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Protecting Adults From Influenza: Tis the Season to Learn From the Pandemic

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Although influenza seasons come and go, one unfortunate constant over the past decade has been a lack of measurable progress in protecting adults from influenza. Despite greater vaccine supply, rising vaccination rates in children, and universal recommendations for all adults to be vaccinated annually, vaccination rates among the general adult population have scarcely budged. This stagnation in population coverage accentuates the value of approaches that improve influenza vaccine efficacy in adults. In this issue of the *Journal of Infectious Diseases* Jackson reports on the comparative immunogenicity of multiple formulations of A(H1N1) 09pdm influenza vaccine among adults [1]. Their study has potential relevance for improved control of seasonal influenza, as well as better preparedness against future pandemic and avian influenza threats.

The availability of inactivated vaccine and the recurring burden of influenza and its complications led the US surgeon general in 1960 to issue the first recommendations for routine annual influenza vaccination of older adults, pregnant women, and others with chronic medical conditions [2]. Vaccination rates among the elderly increased substantially during the 1990s [3] but subsequently plateaued at approximately 60% to 70%. Older adults continue to experience a disproportionate burden of severe illness caused by influenza. Unfortunately, influenza vaccine effectiveness is generally lower among older populations, even during seasons when vaccine strains are well matched to circulating viruses. Efforts to overcome immune senescence and identify formulations with improved immunogenicity and clinical protection have been a focus of researchers, manufacturers, and the government. The potential roles of high-dose antigen formulations as well as adjuvants in improving immune response have been of particular interest with respect to both avian and seasonal influenza vaccines.

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Jackson investigated effects of dose, adjuvant, and age on the immunogenicity of pandemic vaccine [1]. Of note, the study used antigen from 1 manufacturer extemporaneously mixed with an oil-in-water emulsion adjuvant of another, mimicking a potential real-life need to expand vaccine coverage during a pandemic. The immunogenicity of 2 doses of 3.5, 7.5, and 15 μg of split inactivated 2009 H1N1 vaccine with AS03 adjuvant or 7.5 and 15 μg without adjuvant was assessed in adults aged 18–64 and ≥65 years. Confirming the results of earlier 2009 H1N1 vaccine studies, a single dose of unadjuvanted vaccine at either standard (15 μg) or half (7.5 μg) dose induced serum hemagglutination-inhibition (HI) antibody responses in the majority of adults in either age group, although a greater proportion of older adults receiving the standard dose achieved HI titers of ≥40 [4–6]. Rising HI antibody titers were evident as early as 8 days after a single dose of either unadjuvanted or adjuvanted vaccine, consistent with other reports [7]. Adjuvanted vaccine elicited more robust responses in adults aged ≥65 years compared with the standard dose of unadjuvanted vaccine, and a second dose of adjuvanted vaccine boosted titers in seniors as well as in younger adults, with a notable increase in the durability of the response at 6 months. Significantly lower responses were detected within each vaccine group in those aged 36–50 and 51–64 years compared with the youngest group aged 18–35 years.

These results remind us that lower immunity is not just a concern for vaccine responses in seniors and that more immunogenic influenza vaccine would benefit adults of all ages. In addition to age, prior receipt of seasonal influenza vaccine was independently associated with lower postvaccination serum HI antibody titers. A similar finding has been reported for other adjuvanted and nonadjuvanted A (H1N1)pdm09 vaccines in both children and adults [8, 9]. One reason for this may be that A(H1N1)pdm09 vaccines preferentially recall memory B cell responses to crossreactive epitopes in seasonal vaccine viruses, eliciting antibodies that do not effectively inhibit hemagglutination of the pandemic virus. Further research to understand the quality and fine specificity of the antibody response to pandemic vaccines is needed to provide insight into the precise immunologic mechanisms involved.

Although effective emergency response must take center stage in the governmental response to a pandemic, the capacity to conduct scientific investigations during pandemics or similar national disasters is critical to strengthening national preparedness and improving future response efforts. There were many successful examples of such research during the 2009 pandemic influenza response [10]. The National Institutes of Health and their network of Vaccine Treatment and Evaluation Unit (VTEU) investigators carried out important studies during the 2009 pandemic that addressed contemporary public concerns about the monovalent vaccine but also explored the role of dose and adjuvant in improving immunologic response. The pandemic H1N1 vaccination efforts in the United States employed the licensed, standard dose formulations of unadjuvanted vaccines. However, the VTEU network studies helped advance understanding of influenza vaccine performance among primed adults. Fortunately, a single dose of A(H1N1)pdm09 influenza vaccine was sufficient to produce an effective response in most of the population, and neither higher dose formulations nor adjuvants were needed to protect Americans during the pandemic.

Research on new adjuvants has been productive. In addition to potential dose sparing, adjuvants can lead to broader immune response that may confer protection against

heterologous strains. Adjuvanted influenza vaccines have been in use in Europe but have not yet been licensed in the United States. In 2009, their perceived novelty and unproven record in children raised potential alerts among some members of the US public. During the summer of 2009, as part of the preparations for a voluntary national monovalent H1N1 vaccination program, the Centers for Disease Control and Prevention supported public engagement events in communities around the country to garner insights into values that were important to citizens related to pandemic vaccination. The limited knowledge base related to adjuvanted influenza vaccines, particularly among children, was an issue raised frequently at these venues. Because standard antigen, single-dose inactivated vaccine formulations elicited immune responses in adults and most children, the potential dose-sparing benefits that adjuvants might offer did not exceed the expected reduction in public acceptance and the implementation challenges that mixing adjuvant with vaccine at the point of delivery might confer on the US program. However, adjuvanted formulations were used elsewhere and did prove antigen sparing. The very rare occurrence of narcolepsy among some recipients of the adjuvanted monovalent vaccine, Pandemrix, used in Scandinavia is still under investigation. The European Medicine Agency recommended restricting use of Pandemrix on a precautionary basis in those under 20 years of age, though noting that the overall benefit-to-risk ratio remains positive [11].

Public attention to pandemic threats has diminished in the years following the 2009 influenza pandemic. The 2011–2012 influenza season in the United States arrived later than any season since 1982 and caused very modest morbidity. Nevertheless, the challenge of protecting individuals and communities from influenza and its complications continues. There have been incremental expansions in the influenza vaccine armamentarium since the pandemic, including US Food and Drug Administration approvals of high-dose inactivated vaccine (sanofi pasteur), intradermal lower-dose inactivated influenza vaccine (sanofi pasteur), and quadrivalent live-attenuated influenza vaccine that targets 2 B virus lineages (Medimmune). The potential clinical advantages of these products will be assessed in years to come. Meanwhile, consumers, clinicians, and programs alike share enthusiasm for continued research and development of universal influenza vaccines that could overcome the need for annual revaccination. The potential to achieve longer-term protection and prevent pandemics would be transformative compared with the current practice of immunizing more than 120 million Americans each and every year against this unpredictable but serious virus.

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