibody kinetics. However, repeated blood sampling is generally not well received by parents of healthy young children. Future studies should involve children younger than 3 years of age, children seronegative to the vaccine strains, children with various immunocompromised states, comparing 1 intradermal dose with the intramuscular 2-dose regimen in young children, multiple vaccine administrators, longer follow-up, and studies to include efficacy to ascertain that antibodies elicited by different routes of administration are comparable functionally.

This study has provided encouraging data that intradermal injection can elicit comparable immune response against influenza at a much reduced dose in healthy children as young as 3 years of age and is a useful strategy against vaccine shortage. Pandemic vaccines with avian hemagglutinins, especially the nonadjuvanted H5N1 vaccine, are known to be poor immunogens.[27,28] It is not known whether the intradermal route of vaccination will offer any advantages. A recent report of intradermal administration of a subvirion H5N1 vaccine was not immunogenic up to 3 doses in healthy adults.[29] We are currently investigating the cellular response of our subjects to better define the role of intradermal influenza vaccination.

ACKNOWLEDGMENTS

This work was supported by Research Grants Council of Hong Kong grant HKU 7396/03M, Ellison Medical Foundation grant 1D-1A-0036-02, and the Vice Chancellors Development Fund (University of Hong Kong).

We thank the children and parents who participated in the study, our dedicated team of research staff, and Winnie Lau, who single-handedly performed all the intradermal injections.

REFERENCES

1. Simonsen L. The global impact of influenza on morbidity and mortality. *Vaccine.* 1999;17:3–10
2. Wong CM, Yang L, Chan KP, et al. Influenza-associated hospitalization in a subtropical city. *PLoS Med.* 2006;4:e121
3. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med.* 2000;342:232–339
4. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med.* 2000;342:225–231
5. Chiu SS, Lau YL, Chan KH, Wong WHS, Peiris JSM. Influenza related hospitalizations among children in Hong Kong. *N Engl J Med.* 2001;347:2097–2103
6. Communicable Disease Surveillance and Response Global Influenza Programme. Responding to the avian influenza pandemic threat: recommended strategic actions. 2005. WHO/CDS/CSR/GIP/2005.8. Available at: www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_05_8-EN.pdf. Accessed April 7, 2007
7. Redfield RR, Innis BL, Scott RM, Cannon HG, Bancroft WH. Clinical evaluation of low-dose intradermally administered hepatitis B virus vaccine: a cost reduction strategy. *JAMA.* 1985;254:3203–3206
8. Bryan JP, Sjogren MH, Perine PL, Legters IJ. Low-dose intradermal and intramuscular vaccination against hepatitis B. *Clin Infect Dis.* 1992;14:697–707
9. Sabchareon A, Chantavanich P, Pasuralertsakul S, et al. Persistence of antibodies in children after intradermal or intramuscular administration of preexposure primary and booster immunizations with purified Vero cell rabies vaccine. *Pediatr Infect Dis J* 1998;17:1001–1007
10. 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
11. Quilligan JJ Jr, Salgado PF, Alena B. Influenza vaccination in children. *Am J Dis Child.* 1961;101:593–601
12. Klein M, Huang N. The response of infants and children to Asian influenza vaccine administered by intradermal and subcutaneous routes. *J Pediatr.* 1961;58:312–314
13. Mortimer EA Jr. Intradermal injections of influenza vaccines. *Pediatrics.* 1968;42:875
14. Marks MI, Eller JJ. Intradermal influenza immunization. Experience with Hong Kong vaccine. *Am Rev Respir Dis.* 1971;103:579–581
15. Brown H, Kasel JA, Freeman DM, Moise LD, Grose NP, Couch RB. The immunizing effect of influenza A/New Jersey/76 (Hsw1N1) virus vaccine administered intradermally and intramuscularly to adults. *J Infect Dis.* 1977;136:S466–S471
16. Belshe RB, Newman FK, Cannon J, et al. Serum antibody responses after intradermal vaccination against influenza. *N Engl J Med.* 2004;351:2286–2294
17. Kenney RT, Frech SA, Muenz LR, Villar CP, Glenn GM. Dose sparing with intradermal injection of influenza vaccine. *N Engl J Med.* 2004;351:2295–2301
18. Salk JE. Simplified procedure for titrating hemagglutinating capacity of influenza virus and the corresponding antibody. *J Immunol.* 1944;49:87–98

19. Mitchell DK, Ruben FL, Gravenstein S. Immunogenicity and safety of inactivated influenza virus vaccine in young children in 2003–2004. *Pediatr Infect Dis.* 2005;24:925–927
20. Bhushan M, Cumberbatch M, Dearman RJ, Andrew SM, Kimber I, Griffiths CEM. Tumour necrosis factor-α-induced migration of human Langerhans cells: the influence of ageing. *Br J Dermatol.* 2002;146:32–40
21. Beyer WEP, Palache AM, Luchters G, Nauta J, Osterhaus ADME. Seroprotection rate, mean fold increase, seroconversion rate: which parameter adequately expresses seroresponse to influenza vaccination? *Virus Res.* 2004;103:125–132
22. Degano P, Schneider J, Hannan GM, Gilbert SC, Hill AVS. Gene gun intradermal DNA immunization followed by boostering with modified virus Ankara: enhanced CD8+ T cell immunogenicity and protective efficacy in the influenza and malaria models. *Vaccine.* 2000;18:623–632
23. Jackson LA, Austin G, Chen RT, et al. Safety and immunogenicity of varying dosages of trivalent inactivated influenza vaccine administered by needle-free jet injectors. *Vaccine.* 2001;19:4703–4709
24. Chen D, Burger M, Chu Q, et al. Epidermal power immunization: cellular and molecular mechanisms for enhancing vaccine immunogenicity. *Virus Res.* 2004;103:147–153
25. Peachman KK, Rao M, Alving CR. Immunization with DNA through the skin. *Methods.* 2003;31:232–242
26. Stephenson I, Nicholson KG, Wood JM, Zambon MC, Katz JM. Confronting the avian influenza threat: vaccine development for a potential pandemic. *Lancet Infect Dis.* 2004;4:490–508
27. Bresson JL, Perronne C, Launay O, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase 1 randomised trial. *Lancet.* 2006;367:1657–1664
28. Patel SM, Atmar RL, Sahly H, Cate TR, Keitel WA. Randomized, open-label, phase 1 clinical trial comparing the safety, reactogenicity, and immunogenicity of booster immunization with inactivated influenza A/H5N1 vaccine administered by the intradermal (ID) or the intramuscular IIM) route among healthy adults [abstract]. Presented at: IDSA annual meeting; October 12–15, 2006; Toronto, Ontario, Canada. Abstract LB-5, 64

YALE ON $0 A DAY

"Getting into college may be tougher than it used to be. But top schools are offering a growing number of courses free online. Following the lead of the Massachusetts Institute of Technology and other highly competitive schools, more institutions are posting online everything from lecture notes to sample tests, and even making audio and video files of actual lectures publicly available. The sites attract anywhere from thousands to more than one million unique visitors each month. . . . MIT's pioneering 'OpenCourseWare' program, which was launched in 2003, posts the syllabus and class notes for more than 1500 courses online for anyone who wants them. By this November, it aims to publish materials from virtually all 1800 of its courses across all its schools. . . . Starting last fall, the University of Notre Dame in South Bend, Ind., began offering eight courses. . . . Yale University, meanwhile, has announced it will produce digital videos of undergraduate lecture classes and make them available free to the public."

Chaker AM. *Wall Street Journal*. February 16, 2007
Noted by JFL, MD

Immunogenicity and Safety of Intradermal Influenza Immunization at a Reduced Dose in Healthy Children

Susan S. Chiu, J.S. Malik Peiris, Kwok H. Chan, Wilfred Hing Sang Wong and Yu Lung Lau

Pediatrics 2007;119;1076-1082
DOI: 10.1542/peds.2006-3176