Original paper

Whole-cell pertussis vaccine (DTwP) has no influence on allergic diseases and atopic sensitization in children

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Abstract

Introduction: Vaccine opponents indicate that the infant's immune system is inadequately developed to handle multiple vaccines which may overwhelm the immune system, leading to allergic diseases.

Aim: To verify the association between the vaccine antigen overload derived from DTwP and the development of atopic sensitization and allergic diseases.

Material and methods: Data from an earlier established birth cohort in Krakow, followed up to the 6th year of life were used. Allergic diseases such as eczema, hay fever and asthma were diagnosed by a physician and reported every half a year from the 1st to 6th year of life by the child's parent. Skin prick tests (SPT) were performed in children at 5 years of age. The data on infants' vaccination were extracted from the physician's records. The status of vaccine antigen exposure was based on different types of vaccines against pertussis (DTwP or DTaP) in a primary course. Results were determined by multiple logistic regression, adjusted to potential confounders.

Results: The analyzed population consisted of 234 children: 53.4% – boys and 46.6% – girls. Infants up to the age of 8 months were vaccinated with the primary course against pertussis, with DTwP – 60.7%, DTaP – 32.9% and further 6.4% with a mixed course (DTwP + DTaP). There were no significant relationships between any of vaccination groups and allergic disease and allergen sensitivity in the multiple logistic regression model with adjustment to potential confounders.

Conclusions: The exposure to a large number of vaccine antigens derived from DTwP has no influence on the development of allergic diseases and atopic sensitization in children.

Key words: children, pertussis vaccine (whole-cell, acellular), atopic sensitization, allergic diseases.

Introduction

Immunization has an essential impact on public health worldwide. Numerous studies have shown the efficacy of different vaccines to protect children and adults from various infectious diseases. However, some parents choose not to vaccinate their children for different reasons, such as doubts regarding their usefulness, philosophical or religious opinions and concerns over vaccine safety and efficacy [1]. Parents of children at a high risk of atopy are frequently concerned about the effect of immunizations in infancy. Apart from concerns about rare allergic reactions to the vaccine antigens or contaminants themselves, there exists a fear that immunizations may promote the development of allergic disease [2]. In addition, the rising prevalence of atopic disease today has been attributed to an introduction of the increasing number of recommended vaccines in immunization programs. The concern of vaccine opponents is that the infant's immune system is inadequately developed to handle vaccines safely or that multiple vaccines may overwhelm the immune system leading, among other things, to higher atopy sensitization and allergic diseases [3, 4]. In routinely recommended vaccines administered over the past 100 years, the whole cell pertussis vaccine (DTwP) contained the highest number of antigens among the other vaccines, including about 3000 of pertussis antigens. The new, acellular pertussis vaccine (DTaP) consists of no more than 5 antigens (depending on the type of formulation) [5]. In most of the developed countries, the replacement of DTwP with DTaP allowed to significantly decrease the number of vaccine antigens in the recommended programs. Whereas previously recommended programs consisted of more than 3000 antigens, nowadays including more kinds of vaccines, it consists of less than 150 antigens

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(proteins and polysaccharides) [3]. Poland is the only one country in the European Union where infants are vaccinated with DTwP according to the mandatory immunization program. There is an access to DTaP as an alternative option, payable by infant's parents. As a result of that strategy, about half of Polish infants are vaccinated with DTwP, and the rest of them with DTaP. That is why the exposure to the number of vaccine antigens varies significantly between those two groups of children.

Aim

The aim of this study was to verify the hypothesis about the association between the vaccine antigen overload derived from DTwP and the subsequent development of atopic sensitization and allergic diseases.

Material and methods

This is a prospective cohort study, combining environmental monitoring and molecular approaches with comprehensive neurodevelopment and health assessments. In the analysis we used data from an earlier established birth cohort of children in Krakow, being part of the ongoing, collaborative study with the Columbia University in New York, on the vulnerability of fetus and child to environmental factors. This cohort was described in more detail in the previous publications [6, 7].

Briefly, the enrollment (3 November 2000 – 22 August 2003) included only non-smoking women, aged 18–35 years, with singleton pregnancy, without illicit drug use and HIV infection, free from chronic diseases such as diabetes or hypertension and residing in Krakow for at least one year prior to pregnancy. Children were followed up to the 6th year of life. Each year, mother or father were asked to provide information on infants' health and household characteristics to trained interviewers, who carried out detailed, face-to-face standardized interviews. Information on parental atopy was also collected.

Vaccination data

The data on infants' vaccination history (date of vaccination and type of vaccine) were extracted from the physician's records when the children were 3 years old. The status of vaccine antigen exposure was based on different types of vaccines against pertussis (DTwP or DTaP) in a primary course (three vaccine doses up to 8 months of life). Children with longer vaccination delays (25%) were excluded from the study. Children's vaccination status was divided into three groups:

– the vaccination course completed with DTwP included about 3000 pertussis antigens (manufactured in Poland by Biomed Krakow),
– the vaccination course completed with DTaP included up to 5 pertussis antigens (Tripacel Sanofi Pasteur or Infanrix GlaxoSmithKline vaccines),
– the mixed course (DTwP + DTaP).

The exposure to other vaccines was similar in all three groups. Infants have been vaccinated according to the Polish vaccination schedule against hepatitis B and poliomyelitis, usually simultaneously with DTP. All of the used vaccines contained aluminum as an adjuvant.

Atopy

Allergic diseases such as eczema, hay fever and asthma were diagnosed by a physician and reported every half a year from the 1st to 6th year of life by the child's parent.

All skin prick tests (SPT) were performed when children were 5 years old, using four common aeroallergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat and dog hair. Additionally, in a smaller subsample, sensitization to mold as well as tree and grass pollens was also checked. The standardized extracts of allergens were used, including a positive and negative control solution. The technique of the tests was consistent with standards recommended by the European Academy of Allergy and Clinical Immunology. The tests were performed by trained nurses in one of out-patient allergy clinics. The results were read after 15 min by measuring the largest diameter of the wheal. Sensitization status was interpreted as a positive when a wheal had the diameter of 3 mm and not smaller than the histamine control.

Dosimetry of Pb in blood

Lead concentrations were examined in cord blood (at delivery) and in capillary blood (5-year-old children). Whole blood lead concentrations were determined using inductively coupled plasma mass spectrometry CLIA'88 method "Blood lead cadmium mercury ICPMS_ITB001A". This multi-element analytical technique is based on quadrupole ICP-MS technology [8]. More details on blood sample collection and analysis were presented in the earlier publications [7, 9].

Statistical analysis

Descriptive statistics were reported in a standard way (number and proportion; mean and/or median, and standard deviation). Exposure to DTP vaccine (see above) was categorized according to its type. Differences in the distribution of women's and newborns' parameters grouped by categorized DTP status were tested using χ^2 or Fisher's exact test (for nominal variables) and one-way ANOVA or Kruskal-Wallis tests (for continuous variables).

Candidate confounding factors were selected based on the current literature. They include: gender, birth weight (continuous variable), parity, maternal age (continuous variable), education (university vs. non-university), marital status (married vs. unmarried) and poor economical status, maternal or paternal atopy, breastfeeding (child breastfed for at least 6 months), exposure to environmental tobacco smoking (ETS) prenatally and in a 6-year period of life, presence of a dog or a cat at home for at least

a month in a 6-year period, indoor environment (presence of damp or mold at home) and blood lead level (cord blood and measurement at the age of 5 years). Maternal and paternal atopy was defined as reported medical diagnosis of eczema, atopic dermatitis, hay fever or food allergy.

The candidate factors were first evaluated together with the type of DTP vaccination and were retained in further analyses only if they were statistically significant in a consistent way or influenced the course of DTP vaccination. In subsequent multivariable analyses, the set of confounding factors was further optimized, separately for each outcome. Associations were measured by multiple logistic regressions. Odds ratios were estimated either without any other factor than exposure (crude OR) or with the confounding factors (adjusted OR). Statistical analyses were performed using SPSS 22.0 software.

Ethical approval

The parents of all children involved in the study gave their informed consent. The research protocol was approved by the Jagiellonian University Ethical Committee.

Results

The analyzed population consisted of 234 children: 53.4% – boys and 46.6% – girls. Infants up to the age of 8 months were vaccinated with a primary course against pertussis, with DTwP – 60.7%, DTaP – 32.9% and further 6.4% with the mixed course (DTwP + DTaP).

As for study group characteristics, only maternal education, poor economical status, mother's atopy and ETS exposure significantly differed in the primary course of DTP vaccination. Mothers who graduated from university more often vaccinated their children with DTaP (63.6%) and infants of mothers with atopy were more likely to be vaccinated with the mixed course (40.0%). Infants prenatally exposed to ETS have been significantly more often vaccinated with DTwP in the primary course (45.1%) (Table 1). All of those confounders were included in multivariable analysis.

The frequency of allergic diseases and assessed sensitivity for the selected allergens did not differ significantly between groups exposed to DTP in children at the age of 6 years. Hence, the cumulative incidence

Table 1. Characteristics of the study subjects stratified by the type of primary course of DTP

Characteristic		Total number	DTwP	DTaP	Mixed course (DTwP + DTaP)	*P*-value
Gender	Boys	125 (53.4%)	72 (50.7%)	43 (55.8%)	10 (66.7%)	0.436
	Girls	109 (46.6%)	70 (49.3%)	34 (44.2%)	5 (33.3%)	
Parity	1	156 (66.7%)	87 (61.3%)	57 (74.0%)	12 (80.0%)	0.085
	≥ 2	78 (33.3%)	55 (38.7%)	20 (26.0%)	3 (20.0%)	
Gestational age < 37 weeks		5 (2.1%)	1 (0.7%)	4 (5.2%)	0 (0.0%)	0.104
Birth weight [g]		3420.1 ±469.56	3447.7 ±462.65	3376.8 ±487.17	3380.7 ±453.53	0.536
Birth length [cm]		54.7 ±2.78	54.7 ±2.79	54.6 ±2.89	54.8 ±2.21	0.932
Maternal university education		118 (50.4%)	64 (45.1%)	49 (63.6%)	5 (33.3%)	0.013
Mother's age at 2nd trimester		27.5 ±3.61	27.3 ±3.73	28.2 ±3.46	26.7 ±2.92	0.130
Maternal marital status – married		219 (93.6%)	131 (92.3%)	73 (94.8%)	15 (100.0%)	0.610
Poor economical status		13 (5.6%)	12 (8.5%)	0 (0.0%)	1 (6.7%)	0.015
Breastfeeding up to 6 months		165 (70.5%)	98 (69.0%)	56 (72.7%)	11 (73.3%)	0.822
Maternal asthma		3 (1.3%)	1 (0.7%)	2 (2.6%)	0 (0.0%)	0.413
Maternal atopy		59 (25.2%)	28 (19.7%)	25 (32.5%)	6 (40.0%)	0.046
Paternal asthma		7 (3.0%)	5 (3.5%)	1 (1.3%)	1 (6.7%)	0.490
Paternal atopy		43 (18.4%)	26 (18.3%)	12 (15.6%)	5 (33.3%)	0.267
Atopy in any parent		86 (36.8%)	45 (31.7%)	32 (41.6%)	9 (60.0%)	0.055
Prenatal ETS		87 (37.2%)	64 (45.1%)	19 (24.7%)	4 (26.7%)	0.008
ETS during 6 years		48 (20.5%)	36 (25.4%)	11 (14.3%)	1 (6.7%)	0.060
Cord blood lead level [µg/l]		1.44 ±0.70	1.53 ±0.80	1.33 ±0.51	1.29 ±0.42	0.191
Blood lead level at the age of 5 [µg/l]		2.14 ±0.63	2.17 ±0.65	2.08 ±0.61	2.23±0.60	0.580
Pets at home		64 (37.0%)	33 (33.0%)	25 (41.7%)	6 (46.2%)	0.424
Mold indoors		60 (25.6%)	41 (28.9%)	16 (20.8%)	3 (20.0%)	0.371
Damp indoors		75 (32.1%)	48 (33.8%)	23 (29.9%)	4 (26.7%)	0.753

Table 2. Frequency of allergic diseases and allergen sensitivity stratified by the type of DTP course

Frequency	Total		DTwP		DTaP		Mixed course		*P*-value
	N	%	*N*	%	*N*	%	*N*	%	
Prevalence at the age of 6 years:									
Asthma (*n* = 186)	11	5.9	8	7.4	2	3.1	1	7.7	0.446
Eczema (*n* = 186)	13	7.0	8	7.4	4	6.2	1	7.7	1.000
Hay fever (*n* = 186)	50	26.9	31	28.7	16	24.6	3	23.1	0.799
Any positive SPT: *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* cat and dog dander (*n* = 162)	36	22.2	22	25.0	11	17.7	3	25.0	0.558
Any positive SPT: *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* cat and dog dander, mold, tree and grass pollens (*n* = 97)	34	35.1	18	35.3	10	27.0	6	66.7	0.082
Cumulative incidence from the 1st to 6th year of life:									
Asthma (*n* = 234)	22	9.4	11	7.7	8	10.4	3	20.0	0.283
Eczema (*n* = 234)	139	59.4	78	54.9	53	68.8	8	53.3	0.120
Hay fever (*n* = 234)	148	63.2	97	68.3	43	55.8	8	53.3	0.134

of asthma, eczema and hay fever from the 1st to the 6th year of life was similar in the three pertussis vaccination groups (Table 2).

Our univariate analysis showed that only the exposure to DTwP vs. DTaP was associated with a decreased risk of developing eczema in children (calculated for cumulative incidence), (OR = 0.55; 95% CI: 0.31–0.99). There were no significant relationships between any of vaccination groups and allergic disease and allergen sensitivity in the multiple logistic regression model with adjustment for maternal education, poor economical status, mother's atopy, prenatal ETS, parity, breastfeeding, dwelling in damp or moldy conditions (Table 3).

Discussion

In the present study, children vaccinated with DTwP were at a similar risk of atopic disorders as children vaccinated with DTaP. The burden of about 3000 antigens derived from DTwP on the infants' immune system in comparison to 4 antigens included in DTaP had no influence on the development of allergic disease and atopic sensitization in children up to the 6th year of life.

Our results did not confirm that the theoretical issues, raised by many vaccination opponents, such as immune "overload" by a great number of vaccine antigens in infancy is linked with a higher risk of allergy in children [10]. We obtained the consistent results for all of the analyzed allergic diseases (eczema, hay fever, asthma), and performed tests for allergen skin sensitization. In the previous studies, there was inconsistent evidence for a relation between vaccination and the development of allergic disease. Usually most of the children are vaccinated and it is difficult to obtain adequate numbers of unvaccinated infants to examine the vaccination-allergic disease relationship. Hence, unvaccinated children are a highly selected and usually atypical group. It is related to studies on DTwP as well [11–14].

In our cohort, only 5 infants have not received routine vaccination and we excluded them from the study group to avoid the bias of medical and socio-economical confounders related to refraining from vaccination. Therefore, we decided to calculate the relationship between the heavy burden of vaccine antigens derived from DTwP (about 3000 antigens) in comparison to the exposure to DTaP which included up to 5 antigens. That difference in the burden of vaccine antigens was sufficiently significant to conduct our analysis. The rest of vaccine exposure was similar in the two study groups. We realize that the time of vaccination exposure is important in our analysis and that period was limited up to the 8th month of life. Infants with a longer delay in primary DTP vaccination course have been excluded from the study cohort. The relatively short period of vaccination exposure and including in the analysis only the vaccinated children decreased the bias of reverse causation. The onset of allergic disease usually occurred after the vaccination exposure, and any earlier potential symptoms of allergy did not influence the immunization procedures because the entire cohort was vaccinated against pertussis. The crucial reasons for the vaccine choice (DTwP or DTaP) for infants were dependent on socio-economical factors which were included in the analysis as the important confounders.

The previous studies about the relationship between DTwP exposure and allergy had compared vaccinated

Table 3. Risk of allergic diseases and allergen sensitivity according to DTP vaccination status

Frequency		Crude		Adjusted*	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Prevalence at the age of 6 years:					
Asthma (*n* = 186)	DTwP vs. DTaP	2.52 (0.52–12.25)	0.252	2.54 (0.50–12.79)	0.258
	DTwP vs. mixed course	0.96 (0.11–8.35)	0.970	1.25 (0.13–11.89)	0.844
Eczema (*n* = 186)	DTwP vs. DTaP	1.22 (0.35–4.22)	0.754	1.56 (0.42–5.84)	0.508
	DTwP vs. mixed course	0.96 (0.11–8.35)	0.970	0.82 (0.09–7.79)	0.866
Hay fever (*n* = 186)	DTwP vs. DTaP	1.23 (0.61–2.49)	0.559	1.27 (0.60–2.67)	0.536
	DTwP vs. mixed course	1.34 (0.35–5.21)	0.671	1.52 (0.36–6.45)	0.573
Any positive SPT: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat and dog dander (*n* = 162)	DTwP vs. DTaP	1.55 (0.69–3.48)	0.293	1.64 (0.69–3.89)	0.263
	DTwP vs. mixed course	1.00 (0.25–4.03)	1.000	1.14 (0.26–4.97)	0.866
Any positive SPT: *Dermatophagoides pteronyssinus*, *Dermatophagoides* farinae, cat and dog dander, mold, tree and grass pollens (*n* = 97)	DTwP vs. DTaP	1.47 (0.58–3.72)	0.412	1.64 (0.61–4.44)	0.330
	DTwP vs. mixed course	0.27 (0.06–1.22)	0.090	0.24 (0.05–1.15)	0.074
Cumulative incidence from the 1st to 6th year of life:					
Asthma (*n* = 234)	DTwP vs. DTaP	0.72 (0.28–1.88)	0.508	0.85 (0.31–2.30)	0.743
	DTwP vs. mixed course	0.34 (0.08–1.37)	0.129	0.51 (0.11–2.27)	0.373
Eczema (*n* = 234)	DTwP vs. DTaP	0.55 (0.31–0.99)	0.046	0.55 (0.30–1.03)	0.060
	DTwP vs. mixed course	1.07 (0.37–3.10)	0.906	1.24 (0.40–3.82)	0.714
Hay fever (*n* = 234)	DTwP vs. DTaP	1.70 (0.96–3.02)	0.068	1.78 (0.98–3.23)	0.060
	DTwP vs. mixed course	1.89 (0.64–5.52)	0.247	1.97 (0.64–6.04)	0.236

**OR adjusted to parity, breastfeeding, maternal education, maternal atopy, poor economical status, prenatal ETS and indoor mold or damp.*

groups with the unvaccinated one. The studies conducted that way yielded inconsistent results. Our results are consistent with the observations of other authors who did not confirm the influence of DTwP exposure on the development of allergy [11, 15, 16]. Some of them even observed the protective effect of DTwP vaccination with respect to the onset of asthma and other allergic diseases in later life [17–19]. On the other hand, some other reports indicated the adverse effects of DTwP vaccination on the development of allergy [12, 20, 21]. That fact may result from the methodological differences in the epidemiological studies and the ascertainment bias linked with refraining from vaccination as well as the lack of data about the important confounders. The advantage of our study is its design – the prospective cohort study with reliable data on vaccination exposure, allergic disease onset and skin prick test results. We had a possibility to adjust the crude results to many plausible confounders that could influence the development of allergy in early childhood. The advantage of our study is the active, long-term (9-year) survey of the study cohort. In this paper we decided to present the results of a 6-year survey, when children were administered with skin prick tests. The available data on allergic disease onset in children up to the 9th year of life gave us the possibility to calculate the same analysis for older children, as well. We obtained similar results like for the younger children – no relationship between DTwP exposure and the development of allergy.

We realize that study on DTwP seems not so important for the most of the developed countries because they removed that vaccine from their vaccination programs. Poland is the only country in the EU which still uses DTwP in its mandatory vaccination schedule. DTwP is relatively responsible for most of the adverse effects following immunization (AEFI) reported in Poland. Knowing the numbers of AEFI (observed up to 4 weeks after exposure), the Polish community is concerned about the long-term vaccine influence on children's health. On the other hand, still using DTwP we had the possibility to test the hypothesis popular in the other countries of the "overload" of the immune system with vaccine antigens with respect to the development of allergy. DTwP exposure affects the infant's immune system with 10 times more antigens compared to the entire spectrum of other vaccines applied nowadays in vaccination programs of the developed countries [3]. Lack of the effects of DTwP exposure on the development of allergy indirectly indicate that the cumulative number of antigens derived from the increasing number of new-generation vaccines,

including usually only a few antigens, has no harmful influence manifested by an increased risk allergic diseases in children.

Conclusions

The exposure to a large number of vaccine antigens derived from DTwP has no influence on the development of allergic disease and atopic sensitization in children. The results of our study should not be treated as a supportive argument for the continuation of using DTwP which is responsible for too many AEFI in infants. They are further evidence on the vaccines safety which should encourage parents not to avoid or delay effective immunization of children, especially when weighed against the benefits.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Smailbegovic MS, Laing GJ, Bedford H. Why do parents decide against immunization? The effect of health beliefs and health professionals. Child Care Health Dev 2003; 29: 303-11.
2. Heininger U. An internet-based survey on parental attitudes towards immunization. Vaccine 2006; 24: 6351-5.
3. Offit PA, Quarles J, Gerber MA, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? Pediatrics 2002; 109: 124-9.
4. Kennedy A, Basket M, Sheedy K. Vaccine attitudes, concerns, and information sources reported by parents of young children: results from the 2009 HealthStyles survey. Pediatrics 2011; 127 Suppl 1: S92-9.
5. Marzouqi I, Richmond P, Fry S, et al. Development of improved vaccines against whooping cough: current status. Hum Vaccin 2010; 6: 543-53.
6. Jedrychowski W, Whyatt RM, Camann DE, et al. Effect of prenatal PAH exposure on birth outcomes and neurocognitive development in a cohort of newborns in Poland. Study design and preliminary ambient data. Int J Occup Med Environ Health 2003; 16: 21-9.
7. Mrozek-Budzyn D, Majewska R, Kiełtyka A. Early exposure to thimerosal-containing vaccines and children's cognitive development. A 9-year prospective birth cohort study in Poland. Eur J Pediatr 2015; 174: 383-91.
8. CDC: Whole blood lead, cadmium and mercury determined using inductively coupled plasma mass spectrometry, DLS method code: 2003–01/OD. Atlanta, GA: CLIA Methods. Centers for Disease Control and Prevention 2003.
9. Jedrychowski W, Perera FP, Jankowski J, et al. Very low prenatal exposure to lead and mental development of children in infancy and early childhood: Krakow prospective cohort study. Neuroepidemiology 2009; 32: 270-8.
10. Hilton S, Petticrew M, Hunt K. 'Combined vaccines are like a sudden onslaught to the body's immune system': parental concerns about vaccine 'overload' and 'immune-vulnerability'. Vaccine 2006; 24: 4321-7.
11. Nilsson L, Kjellman NI, Bjorksten B. Allergic disease at the age of 7 years after pertussis vaccination in infancy: results from the follow-up of a randomized controlled trial of 3 vaccines. Arch Pediatr Adolesc Med 2003; 157: 1184-9.
12. Kemp T, Pearce N, Fitzharris P, et al. Is infant immunization a risk factor for childhood asthma or allergy? Epidemiology 1997; 8: 678-80.
13. Enriquez R, Addington W, Davis F, et al. The relationship between vaccine refusal and self-report of atopic disease in children. J Allergy Clin Immunol 2005; 115: 737-44.
14. Mommers M, Weishoff-Houben M, Swaen GM, et al. Infant immunization and the occurrence of atopic disease in Dutch and German children: a nested case-control study. Pediatr Pulmonol 2004; 38: 329-34.
15. Nakajima K, Dharmage SC, Carlin JB, et al. Is childhood immunisation associated with atopic disease from age 7 to 32 years? Thorax 2007; 62: 270-5.
16. Henderson J, North K, Griffiths M, et al. Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. BMJ 1999; 318: 1173-6.
17. Anderson HR, Poloniecki JD, Strachan DP, et al.; Group IPS. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. Am J Public Health 2001; 91: 1126-9.
18. Bernsen RM, de Jongste JC, van der Wouden JC. Lower risk of atopic disorders in whole cell pertussis-vaccinated children. Eur Respir J 2003; 22: 962-4.
19. Grüber C, Illi S, Lau S, et al.; Group M-S. Transient suppression of atopy in early childhood is associated with high vaccination coverage. Pediatrics 2003; 111: e282-8.
20. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? JAMA 1994; 272: 592-3.
21. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. Thorax 1998; 53: 927-32.

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