

Does childhood immunization against infectious diseases protect from the development of atopic disease?

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The argument of whether early immunization against infections promotes allergy or protects from it is presently under debate. The relationship between childhood immunization and the development of atopic diseases (asthma, allergic rhinitis and eczema) was examined in a population-based sample of 718 adolescents by taking individual data drawn from personal paediatric records on the schedule and the type of vaccination into account. Atopic diseases were determined using a standardized questionnaire. After adjustment for sex, age, father's socioeconomic status and active smoking, adolescents having been vaccinated ($n = 694$) had a significant lower risk to suffer from asthma or atopic diseases than non-vaccinated adolescents did ($n = 24$) [odds ratio (OR) = 0.30; 95% CI: 0.10, 0.92]. The relationship did not depend on the disease against which the vaccine was used as prophylaxis, the observance of the vaccination schedule or the number of inoculations. A higher protection was observed in the case of live attenuated vaccines (oral poliomyelitis and bacilli Camille-Guerin; OR = 0.26; 95% CI: 0.08, 0.83). These results, in agreement with previous ecological data, support the hypothesis that early vaccines could promote Th1 proliferation in response to the infectious agent contained in it, which inhibits the enhancement of atopic manifestations. Further studies are needed to confirm the phenomenon.

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At present, existing data on the relationship between the use of immunization and the development of allergic diseases are insufficient for conclusions (1–5) because of lack of individual detailed information on the vaccinations. Moreover, consideration of confounding factors was neglected in most studies having provided such data due to the lack of exhaustive information.

Population studies have shown that tuberculosis vaccination [with bacilli Camille-Guerin (BCG)] was either inversely related (6–8) or unrelated to asthma and allergies (9–12). However, clinical studies have reported significant evidence in favour of a negative correlation between the two phenomenon (13–15). For the diphtheria–tetanus–poliomyelitis (DTPolio)

vaccine and pertussis (whooping cough) vaccine (Pert), few studies have been performed. An ecological study found fewer symptoms indicative of allergic disease in children having been vaccinated against diphtheria, tetanus and pertussis compared with those not vaccinated (2). Regarding Pert, other studies have reported no significant relationship between vaccination and allergy (16–18). However, a retrospective study found a risk of asthma four times higher in teenagers who had received Pert than that in non-vaccinated teenagers (19).

We studied at the population level the relationship between childhood immunization against infectious diseases and the prevalence of asthma, allergic rhinitis and eczema by taking into account

individual data on vaccination, namely the infection against which the vaccine was used as prophylaxis, the number of doses, the vaccination schedule observance, and by adjusting for potential confounding factors of the relationships. Whether an inactivated or live attenuated micro-organism or virus was used was also considered because it can be hypothesized that the effect of live vaccines is different from that of inactivated vaccine with respect to the immune response, which can have an influence on the development of asthma and atopic diseases.

Subjects and methods

Population

A total of 718 adolescents randomly chosen in seventh and eighth graders from the West Marne department of France participated in a survey on risk factors for asthma, rhinitis and eczema health. To this extent, they responded to an enriched version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire that had been translated from English in French and back-translated (20). Simultaneously, information on the vaccines was obtained from their personal paediatric record form (the so-called *Carnet de Santé*), systematically provided to parents of children born in France. This personal health record, which is filled by a doctor after each vaccination, allows obtaining the precise date, name and batch of every vaccine. These 718 adolescents constituted the subset of all adolescents having participated in the ISAAC in West Marne ($n = 3947$), whose parents had initially given their consent for a follow-up study. The exact aims of the follow-up had not been provided to the parents so that the estimation of the exposure (immunization) was blinded. Previously, the Commission Nationale Informatique et Liberté had given the authorization to obtain the adolescents' addresses in order to follow them up for vaccinations. Adolescents having participated in the follow-up did not differ significantly from the others in the prevalence of atopic disorders and other sociodemographic characteristics.

Health outcomes

The present analysis involved the entities monitored in the ISAAC, namely asthma, allergic rhinitis (including rhinoconjunctivitis and hay fever) and eczema, which are based on standardized definition previously described (20). For each of these disorders, two definitions were

distinguished: reported symptoms characteristic of the disease over the past 12 months and reported lifetime diagnostic label. In addition, an adolescent was considered to have at least one atopic disease when he or she have ever had reported asthma, allergic rhinitis or eczema.

Vaccination

Individual data on vaccination included the type of immunization as indicated by the disease against which the vaccine was used as prophylaxis, the number of doses, the vaccination schedule observance and the type of vaccine (inactivated or live attenuated, viral or microbial). Vaccinations were performed by GP or paediatricians using national standard vaccine preparations and doses.

In order to test the hypothesis of an early effect of immunization, the three vaccines received before the age of 6 months were considered in the study: the antituberculosis vaccine (BCG), the diphtheria–tetanus–poliomyelitis vaccine (DTPolio) and the pertussis vaccine (Pert). For the DTPolio and Pert vaccines, two types of positive status were defined: having had at least one dose, and having had three doses or more (DTPolio3 and Pert3). An adolescent was considered as vaccinated when he or she had received at least one of the three vaccines (DTPolio, Pert or BCG).

Vaccinations were performed according to the following calendar: (i) first month of life: BCG; (ii) second month: DTPolio and Pert (first injection); (iii) third month: DTPolio and Pert (second injection); (iv) fourth month: DTPolio and Pert (third injection).

For the purpose of the present paper, observance of the vaccination schedule was defined by distinguishing among vaccines and boosters 'on time' (respecting the national vaccination schedule), 'late' (later than expected vaccination schedule), 'early' (earlier than expected vaccination schedule), or 'early and late' (when at least one vaccine was later and one vaccine was earlier than the schedule). To verify the effect of the type of vaccine, the adolescents were separated into three groups and compared with non-vaccinated:

- The 'live' group included those who had received only live attenuated microbial or viral vaccines: (BCG, oral poliomyelitis).
- The 'inactivated' group included those who had received only inactivated microbial or viral vaccines (pertussis, injectable poliomyelitis).
- The 'live + inactivated' group included those who had received both kinds of vaccines.

Epidemiological and statistical analysis

To examine the relationship between immunization and asthma and allergies, four research questions were formulated in our study.

- 1 Are DTPolio, Pert and BCG vaccines related to asthma and allergies in the same manner?
- 2 Does the relationship between asthma and allergies and vaccination vary according to the number of doses/inoculations?
- 3 Does observance of the vaccination schedule affect the relationship to asthma and allergies?
- 4 Does the type of vaccine (inactivated or live attenuated, viral or microbial) influence the relationship to asthma and allergies?

Analyses were performed on the entire group, as well as separately for girls and boys. Comparisons were performed with the chi-square test. The Fisher's test was introduced in the case of small samples. Logistic regression model was used to compute odds ratios (ORs) of the relationships between vaccinations and atopic diseases adjusted for confounders. Confounding factors included sex, age, active cigarette smoking (21), and socioeconomic status (SES) of the father. SES was based on the French National Statistical Institute (INSEE) nomenclature, the category 'intermediate professions' serving as reference, and the categories retirees and other categories being neglected because of the low number of parents in these groups. Environmental tobacco smoking was discarded because of the high rate of missing data. The fitness of each model was checked. To compare the ORs, the Breslow-Day test for homogeneity was used. ORs were calculated with a 95% confidence interval. All statistical calculations were performed using SAS software, version 8.

Results

Characteristics of the sample

Of the 718 adolescents who participated in the study (13.72 ± 1.20 yr), 396 were girls and 322 boys. Among them, 296 had already smoked at least a cigarette. The majority of the adolescents' fathers were blue-collar workers.

Reported asthma, allergic rhinitis and eczema

In the previous year, asthma was the most frequently reported symptom. Among lifetime diagnostic labels, eczema was the most frequent (Fig. 1). Overall, 362 adolescents had reported at least one atopic disease and 356 had not. As

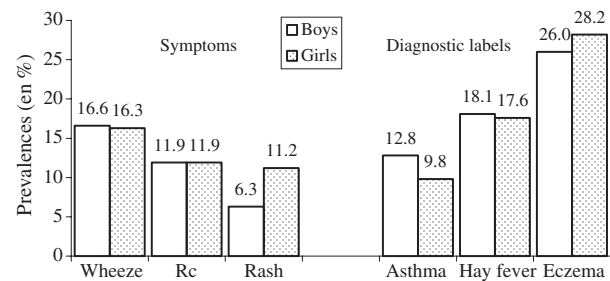


Fig. 1. Prevalence (%) of symptoms and diagnostic labels of asthma, hay fever, and eczema, by gender (n = 718).

Table 1. Sociodemographic characteristics of vaccinated and non-vaccinated adolescents (n = 718)

	Vaccinated (n = 694)	Non-vaccinated (n = 24)
Sex (%)		
Girls (n = 396)	55.2	54.2
Boys (n = 322)	44.8	45.8
Age (mean $\pm$ s.d.)	13.6 $\pm$ 1.2	13.8 $\pm$ 1.1
Age (%)		
12 yr (n = 234)	33.0	25.0
13 yr (n = 228)	31.9	29.2
14 yr (n = 162)	22.1	37.5
15 yr (n = 92)	13.0	8.3
SES of father (%)		
Farmer (n = 118)	18.0	10.0
Artisan (n = 33)	5.0	5.0
White collar (n = 59)	8.9	10.0
Intermediate (n = 101)	15.4	10.0
Employee (n = 70)	10.7	5.0
Blue collar (n = 232)	34.5	50.0
Retiree (n = 13)	1.9	5.0
Unemployed (n = 24)	3.6	5.0
Other (n = 13)	2.0	0.0
Cigarette smoking (%)		
Smoker (n = 296)	41.0	58.3
Non-smoker (n = 415)	59.0	41.7

expected, boys had significantly more asthma than girls. The girls had significantly more symptoms of eczema than the boys did, but there was no significant difference between them in terms of lifetime diagnostic label of eczema (Table 1). There was no statistically significant difference among the age groups. Among the four potential confounding factors, active cigarette smoking was the most closely related to asthma and allergies. Adolescents who smoked reported atopic manifestations significantly more often than the non-smokers did. The adolescents whose father had an intermediate profession tended to report asthma less frequently than the others. In contrast, the children of unemployed men tended to have a high incidence of asthma. The children of blue-collar workers, artisans and unemployed men had hay fever most frequently. Finally, regarding eczema, there was marked

contrast between the children of farmers or men with an intermediate profession (the least often affected) and the children of artisans, business employees or unemployed men (the most frequently affected).

Vaccination

The non-vaccinated group included 24 adolescents (3%). The study of sociodemographic characteristics showed that non-vaccinated were more frequently children of blue collars and active smokers (Table 1). The percentage of immunized pupils was close to 90% for every vaccine (BCG: 90.0%, DTPolio: 93.3%, DTPolio3: 86.5%, Pert: 88.7%, Pert3: 85.1%). Eighty-three per cent of the adolescents had had all three vaccines. Regarding vaccination schedule observance, 175 adolescents were inoculated 'on time'; 319 'late', 144 'early', and 80 'early and late'. Among the vaccinated children, 47 had received only inactivated microbial or viral vaccines, 82 had had only attenuated microbial or viral vaccines, and 565 had had both types of vaccine.

There was no difference between genders regarding the BCG (Table 2). More boys than girls were vaccinated with DTPolio and Pert.

Table 2. Immunization coverage according to gender, age category, and father's socioeconomic status (SES) and smoking habits (n = 718)

	Vaccinated with (%)				
	DTPolio	DTPolio3	Pert	Pert3	BCG
Sex/gender					
Girls (n = 396)	92.9	84.3	86.4	82.1	90.7
Boys (n = 322)	93.8	89.1	91.6*	88.8*	89.4
Age					
12 yr (n = 234)	94.9	90.6	92.3	89.3	91.5
13 yr (n = 228)	94.3	87.3	89.0	86.4	90.8
14 yr (n = 162)	90.7	82.1	87.7	82.7	84.6
15 yr (n = 92)	92.4	82.1	81.5*	76.1*	82.6*
Father's SES					
Farmer (n = 118)	94.9	87.3	92.4	87.3	87.3
Artisan (n = 33)	93.9	90.9	93.9	93.9	93.9
White collar (n = 59)	96.6	94.9	94.9	94.9	93.2
Intermediate (n = 101)	95.1	91.1	94.1	91.1	91.1
Employee (n = 70)	94.3	91.4	88.6	87.1	88.6
Blue collar (n = 232)	92.7	82.8	86.2	82.3	86.2
Retiree (n = 13)	76.9	76.9	69.2	69.2	92.3
Unemployed (n = 24)	95.8	87.5	83.3	83.3	95.8
Other (n = 13)	92.3	76.9	84.6	76.9	92.3
Cigarette smoking					
Smoker (n = 296)	91.8	82.0	84.7	80.3	84.7
Nonsmoker (n = 415)	94.5	89.6**	91.3**	88.2**	93.7***

DTPolio, having had at least one dose of diphtheria-tetanus-poliomyelitis; Pert, having had at least one dose of pertussis vaccine; DTPolio3, having had three doses of diphtheria-tetanus-poliomyelitis; Pert3, having had three doses of Pert; BCG, having had the vaccine against tuberculosis.

*p < 0.05; **p < 0.01; ***p < 0.001

There were significant differences among the four age groups, except regarding DTPolio. For all the vaccines, the children of white-collar workers and those whose father exercised an intermediate profession tended to have the highest rate of vaccination. More non-smokers than smokers had had BCG and Pert vaccination (p < 0.05). The same difference was observed for DTPolio3.

Relationship between vaccination and reported atopic diseases

The vaccinated adolescents reported less asthma, allergic rhinitis and eczema than the non-vaccinated adolescents. Non-vaccinated had a higher prevalence of asthma and atopic manifestations but wheezing in the past year (Table 3). Statistical significance was attained in the case of past year and lifetime eczema. The raw OR for suffering from at least one disease in the vaccinated with respect to the non-vaccinated children was 0.33 (95%CI: 0.13–0.84). The OR between vaccination and atopic diseases adjusted on confounders was 0.30 (95%CI: 0.10–0.92; p = 0.035). In the multivariate logistic model, the OR associated with cigarette smoking was 1.80 (95%CI: 1.27–2.55; p < 0.001). ORs corresponding to gender, age and SES were not significant.

The vaccinated boys were slightly less atopic than the non-vaccinated boys [0.12 (95%CI: 0.01–1.05), p = 0.055] (Table 4). Among the girls (n = 396), there was no significant difference, although the OR was still < 1 [OR = 0.39 (95%CI: 0.10–1.58), p = 0.177].

Figure 2 presents the answers to the four lines of research mentioned in the introduction:

1 Are DTPolio, Pert and BCG vaccines related to asthma and allergies in the same manner?

Table 3. Frequency of symptoms and diagnostic labels of asthma, allergic rhinitis, and eczema according to gender (n = 718)

	Vaccinated (n = 694)	Non-vaccinated (n = 24)
Sex (% girls)	55.2	54.2
Mean age (yr ± s.d.)	13.6 ± 1.2	13.8 ± 1.1
Asthma		
Past year wheeze (%)	16.7	8.3
Lifetime asthma (%)	10.8	20.8
Allergic rhinitis		
Past year RC (%)	11.8	16.7
Lifetime HF (%)	17.4	29.2
Eczema		
Past year rash (%)	8.8	12.5*
Lifetime eczema (%)	26.2	54.2**

RC, rhinoconjunctivitis; HF, hay fever

*p < 0.05; **p < 0.01.

Table 4. Risk of allergy associated with number of vaccinations, by gender (n = 718)

	Girls (n = 396)		Boys (n = 322)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
One vaccine vs. NV*	0.54 (0.10–2.99)	NS	0.04 (0.01–0.79)	0.035
Two vaccines vs. NV	0.28 (0.06–1.31)	NS	0.16 (0.02–1.60)	0.119
Three vaccines vs. NV	0.39 (0.10–1.58)	NS	0.12 (0.01–1.05)	0.055

*Non-vaccinated

Vaccines taken into account were: DTPolio, Pert and BCG

Regardless of the vaccine, the adolescents having received it suffered less significantly from asthma and allergies than the non-vaccinated adolescents did. More precisely, the following results were obtained:

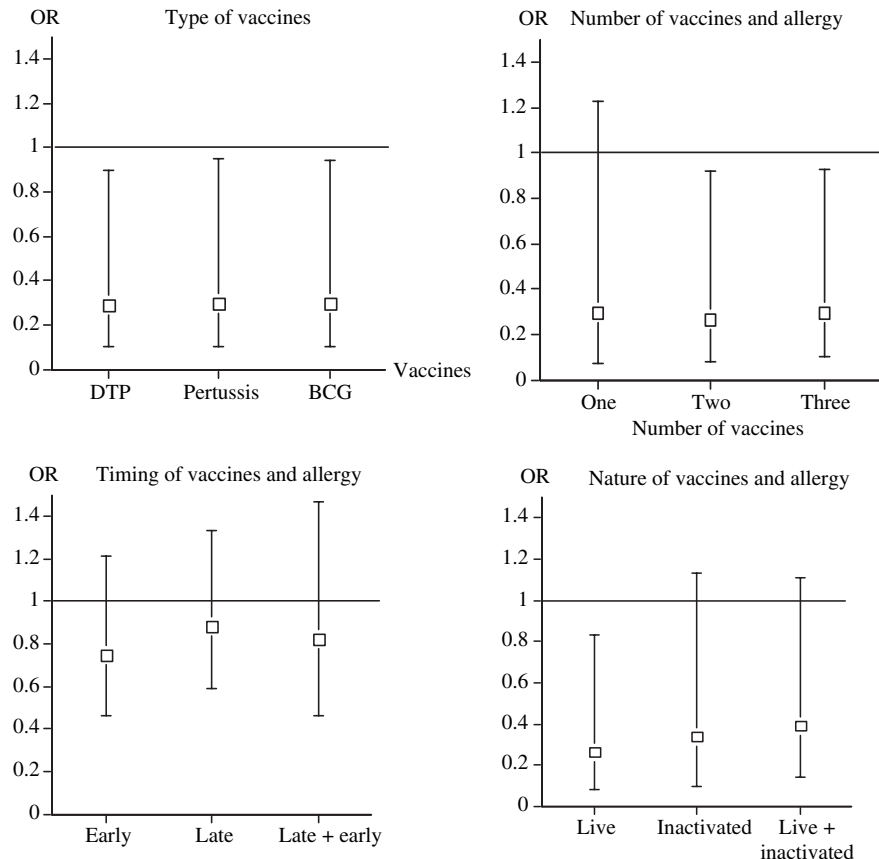
- DTPolio: OR = 0.29 (95%CI: 0.10–0.90), p = 0.033. Boys were more protected than girls [boys: 0.11 (95%CI: 0.01–0.99); girls: 0.37 (95%CI: 0.09–1.49)]
- Pert: OR = 0.30 (95%CI: 0.10–0.94), p = 0.038 [boys: 0.12 (95%CI: 0.01–1.03); girls: 0.39 (95%CI: 0.10–1.60)]
- BCG: OR = 0.30 (95%CI: 0.10–0.93), p = 0.037 [boys: 0.12 (95%CI: 0.01–1.08); girls: 0.40 (95%CI: 0.10–1.56)].

2 Does the relationship between asthma and allergies and vaccination vary according to the number of doses/inoculations?

Eighty-six per cent of the vaccinated adolescents had received three vaccines. Regardless of the number of doses/inoculations, the vaccinated adolescents reported less asthma and atopic disorders than non-vaccinated adolescents although the relationship was not statistically significant in the case of only one dose/inoculation. There was no association between having only one dose/inoculation and having more doses/inoculations as the OR of 'three doses' vs. 'one dose' was 1.00 (95%CI: 0.41–2.44) (NS). In addition, for the DTPolio as for the Pert vaccine, there was no significant difference between the adolescents having had only the first dose (n = 49, and n = 26, respectively) and the adolescents having had all the three doses (n = 621, and n = 611, respectively) [OR = 1.30 (95%CI: 0.68–2.50), and OR = 0.89 (95%CI: 0.35–2.28), respectively]. The ORs of the boys were lower than those of the girls, which remained nevertheless less than 1 (Table 4).

3 Does observance of the vaccination schedule affect the relationship to asthma and allergies?

Fig. 2. Odds-ratios between vaccines and allergy according to four lines of research (n = 718).



Children who observed the vaccination schedule did not have a lower prevalence of asthma or allergies. More precisely:

- 'early' vs. 'on time': OR = 0.75 (95%CI: 0.46–1.21).
- 'late' vs. 'on times': OR = 0.88 (95%CI: 0.59–1.33).
- 'late and early' vs. 'on time': OR = 0.82 (95%CI: 0.46–1.47).

The ORs of the boys were lower than those of the girls.

4 Does the type of vaccine influence the relationship to asthma and allergies?

The children who received only live (attenuated) vaccines reported asthma and allergies less frequently than the other children as shown by the OR values.

- Live (attenuated) vaccine vs. no vaccination: OR = 0.26 (95%CI: 0.08–0.83), $p = 0.022$.
- Inactivated vaccine vs. no vaccination: OR = 0.34 (95%CI: 0.10–1.13), $p = 0.078$.
- Live + inactivated vaccines vs. no vaccination: OR = 0.39 (95%CI: 0.14–1.11), $p = 0.079$.

Furthermore, comparing grouped live vs. inactivated vaccines did not yield any statistical significant difference [OR = 0.80 (95%CI: 0.32–2.01), NS]. Comparisons by gender showed ORs of approximately 0.10 for the boys and ORs of approximately 0.50 for the girls (NS).

Discussion

The present study showed that after adjustment for gender, age, father's SES, and active cigarette smoking, immunized adolescents reported less frequently atopic diseases than non-vaccinated adolescents. That the phenomenon is limited to atopic diseases is supported by that fact that the relationship was not found for wheezing in the past year, which may also be caused by transient infections. We chose to limit the present work to early vaccines to investigate the hypothesis that vaccination early in life would have an influence on the development of the immune system. The fact that the role of immunization might be stronger in early life and progressively fade with maturity was supported by a reinforced relationship for lifetime eczema which is most likely to be first observed in infancy and early childhood and a weakening association with current reported symptoms of itchy rash.

To the best of our knowledge, this is the first population-based study using individual data and taking into account vaccines received before the age of 6 months (namely DTPolio, Pert and BCG) and the development of allergy up to adolescence. Data on inoculations were obtained from the personal paediatric health record and those on reported asthma and allergic diseases from the ISAAC questionnaire.

The findings of prior studies on the relationship between immunization against childhood infections and allergy in adolescence are contradictory. On the one hand there are previous data which are in contrast with ours. However, it is important to note that not all these studies were based on vaccines administered very early in life (2, 12, 19). Furthermore, these studies involved various age groups. Most studies worked with populations relatively younger (10), or much younger than ours (4, 6, 8, 12, 14). Only few studies focused on groups comparable in age with our study population so disposing of a longer lifespan for allergies, which is of importance for girls who become allergic later in life (2, 5, 3). On the other hand, there are findings that are consistent with ours. One study, which was also based on the ISAAC questionnaire, but which took overall vaccination percentages into account (2), reported a significant negative correlation between the percentage of children immunized against diphtheria, tetanus and whooping cough and the prevalence of allergies (asthma, hay fever and eczema). In another study, which was carried out with individual data and involved the same vaccines, similar findings were observed (22). Nevertheless, this concerned an atopy risk-enhanced birth cohort.

Our findings show a sex ratio in the relationship between vaccinations and allergy in favour of boys. So far, data had not been stratified on sex in previous studies, which prevents comparisons. Whether sex could influence the protective effect of vaccination cannot be answered by our data. However, this could also result by chance because of the reduced size of the sample.

The collected data contribute to clarifying the relationship between immunization and allergy beyond the prior level of understanding. The relationship did not depend on the type of immunization. Similarly, in the case of DTPolio or Pert vaccine, there was no difference between adolescents having had one dose and those who had had at least three.

Consequently, one may postulate that the first dose is the one that most affects the immune system. Comparison of allergy according to the observance or non-observance of the vaccination

schedule resulted in no significant findings. In contrast, comparison of the adolescents according to the type of vaccine received showed that those who had only live attenuated vaccines developed allergy significantly less often than those who had inactivated vaccines. This finding supports the hypothesis of action exercised by the vaccine on the development of the immune system early in life. Live attenuated vaccines are thought to promote proliferation of Th1 lymphocytes. This proliferation would inhibit production of immunoglobulin E, which characterizes the body's allergic response. Recent data have shown the importance of early life events in the development of allergic diseases because of their influence on the immune system and target organs (23, 24).

One limitation inherent in our study consists of the small size of the group of non-vaccinated children (24 adolescents) as this could lead to relationships by chance. Nevertheless, statistical methods appropriate for small sample sizes were applied and the fitness of the multivariate models used for assessing the relationships were checked. A small number was expected in our study given that in France vaccination with BCG and DTPolio is compulsory and that the Pert vaccine is strongly recommended. This figure corresponded to official WHO estimations of immunization coverage for the department of the Marne. In spite of the existing obligation, a similar number of non-vaccinated children was found in New Zealand, where findings comparable with ours were observed (16). Another limitation of our study is provided by the fact that unmeasured confounders might be responsible for the observed results. Although our list of confounder factors included various suspected factors (sex, age, active cigarette smoking and SES of the father), the inclusion was not exhaustive. Other major confounders might have been represented by familial history of atopy, passive and environmental tobacco smoking and air pollution. However, results did not change after adjusting for paternal and maternal asthma, which was available in our study, and SES, which is related to tobacco smoking consumption in West Marne. Indeed, direct data on environmental tobacco smoking were not available because of the high rate of missing data. A higher likelihood of being more exposed to air pollution was also excluded because all the adolescents lived in a semi-rural zone.

Another weakness of our study consists of potential unresolved biases for the non-vaccinated group. In our sample, being non-vaccinated was associated with higher active smoking rate and

blue collar SES of the father, which were corrected for in the analyses. Lastly, the study of medical contraindications for the use of vaccination showed that none of the non-vaccinated adolescents included in our sample had records of bronchiolitis, obstructive bronchitis, pneumonia, acute bronchitis or parasitosis potentially related to allergic diseases. A final restriction of our study is that several paediatric vaccines have been excluded from the analysis, which might have had an impact on results. However, we decided to consider overall early life immunization.

Overall, the vaccinated adolescents did not report significantly more atopic diseases than the non-vaccinated adolescents in our population-based sample. Our data support the hypothesis of no evidence for a causal role of childhood vaccination in the occurrence of atopic diseases. Further studies are needed to confirm the phenomenon.

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