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Relation Between Vaccination and Allergic Diseases in Preschool Children in Everyday Primary Care Practice

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TABLE OF CONTENTS

ABBREVIATIONS 7
INTRODUCTION 9
1. MATERIALS AND METHODS 13
1.1 Phase I: Analysis of the Primary Health Care Institution's Statistical Database……...13
1.1.1 Differences in the Scope of Vaccination of Allergic and Non-Allergic Children up to 2 Years and up to 6 Years of Age..... 14
1.1.2 Links of Diagnosed Allergic Diseases with the Time of Each Vaccine Inoculation and the Number of Doses Inoculated 15
1.2 Phase II: Analysis of Medical Histories. Case-Control Study... 16
1.2.1 Analysis of Reactions after Vaccination 16
1.2.2 Vaccination as a Risk Factor of Allergic Diseases…….. 17
2. STATISTICAL ANALYSIS 19
3. RESULTS..... 20
3.1 Phase I: Analysis of the Primary Health Care Institution Statistical Database 20
3.1.1 Dynamics of Diagnosed Allergic Diseases 20
3.1.2 Scope of Vaccination: Vaccinated, Non-Vaccinated, and Partially Vaccinated Children..... 21
3.1.3 Association between the Diagnoses of Allergic Diseases and Vaccination Coverage according to the NIPC until 2 Years of Age 23
3.1.4 Association between Vaccination according to the National Immunoprophylaxis Calendar under 7 Months of Age and Diagnosed Allergic Diseases under 6 Years of Age..... 26

3.1.5 Links of Diagnosed Allergic Diseases with the Time of Each Vaccine Inoculation and Number of Doses Inoculated 28
3.2 Phase II: Analysis of Medical Histories. Case-Control Study.. 35
3.2.1 Frequency and Nature of Adverse Reactions to Vaccination, Recorded in Medical Histories, in Children under 24 Months of Age 35
3.2.2 Association between Early Life Factors, Including Vaccination, and Allergic Diseases 37
4. DISCUSSION..... 45
4.1 Discussion of the Phase I results 45
4.2 Discussion of the Phase II Results..... 50
CONCLUSIONS 55
RECOMENDATIONS 56
LITERATURE 57
PUBLICATIONS 64
ORAL COMMUNICATIONS AND ABSTRACTS IN INTERNATIONAL CONFERENCES AND MEETINGS..... 65
BIOGRAPHY..... 66

ABBREVIATIONS

AB	Antibiotics
AD	Atopic dermatitis
AR	Allergic rhinitis
BA	Bronchial asthma
PCP	Primary care practitioner
BCG	Tuberculosis vaccine: *Bacillus Calmette–Guérin*
CCDA	Centre of Communicable Diseases and AIDS
DTaP-IPV-Hib, DTaP	Diphtheria, tetanus, acellular pertussis – inactivated poliomyelitis – *Haemophilus influenzae b* vaccine
DTaP1	First dose of the DTaP-IPV-Hib vaccine
HB	Hepatitis B vaccine
MMR	Measles, mumps, rubeola vaccine
NIPC	National Immunoprophylaxis Calendar
PCP	Primary care practitioner
SPT	Skin prick test

INTRODUCTION

The rise in the prevalence of allergic diseases worldwide during the recent decades is a concerning issue. The influence of genetic factors on the development of allergic diseases (bronchial asthma, allergic rhinitis, atopic dermatitis) is unquestionable. The growth of allergic sensitization and allergic diseases in society has been actively analysed in the context of environmental factors (1). The first vaccines fall in the period of the "window of opportunity" for the prevention of allergic diseases – it lasts from conception to the sixth month of life (2–4). As a result, immunization, as a planned target effect on a particular response of the immune system during infancy and as an additional risk factor for the development of allergic diseases, raise the interest of scientists and the public.

The methodologies of studies that analyse the link between vaccination and allergic diseases are different and difficult to compare; the conclusions are controversial as well (5–10). During the analysis of the link between vaccination and allergic diseases, a hypothesis has been made that vaccination may disturb the balance of cytokines and direct the response of the immune system toward T_H2 and, at the same time, stimulate the excretion of immunoglobulin E (IgE), including the progress of reactions associated to it, to usually harmless environmental stimuli (allergens) (11, 12). This hypothesis was refuted, and evidence was provided that vaccination affects a specific part of the immune system and leads only to the production of cytokines related to the specific vaccine that has no significant effect on the development of allergies or atopy (13).

Although during the recent years the focus on vaccination of allergic children has increased across the global scholarly literature, this problem still lacks sufficient attention in Lithuania. Physicians and parents still have doubts as to whether allergic diseases that have manifested shortly after vaccination or coincided in its time are related to the vaccination or not. The frequency of the registered adverse events after vaccination in Lithuania is not higher than in other countries, but there still is some fear that allergic children have a higher risk of side effects after vaccination, and this may lead to untimely and incomplete vaccination (14). There are no

contraindications for the vaccination of allergic children, but the absence of clear guidelines at the national level allows the uncertainty and beliefs – not substantiated by scientific evidence – to flourish and permits the spread of fake news.

Relevance and Scientific Novelty

According to the position paper of the European Academy of Allergists and Clinical Immunologists (2017), there still is a lack of data from prospective and retrospective studies on the potential impact of vaccines on the development of allergies. There is a shortage of validated studies or tests allowing to predict and define the clinical expression of the adverse reactions to vaccines (5, 15, 16). There is also a lack of research on how immunization time is related to the development of allergic diseases. The changing composition of the vaccines and their production processes that are being improved prompt researchers to re-examine their safety, efficacy, and links with various diseases, including allergic ones (17).

The relation between vaccination and allergic diseases in Lithuania was analysed only in one prospective study of a small sample and one retrospective study of statistical data (18, 19). There were no studies in Lithuania that analysed whether the frequency and severity of post-vaccination reactions are the same among children with allergic diseases and children without allergic diseases. There are not many such studies in the world. However, they are necessary and relevant in order to assess and define the safety of the immunization of allergic children.

Our work is a "real-life" study that reveals the links between vaccination and allergic diseases diagnosed by primary health care physicians. Real-life studies reflect everyday issues and allow scholars to look into the problems of clinical practice and search for solutions. We have established that atopic dermatitis, diagnosed by a general practitioner or paediatrician during infancy, is associated with the disorders of the routine immunization plan. This study is the first analysis of the links between vaccination and allergies in Lithuania that uses a digital statistical database of a primary health care

institution. On the global scale, digital databases are identified as a potential tool for the recording and analysis of the adverse events of vaccination.

The symptoms that manifest shortly after vaccination, similar to those associated with allergic diseases, can be directly linked to the vaccination; therefore, the precise definition, registration, and testing of these events are of paramount importance (20).

Primary prevention of infectious diseases plays a crucial role in children's health. Allergic children deserve access to the same publicly recommended immunizations as non-allergic patients. Our work has added insights into the ongoing discussion about the risks of allergy development due to vaccination. A comprehensive analysis of the relationship between vaccination and allergic diseases in outpatient practice conducted in our study has revealed how different and complementary to each other outcomes for the same population can be.

Aim of the Study

To thoroughly analyse the links between vaccination and allergic diseases diagnosed under real working conditions in a primary healthcare facility during the pre-school age, and to assess the safety of vaccinating children diagnosed with atopic dermatitis.

Objectives

1. Evaluate the overall frequency of allergic diseases diagnosed at a primary health care institution among vaccinated, partially vaccinated, and non-vaccinated children according to a routine immunization schedule.
2. Analyse the links between atopic dermatitis, allergic rhinitis, or bronchial asthma, diagnosed by primary care practitioners and specialists, and the disorders of a routine immunization schedule.
3. Analyse the links between the start of vaccination during the first 6 months of life and the allergic diseases diagnosed under 6 years of age.

4. Compare the frequency of adverse reactions after vaccination according to the National immuno-prophylaxis calendar among children diagnosed with atopic dermatitis and children with no diagnosed allergic diseases.
5. Determine whether vaccination is a possible independent factor significantly related to the development of allergic diseases.
6. Determine what other factors, acting in parallel with vaccination, are associated with the development of allergic diseases.

Propositions to be Defended

1. Allergic diseases are not more frequently diagnosed in fully vaccinated children in comparison to non-vaccinated or partially vaccinated children.
2. The vaccination of children diagnosed with atopic dermatitis is safe.
3. Routine immunization is not independently associated with the frequency of diagnosing allergic diseases in everyday primary healthcare practice.

1. MATERIALS AND METHODS

The study was conducted from 2015 to 2017 in the Central Polyclinic of Vilnius – partner of the Clinic of Children's Diseases at the Institute of Clinical Medicine of the Faculty of Medicine of Vilnius University.

An authorization to conduct the study was received from the Vilnius Regional Biomedical Research Ethics Committee (09-01-2015 No. 158200-15-757-284) with a supplement to the authorization (04-07-2017 No. 158200-757-PP1-22).

1.1 Phase I: Analysis of the Primary Health Care Institution's Statistical Database

Statistical data about 1294 children born in 2009, retrieved from the polyclinic's database "MEDIS," were analysed. The following data about the research subjects were collected: month of birth, gender, diagnoses of allergic diseases determined by primary care practitioners and physicians-specialists before the children had reached six years of age; periods of their determination (up to 1 year, from 1 to 2 years, from 2 to 6 years, and overall – from birth to 6 years); the vaccination plan (inoculated vaccines, the time of inoculation, and doses), number of visits to PSP and specialists (paediatric pulmonologist, allergist, otorhinolaryngologist). Visits to physicians were picked according to codes of health care specialist services. Diagnoses were picked according to the codes of ICD-AM-10. Only data that have been included in statistical forms of medical histories were retrieved from the electronical database.

Allergic Diseases

Based on the diagnostic codes specified in the protocols for "Diagnosis and Treatment of Children's Atopic Dermatitis," "Diagnostics and Treatment of Children's Allergic Rhinitis," "Diagnostics and Treatment of Children's Bronchial Asthma" of Lithuania (21–23), diagnoses of allergic diseases were selected from the CP database according to the International

Classification of Diseases (ICD-10), diagnosed by physicians under actual working conditions of the primary health care institution. The following disease codes have been selected: atopic dermatitis (L20.8, L20.9), asthma (J45.9, J45.0, J45.1, J45.8), and allergic rhinitis (J30.1, J30.2, J30.3, J30.4). Diagnoses of atopic dermatitis have been analysed in both of such cases: diagnosed by PCP or verified by an allergist; asthma – only if verified by a paediatric pulmonologist; allergic rhinitis – verified by an allergist or otorhinolaryngologist. The diseases with the asthma code (J45.9) in patients under one year of age in our study were named the wheezing diseases. All specialists had consulted children at the same polyclinic after referral from PCP. In order for the study to meet the actual working conditions of the primary health care institution as best as possible, we did not recheck the diagnoses determined by physicians.

1.1.1 Differences in the Scope of Vaccination of Allergic and Non-Allergic Children up to 2 Years and up to 6 Years of Age

In order to assess the differences in the vaccination of allergic and non-allergic children, we checked whether children diagnosed with allergic diseases (atopic dermatitis, allergic rhinitis, and bronchial asthma) are in general different from children who did not have these diseases based on the number of doses of vaccines inoculated before 2 years of age and before 6 years of age. We subsequently analysed whether vaccination with individual vaccines according to the routine immunization schedule is related to the development of allergic diseases (AD, AR, BA) from birth to 6 years of age.

Children born in 2009 were vaccinated according to the Lithuanian Children's Prophylactic Vaccination Calendar, which was in force at that time based on the National Immunoprophylaxis Program for 2009–2013 (24). According to it, all children in CP were vaccinated with vaccines supplied in a centralized manner: BCG (BCG, SSI, Denmark) – within the first 24 hours, HB (Engerix B, GSK) – 2–3 days, 1 month, and 6-months-old, DTaP-IPV-Hib (Infanrix-IPV + Hib, GSK) – 2, 4, 6, and 18 months, MMR (Priorix, GSK) – 15–16.5 months.

According to the general scope of vaccination, patients were classified into groups. (1) Fully vaccinated – children who completed the vaccination schedule before the age of 2 years: one dose of the tuberculosis (BCG) vaccine, three doses of the hepatitis B vaccine (HB1, HB2, HB3), four doses of the DTaP-IPV-Hib vaccine, as well as first dose of the measles, mumps, and rubella vaccine (MMR1). (2) Partially vaccinated: before 2 years of age – children vaccinated according to the schedule but not inoculated with all vaccines specified in the calendar before 2 years of age. (3) Non-vaccinated children: not vaccinated with any of the state-reimbursed vaccines according to the immunization calendar before 2 years of age.

Respectively, children were classified based on receiving vaccination under 6 years of age.

1.1.2 Links of Diagnosed Allergic Diseases with the Time of Each Vaccine Inoculation and the Number of Doses Inoculated

Number of Doses of Vaccine Received before 7 Months of Age

In order to evaluate the links between the disorders of the routine immunization schedule under 7 months of age and allergic diseases, the population was analysed for each vaccine separately. There were 36 non-vaccinated children with BCG. Depending on the received HB vaccine doses, the children were divided into groups of those completely vaccinated with three doses of HB, partially vaccinated, and non-vaccinated with HB under 7 months of age. According to the inoculated doses of the DTaP-IPV-Hib vaccine, children were divided as follows: completely vaccinated – received all 3 doses of the vaccine; partially vaccinated – received one or two doses over the same period; non-vaccinated – did not receive any dose of the DTaP-IPV-Hib vaccine before 7 months of age.

Starting Time of Vaccination

According to the vaccination with the BCG vaccine, the population of the research subjects was divided into groups as follows: vaccinated on time

(at the maternity hospital) or with a 1-month delay. According to the vaccination with the HB vaccine: the group of children who had received the first dose on time (within the first day) and those vaccinated 1 month later. According to the vaccination with the DTaP-IPV-Hib vaccine: vaccinated with the first dose on time (at 2 months of age), with a 1-month delay, i.e., at 3 months of age, and with the vaccination delayed until 4–6 months of age.

1.2 Phase II: Analysis of Medical Histories. Case-Control Study

The medical histories of 289 of children born in 2009 who were diagnosed by specialists with allergic diseases (atopic dermatitis, allergic rhinitis, allergic asthma) were selected from the database (relying on the ICD-AM-10 classification). For the control group, 269 children who had no recorded allergic diseases were selected. A total of 558 medical histories were selected for a retrospective case-control study. The selection of the research sample subjects was based on the availability and completeness of data and the presence of a clear diagnosis of an allergic disease verified by a specialist.

1.2.1 Analysis of Reactions after Vaccination

In order to determine whether vaccination is equally safe for allergic and non-allergic children, we compared the frequency of recorded reactions after vaccination in children with atopic dermatitis diagnosed by an allergist (n=250) and in children who had no diagnosis of any allergic disease (n=269).

Only children with atopic dermatitis with or without diagnosis of asthma or allergic rhinitis were included into analysis. We decided not to include children who have been diagnosed only with allergic rhinitis or asthma, because the period of experienced post-vaccination reactions occurs earlier than the manifestation of these diseases, as opposed to the atopic dermatitis prevalent during the first year of life, when the vaccination is most intense.

The following definition of an adverse reaction after vaccination was used: it is a temporary or permanent health condition disorder that causes changes in physical signs, symptoms and/or laboratory parameters, that commence after immuno-prophylaxis and is believed to be caused by it.

1.2.2 Vaccination as a Risk Factor of Allergic Diseases

We intended to examine whether, in addition to already known factors (allergic anamnesis of the family, harmful environmental effects, factors affecting the development of the foetus in the uterus and during the first months of life, etc.), immunization could be associated with the risk of allergic diseases diagnosed in a primary health care facility. We included into our analysis the method of delivery (natural or SC), birth weight, breastfeeding and its duration, number of siblings, prescription of antibiotics (prescription time, number of prescribed antibiotic courses in different age periods), the mother's age, the presence of other allergic diseases.

Research subjects were classified into groups according to the allergic diseases: AD, BA, and AR. People who were never diagnosed with any allergic disease were deemed non-allergic.

General scheme of the study is shown in Figure 1.

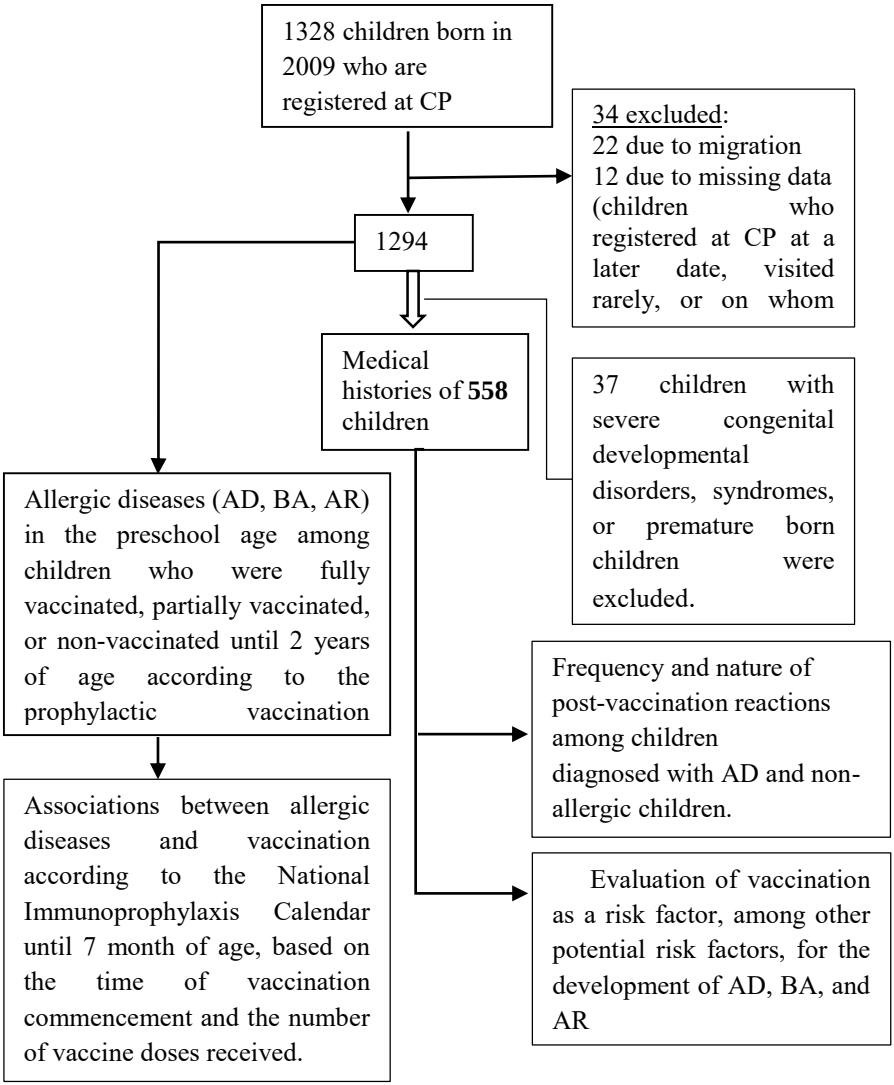

Figure 1. General scheme of the study.

2. STATISTICAL ANALYSIS

Statistical data analysis was performed using the computer software SPSS (21.0 version) statistical data analysis package (IBM, USA) and Microsoft Excel 2013.

The distribution of the data of quantitative variables was tested by using the Shapiro-Wilk test. Differences in the averages of the independent variables distributed normally were measured by using the t test, or the Mann-Witney U test, if the assumption of normality was not met. Averages ± standard deviation were calculated for quantitative variables distributed according normal distribution; in other cases, the median with a quartile difference was calculated.

The spread of the categorical variable frequency was compared using the Chi-square or Fisher's exact tests. The odds ratio and the 95% confidence interval were calculated for the analysis of binary variables.

The possible influence of factors, its size, and significance for the diagnosis of allergic diseases were initially analysed in models of univariate binary logistic regression. Models of multivariate binary logistic regression were developed in order to identify independent prognostic factors as well as the magnitude and significance of their impact on the diagnosis of allergic diseases. The odds ratio (OR) was calculated with 95% of the confidence interval (CI).

A p-value of <0.05 was considered as statistically significant.

3. RESULTS

3.1 Phase I: Analysis of the Primary Health Care Institution Statistical Database

According to a specially formulated request by the researchers, data of 1328 children who were born in 2009 and registered at the polyclinic were retracted by CP Technology and Statistics department specialists. Data of 1294 patients who met the inclusion criteria were analysed. The cohort of the research subjects consisted of 650 girls and 644 boys.

At least one allergic disease – atopic dermatitis, asthma or allergic rhinitis – was diagnosed at least once in 417 (32%) children before 6 years of age. All three allergic diseases affected 30 (2.3%) children, two were diagnosed in 84 (6.5%) children, and 303 (23.5%) children were diagnosed with one of these diseases.

The predominant final diagnosis in the CP database was atopic dermatitis, confirmed by an allergist in 21.0% (n=272) of children under 6 years of age. The second most frequent final diagnosis was bronchial asthma – 14.2%. Allergic rhinitis has been diagnosed in 9.6% of children. These diagnoses were collected only from the records of specialists (paediatric pulmonologists, allergists, and otorhinolaryngologists). Atopic dermatitis in the pre-school age was diagnosed by a PCP at least once in 357 (27.6%) children, in which 73.1% (n = 272) of cases were confirmed by an allergist.

3.1.1 Dynamics of Diagnosed Allergic Diseases

PCPs have diagnosed atopic dermatitis in 205 (15.5%) of children in infancy. An allergist confirmed this diagnosis in 126 (61.5% of PCP cases) of children younger than 1 year of age. In the second year of life, a PCP had diagnosed atopic dermatitis in 123 children, and an allergist had confirmed 116 new AD cases during that year (Table 1). Table 1 shows the dynamics in the diagnoses of bronchial asthma and allergic rhinitis diagnosed by specialists at different age periods as well.

Table 1. The frequency of diagnoses of allergic diseases in different age periods.

Events of atopic diseases	No. of cases	%
Atopic dermatitis until 6 y by a PCP	**357**	**27.6**
Until 1 year	**205**	**57.4**
1–2 years	**123**	**34.5**
2–6 years	**29**	**8.1**
AD diagnosed by an allergist until 6 y	**272**	**21.0**
Until 1 year	**126**	**46.4**
1–2 years	**116**	**42.6**
2–6 years	**30**	**11.0**
Asthma until 6 years	**184**	**14.2**
Wheezing illness until 1 y of age	**11**	**6.0**
1–2 years	**60**	**32.6**
2–6 years	**113**	**61.4**
Allergic rhinitis	**124***	**9.6**
Allergic rhinitis until 1 year	**0**	**-**
1–2 years	**14 (8)***	**11.3**
2–6 years	**110**	**88.7**

*Starting from the 2nd year of life, 8 from 14 children with allergic rhinitis were proved to have a disease, and 6 were neglected. Therefore, the general number of allergic rhinitis from the database during the first six years of life is 124, although only 118 of children had it finally confirmed.

3.1.2 Scope of Vaccination: Completely Vaccinated, Non-Vaccinated, and Partially Vaccinated Children

We evaluated the overall vaccination coverage according to the NIPC in the study population up to 2 years of age and up to 6 years of age. Until 2 years of age, there were 17.6% of children who were partially vaccinated or

non-vaccinated (Figure 2), but the proportion of such children up to 6 years of age decreased to 6.2% (Figure 3).

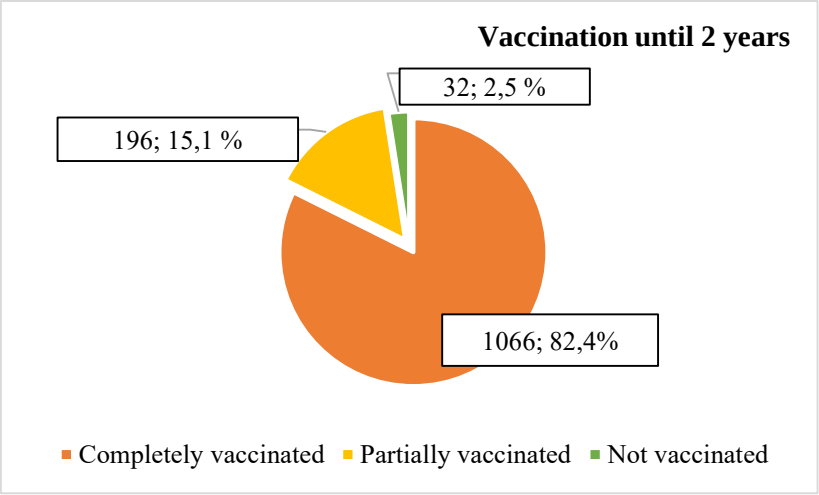

Figure 2. Vaccination until 2 years of age.

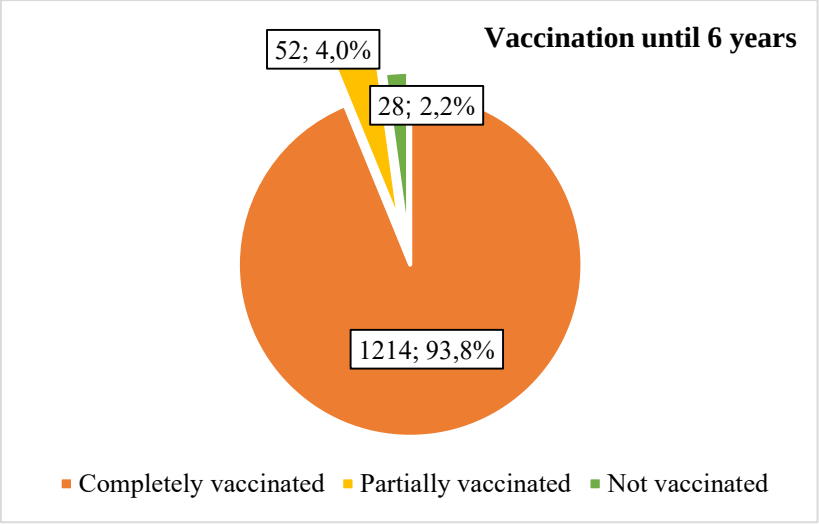

Figure 3. Vaccination until 6 years of age.

The relative majority of specialist-confirmed diagnoses of all analysed allergic diseases over the period of 6 years has been among the non-vaccinated children until 2 years of age. However, comparing all three groups of children (completely vaccinated, non-vaccinated, and partially vaccinated according to NIPC), the overall frequency of diagnosed allergic diseases did not differ significantly ($p > 0.05$ among each group) (Figure 4).

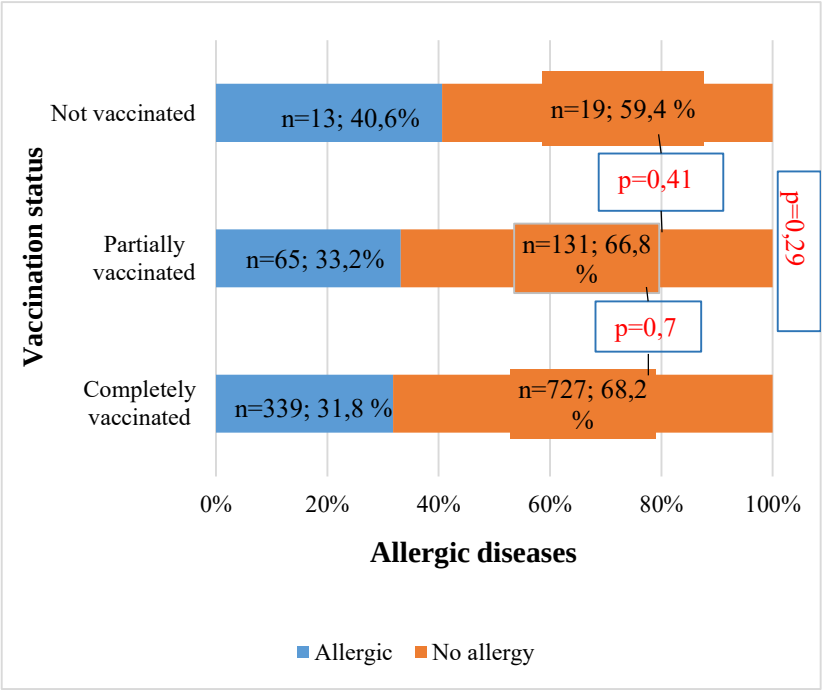

Figure 4. The frequency of allergic diseases in the final statistical data of the digital databases of clinics among completely vaccinated, partially vaccinated, and non-vaccinated children until 2 years of age.

3.1.3 Association between the Diagnoses of Allergic Diseases and Vaccination Coverage according to the NIPC until 2 Years of Age

The total number of allergic diseases among completely vaccinated, non-vaccinated, and partially vaccinated children have no significant differences,

but we identified certain differences when analysing each allergic disease individually. Of the 196 children who were partially vaccinated before the age of 2, 21.9% (n = 43) were diagnosed with AD by a PCP during their first year of life. When compared to the group of completely vaccinated children, AD before 1 year of age was diagnosed in 14.4% ($p = 0.008$). And up until 6 years of age, respectively, an AD diagnosis was determined in 36.2% of partially vaccinated and 25.8% of completely vaccinated children ($p = 0.003$). PCPs and allergists have diagnosed AD in non-vaccinated children more frequently at the age of 2–6 years, but this group did not differ statistically significantly from partially vaccinated or completely vaccinated children. The frequency of other diseases diagnosed among the fully vaccinated, non-vaccinated, and partially vaccinated children had no statistically significant differences (Table 2).

Table 2. The proportions of separate allergic diseases between children who were non-vaccinated, partially vaccinated, and completely vaccinated until 2 years of age.

Diagnosis	Non-vaccinated	Partially vaccinated	Completely vaccinated	p value
No. of children	32	196	1066	
	YES (%)/No	YES (%)/No	YES (%)/No	
Atopic dermatitis by PCP				
Until 6 years	11 (34.4%) /21	71 (36.2%) /125*	275(25.8%) /791*	0.008
Until 1 year	8 (25.0)/24	43 (21.9) /153**	154 (14.4) /912**	0.016
1–2 years	8 (25.0)/24	35(17.9)/161	167 (15.7)/899	0.29
2–6 years	5 (15.6)/ 27***	19 (9.7)/176	76(7.1)/991 ***	0.09
Atopic dermatitis by allergist				
Until 6 years	10(31.3)/22	46 (23.5) /150	216(20.3) /850	0.21
Until 1 year	3 (9.4)/29	22(11.22)/ 174	101 (9.5)/965	0.75
1–2 years	7 (21.9)/25	24(12.2)/ 172	133(12.5)/933	0.28
2–6 years	4 (12.5)/28	12 (6.1)/184	59 (5.5)/1007	0.25
Bronchial asthma				
Until 6 years	1 (3.1)/31	31(15.8)/165	152(14.3)/914	0.16
Wheezing illness until 1 year	0/32	3 (1.5)/192	8 (0.8)/1057	-
BA at 1–2 years	1(3.1)/30	10 (5.1)/183	50 (4.7)/1016	0.031
BA at 2–6 years	3 (9.4)/29	23(11.7)/172	132(12.4)/934	0.28
Allergic rhinitis				
Until 6 years	3 (9.4)/29	19 (9.7)/177	102 (9.6)/964	0.98
1–2 years	1(3.1)/30	2 (1.0)/192	11 (1.0)/1055	0.012
2–6 years	3 (9.4)/29	18 (9.2)/177	96 (9.0)/970	0.99

AD until 6 years was diagnosed by a PCP statistically significantly more often in partially vaccinated children than in completely vaccinated children until 2 years of age (*p=0.003). An AD diagnosis until 1 year of age by a PCP was more often made in the partially vaccinated group (**p=0.008). In the age group of 2–6 years, AD was diagnosed by a PCP more often in non-vaccinated than in completely vaccinated children (***p=0.07).

The links between allergic diseases and each vaccine separately were analysed further. The scope of vaccination of children under 2 years of age

not with all vaccines was 90%, but children at six years of age had been given at least 95% of the NIPC's coverage. Based on the data belonging to the Lithuanian Department of Statistics, vaccination coverage with individual vaccines according to the NIPC in 2009–2010 at CP did not differ from the general Lithuanian data.

3.1.4 Association between Vaccination according to the National Immunoprophylaxis Calendar under 7 Months of Age and Diagnosed Allergic Diseases under 6 Years of Age

The number of children based on vaccination time and the number of doses given with every vaccine that should be inoculated until the 7th month are shown in Table 3.

Table 3. Vaccination starting time and number of vaccine doses received.

Vaccine	No. of children	%
BCG		
BCG vaccination time	1294	
On time	1157	89.4
During the first month	92	7.1
Later (2–15 months)	9	0.7
Non-vaccinated	36	2.8
HB		
Doses of HB received until the 7th month	1238	
Completely vaccinated (3 doses)	1014	78.4
Partially vaccinated (1–2 doses)	224	17.3
Non-vaccinated:	56	4.3
Not until the 7th month, but vaccinated later	20	35.7
Never vaccinated	36	64.3
Time of the first HB dose	1258	
On time	1201	95.5
During the first month of life	40	3.2
From the second month	17	1.3
DTaP-IPV-Hib		
Doses of DTaP-IPV-Hib received until the 7th month		
Completely vaccinated (3 doses)	1016	78.5
Partially vaccinated	214	16.5
1 dose	52	24.3
2 doses	162	75.7
Non-vaccinated	64	5.0
Until the 7th month	25	39.0
Never vaccinated	39	61.0
Time of the 1st DTaP-IPV-Hib dose:	1230	95.0
On time	851	69.2
Slightly delayed	324	26.3
Delayed	55	4.5

3.1.5 Links of Diagnosed Allergic Diseases with the Time of Each Vaccine Inoculation and Number of Doses Inoculated

We found that children who were inoculated with the BCG vaccine one month later were diagnosed with atopic dermatitis by an allergist 2.83 times more often at the age of 2–6 years than those vaccinated on time (p=0.03). BCG inoculation time was not significantly linked to the incidence of asthma and allergic rhinitis (Table 4).

Children whose vaccination with the first dose of the hepatitis B vaccine was delayed by a month were diagnosed with a case of asthma 2.3 times more frequently (p = 0.02) (Table 5). The increase in the chance of allergic rhinitis with respect to the time of vaccination in this age group was statistically insignificant.

We established that atopic dermatitis was diagnosed by PCPs 2.2 times more often in the group of children who had not been vaccinated with the HB vaccine than children who had received all 3 doses of the vaccine (p=0.02). The group of children under one year of age stood out: OR 2.57 (95% CI: 1.24-5.34), p=0.01. This tendency was also seen in the case of AD diagnosed by an allergist in children of 1 to 2 years of age: the diagnosis of atopic dermatitis was relatively more frequent among non-vaccinated children (p=0.03) (Table 6).

There was no difference in the relative frequency of atopic dermatitis between children in the analysed age groups vaccinated with DTaP1 on time and those vaccinated one month later. However, in general, asthma in the pre-school age was diagnosed more frequently in the group of children vaccinated with a one-month delay: OR 0.64 (95% CI: 0.43-0.95), p = 0.03. The frequency of allergic disease diagnosing did not change when comparing the group with an even further delayed start of DTaP vaccination to the children vaccinated on time (Table 7).

In the group of partially vaccinated children, the frequency of AD diagnosed by a PCP (OR 1.53 (95% CI: 1.05-2.23); p = 0.03), and the wheezing disease (J45.9) frequency (OR 4.02 (95% CI: 1.22-13.29); p = 0.01) in the group of children younger than one year of age, was statistically significantly higher in comparison to completely vaccinated children.

Atopic dermatitis, diagnosed by an allergist, was relatively more prevalent in the group of partially vaccinated children under 1 year of age (OR 1.24 (95% CI: 0.77-1.99), but no significant difference from completely vaccinated children was found (p = 0.38) (Table 8).

Table 4. Distribution of the diagnosed atopic diseases in different age periods according to BCG vaccination timing and fact

	BCG on time	**BCG 1 month later**	**OR (95% CI)**	***p value***	**Non-vaccinated BCG**	**OR (95% CI)**	***p value***
Number of children Overall: 1285	1157 (90.0%)	92 (7.2%)			36 (2.8%)		
Diagnosis of allergic disease	n (%)	n (%)	1 month later vs. on time		n (%)	Non-vaccinated vs. vaccinated on time	
AD 0–6 years PCP overall	316 (27.3)	28 (30.4)	1.16 (0.73-1.45)	*0.52*	12 (33.3)	1.33 (0.66-2.69)	*0.43*
Until 1 year	177 (15.3)	19 (20.7)	1.44 (0.85-2.45)	*0.17*	9 (25.0)	1.85 (0.85-3.99)	*0.11*
1–2 years	114 (9.9)	6 (6.5)	0.64 (0.27-1.49)	*0.30*	2 (5.6)	0.54 (0.13-2.27)	*0.39*
2–6 years	25 (2.2)	3 (3.3)	1.53 (0.45-5.15)	*0.49*	1 (2.8)	1.29 (0.17-9.82)	*0.80*
AD 0–6 years allergist	239 (20.7)	21 (22.8)	1.14 (0.68-1.89)	*0.62*	11 (4.4)	1.69 (0.82-3.48)	*0.15*
Until 1 year	112 (9.7)	11 (12.0)	1.27 (0.66-2.45)	*0.48*	3 (8.3)	0.85 (0.26-2.81)	*0.79*
1–2 years	104 (9.0)	5 (5.4)	0.58 (0.23-1.47)	*0.25*	6 (16.7)	2.03 (0.82-4.98)	*0.12*
2–6 years	23 (2.0)	5 (5.4)	2.83 (1.05-7.64)	***0.03***	2 (5.6)	2.90 (0.66-12.8)	*0.14*
Asthma 0–6 years overall	167 (14.4)	13 (14.1)	1.02 (0.61-1.72)	*0.94*	2 (5.6)	2.60 (0.67-10.01)	*0.13*
Wheezing illness until 1 y.	11 (1.0)	0 (0)	-	*0.35*	0 (0)	-	*0.56*
1–2 years	57 (4.9)	5 (5.4)	0.91 (0.37-2.21)	*0.83*	0 (0)	-	*0.17*
2–6 years	101 (8.7)	8 (8.7)	1.00 (0.50-1.20)	*0.99*	2 (5.6)	1.57 (0.40-6.12)	*0.50*
AR 0–6 years overall	107 (9.2)	14 (15.2)	0.61 (0.36-1.02)	*0.06*	3 (8.4)	1.11 (0.37-3.33)	*0.85*
1–2 years	12 (1.0)	2 (2.2)	0.48 (0.11-2.10)	*0.32*	0 (0)	-	*0.54*
2–6 years	94 (8.1)	12 (13.0)	0.62 (0.36-1.09)	*0.10*	3 (8.3)	0.97 (0.32-2.93)	*0.96*

Table 5. Association between the allergic diseases and the time of the first HB dose.

	HB1 vaccinated 1 month later	**HB1 vaccinated on time**	**OR (95% PI)**	***p value***
Number of children	N=40 (3.2%)	N=1201 (96.8%)		
Allergic disease	n (%)	n (%)		
AD 0–6 years PCP overall	14 (35.0)	324 (27.0)	1.46 (0.75-2.83)	*0.26*
Until 1 year	10 (25.0)	184 (15.3)	1.84 (0.89-3.83)	*0.10*
1–2 years	3 (7.5)	117 (9.7)	0.75 (0.23-2.47)	*0.64*
2–6 years	1 (2.5)	23 (2.8)	1.31 (0.17-9.97)	*0.79*
AD 0–6 years allergist	8 (20.0)	249 (20.7)	0.96 (0.44-2.10)	*0.91*
Until 1 year	6 (15.0)	117 (9.7)	1.63 (0.67-3.98)	*0.27*
1–2 years	1 (2.5)	108 (9.0)	0.26 (0.03-1.91)	*0.15*
2–6 years	1 (2.5)	24 (2.0)	1.26 (0.17-9.53)	*0.82*
Asthma 0-6 m. overall	11 (27.5)	170 (14.2)	2.30 (1.13-4.69)	***0.02***
Wheezing illness until 1 y.	0 (0)	11 (9.1)	-	*0.54*
1–2 years	4 (10.0)	57 (4.7)	2.23 (0.77-6.48)	*0.13*
2–6 years	7 (17.5)	104 (8.7)	2.24 (0.97-5.18)	*0.05*
AR 0–6 years overall	8 (20.0)	111 (9.2)	2.45 (1.10-5.46)	***0.02****
1–2 years	2 (5.0)	11 (0.9)	5.69 (1.22-26.56)	***0.01****
2–6 years	6 (15.0)	99 (8.2)	1.96 (0.81-4.79)	*0.13*
AR 2–6 years overall	6 (15.0)	106 (8.8)	1.82 (0.75-4.44)	*0.18*

*Allergic rhinitis is not a usual diagnosis in children under 2 years; therefore, we suggest to rely on the frequency of AR at the age of 2–6 years rather than the period from birth to 6 years.

Table 6. Distribution of the allergic diseases between the children who have received all three doses of HB and those who had not completed vaccination until the 7th month.

	Non-vaccinated HB	**All three doses of HB until 7 months**	**OR (CI 95%)**	***p value***
Number of children	N=36 (3.4%)	N=1014 (96.6%)		
Allergic disease	n (%)	n (%)		
AD 0–6 years by PCP overall	16 (44.4)	267 (26.3)	2.24 (1.14-4.38)	***0.02***
Until 1 year	11(30.6)	148 (14.6)	2.57 (1.24-5.34)	***0.01***
1–2 years	3 (8.3)	99 (9.8)	0.84 (0.25-2.79)	*0.78*
2–6 years	2 (5.6)	20 (2.0)	2.92 (0.66-13.01)	*0.14*
AD 0-6 years by allergist	12(33.3)	205 (20.2)	1.97 (0.97-4.01)	*0.06*
Until 1 year	3 (8.3)	93 (9.2)	0.90 (0.27-2.99)	*0.86*
1–2 years	7 (19.4)	91 (9.0)	2.45 (1.04-5.75)	***0.03***
2–6 years	2 (5.6)	20 (2.0)	2.92 (0.66-13.01)	*0.14*
Asthma 0–6 years overall	1 (2.8)	148 (14.6)	0.17 (0.02-1.23)	*0.05*
Wheezing illness until 1 y.	0 (0)	7 (0.7)	-	*0.62*
1–2 years	0 (0)	51 (5.0)	-	*0.17*
2–6 years	1 (2.8)	90 (9.0)	0.29 (0.04-2.17)	*0.20*
AR 0–6 years overall	3 (8.3)	97 (9.6)	0.86 (0.26-2.85)	*0.80*
1–2 years	0 (0)	12 (1.2)	-	*0.51*
2–6 years	3 (8.3)	84 (8.3)	1.01 (0.30-3.35)	*0.99*

Table 7. Allergic diseases at different age periods according to the time of the first DTaP-IPV-Hib dose inoculation.

	DTaP the 1st dose on time	**DTaP the 1st dose 1 month later**	**OR (95% PI) 1 month later vs. on time**	**DTaP-IPV-Hib delayed**	**OR (95% PI) Delayed vs. on time**
Number of children N=1230	N=851(69.2%)	N=324 (26.3%)		N=55 (4.5%)	
Allergic disease	n (%)	n (%)		n (%)	
AD 0–6 years by PCP overall	235 (27.6)	81 (25.0)	0.87 (0.65-1.17)	19 (34.5)	1.38 (0.78-2.46)
Until 1 year	134(15.7)	47 (14.5)	0.91 (0.63-1.30)	10 (18.2)	1.19 (0.58-2.42)
1–2 years	79 (9.3)	29 (9.0)	0.96 (0.61-1.50)	9 (16.4)	1.91 (0.90-4.05)
2–6 years	22 (2.6)	5 (1.5)	0.59 (0.22-1.57)	0 (0)	-
AD 0–6 years by allergist	181(21.3)	60 (18.5)	0.84 (0.61-1.16)	12 (21.8)	1.03 (0.53-2.00)
Until 1 year	87 (10.2)	27 (8.3)	0.80 (0.51-1.25)	4 (7.3)	0.69 (0.24-1.95)
1–2 years	73 (8.6)	26 (8.0)	0.93 (0.58-1.48)	8 (14.5)	1.81 (0.83-3.99)
2–6 years	21 (2.5)	7 (2.2)	0.87 (0.37-2.07)	0 (0)	-
Asthma 0–6 years overall	132 (15.5)	34 (10.5)	**0.64 (0.43-0.95) ***	12 (21.8)	1.52 (0.78-2.96)
Wheezing illness until 1 y.	10 (1.2)	1 (0.3)	0.26 (0.03-2.04)	1 (1.8)	1.56 (0.20-12.38)
1–2 years	40 (4.7)	10 (3.1)	0.65 (0.32-1.31)	4 (7.3)	1.59 (0.55-4.62)
2–6 years	81 (8.3)	22 (6.8)	0.69 (0.42-1.13)	7 (12.7)	1.39 (0.61-3.16)
AR 0–6 years overall	85 (10.0)	25 (7.7)	0.75 (0.47-1.20)	6 (10.9)	1.10 (0.46-2.65)
1–2 years	11 (1.3)	3 (0.9)	0.71 (0.19-2.57)	0 (0)	-
2–6 years	74 (8.7)	22 (6.8)	0.76 (0.47-1.25)	6 (11.0)	1.29 (0.53-3.10)

If the 1st dose of DTaP-IPV-Hib was delayed by 1 month, the risk for an asthma diagnosis decreased in comparison to timely vaccinated children (* p=0.03).

Table 8. Distribution of the diagnosed allergic diseases between the children who have received all three doses of DTaP-IPV-Hib with those who did not complete their vaccinations until the 7th month or were not vaccinated at all.

	Completely vaccinated with 3 doses of DTaP until 7 months	**Partially vaccinated until the 7th month**	**OR (95% CI)**	***p value***	**Non-vaccinated with DTaP until the 7th month**	**OR (95% CI)**	***p value***
Number of children: N=1294	N=1016 (82.6%)	N=214(17.4%)			N=64 (5.9%)		
Allergic disease	n (%)	n (%)	Partially vs. completely		n (%)	Non-vaccinated vs. completely	
AD 0–6 years by PCP overall	268 (26.4)	67 (31.3)	1.27 (0.92-1.75)	*0.14*	22 (34.4)	1.46 (1.86-2.49)	*0.16*
Until 1 year	147 (14.5)	44 (20.6)	1.53 (1.05-2.23)	***0.03***	14 (21.9)	1.66 (0.89-3.07)	*0.11*
1–2 years	99 (9.7)	18 (8.4)	0.85 (0.50-1.44)	*0.55*	6 (9.4)	0.96 (0.40-2.28)	*0.92*
2–6 years	22 (1.7)	5 (2.3)	1.08 (0.40-2.89)	*0.88*	2 (3.1)	1.46 (0.34-6.34)	*0.61*
AD 0–6 years by allergist	208 (20.5)	45 (21)	1.03 (0.72-1.49)	*0.85*	19 (29.7)	1.64 (0.94-2.86)	*0.08*
Until 1 year	94 (9.3)	24 (11.2)	1.24 (0.77-1.99)	*0.38*	8 (12.5)	1.40 (0.65-3.03)	*0.39*
1–2 years	91 (9.0)	16 (7.5)	0.82 (0.47-1.43)	*0.49*	9 (14.0)	1.66 (0.80-3.48)	*0.17*
2–6 years	23 (2.3)	5 (2.3)	1.03 (0.39-2.75)	*0.95*	2 (3.1)	1.39 (0.32-6.04)	*0.66*
Asthma 0–6 years overall	145 (14.3)	33 (15.4)	1.10 (0.73-1.65)	*0.66*	6 (9.4)	0.62 (0.26-1.47)	*0.27*
Wheezing illness until 1 y.	6 (0.6)	5 (2.3)	4.02 (1.22-13.29)	***0.01***	0 (0)	-	*0.54*
1–2 years	48 (4.7)	11 (5.1)	1.09 (0.56-2.14)	*0.80*	3 (4.7)	0.99 (0.30-3.28)	*0.99*
2–6 years	92 (9.1)	18 (8.4)	0.92 (0.54-1.56)	*0.76*	3 (4.7)	0.49 (0.15-1.60)	*0.23*
AR 0-6 years overall	95 (9.4)	21 (9.8)	1.05 (0.64-1.73)	*0.83*	8 (12.5)	1.38 (0.64-2.99)	*0.41*
1–2 years	13 (1.3)	0 (0)	-	*0.09*	1 (1.6)	1.24 (0.16-9.67)	*0.83*
2–6 years	81 (8.0)	21 (9.8)	1.26 (0.76-2.08)	*0.37*	7 (10.9)	1.42 (0.63-3.21)	*0.40*

3.2 Phase II: Analysis of Medical Histories. Case-Control Study

The group of 250 children diagnosed with AD with or without other allergic diseases included 116 girls and 134 boys. The group of children who had not been diagnosed with allergic diseases as confirmed by the allergist included 142 girls and 127 boys. There was no statistically significant difference between the distribution of genders. Some of the children in the group diagnosed with AD were also diagnosed with other allergic diseases: AD and BA were diagnosed in 41 (16.4%) child, AD with AR were diagnosed in 28 (11.2%) children, AD with AR and BA in 26 (10.4%). More than a half of children with the diagnosis of AD, i.e., 134 (52.6%) were diagnosed with atopic dermatitis during the first year of life.

3.2.1 Frequency and Nature of Adverse Reactions to Vaccination, Recorded in Medical Histories, in Children under 24 Months of Age

After reviewing all medical histories of the research subjects and control group (n=519), reactions after vaccination identified by physicians were found in 28 children under 2 years of age. Post-vaccination reactions to one vaccine were documented in 26 children, and in 2 children – to two inoculations of the same vaccine (one to DTaP2 and DTaP3, another to DTaP1 and DTaP3). Thus, the total number of adverse reactions to vaccines, documented in medical histories, was 30. Post-vaccination reactions were recorded in 10 (35.7%) girls and 18 (64.3%) boys ($p = 0.141$). Adverse reactions to vaccines were reported in 16 (6.4%) children with AD and 8 (3.0%) children without any allergic diseases. Children diagnosed with AD experienced 18 adverse reactions to vaccination, while non-allergic children – 14 ($p = 0.063$). There was no statistically significant difference between groups in the frequency of adverse reactions after vaccination with every vaccine (Table 9).

Table 9. Comparison of the adverse reactions rate after vaccination, between children with atopic dermatitis and non-allergic children.

Vaccine	Number of reactions/number of children vaccinated	In children with AD	In non-allergic children	OR (CI 95%)
BCG	3/496	1/241	2/255	0.53 (0.05-5.82)
HB1	0/495	0/240	0/255	-
HB2	1/491	1/237	0/254	*p=0.30*
HB3	1/481	1/235	0/246	*p=0.31*
DTaP1	6/491	2/240	4/251	0.52 (0.09-2.88)
DTaP2	7/485	5/237	2/248	2.62 (0.50-13.61)
DTaP3	5/485	4/237	1/248	4.12 (0.46-37.71)
DTaP4	4/471	2/231	2/240	1.04 (0.15-7.44)
MMR1	3/476	2/234	1/242	2.07 (0.17-22.97)
Total	30/4371	18/2132	12/2239	1.58 (0.76-3.28)

Egg Allergy and Vaccination

Sensitization to food or environmental allergens was confirmed for 139 children in the group diagnosed with AD, of those 43 (30.9%) were sensitized to eggs (sensitization confirmed by positive SPT). Two of the 43 egg-sensitized children were not vaccinated with the MMR vaccine, although contraindications were not indicated neither in their medical histories nor in the database system. Of the 43 children, 39 were completely vaccinated and 4 were vaccinated partially. Of the 4 partially vaccinated children one was vaccinated

only with the BCG vaccine, two children were not vaccinated with the DTaP4 vaccine, and another child was not vaccinated with the MMR1 and DTaP4 vaccines.

3.2.2 Association between Early Life Factors, Including Vaccination, and Allergic Diseases

We have selected medical histories of 289 children who have been diagnosed with allergic diseases. We excluded 49 children from the group, who (1) were diagnosed with AD by an allergist before 2 months of age, i.e., prior to the vaccination with DTaP-IPV-Hib (24 children); (2) were diagnosed with AD by a PCP before 2 months of age, which was subsequently confirmed by an allergist (22 children); (3) commenced vaccination at the time of AD diagnosis (2 children); (4) were diagnosed with AD after 2 months of age, but prior to the commencement of vaccination (1 child).

Of the 240 children selected, 203 were diagnosed with AD, 62 were diagnosed with AR, and 76 were diagnosed with BA. Of 203 children diagnosed with atopic dermatitis, 47 (23.2%) were diagnosed with asthma and 43 (21.2%) with allergic rhinitis. Atopic dermatitis was diagnosed by an allergist in 88 children in the first year of life, in 74 children in the second year of life, and in 41 children after their second birthday. The control group consisted of 269 children with no diagnoses of allergic diseases.

Association between Early Risk Factors and Allergic Diseases

For this part of the study, we have selected the factors that undoubtedly occurred before the onset of allergic diseases: the method of delivery (birth through natural means as a protective factor), gender (male), birth pathology, presence of older siblings, time of vaccination with DTaP1, breastfeeding, weight at birth and weight at discharge (difference by one hundred grams); we later added the prescription of antibiotics during the first year of life.

Analysing one factor after another in univariate binary logistic regression models, we found that the risk of allergic disease diagnosis was slightly increased before 7 months of age by every dose of inoculated vaccines (OR 1.337; 95% CI: 1.005-1.778, p=0.046). A DTaP1 delay by a month later than specified in the NIPC tended to the 0.786 lower risk of diagnosis of allergic disease, but was statistically insignificant (p = 0.217). In the univariate binary logistic regression model, allergic diseases were diagnosed more frequently (OR 5.050; 95% CI: 1.672-15.25, p = 0.004) if congenital infection was diagnosed at birth, but in the models of multivariate analysis, this factor was not statistically significant. The antibiotic prescription fact during infancy – OR 1.609 (95% CI: 1.123-2.306, p=0.010), same as the number of prescribed courses of antibiotics during the infancy – OR 1.480 (95% CI: 1.200-1.824, p=0.0001), were associated with a higher overall risk of having a diagnosis of allergic disease at a preschool age. But in the multivariate binary logistic regression model, only the number of antibiotic prescriptions was associated with a higher risk of allergic disease: OR 1.463 (95% PI: 1.15-1.903, p=0.002) (Table 10).

Table 10. Early-life factors associated to the diagnoses of the allergic diseases.

N=509	Univariate analysis		Multivariate analysis	
Factor	OR (95% CI)	*p*	OR (95% CI)	*p*
Vaccination			I model: N=442	
DTaP1 vaccination	1.649 (0.746-3.647)	0.216		
DTaP1 on time vs. not on time	1.174 (0.582-2.368)	0.654		
DTaP1 timing: 1 month later	0.768 (0.505-1.168)	0.217		
BCG vaccination	1.407 (0.599-3.317)	0.432		
HB1 vaccination	1.358 (0.598-3.083)	0.464		
DTaP1 timing from 2 month	1.001 (0.958-1.047)	0.948		
DTaP doses received until the 7th month	1.167 (0.957-1.423)	0.127		
DTaP1 on time vs. non-vaccinated	1.668 (0.753-3.694)	0.207		
DTaP3 on time vs. delayed	1.020 (0.652-1.597)	0.930		
HB3 on time	1.034 (0.649-1.616)	0.918		
Demographic data			II model: N= 372	
Gender: boy	1.295 (0.913-1.835)	0.147		
Month of birth (1)	1.036 (0.982-1.092)	0.195		
Birth circumstances				
Birth at hospital	0.891 (0.220-3.600)	0.871		
Delivery (SC)	1.011 (0.647-1.681)	0.961		
Birth weight (100 g)	1.023 (0.987-1.060)	0.212		
Weight at the discharge (100 g)	1.038 (0.997-1.080)	0.073	1.045(0.997-1.094)	0.067
Birth pathologies	1.606 (0.959-2.690)	0.072		
Congenital infection	5.050 (1.672-15.25)	0.004		
Mothers age (a year)	0.995 (0.962-1.029)	0.763		
Early life factors			III model: N= 347	
Number of siblings	1.006 (0.780-1.297)	0.964		
Breastfeeding	0.392 (0.119-1.289)	0.123		
AB prescription in infancy	1.609 (1.123-2.306)	0.010		
Frequency of AB prescription in infancy	1.480 (1.200-1.824)	0.0001	1.463 (1.15-1.903)	0.002

In the univariate logistic regression models, we found that birth pathologies were associated with a 1.724 times higher risk of AD diagnosis. Congenital infection increased the risk of AD diagnosis by 5.325 times. The fact of antibiotics prescription and the frequency of prescriptions were also associated with a higher risk of AD diagnosis. We found that breastfeeding was a protective factor for AD diagnosis: OR 0.332 (95% CI: 1.101-1.093).

Each additionally prescribed course of antibiotics during the first year of life independently increased the risk of diagnosis of AD by 1.448 times ($p = 0.003$), but the fact of the prescription of antibiotics itself was not associated with an increase in AD risk in multiple binary logistic regression models. Congenital infection with the effect of other factors was not a statistically significant risk factor for atopic dermatitis (Table 11).

Table 11. Association between early life factors and atopic dermatitis.

N= 472	**Univariate analysis (for AD without BA and AR comparing to non-allergic children).**		**Multivariate analysis**	
Factor	OR (95% CI)	*p*	OR (95% CI)	*p*
Vaccination			I model: N=413	
BCG vaccination	1.338(0.550-3.254)	0.520		
DTaP1 vaccination	1.546 (0.680-3.516)	0.299		
DTaP1 on time/ delayed	1.242 (0.588-2.625)	0.570		
DTaP1 time from 2 months (monthly)	1.007 (0.963-1.054)	0.755	-	
DTP1 time: 1 month later	0.841 (0.545-1.298)	0.434		
HB1 vaccination	1.273 (0.546-2.970)	0.577		
HB1 monthly	0.711 (0.235-2.158)	0.547	-	
HB3 on time	0.901 (0.381- 2.130)	0.813	-	
DtaP3 on time / delayed	0.818 (0.334-2.008)	0.662	-	
Demographic data			II model: N=346	
Gender: boy	1.295 (0.913-1.835)	0.147		
Month of birth (1)	1.036 (0.982-1.092)	0.195	-	
Birth circumstances				
Birth at hospital	1.006 (0.223-4.547)	0.993		
Delivery (SC)	1.145 (0.724-1.810)	0.564		
Birth weight (100 g)	1.024 (0.987-1.063)	0.209		
Weight at the discharge (100 g)	1.037 (0.995-1.081)	0.087	II 1.048 (0.998-1.099) III 1.045 (0.994-1.098)	 0.058 0.082
Birth pathologies	1.724 (1.015-2.930)	0.044		
Congenital infection	5.325 (1.737-16.22)	**0.003**		
Early life factors			III model: N=324	
Number of siblings	1.037 (0.796-1.352)	0.786		
Breastfeeding	0.332 (0.101-1.093)	0.070		
AB prescription in infancy	1.561 (1.072-2.275)	**0.020**		
Frequency of AB prescription in infancy	1.460 (1.183-1.824)	**0.001**	1.448 (1.124-1.866)	0.003
Allergy				

Anamnesis of allergy is not included in the models of multiple logistic regression due to the small sample of research subjects who had such data.

In the models of the multivariate binary logistic regression, we established that antibiotic prescription in infancy twice (p = 0.009) and each additional antibiotic prescription increased the risk of asthma diagnosis by 1.59 times (p = 0.002) in the preschool age. We observed a trend that every month that the inoculation of DTaP1 was postponed was related to the reduction of asthma risk, but it was statistically insignificant. Postponing the first dose of DTaP from the second to the third month of life, i.e., by one month, was significantly linked with a reduction in the risk of asthma diagnosis: OR 0.385 (95% CI: 0.186-0.795), p = 0.01. The male gender was associated with a 1.5 time higher risk of asthma diagnosis, but this factor did not reach the level of statistical significance (Table 12).

DTaP1 delay for 1 month in the multivariate regression model with all analysed factors included did not remain significant for asthma risk reduction. The only factor remaining in the complete model, which was significantly linked to the increase of asthma risk by 1.5 times, was the frequency of antibiotics prescription during infancy (p = 0.033) (Table 12).

Table 12. Association between early life factors and bronchial asthma.

N = 345	Univariate analysis		Multivariate analysis	
Factor	OR (95% CI)	*p*	OR (95% CI)	*p*
Vaccination			I model: N=248	
BCG vaccination	4.118 (0.533-31.827)	0.175		
BCG on time vs. 1 month later	0.821 (0.312-2.164)	0.691		
DTaP1 on time/ delayed	1.163 (0.419-3.226)	0.772		
DTaP1 time from 2 months (monthly)	0.808 (0.590-1.107)	0.184		
DTP1 time: 1 month later	0.385 (0.186-0.795)	**0.010**	I 0.397 (0.192-0.823) II 0.479 (0.234-1.057)	0.013 0.069

HB1 vaccination	4.429 (0.576-34.082)	0.153		
HB1 monthly	0.945 (0.782-1.142)	0.557		
HB3 on time	1.168 (0.594-2.296)	0.659		
DTaP3 time monthly	0.976 (0.926-1.029)	0.374		
DTaP until the 7th month according to the vaccination plan vs. plan disturbed	1.397 (0.756-2.579)	0.286		
Number of vaccine doses received until 7 months	1.499 (0.865-2.569)	0.149		
Vaccinated vs. partially and non-vaccinated	1.699 (0.864-3.344)	0.125		
Demographic data			II model: N=234	
Gender: boy	1.584 (0.947-2.650)	0.080		
Month of birth (1)	1.037 (0.959-1.121)	0.366		
Birth circumstances				
Delivery (SC)	1.256 (0.675-2.337)	0.471		
Birth weight (100 g)	1.013 (0.962-1.067)	0.616		
Weight at the discharge (100 g)	1.032 (0.973-1.095)	0.290		
Birth pathologies	1.708 (0.839-3.476)	0.140		
Congenital infection	4.762 (1.242-18.25)	**0.023**	-	
Discharge from the hospital day	1.053 (0.939-1.179)	0.378		
Mother's age (year)	0.984 (0.937-1.033)	0.521		
Early life factors			III model: N=226	
Number of siblings	0.738 (0.476-1.146)	0.716		
AB prescription in infancy	2.000 (1.193-3.353)	**0.009**		
Frequency of AB prescription in infancy	1.591 (1.188-2.130)	**0.002**	1.484 (1.032-2.135)	0.033

Risk factors for the Diagnosing of Allergic Rhinitis

Although bronchial asthma and allergic rhinitis are related conditions (up to 30% of children with allergic rhinitis had asthma as well), a one-month delay in DTaP1 had no effect on the frequency of allergic rhinitis diagnoses. Antibiotic prescription during the first year

of life increased the risk of AR by 1.6 times (in the models of multivariate binary logistic regression) (p = 0.02) (Table 13).

Table 13. Association between early life factors and allergic rhinitis.

N=331	Univariate analysis		Multivariate analysis	
Factors	OR (95% CI)	*p*	OR (95% CI)	*p*
Vaccination			I model: N=282	
BCG vaccination	3.349 (0.432-25.96)	0.247		
BCG on time vs. 1 month later	0.655 (0.247-1.737)	0.395		
DTaP1 vaccination	2.151 (0.486-9.525)	0.313		
DTaP1 on time/delayed	1.147 (0.375-3.504)	0.810		
DTaP1 time from 2 months (monthly)	0.896 (0.721-1.114)	0.323		
DTP1 time: 1 month later	0.640 (0.318-1.287)	0.210		
HB1 vaccination	3.602 (0.467-27.80)	0.219		
HB1 monthly	0.885 (0.331-2.364)	0.807		
HB3 on time	1.224 (0.579-2.589)	0.596		
Demographic data			II model: N=240	
Gender: boy	1.229 (0.707-2.136)	0.465		
Month of birth (1)	1.009 (0.927-1.098)	0.844	-	
Birth circumstances	0.921 (0.101-8.384)	0.942		
Birth at hospital	0.940 (0.458-1.933)	0.867		
Delivery (SC)	1.059 (0.999-1.123)	0.055	(II) 1.100 (1.002-1.183) (III) 1.094 (1.012-1.182)	0.011 0.024
Birth weight (100 g)	1.065 (1.000-1.136)	0.051		
Birth pathologies	1.226 (0.531-2.830)	0.633		
Congenital infection	5.556 (1.444-21.38)	0.013		
Discharge day	1.007 (0.879-1.153)	0.924		
Mothers age (a year)	0.991 (0.939- 1.045)	0.737		
Early life factors			III model: N=216	
Number of siblings	0.878 (0.572- 1.345)	0.549		
Breastfeeding	0.444 (0.079-2.487)	0.356		
AB prescription in infancy	2.000 (1.143-3.498)	**0.015**	(III) 1.610 (1.078-2.406)	0.02
AB prescription times during infancy	1.593 (1.178-2.154)	**0.003**		

4. DISCUSSION

A comparative analysis of studies analysing vaccination links with allergic diseases is difficult due to the different combinations of vaccine components examined (25–28). Even the research subjects included in the sample of the same study may differ according to the components of the inoculated vaccines (e.g., some research subjects are vaccinated with whole cell pertussis vaccine, while others with an acellular vaccine), the national prophylactic vaccination calendars of children are also supplemented with new vaccines and some research subjects are vaccinated according to one plan, while others are vaccinated according to another (28, 29). In our study, all children were vaccinated according to the NIPC of Children of the Republic of Lithuania, which was in effect in 2009–2010, the number of planned vaccines and the composition of specific vaccines did not differ for any child. Study results may also vary due to regional-socio-economic and genotypic peculiarities of the study populations (30).

4.1. Discussion of the Phase I results

Vaccination Coverage and Frequency of Allergic Diseases

In the first phase of the study, we determined that the frequency of diagnoses of allergic diseases before the age of 6 years is not related to the coverage of vaccination before the age of 2 years and before the age of 6 years. This means that children vaccinated with NIPC vaccines are not more allergic than non-vaccinated or partially vaccinated children. No associations with national immunization rates were found in the International Study of Asthma and Allergies in Childhood (31), as well as in a more recent large-scale prospective study (32).

By analysing the data in the polyclinic ‘s electronical database and further examining each allergic disease separately, we found that AD was diagnosed by PCPs in non-vaccinated or partially vaccinated children more frequently than in children up to 2 and up to 6 years of age who were fully vaccinated according to the routine immunization schedule. In the group of partially vaccinated children of up to 2 years, 21.9% of children under 1 year of age were diagnosed with AD by a PCP when compared to 14.4% in the group of completely vaccinated children ($p = 0.008$). This trend remained all the way up to 6 years of age. To sum up these results, we can say that vaccinated children suffer from allergic diseases as often as non-vaccinated ones, but atopic dermatitis, diagnosed by primary care practitioners, may be associated with disorders of the routine immunization schedule.

We assumed that the diagnosing of allergic diseases in the primary health care may be related to the disorders of the NIPC. Therefore, we analysed in detail the links between vaccination with individual vaccines and atopic dermatitis, diagnosed both by PCPs and allergists (as the first atopic disease diagnosed at the earliest), as well as with the diagnoses of BA and AR diagnosed by the specialists.

There was no statistically significant difference in the frequency of PCP diagnoses of allergic diseases among children vaccinated with BCG and children who were not vaccinated with it. A MIRIAM study (in Germany) with a sample size similar to ours ($n = 1673$) did not identify links of BCG vaccination with any allergic diseases in studied children from 5 to 7 years of age (33). The results of studies conducted in Germany, Spain, and the United Kingdom have demonstrated the protective effect of BCG on the development of asthma in pre-school children (30, 34, 35). Systematic reviews have not identified the protective effects of BCG against the development of asthma (36, 37).

We found that the atopic dermatitis was diagnosed by PCP in the group of children who were not vaccinated with the HB vaccine statistically significantly more often when compared to children under

the age of 7 months who received all 3 doses of the vaccine (95% CI: 1.14-4.38), p = 0.02. This trend was also seen in children who were diagnosed with AD by an allergist at the age of 1 to 2 years: the diagnosis of atopic dermatitis was 2.5 times more frequent in the group of non-vaccinated children (p = 0.03). Such results allow to presume that the HB vaccine is not related to the development of allergic diseases. There is very little research on the link between the hepatitis B vaccine and atopic diseases. Usually this vaccine is analysed in combination with others (29, 38). To date, no significant correlation between vaccination with the HB vaccine and allergic diseases has been established.

It is likely that vaccination for children, who were suspected of having atopic dermatitis during the first months of their life, could have been delayed more often during the first six months of their life. The increase of atopic dermatitis by 1.5 times (p = 0.03) and asthma by 4 times (p = 0.01) in the first year of life in the group of children who were not fully vaccinated with the DTaP-IPV-Hib vaccine before 7 months of age when compared to the fully vaccinated, which was established in our study, may have been caused by a refusal to vaccinate due to transient disorders of the skin and respiratory system. In a study of children hospitalized for wheezing, E. Ozkaya found that wheezing episodes during the first three years of life increased the likelihood that children would not be fully vaccinated with BCG, HB, Hib, and MMR even up to 10.6 times (39).

In order to evaluate whether vaccination disorders might have been associated with wheezing in infancy due to recurrent infections (which may “hide” under the diagnosis of asthma until the first year of age) or with a PCP-diagnosed atopic dermatitis (in order to avoid exacerbations), we compared the frequency of allergic diseases between children vaccinated and not vaccinated with DTaP-IPV-Hib before 7 months of age. There was no difference in the ratio of PCP- and allergist-diagnosed AD in vaccinated and non-vaccinated children. This indicates that prophylactic vaccination of infants with vaccines containing the acellular pertussis component is not associated

with a more frequent diagnosing of allergic diseases. We can assume that interferences of the routine vaccination plan, same as in the study conducted by E. Ozkaya and co-authors, were related to transient health conditions.

Links of Diagnosed Allergic Diseases with Time of Each Vaccine Inoculation

The first six months of life are a certain "window of opportunity" where the impact of allergic disease-inducing or protective factors is crucial. AD is usually diagnosed during the first year of life, which coincides with the intense vaccination of infants. We did not study the reasons for postponing or delaying vaccination but analysed the links between the postponing of vaccination with individual vaccines and allergic diseases.

We found that BCG vaccination delay by a month was associated with atopic dermatitis as diagnosed by an allergist 2.8 times more often at the age of 2 to 6 years ($p = 0.03$). However, there was no statistically significant difference in the frequency of PCP-diagnosed AD during the same age period, between children vaccinated on time and those vaccinated 1 month later. It should be noted that at all age periods analysed, PCPs had diagnosed atopic dermatitis in a higher number of children than allergists, except for the period of 2 to 6 years, so it could mean that the allergists later verified the diseases suspected by PCPs. According to the results of the research of a cross-section by D. Dilli and co-authors, the time of vaccination with BCG and HB vaccines during the first two months of life was not associated with the development of atopy, but it was noticed that the risk of wheezing was lower in the group of children who were previously vaccinated with BCG (right after birth) when compared to children vaccinated with this vaccine at 2 months of age (40).

In our study, the children whose vaccinations with the first HB dose were delayed by 1 month were diagnosed with asthma over the period of 2–6 years of age 2.8 times more often (95% CI: 1.38-5.78,

p=0.003). Same as in the case of the delayed BCG vaccination, we believe that there may have been reasons (such as congenital pathology, etc.) that could lead to the delay of vaccination and have an effect on the development of allergic diseases. We also found that allergic rhinitis was diagnosed 2.45 times more often in children who were vaccinated with HB1 a month later, but we would be critical of this result. The diagnosis of allergic rhinitis at an early age (1–2 years) is questionable, and a significant difference in proportions may be due to the very small sample of the group of children that were vaccinated later (n = 8).

The frequency of asthma diagnosis from birth to 6 years of age was generally lower if children were vaccinated with DTaP-IPV-Hib one month later: OR 0.64 (95% CI: 0.43-0.95, p=0.03). However, there was no statistically significant difference in the frequency of asthma diagnoses for children who had been vaccinated with DTaP-IPV-Hib even later when compared to children who were vaccinated on time. The negative correlation between the reception of the first dose of DTP-IPV-Hib at infancy and asthma was first of all described by K. L. McDonald. The postponing of vaccination with the first dose of DTP reduced the risk of diagnosing asthma before 7 years of age. This trend was even more clear if all three first doses of the vaccine were postponed (OR 0.39; CI 95%: 0.18-0.86) (41). However, the results of the study caused doubt for other scientists, as the asthma description chosen by the researchers was based on the need of parents to contact a medical facility when a child with asthma experienced the symptoms (42). The results of the meta-analysis study did not indicate any correlation between the time of vaccination and asthma (43).

The results of our study resemble the results of the most recent study with a representative sample (n = 4433) cohort conducted in Australia. It was established that vaccination with DTaP (combined with IPV, Hib and HB) when delayed by one month (109 (2.5%) children of the general sample) is associated with a decrease in eczema (atopic dermatitis) (OR 0.55; 95% CI: 0.33-0.91) and reduced the need

for eczema medication (OR 0.41, 95% CI: (c. p. 0.22-0.76) at one year of age (44).

According to the Global Infant Immunization Program, the expected start of vaccination with DTaP-IPV-Hib in Lithuania is at 2 months of age, which is a common practice in Europe and in many countries around the world. We could speculate that a slight delay in vaccination, by no more than one month, could be a protective factor for an allergic march – in children with a risk of atopy, for example. However, the lack of strong evidence leaves the question open of whether the delayed vaccination with DTaP-IPV-Hib would be beneficial to individual patients and how it would affect universal immune protection (45). It must be kept in mind that the postponement of vaccination times and the delay of the vaccine-induced protection increases the risk of contracting the diseases that are managed with vaccines, and the benefits of early vaccination outweigh any possible or only suspected risk of progression of allergic diseases (46, 47).

4.2 Discussion of the Phase II Results

Adverse Reactions to the Vaccines

Changes in health conditions that manifest shortly after vaccination are very rarely associated with allergic reactions. Whatever they are, they have a major impact on parents' decisions on the further vaccination of their children (39). One of our research subjects had experienced a post-vaccination reaction after a dose of DTaP2 – sluggishness and drowsiness. After this reaction, the parents stopped further vaccination of the child.

The frequency of adverse reactions to vaccines reflect the safety of vaccines. The fact that after the review of 519 medical histories during the study we found 30 documented post-vaccination reactions experienced by 28 children over 1.5 years, when one BCG, three HB, four DTaP-IPV-Hib, and one MMR vaccine doses are inoculated, showed that the reporting of reactions after immunization is not

sufficient, or that most reactions are mild, do not pose a threat to health, and quickly pass on their own. According to the data of CCDA, 36 to 80 post-vaccine reactions are registered every year in Lithuania, both for children and adults. Based on the frequency of officially registered post-vaccination reactions, our country does not differ from other countries (48).

Recent data suggest that children who are allergic to an egg white can be vaccinated safely with the MMR vaccine at primary health care centres (49–51). In addition, the latest results from the *Europrevall* study showed that an egg white allergy is not as common as previously thought, and more than half of all children who were allergic to egg whites are starting to tolerate it even before their first birthday (52).

Based on the data of our study, children who were allergic to the egg white and who were vaccinated did not experience any adverse effects after the vaccination. Four children who were allergic to egg whites were vaccinated only partially, although no contraindications were specified in medical histories. Based on the results of the study conducted in Ireland, during the vaccination of children with a possibly increased risk, for whom an allergy was suspected, only 1.3% experienced adverse reactions to the MMR vaccine; all of those were mild and were not caused by the immune mechanisms of the allergy (49).

The difference between the reactions after vaccination recorded in the medical histories of the polyclinic and the CCDA data shows that the current recording of such reactions is rather complicated and inadequate. The recording of adverse reactions after vaccination could be facilitated by the digital data storage and automatic forwarding systems as well as mobile applications.

Association between Early Life Factors (Including Vaccination) and Allergic Diseases

For the second phase of the study, the medical histories of children whose diagnoses of allergic diseases raised no doubts were selected.

During the first year of life, none of the selected children were diagnosed with allergic rhinitis or bronchial asthma. Furthermore, children who were diagnosed with atopic dermatitis even before the vaccination with the DTaP-IPV-Hib vaccine were excluded from the group of research subjects. Therefore, vaccination as a factor in all cases was prior to the diagnosing of an allergic disease and could be analysed as a protective or risk factor.

It is difficult to analyse the links between vaccination during the first year of life and allergic diseases over the time in the same sample of children in different age periods. This could be the reason why there are not many studies of such kind (35, 41, 53, 54). Usually children of different ages are examined at one specific point in time or by parents questionnaires, but no continuous or periodic observations of the same children are performed (26, 55–58).

After a comprehensive multiple binary logistic regression analysis, the postponement of first dose of DTaP-IPV-Hib by one month was not statistically significantly associated with a reduction in asthma risk, and postponement of HB1 and BCG were not a significant risk factor for the diagnosis of allergic diseases. A recent study has established links between a one-month postponement of immunization with the DTaP vaccine and the development of eczema (44). Hence, there is a particular focus on the early effects of various factors related to the development of the immune system. However, when assessing the vaccination in the context of other factors, the evidence that delaying of vaccination with one vaccine or another would be significant to the prevention of the development of allergic diseases is insufficient.

We analysed the fact of antibiotic prescription, which we were able to verify by conducting an analysis of medical histories. We found that during the first year of life, each course of antibiotics prescribed increased the risk of the analysed allergic diseases. A frequent prescription of antibiotics is possibly associated with a higher morbidity with respiratory infections, but that was not a subject of our study. Retrospectively, it was difficult to assess whether certain

diseases or antibiotics themselves were associated with further developments of allergies. It was shown that infection may be associated with the progression of allergic diseases (59).

The first year of life is a crucial time for beginning antibiotic consumption. We did not find any association between the diagnosis of asthma or atopic dermatitis before 6 years of age and the antibiotic administration fact. However, these diseases were diagnosed more often in children who were prescribed antibiotics in their first year of life more often: BA – 1.48 times ($p = 0.033$), AD – 1.45 times ($p = 0.008$). A continuous study of parents and children by AVON found that children who were more often prescribed antibiotics at 0–2 years of age were diagnosed with asthma 1.75 times more often at 7.5 years of age. (60). According to a prospective birth cohort study PASTURE, exposure to antibiotics in the first year of life (aOR 2.73; 95% CI 1.66-4.49) and the number of doses received were strongly positively associated with AD up to 4 years. A tendency of a positive association between antibiotic intake in infancy and asthma between 3 and 6 years was also observed (aOR 1.65; 95% CI 0.95-2.86) (61).

In analysing the pathology immediately after birth, we found that a congenital infection was associated with an increase in the frequency of all allergic diseases examined in the models of the univariate binary logistic regression, i.e. it could be one of the potential risk factors for allergic diseases. However, in the multivariate logistic regression models, congenital infections did not appear as an independent significant risk factor for the diagnosing of allergic diseases. It has been established that the impact of early infection on the microbiota, which is important for the development of the immune balance right after birth, can result in a development of atopic diseases as the individual grows (62, 63). T. Sobko and co-authors showed that sepsis in the new born is associated with a higher risk of asthma and eczema, and that an early prescription of antibiotics may increase this risk even more (64).

The results of our study revealed what a comprehensive subject is the link between vaccination and allergic diseases, and how one or the

other conclusion cannot be interpreted unambiguously. It is expedient to continue prospective research on this subject by including more factors that act at the same time, such as the morbidity of infectious diseases during infancy, the confirmation of antibiotics consumption, the duration of consumption, etc. The adaptation of digital databases of health care institutions for such research would expand the prospects of not only regional but international research as well.

CONCLUSIONS

1. The frequency of allergic diseases in general, diagnosed among children vaccinated according to the prophylactic vaccination calendar and among non-vaccinated children, did not differ.
2. Atopic dermatitis diagnosed by primary care physicians during infancy and wheezing diseases diagnosed by pulmonologists are associated with disorders of the routine immunization plan for the DTaP-IPV-Hib vaccine. In children who have not been vaccinated with the HB vaccine before 7 months of age, atopic dermatitis was diagnosed more frequently by primary care physicians during infancy, and by allergists – during the second year of life.
3. For children vaccinated with BCG a month later, an allergist has diagnosed atopic dermatitis at 2 to 6 years statistically significantly more frequently. For children vaccinated with HB1 a month later, asthma was diagnosed at 2 to 6 years of age statistically significantly more frequently. The inoculation of the first dose of DTaP-IPV-Hib delayed by one month was associated with a lower frequency of asthma diagnosis in the pre-school age (compared to the children who were vaccinated on time).
4. There was no difference in the frequency of adverse reactions to vaccines among children diagnosed with atopic dermatitis and children with no allergic diseases diagnosed.
5. The first dose of the DTaP-IPV-Hib vaccination, when delayed by one month, is not an independent protective factor for bronchial asthma. BCG delay by a month is not an independent risk factor for atopic dermatitis, and a HB1 delay is not an independent risk factor for asthma.
6. The number of antibiotic courses prescribed during infancy is a significant independent risk factor for atopic dermatitis and asthma, and the fact of antibiotics prescription during infancy is a significant independent risk factor for allergic rhinitis.

RECOMENDATIONS

1. Based on the findings of our study and international recommendations – allergic diseases, allergic reactions, or sensitization are not related to the components of vaccines; therefore, children with allergic diseases can be safely vaccinated. It is advisable to supplement the National recommendations on the absolute and relative, both permanent and temporary contraindications for the immunisation of children with allergies.
2. Based on the results of our real-life study, children vaccinated with the DTaP-IPV-Hib vaccine with the delay of a month later than specified in the NIPC were diagnosed with asthma more rarely, but the delay of vaccination is not an independent protective factor for asthma. It would be advisable to expand and to conduct the study prospectively.
3. We recommend that children with atopic dermatitis be vaccinated according to the national immuno-prophylaxis calendar – their vaccination is safe, as the frequency of adverse reactions after vaccination does not differ from that of children without allergic diseases.
4. The adaptation of digital statistical databases and systems used in health care institutions to record adverse reactions to vaccines and their automatic forwarding to CCDA and other responsible institutions would greatly facilitate the analysis of these events. It is advisable to improve data collection and to ensure the possibility for collaboration with researchers who use digital health databases abroad.
5. It is necessary to follow the protocols for diagnosis and treatment of diseases or algorithms established and approved by health care institutions in order to improve the quality of the prescription of antibacterial preparations in Lithuanian health care institutions. It is fundamental to prescribe antibiotics to children responsibly, especially during infancy.

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1. Jagelaviciene A, Usonis V. Relationship between vaccination and atopy. Acta Medica Lituanica 2014: 21 (3): 116–122
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4. Mark A. Katz, Diana Marangu, Engi F. Attia, Jorgen Bauwens, Luis J. Bont, Annamaria Bulatovic, Julian Crane, Alexander Doroshenko, Bernard E. Ebruke, Kathryn M. Edwards, Librada Fortuna, Agne Jagelaviciene et al. Acute wheeze in the pediatric population: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2019; 37(2):392–399
5. Jagelavičienė A, Kučinskaitė J, Krživickytė A, Rudzevičienė O, Usonis V. Adverse events after vaccination in atopic children – do we know enough? Forthcoming (accepted for publication on 2019-05-02) in *Vaikų pulmonologija ir alergologija*.

Oral Communications and Abstracts in International Conferences and Meetings

1. Jagelavičiene A, Usonis V. "Relationship between Vaccination and Atopy," abstract and oral presentation at the 2nd international conference *Evolutionary Medicine: Perspectives in Understanding Health and Disease*. Vilnius, Lithuania 2014.
2. Jagelavičienė A, Usonis V. "Pneumococcal Vaccination for Children with Asthma." E-poster and abstract at the 3rd international conference *Evolutionary Medicine: Pre-Existing Mechanisms and Patterns of Current Health Issues*. Vilnius, Lithuania, 2016.
3. Jagelaviciene A, Drevinskiene L, Zalnierunaite-Lavrinovic L, Stankevicius T, Usonis V. "Vaccination Status in Allergic Children." Poster and Abstract at the International School of Allergy (EAACI Allergy School), Drug Allergy in Children. Zagreb, Serbia, 2016.
4. Jagelaviciene A, Usonis V. "Vaccination of Allergic Children in Real Life." Poster at the 2nd International Conference of Communicable Diseases. Vilnius, Lithuania, 2017.
5. Jagelaviciene A, Usonis V. "DTaP (Diphtheria, Tetanus, Acellular Pertussis) Vaccine Coverage until 7 Months and Its Relation to Atopic Dermatitis." Poster presentation and abstract at the Paediatric Allergy and Asthma Meeting. London, United Kingdom, 2017.
6. Kučinskaitė J, Krživickytė A, Jagelavičienė A, Usonis V. "The Onset of Atopic Dermatitis Is Not Related to the Doses of Vaccines Received during the First Seven Months of Life." The abstract and poster were presented at the 4th international conference *Health and Diseases in a Changing Environment*. Vilnius, Lithuania, 2018.
7. Jagelavičienė A, Kučinskaitė J, Krživickytė A, Usonis V. "Atopic march in Preschool Age. What Is the Role of Vaccines?" Oral presentation at the 4th international conference *Health and Diseases in a Changing Environment*. Vilnius, Lithuania, 2018.

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2015–07	Paediatric HERMES Summer School, Barcelona, Spain
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2017–09	EAACI Allergy School: Drug Allergy in Children (poster prize winner)

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