Effect of acellular pertussis vaccine on the development of allergic sensitization to environmental allergens in adults

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Background: Exposure of children to pertussis antigens caused by infection or vaccination with whole-cell pertussis vaccine may increase the serum IgE level and predispose to sensitization to the prevalent environmental allergens. Acellular pertussis vaccine (APV) that may be given to adults may have a similar effect.
Objective: The purpose of this study was to determine whether APV will cause an increase in environmental sensitization measured by an increase of serum-specific IgE to the allergens to which adults are exposed during the vaccination period.
Methods: One hundred adult hospital employees were randomized to receive either a 2-component APV composed of pertussis toxin and filamentous hemagglutinin or a meningococcal vaccine as a control. Serum-specific IgE level to 2 indoor allergens, cat and dust mite, and 2 outdoor allergens prevalent during the immunization season, *Alternaria* species and ragweed, was measured by an RIA on sera collected before and 1 month after vaccination.
Results: The group that received the APV had no significant change in their serum-specific IgE levels to cat, dust, *Alternaria* species, or ragweed 1 month after vaccination.
Conclusion: A 2-component APV did not predispose to an increase of allergen-specific IgE in an adult population. (J Allergy Clin Immunol 1999;170-5.)

Key words: *Adult, allergens, Bordetella pertussis, hypersensitivity, IgE, hospital personnel, pertussis toxin, pertussis vaccine, RAST, vaccines*

Abbreviation used
APV: Acellular pertussis vaccine

Pertussis may cause primary and secondary infection in an adult population. The prevalence of pertussis was found to be 12% in patients 18 years or older who had a complaint of cough for 2 weeks or longer.[1] Subclinical infection is also common in adults, occurring at a rate of 25% of adults living in households in which a culture-positive patient was detected.[2] Adults were the source of infection in 11.2%[2] to 15%[3] of households. Adults seem to become susceptible to reinfection 20 years after a previous pertussis infection.[3] Most adults who report childhood immunization against pertussis have low antibody titers that are comparable with titers of unimmunized adults.[4] Adults, particularly hospital employees, are therefore at risk of acquiring the disease from infected children or adults, with subsequent risk of transmission to susceptible patients.[4] During a regional epidemic of pertussis in 1993, pertussis occurred in 2% of adult hospital employees of a children's hospital.[5]

Whole-cell pertussis vaccines have been used to immunize children against pertussis infection. The whole-cell pertussis vaccine is made from a suspension of inactivated *Bordetella pertussis* and contains several immunogens, including pertussis toxin, filamentous hemagglutinin, pertactin, and fimbrial protein. Whole-cell pertussis vaccines are contraindicated in adults because of the high rate of adverse reactions. Acellular pertussis vaccines (APVs) were approved and licensed in the United States in 1991. They contain one or more of the following highly purified, chemically inactivated pertussis immunogens: pertussis toxoid, filamentous hemagglutinin, fimbrial protein, and pertactin. Immunization of adult hospital employees with APV has been shown to be effective in raising their antibody titers while being associated with minimal immediate side effects.[6,7]

Killed *Bordetella pertussis* organisms have been shown to increase the sensitivity of rats and mice to histamine and their potential for IgE production. The treatment of mice with *Bordetella pertussis* vaccine facilitated the induction of anaphylactic shock but only when the vaccine was given at the same time as the sensitizing antigen.[8,9]

Several studies have shown that similar effects are observed in children after pertussis vaccination or infection. Increased skin sensitivity to histamine 7 days after vaccination occurred in children receiving the diphtheria pertussis tetanus vaccine but did not occur in those receiving the diphtheria tetanus vaccine.[10] Children who had pertussis infections were found to have increased production of IgE over the following year, as compared with age-matched control subjects. Children with a personal or family history of atopy were at a significant risk for

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increased IgE level or new allergic sensitization.[11] The change in total IgE level after pertussis infection differed according to the patient's age at the time of infection.[12]

APV contains the 2 pertussis antigens, pertussis toxin and filamentous hemagglutinin, that have been implicated as the cause of sensitization after pertussis infection or vaccination with the whole-cell pertussis vaccines. Therefore APV may also predispose to the development of allergic sensitization. When APV became available for adult vaccination, vaccination of adult hospital employees during pertussis outbreaks was advocated. This study was designed to examine whether allergic sensitization will develop or increase in adults receiving APV.

The hypothesis of this investigation was that, similar to the effects of exposure to pertussis in children, APV given to adults will increase their allergic sensitization. Because the increase in sensitization occurs to the allergens to which the subjects are exposed during the vaccination period, 2 indoor allergens, cat and dust mite, and 2 outdoor allergens prevalent in the fall in our area, *Alternaria* species and ragweed, were chosen for the study. Serum-specific IgE to the allergens was measured before and 1 month after vaccination of adult hospital employees in a double-blind, placebo-controlled randomized trial of APV versus meningococcal vaccine as a control. Because atopy was shown to be a risk factor for the sensitizing effects of pertussis exposure in children, the second part of the study hypothesis was that atopic adults are at higher risk than nonatopic adults. Study subjects who had one or more detectable serum-specific IgE levels to environmental allergens before vaccination were separated into an atopic group, and their results were examined separately.

METHODS

Subjects

This study was conducted as part of an epidemiologic study to determine the effectiveness of immunization of adult hospital employees to pertussis in outbreak control, as well as to determine the safety of APV given to adults. In the fall of 1993, 400 adult hospital employees were randomized to receive either a divalent APV or a meningococcal polysaccharide vaccine as a control. Serum was collected from each subject before vaccination and 1 month after vaccination. The prevaccination and postvaccination sera were stored at −70°C. Sera collected from 51 individuals in the APV group and from 49 individuals in the control group were randomly selected for the present study. The study was approved by the institutional review board.

Vaccines

APV (lot AP-3) was manufactured by the University of Massachusetts Biological Laboratories. The vaccine contains 25 μg of chemically inactivated pertussis toxoid and 3 μg of filamentous hemagglutinin adsorbed to aluminum phosphate per 0.5-mL dose. Licensed Meningococcal Polysaccharide Vaccine Groups A,C,Y and W-135 Combined (Menomune -A/C/Y/W-135; Connaught Laboratories, Inc, Swiftwater, Pa) was used as the control. The vaccine contains 50 μg of each polysaccharide in isotonic sodium chloride solution preserved in thimerosal per 0.5-mL dose. The vaccines were given by intramuscular injection in the deltoid region of the arm.

RAST testing

Serum-specific IgE to cat, dust, *Alternaria* species, and ragweed was assayed in the collected sera. Serum-specific IgE to each individual antigen was assayed simultaneously on sera collected before and after immunization from subjects immunized with the APV and those immunized with the control vaccine. All assays were done in duplicate. The RAST assays were performed by using the Phadebas RAST System (Pharmacia AB, Uppsala, Sweden). The allergen disks were placed in glass tubes, and 50 μL of the sera was added. The tubes were covered with a plastic film and incubated at room temperature for 3 hours. Two and half milliliters of washing solution was then added to all tubes, and the tubes were allowed to stand for 10 minutes. All liquid was then completely removed. The washing procedure was repeated 2 more times. Fifty microliters of anti-IgE iodine 125 (^{125}I) solution was added to all tubes. Fifty microliters of anti-IgE ^{125}I solution was added to 2 empty tubes that were capped immediately. These 2 tubes were set aside and used to measure total radioactivity of the anti-IgE ^{125}I solution. All tubes were covered with a plastic film and incubated overnight for 16 to 24 hours at room temperature. The tubes were then washed 3 times as above. Disk-bound radioactivity and total radioactivity of the anti-IgE ^{125}I solution were determined by counting the tubes for 1 minute in a gamma counter. Percentage binding of anti-IgE ^{125}I for each sera, which is reflective of the serum-specific IgE for each antigen, was calculated as follows: disk count/total anti-IgE ^{125}I solution count × 100. The mean of each duplicate sample was used for calculation.

By using the manufacturer's instructions as a guide, the percentage binding of anti-IgE ^{125}I was interpreted as follows in RAST scores: less than 1.5%, absent or undetectable; 1.5% to 7%, low; 8% to 19%, moderate; 20% to 30%, high; greater than 31%, very high.

Statistical analysis

Sample size. RAST to *Alternaria* species was initially performed on a random sample of serum from 100 subjects (51 from the APV group and 49 from the control group) before and after vaccination. The observed mean and SD were used to calculate the power of the study in a 2-tailed paired *t* test for the within-group analysis and a nonpaired *t* test for the between-group analysis. With the α value set at .05, the study had a power (1-β) of 92% to yield a statistically significant difference when testing a mean difference of 0.4 (SD, 0.8) in the percentage binding of anti-IgE ^{125}I between the prevaccination and postvaccination sera within each group. It also had a power of 81% to yield a statistically significant result when testing a mean difference of 0.4 (SD within groups, 0.7) in the percentage binding of anti-IgE ^{125}I in the postvaccination sera between the 2 groups.

Statistical method. The percentage binding of anti-IgE ^{125}I for all sera obtained was transformed by taking the $\log_{10}$ to normalize the data. The means of the APV and control group for both prevaccination and postvaccination measurements were compared by using a repeated-measures ANOVA. Multiple comparisons were then conducted for those cases in which the ANOVA indicated a significant effect. Similar analyses were conducted on the atopic subjects only. The frequency of subjects whose RAST scores indicated new allergic sensitization (from a negative to a positive score) and those who moved up on their RAST scores (from a positive to a higher positive score) after vaccination were compared between the APV and control group by using either a Fisher exact test or a χ^2 test for the antigens in which the number of cells was greater than zero. All data analysis was conducted with SAS/STAT window version 6.12.

RESULTS

Sera from 49 subjects were tested in the control group, and 51 subjects were tested in the APV group (Table I).

TABLE I. Percentage binding of anti-IgE ^{125}I in control and APV groups before vaccination and 1 month after vaccination

	Percentage binding of anti-IgE ^{125}I (mean ± SEM)			
	Control vaccine (n = 49)		APV (n = 51)	
	Before	After	Before	After
Alternaria species	0.74%* ± 0.16%	1.02% ± 0.16%	0.79% ± 0.11%	0.9% ± 0.11%
Ragweed	2.09% ± 0.74%	2.01% ± 0.72%	1.61% ± 0.53%	1.69% ± 0.59%
Dust mite	2.99% ± 0.92%	3.17% ± 0.98%	1.76% ± 0.67%	1.75% ± 0.6%
Cat	1.63% ± 0.5%	1.52% ± 0.49%	2.4% ± 0.81%	2.43% ± 0.82%

*Percentage binding of anti-IgE ^{125}I is interpreted as follows in RAST score: less than 1.5%, negative; 1.5% to 7%, low; 8% to 19%, moderate; 20% to 30%, high; greater than 31%, very high.

TABLE II. Number of subjects who acquired new allergic sensitization after vaccination in control and APV groups

	Alternaria species	Ragweed	Cat	Total	Percent
Control (n = 49)	4	1	0	5	10.2
APV (n = 51)	3	0	1	4	7.9

Before vaccination, there was no statistically significant difference between the percentage binding of anti-IgE ^{125}I of the sera of the APV group and the control group to any of the antigens tested.

Compared with the prevaccination sera, the postvaccination sera from the control group showed a statistically significant rise in percentage binding of anti-IgE ^{125}I to *Alternaria* species (P = .001) and a statistically significant decline in percentage binding of anti-IgE ^{125}I to cat dander (P = .001) after vaccination. There was a statistically significant effect for *Alternaria* species between the prevaccination and postvaccination sera in the percentage binding of IgE ^{125}I when the subjects from both the APV and control group were pooled ($F[1,98] = 8.23$, P = .0051). There was no statistically significant difference between the prevaccination and postvaccination sera in percentage binding of IgE ^{125}I to the ragweed or dust antigens in the control group and to all the antigens tested in the APV group. There was no statistically significant difference between the APV and control groups in percentage binding of IgE ^{125}I to all antigens tested in the postvaccination sera.

Defining atopy as one or more positive RAST results to an environmental allergen, the results for the atopic subjects in each group were analyzed separately. Before vaccination, 33% of the subjects were atopic, with 16 atopic subjects in the control group and 17 in the APV group. After vaccination, 37% of the subjects were atopic, with 19 atopic subjects in the control group and 18 in the APV group. The χ^2 test result of the frequency of subjects in both groups who acquired new allergic sensitization after vaccination for the *Alternaria* species, ragweed, and cat antigens was not significant (Table II); no subjects acquired new allergic sensitization to dust mite antigen in either group. In the subjects identified as atopic at the prevaccination measurement, there was no significant difference in the percentage binding of IgE ^{125}I between prevaccination and postvaccination sera in each group nor between the postvaccination sera from the APV and control groups for all the antigens tested. There was a statistically significant effect for *Alternaria* species between the prevaccination and postvaccination sera in the percentage binding of IgE ^{125}I when the atopic subjects from both the APV and control groups were pooled ($F[1,12] = 5.21$, P = .0415).

The degree of sensitization, as reflected by the RAST score to each antigen, is shown in Table III for the total number of subjects in each group and in Fig 1 for the atopic subjects in each group. The RAST score increased after vaccination to ragweed in one subject in both the APV and control groups and to dust mite in 2 subjects in the control group. The Fischer exact test result of the frequency of subjects whose RAST scores increased for ragweed and dust mite was not significant.

DISCUSSION

The adjuvant effect in promoting IgE production of various components of pertussis has been established in in vitro human T-lymphocyte cultures[13] and in animal models.[14-16] Redhead et al[17] found that an acellular vaccine consisting of the pertussis toxin, filamentous hemagglutinin, and pertactin induced a T_{H2} cell response in mice. The same effect was found after vaccination with pertussis vaccines in children. Odelram et al[18] found that vaccination of children with a 2-component APV produced higher pertussis IgE antibodies than vaccination with a monocomponent vaccine and that a rise in total serum IgE correlated with the rise in pertussis IgE, particularly in the children who were atopic. The change in total serum IgE after pertussis infection was also found to differ according to the age at the time of infection. Compared with control subjects, children 0 to 2 years of age had no significant change, whereas children 3 to 12 years of age had a significant rise in their serum IgE levels.[12] It was therefore important to determine the possible change in the IgE response in adults. The change in allergen-specific IgE, rather than that in total IgE, was chosen for this study so that a more clinically relevant outcome can be determined.

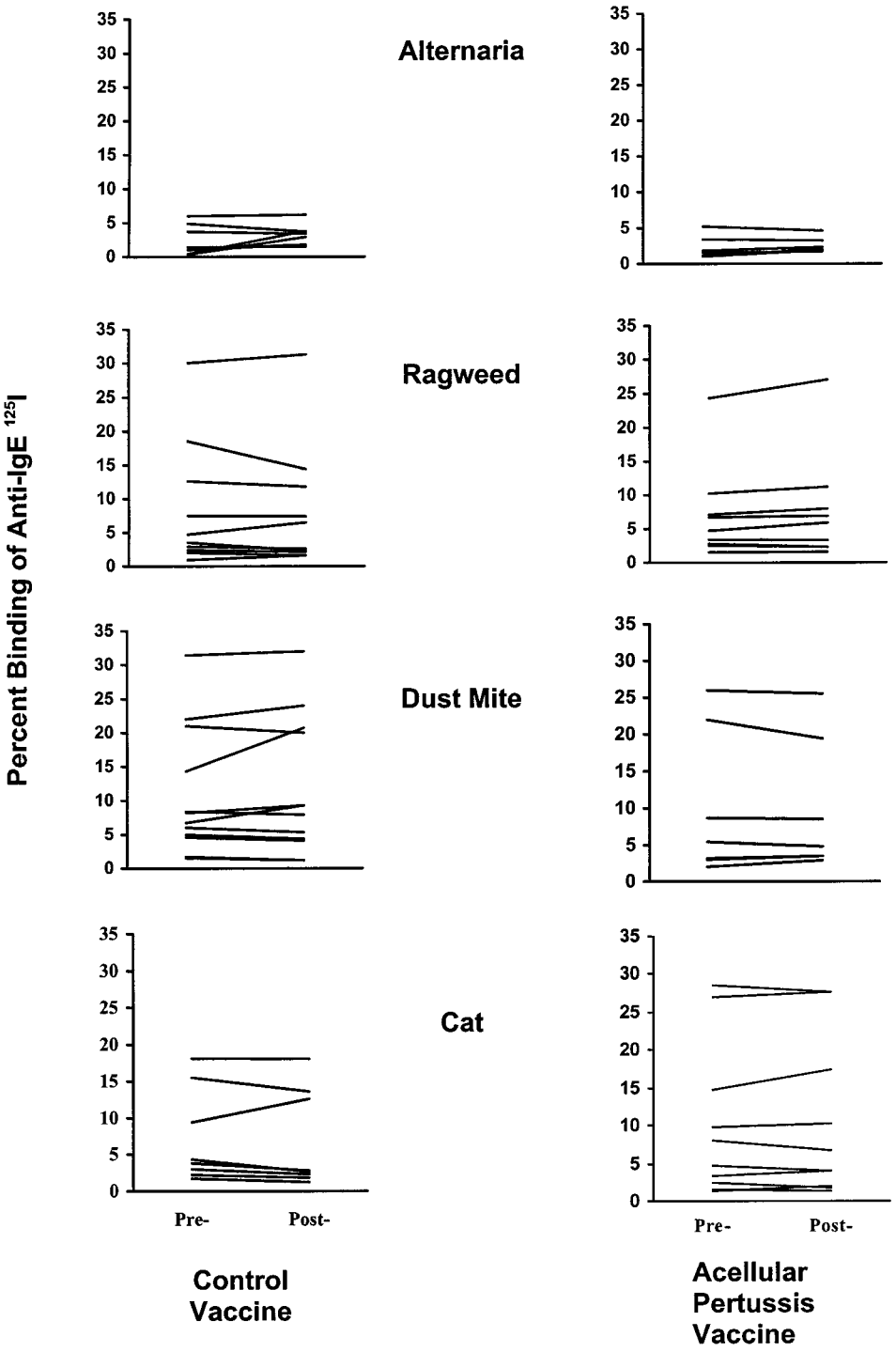

FIG 1. RAST results to the allergens tested for the atopic subjects before and after vaccination in the APV and the control vaccine group. RAST results are expressed as percentage binding of anti-IgE ^{125}I, which is interpreted in RAST scores as follows: less than 1.5%, negative; 1.5% to 7%, low; 8% to 19%, moderate; 20% to 30%, high; and greater than 31%, very high.

The randomly selected study subjects represented an adequate sample of the adult population. In particular, the 32% prevalence of atopy, as defined by evidence of IgE sensitization to one or more environmental allergens at baseline, was similar to the published figures of atopy in the general population.[19,20] The results of this study showed that a 2-component APV given to adults did not cause an increase in the serum-specific IgE response to the environmental allergens to which the subjects were exposed during the vaccination period. The results were

TABLE III. Number of subjects by RAST score to each antigen in control and APV groups before vaccination and 1 month after vaccination

	No. of subjects															
	Alternaria species				Ragweed				Dust mite				Cat			
	Control vaccine (n = 49)		APV (n = 51)		Control vaccine (n = 49)		APV (n = 51)		Control vaccine (n = 49)		APV (n = 51)		Control Vaccine (n = 49)		APV (n = 51)	
Group	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
RAST score																
Low (1.5%-7%)*	3	7	4	7	6	7	7	6	5	3	4	4	5	5	3	5
Moderate (8%-19%)	0	0	0	0	2	2	1	2	3	3	1	2	3	3	3	2
High (20%-30%)	0	0	0	0	1	0	1	1	2	3	2	1	0	0	2	2
Very high (>31%)	0	0	0	0	0	1	0	0	1	1	0	0	0	0	0	0
Total positive RAST results >1.5%	3	7	4	7	9	10	9	9	11	10	7	7	8	8	8	9
Negative RAST results <1.5%	46	42	47	44	40	39	42	42	38	39	44	44	41	41	43	42

*Percentage binding of anti-IgE ^{125}I.

not different in the study population as a whole or in the group of atopic subjects. The rise in serum-specific IgE to *Alternaria* species was quite mild and resulted in changing the RAST score from negative to low in 4 subjects in the control group and in 3 subjects in the APV group. The analysis indicated that the effect was related to *Alternaria* species and not to the other allergens tested. It indicated a response by the whole subject population, regardless of the vaccination received, to the prevalence of *Alternaria* species in the region throughout the fall and beyond it. A similar change was not seen in the response to ragweed and may be due to the subject recruitment for study extending beyond the ragweed season in our area. This may have led to several of the subjects' prevaccination and postvaccination titers being assayed outside the season. The changes that occurred in serum-specific IgE to the other allergens were mild and not statistically significant. They were comparable in both groups, indicating that APV had no distinct effect on specific allergen sensitization.

The discrepancy between the results of this study and the previously shown effects of pertussis exposure on promoting IgE synthesis may have several explanations. The difference may be due to the difference in age of the subjects at the time of vaccination. Previous studies had examined children, whereas this study was confined to adults. In a study of the immune response of adult medical personnel immunized with a 2-component APV similar to the one used in our study, Lin and Chiang[21] showed a predominant activation of T_{H1} cells, as reflected in increased production of IFN-γ after vaccination. Ausiello et al[22] have shown that T cells from adults without a previous record of infection or vaccination proliferated in culture when exposed to *Bordetella pertussis*. The cytokine profile was that of a T_{H1} response, as shown by IFN-γ and IL-2 production. This indicated that healthy adults may have been unknowingly exposed to *Bordetella pertussis* and that they have acquired a protective T_{H1} response. It may be speculated that another exposure by vaccination may generate the same T_{H1} response.[22] Finally, to our knowledge, no previous studies have examined antigen-specific responses, rather than total IgE, in humans in response to pertussis vaccination.

A clinical correlate to the current study, although in a pediatric population, is the study by Nilsson et al,[22] who followed, by means of clinical parameters (eg, questionnaires, skin test reactivity, and physical examinations), the effect of pertussis vaccines and pertussis infection on atopic disease in children aged 2 months to 2.5 years. The children were vaccinated with a 2-component acellular vaccine, a 5-component acellular vaccine, a whole-cell pertussis vaccine, and a placebo. They found no evidence of increased clinically significant allergic manifestation after any of the pertussis vaccines, although they found a statistically significant difference in the incidence of asthma in children who had a proven pertussis infection. It therefore appears that, regardless of the effect of pertussis on total IgE, vaccination with APV does not lead to a rise in serum-specific IgE responses to environmental allergens to which the subject is exposed during the period of vaccination and that there is no clinically significant increase in the signs and symptoms of allergy.

Our study is the first to address the question of an increase in allergic sensitization in an adult population after pertussis vaccination. We found that a divalent APV containing highly purified, chemically inactivated pertussis toxoid and filamentous hemagglutinin given to adults did not result in a rise in allergen-specific serum IgE levels in the immunized subjects.

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