ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
August 2015; 14(4):402-409.

The Effect of Preventive Immunization on the Incidence of Allergic Conditions

Grażyna Dulny[1], Adam J. Sybilski[1], Marta Zalewska[1], Filip Raciborski[2], Jarosław Komorowski[1], Barbara Piekarska[1], Agnieszka Lipiec[1], and Bolesław Samoliński[1]

[1] Department of the Prevention of Environmental Hazards and Allergology, Medical University of Warsaw, Poland
[2] Department of Epidemiology and Health Promotion, Institute of Rheumatology, Warsaw, Poland

Received: 28 October 2014; Received in revised form: 2 November 2014; Accepted: 6 December 2014

ABSTRACT

The purpose of this study was to assess the effect of preventive immunization on the incidence of allergies in Poland.

18617 (53.8% female, 24.2% 6-7 years old, 25.4% 13-14 years old, 50.4% 20–44 years old) were selected by stratified cluster sampling method in 8 cities and 1 rural area. 4783 of whom underwent objective outpatient screening assessments. Study subjects were evaluated for any association between preventive immunization against rubella, measles, typhoid fever, smallpox and incidence of atopic dermatitis, allergic rhinitis, and asthma.

There was no increased risk of allergy incidence in the majority of vaccinated subjects against rubella, measles, typhoid fever, or smallpox (OR from 0.42 (p<0.0001) to 1.34 (p<0.0001) with 95% CI from 0.27–0.65 to 1.19–1.50). Slightly increased risk of asthma was after vaccination against typhoid (OR=1.27; p<0.0001) and smallpox (OR=1.21; p=0.02). The risk of atopic dermatitis (AD) was also evaluated following vaccination against rubella (OR=1.34; p<0.0001), typhoid (OR=1.13; p=0.005), varicella (OR=1.18; p=0.003); rhinitis and AR following vaccination against measles (respectively OR=1.22; p<0.0005 and OR = 1.21; p=0.0002). No higher risk of allergic diseases was demonstrated in vaccinated individuals diagnosed by doctor in an outpatient setting.

These data do not demonstrate a causal relationship between vaccinations and allergic conditions.

Keywords: Allergy; Immunization; Measles; Rubella; Smallpox; Vaccination

INTRODUCTION

Allergic conditions constitute one of the most important problems of modern medicine.

In the past 3 decades, we have witnessed a dramatic increase in the prevalence of asthma and allergic diseases worldwide, most notably in countries with a western lifestyle. These studies indicate that in many nations over 30% of the study population may be affected with allergies.[1-3] Most cases of allergic diseases first appear in childhood, with 80% to 90% of patients diagnosed by 6 years of age. The incidence of allergies is associated with a combination of genetic

Corresponding Authors: Adam J. Sybilski, MD, PhD; Department of Pediatric and Neonatology, Central Clinical Hospital of Ministry of Internal Affair, Wołoska 137, 02-507 Warsaw, Poland. Tel: (+4822) 5081 220, Fax: (+4822) 5081 222, E-mail: adam.sybilski@cskmswia.pl

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

and environmental factors. Preventive vaccinations are also considered in the etiology of allergies. The association between vaccination uptake and the risk of atopic diseases was first proposed in 1994.[4] Up to now, several studies have suggested either a provocative or protective effect of immunization depending on the specific vaccine, the target population, and the age at which the vaccine was administered.[5-8] Some studies indicated a possible atopy-protective effect of immunization.[9-11]

Although current evidence suggests that virus vaccination does not lead to an increase or decrease incidence of asthma or atopy in children receiving vaccines, the cross-sectional, population-based cohort studies are required.

In Poland, mandatory vaccinations were initiated after 1945. At first, they were conducted as part of immunization initiatives, then – beginning from 1963 – they were part of immunization programs (Table 1).[12]

The objective of this study, as a part of the Epidemiology of Allergic Disorders in Poland (ECAP study), was to determine the possible association of rubella, measles, typhoid fever and smallpox preventive immunization with the incidence of allergic diseases in Poland.

MATERIALS AND METHODS

Study Population

ECAP used the methodology of The International Study of Asthma and Allergies in Childhood (ISAAC) and The European Community Respiratory Health Survey (ECRHS). The study areas were selected according to the ECRHS guidelines. ECAP involved the populations of eight largest urban agglomerations in Poland (each with over 150 000 inhabitants) and additionally one rural region, also with a population of over 150 000 since the rural population accounts for 39% of the entire Polish population. The study areas were specifically chosen but the study subjects were selected by stratified random sampling based on the national identification number (PESEL). According to the ISAAC and ECRHS protocols, the study included three groups of respondents: children aged 6-7 years and 13-14 years, and adults (20-44 years).

The first part of project (a questionnaire survey) was carried out on a group of 22703 subjects with the response rate of 64.4% and eventually 18 617 completed questionnaires were accepted. The study involved two age groups of children, 6-7 year olds and 13-14 year olds, and adults aged 20 – 44. There were 4510 (24.2%) 6-7 year olds, 4721 (25.4%) 13-14 year olds and 9386 (50.4%) adults. Of the respondents, 10 011 (53.8%) were female and 8606 (46.2%) were male. In the medical evaluation part of the study, 4783 patients (25.7% of the respondents) were assessed on an outpatient basis, including 1329 6-7 year olds, 1321 13-14 year olds and 2133 adults. The study group design is shown in Table 2.

Table 1. Mandatory preventive vaccinations administered in Polish children aged 0–18 between 1945 and 2008.[14]

Vaccine type	Immunization prior to 1963	Added into immunization schedule	Removed from immunization schedule
DTP	initiative-based	1963	still administered
BCG	initiative-based	1963	still administered
Smallpox	initiative-based	1963	1979
Typhoid fever	initiative-based	1963	1974
Poliomyelitis	initiative-based	1972	still administered
Measles	not administered	1975	still administered
Rubella	not administered	in girls between 1988 and 2004; in everyone since 2005	still administered
Hepatitis B	not administered	1994	still administered
Mumps	not administered	2005	still administered
Haemophilus influenza b (HIB)	not administered	2007	still administered

DTP: Diphtheria-Tetanus-Pertussis vaccine, BCG: Bacille Calmette-Guérin vaccine

Table 2. Baseline characteristics of the study population.

Year of birth		Total		6-7 years old 1999–2002		13-14 years old 1992–1995		20-44 years old 1962–1987	
Questionnaire survey									
Total	n (%)	18617	(100.0)	4510	(24.2)	4721	(25.4)	9386	(50.4)
female	n (%)	10011	(53.8)	2218	(22.2)	2275	(22.7)	5518	(55.1)
male	n (%)	8606	(46.2)	2292	(26.6)	2446	(28.4)	3868	(44.9)
Medical evaluation									
Total	n (%)	4783	(100.0)	1329	(27.8)	1321	(27.6)	2133	(44.6)
female	n (%)	2608	(54.5)	657	(25.2)	639	(24.5)	1312	(50.3)
male	n (%)	2175	(45.5)	672	(30.9)	682	(31.4)	821	(37.7)

Questionnaire-based Survey

The questionnaire was based on the translated and validated questionnaires ECRHS and ISAAC. According to ECRHS and ISAAC, the diagnosis of allergic diseases was based on assumptions of these studies described in detail in previous reports.[1] Details of the definition of the diseases are shown in the Appendix.

The responses to these survey questions were analyzed in the age groups subject to immunization, stratified by the response to the following "*Have you been vaccinated according to the Immunization Schedule?"*. We compared the incidence of allergic diseases (asthma, allergic rhinitis, atopic dermatitis (AD)) in vaccinated and non-vaccinated respondents. Due to the schedule of vaccination and the percentage of vaccinated individuals (nearly 99%), for each vaccination we adopted different criteria comparison groups. We compared the groups that had in their schedule mandatory vaccination with a group of no required vaccination.

Medical Evaluation

Allergologists diagnosed asthma according to the GINA criteria, allergic rhinitis using the ARIA criteria and AD using the Hannifin and Rajka criteria. In addition, based on the results of these outpatient assessments and skin prick test (SPT), respondents were sub-grouped with allergic asthma confirmed with SPT and allergic rhinitis confirmed with SPT. SPT was performed for 15 most common airborne allergens (*Allergopharma, Reinbek, Germany*).[1]

The above categories of diagnoses were analyzed in the age groups subject to vaccination, with respect to the following question from the outpatient survey: *Have you been vaccinated according to the Immunization Schedule?"*

From among the vaccines that the analyzed age groups were subjected to, the study considered those that were introduced into or removed from the mandatory immunization schedule for the age group from 0 to 18-year-olds between 1962 and 2002. According to these criteria, individuals vaccinated against smallpox, typhoid fever, measles, and rubella were qualified for analysis.

Every respondent who answered "Yes" to the survey question: "*Have you been vaccinated according to the Immunization Schedule"* and belonged to the age group subject to mandatory immunization between 0 and 18 years, was qualified into the group vaccinated against the evaluated diseases.

Statistical Analysis

The differences in the incidence of allergies considered in relation with immunization against rubella, measles, typhoid fever, and smallpox were expressed as odds ratio (OR) with 95% confidence intervals (95% CI). The statistical analysis was conducted with a chi-square (χ^2) test. The differences with the p value of <0.05 were considered to be statistically significant.

RESULTS

The prevalence of allergic diseases in the study population is shown in Table 3.

The association of rubella, measles, typhoid fever and smallpox preventive immunization with the prevalence of allergic diseases is shown in Table 4.

Table 3. Prevalence of allergic diseases in the study population. Data are presented as percentages.

	Age groups		
	6–7 years old	**13–14 years old**	**Adults**
Diagnosis by questionnaire			
Reported asthma	4.4	6.2	4.0
Symptomatic asthma	19.2	15.9	13.8
Symptomatic allergic rhinitis	23.7	24.6	21.0
Symptoms of rhinitis	37.8	34.5	36.0
Reported atopic dermatitis	45.9	39.1	33.7
Atopic dermatitis	5.3	4.3	3.0
Doctor's diagnosis			
Asthma	11.4	11.8	9.7
Objectively diagnosed allergic rhinitis	23.8	30.1	30.0
Objectively diagnosed atopic dermatitis	8.7	9.0	3.6
Allergic asthma	5.3	7.6	6.6
Allergic rhinitis	18.3	26.4	25.9

Table 4. Relationship between immunization status and the prevalence of allergic diseases in study group. Data are presented as OR (95% CI). Reference category is unvaccinated. Statistically significant values are shown in bold.

		Rubella	**Measles**	**Typhoid fever**	**Smallpox**
Diagnosis by questionnaire					
Reported asthma	OR	**0.68** (0.54–0.87)	1.02 (0.82–1.26)	1.00 (0.81–1.24)	0.78 (0.59–1.01)
	P	0.002	0.87	1	0.07
Symptomatic asthma	OR	**0.80** (0.66–0.97)	**0.80** (0.71–0.91)	**1.27** (1.12–1.44)	**1.21** (1.03–1.41)
	P	0.026	0.0007	0.0001	0.02
Symptomatic allergic rhinitis	OR	**0.73** (0.64–0.83)	**1.21** (1.06–1.34)	**0.83** (0.75–0.92)	0.93 (0.82–1.05)
	P	<0.0001	0.0002	0.0003	0.25
Symptoms of rhinitis	OR	**0.77** (0.68–0.87)	**1.22** (1.11–1.32)	**0.83** (0.76–0.90)	**0.89** (0.80–0.99)
	P	<0.0001	<0.0005	<0.0005	0.03
Self-reported atopic dermatitis	OR	**1.34** (1.19–1.50)	0.91 (0.84–1.0)	**1.13** (1.04–1.24)	**1.18** (1.06–1.31)
	P	<0.0001	0.05	0.005	0.003
Atopic dermatitis	OR	1.24 (0.94–1.65)	0.90 (0.71–1.14)	1.12 (0.88–1.43)	1.01 (0.74–1.36)
	P	0.1315	0.39	0.36	1
Doctor's diagnosis					
Asthma	OR	**0.67** (0.47–0.95)	0.94 (0.7–1.25)	1.05 (0.79–1.41)	0.80 (0.55–1.16)
	P	0.0238	0.66	0.7645	0.26
Allergic rhinitis	OR	**0.70** (0.55–0.89)	1.10 (0.92–1.33)	0.90 (0.74–1.08)	0.96 (0.76–1.20)
	P	0.0032	0.32	0.2716	0.73
Atopic dermatitis	OR	1.22 (0.84–1.78)	1.19 (0.74–1.90)	0.85 (0.53–1.36)	0.91 (0.52–1.61)
	P	0.3363	0.48	0.5574	0.77
Allergic asthma confirmed with SPT	OR	**0.42** (0.27–0.65)	1.17 (0.82–1.67)	0.84 (0.59–1.20)	**0.67** (0.43–1.04)
	P	<0.0001	0.42	0.3681	0.08
Allergic rhinitis confirmed with SPT	OR	**0.60** (0.47–0.77)	1.14 (0.93–1.38)	0.87 (0.71–1.05)	0.97 (0.77–1.23)
	P	<0.0001	0.21	0.1614	0.81

Immunization against Rubella

The evaluation of the relationship between vaccinations against rubella and allergies revealed lower incidence of reported asthma (OR=0.68; p=0.002), symptomatic asthma (OR=0.8; p=0.026), symptomatic allergic rhinitis (OR=0.73; p<0.0001), symptoms of rhinitis (OR=0.77; p<0.0001), in individuals vaccinated against rubella as opposed to the nonvaccinated individuals. The similar data we received for asthma (OR=0.67; p=0.02) and allergic rhinitis (OR=0.7; p=0.003) diagnosed by doctor and asthma (OR=0.42; p<0.0001) and allergic rhinitis (OR=0.6; p<0.0001) confirmed by SPT. The group vaccinated against rubella was shown to have a higher incidence of self-reported eczema (OR=1.34; p<0.0001). However, the incidence of such allergic conditions as AD diagnosed by doctor was shown to be slightly higher in the vaccinated vs. the nonvaccinated group, although the difference was not statistically significant.

Immunization against Measles

Our analysis demonstrated that the incidence of symptomatic asthma (OR=0.8; p=0.0007) was lower in the individuals vaccinated against measles vs. those nonvaccinated. Individuals vaccinated against measles were shown to have a higher risk of developing such allergic conditions as allergic rhinitis (OR=1.21; p=0.0002) and symptoms of rhinitis (OR=1.22; p<0.0005).

Immunization against Typhoid Fever

Our analysis demonstrated lower risk of symptomatic allergic rhinitis (OR=0.83; p=0.0003) and symptoms of rhinitis (OR=0.83; p<0.0005) in vaccinated individuals. We observed higher risk of symptomatic asthma (OR=1.27; p=0.0001) and self-reported eczema (OR=1.13; p=0.005) in the vaccinated vs. the nonvaccinated group.

Immunization against Smallpox

We observed lower risk of symptoms of rhinitis (OR=0.89; p=0.03) in the individuals vaccinated against smallpox vs. that in the nonvaccinated group. The risk of developing such allergic conditions as symptomatic asthma (OR=1.21; p=0.02) and self-reported eczema (OR=1.18; p=0.003) was shown to be higher in the individuals vaccinated against smallpox.

DISCUSSION

The possible effects of immunization on subsequent development of asthma and atopy remain a matter of controversy. In 1994, JAMA published a letter to editors sent by Odent et al. entitled: Pertussis vaccination and asthma: is there a link? as a response to the article by Ellis and Douglas on new vaccine production technologies.[4,13] They presented their observational study results in 448 children and concluded that relative risk of severe asthma in vaccinated against pertussis children was 5.43 (p=0.0005). Further 3 of 112 children who were nonvaccinated against pertussis but had received other vaccines were diagnosed with asthma, compared with only 1 asthma diagnosis among 91 children who had not received any vaccines – the difference was not statistically significant.[4]

Since Odent's report, there have been many studies to evaluate the relationship between allergies and immunization. Although some studies have suggested that immunization might increase the risk for atopic disease, a number of studies have found no association or have even reported a protective effect for immunization against atopy.[14-16] The focus is particularly on BCG vaccination. According to a recent published meta-analysis and the study carried out by Linehan et al., single BCG vaccination could be a protective factor for asthma.[9,10] But other reports did not confirm this observation[17,18] or found a uniform positive association between TB and allergic disease outcomes, including eczema on skin examination.[19,20]

At the same time, there was no association between BCG revaccination (a second dose of BCG) and asthma, allergic rhinitis and/or atopic eczema.[21] To date, it is unclear whether this possible association is attributable to a causal relationship, and further longitudinal studies are required. In our study, we have not assessed the association between BCG vaccination and allergies, due to the almost 100% of BCG vaccinated children in Poland.

McDonald et al. discovered a negative association between delay in administration of the first dose of whole-cell diphtheria, pertussis, tetanus immunization in childhood and the development of asthma. The association was greater with delays in all of the first 3 doses.[22] No evidence for an increased risk of wheeze or asthma in children vaccinated against pertussis compared with nonvaccinated children was found by

Spycher et al.[23] It follows that the results are inconclusive. To our knowledge, there are a few studies assessing other vaccinations.[15,16] That was the reason for taking this subject in the ECAP project.

Our cross-sectional, observational, retrospective study was designed on the basis of international epidemiological studies (ISAAC and ECRHS), which are international, multicenter and the most reliable research on the prevalence of allergic diseases in the world.[3,24] The basic tool of ECAP is a validated questionnaire, which is recognized as an objective method of diagnosis. In addition, we conducted a verification of the results by the second phase of the study - to examine outpatient. However, we should not forget, that the selection of the respondents to the outpatient examination in screening study is often biased. Sick people are more likely to engage in this type of study than healthy ones.[25] The use of two research methods - a questionnaire and examine outpatient - allowed for a maximum objectification of the results and increases the value of the merits of the ECAP project.

For ethical reasons, the only possibility to carry out research on the relationship between vaccination and the occurrence of diseases is an observational study (retrospective or prospective). In Poland, it is very difficult to design and conduct studies on the effect of preventive vaccination in children 0 to 18 years old on the incidence of allergies, because the proportion of vaccinated children exceeds 90%. Therefore, our study considered preventive vaccinations intended for children aged 0–18 that were introduced into or removed from the Polish immunization schedule within the analyzed period (1962–2002). Thus, our analysis focused on immunization against rubella, measles, typhoid fever, and smallpox. We compared the vaccinated and unvaccinated persons. Due to the schedule of mandatory vaccinations and a very high percentage of vaccinated children (nearly 99%), we had compared the respondents were born in different year periods (measles, smallpox, typhoid fever), or girls and boys (rubella). In another case, the group of unvaccinated would be too small for analysis.

The results generally demonstrated comparable incidence rates of allergic conditions in the groups vaccinated and nonvaccinated against measles, typhoid fever, and smallpox. Higher incidence rates of allergic conditions in the vaccinated groups were demonstrated only in a few cases diagnosed by questionnaire responses. We found higher risk of symptomatic asthma and self-reported eczema in vaccinated persons against typhoid fever and smallpox. In participants vaccinated against measles, we found a higher risk of symptoms of rhinitis and allergic rhinitis. At the same time, in a few incidents, we found decreased risk of rhinitis and asthma. Neither increase nor decrease in the risk of allergic conditions diagnosed based on an outpatient assessment, was demonstrated in vaccinated vs. nonvaccinated individuals. These results may be explained based on the varied degrees of sensitivity and specificity of questions serving as the basis for diagnosing the evaluated conditions. The survey questions serving as the basis for diagnosing symptomatic asthma, self-reported eczema, symptoms and allergic rhinitis were more sensitive and less specific in comparison to those for diagnosing these conditions based on objective tests conducted in an outpatient setting. These differences may also be a result of comparing the incidence of allergic conditions in different age groups, and – as our study demonstrated – the incidence rates of allergy in different age groups differed. Koppen et al. reviewed the results of studies available in the MEDLINE database on the relationship of childhood immunization with vaccines containing pertussis, measles, or tuberculosis. The authors analyzed studies in terms of their robustness and methodological adequacy (randomization, control group status, sample size). A total of 12 studies on pertussis immunization, 9 studies on measles immunization, and 8 studies on tuberculosis immunization were analyzed. The studies that were found to be methodologically adequate, demonstrated no relationship between immunization and allergies.[14]

A little different results and conclusions, we received analyzing the vaccinated and unvaccinated group against rubella. The risk of rhinitis and asthma (diagnosis by the questionnaire and medical examination) was lower in vaccinated subjects. Similar results were obtained by Mommmers et al., who analyzed the relationship between immunization status and the incidence of allergic conditions. They found lower levels of IgE in children vaccinated against rubella (OR=0.80).[15] In contrast to rhinitis and asthma, AD and self-reported eczema were more common in vaccinated people in our study.

Gruber et al., who evaluated the relationship between vaccinations administered during the first year of life and the development of AD and hypersensitivity,

Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

concluded that there was no relationship between the development of AD and the administered vaccines (rubella, diphtheria, tetanus, pertussis, polio, *Haemophilus influenza b* (HIB) infection, hepatitis B, measles, mumps, chickenpox, tuberculosis, meningococcal and pneumococcal infections). The study also failed to show a relationship between the administered vaccines and IgE level elevation in the second year of life.[16] Our findings could be a result of the higher AD and lower asthma and rhinitis incidence in females compared to that in males, as demonstrated in the ECAP study,[1] so it requires further detailed research and clarification.

In conclusion, our cross-sectional study using the ISAAC and ECRHS standards generally showed no causal relationship between immunization and the incidence of allergic conditions. We observed only slight higher risk of symptomatic asthma and self-reported eczema in vaccinated persons against typhoid fever and smallpox. In respondents vaccinated against measles, we found a higher risk of symptoms of rhinitis and allergic rhinitis. Rhinitis and asthma were negatively associated with typhoid fever and smallpox vaccines. Rubella vaccination reduces the risk of asthma and rhinitis. The risk of self-reported eczema was increased in vaccinated against rubella, typhoid fever, and smallpox. Further study of the relationship between the possible association of rubella, measles, typhoid fever and smallpox preventive immunization with the incidence of allergic diseases should be carried out.

REFERENCES

1. Sybilski AJ, Raciborski F, Lipiec A, Tomaszewska A, Lusawa A, Samel-Kowalik P, et al. Epidemiology of atopic dermatitis in Poland according to Epidemiology of Allergic Disorders in Poland (ECAP) study J Dermatol 2015; 42(2):140-7.
2. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. CMAJ 2009; 181(9):E181-90.
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006; 368(9537):733-43.
4. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: is there a link? JAMA 1994; 272(8):592–3
5. Sánchez-Solis M, García-Marcos L. Do vaccines modify the prevalence of asthma and allergies? Expert Rev. Vaccines 2006; 5(5):631-40.
6. Spycher BD, Silverman M, Egger M, Zwahlen M, Kuehni CE. Routine Vaccination Against Pertussis and the Risk of Childhood Asthma: A Population-Based Cohort Study. Pediatrics 2009; 123(3):944-50.
7. Arnoldussen DL, Linehan M, Sheikh A. BCG vaccination and allergy: A systematic review and meta- analysis. J Allergy Clin Immunol 2011; 127(1): 246-53
8. Datau EA, Mewengkang H, Matheos JC, Purnawan I, Wibisono M, Wongdjaja K, et al. Clinical Efficacy and Laboratory Improvement of Bacillus Calmette-Guerin Vaccination on Adult Atopic Asthma. World Allergy Organ J 2008; 1(4):63-9.
9. El-Zein M, Parent ME, Benedetti A, Rousseau MC. Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. Int J Epidemiol 2010; 39(2):469-86.
10. Linehan MF, Frank TL, Hazell ML, Francis HC, Morris JA, Baxter DN, et al. Is the prevalence of wheeze in children altered by neonatal BCG vaccination? J Allergy Clin Immunol 2007; 119(5):1079-85.
11. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? Pediatr Allergy Immunol 2005; 16(3):193–200.
12. Czarkowski MP, Cielebąk E, Kondej B, Staszewska E Biuletyn Szczepienia Ochronne, Warszawa: PZH, 1999-2010.
13. Ellis RW. Douglas RG. New vaccine technologies. JAMA 1994; 271(12):929-31.
14. Koppen S, de Groot R, Neijens HJ, Nagelkerke N, van Eden W, Rümke HC. No epidemiological evidence for infant vaccinations to cause allergic disease. Vaccine 2004; 22(25-26):3375-85.
15. Mommers M, Weishoff-Houben M, Swaen GM, Creemers H, Freund H, Dott W, et al. Infant Immunization and the Occurrence of Atopic Disease in Dutch and German Children. Pediatr Pulmonol 2004; 38(4):329-34.
16. Grüber C, Warner J, Hill D, Bauchau V. EPAAC Study Group. Early atopic disease and early childhood immunization-is there a link? Allergy 2008; 63(11):1464-72.
17. Arnoldussen DL, Linehan M, Sheikh A. BCG vaccination

and allergy: a systematic review and meta-analysis. J Allergy Clin Immunol 2011; 127(1):246-53.
18. Balicer RD, Grotto I, Mimouni M, Mimouni D. Is childhood vaccination associated with asthma? A meta-analysis of observational studies. Pediatrics 2007; 120(5):e1269-77.
19. Flohr C, Nagel G, Weinmayr G, Kleiner A, Williams HC, Aı¨t-Khaled N, et al. Tuberculosis, bacillus Calmette–Gue´ rin vaccination, and allergic disease: Findings from the International Study of Asthma and Allergies in Childhood Phase Two. Pediatr Allergy Immunol 2012; 23(4):324–31.
20. Miyake Y, Arakawa M, Tanaka K, Sasaki S, Ohya Y. Tuberculin reactivity and allergic disorders in schoolchildren, Okinawa, Japan. Clin Exp Allergy 2008; 38(3):486-92.
21. de Andrade CR, da Cunha SS, Alvim CG, Fontes MJ, Bedran R, Binato HA, et al. Does BCG revaccination protect against the development of asthma? Respir Med 2013; 107(2):317-9.
22. McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. J Allergy Clin Immunol 2008; 121(3):626-31.
23. Spycher BD, Silverman M, Egger M, Zwahlen M, Kuehni CE. Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study. Pediatrics 2009; 123(3):944-50.
24. Variations in the prevalence of respiratory symptoms, self-reported asthma, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; 9:687-95.
25. Burney P. The changing prevalence of asthma? Thorax 2002; 57(Suppl 2):36-9.