

Transient Suppression of Atopy in Early Childhood Is Associated With High Vaccination Coverage

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ABSTRACT. *Objective.* To analyze prevalences of allergic sensitization and atopic disease in relation to vaccination coverage.

Methods. A German atopy risk-enhanced birth cohort of 1314 neonates who were born in 1990 in 5 German cities was studied. A total of 943 children participated in the follow-up visit at 5 years of age. Atopic symptoms and diagnoses (derived from structured interviews), total serum immunoglobulin E, and specific immunoglobulin E against 9 common allergens (CAP Radio-Allergo-Sorbent Test Fluoro-Enzyme Immunoassay) were evaluated. Children were grouped into dose percentiles according to cumulative doses of any vaccine given up to 5 years of age (<10%, 0–11 doses; 10%–50%, 12–14 doses; 51%–90%, 15–20 doses; >90%, 21–27 doses).

Results. The cumulative vaccine dose was inversely related to atopic dermatitis prevalences at 6 months (13.8%, 5.2%, 5.1%, and 4.5%), 2 years (16.9%, 10.9%, 7.4%, and 3.7%), 3 years (27.6%, 16.4%, 13.5%, and 4.5%), and 5 years (28.3%, 16.0%, 9.3%, and 11.9%). Asthma followed a similar pattern at age 3 (22.4%, 8.6%, 6.7%, and 6.3%), age 4 (20.0%, 8.6%, 8.9%, and 8.1%), and age 5 (20.8%, 12.6%, 10.3%, and 5.5%). Allergic sensitization rates were inversely related to the cumulative vaccine dose at age 2 (37.5%, 29.1%, 23.8%, and 12.9%).

Conclusion. Children with a higher vaccination coverage seemed to be transiently better protected against development of atopy in the first years of life. *Pediatrics* 2003;111:e282–e288. URL: <http://www.pediatrics.org/cgi/content/full/111/3/e282>; child, preschool, vaccination, asthma, atopic dermatitis, immunoglobulin E.

ABBREVIATIONS. IgE, immunoglobulin E; OR, odds ratio; CI, confidence interval.

There has been much recent debate about the possible promotion of allergy by common childhood vaccinations. A substantial proportion of children predisposed to allergy may not be fully vaccinated because of such apprehension.¹

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Promotion of allergy may occur directly, by administering potentially proallergic vaccines, or indirectly, by hindering the Th1-promoting effect of infectious agents against which the child is vaccinated. Pertussis toxin, which is included in all pertussis vaccines, is a classic adjuvant for immunoglobulin E (IgE) formation in animal models² and has been linked with a shift toward Th2-like cytokines in humans.³ Indirect evidence for a role of missing infections that were prevented by immunizations comes from epidemiologic studies showing an association of declining rates of infection with rising prevalences of allergic disease.^{4,5} In fact, some recent cross-sectional studies suggest a proallergic effect of early childhood vaccinations.^{6,7} Retrospective studies indicate a lower prevalence of atopy among children with a lower vaccination coverage.^{6,8,9} Some of these studies are hampered by small sample sizes. This study prospectively investigated the association between childhood vaccinations and atopy and prevalences of atopic disease in children from a large observational birth cohort (MAS-90) up to the age of 5 years.

METHODS

Patients

At 6 obstetric departments of 5 German cities (Berlin, Düsseldorf, Freiburg, Mainz, and Munich), cord-blood IgE values were obtained from 6401 (84%) of the total of 7609 infants born between January 1 and December 31, 1990. Parents of 6019 neonates each filled out a questionnaire that comprised diagnoses and relevant symptoms of atopic diseases and of allergy tests. Of all newborns, those with at least 2 atopic family members and/or a cord-blood IgE value ≥ 0.9 kU/L were assigned to a high-risk group ($N = 920$). A control group of 1619 infants was simultaneously drawn by a dynamic randomization procedure from the remaining newborns. After premature infants, newborns with major health problems, twins, or newborns from families who could not speak German were excluded, 1985 infants remained eligible and were invited to take part in a prospective observational study (MAS-90). Of these, 1314 (66%) participated and constituted the basis of the cohort: 499 (38%) infants belonged to the high-risk group, and 815 (62%) infants belonged to the control group with no or lower atopy risk.

The cohort infants and their parents were regularly seen for follow-up visits at ages 3, 6, 12, and 18 months and 2, 3, 4, and 5 years. At each visit, parents completed a questionnaire and gave a structured interview about their child's diseases and atopic symptoms. To keep the reporting bias low, parents kept a diary in which details were recorded whenever the child became sick. The study coordinators monitored the diary at the indicated examination intervals. At each visit, the children received a standardized physical examination by trained study physicians. The parents of

all children involved in the study gave their informed consent. The research protocol was approved by the local ethics committee.

Definition of Atopic Diseases

Atopic dermatitis was diagnosed from a combination of dry skin and at least 3 of 9 typical signs (itching, erythema, red papules, vesicles, rhagades, excoriation, squamae, lichenification, and perifollicular accentuation) in at least 3 of 26 typical anatomic sites (eg, cheeks, infra-auricular, extensor, or flexural areas). A positive definition of asthma required at least 2 wheezing episodes. Allergic rhinitis was defined as stuffy and/or runny nose in combination with conjunctivitis, without a cold, lasting for 2 or more months during the preceding observation period, plus diagnosis by a physician.¹⁰

Vaccinations

The German vaccination schedule, as officially recommended in 1990, is summarized in Table 1. As in many other countries, covaccination for diphtheria/tetanus with or without pertussis and measles/mumps with or without rubella was common. Pertussis vaccination, not officially recommended in 1990, was recommended again in 1991. Diphtheria/tetanus/pertussis immunizations were recommended at ages 3, 4, 5, and 15 months. The vaccination histories of the children, however, varied. Corresponding to the observational study design, there was no intervention regarding timing of vaccination and selection of vaccine preparations. Vaccinations were recorded from official vaccination documents, which were available for all children in the cohort. Infants with documented vaccination were regarded as vaccinated; others were regarded as nonvaccinated.

Determination of IgE

Venous blood samples were obtained at birth (cord-blood) and at 1, 2, 3, and 5 years. Sera were analyzed for total IgE and specific IgE against 9 common allergens: inhalant outdoor (birch and grass), indoor (mite, cat, and dog), and food (egg, milk, wheat, and soy). Analysis was performed in 1 laboratory by CAP Radio-Allergo-Sorbent Test Fluoro-Enzyme Immunoassay (Pharmacia, Freiburg, Germany). A child was considered sensitized when the specific IgE antibody titer of 1 or more of the 9 allergens tested was ≥ 0.35 kU/L. Cord-blood IgE levels were categorized as not elevated (<0.9 kU/L) or elevated (≥ 0.9 kU/L).

Statistical Methods

χ^2 tests were applied to compare prevalences between groups, and Mantel-Haenszel tests were applied for analyzing trends across categories. The Mann-Whitney *U* test was used for comparisons of continuous variables. For longitudinal analyses, we used generalized estimation equation models to adjust for repeated measures. To take the stratified sampling scheme into account and to assess participation bias and potential effect modification, we initially stratified all multivariate analyses for elevated cord-blood IgE concentration, family history of atopy, and social status (defined as low, middle, or high parental education).

When the results were similar over strata, however, we calculated the multivariate models in the total sample with indicator variables included for high risk of atopy at birth (elevated cord-blood IgE concentration or 2 or more atopic family members) and parental education. Statistical significance was defined by a 2-sided α level of 0.05. Statistical analysis was performed by using SPSS software version 10.0 (SPSS Inc, Chicago, IL) and SAS software version 6.12 (SAS Institute, Cary, NC).

RESULTS

Response Rates and Characteristics of Study Subjects

Of the 1314 children in the MAS-90 birth cohort, 943 (71.8%) children participated in a follow-up visit at the age of 5 years. Serum was available from 64.3% of the participating children at age 5; 43.3% of the participants had no atopic sibling or parent, 35.8% had 1 atopic family member, and 20.9% had 2 or more atopic family members.

To assess potential participation bias, we compared sociodemographic characteristics of participants with those of children lost to follow-up. Participating children did not differ significantly from the whole cohort in terms of gender, atopic family history, cord-blood IgE levels, sibship size, and typical childhood infections (measles, mumps, rubella). Pertussis infection was more prevalent among participants than among nonparticipants (10.2% vs 5.1%; $P = .005$), as was prolonged breastfeeding (>6 months, 31.0% vs 11.5%; $P < .001$).

Vaccination Coverage

Vaccination coverage rates are displayed in Table 1. Coverage was low for *Haemophilus influenzae* type b and pertussis vaccination.

Measles/Mumps

Allergic disease prevalences tended to be lower among children who were vaccinated against measles and mumps. A significantly reduced prevalence of asthma was observed at 1 year (5.0% vs 10.2%; $P = .050$) and 3 years (7.3% vs 17.0%; $P = .003$). The prevalence of atopic dermatitis was significantly reduced at 6 months (4.7% vs 12.0%; $P = .012$), 18 months (7.2% vs 18.2%; $P = .001$), 3 years (13.1% vs 21.6%; $P = .043$), and 5 years (Table 2). Allergic rhinoconjunctivitis prevalences were below 3% up to

TABLE 1. Recommended Minimum of Vaccination Doses for a Sufficient Protection Against Communicable Diseases and Vaccination Coverage up to the Age of 5 Years Among the 943 Study Subjects

Vaccine	Recommended Vaccination Doses (n)	Never Vaccinated (%)	Received Doses as Recommended or More (%)
Diphtheria	3*	0.8	97.6
Tetanus	3*	0.7	98.0
Pertussis	3*	59.7	33.3
Measles	1*	10.4	89.6
Mumps	1*	10.2	89.8
Rubella	1*	19.3	80.7
Polio (OPV)	3*	1.1	96.3
HiB	3†	13.0	66.3
Tick-borne encephalitis	3†	89.8	5.4

OPV indicates oral polio vaccine; HiB, *Haemophilus influenzae* type b.

* Officially recommended at cohort study start (1990).

† No officially recommended vaccination (1990); number of shots as recommended by manufacturer.

TABLE 2. Prevalences of Allergic Disease and Allergic Sensitization at 5 Years of Age in Relation to Vaccination Status

	Nonvaccinated		Vaccinated		P Value
	n	%	n	%	
Pertussis					
Asthma	64/527	12.1	34/366	9.3	.180
Atopic dermatitis	78/527	14.8	34/366	9.3	.014
Allergic rhinoconjunctivitis	29/527	5.5	18/366	4.9	.816
Allergic sensitization	134/368	36.4	79/238	33.2	.418
Measles/mumps*					
Asthma	14/85	16.5	84/802	10.5	.135
Atopic dermatitis	19/85	22.4	92/802	11.5	.007
Allergic rhinoconjunctivitis	10/85	11.8	35/802	4.4	.007
Allergic sensitization	21/48	43.8	189/554	34.1	.179
Rubella					
Asthma	23/169	13.6	75/724	10.4	.224
Atopic dermatitis	30/169	17.8	82/724	11.3	.023
Allergic rhinoconjunctivitis	13/169	7.7	34/724	4.7	.168
Allergic sensitization	39/100	39.0	174/506	34.4	.377
HiB					
Asthma	13/111	11.7	85/782	10.9	.918
Atopic dermatitis	17/111	15.3	95/782	12.1	.430
Allergic rhinoconjunctivitis	8/111	7.2	39/782	5.0	.451
Allergic sensitization	27/76	35.5	186/530	35.1	.941

HiB indicates *Haemophilus influenzae* type b.

* Five children who received mumps vaccination without covaccination against measles and 1 child who received measles vaccination without covaccination against mumps were excluded from this analysis.

age 4, but at 5 years, >5% had allergic rhinoconjunctivitis and the prevalence among vaccinated children was less than half the prevalence among nonvaccinated children (Table 2).

Sensitization rates and total IgE levels were lower among measles/mumps-vaccinated children at all examination dates. Statistical significance was achieved for sensitization at 2 years (41.3% vs 23.0%; $P = .009$) and for total IgE at 1 year (6.1 kU/L vs 10.7 kU/L, $P = .019$) and at 5 years (Table 3).

In a longitudinal analysis of children with a family history of atopic disease, children who were vaccinated for measles/mumps were less likely to experience atopic dermatitis up to age 5 than nonvaccinated children (odds ratio [OR]: 0.50; 95% confidence interval [CI]: 0.29–0.86, adjusted for parental education), whereas among children with negative family history, no statistically significant advantage was found for vaccinated compared with nonvaccinated children (OR: 0.65; 95% CI: 0.34–1.23). Sensitization up to age 5 was also less likely among children with atopic family members (OR: 0.56; 95% CI: 0.34–0.93), but among children without atopic family history, we found no inverse relationship between measles/mumps vaccination and risk of sensitization (OR: 0.81; 95% CI: 0.40–1.62). No significant differences were found for measles/mumps vaccination status

and other outcome parameters (asthma, allergic rhinoconjunctivitis, total serum IgE).

Rubella

Prevalence rates of atopic dermatitis tended to be lower among vaccinated children at most examination intervals. Statistical significance was achieved at 6 months (4.6% vs 10.0%; $P = .008$), 2 years (7.6% vs 12.4%; $P = .039$), 3 years (12.6% vs 20.2%; $P = .009$), and 5 years (Table 2). No statistically significant differences were observed with regard to asthma or allergic rhinoconjunctivitis at 5 years (Table 2) or any other time point (data not shown). No statistically significant differences were found for allergic sensitization rates (Table 2) or total serum IgE levels (Table 3) at 5 years or any other examination date (data not shown).

Pertussis

At 5 years of age, allergic disease prevalences tended to be lower among pertussis-vaccinated children than in nonvaccinated children; the group difference was statistically significant for atopic dermatitis (Table 2). Period prevalence of atopic dermatitis was also significantly lower at 2 years (vaccinated versus nonvaccinated: 5.6% vs 10.5%; $P = .009$) and 3 years (10.9% vs 16.2%; $P = .025$). These differences

TABLE 3. Total IgE Levels at 5 Years of Age in Relation to Vaccination Status

	Total IgE Levels at 1 Year of Age in Relation to Vaccination Status							<i>P</i> Value	
	Nonvaccinated			Vaccinated					
	<i>N</i>	Total Serum IgE (kU/L)		<i>N</i>	Total Serum IgE (kU/L)				
		P25	Median	P75		P25	Median	P75	
Pertussis	368	15.6	45.3	109.5	238	14.2	32.0	96.0	.119
Measles/mumps*	47	21.2	80.8	326.5	555	14.5	37.5	99.9	.015
Rubella	99	17.6	40.1	127.5	507	14.8	37.8	102.8	.429
HiB	76	13.9	31.7	102.0	530	15.1	40.7	106.5	.285

* Five children who received mumps vaccination without covaccination against measles and 1 child who received measles vaccination without covaccination against mumps were excluded from this analysis.

were dose-dependent (at 2 years: 0–2 doses [10.0%], 3 doses [8.6%], 4–6 doses [3.0%], $P = .006$ for trend; at 3 years: 0–2 doses [16.4%], 3 doses [12.1%], 4–6 doses [7.1%], P for trend = 0.002). In comparison with children with <3 doses, the longitudinal risk was lowest for those who received 4 or more doses (OR: 0.61; 95% CI: 0.42–0.89). No statistically significant differences were found for asthma or allergic rhinoconjunctivitis prevalences.

After the first birthday, there was a tendency toward an inverse relationship between pertussis doses and the sensitization rate, which achieved statistical significance at 2 years (0–2 doses, 27.8%; 3 doses, 20.6%; 4–6 doses, 16.3%; $P = .01$ for trend), but in the longitudinal model, statistical significance was not reached (data not shown). The median of total serum IgE levels was significantly lower in the vaccinated group at 1 year (vaccinated versus nonvaccinated: 5.2 kU/L vs 7.2 kU/L; $P = .005$) and at 2 years (13.3 kU/L vs 20.8 kU/L; $P = .001$). Statistical significance was not reached at 3 years (20.5 kU/L vs 26.5 kU/L; $P = .113$) or at 5 years (Table 3).

Diphtheria/Tetanus

At 5 years of age, vaccinated children were not more afflicted with atopic disease than nonvaccinated children (data not shown). Similarly, no statistically significant differences were found earlier in life (data not shown). In a longitudinal multivariate analysis adjusting for potential confounders and repeated measures, however, the risk for atopic dermatitis was lower for diphtheria/tetanus-vaccinated children who received 3 doses (OR: 0.51; 95% CI: 0.24–1.07) or at least 4 doses (OR: 0.35; 95% CI: 0.16–0.78) as compared with children who received <3 doses.

After the first birthday, there was a tendency toward an inverse relation of diphtheria/tetanus doses and allergic sensitization rate that reached statistical significance at 2 years (0–2 doses, 35.7%; 3 doses, 26.0%; 4–6 doses, 17.8%; $P = .037$ for trend) and 5 years (0–2 doses, 58.3%; 3 doses, 36.2%; 4–6 doses, 29.0%; $P = .043$ for trend). Children who had received 4 or more diphtheria/tetanus doses had significantly lower total IgE levels (median) than children who had received fewer doses (at 1 year: 5.1 kU/L vs 6.5 kU/L, $P = .016$; at 2 years: 10.8 kU/L vs 19.5 kU/L, $P < .001$).

Haemophilus influenzae Type b

At 5 years of age, no statistically significant differences between vaccinated and nonvaccinated children were found for clinical manifestations of atopy, allergic sensitization rates (Table 2), or total serum IgE levels (Table 3). Similarly, no statistically significant differences were found at earlier examinations (data not shown).

Polio

The cohort included few nonvaccinated children for polio. No statistically significant differences were found between vaccinated and nonvaccinated children at 5 years or at earlier time points for clinical manifestations of atopy or allergic sensitization (data

not shown). Total serum IgE levels (median) were higher among vaccinated children at 2 years of age (17.7 kU/L vs 8.2 kU/L; $P = .037$) but not at 5 years (38.2 kU/L vs 29.5 kU/L; $P = .229$). No dose-response relationship was found (data not shown).

There was an inverse association of polio vaccination status (3 or more doses up to age 3) and the risk for asthma up to age 5 (OR: 0.58; 95% CI: 0.36–0.94, adjusted for high risk of atopy at birth and parental education). No corresponding associations were found between polio vaccination status and the other outcome variables.

Cumulative Dose of Vaccines That Contain Aluminum

Apart from diphtheria/tetanus/pertussis vaccines, relatively few children received other aluminum-containing vaccines (hepatitis B, $N = 1$; tick-borne encephalitis vaccine, $N = 96$). No dose-response relationship was found regarding atopic manifestations, total serum IgE, or allergic sensitization at 5 years of age or earlier (data not shown).

Effect of the Cumulative Dose of Any Vaccine

To assess a possible effect of the cumulative dose of any vaccine up to 5 years of age, we grouped children into dose percentiles (<10%, 0–11 doses; 10%–50%, 12–14 doses; 51%–90%, 15–20 doses; >90%, 21–27 doses). The cumulative vaccine dose was inversely related to atopic dermatitis prevalences at 6 months (13.8%, 5.2%, 5.1%, and 4.5%, respectively; $P = .049$), 2 years (16.9%, 10.9%, 7.4%, and 3.7%, respectively; $P = .010$), 3 years (27.6%, 16.4%, 13.5%, and 4.5%, respectively; $P < .001$), and 5 years (28.3%, 16.0%, 9.3%, and 11.9%, respectively; $P < .001$). The longitudinal risk for atopic dermatitis was reduced with higher vaccination coverage (Fig 1). Asthma followed a similar pattern at age 3 (22.4%, 8.6%, 6.7%, and 6.3%, respectively; $P = .001$), age 4 (20.0%, 8.6%, 8.9%, and 8.1%, respectively; $P = .05$), and age 5 (20.8%, 12.6%, 10.3%, and 5.5%, respectively; $P = .025$). The longitudinal risk was significantly reduced with increasing vaccination coverage (Fig 2). Only 7 children had allergic rhinoconjunctivitis at age 3 when prevalences were 1.7%, 0.8%, 0.2%, and 2.7%, respectively ($P = .040$). No statistically significant associations were found between allergic rhinoconjunctivitis and cumulative vaccine doses thereafter. Doses were also inversely related to total serum IgE levels (median) at age 1 (9.2 kU/L, 7.1 kU/L, 6.2 kU/L, and 4.7 kU/L, respectively; $P = .034$) and at age 2 (21.4 kU/L, 17.2 kU/L, 19.2 kU/L, and 10.3 kU/L, respectively; $P = .031$). Allergic sensitization rates were inversely related to the cumulative vaccine dose at age 2 (37.5%, 29.1%, 23.8%, and 12.9%, respectively; $P = .021$) and longitudinally the risk for sensitization was reduced (Fig 3).

Sociodemographic Characteristics of Children With High Vaccination Coverage

There was an inverse relationship between older siblings and general vaccination coverage. The proportion of children with older siblings in the dose percentiles (<10%, 0–11 doses; 10%–50%, 12–14 doses; 51%–90%, 15–20 doses; >90%, 21–27 doses) was

Fig 1. Risk (OR, 95% CI) for atopic dermatitis up to the age of 5 years in relation to cumulative vaccination doses, adjusted for high atopy risk at birth and parental education.

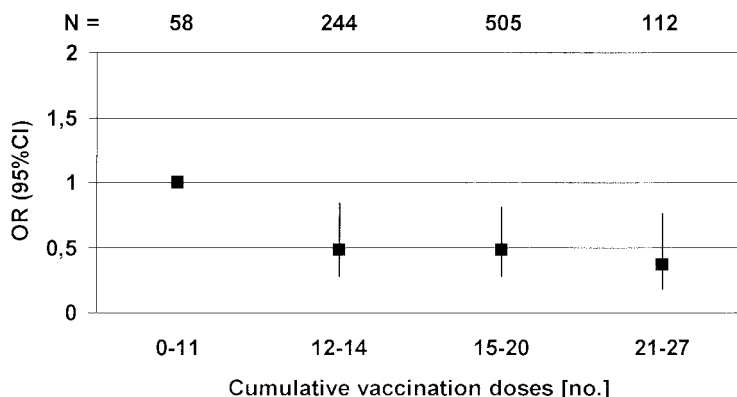
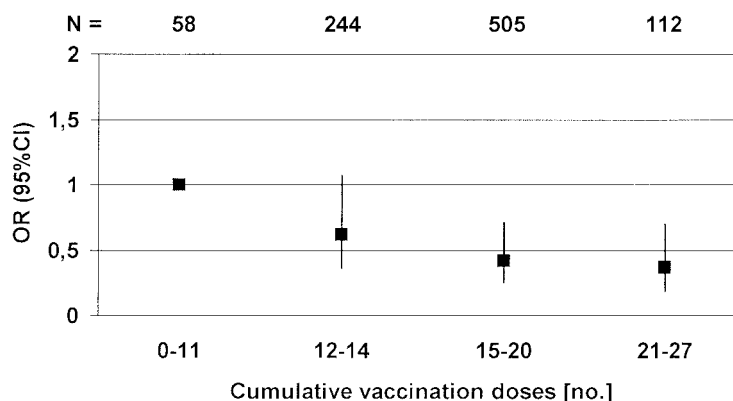


Fig 2. Risk (OR, 95% CI) for asthma up to the age of 5 years in relation to cumulative vaccination doses, adjusted for high atopy risk at birth and parental education.

64.3%, 55.2%, 40.8%, and 41.5%, respectively ($P < .001$ for trend). No statistically significant trend was seen for parental smoking habits, parental education, or atopic family history.

DISCUSSION

This study revealed no evidence for an allergy-promoting effect of common childhood vaccines in a prospectively followed atopy risk-enhanced birth cohort. Moreover, children with a better vaccination coverage seemed to be better protected against development of atopy in their second and third years of life. The mechanism through which vaccinations early in life could have modified the natural course of allergy remains to be elucidated. A biologically plausible explanation may be that some vaccines similar to infections act directly by induction of a cytokine shift toward Th1 and away from atopy. Although we tested for reverse causation, it is also possible that a better vaccination coverage serves as a marker for a yet unidentified cause that underlies the observed inverse relation of vaccination coverage and allergy.

The potential of several vaccines to modify the risk for atopy has been investigated recently. Diphtheria/tetanus vaccination elicits an IgE response directed against the vaccinated toxoids as part of the regular immune response, but this is exaggerated in individuals predisposed to atopy.¹¹ Pertussis vaccination elicits an IgE response to pertussis toxin, more pronounced after vaccination with acellular than whole cell vaccines.¹² To date, however, there is no evidence of a promoting effect extending to unrelated

allergens or atopic disease.¹³ In contrast, we were able to show earlier that immunization with whole-cell pertussis vaccine in our children downregulated the IgE response to the covaccinated diphtheria and tetanus toxoids.¹⁴ A recent epidemiologic study relating national pertussis immunization rates to the national prevalence of allergic diseases indicated a possible suppressive effect of whole-cell pertussis vaccine on allergic disease.¹⁵ In our study, pertussis vaccination was associated in a dose-dependent manner with a lower prevalence of early atopic dermatitis and allergic sensitization as well as with lower total serum IgE levels. Thus, vaccination with pertussis vaccine may have a transitory inhibitory effect on allergy, possibly as a result of cell-wall constituents lacking in acellular vaccines.

Measles vaccination, coadministered in many countries with vaccination against mumps and rubella, induces a Th2-type cytokine response.¹⁶ Previous epidemiologic data suggested a possible suppressive effect of measles infection or vaccination on allergic sensitization or allergic disease.^{15,17,18} In our study, we found a trend toward less atopic dermatitis or asthma among measles/mumps-vaccinated children in comparison with nonvaccinated children. A risk reduction with regard to allergic sensitization and asthma was particularly evident in children with an inherited risk for atopy. Well-controlled prospective trials could possibly confirm a mild allergy-preventing effect of measles vaccination.

In our study, the risk for allergic sensitization and early atopic disease decreases with increasing cumulative vaccination doses. It is a matter of speculation

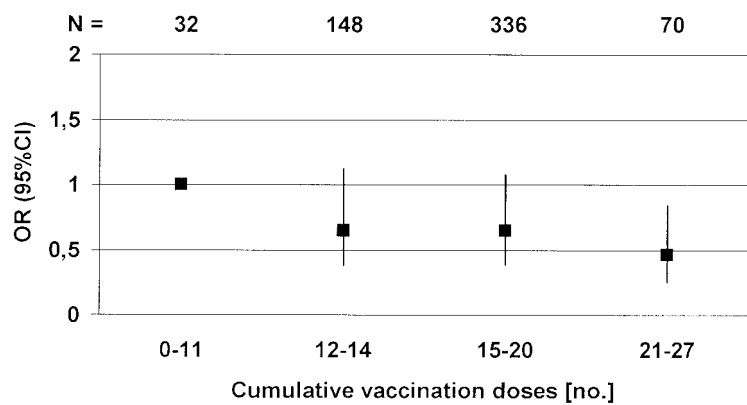


Fig 3. Risk (OR, 95% CI) for allergic sensitization up to the age of 5 years in relation to cumulative vaccination doses, adjusted for high atopy risk at birth and parental education.

whether the inverse trend is expression of a synergism of vaccines that were associated with lower allergy prevalence or whether vaccination coverage marks lifestyle factors that we could not identify. That measles/mumps vaccination was associated with lower disease prevalences even before the first birthday (ie, before measles/mumps vaccination was administered) casts some doubt on the extent of a causal role of this vaccine. Although many variables known to be potential risk modifiers have been studied in this cohort, no other environmental or lifestyle factor that could serve as an explanation was identified. More vaccinated children had fewer older siblings. Higher sibship, however, would be expected to correlate inversely with the prevalence of atopy,¹⁹ although the effect was not strong in our cohort.²⁰ Testing for reverse causation, we found no evidence for delayed vaccination of children who experienced atopic dermatitis in the first 2 years of life (data not shown).

From infancy on, the incidence of atopic dermatitis in our cohort was more frequent among children with first-degree relatives with the same phenotype.²¹ In contrast, recurrent wheezing during the first 2 years of life was associated with serologic evidence of respiratory syncytial virus infection,²² and thereafter, a positive family history of asthma became a risk factor.²¹ In this study, the risk of both allergic sensitization and (more clear-cut after infancy) asthma symptoms was reduced in children with a higher vaccination coverage (Figs 2 and 3), suggesting that vaccinations may have a stronger impact on allergic than on nonallergic asthma.

CONCLUSION

We found an inverse relationship between cumulative vaccine doses received and atopy. In particular, measles/mumps, pertussis, and diphtheria/tetanus vaccinations were associated with a transient reduction of atopy, whereas vaccination against polio and *Haemophilus influenzae* had no effect. Thus, regular childhood vaccination regimens may help to overcome a transient atopy-associated deficiency in Th1 function.²³ Parents often report occurrence or deterioration of atopic dermatitis or obstructive bronchitis subsequent to early childhood vaccinations. The incidence of these conditions coincides naturally with the period in which childhood vacci-

nations are scheduled.²¹ Our study demonstrates no evidence for a causal role of childhood vaccinations in the occurrence of early atopic disease. Parents should be encouraged not to delay effective immunization of their children because of a suspicion that vaccines could promote allergy in the first years of life.

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