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Influenza Vaccine in Pediatric Recipients of Hematopoietic-Cell Transplants

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Pediatric HCT Flu Study Group*

TO THE EDITOR:

Pediatric recipients of hematopoietic-cell transplants (HCT) are at high risk for influenza-related illness and death. They also have weaker humoral immune responses to influenza vaccination than healthy children, which suggests that alternative vaccine regimens are needed.[1] Previous phase 1 studies showed that high-dose influenza vaccines are immunogenic in some high-risk populations without evident safety concerns, but data are lacking for pediatric recipients of HCT.[2-4]

We conducted a phase 2, multicenter, double-blind, randomized, controlled trial (Pediatric HCT Flu Study; ClinicalTrials.gov number, NCT02860039) that compared immunogenicity and safety between high-dose trivalent influenza vaccine (HD-TIV) and standard-dose quadrivalent influenza vaccine (SD-QIV) in children and adolescents 3 to 17 years of age who had received an allogeneic HCT 3 to 35 months earlier. The trial was conducted over three influenza seasons (2016 through 2019). The protocol (available with the full text of this letter at NEJM.org) was approved by the institutional review board at each site, and written informed consent was obtained from parents or legal guardians. Each participant received two vaccine doses, 28 to 42 days apart. Hemagglutination-inhibition (HAI) titers to all four vaccine-specific influenza antigens (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata) were measured before each vaccine dose and 28 to 42 days after the second dose. The primary immunogenicity end point was the adjusted geometric mean ratio (GMR [HD-TIV vs. SD-QIV]) of HAI titers to influenza A antigens 28 to 42 days after the second dose. Solicited injection-site reactions and systemic adverse events were assessed for 7 days after each dose.

A total of 170 participants were randomly assigned to receive two vaccine doses of either HD-TIV (85 recipients) or SD-QIV (85 participants) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The median age of the participants was 10.9 years, 76 (45%) were female, 117 (69%) were White, 36 (21%) were Hispanic or Latino, and the median time from transplantation to enrollment was 7.8 months (Table S1). As compared with two doses of SD-QIV, two doses of HD-TIV were associated with significantly higher geometric mean titers to A/H1N1 (adjusted GMR, 1.65; 95% confidence interval [CI], 1.06 to 2.57; P = 0.03) and A/H3N2 (adjusted GMR, 2.11; 95% CI, 1.32 to 3.38; P = 0.002) and numerically higher titers to B/Victoria (adjusted GMR, 1.46; 95% CI, 0.93 to 2.31; P = 0.10) (Fig. 1 and Table S2) but lower titers to B/Yamagata (which is not included in HD-TIV). The HD-TIV group had a higher frequency of mild or moderate injection-site reactions after the second vaccine dose (Fig. S2). The frequency of any severe reaction was similar in the two groups: 7.5% with HD-TIV and 6.0% with SD-QIV after dose 1 and 7.6% with HD-TIV and 6.4% with SD-QIV after dose 2.

We found that two doses of HD-TIV resulted in higher antibody responses to influenza A antigens than two doses of SD-QIV in pediatric recipients of HCT. The overall safety profile was similar, with a slightly higher number of mild or moderate injection-site reactions after the second dose of HD-TIV than after the second dose of SD-QIV. Influenza is associated with substantial morbidity and mortality in this high-risk population. Improvement of vaccine strategies is critical, and the administration of two doses of high-dose inactivated influenza vaccine could be a practical strategy to increase immune responses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Influenza Vaccine in Pediatric Recipients of Hematopoietic-Cell Transplants

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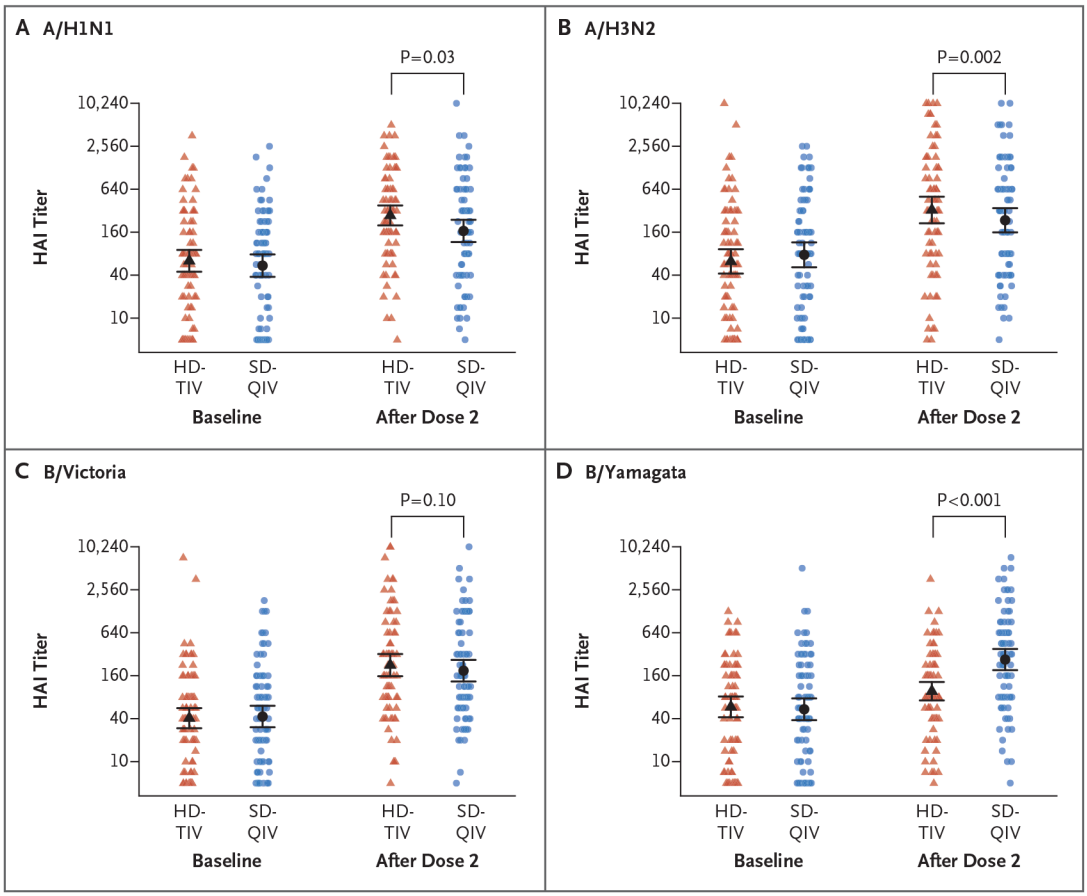

Figure 1. Hemagglutination-Inhibition Titers to Influenza Antigens.

Depicted are the raw data along with group- and time-specific estimates of the geometric mean titers for hemagglutination inhibition (HAI) along with 95% confidence intervals (indicated by I bars). P values are for the adjusted geometric mean ratios comparing high-dose trivalent influenza vaccine (HD-TIV) with standard-dose quadrivalent influenza vaccine (SD-QIV). B/Yamagata is not included in HD-TIV.