

A Randomized Controlled Trial of the Effect of Pertussis Vaccines on Atopic Disease

Lennart Nilsson, MD; N.-I. Max Kjellman, MD, PhD; Bengt Björkstén, MD, PhD

Background: Pertussis vaccination in infancy has been suggested to increase the risk for development of asthma and allergy.

Objective: To assess sensitization rates and development of atopic diseases in a prospective randomized controlled trial of pertussis vaccine.

Patients and Methods: A total of 669 children were randomized to 1 of 4 vaccine groups (2-component acellular pertussis, 5-component acellular pertussis, whole-cell pertussis vaccines, and placebo [diphtheria and tetanus toxoids]). Diphtheria and tetanus toxoids were also given to the children in the pertussis vaccine groups. The children were evaluated by means of questionnaires at age 2 months, 7 months, and 2½ years; skin prick tests at age 7 months and 2½ years; and blinded clinical investigation at age 2½ years. The families were contacted at regular intervals to assess possible adverse effects after the vaccinations and symptoms of whooping cough.

Results: The cumulative incidence of atopic diseases was 30% and incidence rates were similar in the 4 groups after adjusting for family history. Exposure to environmental tobacco smoke and home dampness did not confound these results. The frequency of adverse effects did not differ appreciably between atopic and nonatopic children, with the exception that a nodule at the vaccination site was more frequent after whole-cell pertussis vaccination in the nonatopic children. Among 47 children with proven pertussis, atopic disease appeared in 19 (40%). Of these 47 children, 9 (19%) developed asthma, as compared with 58 (9%) noninfected children ($P = .03$).

Conclusions: We found no support for a drastic increase in allergic manifestations after pertussis vaccination. There was a positive association between whooping cough and asthma by 2½ years of age. There seems to be little reason to withhold pertussis vaccination from infants, irrespective of family history of allergy.

Arch Pediatr Adolesc Med. 1998;152:734-738

Editor's Note: This study should help to allay fears of increased atopy with pertussis vaccine; in fact, if that was the reason you used not to immunize, the data on atopy following pertussis vaccination should stimulate you to do so.

Catherine D. DeAngelis, MD

THE ETIOLOGY of asthma and allergy is multifactorial and a consequence of an interaction between genetic susceptibility and environmental factors, particularly those encountered early in life.^{1,2} Tobacco smoke is a major adjuvant factor for the development of asthma and allergy; avoidance of environmental tobacco smoke is essential in both primary and secondary prevention.³ Other potential adjuvants include certain infections and vaccinations.¹ *Bordetella pertussis* may be particularly important in this respect, as judged from experiments in animals⁴⁻⁷ and experiences in humans.⁸⁻¹²

In children, IgE antibodies to pertussis toxin are commonly found after infection and immunization.¹² It was recently suggested that whole-cell pertussis vaccination in infancy may increase the risk of

asthma 5-fold, from 2% to more than 10% during childhood.¹¹ However, in a study of nearly 10 000 children, a questionnaire survey with 3 questions on allergy symptoms did not support these findings.¹³ As part of a study of the efficacy of 3 pertussis vaccines, we prospectively studied the development of atopic disease and sensitization during the first 2½ years of life in relation to type of vaccine and possible confounders, including the effect of pertussis infection. Adverse effects related to pertussis vaccination were also considered, to evaluate both advantages and disadvantages of pertussis immunization.

RESULTS

Atopic disease was verified in 201 children (30%) during the first 2½ years of life. Atopic dermatitis occurred in 140 children (21%), and 67 children (10%) had bronchial asthma. Allergic rhinoconjunctivitis was found in 14 (2%), urticaria in 15 (2%), and food allergy in 12 (2%) of the children. Ninety-one children (14%) had a positive SPT to at least 1 allergen at 7 months of age. The prevalence of positive SPTs decreased with older age, as only 63 children

From the Division of Pediatrics, Department of Health and Environment, Faculty of Health Sciences, University Hospital, Linköping, Sweden.

PATIENTS AND METHODS

PATIENTS

In a Swedish pertussis vaccine trial of 9829 children at 14 study centers, 788 infants in Linköping, Sweden, were randomized to a double-blind comparison of the effects of 2-component acellular pertussis vaccine (2-c, SmithKline Beecham, Rixensart, Belgium), 5-component acellular pertussis vaccine (5-c, Connaught Ltd, Toronto, Ontario), whole-cell pertussis vaccine (WC, Connaught Laboratory Inc, Swiftwater, Pa), and diphtheria and tetanus toxoids vaccine (DT, Swedish National Bacteriological Laboratory, Stockholm) used as placebo.¹⁴ The families of 711 infants also agreed to be included in the allergy study and 699 infants received 3 doses of vaccine as scheduled. The 2-c vaccine was given to 188 children, 184 received the 5-c vaccine, 143 the WC vaccine, and 184 children received only DT. In all, 17 families moved from the area, and 6 families decided to withdraw during the study period, and 7 children had incomplete follow-up data, leaving 669 children who were followed up from 2 months up to 2½ years of age. The demographics of the 30 children who were unavailable for follow-up did not differ significantly from that of the remaining children.

The children received their first vaccine dose in the trial at age 2 months (56-92 days), and were evaluated at age 7 months (1 month after dose 3), and at about age 2½ years (mean, 2 years 5 months; range, 2 years 3 months to 2 years 8 months). The parents received questionnaires regarding tobacco smoke exposure of the children, home dampness (defined as problems in the house, such as leaking pipes or condensation on 2-glass window panes at temperatures below 0°C), pets in the house, type of feeding, and possible allergic symptoms in the children at 7 months and at 2½ years of age. The questions regarding symptoms in the skin, nose, and bronchi (**Figure 1**) were modified from the International Study of Asthma and Allergies in Childhood ("ISAAC") questionnaires.¹⁵

Skin prick tests (SPTs) were performed in duplicate on the volar aspect of the forearm with milk, egg white, and cat dander antigens at 7 months (n = 669), and with egg, cat dander, dog dander, 2 mites (*Dermatophagoides pteronyssinus* and *D farinae*), and timothy and birch antigens at 2½ years of age (n = 666). Undiluted cow's milk and hen's egg and Soluprick SQ extracts (10 HEP; Allergologisk Laboratorium A/S, Hørsholm, Denmark) for other allergens were used according to the recommendations by the European Academy of Allergy and Clinical Immunology.¹⁶ Tests were regarded positive if skin wheals had a mean diameter of 3 × 3 mm or more after 15 minutes. Histamine dihydrochloride, 10 mg/mL, and blank lancets were included as positive and negative controls. No antihistamine should have been used during 3 days preceding the SPT.

Physical examinations and, if needed, additional tests, were performed at 2½ years of age and when bronchial asthma or allergy was suspected by the study nurses.

The parents of all participating children gave their informed consent. The study was approved by the Human Research Ethics Committee of the Medical Faculty at the University of Linköping.

DIAGNOSTIC CRITERIA

The diagnoses were made on the basis of questionnaires, clinical findings, and information in medical records. Bronchial asthma was defined as at least 3 episodes of obstructive bronchitis before 2 years of age or 1 episode of bronchial obstruction after 2 years of age in the absence of other explanations. Atopic dermatitis was defined as persisting or recurring itching eczema for 6 months or more. A child was regarded as having allergic rhinoconjunctivitis in the case of an affirmative answer to both of the following questions: "Has your child, during the last 12 months, suffered from sneezing, rhinorrhea, or blocked nose without having a cold?" and "Have the nose complaints, during the last 12 months, been accompanied by itching or running eyes?" Urticaria was defined as allergic if appearing after exposure to a particular allergen and with a positive SPT to the same allergen. The diagnostic criteria for food allergy included diarrhea, vomiting, urticaria, or Quincke edema after ingestion of a specific food at least once, and demonstrable IgE antibodies to the same food.

The diagnosis of pertussis (whooping cough) was used according to criteria established by the World Health Organization.¹⁷ The families were contacted by telephone every 6 weeks. Blood samples for serological analyses and nasopharyngeal cultures for *B pertussis* were made after 7 days of coughing. A case of pertussis was defined as the presence of paroxysmal cough for at least 21 consecutive days plus 1 of the following criteria: isolation of *B pertussis* in culture, an increase of 100% or more in IgG or IgA antibodies against pertussis toxin, an increase of 100% or more in IgG or IgA antibodies against filamentous hemagglutinin (in the absence of positive results for *Bordetella parapertussis* on culture or polymerase chain reaction analysis), or documented contact with an infected household member with culture-confirmed *B pertussis* infection who began to cough within 28 days before or after the onset of cough in the study child.

The investigation was blinded to the families, nurses, and investigating physicians through the use of coded bottles until the diagnoses were established in all the children.

STATISTICAL ANALYSIS

Statistical comparisons were made using χ^2 tests and Fisher exact tests. Adjustments for differences in family history of atopic disease were performed in the main comparisons between study groups using a logistic regression model (version 3.1 of JMP, SAS Institute Inc, Cary, NC). Study group differences were taken into account by introducing indicator variables, as were differences in family history. An additive model containing such indicators seemed to be adequate and was used.

Sample sizes gave approximately an 80% chance of detecting a 50% treatment group increase above the control group level of atopic diseases during the first 2½ years of age when using a 1-sided test of significance at the 5% level.¹⁸ As the main purpose of the study was to detect considerable increases in the risk of atopic disease by pertussis vaccination, 1-sided tests and 1-sided confidence limits that delimit the increase in risk in an upward direction were used.

(9%) had a positive SPT at 2½ years of age ($P = .02$). At least 1 positive SPT was recorded in 17% of the children, the most common reaction being to egg white, both at 7 months (80/669 [12%]) and at 2½ years of age (41/666 [6%]). A

family history of allergy was associated with an increased prevalence of positive SPTs at 7 months of age. Thus, 26 (9%) of 279, 46 (15%) of 308, and 19 (23%) of 82 children with no, single, and double parental history, respectively, had

1. Has your child *ever* had wheezing or whistling in the chest? No/Yes
2. Has your child had wheezing or whistling in the chest at any time during the last 12 months? No/Yes
3. How many episodes with wheezing has your child had during the last 12 months? None/1-3/4-12/>12
4. During the last 12 months, how often, on average, has your child been disturbed by wheezing? Never/Less than 1 night per week/1 or more nights per week
5. During the last 12 months, has the wheezing of your child ever been so severe that he or she only could say 1 to 2 words between the breathings? No/Yes
6. During the last 12 months, has your child had wheezing in the chest during or after exercise? No/Yes
7. During the last 12 months, has your child had dry cough in the nights without having a cold or an infection? No/Yes
8. Has your child ever had wheezing at any time after 2 years of age? No/Yes
9. Has your child ever had 3 diagnosed episodes of bronchitis before 2 years of age? No/Yes
10. Has your child ever had treatment with inhaled Lomudal (cromolyn sodium) or inhaled steroids? No/Yes
11. Has your child ever had a diagnosis of bronchial asthma according to a physician? No/Yes

Figure 1. Questions for a diagnosis of bronchial asthma. Boldface items indicate responses supporting the diagnosis. A cumulative diagnosis of "bronchial asthma" by 2½ years of age in 67 children was based on a confirmative answer to the following questions: question 1 and one or more of questions 3, 4, 5, 6, and 7 and one or both of questions 8 and 9 ($n = 56$); question 1 and at least question 11 and confirmed by the medical record of the child ($n = 5$); question 1 and at least question 8, 9, or 10 and confirmed by the medical record of the child ($n = 5$); question 11 and confirmed by the medical record of the child ($n = 1$).

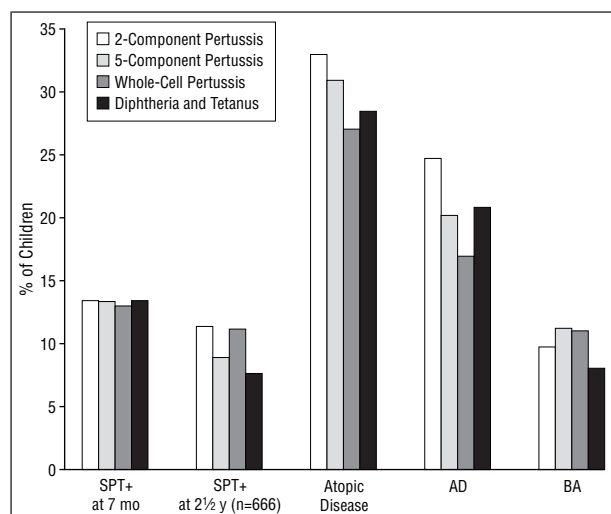


Figure 2. Atopic manifestations in 669 children during the first 2½ years of age in relation to type of pertussis vaccine. No significant differences were seen between the vaccine groups. AD indicates atopic dermatitis; BA, bronchial asthma; and SPT+, positive skin prick test.

a positive SPT ($P = .004$). The corresponding figures for a positive SPT at 2½ years were 8%, 9%, and 19% depending on heredity ($P = .02$). The cumulative incidence of atopic manifestations was similar in children with a maternal and paternal history of atopic disease (36% vs 37%).

The cumulative incidence of atopic disease at 2½ years of age, as well as the individual manifestations, were similar in the 3 pertussis vaccine groups and the DT group (**Figure 2**). The cumulative incidence of positive SPTs at 7 months and 2½ years of age did not differ significantly between the groups (Figure 2). Using unadjusted data, a positive SPT at 2½ years was found in 12% of the children who had received the 2-c vaccine, as compared with 8% in the DT group ($P = .20$). Similarly, atopic dermatitis was

Table 1. Demographic Data of 669 Children Immunized With 3 Injections of 1 of 3 Pertussis Vaccines or Placebo*

Demographic Features	Vaccine Group Assignment, % of Children			
	2-c (n = 182)	5-c (n = 178)	WC (n = 137)	DT (n = 172)
Family history of allergy	59.9	62.4	58.4	52.3
Maternal asthma	7.7	8.4	13.9	8.1
Paternal asthma	9.9	7.9	5.1	10.5
Smoking mother	18.7	15.8	19.0	18.7
Smoking father	15.4	18.9	13.1	17.5
Dampness at home	14.3	12.4	13.1	14.0
Pet at home	28.0	24.2	19.0	27.3
Male sex	57.1	50.6	55.5	52.9

*No significant differences were found between vaccine groups (χ^2 test). 2-c indicates 2-component acellular pertussis vaccine; 5-c, 5-component acellular pertussis vaccine; WC, whole-cell pertussis vaccine; and DT, diphtheria and tetanus toxoids vaccine (used as placebo).

Table 2. Occurrence of Any Atopic Disease During the First 2½ Years of Age in 669 Children in Relation to Vaccination and Parental History of Bronchial Asthma, Atopic Dermatitis, or Allergic Rhinitis*

Parental History	No. of Subjects	Vaccine Group Assignment, % of Children		
		2-c or 5-c	WC	DT
None	279	25.0	21.1	22.0
Mother	241	37.5	32.1	34.6
Father	227	38.4	35.7	33.3

*No significant differences were found between the vaccine groups. Abbreviations are explained in the footnote to Table 1.

more frequent in children vaccinated with the 2-c vaccine than in the WC-vaccinated children ($P = .08$).

The prevalence of environmental tobacco smoke, dampness in the home, indoor pets, preterm birth, and gender did not differ significantly between the 4 groups (**Table 1**). There were, however, fewer children with a family history of allergic disease in the DT-vaccinated children than in the 2 acellular vaccine groups (90/172 vs 220/360; $P = .05$). When stratifying for family history of allergic disease, no significant differences in atopic manifestations were found between the children in the different vaccine groups (**Table 2**).

Risk estimates for atopic disease during the first 2½ years of life were obtained using a logistic regression model (**Table 3**). The risk in the DT group was estimated to be 22.5% in children with no parental history of allergic disease. The risk was estimated to decrease by 1.7 percentage points for the WC vaccine (upper 95% confidence limit, 6.2 percentage points). The figures correspond to an 8% reduction and 28% increase, respectively. The corresponding figures for children immunized with a component vaccine was an increase by 2.3 percentage points (single-sided upper 95% confidence limit, 9.3), corresponding to a 10% and 41% increase, respectively. The percentages all refer to children with no parental history of allergic disease. The pattern was similar in children with single and double heredity.

The prevalence of adverse effects was similar in atopic and nonatopic children, with the exception that a nodule

Table 3. Estimated Risk (From a Regression Model) for Atopic Disease During the First 2½ Years of Age*

Parental History of Allergic Disease	Estimated Risk in Control Group	Estimated Increase in Risk in Treatment Groups		Upper 95% Confidence Limits of Increase		Upper 70% Confidence Limits of Increase	
		WC	2-c and 5-c	WC	2-c and 5-c	WC	2-c and 5-c
None	22.5	-1.7	2.3	6.2	9.3	1.0	4.4
1 Parent	31.6	-2.1	2.9	7.5	11.0	0.8	5.4
Both parents	41.4	-2.3	3.2	8.1	11.7	0.9	5.9

*Abbreviations are explained in the footnote to Table 1. Estimated risks in the control group are expressed as percentage values. Estimated changes in risk are expressed as a reduction or increase in these percentage points. For example, a risk increase of 2.3 corresponds to a 10% increase over the control group in the children receiving component vaccine.

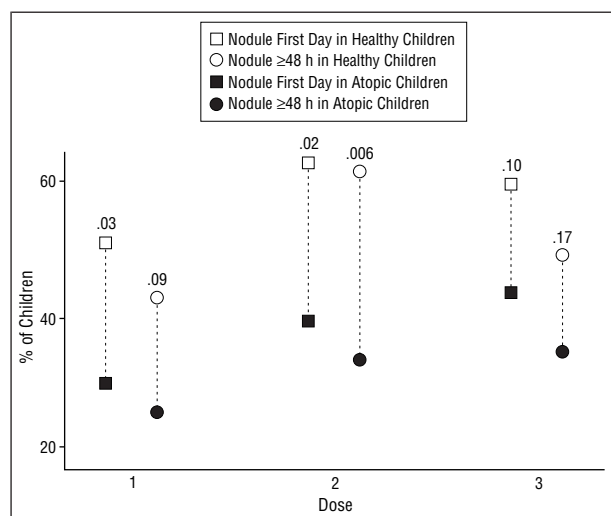


Figure 3. Prevalence of a nodule at injection site after each of 3 injections with whole-cell pertussis vaccine (at 2, 4, and 6 months of age) in 137 children, stratified according to the presence or absence of atopic disease during the first 2½ years of life. Values at the top of symbols indicate levels of significance for differences between children with and without atopic disease. No significant differences were found between atopic and nonatopic children in any of the other groups.

at the injection site after WC vaccination was more often reported in the nonatopic children (**Figure 3**). The most common adverse effects of the vaccines were redness (mean for all vaccine groups, 14%, 31%, and 39% after the first, second, and third injections, respectively), swelling (19%, 42%, and 48%), and fever (22%, 30%, and 33%). The incidence of adverse effects increased significantly with each dose given (for swelling and redness, $P < .001$) in children vaccinated with acellular pertussis vaccines or DT vaccine. The WC vaccine was associated with a similar high incidence of adverse effects after all 3 injections.

Forty-seven children had verified pertussis during the study period, 25 children in the DT group, 13 in the 2-c group, 8 in the WC group, and 1 in the 5-c group ($P < .001$). Pertussis was associated with an increased cumulative incidence of bronchial asthma, ie, 19% vs 9% in uninfected children ($P = .03$). Other atopic diseases also tended to be more frequent, although not significantly, among the children with confirmed whooping cough (40% vs 29%; $P = .10$).

COMMENT

The incidence of sensitization and manifestations of atopic diseases during the first 2½ years of life was largely simi-

lar after vaccination with any of 3 pertussis vaccines and placebo. There were several reasons to suspect that pertussis immunization could be associated with an increased risk for atopic manifestations. First, pertussis toxin is a potent adjuvant for IgE induction in animals,⁷ and second, a strong IgE response can be obtained to pertussis toxin from purified vaccines.⁸ Furthermore, primed T cells from children immunized with acellular vaccines secrete high levels of interleukin 5 and relatively low levels of interleukin 2 and interferon γ following specific antigen stimulation in vitro, ie, a mixed T_H1/T_H2 cytokine profile.¹⁹

Experiments in mice have shown that injection of *B pertussis* induces susceptibility to various chemicals,²⁰⁻²² and cold air,²³ indicating a functional β -receptor blockade. The immunological effects could possibly be explained by increased intracellular levels of cyclic adenosine monophosphate in lymphocytes induced by *B pertussis*²⁴ and thereby a shift toward a T_H2 -like response.²⁵

On the other hand, peripheral blood T cells from children with whooping cough secrete interferon γ but not interleukin 5 on antigen stimulation, implying that immunity generated by natural infection is mediated by T_H1 -like cells.²⁶ Analysis of blood samples from children after immunization with WC pertussis vaccines revealed a similar cytokine profile.¹⁹

It is well known that families with allergic diseases tend to be overrepresented in allergy studies. There was, however, no significant difference regarding symptoms associated with allergy between participants in the present study related to allergy and the children who only participated in the efficacy part of the pertussis trial.¹³

We intended to study whether pertussis vaccination of infants would increase the risk of atopic disease and were fortunate to obtain data in a randomized and controlled experiment. Even though 669 children completed the trial, the estimated risk levels had large margins of error. Aiming at an 80% power to detect a 10% increase in risk rate, a treatment group and a control group with nearly 4000 infants in each would have been needed. As each group in our study consisted of about 175 infants, any true differences would have to be nearly 50% to obtain an 80% power of detecting the differences. This is acceptable as the main purpose of the investigation was to detect a largely increased risk similar to that reported by Odent et al¹¹ for a WC vaccine. A similar vaccine was included in the present study.

The study reported by Odent et al¹¹ was retrospective and not randomized. Considering the relatively small

size of the study groups and that there were only 30 cases of asthma, it is not surprising that they were not able to conduct a comprehensive analysis of possible bias. In contrast, our study was prospective and the problems of bias were addressed through randomization. The results indicate that it is unlikely that WC pertussis vaccination increases the risk of atopic disease to up to 2½ years by more than 4% (single-sided upper 70% confidence limit). It may be argued that the observation period was too short to detect allergic respiratory disease. There is reason to believe, however, that a majority of the children who will develop asthma or rhinitis during the next few years were already identified as atopic during the observation period since they were often already sensitized and/or have had atopic dermatitis during infancy.²⁷ It seems presently reasonable to conclude that WC pertussis vaccination is not associated with a major increase in the risk of atopic disease.

Because observed results were similar for the 2 acellular vaccines, the groups were merged in the final analysis. The estimated risks of atopy following acellular pertussis vaccination were about 10% larger than the estimated control group risk levels. Our results indicate a possible small increase in the risk of atopic disease after acellular pertussis vaccines. The upper 95% confidence limit for an increased risk was considerable, however. In the large Swedish pertussis vaccine trial,¹⁴ the parents answered questions concerning symptoms of itching and wheezing in 9617 children. Similar frequencies of the symptoms were reported from all the 4 vaccine groups. With the acellular vaccines, the upper 95% confidence limit was 5.7% above the level in the control group for wheezing and 13.5% for itching. These results suggest that any negative effects of acellular vaccines are not much larger than 10%. Whooping cough is a debilitating disease and, in infancy, there may be serious complications. The reasonable conclusion seems to be that acellular vaccines would at most be associated with a small to moderate increase in atopy.

We also observed an association between pertussis and asthma. This could, for instance, be due to a causal relationship in that pertussis might increase the risk of later becoming asthmatic, eg, by inducing β -receptor blockade.²⁸ It might also be due to transient bronchial hyperreactivity after whooping cough.²⁹

At present, we recommend pertussis vaccination during early infancy, independent of any family history of atopic disease.

Accepted for publication March 10, 1998.

This work was supported by grants from the Swedish National Association Against Chest and Heart Disease, the Medical Research Fund of the County of Östergötland, the Swedish Asthma and Allergy Association, the Queen Silvia's Jubilee Fund, the First of May Flower Annual Campaign, the Samaritan Foundation, the Swedish Association for Allergology, and the National Institute of Public Health, Stockholm.

The efficacy study¹⁴ was supported by a grant from the National Institutes of Health, Bethesda, Md.

Special thanks to the nurses Ulla Larsson, RN; Meta Philipsson, RN; Lena Spetz, RN; and Kicki Helander, RN; for excellent assistance, and to the statisticians Olle Eriks-

son, ScB; and Erik Leander, PhD; Linköping University, for advice and assistance.

Reprints: Lennart Nilsson, MD, Department of Health and Environment/Pediatrics, University Hospital, 581 85 Linköping, Sweden.

REFERENCES

- Holt PG. Environmental factors and primary T-cell sensitisation to inhalant allergens in infancy: reappraisal of the role of infections and air pollution. *Pediatr Allergy Immunol.* 1995;6:1-10.
- Ruffilli A, Bonini S. Susceptibility genes for allergy and asthma. *Allergy.* 1997;52:256-273.
- Halken S, Høst A, Nilsson L, Taudorf E. Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy.* 1995;50:97-105.
- Redhead K, Watkins J, Barnard A, Mills KHG. Effective immunization against *Bordetella pertussis* respiratory infection in mice is dependent on induction of cell-mediated immunity. *Infect Immun.* 1993;61:3190-3198.
- Munoz JJ, Peacock MG. Action of pertussigen (pertussis toxin) on serum IgE and Fc ϵ receptors on lymphocytes. *Cell Immunol.* 1990;127:327-336.
- Mu HH, Sewell WA. Regulation of DTH and IgE responses by IL-4 and IFN-gamma in immunised mice given pertussis toxin. *Immunology.* 1994;83:639-645.
- Pauwels R, Van der Straeten M, Platteau B, Bazin H. The non-specific enhancement of allergy: in vivo effects of *Bordetella pertussis* vaccine on IgE synthesis. *Allergy.* 1983;38:239-246.
- Hedenskog S, Björkstén B, Blennow M, Granström G, Granström M. Immunoglobulin E response to pertussis toxin in whooping cough and after immunization with a whole-cell and an acellular pertussis vaccine. *Int Arch Allergy Appl Immunol.* 1989;89:156-161.
- Schuster A, Hofmann A, Reinhardt D. Does pertussis infection induce manifestation of allergy? *Clin Invest.* 1993;71:208-213.
- Wjst M, Dold S, Reitmeir P, Fritzsche C, von Mutius E, Thiemann HH. Pertussis infection and allergic sensitization. *Ann Allergy.* 1994;73:450-454.
- Odent MR, Culpin EE, Kimel T. Pertussis vaccination and asthma: is there a link? *JAMA.* 1994;272:591-592.
- Odelram H, Granström M, Hedenskog S, Duchon K, Björkstén B. Immunoglobulin E and G responses to pertussis toxin after booster immunization in relation to atopy, local reactions and aluminum content of the vaccines. *Pediatr Allergy Immunol.* 1994;5:118-123.
- Nilsson L, Kjellman N-IM, Storsaeter J, Gustafsson L, Olin P. Lack of association between pertussis vaccination and symptoms of asthma and allergy [letter]. *JAMA.* 1996;275:760.
- Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med.* 1996;334:349-355.
- Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Resp J.* 1995;8:483-491.
- Dreborg S, Frew A. Allergen standardization and skin tests. *Allergy.* 1993;48 (suppl 14):49-82.
- WHO Meeting on Case Definition of Pertussis, Geneva, 10-11 January 1991. Geneva, Switzerland: World Health Organization; 1991:4-5.
- Altman DG. *Practical Statistics for Medical Research.* London, England: Chapman & Hall; 1991.
- Ryan M, Murphy G, Ryan E, Nilsson L, Shackley F, Gothefors L, et al. Distinct T-cell subtypes induced with whole cell and acellular pertussis vaccines in children. *Immunology.* 1998;93:1-10.
- Parfentjev IA, Goodline MA. Histamine shock in mice sensitized with *Hemophilus pertussis* vaccine. *J Pharm Exp Pathol.* 1948;92:411-413.
- Kind LS. The altered reactivity of mice after inoculation with *Bordetella pertussis* vaccine. *Bacteriol Rev.* 1958;22:173-182.
- Malkiel S, Hargis BJ. Sensitization of the mouse to bradykinin. *Proc Soc Exp Biol Med.* 1967;125:565-567.
- Munoz J, Schuchardt LF. Effect of *H pertussis* on sensitivity of mice to cold stress. *Proc Soc Exp Biol Med.* 1957;94:186-190.
- Friedman E, Farfel Z, Hanski E. The invasive adenylate cyclase of *Bordetella pertussis*: properties and penetration kinetics. *Biochem J.* 1987;243:145-151.
- Fedyk ER, Adawi A, Looney RJ, Phipps RP. Regulation of IgE and cytokine production by cAMP: implications for extrinsic asthma. *Clin Immunol Immunopathol.* 1996;81:101-113.
- Ryan M, Murphy G, Gothefors L, Nilsson L, Storsaeter J, Mills KHG. *Bordetella pertussis* respiratory infection in children is associated with preferential activation of type 1 Th cells. *J Infect Dis.* 1997;175:1246-1250.
- Hattevig G, Kjellman B, Björkstén B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol.* 1993;4:182-186.
- Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J Allergy.* 1968;42:203-232.
- Ellis EF. Acute bronchopulmonary infections. In: Bierman CW, Pearlman DS. *Allergic Diseases From Infancy to Adulthood.* Philadelphia, Pa: WB Saunders Co; 1988:537.