

CORRESPONDENCE



Responses to 2009 H1N1 Vaccine in Children 3 to 17 Years of Age

TO THE EDITOR: The current 2009 pandemic influenza A (H1N1) virus is associated with substantial morbidity in children, with 45% of hospitalizations occurring in patients under 18 years of age.¹ One possible reason for this trend is a lack of preexisting immunity against the 2009 H1N1 virus among children.² Experience with other pandemic vaccines has suggested that two doses of vaccine for children and adults would be needed to meet the licensure criteria of the Center for Biologics Evaluation and Research (CBER).³ According to these criteria, the lower bound of the two-sided 95% confidence interval should meet or exceed 40% in subjects achieving seroconversion on hemagglutination-inhibition (HI) assay and should meet or exceed 70% in subjects with an HI antibody titer of 1:40 or more. Data from recent studies^{4,5} have shown that in adults one 15- μ g dose of influenza A/California/2009 (H1N1) vaccine (CSL Biotherapies and Novartis) met licensing criteria.

In a randomized, single-center study in Costa Rica, we tested various doses of egg-based 2009 H1N1 vaccine (Novartis) in subjects ranging in age from 3 to 64 years, including 194 subjects between the ages of 3 and 8 years and 196 subjects between the ages of 9 and 17 years (ClinicalTrials.gov number, NCT00973700). The vaccines were formulated with or without the adjuvant MF59 that was used in a European licensed influenza vaccine (Novartis). The study was approved by the ethics committee of the Universidad de Ciencias Médicas. Parents of all subjects provided written informed consent.

Subjects in the two age groups, who were more than 99% Hispanic, were randomly assigned (in a 2:3:2 ratio) to receive one 7.5- μ g hemagglutinin dose with adjuvant or either one or two 15- μ g doses without adjuvant. After vaccination, local and systemic events were gener-

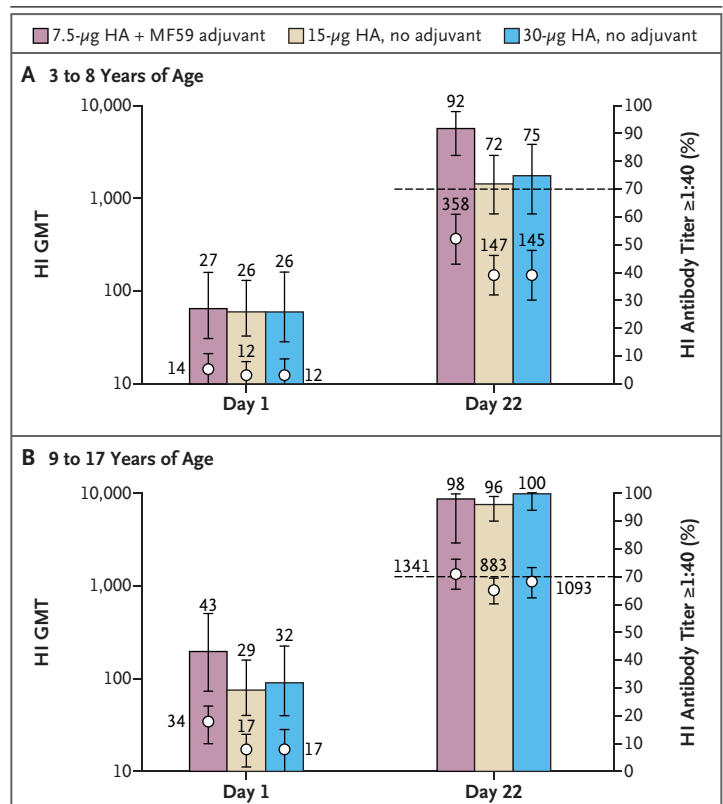


Figure 1. Immunogenicity of Three Regimens of 2009 H1N1 Vaccine, According to Age Group.

Shown are geometric mean titers (GMT) measured by means of hemagglutination-inhibition (HI) assay (circles, with numbers indicating values) and the proportion of subjects with an HI antibody titer of 1:40 or more (bars, with numbers indicating percentages) among 194 children between the ages of 3 and 8 years (Panel A) and 196 children between the ages of 9 and 17 years (Panel B) before the administration of one dose of 2009 H1N1 influenza vaccine (day 1) and at 22 days. Children (in a 2:3:2 ratio) received one 7.5- μ g dose of hemagglutinin (HA) with MF59 adjuvant, one 15- μ g dose without adjuvant, or two 15- μ g doses (totaling 30 μ g) without adjuvant in each age group. The I bars indicate 95% confidence intervals. The dotted line indicates the vaccine-efficacy cutoff point for the criterion of the Center for Biologics Evaluation and Research, which states that the lower bound of the two-sided 95% confidence interval should be at least 70% for the HI antibody titer of 1:40 or more.

ally mild to moderate. Less than 4% of subjects reported having severe events in any of the vaccine or age groups, and no vaccine-related serious adverse events were reported (for details, see the Supplementary Appendix, available with the full text of this letter at NEJM.org). By day 22, all three vaccine regimens had elicited increases in HI titers in the two age groups (Fig. 1). Rates of seroconversion were greater than 70% in all age and vaccine groups. After a single dose of vaccine, all three vaccine regimens met the CBER criterion for the HI antibody titer among subjects 9 to 17 years of age, but only the 7.5- μ g dose of vaccine with adjuvant met this criterion among children 3 to 8 years of age.

These preliminary data support the use of one 15- μ g dose of 2009 H1N1 vaccine without adjuvant in children between the ages of 9 and 17 years. However, in children 3 to 8 years of age, only the 7.5- μ g dose of 2009 H1N1 vaccine with adjuvant met both the immunogenicity criteria after one dose, and the criterion for the HI antibody titer was not met by either one or two 15- μ g doses without adjuvant. The use of adjuvant may provide a rapid immune response at a lower hemagglutinin dose than that required in vaccine without adjuvant. This may increase the availability of vaccine for rapid immunization in

young children, an age group that is at substantial risk for hospitalization associated with influenza.

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