Safety and Immunogenicity of Trivalent Inactivated Influenza Vaccine in Infants

A Randomized Double-Blind Placebo-Controlled Study

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Background: Infants less than 6 months of age are at high risk for influenza disease and influenza-related complications, but no vaccine is licensed for this population.

Methods: A double-blind, randomized, placebo-controlled trial was conducted in 1375 healthy US infants 6 to 12 weeks of age. Subjects received 2 doses of trivalent inactivated influenza vaccine (TIV, Fluzone, sanofi pasteur; N = 915) or placebo (N = 460) 1 month apart in combination with indicated concomitant vaccines. Solicited adverse events were collected for 7 days following vaccination, and unsolicited adverse events for 28 days. Hemagglutination-inhibition antibodies to all 3 vaccine strains were measured following the second TIV/placebo dose.

Results: No significant differences were seen between TIV and placebo groups for any safety outcome. Fever ≥38°C within 3 days of vaccination was seen in 11.2% versus 11.7% of TIV versus placebo recipients. Serious adverse events within 28 days were reported in 1.9% of TIV and 1.5% of placebo recipients. Antibody responses to childhood vaccines were similar in both groups. Increased influenza-specific antibody responses in TIV recipients compared with placebo recipients were seen against all 3 strains in TIV recipients ($P < 0.001$), with better responses to influenza A strains noted. Reciprocal geometrical mean titer to H1N1, H3N2, and B were 33, 95, and 11 in TIV recipients versus 7, 9, and 5 for placebo recipients. Over 90% of TIV recipients had antibody ≥1:40 for at least 1 vaccine strain and 49.6% for 2 strains, versus 16.4% and 0.9% in placebo-recipients.

Conclusions: TIV administered to young infants beginning at 6 to 12 weeks of age is safe and immunogenic.

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Influenza-related hospitalization and mortality rates remain highest in the very young and the very old.[1,2] A study conducted during 2003 to 2004 found the highest pediatric influenza mortality rates in the youngest infants.[3] Similarly, the highest rates of medically attended illnesses during influenza outbreaks are in children less than 6 months of age with underlying conditions.[1,4,5] Nearly 1 million infants each year are between the ages of 6 weeks and 6 months during periods when influenza vaccines are routinely administered, yet neither influenza vaccine nor antiviral therapy is available for these young children. Vaccination strategies proposed for influenza pandemics also serve to emphasize the lack of prevention available for this vulnerable population.[6]

Trivalent inactivated influenza vaccine (TIV) has been found to be safe, immunogenic, and effective in children >6 months of age when given as 2 doses separated by 1 or more months.[7–12] However, data evaluating TIV in children under 6 months of age are quite limited. One small study in 113 children <2 years of age with bronchopulmonary dysplasia or congenital heart disease demonstrated that 2 doses of TIV elicited good antibody responses to H3N2 but poorer responses to H1N1 and B[13]; only a few infants were <6 months old. A pilot study in 42 infants who received TIV at 10 to 22 weeks of age, demonstrated good safety but only moderate immunogenicity in 2-month-old infants given TIV separately from routine immunizations with some potential inhibition by maternal antibodies.[14] In a pilot study comparing TIV vaccine in 2 versus 6-month-old infants, immunization in 2-month-old was safe and immunogenic.[15] Immune responses were similar in seronegative 2-month-olds and 6-month-old infants, although less immunogenic in infants with preexisiting maternal antibody.

Strategies to protect young infants include immunization of pregnant women with TIV[16] and "cocooning" infants by vaccinating family members. Maternal immunization offers an excellent option for protecting both pregnant women and young infants against influenza,[16,17] although current acceptance of this approach is low[18] and the proportion of women immunized during pregnancy has not greatly increased over the past 5 years.[18–20] Another obvious approach to protect infants from complications of influenza is earlier vaccination. Because routine childhood immunization in the United States begins at 2 months of age, initiating influenza vaccination coincidentally with routine childhood immunizations is both practical and convenient. This multicenter placebo-controlled study was designed and conducted to evaluate the safety and immunogenicity of 2 doses of licensed inactivated trivalent subvirion influenza vaccine delivered in-season to healthy infants.

METHODS

Study Design

This was a prospective, multicenter, double-blind, randomized, placebo-controlled trial designed to compare the safety and immunogenicity of a licensed 2005 to 2006 trivalent inactivated influenza vaccine (Fluzone; TIV) to placebo in infants. The study protocol was reviewed by the Food and Drug Administration, and was approved by each institutional review board. Informed consent was obtained from a parent or guardian. Children were randomized 2:1 to receive TIV or placebo using a computer-generated randomization list provided to an interactive voice response system, which was accessed by each site's study personnel. The investigational vaccine and control product were identical in appearance and labeling, with lot numbers corresponding to the group assignment (investigational or control) assigned to each subject. Study personnel, family, and sanofi pasteur personnel associated with the trial remained blinded throughout the trial.

All children were enrolled at 6 to 12 weeks of age to receive 2 doses of TIV or placebo a month apart (Table 1). Routine childhood vaccines were administered concomitantly with study vaccine at the first visit and without study vaccine at 4 and 6 months of age. Concomitant childhood vaccines are listed in Table, Supplemental Digital Content 1, http://links.lww.com/INF/A222. All vaccines were administered in specified anatomic sites to facilitate reaction assessment, with TIV given in the upper right thigh. Blood was drawn at 4 months of age for determination of influenza antibodies and at 7 months for responses to childhood vaccines.

The primary objective of this study was to demonstrate safety and immunogenicity of 2 doses of TIV administered to infants with concomitant childhood vaccines. We hypothesized that rates of fever ≥38.0°C would be noninferior in children receiving TIV compared with placebo and that antibody responses to TIV would be superior to placebo as measured by the proportion in each group achieving hemagglutination-inhibition titer of ≥1:40 to at least 1 influenza antigen following the second TIV dose.

The estimated projected sample size was 1380 subjects, randomized 2:1 to receive TIV or placebo. Healthy infants were recruited from participating clinics throughout the United States between September 2005 and December 2005. Infants were required to be healthy, 6 to 12 weeks of age at enrollment, born at ≥36 weeks gestation with a birth weight of >2.5 kg, and have no egg allergies.

Vaccines

All vaccines except HepB and pneumococcal conjugate vaccine (PNC) were provided by the study sponsor. The 2005 to 2006 pediatric formulation of preservative-free Fluzone TIV (sanofi pasteur, Swiftwater, PA) was used. Each 0.25 mL dose contained 7.5 μg hemagglutinin (HA) of A/New Caledonia/20/99 (H1N1); A/New York/55/2004 (H3N2), and B/Jiangsu/10/2003. The placebo was 0.25 mL sterile with 0.9% sodium chloride. TIV or placebo was administered as a separate intramuscular injection in the right anterolateral thigh using a 25 G, 1.0 inch needle. Concomitant vaccines are listed in Table 1. The Hib vaccine was given as a separate injection. Vaccination with HepB (provided by each patient's health care provider) and inactivated polio vaccine (IPV) (IPOL, sanofi pasteur) was permitted at study visits 1 or 2, or at least 7 days apart from study visits 1 or 2.

Safety

Safety outcomes included immediate reactions at the time of vaccination, solicited local and systemic reactions for 7 days, unsolicited adverse events for 28 days, and serious adverse events (SAEs) using previously defined criteria.[8,9] Parents maintained a study diary for 7 days. Potentially serious adverse reports were collected through the final parental contact 6 months following the final study visit.

Immunogenicity

Blood samples were obtained at Study Visit 3 and Visit 4. Sera were separated within 2 hours of collection and stored frozen in a monitored freezer at −20°C. Antibody responses to influenza antigens on blood obtained at Study Visit 3 were determined by an HAI performed at sanofi pasteur (Swiftwater, PA) using vaccine antigens provided by Centers for Disease Control.[15]

Antibody concentrations to other childhood vaccines were obtained from blood obtained at 7 months of age. Pertussis antibody concentrations to 4 antigens were determined by an indirect enzyme-linked immunosorbent assay (ELISA) method. Antidiphtheria antibody responses were measured by Vero cell protection assay and antitetanus titers determined by indirect ELISA, expressed as International Units (IU)/mL compared with World Health Organization standard. Antibody polyribosylribitol phosphate (PRP) concentrations were determined using a Farr-type radioimmunoassay. Type 4, 6B, 9V, 14, 18C, 19F, and 23F pneumococcal antibody concentrations were measured by IgG ELISA and specific poliovirus antibodies by neutralization.

Sample Size and Data Analysis

The planned enrollment of 1380 subjects (randomized 2:1 to receive TIV:placebo) was designed to obtain at least 1200 evaluable subjects, allowing an attrition rate up to 13%. The associated power of this study was 81%, (assuming an incident rate of fever ≥38°C of 10%), to detect a noninferiority criterion of 5%, or

TABLE 1. Study Design of Placebo-Controlled Evaluation of Trivalent Inactivated Influenza Vaccine Versus Placebo in Infants Beginning at 2 Months of Age

	Study Visit 1	Study Visit 2	Study Visit 3	6 mo Vaccinations	Study Visit 4
Age (approx.)	2 mo	3 mo	4 mo	6 mo	7 mo (21–42 d after 6 mo vaccinations)
Study vaccines	TIV or Placebo	TIV or Placebo	—	—	—
Concomitant vaccines	DTaP, Hib, PNC, IPV, HepB, IPV*	HepB*	DTaP, Hib, IPV, PNC; (optionally HepB, IPV)	DTaP, Hib, IPV, PNC; (optionally HepB, IPV)	—
Blood drawn	—	—	Yes	—	Yes

*Vaccination with hepatitis B (HepB) and inactivated polio vaccines (IPOL, sanofi pasteur) was permitted during study visits 1 or 2 or any time in-between as long as the vaccination was at least 7 days apart from Study visits 1 and 2.

DTaP indicates diphtheria toxoid-tetanus toxoid-acellular pertussis, (DAPTACEL, sanofi pasteur, Swiftwater, PA); Hib, *H. influenzae* type b conjugate (ActHIB; sanofi pasteur, Swiftwater, PA); IPV, inactivated polio vaccine (IPOL, sanofi pasteur, Swiftwater, PA); PNC, pneumococcal conjugate vaccine, (Prevnar, Wyeth Lederle, Pearl River, NY); HepB, Hepatitis B vaccine.

approximately ruling out a relative risk of ≥1.5-fold increased rate of fever in TIV recipients.

Descriptive and exploratory analyses examined demographic characteristics and frequency and percentage of subjects with local and systemic reactions. The Geometric Mean Titer (GMT) and potential seroprotection rate (proportion of subjects with a postimmunization titer ≥1:40) were determined for each influenza vaccine antigen and 95% confidence intervals (CI) calculated. Seroprotective levels were predefined for antigens in the childhood vaccines: ≥0.15 μg/mL for PRP; ≥0.01 IU/mL for diphtheria and tetanus; ≥4 EU/mL for pertussis toxoid, fimbriae (FIM), and pertactin (PRN); ≥3 EU/mL for filamentous hemagglutinin; ≥1:8 for polioviruses; and ≥0.15 μg/mL for each pneumococcal antigen.

The full data analysis set, considered the "Intention to Treat" (ITT) population, included all randomized subjects who received at least 1 dose of study vaccine/placebo, and had a valid serology result from Visit 3 or 4. The safety analysis included all subjects receiving at least 1 injection of TIV/placebo. Analyses of the primary hypotheses were performed with 2-sided 95% asymptotic CI of the difference in 2 proportions. In the fever analysis, noninferiority of TIV to placebo was established if the upper bound of the 95% CI of TIV minus placebo was below 5%. In the seroprotection primary analysis, superiority of TIV to placebo was established if the lower bound of the 95% CI of TIV minus placebo was above 0. In exploratory analyses, the Pearson χ^2 test was used for categorical data analysis, Student *t* test for inferential analysis of continuous data, and the log-rank test to analyze the antibody titer reverse cumulative distribution curves (SAS version 8.2, SAS Institute, Cary, NC).

RESULTS

Subjects

A total of 1374 infants were enrolled; 915 were randomized into the TIV group and 459 into the placebo group (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/A223). One subject randomized to receive TIV received 2 doses of placebo, and 1 subject was not randomized but received TIV. Thus, a total of 1375 subjects were analyzed in the Safety Analysis of subjects receiving at least 1 dose of study drug; 163 did not complete the study to Visit 4 (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/A223). Overall, 103 withdrew from the study voluntarily (65 TIV, 38 placebo), 22 were lost to follow-up (16 TIV, 6 placebo), 26 were withdrawn by the investigator for noncompliance (19 TIV, 7 placebo), 5 (4 TIV, 1 placebo) withdrew due to serious adverse events, and 7 (4 TIV, 3 placebo) withdrew because of other adverse events.

A total of 1304 subjects (869 TIV recipients; 435 placebo) received 2 doses of TIV or placebo, and 1096 of these (79.8% of all enrolled subjects; 84% of those receiving 2 TIV doses) had serology test results from Visit 3 or 4. These 1096 subjects were considered the ITT population (747 in TIV Group, 349 in placebo group). Of the 1304 subjects, 985 completed the study per protocol (receipt of concomitant vaccines within the appropriate time frame; serological results available at Study Visit 3; all study visits at the correct times).

Subjects in both the Safety and ITT populations were well balanced by age, sex, race, ethnicity, and history of maternal influenza vaccine (Table, Supplemental Digital Content 3, http://links.lww.com/INF/A224). In the TIV group, 45.6% of mothers never received influenza vaccine, 38.7% received vaccine ≥6 months prior to delivery, and 1% received vaccine within 6 months of delivery compared with 45.1%, 38.6%, and 2.3% of mothers in the placebo group.

Altogether, 90.6% of subjects in the TIV and 89.3% of those in the placebo group received 3 doses of DTaP, and 89% to 90% of participants in both groups received 3 doses of Hib, IPV, and pneumococcal conjugate vaccine. Use of antibiotics and antipyretics was similar in both groups.

Safety

Safety profiles were similar in the TIV and placebo groups in terms of immediate adverse events, solicited local and systemic reactions, unsolicited adverse events, and SAEs (Fig. 1). Two subjects in the TIV Group experienced unsolicited adverse events within 20 minutes of vaccination, including one with a nonsevere allergic reaction and other with colic.

Similar proportions of subjects in both groups experienced local injection site reactions within 3 days (Fig. 1), with over 75% of local reactions reported on the day of injection. Most local reactions were mild in intensity and resolved within 2 days. The incidence of local reactions decreased with the second TIV dose (Fig. 1). Similar proportions of subjects in each group (63% in TIV, 65% in placebo group) reported reactions at the DTaP site within 3 days of vaccination.

Fever was the end point for the primary safety hypothesis. The incidence of fever within 3 days was similar in both groups after both doses (Fig. 1). Fever was most commonly reported on the day of injection, but the incidence rapidly decreased such that fever was unusual by day 2 (0.3%–0.7% in each group after either dose). The difference in the group fever rates was −0.47% (95% CI, −4.14–3.20), satisfying the predefined criteria of noninferiority. The incidence of fever was significantly lower following the second dose of TIV/placebo than following the first dose: 2.3% (19/839, 95% CI: 1.4–3.5) in the TIV group versus 3.8% (16/416, 95% CI: 2.2–6.2) in the placebo group. At postdose 2, an ad hoc noninferiority analysis of TIV versus placebo produced a fever rate difference of −1.58% (95% CI: −3.69–0.52), achieving the predefined noninferiority criterion.

The percentage of subjects who experienced at least 1 solicited systemic reaction within 3 days of TIV/placebo was 93.4% in the TIV and 92.7% in the placebo group (Table, Supplemental Digital Content 4, http://links.lww.com/INF/A225). No systemic reaction was serious. Rates of solicited systemic reactions within 3 days of Dose 1 and 2 of TIV/placebo were similar in both groups, although higher reaction rates were reported following Dose 1 of TIV, when multiple vaccines were administered.

Unsolicited adverse events (AEs) occurring within 28 days after any study treatment administration were common, but were not significantly different between the 2 groups. Four serious AE's in TIV recipients lead to study withdrawal: 1 patient developed a hypersensitivity reaction 20 minutes after receiving the first dose of TIV, which was administered simultaneously with DTaP, Hib, and PNC. This urticarial reaction resulted in hives and swelling in 1 ear, requiring treatment with diphenhydramine. The other subjects were withdrawn from the study for unrelated reasons including accidental asphyxiation, urinary tract infection, and formula or milk protein intolerance. The single withdrawal in the placebo group was due to intussusception 118 days postvaccination. Altogether, 1.9% of subjects in the TIV group and 1.5% of subjects in the placebo group experienced a serious adverse event within 28 days. Only 1 of 17 reported SAEs in the TIV group was considered TIV-related, an immediate moderate allergic reaction (described above). Pneumococcal conjugate vaccine (PNC) was the most common SAE reported in both groups, documented in over 50% of all events. The single unrelated death (accidental asphyxiation) occurred 24 days following TIV.

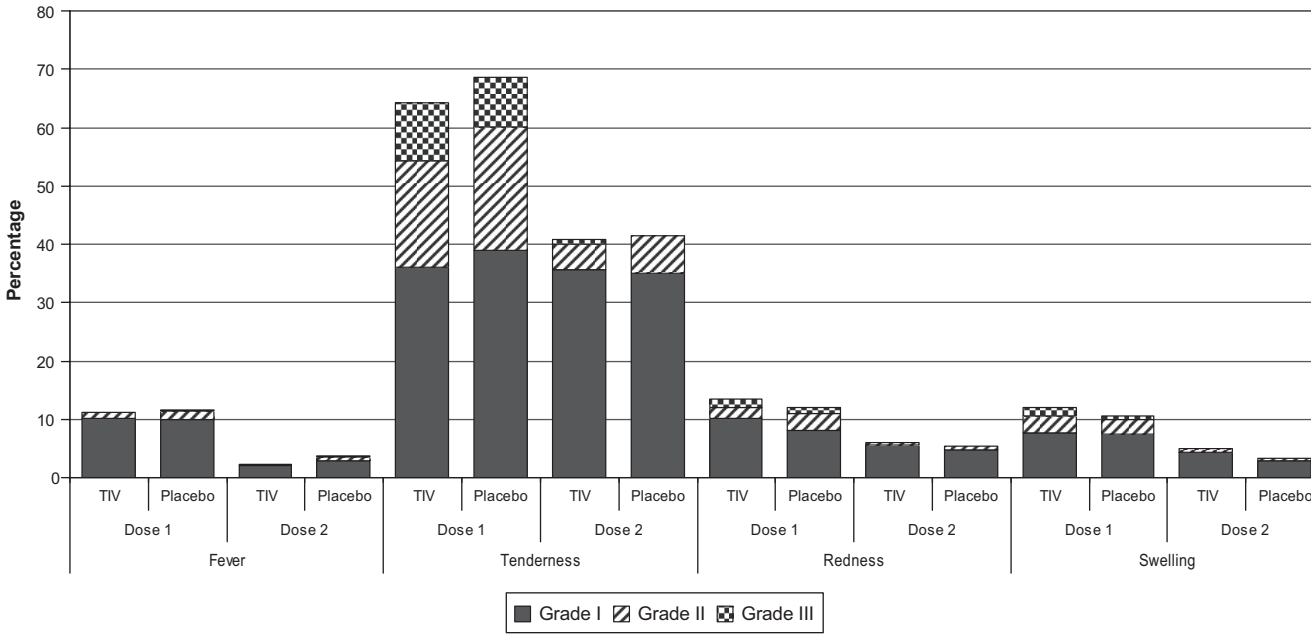

FIGURE 1. Percentage of participants with fever or local reactions (tenderness, redness, or swelling) following first and second doses of TIV/Placebo. No significant differences were noted between TIV and placebo groups at either dose 1 or dose 2 for fever or any local reaction.

Immunogenicity

Study vaccine immunogenicity is reported for the 1096 subjects in the ITT population. The number of patients who completed the study per protocol and had antibody responses to childhood vaccine antigens included 90.4% of TIV recipients in the ITT population and 88.8% of placebo recipients (Fig. 2). The ITT subjects in the TIV group exhibited statistically superior seroresponse rates to influenza antigens compared with placebo recipients. Overall, 90.2% (671/744) of TIV recipients achieved potential seroprotection (titer ≥1:40) following the second TIV dose to at least one influenza strain compared with 16.4% (57/347) of subjects in the placebo group. The 95% CI of difference in rates between groups (69.3%, 78.2%) easily achieved the superiority criterion of greater than 0.

Seroprotection rates to individual influenza vaccine antigens were significantly higher in the TIV group than the placebo group: 50.1%, 85.6%, and 10.9% for A/New Caledonia/20/99, A/New York/55/2004, and B/Jiangsu/10/2003, respectively, versus 6.9%, 10.1%,

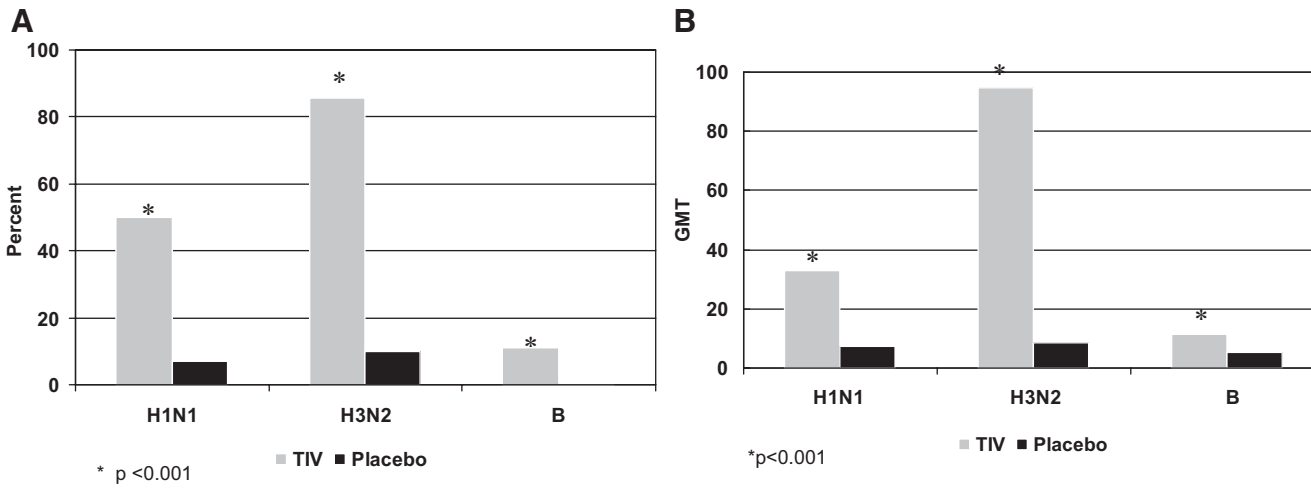

FIGURE 2. Immunogenicity of trivalent inactivated influenza vaccine (TIV) versus Placebo groups against the 3 influenza vaccine strains in the intention to treat population. A, Percentage of TIV and placebo recipients with potential seroprotection (titers ≥1:40) after the second dose of TIV/placebo. Responses in TIV group significantly greater than that of placebo group for all 3 antigens, $P < 0.001$. B, Geometric Mean Titer (GMT) after second dose of TIV or placebo. TIV significantly elevated compared with GMT, $P < 0.001$.

and 0.3% ($P < 0.001$). Nearly 50% of infants who received TIV had antibody ≥1:40 for at least 2 vaccine antigens, versus 16.4% and 0.9% in the placebo group, respectively. GMTs were significantly higher for all 3 influenza antigens ($P < 0.001$ for each strain). The reciprocal GMT for influenza recipients was 33, 95, and 11 for H1N1, H3N2, and B versus 7, 9, and 5 for placebo recipients.

The distribution of antibody titers in infants following the second dose of TIV or placebo is shown in the reverse cumulative distribution curves (Fig., Supplemental Digital Content 5, http://links.lww.com/INF/A226), demonstrating a high percentage of individuals with good antibody responses to influenza A/H1N1 and A/H3N2 and a markedly less robust response to the B antigen ($P < 0.001$, each strain).

Concomitant Vaccines

Administration of TIV at 2 and 3 months of age did not interfere with responses to the concomitant vaccines administered routinely during infancy: post-third-dose antibody responses to all antigens in the DTaP, Hib, IPV, Hep B, and PNC vaccines were not significantly different between the TIV and placebo groups in both the ITT and per-protocol populations. Prespecified seroprotection rates to concomitant vaccine antigens were excellent and uniformly high in both groups. Seroprotection rates in the ITT population to diphtheria, tetanus, PRP, and 3 polioviruses were 100%, 100%, 96.8%, and 100% in the TIV group and 100%, 100%, 96.5, and 100% in the placebo group. Similarly, antibody responses ≥ lower limit of quantitation to pertussis toxoid, filamentous hemagglutinin, PRN, and FIM were between 97% and 100% in subjects in both groups. Responses and GMT to all 7 pneumococcal antigens were likewise very good and similar in both groups (≥99% of subjects with antibody >0.15 μg/mL to serotypes 4, 9V, 14, 18C, and 19F; 94.8% to 98.4% of subjects with antibody >0.15 μg/mL to Serotypes 6B and 23F).

DISCUSSION

This study, designed to assess the safety and immunogenicity of TIV in a young population, showed that currently formulated TIV can be administered safely to 6 to 12-week-old infants concomitantly with routine childhood vaccines. TIV was immunogenic in young children and did not inhibit antibody responses to routine vaccines administered concurrently at the first immunization visit. The superiority of TIV to placebo in these infants was demonstrated by higher rates of seroprotection and higher GMTs, a response best illustrated by the reverse cumulative distribution curves for each antigen (Fig., Supplemental Digital Content 5, http://links.lww.com/INF/A226). Results from this study are encouraging for future prospective studies that could evaluate actual efficacy of TIV in young children.

TIV vaccine was well tolerated by infants in this large, placebo-controlled study, again demonstrating the safety of this vaccine in children at all ages.[7–10] Specifically, rates of fever following TIV were noninferior to those following placebo after the first dose when multiple childhood immunizations were administered, and after the second dose, when very few concomitant vaccines were given. The higher rate of reactions following the first dose of TIV and placebo is likely related to the administration of multiple concomitant vaccines including PNC at 2 months of age compared with no other vaccine or the relatively nonreactogenic HepB vaccine concurrently with the second dose of TIV/placebo. Fever following vaccination therefore is more likely attributable to other childhood vaccines rather than TIV. We have previously documented the impact of PNC as a major contributor to fever in young children receiving multiple childhood vaccines including influenza vaccine.[8]

TIV produced a good immunologic response in young infants vaccinated in the fall during the routine influenza vaccination season. In the 2005 to 2006 season, influenza activity was not widespread until early January 2006, indicating that wild-type disease was unlikely to have impacted our study results.[21] Our results contrast with those observed by Halasa et al,[14] in a smaller study of 42 infants immunized during 2 influenza seasons without concomitant vaccines. In that study, interference by maternal antibody may have contributed to the poor antibody response in infants. The enrollment of infants during 2 separate influenza seasons may also have complicated the serological analysis. Inhibition of the infant immune response by maternal antibody is an important consideration and has been recognized in other studies of infant vaccination, notably with hepatitis A,[22] diphtheria-tetanus-pertussis,[23] Hib,[24] and live attenuated measles vaccines,[25] as well as studies of influenza vaccine.[14,15] Despite decreased antibody production in the presence of increased concentrations of maternal antibody, some of these vaccines have demonstrated priming in infants, with brisk responses upon antigen reexposure.[25] The impact of influenza immunization in young infants with or without high amounts of maternal antibody could be potentially assessed in prospective efficacy studies.

Seroprotective antibody concentrations in infants are not known. Potential protective antibody concentrations in infants against influenza may be similar to those reported in adults, but multiple biologic factors would be expected to impact the ability of young infants to be protected against respiratory infection due to influenza, including maturation of cell-mediated immunity. Nonetheless, rates of antibody ≥1:40 as determined by HAI in this study suggest that infant immunization could be potentially effective against influenza A H3N2 and H1N1 strains. The response to B/Jiangsu/10/2003, was lower but similar to B responses reported in older children following TIV.[26] In studies conducted with TIV in 6 to 23-month-old infants, older children, and even adults, poor responses to the B component of influenza vaccines are common.[8,9,27] Despite the poor humoral response to influenza B in infants, it is plausible that the B component could still prime against influenza B. This awaits further study.

The administration of TIV to 6- to 12-week-old infants was well accepted by pediatricians and families, and enhanced by coadministration of TIV with routine vaccines. Increased publicity regarding pandemic influenza, and experience with pediatric influenza vaccination[28] assisted in TIV acceptance. Although we administered the second dose of TIV at an unscheduled visit at age 3 months, TIV could potentially be administered at any visit between 2 and 6 months—an approach likely to increase the amount of vaccine uptake and potentially protect more young children against influenza.

This study demonstrates that influenza vaccine is safe and immunogenic in infants. Administration of TIV starting at 2 months of age could enhance protection from influenza in this vulnerable population. Efforts are being made to increase protection against influenza in elderly patients,[29] but improved vaccine strategies including novel timing strategies, more immunogenic vaccines with improved adjuvants, and/or or increased antigenic contents are also urgently needed. Based on the results of this study, potential protection against influenza could be safely obtained in infants less than 6 months of age who receive a standard infant dose of inactivated influenza vaccine. An efficacy study evaluating protection from influenza disease in this young and vulnerable age group is warranted.

REFERENCES

1. Neuzil KM, Mellen BG, Wright PF. The effect of influenza on hospitalizations, outpatient visits, and antibiotic prescriptions in children. *N Engl J Med*. 2000;342:225–231.

2. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292:1333–1340.
3. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. *N Engl J Med*. 2005;353:2559–2567.
4. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med*. 2000;342:232–239.
5. O'Brien MA, Uyeki TM, Shay DK, et al. Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics*. 2004;133:585–593.
6. US Department of health and human Services. Guidance on allocating and targeting pandemic influenza vaccine. Available at: www.pandemicflu.gov/vaccine/allocationguidance.pdf.
7. Ruben F. Inactivated influenza virus vaccines in children. *Clin Infect Dis*. 2004;38:678–688.
8. Englund JA, Walter EB, Gbadebo A, et al. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics*. 2006;118:e579–e585.
9. Walter EB, Neuzil KM, Zhu Y, et al. Influenza vaccine immunogenicity in 6- to 23-month-old children: are identical antigens necessary for priming? *Pediatrics*. 2006;118:e570–e578.
10. Neuzil KM, Dupont WD, Wright PF, et al. The efficacy of inactivated and cold-adapted vaccines against influenza A infection 1985–1990: the pediatric experience. *Pediatr Infect Dis J*. 2001;20:733–740.
11. Kempe A, Daley MF, Crane LA, et al. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003–2004 season. *J Pediatr*. 2006;149:755–762.
12. CDC. Surveillance for laboratory-confirmed, influenza-associated hospitalizations–Colorado, 2004–05 influenza season. *MMWR Recomm Rep*. 2005;54:535–537.
13. Groothuis JR, Levin MJ, Rabalais GP, et al. Immunization of high-risk infants younger than 18 months with split product influenza vaccine. *Pediatrics*. 1991;87:823–828.
14. Halasa NB, Gerber MA, Chen Q, et al. Safety and immunogenicity of trivalent inactivated influenza vaccine (TIV) in infants. *J Infect Dis*. 2008;197:1448–1454.
15. Walter EB, Englund JA, Blatter M, et al. Trivalent inactivated influenza virus vaccines given to 2-month old children: an off-season pilot study. *PIDJ*. In press.
16. Englund JA, Mbawuike IN, Hammill H, et al. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis*. 1993;168:647–656.
17. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal immunization in mothers and infants. *N Engl J Med*. 2008;350:1555–1564.
18. Fiore AE, Shay DK, Broder K, et al. Prevention and control of influenza: recommendation of the Advisory Committee on Immunmization Practices (ACIP), 2008. *MMWR Recomm Rep*. 2008;57:1–60.
19. Munoz FM, Greisinger AJ, Wehmanen OA, et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol*. 2005;192:1098–1106.
20. Englund JA. Maternal immunization with inactivated influenza vaccine: rationale and experience. *Vaccine*. 2003;21:3460–3464.
21. CDC. Weekly report: influenza summary update, May 2006. www.cdc.gov/flu/weekly/weeklyarchives2005–2006/weekly20.htm, Accessed May 18, 2009.
22. Dagan R, Amir J, Mijalovsky A, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. *Pediatr Infect Dis J*. 2000;19:1045–1052.
23. Englund JA, Anderson EL, Reed GF, et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. *Pediatrics*. 1995;96:580–584.
24. Englund JA, Glezen WP, Thompson C, et al. *Haemophilus influenzae* type b-specific antibody in infants after maternal immunization. *Pediatr Infect Dis J*. 1997;16:1122–1130.
25. Johnson CE, Nalin DR, Chui LW, et al. Measles vaccine immunogenicity in 6- versus 15-month-old infants born to mothers in the measles vaccine era. *Pediatrics*. 1994;93:939–944.
26. Neuzil KM, Jackson LA, Nelson J, et al. Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naive 5–8-year-old children. *J Infect Dis*. 2006;194:1032–1039.
27. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine*. 2007;25:7656–7663.
28. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-10):1–42.
29. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. *Am J Epidemiol*. 2001;154:155–160.

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