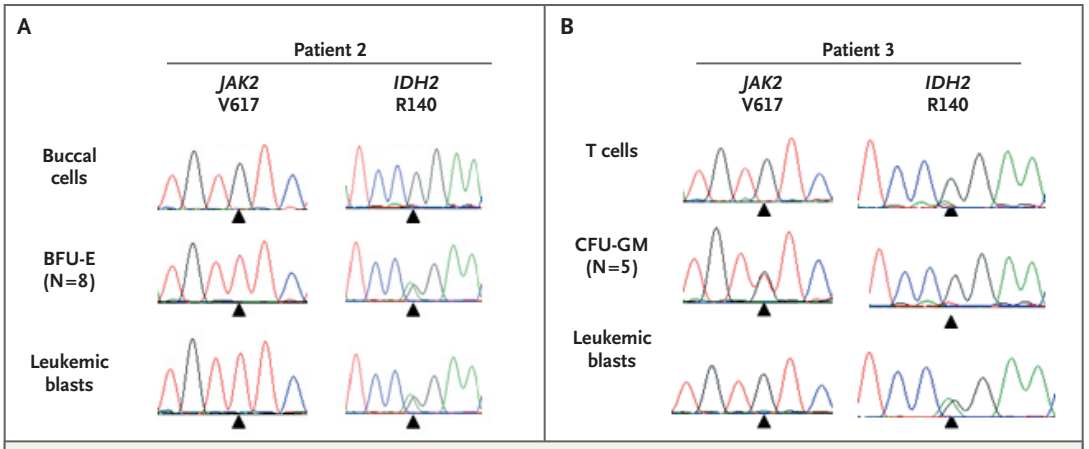

Figure 1. Mutations in *IDH1* and *IDH2* in Patients with Leukemia Evolving from a Myeloproliferative Neoplasm Harboring a Mutation in *JAK2*.

Studies of cells from Patient 2 show wild-type *JAK2* and *IDH2* in buccal cells and coexisting *JAK2* and *IDH2* mutations in erythroid colonies and leukemic blasts (Panel A). Studies of cells from Patient 3 show wild-type *JAK2* and *IDH2* in T cells, with analysis of progenitor colonies and leukemic blasts showing that mutations in *IDH2* and *JAK2* may be present in separate clonal expansions (Panel B). BFU-E denotes erythroid burst-forming unit, and CFU-GM granulocyte–macrophage colony-forming unit.

180 unselected patients with chronic-phase polycythemia vera or essential thrombocythemia. Among the five patients with *IDH* mutations, three harbored an *IDH1* R132C substitution and two harbored a novel *IDH2* R140Q mutation affecting a residue conserved in mouse, yeast, and plant homologues.

In Patient 2, an *IDH2* R140Q mutation was detected in erythroid colonies with a *JAK2* mutation as well as in leukemic blasts (Fig. 1A), indicating that this alteration was acquired early during the progression to leukemia and is not responsible for the block in cellular differentiation that occurs in acute leukemia. Leukemic cells arising from myeloproliferative neoplasms with a *JAK2* mutation are commonly *JAK2* wild-type,[4] although the mechanism by which they become wild-type is unknown. Among the five samples of leukemia cells carrying an *IDH* mutation, three samples lacked the *JAK2* mutation. In two of these three samples, an *IDH* mutation was present in leukemic blasts with wild-type *JAK2* but absent from progenitor colonies with a *JAK2* mutation (Fig. 1B), establishing the presence of two separate clonal expansions in each patient. In these cases, the separate *JAK2*-mutant and *IDH*-mutant clones may represent the shared progeny of an ancestral abnormal clone or the coexistence of two distinct disorders with independent origins.[5]

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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-μg 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-μg hemagglutinin dose with adjuvant or either one or two 15-μg doses without adjuvant. After vaccination, local and systemic events were generally 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-μg 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-μg 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-μg 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-μg 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.

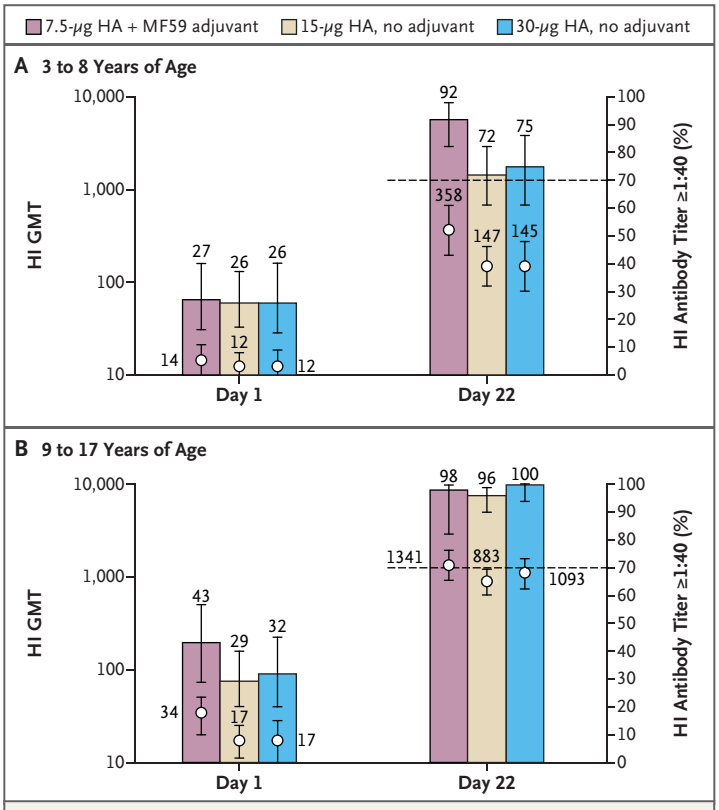

Figure 1. Immunogenicity of Three Regimens of 2009 H1N1 Vaccine, According to Age Group.

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-μg dose of hemagglutinin (HA) with MF59 adjuvant, one 15-μg dose without adjuvant, or two 15-μg doses (totaling 30 μg) 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.

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The following subspecialty examinations will be held in various cities on March 22: "Adolescent Medicine," "Neonatal-Perinatal Medicine," and "Pediatric Nephrology."

Contact the American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513; or call (919) 929-0461; or fax (919) 929-9255; or e-mail abpeds@abpeds.org; or see http://www.abp.org.

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

The "8th Annual Meeting" will be held in San Francisco, June 16–19.

Contact the International Society for Stem Cell Research, 111 Deer Lake Rd., Suite 100, Deerfield, IL 60015; or call (847) 509-1944; or fax (847) 480-9282; or e-mail isscr@isscr.org; or see http://www.isscr.org/.

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The "21st Annual Meeting" will be held in Tampa, FL, March 17–20. Deadline for early registration is Feb. 3.

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Contact the organizing secretariat, Meet and Work Srl, Piazza del Sole e della Pace 5, 35031 Abano Terme (Padova), Italy; or call (49) 860 1818; or fax (49) 860 2389; or see http://www.nhs2010.org; or e-mail nhs@polimi.it.

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