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PROSPECTIVE EPIDEMIOLOGIC STUDY ON RESPIRATORY DISEASES IN CHILDREN AND IMMUNIZATION AGAINST MEASLES

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Abstract.
Background: A hypothesis that vaccination with live attenuated measles virus performed in early childhood may prevent allergic sensitization has been explored in the course of a 3-year follow-up study in Kraków (Poland) among 1005 school children. **Materials and Methods:** The basic respiratory health end-points were chronic respiratory symptoms, allergy, asthma and susceptibility to acute respiratory infections. Information about immunization status of children was extracted from individual vaccination records kept by school nurses. The study showed the highest rates of chronic respiratory symptoms in non-vaccinated children who contracted measles while the lowest rates in those vaccinated who did not contract the disease. **Results and Conclusions:** Risk of allergy diagnosed by a physician in vaccinated children after adjustment to potential confounders was about half of that in the reference group (OR = 0.58 95% CI: 0.42–0.80), the same was found for asthma diagnosed by a physician (OR = 0.50 95% CI: 0.24–1.00), and for susceptibility to respiratory infections (OR = 0.51 95% CI: 0.36–0.72). Our data provide indirect evidence that infection with attenuated measles virus is able to alter immunological reactions being responsible for the manifestation of respiratory symptoms and allergy.

Key words:
Measles immunization, Allergy, Acute respiratory infection, Asthma and chronic respiratory symptoms

INTRODUCTION

Shaheen et al.[1] showed that African children infected with measles in the first year of life had a third less positive allergen skin test reactivity when examined between the age of 13–19 years than their uninfected siblings immunized against measles later in childhood. A possible explanation for this observation is that measles inoculation in early life strongly drives T cell responses in the direction of Th1 cells producing IFN-y that inhibits the development of Th2 responses and IgE production [2,3].

The African study is in agreement with other studies showing that early exposure to respiratory infections is associated with decreased rates of atopic diseases [2–7]. On the other hand, there are data indicating that the measles vaccine itself may protect against health conditions other than measles. It has been observed that in developing countries measles vaccine reduces mortality by at least 30%; mortality is much lower in the immunized than in non-immunized children [8–11].

An observation that measles immunization provides non-specific immune stimulation sufficient to decrease mortal-

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ity from other diseases is of great interest. However, the studies mentioned above did not consider health conditions against which measles vaccine might be protective and did not rule out important potential confounders. The more likely explanation for these findings could be the fact that measles immunization is just a marker of other environmental or socio-cultural factors determining health and health-conducive behavior in a given population.

The main purpose of our study was to explore a hypothesis that not only natural infection prevents allergic diseases but also measles vaccination performed in early childhood may protect the child against respiratory infections and the development of atopy. This hypothesis has been probed in the course of the Kraków cohort study on the occurrence of respiratory diseases in school children. As the risk of respiratory infections and allergy may be related to inhaled pollutants, overcrowded households or malnutrition, a set of these potentially modifying or confounding variables was considered in the risk assessment analysis.

MATERIALS AND METHODS

The epidemiologic cohort study was conducted in Kraków, a city in the south of Poland with approximately 750 000 inhabitants. The children of Caucasian origin from twelve primary schools located in two areas of the city, in the center and on its outskirts, were selected. All 9-year-old children (1165) from the schools located in these two areas attending the second grade were included in the study, and the list of their names and addresses was prepared. Of the 1129 eligible parents, 97% agreed to be interviewed on the respiratory health of their children and household characteristics. Standardized interviews with health questionnaire on children's health status were held with parents [12].

The baseline field health survey was performed in 1995, and the annual follow-up was conducted over subsequent two years (1996–1997). Health assessment was based on standardized interviews. The basic respiratory health endpoints were acute and chronic respiratory symptoms, allergy and asthma.

Respiratory infections of the upper (pharyngitis, sinusitis, tonsillitis, otitis) and lower (laryngitis/tracheitis, bronchitis, and pneumonia) respiratory tract that occurred in each year of the follow-up were recorded at interviews. A predisposition (susceptibility) to acute respiratory infections in children was defined as frequent spells (9 or more) of respiratory episodes experienced by a given child over the follow-up. This reflected the number of infection spells exceeding the third quartile of the distribution of number of infection spells.

The data on chronic respiratory symptoms in children were grouped as follows: 1) chronic cough (cough for three consecutive months or more during the year); 2) chronic phlegm (phlegm production for 3 consecutive months or more during the year); 3) wheezing or whistling in chest apart from respiratory infections or colds; and 4) attacks of wheezing with feeling of shortness of breath).

Chronic symptoms were assessed separately in each annual survey as present (+) or absent (–), and the subjects were classified into the following three categories according to the pattern of the symptoms reported:

1. Healthy: symptoms never present; before 1995 and in the years 1995–1997; (– – –)
2. Intermittent symptoms: symptoms reported only once in 1995, 1996 or 1997; (– –+), or (+– –) or (–+–),
3. Continual symptoms present at least in two surveys (1995–1997); (+ + +) or (+ +–) or (+–+), (–+ +).

The children were defined as those suffering from asthma or allergy if their mothers reported at interview any occurrence of asthma or allergy (irrespective of the type of allergy and diagnostic methods used by a physician).

In the indoor air quality assessment, three main variables were considered: environmental tobacco smoke (ETS), home heating system (gas or coal stove vs. central heating) and the presence of dampness or moulds on the apartment walls. Exposure to ETS was expressed as the presence of at least one regular cigarette smoker in the child's family (parents or guardians). The definition of a household with damp and mould problems was based on questions about moisture stains and/or visible mould growth on the walls noticed in a household (moisture stains or moulds growth larger than 1 m^2).

The children were classified in two groups: those living in the city center and exposed to high outdoor pollution, and those living on the city outskirts with low pollution. The residence area with busy streets or bus stops or parking lots located in the vicinity was defined as an area with heavy traffic pollution.

Information about the immunization status of children was derived from individual vaccination records kept by a school nurse in each of the schools included in the study. According to the measles vaccination schedule, the first dose of Schwartz vaccine (Rouvax) was given to infants at 13–15 months of age and the second dose was given at the age of 8 years. Based on the careful evaluation of the records, three vaccination cohorts were initially established: 1) non-vaccinated (39 children), 2) vaccinated partially with the first dose only (184 children), and 3) fully vaccinated with both doses of vaccine (782 children).

Statistical analysis

In the statistical analysis both non-vaccinated and partially vaccinated cohorts were combined and treated as the reference group.

At the first stage of the statistical analysis, we carried out the univariate descriptive statistics on the children's characteristics, the frequency of respiratory symptoms by vaccination status and the occurrence of measles. At the second stage, we used multivariate logistic regression (MLR) analysis to calculate the prevalence odds ratio for allergy, asthma and respiratory symptoms adjusted to potential confounders when comparing different vaccination/disease categories [13]. Beside the vaccination status, the following independent variables were included in the MRL model: gender, parental education, ETS, household heating system and moulds/dampness problems, residence in the city area, and the level of traffic pollution. Initially, the confounding variables were considered separately and then all of them were included in one MRL model to appraise their joint confounding effects. Descriptive and multivariate analysis was done with BMDP programs.

RESULTS

After excluding children with vaccination records lost to follow-up, the total study group included 1005 children

Table 1. Environmental characteristics of the study groups (%) by the vaccination and measles status

Variables	V(–), M(–) n = 174	V(–), M(+) n = 49	V(+), M(–) n = 710	V(+), M(+) n = 72
Gender				
Boys	56.2	67.3	50.7	51.4
Girls	44.8	32.7	49.3	48.6
Parents' education				
Elementary	32.8	36.7	22.8	31.9
High school	44.3	49.0	42.5	41.7
University	23.0	14.3	34.6	26.4
Smoking of mothers during pregnancy	18.4	18.4	14.3	16.7
Environmental tobacco smoke	79.3	77.6	69.4	80.6
Residence in highly polluted city area	50.0	53.1	44.9	41.7
Household heating system				
Central heating	77.0	71.4	80.0	77.8
Coal/gas heating	23.0	28.6	20.0	22.2
Traffic pollution				
Low	28.7	18.4	26.8	19.4
High	71.3	81.6	73.2	80.6
Crowding category				
<10 m^2/person	31.0	34.7	26.6	16.7
≥ 10 m^2/person	69.0	65.3	73.4	83.3

V – vaccination status.
M – measles status.

Table 2. Prevalence of chronic respiratory symptoms and number of acute respiratory infections over the follow-up

Variables	V(–), M(–) n = 174	V(–), M(+) n = 49	V(+), M(–) n = 710	V(+), M(+) n = 72
Chronic cough				
Intermittent	15.5	16.3	9.9	11.1
Continual	4.0	14.3	2.6	1.4
				Chi^2 = 27.922
				P = 0.0001
Chronic phlegm				
Intermittent	7.5	14.3	3.0	5.6
Continual	2.9	2.0	0.6	2.8
				Chi^2 = 27.537
Wheezing independent from infections				P = 0.0001
Intermittent	5.7	24.5	6.5	8.3
Continual	8.1	6.1	2.7	1.4
				Chi^2 = 36.312
Attacks of dyspnea with whistling				P = 0.0000
Intermittent	5.7	14.3	4.5	8.3
Continual	5.7	6.1	1.8	0.0
				Chi^2=23.045
				P=0.0008
Asthma diagnosed by physician	6.3	6.1	3.2	2.8
				Chi^2 = 4.458
				P = 0.22161
Allergy diagnosed by physician	41.4	46.9	30.3	25.0
				Chi^2 = 14.309
				P = 0.0025
Acute respiratory infections				
Spells of upper respiratory tract infections >7	20.1	31.9	12.5	20.8
				Chi^2 = 24.156
				P = 0.0041
Spells of lower respiratory tract infections >7	17.2	30.4	11.0	11.1
				Chi^2 = 26.902
				P = 0015

V – vaccination status.
M – measles status.

(526 boys and 471 girls). Three children who contracted measles after entering the study were also excluded. The children were 9 years old at the entry to the study and the median time of measles infection was 4 years. In the non-vaccinated group, boys slightly outnumbered girls, children's parents had more often lower education, and their households were more crowded. There was no difference across groups with respect to other environmental factors such as atmospheric or traffic pollution, household heating system, smoking of mothers during pregnancy or ETS (Table 1).

Table 2 shows the occurrence of different chronic respiratory symptoms (chronic cough, chronic phlegm, and wheezing independent of infections and colds, attacks of dyspnea with wheezing), asthma, allergy, and the number of episodes of acute respiratory infections that were broken down by the vaccination status and the occurrence of measles. The study showed the highest rates of chronic symptoms in children, who being non-vaccinated contracted measles, and the lowest rates in vaccinated children. In a group of vaccinated children who became ill, a slightly higher prevalence of respiratory symptoms and a higher number of infection episodes were found. It is worth mentioning that all kinds of symptoms with respect to their persistence (intermittent and continual) showed the same pattern of occurrence (Figs. 1 and 2).

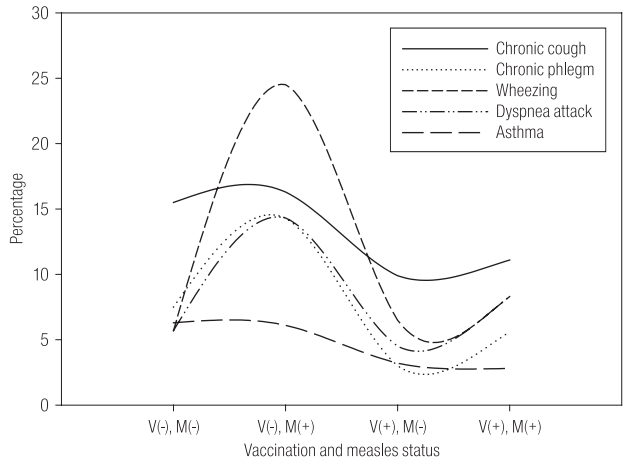

Fig. 1. Chronic respiratory symptoms (intermittent) over the follow-up (by vaccination and measles status).

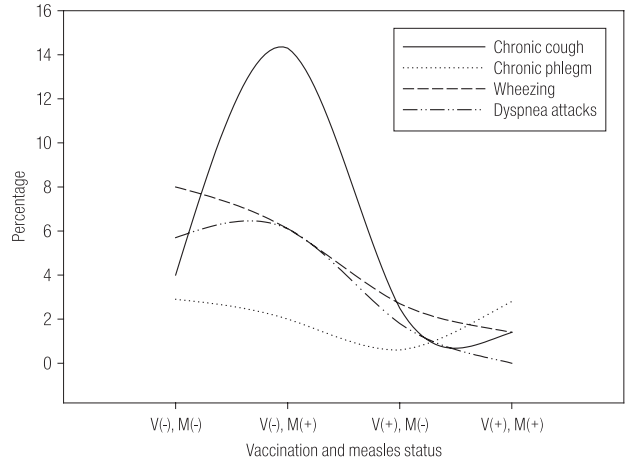

Fig. 2. Chronic respiratory symptoms (continual) over the follow-up (by vaccination and measles status).

It is important to note that allergy followed the same trend as that described for chronic respiratory symptoms. The highest prevalence was observed in non-vaccinated children with measles infection reported in the past (46.9%) but it was markedly lower in the vaccinated children both without (30.3%) and with measles (25.0%). The frequency of medical diagnosis of asthma was twice as low in the vaccinated than in non-vaccinated children (6.3% vs. 3.2%).

At the final stage of the statistical analysis, the multivariate logistic regression was performed in the group of children with chronic respiratory symptoms reported at least once in the follow-up. Allergy, asthma and susceptibility to respiratory infections were introduced in turn into the statistical models as dependent variables. Together with the vaccination status a set of independent variables such as child's gender, parental education, ETS, maternal smoking during pregnancy, household heating system, outdoor air quality, traffic pollution in the residence area, and dampness or mould problems in the household was included in the MLR model.

The results of the analysis demonstrate that vaccinated children were at much lower risk of chronic respiratory symptoms, allergy and asthma diagnosed by a physician,

Table 3. Odds ratio of chronic respiratory symptoms (continual or intermittent), allergy, asthma and susceptibility to respiratory infections over a 3-year follow-up in children related to their vaccination status (vaccinated vs. non-vaccinated) and measles infection strata. Estimated ORs adjusted in the multiple logistic models to gender, education of parents, outdoors air traffic pollution, ETS, smoking of mothers during pregnancy, and moulds on the house walls

Health outcome	OR	95 % CI	P
Chronic cough			
Total study sample	0.22	0.12–0.45	0.0000
Measles (–)	0.35	0.14–0.87	0.0233
Measles (+)	0.17	0.05–0.56	0.0035
Chronic phlegm			
Total study sample	0.26	0.11–0.64	0.0034
Measles (–)	0.48	0.11–2.18	0.3443
Measles (+)	0.33	0.08–1.39	0.1257
Wheezing			
Total study sample	0.23	0.11–0.46	0.0000
Measles (–)	0.38	0.14–1.08	0.0682
Measles (+)	0.16	0.04–0.58	0.0049
Dyspnea attacks with wheezing			
Total study sample	0.33	0.14–0.75	0.0078
Measles (–)	0.51	0.15–1.79	0.2945
Measles (+)	0.27	0.07–1.04	0.0551
Allergy			
Total study sample	0.58	0.42–0.80	0.0008
Measles (–)	0.61	0.43–0.87	0.0056
Measles(+)	0.40	0.17–0.92	0.0297
Asthma			
Total study sample	0.50	0.24–1.00	0.05054
Measles (–)	0.46	0.22–0.99	0.04919
Susceptibility to respiratory infections			
Total study sample	0.51	0.36–0.72	0.0002
Measles (–)	0.57	0.39–0.85	0.0055
Measles (+)	0.35	0.13–0.90	0.0279

and also at lower risk of frequent episodes of respiratory infections (Table 3). In the total sample, the lowest adjusted odds ratio (OR) was found for chronic cough (OR = 0.22 95% confidence interval (CI) 0.12–0.45) and wheezing (OR = 0.23 95% CI 0.11–0.46). Generally, OR was also lower in children with past measles than in those who were not vaccinated. In vaccinated children, adjusted risk for allergy was 0.58 (95% CI: 0.42–0.80), for asthma 0.50 (95% CI: 0.24–1.00), and for susceptibility to respiratory infections 0.51 (95% CI: 0.36–0.72).

DISCUSSION

The study showed the highest rates of chronic respiratory symptoms in non-vaccinated children who contracted measles, while the lowest rates were observed in vaccinated children who did not contract disease. In vaccinated children who became ill, the prevalence of chronic respiratory symptoms and episodes of infections was insignificantly higher. It is worth mentioning that all kinds of respiratory symptoms with respect to their persistence (intermittent and continual) showed the aforementioned trend and the prevalence of medical diagnosis of allergy and asthma followed the same pattern. The frequency of medical diagnosis of asthma was twice as low in the vaccinated as in non-vaccinated children. Adjusted risk estimates for allergy, asthma and susceptibility to respiratory infections in the vaccinated children were about half of that found in the reference group.

The results of our study support a hypothesis that measles immunization provides non-specific immune stimulation sufficient to decrease the risk of allergy and respiratory morbidity due to acute and chronic diseases. Our data provide an indirect evidence that inoculation of live attenuated measles virus alters T helper-mediated responses leading to IgE antibody responses that contribute to the manifestation of atopic disease. Assuming that measles vaccination may protect against allergic manifestations in children, it would be difficult to explain the rising trends of atopy observed over the last twenty years in the countries of western Europe [14].

We think that the results of our study are consistent with observations made in developing countries which show that measles immunization may be implicated in a spectacular reduction of 30 to 86% in infant mortality from other conditions than measles [1]. However, we could not confirm the findings that measles infection in the first year of life protects against allergic manifestations in later years of life, since in our study groups there were no children with measles infection passed in infancy.

The outcome of our study is in agreement with the evidence produced by Paunio et al. [15] who found that common allergic diseases were substantially more prevalent in children and adolescent persons with history of measles. Finally, we would like to refer to the ecological analysis of pooled data of national and local immunization rates from 91 centers and 38 countries. The analysis revealed no association between immunization against diphtheria, tetanus toxoids and pertussis (DTP) and atopic disease [16]. However, the ecological approach is burdened with many drawbacks typical of this kind of study and thus associations at the individual level cannot be excluded.

Epidemiologic studies on respiratory health in children and adults largely focus on environmental factors such as outdoor and indoor qualities, whereas the role of host factors is often neglected in the risk assessment analysis. Our study shows that immunization status and contraction of measles are strong determinants of the distribution of acute and chronic respiratory symptoms in the children population, and this variable should be regarded as a predictor of many health events. This issue deserves careful consideration in view of the fact that adult chronic diseases stem from the fetal and infant disorders [17]. Our study was limited to children population, but we think that vaccination against measles in childhood may also have beneficial effects on health status of adults and make them better protected against allergy-related health disorders.

It is not likely that the results of our study could be explained by bias due to different health-conducive behavior in the vaccinated and non-vaccinated children since it was to a great extent controlled by parental education. The latter variable may be considered as a marker of sociocultural determinants and better preventive health care within the family. It is debatable whether the apparent benefits from measles immunization might be due to bet-

ter nutrition of children, but again this would be related to the socioeconomic confounding factor. Neither outdoor/indoor air quality, nor ETS and maternal smoking during pregnancy could explain differences in the prevalence pattern of symptoms and diseases that occurred in vaccinated and non-vaccinated children.

The study has some limitations that could result from a potential differential selection bias in the groups of vaccinated and non-vaccinated children. The children from the latter group had more spells of recurrent respiratory infections and allergy. Parents preoccupied with the health of their children could have delayed and even avoided measles vaccination. If the proportion of chronically ill children would reach a high level, then the estimated beneficial effect of vaccination would have been inflated. It was difficult to precisely assess the importance of this bias since the vaccination records did not contain medical certificates confirming contraindications against measles vaccination. We found that the proportion of those vaccinated in the group of allergic children was 81.1% and that it was lower (71.0%) in the group of non-allergic children. Since the difference in the prevalence of vaccinations in groups under comparison (10.1%) appeared to be insignificant (95% CI 4.5–15.0), we may assume unlikely to find explanation of our findings in the selection bias.

Errors in the diagnosis of allergy and measles resulting from false information obtained from interviewed children's mothers may be regarded as another source of weakness of the study, but it is unlikely that such diagnostic errors differed across vaccinated and non-vaccinated groups of children. There was no information about the temporal relationship between measles immunization and the occurrence of respiratory symptoms and allergy. However, one has to remember that the first dose of the vaccine is routinely given to infants very early, at the age of 13-15 months whereas chronic respiratory symptoms occur much later.

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