Better Influenza Vaccines for Older People: What Will It Take?

Janet E. McElhaney1,2 and Jan P. Dutz2

1University of Connecticut School of Medicine, Farmington; 2University of British Columbia, Vancouver, British Columbia, Canada

(See the article by Holland et al., on pages 650–8.)

Of all infectious diseases, influenza is foremost in its association with an age-related increase in serious consequences leading to hospitalization, debilitating complications, and death. Current influenza vaccines are both effective [1] and cost saving [2]; however, in spite of widespread influenza vaccination programs, rates of hospitalization for acute respiratory illnesses and cardiovascular diseases have been increasing in the population aged ≥ 65 years during the influenza season [3]. Given that current influenza vaccines are only 30%–40% effective in this population, there appears to be a considerable margin for improvement. However, in spite of recent advances in vaccine development, the same technology has been used to produce seasonal influenza vaccines for the past 40 years.

A decrease in immune function is a hallmark of aging and affects the ability to resist influenza virus infection and to respond to vaccination. It is recognized that multiple components of immune function, particularly cell-mediated immunity, are affected during the aging process. As a consequence, there has been a paradigm shift in understanding the limitations of antibody titers as a sole measure of the efficacy of influenza vaccine in older people [4]. Adequate antibody titers may not provide sterilizing immunity in this population [5]. Furthermore, statistically significant increases in antibody titers that correlate with protection in response to vaccination may not translate to clinically important improvements in influenza outcomes in older adults [6]. Thus, the goal of vaccination may be to provide clinical protection against illness mediated by both humoral and cellular immune mechanisms. The challenge to new vaccine development is that antibody titers, when used as a predictor of vaccine efficacy, may fail to detect important changes in cellular immunity that enhance vaccine-mediated protection in older people.

Why might antibody and cell-mediated immune responses to vaccination both be important to protection against influenza in older adults? Influenza virus stimulates an antiviral response in both B and T lymphocytes, resulting in humoral and cell-mediated immunity, respectively. Virus-activated T cells, through cytokine mediators, stimulate B cells to differentiate and produce antibodies specific for a particular vaccine strain. These specific antibodies bind to the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA), to neutralize the virus particle. On an annual basis, influenza vaccines must be updated to include the predicted circulating strains of influenza A/H3N2 and A/H1N1 and influenza B virus. The antibody responses to influenza vaccination evaluated by the hemagglutination inhibition assay have not been shown to be different in healthy young adults and older adults, with regard to the response to influenza A/H3N2 strains, whereas titers of antibody to A/H1N1 strains have been found to be lower in older adults than in young adults [7]. These results would suggest that young adults and older adults receive comparable antibody-mediated protection against A/H3N2 strains; however, the results are in sharp contrast to the observed clinical outcomes in older adults. Influenza A/H3N2 strains have, by far, the greatest influence on hospitalization rates, relative to influenza B and A/H1N1 strains [3]. In addition, although successive annual influenza vaccinations may limit the antibody response, protection against influenza improves [8–10], suggesting that cellular immune mechanisms may also be important for protection in older adults. Although antibody responses to influenza vaccination have been correlated with alterations in T cell function [11, 12],
the mechanism for the overall decrease in vaccine-mediated protection in older adults has not yet been established.

T cell–mediated immune responses are also protective against influenza virus infection and illness [13]. In contrast to the strain-specific antibody response of B cells, T helper (Th) cells and cytotoxic T lymphocyte (CTL) responses are much more cross-reactive against different virus strains [14]. T cell stimulation occurs when virus is taken up and processed by such antigen-presenting cells as macrophages and dendritic cells (DCs). The resulting peptides are presented on the major histocompatibility complex (MHC) to activate T cells. Protein sequences within HA, NA, and internal viral proteins (matrix and nucleoproteins) that stimulate Th cells and CTLs are largely conserved across subtypes of influenza A (A/H3N2 and A/H1N1) and within the strains of influenza A or B virus [15], thus stimulating cross-protective immunity.

Th cell–mediated immune responses to influenza virus play a key role in both humoral and CTL responses to influenza vaccination. Th1 cells effectively stimulate antibody responses, interferon (IFN)–γ production, and CTL memory, whereas Th2 cells stimulate antibody responses; Th2 cells also produce interleukin (IL)–10 which suppresses the Th1 response. With aging, a decrease in cytokine production by Th1 cells, relative to production by Th2 cells, occurs; a reduced ratio of IFN-γ to IL-10 responding to influenza challenge correlates with an increased risk for influenza illness in older adults [5]. Also important to vaccine development, Th cells and CTLs recognize viral peptides on MHC II and MHC I, respectively; thus, they have different requirements for effective antigen presentation. Although peptides from live virus are effectively presented on both MHC I and MHC II, split-virus vaccines require antigen cross-presentation within the DCs and generally stimulate a weak CTL response [16] that depends on previous priming with natural infection [17]. Studies in humans have confirmed that CTL responses effectively clear influenza virus, even in the absence of protective antibodies to the infecting virus, and that they are important for recovery from influenza infection [18]. In older individuals, higher levels of cytolytic mediators correlate with protection against influenza [5]. Thus, influenza vaccinations that produce a shift toward a Th1 response and effectively stimulate both antibody production and CTL memory should improve protection in older adults.

**Vaccine design strategies to enhance protection: using the skin.** Novel vaccines can be designed to enhance the cell-mediated immune response through changes in the dose, type (live attenuated, killed, split, particle, or subunit viral proteins, with or without adjuvants), or route of delivery of the viral antigens. As the abundance and function of antigen-presenting cells within the skin have been appreciated, they have become an increasingly attractive target of immunization strategies using either DNA constructs [19] or proteins [20, 21]. In this issue of the *Journal*, Holland et al. [22] report a trial of split-virus influenza vaccine, wherein adults >60 years of age were randomized to receive the standard intramuscular injection of vaccine versus intradermal injection, demonstrating the superiority of intradermal injection, demonstrating the superior potency of intradermal injection on the basis of antibody criteria. The investigators are to be commended for recruiting “healthy” older adults, including those with the chronic diseases common in this population. This type of recruitment will help to ensure that the results can be replicated in the general population of older persons. Although alternate correlates of protection could not be measured in the study, intradermal administration of the vaccine may provide a novel strategy for also improving cell-mediated immune responses to influenza vaccination.

Why might intradermal administration of antigen improve vaccine immunogenicity? Langerhans cells, the abundant DCs within the epidermis, have long been thought to mediate skin immune responses. Recent findings in the mouse, however, suggest that Langerhans cells are not required for either humoral- or cell-mediated immunity after gene gun immunization [23] or protein immunization [24]. Langerhans cells may also be dispensable for contact hypersensitivity responses, a model of cell-mediated immune response in the skin [25]. This has resulted in a shift in importance toward dermal DCs as potential primary stimulators of skin immune responses [26]. Distinct populations of plasmacytoid DCs, immunostimulatory dermal DCs, and phagocytic macrophages have been identified within the dermis [27, 28]. Thus, in the human dermis, immunostimulatory DCs may be identified by the expression of the blood DC antigen–1 marker (also known as “CD1c”). These cells are fully able to support T cell activation in the form of an allogeneic response. The proportional role of the dendritic-like macrophages and the plasmacytoid DCs in skin immune responses remains to be clarified.

The relative importance of the dermal immune system in the optimization of vaccine responses suggested by the recent identification of highly immunostimulatory DCs within the dermis is supported by observations in clinical vaccinology. Thus, intradermal vaccination is effective in the induction of protective antibodies to cellular vaccine in the preexposure [29] or postexposure prophylaxis for rabies [30] at roughly one-fifth the dose required by intramuscular administration. Intradermal immunization also improves the efficacy of antibody production to hepatitis B virus vaccine and influenza vaccinations. The mechanisms for this improvement in efficacy are still unknown, but they presumably involve the activation of the dermal DCs and/or dendritic-like macrophages and the efficient shuttling of antigen to the draining lymph nodes where B cells reside. Because DCs are the prime activators of naive T cells, more efficient induction of cell-mediated immune responses by intradermal administration of vaccine is anticipated but remains to be demonstrated. Such an enhanced cellular immune re-
response is likely important in the immune protection of older adults from viral infection, including that due to influenza virus.

**New tests are needed for new vaccine technologies.** A major challenge to new vaccine development for older adults is to stimulate the senescent immune response in ways that may not be measured using such standard techniques as antibody titers to predict vaccine efficacy. Furthermore, antibody responses to vaccination as a correlate of protection may fail to detect important changes in cellular immunity and enhanced vaccine-mediated protection against influenza illness in older people. Future efforts to develop alternative correlates of clinical protection against influenza are needed for more effective translation of novel vaccination strategies to improve protection against influenza in older adults.

**References**