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2009 Influenza A(H1N1) Monovalent Vaccines for Children

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THE 2009 INFLUENZA A(H1N1) VIRUS WAS FIRST IDENtified 8 months ago,[1] but the virus has already had a substantial effect on human health. Influenza activity in the United States has remained higher than normal since May, and measures of severe illness such as hospitalizations and deaths during the summer and fall have been equal to or higher than rates usually observed in a typical winter influenza season in all age groups except older adults.[2] Even though influenza activity has decreased in recent weeks in some states, there remains the possibility of continued activity through the traditional winter influenza season and the prospect of normal winter circulation of seasonal influenza viruses.

The 2009 influenza A(H1N1) pandemic highlights the role of children in influenza epidemiology. Serological studies suggested that children had no measurable immunity against H1N1 prior to the outbreak.[3] In addition, children have been a primary source of illness in community outbreaks of pandemic influenza, as indicated by the association between outbreaks in schools or summer camps and influenza activity in the community.[4] Children also have developed severe influenza A(H1N1)–related complications more frequently than is usually seen for seasonal influenza and reports of pediatric deaths and hospitalizations continue to increase.[2] As of December 5, 2009, 224 laboratory-confirmed deaths among children had been reported to the Centers for Disease Control and Prevention, far surpassing any recent influenza season,[2] and the actual number of pediatric deaths due to the influenza A(H1N1) virus pandemic is likely to be considerably higher.[5] Children have been among the primary groups targeted for the limited amount of vaccine available in most areas.[6]

A logistical challenge for immunization programs and clinicians who provide vaccinations is the need for 2 doses in young children.[6] For seasonal influenza vaccine, 2 doses are recommended for all children younger than 9 years who are being vaccinated for the first time, based on immunogenicity and vaccine effectiveness studies that indicate better protection with a 2-dose schedule for young children.[7] For the 2009 influenza A(H1N1) monovalent vaccines, the current recommendation is based on these seasonal vaccine studies even though the age group recommended for 2 doses is children younger than 10 years.[6,8]

The report by Nolan and colleagues[9] in this issue of *JAMA* indicates that a single 15-μg dose of an unadjuvanted inactivated influenza A(H1N1) vaccine can elicit significant increases in influenza-specific antibody in more than 90% of healthy infants and young children. A second dose given 21 days later yielded significantly higher antibody levels.[9] Data indicating that influenza A(H1N1) vaccines are immunogenic at licensed doses and schedules is excellent news for children, parents, health care professionals, and public health workers who have participated in pediatric immunization programs. Also reassuring are the findings from the safety analyses reported by Nolan et al,[9] which indicate that this unadjuvanated vaccine is well tolerated with a safety profile similar to the seasonal influenza vaccine—an expected result given that the pandemic vaccine manufacturing process is identical to that used for seasonal vaccines.[6]

Although the finding that a single dose is immunogenic in most young children is encouraging, it is premature to assume that only 1 dose will be needed to provide adequate protection for all young children based on these data. Rather, the results from this study must be considered in the context of prior studies of seasonal vaccine immunogenicity and effectiveness in children.

The hemagglutination inhibition (HI) test used in the study by Nolan et al[9] is the primary accepted measure of influenza immunogenicity. The test measures how well antibodies in serum from vaccinated (or previously infected) persons are able to compete with animal-derived red blood cells in binding influenza viruses. The ability of sera to inhibit binding by red blood cells at higher dilutions indicates a higher amount of virus-specific antibody in the specimen. An HI titer of 1:40 or greater in Nolan et al[9] and in most other studies is understood to represent the level at which approximately 50% of individuals will be protected after receiving a seasonal influenza vaccine; and higher levels of antibody generally correlate with greater protection.[10]

The evidence that led to the 2-dose recommendation for vaccine-naive children receiving seasonal influenza vaccine was based on immunogenicity data and has been supported by effectiveness data. Infants and young children not previously vaccinated with seasonal vaccine have a lower immune response to 1 dose of vaccine compared with older children and adults.[11,12] Based on the immunogenicity data alone, a possible conclusion is that only 1 dose of the 2009 influenza A(H1N1) vaccine provides protection to a substantial proportion of previously unvaccinated children in some seasons. However, studies of vaccine effectiveness have consistently demonstrated that 2 doses of seasonal influenza vaccine provide better protection than 1

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dose. In most vaccine effectiveness studies among previously unvaccinated young children, significant protection after 1 dose has not been demonstrated.[13-15] In addition, the HI test can be technically challenging and is not fully standardized, and variability of HI titer measurement makes it difficult to interpret differences in HI titer results between studies and for different virus strains.[10]

Several other notes of caution are warranted when considering the use of a single dose of unadjuvanted influenza A(H1N1) monovalent vaccine for young children. The hemagglutinin antigen content administered to 6-month-old infants and children younger than 3 years in this study[9] was 15 µg, the equivalent of 2 doses of the 7.5-µg vaccine currently licensed in the United States for this age group.[16] Furthermore, among the children aged 3 years or older, antibody levels in the study by Nolan et al[9] were approximately 30% lower than those measured using the same assay in adults who also received the 15-µg dose of the H1N1 vaccine.[17] Studies using other H1N1 vaccines also have yielded lower antibody responses in children compared with adults after 1 dose. For example, preliminary data from the ongoing US National Institutes of Health studies using a different H1N1 vaccine indicated that only 25% of 6-month-old infants and children younger than 3 years and 55% of 3- to 9-year-olds had HI titers of 1:40 or greater when measured 3 weeks after a single 15-µg dose. Significant increases in influenza-specific antibody were observed after 2 doses in more than 90% of healthy infants and young children.[18] In contrast, preliminary results indicate that 80% to 96% of 18- to 64-year-old adults participating in a National Institutes of Health study responded within 8 to 10 days with an HI titer of 1:40 or greater.[19] Variability exists in first dose response rates, but it appears that 2 doses consistently ensures that nearly all children achieve an HI titer of at least 1:40 or, preferably, greater.

In addition, in the report by Nolan et al[9] a higher proportion of children than expected (9%-14% of children <3 years and 28%-33% of children aged 3-9 years) had baseline prevaccination HI titers of 1:40 or greater, raising the possibility of previous subclinical infection with the pandemic H1N1 virus among some study participants during the pandemic wave that preceded study enrollment in Australia, or perhaps an unusually sensitive HI test. Moreover, and most importantly, lower immunogenicity is expected in children with chronic medical conditions who are at substantially higher risk of severe influenza-related complications. At least 60% of children who have been hospitalized or died in the United States during the 2009 pandemic have had 1 or more chronic medical conditions.[20,21]

The rapid development of a specific 2009 influenza A(H1N1) vaccine, and the demonstration that it is highly immunogenic and minimally reactogenic, is an important achievement. The immunogenicity data presented by Nolan et al[9] suggest that at least some children will be protected after a single 15-µg dose of the H1N1 vaccine used in this study, but the findings cannot be generalized with confidence to all children, epidemiological circumstances in every country, or different vaccine formulations. In recent years, important gaps in influenza knowledge and pandemic preparedness have been addressed, but significant challenges remain. Among those challenges is development of an easily measurable correlate of immunity that can consistently predict clinical vaccine effectiveness in all age groups. Until that objective is achieved, it remains prudent to continue to follow current recommendations for administering 2 doses to infants and young children while awaiting definitive vaccine effectiveness data.[6,8]

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