

plants, ex vivo expansion of cord-blood stem cells, and cotransplantation of CD34+ cells from a haploidentical donor are ongoing. It is realistic to anticipate that the current results for cord-blood transplantation in adults with hematologic cancers will contribute to more extended use in the coming years for many patients in need.

From the Hematology Department, Hospital Universitario La Fe, 46009 Valencia, Spain.

1. Bone Marrow Donors Worldwide homepage. (Accessed November 4, 2004, at www.bmdw.org.)
2. Bone marrow transplants: despite recruitment successes, national programs may be underutilized. Washington, D.C.: General Accounting Office, 2002. (GAO-03-182.)
3. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood* 2003;101:4233-44.
4. Netcord inventory and use, July 2004. (Accessed November 4, 2004, at <https://office.de.netcord.org/inventory.gif>.)
5. Laughlin MJ, Barker J, Bambach B, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *N Engl J Med* 2001;344:1815-22.
6. Sanz GF, Saavedra S, Planelles D, et al. Standardized unrelated donor cord blood transplantation in adults with hematologic malignancies. *Blood* 2001;98:2332-8.
7. Ooi J, Iseki T, Takahashi S, et al. Unrelated cord blood transplantation for adult patients with de novo acute myeloid leukemia. *Blood* 2004;103:489-91.
8. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. *N Engl J Med* 1997;337:373-81.
9. Rubinstein P, Carrier C, Scaradavou A, et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med* 1998;339:1565-77.
10. Rocha V, Cornish J, Sievers EL, et al. Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. *Blood* 2001;97:2962-71.
11. Barker JN, Davies SM, DeForr T, Ramsay NKC, Weisdorf DJ, Wagner JE. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. *Blood* 2001;97:2957-61.
12. Rocha V, Labopin M, Sanz G, et al. Outcomes after transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med* 2004;351:2276-85.
13. Laughlin MJ, Eapen M, Rubinstein P, et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N Engl J Med* 2004;351:2265-75.
14. Gluckman E, Rocha V, Arcece W, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol* 2004;32:397-407.
15. Takahashi S, Iseki T, Ooi J, et al. Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematological malignancies. *Blood* (in press).

Copyright © 2004 Massachusetts Medical Society.

Intradermal Influenza Vaccination — Can Less Be More?

John R. La Montagne, Ph.D.,* and Anthony S. Fauci, M.D.

The current shortfall in anticipated doses of vaccine for the upcoming influenza season¹ makes the reports by Belshe et al.² and Kenney et al.³ in this issue of the *Journal* particularly timely. These studies raise the possibility of using alternative routes of immunization (e.g., intradermal, as opposed to intramuscular, administration) with smaller doses of vaccine as a means of “stretching” available doses of influenza vaccine in times of shortages. In addition, the studies indirectly raise provocative issues regarding the potential effect of these alternative routes of immunization in targeting specialized cells of the immune system to enhance the immunogenicity of certain vaccine antigens, particularly in populations such as the elderly and those with chronic diseases, who may not have a robust response to antigenic challenge.

Influenza remains a major health problem in the United States, resulting each year in an estimated 36,000 deaths and 200,000 hospitalizations.⁴ Those who have been shown to be at high risk for the complications of influenza infection are chil-

dren 6 to 23 months of age; healthy persons 65 years of age or older; adults and children with chronic diseases, including asthma, heart and lung disease, and diabetes; residents of nursing homes and other long-term care facilities; and pregnant women.⁴ It is for this reason that the Centers for Disease Control and Prevention (CDC) has recommended that these groups, together with health care workers and others with direct patient-care responsibilities, should be given priority for influenza vaccination this season in the face of the current shortage.¹ Other high-priority groups include children and teenagers 6 months to 18 years of age whose underlying medical condition requires the daily use of aspirin and household members and out-of-home caregivers of infants less than 6 months old.¹ Hence, in the case of vaccine shortages resulting either from the unanticipated loss of expected supplies or from the emergence of greater-than-expected global influenza activity — such as pandemic influenza, which would prompt a greater demand for vaccination⁵ — the capability of extending ex-

isting vaccine supplies by using alternative routes of vaccination that would require smaller doses could have important public health implications.

In a previous report, Treanor et al. demonstrated that one half the standard dose of trivalent influenza vaccine elicited immune responses similar to those elicited by the full dose when each was administered intramuscularly.⁶ In that investigation, healthy persons between the ages of 18 and 49 years were studied. Both of the current studies^{2,3} clearly show that intradermal vaccination may have greater immunogenicity than intramuscular vaccination. Of note, the study by Belshe et al.² further shows the potential applicability of this approach in healthy persons older than 60 years of age, despite the fact that the responses in this group were generally somewhat less robust than those in younger adults. This finding is particularly relevant, since more than 90 percent of the 36,000 influenza-related deaths in the United States each year occur among persons older than 65 years,⁷ and shortages of vaccine are especially problematic for this population.

Beyond the issue of alleviating real and potential shortages of influenza-vaccine supplies is the possibility of pursuing vaccination strategies that would induce optimal immunity among populations of persons who not only are at greatest risk for complications but who also generally do not mount an optimal immune response. On the basis of the current studies as well as previous reports on the use of intradermal immunization against influenza, hepatitis B, rabies, and other infectious diseases,^{2,3,8} it is becoming clear that use of the intradermal route may at least partially overcome the relatively poor influenza-specific immune responses seen in certain at-risk populations, particularly the elderly, in whom the immune response in general is known to diminish with age.⁹ Moreover, in times of shortage, the dose-sparing intradermal approach might be particularly well suited to the young, healthy persons included in the CDC's high-priority group for vaccination, such as health care workers, as well as to younger, otherwise healthy populations in general.

The dermis contains copious numbers of cutaneous dendritic cells that are important for an intradermal route of immunization.¹⁰ Dendritic cells are the most potent antigen-presenting cells for eliciting primary immune responses. Dendritic cells are thought to induce cell-mediated immune responses, particularly CD4+ and CD8+ T-cell

responses¹⁰; however, they have also been shown to enhance antibody production by B cells through the efficient induction of CD4+ T-cell modulation of B cells.¹¹ It will be important to conduct further basic and clinical research in order to determine the potential role that dendritic cells play in optimizing immune responses to intradermal vaccination and whether it could ultimately translate into a clinical benefit for healthy persons and for those in groups at high risk for influenza-related illness and death, particularly those whose immune response is compromised by disease or age.

In addition to the basic research and clinical challenges that the current studies bring to mind, there are technical challenges that must be addressed, including the special training of personnel who would be needed to administer vaccinations through the intradermal route effectively. There is also the issue of regulatory challenges that must be addressed to allow, under special circumstances, a degree of flexibility in the administration of vaccine by a route that was not originally used in the critical path toward licensure of a given product. The latter issue should be addressed by careful design and execution of the appropriate clinical trials in a broad range of relevant populations.

Influenza is an unremitting challenge to the health of our nation and the world. The possibility of a pandemic outbreak related to the emergence of influenza strains to which there is little or no baseline immunity in the population is an ever-present threat. The current epizootic in the Far East caused by avian influenza virus A (H5N1) has led to real concern about the possibility of a new pandemic of influenza.¹² Technological innovation, such as the use of new vaccines delivered by the intradermal route, offers great promise to change and improve on current immunization strategies. It is our responsibility to pursue these and other approaches in order to advance our ability to meet the inevitable challenges of emerging and reemerging infectious diseases, particularly influenza.

This article was published at www.nejm.org on November 4, 2004.

From the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

*Deceased.

1. Influenza vaccination recommendations, 2004–05 influenza season. *MMWR Morb Mortal Wkly Rep* 2004;53:923-4.
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. 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.
4. Centers for Disease Control and Prevention. Key facts about the flu and flu vaccine. (Accessed November 4, 2004, at <http://www.cdc.gov/flu/keyfacts.htm>.)
 5. Treanor J. Weathering the influenza vaccine crisis. *N Engl J Med* 2004;351:2038-40.
 6. Treanor J, Keitel W, Belshe R, et al. Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. *Vaccine* 2002;20:1099-105.
 7. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179-86.
 8. Nagafuchi S, Kashiwagi S, Imayama S, Hayashi J, Niho Y. Intradermal administration of viral vaccines. *Rev Med Virol* 1998;8:97-111.
 9. Pawelec G, Ouyang Q, Wagner W, Biol D, Wikby A. Pathways to a robust immune response in the elderly. *Immunol Allergy Clin North Am* 2003;23:1-13.
 10. Steinman RM, Pope M. Exploiting dendritic cells to improve vaccine efficacy. *J Clin Invest* 2002;109:1519-26.
 11. Dubois B, Bridon JM, Fayette J, et al. Dendritic cells directly modulate B cell growth and differentiation. *J Leukoc Biol* 1999;66:224-30.
 12. Li KS, Guan Y, Wang J, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature* 2004;430:209-13.
- Copyright © 2004 Massachusetts Medical Society.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal's* Web site at www.nejm.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.
