Effectiveness of Inactivated Influenza Vaccine in Preventing Acute Otitis Media in Young Children

A Randomized Controlled Trial

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Context Acute otitis media (AOM) frequently complicates influenza infection. Previous studies have found influenza vaccine effective in reducing the occurrence of AOM in children mainly older than 2 years.

Objective To evaluate the effectiveness of inactivated influenza vaccine in preventing AOM in children aged 6 to 24 months.

Design, Setting, and Patients Randomized, double-blind, placebo-controlled trial of 786 children aged 6 to 24 months enrolled at Children's Hospital of Pittsburgh before the 1999-2000 (411 children) and 2000-2001 (375 children) respiratory seasons (defined as December 1 through March 31 of the respective following year). Children received influenza vaccine or placebo in a 2:1 ratio. The first cohort was observed for 1 year and the second cohort until the end of the ensuing respiratory season.

Intervention Two doses (0.25 mL each) of inactivated trivalent subvirion influenza vaccine or placebo were administered intramuscularly approximately 4 weeks apart.

Main Outcome Measures Proportion of children who developed AOM, monthly occurrence rate of AOM, estimated proportion of time with middle ear effusion, and utilization of selected health care and related resources.

Results Of the 66 children in the vaccine group from whom serum samples were collected, seroconversion against strains in the vaccine formulations developed in 88.6% to 96.8%, depending on the specific strain. The efficacy of the vaccine against culture-confirmed influenza was 66% (95% confidence interval [CI], 34%-82%) in 1999-2000 and –7% (95% CI, –247% to 67%) in 2000-2001; however, influenza attack rates differed between these 2 periods (in the placebo group, 15.9% and 3.3%, respectively). Compared with placebo, influenza vaccine did not reduce the proportion of children who had at least 1 episode of AOM during the respiratory season (in the first cohort: vaccine, 49.2% vs placebo, 52.2%; $P=.56$]; in the second cohort: vaccine, 55.8% vs placebo, 48.3%; $P=.17$). The vaccine also did not reduce the monthly rate of AOM; the estimated proportion of time with middle ear effusion; or the utilization of selected health care and related resources. There were also no differences between the vaccine and placebo groups regarding any of these outcomes during peak influenza periods. The vaccines administered to both cohorts of children were well tolerated.

Conclusion Administration of inactivated trivalent influenza vaccine to children aged 6 to 24 months did not reduce their burden of AOM or their utilization of selected health care and related resources.

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VIRUSES THAT CAUSE RESPIRATORY tract infections are often present in the middle ear exudate of children with acute otitis media (AOM).[1] These viruses may play an important role in the pathogenesis of AOM and may slow the response to antimicrobial therapy.[2,3] Accordingly, it seems reasonable to expect that the administration of vaccines effective against viral infections might also serve to lessen morbidity from AOM.

Influenza vaccines (inactivated trivalent administered intramuscularly or intranasally or live attenuated trivalent administered intranasally) have been found effective in preventing AOM in 4 previous studies involving children mainly

See also p 1633 and Patient Page.

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older than 2 years; reductions of 30% to 44% in the occurrence of AOM episodes were reported.[4-7] However, certain important limitations of those studies may preclude generalizability of their results, particularly to children aged 6 to 24 months. These limitations include small sample size, enrollment only of otitis-prone children or day-care attendees, nonrandomized allocation of participants, single or incomplete blinding, dependence on parental reporting of episodes rather than active surveillance, and lack of standardized criteria for the diagnosis of AOM.

We undertook our study to determine whether inactivated trivalent influenza vaccine administered intramuscularly is effective in reducing the occurrence of AOM and other forms of otitis media in the children most vulnerable to the disease, namely, those aged 6 to 24 months. The study was designed to evaluate the effect of the vaccine during the influenza season, the broader respiratory season, and the 1-year period following vaccination. Although the vaccine does not protect against infections other than influenza, we hypothesized that preventing episodes of AOM associated with influenza might, by preserving normal middle ear status, reduce the occurrence of subsequent episodes of AOM associated with other respiratory viral infections. Secondary objectives of the study were to evaluate the vaccine's safety, immunogenicity, and efficacy against culture-proven influenza in these young children, as well as the effects of vaccination on the children's utilization of selected health care and related resources.

METHODS

Participants

The study was approved by the Children's Hospital of Pittsburgh Human Rights Committee. We recruited healthy children aged 6 to 24 months from the hospital's primary care center and from the community at large. Research personnel informed parents in the primary care center about the study, and advertisements were placed on the radio and in the regional newspaper. Written informed consent was obtained from the parent(s) of each enrolled child. We excluded children who had been born prematurely or had a craniofacial abnormality; or who had or were living with persons who had any medical condition placing them at high risk of complications of influenza[8]; or who had a neurologic disorder, a history of tympanostomy tube insertion, hypersensitivity to egg protein or thimerosal, or a febrile illness or severe respiratory illness within the preceding 48 hours.

Procedures

We enrolled 2 cohorts of children: during the periods October 4, 1999, to November 30, 1999, and September 5, 2000, to December 8, 2000. We stratified the children according to whether they were prone to otitis (ie, had a history of at least 3 episodes of AOM in the preceding 6 months or 4 episodes in the preceding 12 months) and whether they were attending day care (defined as exposed to 3 or more nonfamily children for at least 10 hours per week). We also stratified children in the second cohort according to whether they had received at least 1 dose of the then newly available pneumococcal conjugate vaccine. Within each stratum, we randomly assigned the children in blocks of 9, using a computer-generated list, to either the vaccine group or the placebo group in a 2:1 ratio. To each child we administered 2 doses, approximately 4 weeks apart, of either vaccine or placebo (0.25 mL each) intramuscularly. Administration was performed by nonblinded research nurses who were not involved in subsequent clinical follow-up of the children. Assignments to treatment groups were not revealed to parents, investigators, research personnel conducting clinical follow-up, or nonstudy health care providers, all of whom remained blinded throughout the study. Randomization lists were kept in locked files not accessible to blinded personnel.

Vaccine

Inactivated trivalent subvirion influenza vaccine (Fluzone) was supplied by Aventis Pasteur (Swiftwater, Pa). Strains in the 1999-2000 formulation were A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2), and B/Yamanashi/166/98; and in the 2000–2001 formulation, A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), and B/Yamanashi/166/98. The placebo, also supplied by Aventis Pasteur, consisted only of a standard diluent.

Surveillance for Otitis Media

Surveillance for the occurrence of otitis media following administration of the second dose of vaccine or placebo was maintained in the first cohort of children through biweekly visits until the end of the ensuing respiratory season, ie, March 31, 2000, and through monthly visits thereafter until November 15, 2000. Surveillance in the second cohort was maintained through biweekly visits until March 31, 2001. Parents were instructed to contact study staff if any sign or symptom of either an upper respiratory tract infection or AOM developed so that an interim visit could be arranged. Acute care visits were defined as those that resulted from the presence of fever (at least 38°C) within 72 hours or the occurrence of otalgia or that substituted for an illness-related visit to the children's primary care clinicians. All examinations were conducted by study clinicians using pneumatic otoscopy, supplemented by tympanometry and spectral gradient acoustic reflectometry. The diagnosis of middle ear effusion was based on the presence of 2 of 4 elements: decreased or absent tympanic membrane mobility, yellow or white discoloration of the tympanic membrane, opacification of the tympanic membrane not due to scarring, and visible bubbles or air-fluid levels. The diagnosis of AOM was based on the presence of purulent otorrhea of recent onset not due to otitis externa or of middle ear effusion accompanied by 1 or more of the following: ear pain, marked redness of the tympanic membrane, and substantial bulging of the tympanic membrane. We prescribed treatment for AOM according to published guidelines.[9] Decisions regarding myrin-

gotomy and tympanostomy tube insertion were not part of the study protocol and were made by the children's primary care clinicians.

Influenza Surveillance

To diagnose influenza, we performed throat cultures during visits at which patients had symptoms or signs of an upper respiratory tract infection accompanied by fever (at least 38°C), AOM, or both. The culture swabs were placed into viral transport media and immediately refrigerated. Within 4 hours, monkey kidney cell culture tubes were inoculated with processed throat specimens. On weekends and after routine hours, throat swabs were stored in viral transport media at 4°C until the next business day. Cultures were maintained at between 33°C and 35°C, examined daily for cytopathic effect, and tested for hemadsorption at 4, 7, and 14 days after inoculation and anytime cytopathic effect was observed. Typing and subtyping of influenza strains were performed using standard techniques.[10] No attempt was made to culture other viral pathogens.

Immunogenicity

At the beginning of the enrollment period each year, research personnel asked consecutive parents for additional permission to obtain blood samples from their children. Samples were collected from 53 children in the first cohort and 40 children in the second cohort immediately before administering the first dose of vaccine or placebo and again 4 weeks after the second dose. Serum samples were tested by blinded personnel in a laboratory at East Virginia Medical School, Norfolk, Va, for the presence of antibody to the 3 influenza serotypes using a standardized hemagglutination-inhibition assay.[11] Seroconversion was defined as a 4-fold increase in antibody titers and/or a postimmunization antibody titer greater than 1:40.

Safety Evaluation

Monitoring of unexpected adverse events was conducted at each visit by review of the child's medical record and interview with the parent. The occurrence of minor adverse reactions (eg, injection site reactions, low-grade fever, crying) was not systematically recorded.

Health Care Utilization

At each visit, parents were asked about any illnesses their child had since the preceding visit, visits to primary care clinicians and emergency departments, hospitalizations, use of antibiotics, and whether the study visit substituted for a clinician visit. Parents were also asked about illnesses in other family members, time lost from work, or a need for alternative child-care arrangements because of the child's illness.

Statistical Analysis

The study's primary outcome measure was the proportion of children who had at least 1 episode of AOM during the ensuing respiratory season. To detect a 33% reduction in the proportion of such children (eg, 30% of control children vs 20% of immunized children), with 2-tailed α level of .05 and β level of .20, we calculated that 466 evaluable children in the vaccine group and 232 evaluable children in the placebo group were needed during the 2-year study period. To determine the efficacy of the vaccine against influenza, the analysis was conducted for cases that occurred at any time following administration of the first dose and were based on person-months at risk; confidence intervals (CIs) for vaccine efficacy were based on an assumption of asymptotic normality of the log of the ratio of Poisson rates.[12] Otitis media–related outcomes were included in analyses if they occurred at least 2 weeks following administration of the second dose.

We based results on an intention-to-treat analysis that included all available data from all participants. The number of episodes of AOM for each child was calculated by totaling episodes that presented acutely and episodes defined as new because evidence of AOM persisted for more than 28 days, or supervened in the course of otitis media with effusion, or recurred after documented resolution of an episode. We estimated the proportion of days with middle ear effusion based on the diagnosis at each visit and on interpolations for intervals between visits, provided that the intervals did not exceed 60 days. If an interval between 2 visits exceeded 60 days, we assumed the status at the first visit to have continued for 30 additional days and the status at the second visit to have prevailed for 30 days preceding that visit. Middle ear status for the remaining days in the interval was considered indeterminate.

We used a logistic regression model that included adjustment for the stratification variables to compare by treatment groups the proportion of children who had at least 1 episode of AOM. We assessed differences between monthly rates of episodes of AOM and of febrile respiratory tract infections using a Poisson regression model in which the stratification variables were included as independent variables. We used a weighted regression model to compare mean proportions of days with middle ear effusion, with weights equal to the lengths of observed time, after first applying an arcsine transformation to obtain a distribution that better approximated a normal distribution.

For health care resource utilization outcomes, we compared treatment groups applying the method of generalized estimated equations.[13] Analyses were performed with SAS version 8.2 (SAS Institute Inc, Cary, NC).

The level of significance for all outcomes was .05.

RESULTS

Study Population

The first cohort of the study included 411 children and the second cohort included 375 children. Of these, 373 (91%) and 346 (92%) completed the study, defined as having a final visit after August 2000 for the first cohort and during March 2001 for the second cohort (FIGURE). Selected demographic and clinical characteristics of the children are summarized in TABLE 1. Approximately half were aged 6 to 12 months at enrollment. There were no significant differences in characteris-

tics between the vaccine and placebo groups in either of the 2 cohorts.

Immunogenicity of Vaccine

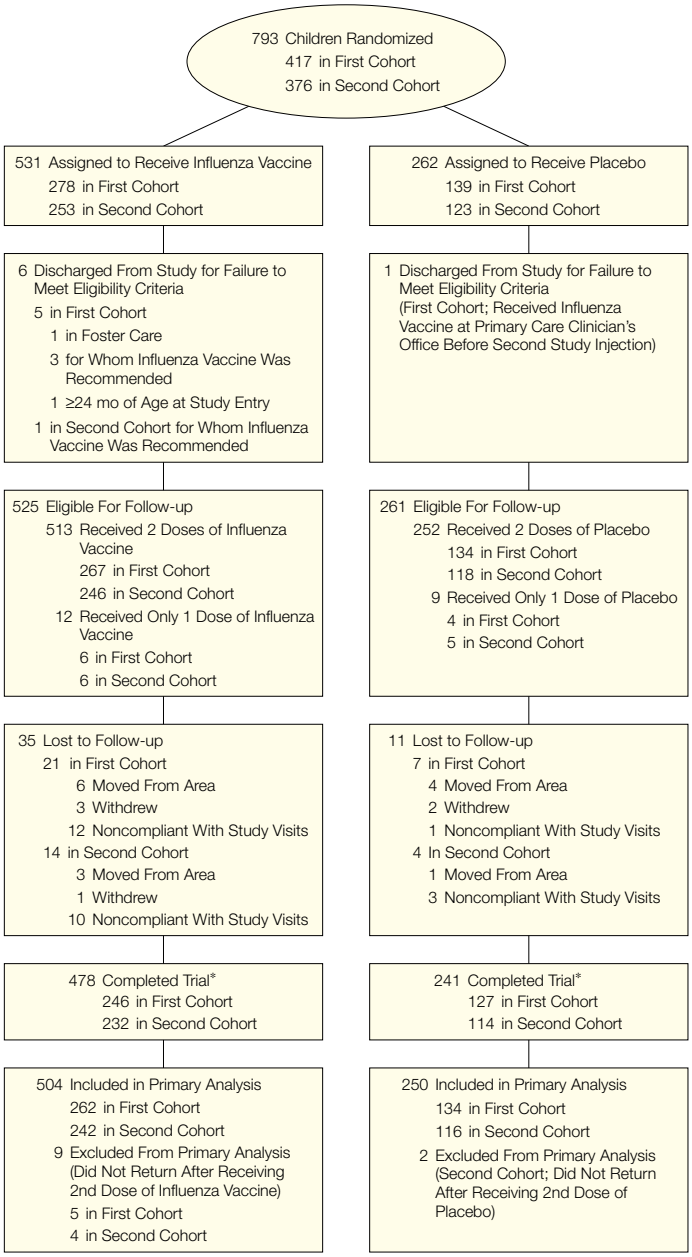
Of the 66 children in the vaccine group from whom serum samples were collected, seroconversion (defined as a hemagglutination-inhibition titer of ≥1:40, a 4-fold or greater increase in antibody titer, or both) against strains in the vaccine formulations developed in 88.6% to 96.8%, depending on the strain (TABLE 2).

Efficacy

Influenza. Throat cultures for influenza virus were obtained in 1113 (88%) of 1260 episodes of illness in which fever, AOM, or both were present. During the first year of the study, influenza was epidemic in the community. The influenza season was defined as the 6-week period (January 3 to February 15, 2000) during which 25 (67%) of the 37 culture-proven cases of influenza occurred; the other 12 cases occurred during the remaining 25 weeks of surveillance. During the second year, influenza occurred infrequently and there was no clustering of cases. The influenza season was defined as the 13-week period (January 4 to March 30, 2001) during which 11 (85%) of the 13 culture-proven cases occurred; the other 2 cases occurred during the remaining 16 weeks of surveillance. In the first cohort, culture-proven influenza was identified in 15 (5.5%) of 273 children in the vaccine group and 22 (15.9%) of 138 children in the placebo group. In the second cohort, corresponding values were 9 (3.6%) of 252 children in the vaccine group and 4 (3.3%) of 123 children in the placebo group. Accordingly, efficacy rates against influenza were 66% (95% confidence interval [CI], 34%-82%) in the first cohort and –7% (95% CI, –247% to 67%) in the second cohort. In the first cohort, efficacy rates against influenza in children aged 6 to 12 months, 13 to 18 months, and 19 to 24 months were 63%, 66%, and 69%, respectively. Of the 37 cases that occurred in the first cohort, 14 were caused by A/Beijing, 18 by A/Sydney, and 5 were not typed. Of the 13 cases that occurred in the second cohort, 5 were caused by A/New Caledonia, 5 by B/Yamanashi, 1 by A/Panama, and 2 were not typed. Circulating influenza strains were well matched with vaccine strains in the 2 respiratory seasons during which the study was conducted. All of the 24 cases in the vaccine group and 24 of the 26 cases in the placebo group occurred 2 weeks or longer after the second dose of vaccine or placebo.

Respiratory Tract Infections. In the first cohort, no differences in rates of febrile respiratory tract infections were noted between the influenza vaccine and placebo groups during the influenza sea-

Figure. Flow of Patients Through the Trial



Asterisk indicates defined as having a final visit after August 2000 for the first cohort and during March 2001 for the second cohort.

Table 1. Characteristics of Children Eligible for Follow-up in in Both Cohorts

Characteristic	No. (%) of Children					
	Cohort 1 (n = 411)		Cohort 2 (n = 375)		Total (N = 786)	
	Vaccine (n = 273)	Placebo (n = 138)	Vaccine (n = 252)	Placebo (n = 123)	Vaccine (n = 525)	Placebo (n = 261)
Demographics						
Age at entry, mo						
6-12	119 (43.6)	57 (41.3)	150 (59.5)	62 (50.4)	269 (51.2)	119 (45.6)
13-18	83 (30.4)	45 (32.6)	61 (24.2)	38 (30.9)	144 (27.4)	83 (31.8)
19-24	71 (26.0)	36 (26.1)	41 (16.3)	23 (18.7)	112 (21.3)	59 (22.6)
Male	128 (46.9)	75 (54.3)	139 (55.2)	70 (56.9)	267 (50.9)	145 (55.6)
Female	145 (53.1)	63 (45.7)	113 (44.8)	53 (43.1)	258 (49.1)	116 (44.4)
Race						
White	140 (51.3)	77 (55.8)	128 (50.8)	56 (45.5)	268 (51.1)	133 (51.0)
Black	116 (42.5)	52 (37.7)	102 (40.5)	58 (47.2)	218 (41.5)	110 (42.1)
Other	17 (6.2)	9 (6.5)	22 (8.7)	9 (7.3)	39 (7.4)	18 (6.9)
Maternal education						
Less than high school	25 (9.2)	11 (8.0)	31 (12.3)	15 (12.2)	56 (10.7)	26 (10.0)
High school graduate with or without technical or other training	173 (63.4)	90 (65.2)	147 (58.3)	74 (60.2)	320 (61.0)	164 (62.8)
College graduate	74 (27.1)	37 (26.8)	74 (29.4)	34 (27.6)	148 (28.2)	71 (27.2)
Unknown	1 (0.4)	0	0	0	1 (0.2)	0
Health insurance status						
Private	121 (44.3)	69 (50.0)	121 (48.0)	65 (52.9)	242 (46.1)	134 (51.3)
Medicaid	140 (51.3)	60 (43.5)	127 (50.4)	56 (45.5)	267 (50.9)	116 (44.4)
None	12 (4.4)	9 (6.5)	4 (1.6)	2 (1.6)	16 (3.0)	11 (4.2)
Health care provider						
Children's Hospital of Pittsburgh clinics	143 (52.4)	61 (44.2)	120 (47.6)	62 (50.4)	263 (50.1)	123 (47.1)
Private practitioner	130 (47.6)	77 (55.8)	132 (52.4)	61 (49.6)	262 (49.9)	138 (52.9)
Exposure to household cigarette smoke						
Yes	95 (34.8)	56 (40.6)	87 (34.5)	48 (39.0)	182 (34.7)	104 (39.8)
No	178 (65.2)	82 (59.4)	165 (65.5)	75 (61.0)	343 (65.3)	157 (60.2)
Other children in household						
Yes	186 (68.1)	91 (65.9)	145 (57.5)	75 (61.0)	331 (63.0)	166 (63.6)
No	87 (31.9)	47 (34.1)	107 (42.5)	48 (39.0)	194 (37.0)	95 (36.4)
Recurrent AOM*						
Yes	66 (24.2)	33 (23.9)	40 (15.9)	21 (17.1)	106 (20.2)	54 (20.7)
No	207 (75.8)	105 (76.1)	212 (84.1)	102 (82.9)	419 (79.8)	207 (79.3)
Day care†						
Yes	75 (27.5)	39 (28.3)	68 (27.0)	34 (27.6)	143 (27.2)	73 (28.0)
No	198 (72.5)	99 (71.7)	184 (73.0)	89 (72.4)	382 (72.8)	188 (72.0)
Had received ≥1 dose of pneumococcal conjugate vaccine						
Yes	NA	NA	179 (71.0)	83 (67.5)	179 (71.0)	83 (67.5)
No	NA	NA	73 (29.0)	40 (32.5)	73 (29.0)	40 (32.5)
Middle ear status at the time of the second dose of vaccine or placebo‡						
AOM	40 (15.0)	19 (14.3)	31 (12.6)	10 (8.5)	71 (13.8)	29 (11.6)
Otitis media with effusion	42 (15.7)	24 (18.0)	46 (18.7)	17 (14.4)	88 (17.2)	41 (16.3)
Normal	185 (69.3)	90 (67.7)	169 (68.7)	91 (77.1)	354 (69.0)	181 (72.1)

Abbreviations: AOM, acute otitis media; NA, not applicable.
*Defined as ≥3 AOM episodes in the preceding 6 months or 4 episodes in the preceding 1 year.
†Defined as ≥10 h/wk with ≥3 other children.
‡Data are not available for children withdrawn from the study before receiving the second dose of vaccine or placebo.

son (0.23 vs 0.25 episodes per person-month, respectively, $P=.71$) or during the respiratory season (0.21 vs 0.22 episodes per person-month, respectively, $P=.66$). However, in the second cohort, rates were actually higher in the vaccine group than in the placebo group during the influenza season (0.23 vs 0.17 episodes per person-month, respectively, $P=.03$) and during the respiratory season (0.22 vs 0.17 episodes per person-month, respectively, $P=.10$).

Episodes of AOM. TABLE 3 shows that in the first cohort, there were no differences overall between the vaccine group and the placebo group in the proportions of children who had at least 1 episode of AOM during the ensuing influenza season (30.5% vs 29.9%, $P=.89$), during the respiratory season (49.2% vs 52.2%, $P=.56$), or during the entire 1-year follow-up period (57.3% vs 61.9%, $P=.35$).

The difference between the vaccine and placebo groups in the proportion of children with AOM during the respiratory season was 3.0% (95% CI, –13.4% to 7.4%). Within the subgroup of children in the first cohort aged 19 to 24 months, the proportions who had at least 1 episode of AOM during the ensuing influenza and respiratory seasons were suggestively lower in the vaccine group than in the placebo group (19.4% vs 34.3%, $P=.10$; and 36.8% vs 54.3%, $P=.09$, respectively), and during the 1-year follow-up period, significantly lower (44.1% vs 65.7%, $P=.04$). Nevertheless, tests for interaction between vaccine effectiveness and age group produced nonsignificant results. In the second cohort there were no significant differences between the vaccine and placebo groups in the proportions who had at least 1 episode of AOM.

TABLE 4 shows data from both cohorts concerning the distribution of observed episodes of AOM and the mean monthly rates of occurrence of episodes of AOM during the influenza and respiratory seasons, and from the first cohort, values for the entire follow-up year. None of the differences between the vaccine and placebo groups was statistically significant.

Table 2. Geometric Means of Reciprocals of Serum Antibody Titers to Influenza and Children Who Were Seroprotected According to Cohort and Treatment Group

Treatment Group, Timing, and Outcome Measure*	Vaccine Type/Serotype					
	A/H1N1	A/H3N2	B	A/H1N1	A/H3N2	B
Vaccine	**First Cohort (n = 35)**			**Second Cohort (n = 31)**		
Prevaccination						
Mean of reciprocals of titers	5.0	18.5	9.8	5.0	9.5	5.0
Seropositive, No. (%)	0	4 (11.4)	6 (17.1)	0	7 (22.6)	0
Postvaccination						
Mean of reciprocals of titers	46.8	68.3	130	44.3	69.2	42.8
Seroprotected, No. (%)	32 (91.4)	31 (88.6)	32 (91.4)	28 (90.3)	30 (96.8)	28 (90.3)
Placebo	**First Cohort (n = 18)**			**Second Cohort (n = 9)**		
Prevaccination						
Mean of reciprocals of titers	5.0	22.4	12.8	5.0	9.3	5.4
Seropositive, No. (%)	0	4 (22.2)	4 (22.2)	0	2 (22.2)	0
Postvaccination						
Mean of reciprocals of titers	5.0	23.8	13.6	5.0	7.9	5.4
Seroprotected, No. (%)	0	4 (22.2)	6 (33.3)	0	1 (11.1)	0

*Prevaccination seroprotection was defined as the presence of a titer of 1:40 or higher; postvaccination seroprotection was defined as the presence of a titer of 1:40 or higher or a 4-fold increase in antibody titer.

The proportions of children who had an episode of AOM within 1 week of having a positive throat culture for influenza were similar between groups with 13 (54.2%) of 24 in the vaccine and 12 (48.0%) of 25 in the placebo groups ($P=.88$). Acute otitis media was diagnosed at 465 (36.8%) of 1262 acute care visits vs 468 (9.6%) of 4881 routine visits ($P<.001$). That fact notwithstanding, to test the possibility that a vaccine-vs-placebo difference might have been obscured by the inclusion, in the overall analysis, of more or less subclinical cases of AOM diagnosed at other than acute care visits, we further considered the effectiveness of the vaccine in an analysis limited to acute care visits during the influenza and respiratory seasons of each year of the study. Again, there were no differences between the vaccine group and the placebo group in the proportions of children who experienced at least 1 episode of AOM during the 2 influenza seasons (35.6% vs 37.1% and 42.9% vs 31.0%, respectively) or during the 2 respiratory seasons (45.9% vs 41.8% and 44.8% vs 34.2%, respectively).

TABLE 5 shows that there were no significant differences between the vaccine group and the placebo group in the proportions of days with middle ear effusion during the influenza and respiratory seasons.

Table 3. Children Who Experienced at Least 1 Episode of AOM According to Age at Enrollment, by Follow-up Period, and Treatment Group

Cohort, Follow-up Period, and Age Group	No./Total (%) of Children With >1 Episode of AOM		*P* Value
	Vaccine	Placebo	
	First Cohort		
Influenza season*			
All children	79/259 (30.5)	40/134 (29.9)	.89
6-12 mo	35/117 (29.9)	17/54 (31.5)	.84
13-18 mo	31/75 (41.3)	11/45 (24.4)	.06
19-24 mo	13/67 (19.4)	12/35 (34.3)	.10
Respiratory season†			
All children	129/262 (49.2)	70/134 (52.2)	.56
6-12 mo	61/117 (52.1)	27/54 (50.0)	.79
13-18 mo	43/77 (55.8)	24/45 (53.3)	.79
19-24 mo	25/68 (36.8)	19/35 (54.3)	.09
1-Year follow-up period			
All children	150/262 (57.3)	83/134 (61.9)	.35
6-12 mo	72/117 (61.5)	32/54 (59.3)	.78
13-18 mo	48/77 (62.3)	28/45 (62.2)	.99
19-24 mo	30/68 (44.1)	23/35 (65.7)	.04
	Second Cohort		
Influenza season*			
All children	125/239 (52.3)	49/116 (42.2)	.07
6-12 mo	78/142 (54.9)	27/56 (48.2)	.39
13-18 mo	27/59 (45.8)	14/38 (36.8)	.39
19-24 mo	20/38 (52.6)	8/22 (36.4)	.23
Respiratory season†			
All children	135/242 (55.8)	56/116 (48.3)	.17
6-12 mo	83/142 (58.5)	32/56 (57.1)	.87
13-18 mo	31/61 (50.8)	14/38 (36.8)	.18
19-24 mo	21/39 (53.8)	10/22 (45.5)	.53

Abbreviation: AOM, acute otitis media.
*Influenza season was defined as January 3 to February 15, 2000, for the first cohort and as January 4 to March 30, 2001, for the second cohort.
†For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.

Health Care Utilization

TABLE 6 shows that in neither cohort were there any statistically significant differences between the vaccine group and the placebo group during ensuing respiratory seasons regarding utilization of selected health care resources. During the second year of the study the rate of hospitalization was actually higher in the vaccine group than in the placebo group.

Table 4. Observed Episodes of AOM by Follow-up Period, Cohort, and Treatment Group

Observations of AOM	Vaccine	Placebo	*P* Value
First Cohort			
Influenza season*			
No. of children	259	134	
Episodes, No. (%) of children			
0	180 (69.5)	94 (70.1)	
1	65 (25.1)	32 (23.9)	
2	14 (5.4)	8 (6.0)	
≥3	0	0	
Total No. of episodes	93	48	
Mean monthly rate of AOM episodes	0.25	0.25	>.99
Respiratory season†			
No. of children	262	134	
Episodes, No. (%) of children			
0	133 (50.8)	64 (47.8)	
1	62 (23.7)	41 (30.6)	
2	40 (15.3)	16 (11.9)	
≥3	27 (10.3)	13 (9.7)	
Total No. of episodes	231	113	
Mean monthly rate of AOM episodes	0.24	0.23	.65
1-Year follow-up			
No. of children	262	134	
Episodes, No. (%) of children			
0	112 (42.7)	51 (38.1)	
1	48 (18.3)	35 (26.1)	
2	45 (17.2)	23 (17.2)	
≥3	57 (21.8)	25 (18.7)	
Total No. of episodes	370	175	
Mean monthly rate of AOM episodes	0.14	0.13	.37
Second Cohort			
Influenza season*			
No. of children	239	116	
Episodes, No. (%) of children			
0	114 (47.7)	67 (57.8)	
1	84 (35.1)	31 (26.7)	
2	37 (15.5)	16 (13.8)	
≥3	4 (1.7)	2 (1.7)	
Total No. of episodes	170	69	
Mean monthly rate of AOM episodes	0.28	0.23	.19
Respiratory season†			
No. of children	242	116	
Episodes, No. (%) of children			
0	107 (44.2)	60 (51.7)	
1	75 (31.0)	30 (25.9)	
2	41 (16.9)	21 (18.1)	
≥3	19 (7.9)	5 (4.3)	
Total No. of episodes	216	87	
Mean monthly rate of AOM episodes	0.27	0.23	.15

Abbreviation: AOM, acute otitis media.
*Influenza season was defined as January 3 to February 15, 2000, for the first cohort and as January 4 to March 30, 2001, for the second cohort.
†For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.

Safety

During the 2 years of the study, 39 children in the vaccine group and 12 children in the placebo group underwent insertion of tympanostomy tubes, and 27 and 12 children, respectively, were hospitalized for other reasons. Three adverse events occurred that were considered serious and possibly related to receipt of influenza vaccine: 1 child had 2 brief episodes of unexplained staring on the day of the first vaccination; 1 child had mild intercostal retractions and wheezing 1 day after the second vaccination, and 1 child developed acute gastroenteritis 3 days after the first vaccination.

COMMENT

In our study, influenza vaccination in a group of healthy children aged 6 to 24 months failed to affect the overall occurrence of AOM, although during an epidemic season the vaccine might have provided a measure of protection against AOM to children aged 19 to 24 months and provided some measure of protection against influenza across the age spectrum studied. The results in our study of whether influenza vaccination affects AOM are thus at variance with the results of previous studies in which use of the vaccine reportedly provided an approximate one-third reduction in AOM occurrence.[4-6] The discordant results may be attributable to some of the methodological differences between studies, the most important of which may involve age. More than 75% of the children we enrolled were aged 18 months or younger (mean age, 14 months) compared with mean ages ranging from 20 to 43 months in 3 of the earlier studies.[4-6] Two age-related factors may have been operative. First, the proportion of viral respiratory infections due to influenza virus may be lower in younger children than in older children, so that in younger children the consequences of noninfluenza viral infections may have obscured any effect of influenza vaccination. Evidence that most episodes of respiratory tract infection in the children in our study were caused by viruses other than influenza consists of the facts that during the respiratory sea-

sons, more than 90% of the children with febrile illnesses whom we tested were culture-negative for influenza virus and that during the second year of our study, the incidence of influenza never reached epidemic proportions. Differences between our results and those of a recently reported study that evaluated the efficacy of an intranasally administered, inactivated, virosomal influenza vaccine[7] may be attributable to the generally younger age of our participants; the inclusion in that study only of otitis-prone children who had had an episode of AOM within 2 to 8 weeks; and differences in the manufacture, contents, and route of administration of the vaccines.

A second age-related factor could be that, although satisfactorily immunogenic in young children, influenza vaccine may for other reasons be less effective in preventing influenza—and accordingly, influenza-related otitis media—in younger children than in older children. In a recent study by Hurwitz et al,[14] children aged 24 to 60 months were randomized to receive either inactivated influenza vaccine or placebo and were observed during the ensuing winter for influenza infection, using serologic criteria for the diagnosis. The investigators found no reductions in vaccinated children in respiratory-related events, including ear infections, physician visits, antibiotics prescribed, or missed day-care attendance by children or work attendance by parents. Children with prevaccination titers of 1:5 or lower were less likely to achieve a 4-fold increase in antibody titer after vaccination than children with prevaccination titers of 1:10 or more. In addition, children aged 36 months or older were more likely to respond to vaccination than were younger children. Overall, efficacy of the inactivated vaccine against serologically confirmed influenza was only 31% to 45%, and efficacy was greater in children with prevaccination titers of 1:10 or higher than in those with titers of 1:5 or less.

Table 5. Estimated Proportion of Days With Middle Ear Effusion by Follow-up Period, Cohort, and Treatment Group*

	Influenza Season†				Respiratory Season‡				1-Year Follow-up	
	First Cohort		Second Cohort		First Cohort		Second Cohort		First Cohort	
Days With Middle Ear Effusion	Vaccine (n = 258)	Placebo (n = 133)	Vaccine (n = 239)	Placebo (n = 116)	Vaccine (n = 262)	Placebo (n = 134)	Vaccine (n = 241)	Placebo (n = 116)	Vaccine (n = 262)	Placebo (n = 134)
Days classified as effusion present, No. (%) of children										
0	112 (43.4)	50 (37.6)	65 (27.2)	32 (27.6)	76 (29.0)	28 (20.9)	59 (24.5)	29 (25.0)	59 (22.5)	21 (15.7)
1-25	24 (9.3)	19 (14.3)	42 (17.6)	21 (18.1)	47 (17.9)	46 (34.3)	48 (19.9)	29 (25.0)	98 (37.4)	67 (50.0)
26-50	40 (15.5)	19 (14.3)	50 (20.9)	33 (28.4)	54 (20.6)	22 (16.4)	59 (24.5)	31 (26.7)	56 (21.4)	26 (19.4)
51-75	31 (12.0)	14 (10.5)	39 (16.3)	17 (14.7)	47 (17.9)	15 (11.2)	32 (13.3)	18 (15.5)	30 (11.5)	12 (9.0)
≥76	51 (19.8)	31 (23.3)	43 (18.0)	13 (11.2)	38 (14.5)	23 (17.2)	43 (17.8)	9 (7.8)	19 (7.3)	8 (6.0)
Total days per follow-up period classified as effusion present, mean (SD), %	34.0 (38.4)	36.6 (38.6)	37.1 (33.4)	31.7 (29.3)	34.8 (32.5)	33.3 (31.9)	36.2 (32.1)	30.9 (27.7)	26.5 (26.1)	24.6 (23.6)
P value§	.49		.14		.85		.14		.92	

*Percentages may not sum to 100 due to rounding.
†Influenza season was defined as January 3 to February 15, 2000, for the first cohort and as January 4 to March 30, 2001, for the second cohort.
‡For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.

Table 6. Selected Measures of the Potential Economic Impact of Influenza Vaccine During the Ensuing Respiratory Season*

	First Cohort		Second Cohort		Total	
Measure	Vaccine (n = 267)	Placebo (n = 134)	Vaccine (n = 246)	Placebo (n = 118)	Vaccine (n = 513)	Placebo (n = 252)
Visits to primary care physicians, mean (SD)†	1.97 (1.69)	2.07 (1.52)	2.2 (1.75)	2.12 (1.77)	2.08 (1.72)	2.10 (1.64)
Visits to emergency departments, mean (SD)	0.19 (0.48)	0.18 (0.49)	0.3 (0.58)	0.31 (0.56)	0.25 (0.54)	0.24 (0.53)
Children hospitalized, No. (%)‡	33 (12.4)	17 (12.7)	33 (13.4)	7 (5.9)§	66 (12.9)	24 (9.5)
Courses of antibiotics, mean (SD)	1.79 (2.36)	1.92 (2.37)	2.04 (2.57)	1.66 (1.76)	1.91 (2.46)	1.80 (2.11)
Instances of illness in any family member other than the child, mean (SD)	2.74 (1.95)	2.59 (1.73)	2.86 (1.98)	2.73 (1.90)	2.80 (1.96)	2.65 (1.81)
Visits at which parents reported missing work, No./Total (%)‖	105/2004 (5.2)	58/1056 (5.5)	166/1767 (9.4)	57/878 (6.5)	271/3771 (7.2)	115/1934 (5.9)
Visits at which parents reported making other than usual day-care arrangements, No./Total (%)	50/2004 (2.5)	31/1056 (2.9)	71/1767 (4.0)	33/878 (3.8)	121/3771 (3.2)	64/1934 (3.3)

*Treatment groups were compared applying the method of generalized estimating equations.[13] For each cohort, the respiratory season was defined as the period from December 1 through March 31 of the respective following year.
†Includes study visits that were substituted for primary care physician visits.
‡Reasons for hospitalization include bilateral myringotomy and placement of tympanostomy tubes.
§Vaccine vs placebo (second cohort), $P = .05$.
‖Limited to working families.

By comparison, in both cohorts in our study, the seroconversion rate to each vaccine serotype was approximately 90%, and the vaccine was not more likely to induce significant antibody responses in older than in younger children. Nonetheless, among the few children in our study whom we tested, those who had prevaccination hemagglutination-inhibition titers of 1:10 or higher (36% in the first cohort and 8% in the second cohort) also had the highest postvaccination titers. It seems possible that lack of previous exposure to influenza viruses on the part of our study population contributed, in the second year of the study, to the vaccine's inability to prevent influenza, and in both years, to its inability to reduce the incidence of AOM. Finally, it is possible, although not likely, that the vaccines formulated for the 1999-2000 and 2000-2001 seasons were not as effective overall in preventing influenza as vaccines formulated in previous years.

Given that our study did not find a significant difference between vaccine and placebo, it is important to consider the magnitude of difference we were able to detect. The 95% CIs for detecting a difference between the vaccine and placebo groups in the proportion of children with AOM during the respiratory season were –13.4% to 7.4% for the first cohort, –3.5% to 18.5% for the second cohort, and –5.7% to 9.5% for the combined cohorts. Accordingly, our study cannot statistically eliminate the possibility of a decrease in the proportion of children with AOM of 13.4% for the first, 3.3% for the second, and 5.7% for the combined cohorts. An additional consideration is that only 15.9% of children in the placebo group in the first cohort and 3.6% in the second cohort had influenza, and therefore, only a small reduction of AOM could be expected in the vaccine group.

Our study had a number of limitations beyond the fact that, during its second year, the incidence of influenza in the community never reached epidemic proportions. First, we performed cultures for influenza using throat swabs, a method chosen as less invasive than using nasopharyngeal swabs, which may have resulted in underidentification of the virus. Second, because our surveillance, although relatively intensive, relied to some extent on parents' initiating visits for illness, episodes of either influenza or AOM might have been missed. And third, our study was not powered to rule out the possibility of differences in efficacy within specific age subgroups.

Recently, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics issued statements encouraging the vaccination of children aged 6 to 23 months against influenza,[8] based on reports that hospitalization rates in such children increase during periods of influenza activity.[15-17] Our study was not designed or powered to detect differences in hospitalization rates. Although influenza vaccination did not reduce the occurrence of AOM in the children we studied, the limited protection we found against the occurrence of influenza itself may be viewed as lending support to immunize healthy infants and young children.

Author Contributions: Dr Hoberman, as principal investigator, had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hoberman, Greenberg, Paradise, Rockette, Lave.
Acquisition of data: Hoberman, Greenberg, Kearney, Colborn, Haralam, Byers, Zoffel, Fabian, Bernard, Kerr.
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Study supervision: Hoberman, Greenberg, Kearney.
Consultation: Paradise.
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REFERENCES

1. Heikkinen T, Thint M, Chonmaitree T. Prevalence of various respiratory viruses in the middle ear during acute otitis media. *N Engl J Med*. 1999;340:260-264.
2. Chonmaitree T, Owen MJ, Howie VM. Respiratory viruses interfere with bacteriological response to antibiotics in children with acute otitis media. *J Infect Dis*. 1990;162:546-549.
3. Chonmaitree T, Owen MJ, Patel JA, Hedgpeth D, Horlick D, Howie VM. Effect of viral respiratory tract infection on outcome of acute otitis media infection. *J Pediatr*. 1992;120:856-862.
4. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. *N Engl J Med*. 1998;338:1405-1412.
5. Clements DA, Langdon L, Bland C, Emmanuel W. Influenza A vaccine decreases incidence of otitis media in 6- to 30-month-old children in day care. *Arch Pediatr Adolesc Med*. 1995;149:1113-1117.
6. Heikkinen T, Ruuskanen O, Waris M, Zieger T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. *AJDC*. 1991; 145:445-448.
7. Marchisio P, Cavagna R, Maspes B, et al. Efficacy of intranasal virosomal influenza vaccine in the prevention of recurrent acute otitis media in children. *Clin Infect Dis*. 2002;35:168-174.
8. Bridges CB, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2002;51(RR-3):1-31.
9. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance: a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis J*. 1999;18:1-9.
10. Couch RB, Kasel JA. Influenza. In: Lennette EH, Lennette DA, Lennette ET, eds. *Diagnostic Procedures for Viral, Rickettsial, and Chlamydial Infections*. 7th ed. Washington, DC: American Public Health Association; 1995:431-446.
11. WHO Collaborating Center for Influenza, Biological Products Division. *The Hemagglutination Inhibition Test for Influenza Viruses*. Version 31 rev. Atlanta, Ga: Centers for Disease Control and Prevention; 1981:1-21.
12. Ewell M. Comparing methods for calculating confidence intervals for vaccine efficacy. *Stat Med*. 1996; 15:2379-2392.
13. Liang KY, Zejer SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73: 13-22.
14. Hurwitz ES, Haber M, Chang A, et al. Studies of the 1996-1997 inactivated influenza vaccine among children attending day care: immunologic response, protection against infections, and clinical effectiveness. *J Infect Dis*. 2000;182:1218-1223.
15. 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.
16. McIntosh K, Lieu T. Is it time to give influenza vaccine to healthy infants? *N Engl J Med*. 2000;342:275-276.
17. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med*. 2000;342:225-231.