

## EDITORIAL



## Pandemic Influenza Vaccine Policy — Considering the Early Evidence

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“Policy decisions regarding influenza rest on judgments about the behavior of the virus, the impact of the disease and our ability to interdict its course. But the virus is capricious, the disease elusive, and our remedies imperfect,” said a report on the 1976 swine-flu epidemic at Fort Dix.<sup>1</sup>

Two peer-reviewed articles now publicly available at NEJM.org, by Greenberg et al. (ClinicalTrials.gov number, NCT00938639)<sup>2</sup> and Clark et al. (NCT00943358),<sup>3</sup> describe preliminary data on the immunogenicity of the influenza A (H1N1) 2009 monovalent vaccine. These data have been eagerly anticipated, as governments, public health officials, and other stakeholders respond to the first influenza pandemic in over 40 years. The authors and their collaborators are to be commended for their prompt execution of the trials and rapid sharing of the results.

The study by Greenberg et al. shows that a single dose of nonadjuvanted vaccine containing the usual 15  $\mu\text{g}$  of hemagglutinin (HA) antigen is immunogenic in a high proportion of healthy young and middle-aged adults.<sup>2</sup> These findings are welcome and reassuring, as there is little evidence of cross-reactive antibody against the novel 2009 pandemic influenza A (H1N1) virus in the general population, and the need for two doses had been predicted. Without a nonimmunized control group, it is impossible to determine whether subclinical infection may have boosted the immune response elicited by the vaccine. The study was conducted in Australia during a time when the pandemic virus was circulating, and one participant had laboratory-confirmed infection with the 2009 H1N1 virus during the course of the study. Therefore, responses could be somewhat lower if vaccine is administered under different epidemiologic circumstances.

In the study by Clark et al., one or two doses of an adjuvanted influenza vaccine containing 7.5  $\mu\text{g}$  of HA (50% of the standard dose), administered on various schedules, elicited robust antibody titers.<sup>3</sup> Although two doses (for a total of 15  $\mu\text{g}$  of HA) yielded higher antibody levels than one dose, the seroprotective titer was attained in at least 80% of subjects in every group. Without a nonadjuvanted control group, it is impossible to determine the contribution of the adjuvant to these responses. Two previous studies comparing half-dose to full-dose seasonal vaccines support the finding that nonadjuvanted influenza vaccine may be immunogenic at a dose of 7.5  $\mu\text{g}$ .<sup>4,5</sup> Pending data from the nonadjuvanted group studied by Clark et al. are vital to understanding the contribution of adjuvant to the immunogenicity of this vaccine.

Antibody levels as measured by both the hemagglutination-inhibition assay and the micro-neutralization assay correlate with protection against clinical illness from influenza infection. However, for any individual strain, it is not possible to determine a threshold above which protection can be ensured. The robustness and consistency of the antibody responses, and the use of internationally standardized reagents and controls, are reassuring and lend credibility to the results of Greenberg et al. and Clark et al.

The obvious advantage of a one-dose schedule is that, in the current time of vaccine scarcity, it doubles the number of people who may be vaccinated with a fixed amount of vaccine. Another clear advantage to the one-dose schedule is that antibody responses develop sooner. In the present situation of widespread circulation of the 2009 H1N1 virus occurring in many areas of the world, achieving protection 3 to 4 weeks earlier

with one dose, rather than later on a two-dose schedule, is advantageous. From a logistic standpoint, administering one dose will greatly simplify vaccination programs and should reduce costs.

These immunogenicity data are difficult to extrapolate to children or to adults who have underlying immune suppression or high-risk conditions, for whom influenza vaccine is recommended. Experience with traditional seasonal vaccines tells us that the immune responses in older children, pregnant women, and immunocompetent adults with chronic conditions are roughly similar to those of healthy nonpregnant adults.<sup>6,7</sup> On this basis, the new data suggest that the standard 15- $\mu$ g HA dose of the 2009 H1N1 vaccine should be immunogenic in those groups. The immune responses in children are unknown. Owing to the recognized morbidity associated with the 2009 H1N1 virus in children, this population is recommended to be among the first to receive vaccine in the United States.<sup>8,9</sup> Younger children generally have inferior responses to inactivated vaccines, as compared with healthy adults, and children under 9 years of age are recommended to receive two doses the first year that they receive influenza vaccine.<sup>9</sup> Immunogenicity data in young children are critical to guide policy decisions.

In our current global situation, in which demand for influenza vaccine greatly exceeds supply, dose-sparing strategies are needed.<sup>10</sup> Fewer or partial doses and the use of adjuvants can all contribute to increased global vaccine supply. The studies by Greenberg et al. and Clark et al. provide evidence that such strategies may be successful for the current pandemic. On the basis of these data, it would be appropriate to begin vaccination with the use of one dose of the usual antigen content. In children, two doses may be needed, but vaccine should not be held in reserve to be used for a second dose.<sup>9</sup> Although the adjuvanted vaccines are not licensed and not expected to be licensed for the coming season in the United States, they have been used in other countries, and their use could increase the number of persons who receive the benefit of vaccination. The adjuvant used by Clark et al., MF59, represents a class of oil-in-water adjuvants with demonstrated immunogenicity when combined with avian influenza strains that have HA-antigen contents as low as 3.75  $\mu$ g. Immunogenicity data for the 3.75- $\mu$ g dose of vaccine

are pending, but positive results would allow supplies to be stretched even further.

Both vaccines tested have generally acceptable side-effect and adverse-event profiles, with pain or tenderness at the injection site being the most common adverse event observed. The local reactions seen with the adjuvanted vaccines were moderately higher than those generally seen with nonadjuvanted vaccines.<sup>7</sup> Any association of uncommon adverse events with the vaccine cannot be ascertained in studies of this size. It is reassuring that the manufacturing process for these vaccines is identical to that used for seasonal vaccines, which have a strong record of safety. Although concerns linger about the association of the 1976 swine influenza vaccine with the Guillain-Barré syndrome, the syndrome was rare, with approximately 1 case for every 100,000 persons vaccinated. The rate was even lower among persons under 25 years of age.<sup>11</sup> One notable difference is that in 1976, we did not have a pandemic influenza virus that was spreading quickly throughout the world, and causing illness and death, as we do today. A plan for robust and comprehensive safety surveillance should be in place to detect uncommon events rapidly during the upcoming vaccination campaigns, so that risk-benefit ratios can be reassessed.

Additional studies are ongoing that will address the immunogenicity of live-attenuated vaccines, and additional inactivated vaccines, in various age groups and on various schedules and in combination with seasonal influenza vaccines. The desire to see all the available data must be balanced with the need to deploy vaccine quickly to reduce morbidity associated with the pandemic. Likewise, the need to make timely decisions must be balanced with thoughtful, transparent debate and openness to changing direction as new data emerge.<sup>1</sup>

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From PATH, Seattle.

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