ARTICLE

Allergic Disease and Atopic Sensitization in Children in Relation to Measles Vaccination and Measles Infection

Helen Rosenlund, MSc[a,b], Anna Bergström, PhD[a], Johan S. Alm, MD, PhD[c,d], Jackie Swartz, MD[e], Annika Scheynius, MD, PhD[f], Marianne van Hage, MD, PhD[g], Kari Johansen, MD, PhD[h], Bert Brunekreef, PhD[i,j], Erika von Mutius, MD[k], Markus J. Ege, MD[k], Josef Riedler, MD[l], Charlotte Braun-Fahrländer, MD[m], Marco Waser, PhD[m], Göran Pershagen, MD, PhD[a,n], and the PARSIFAL Study Group

[a]Institute of Environmental Medicine, [b]Centre for Allergy Research, and [c]Section of Pediatrics, Department of Clinical Science and Education, Karolinska Institutet, Stockholm, Sweden; [d]Section of Pediatrics, Sachs' Children's Hospital, Södersjukhuset, Stockholm, Sweden; [e]Vidar Clinic, Järna, Sweden; [f]Clinical Allergy Research Unit and [g]Clinical Immunology and Allergy Unit, Department of Medicine Solna, Karolinska Institutet and University Hospital, Stockholm, Sweden; [h]Department of Virology, Swedish Institute for Infectious Disease Control, Solna, Sweden; [i]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, Netherlands; [j]Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht, Netherlands; [k]Dr von Hauner Children's Hospital, University of Munich, Munich, Germany; [l]Children's Hospital, Schwarzach, Austria; [m]Institute of Social and Preventive Medicine, University of Basel, Basel, Switzerland; [n]Department of Occupational and Environmental Health, Stockholm County Council, Stockholm, Sweden

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Measles infection may have an immunosuppressive effect and, therefore, might affect the development of allergy, but the scientific evidence is inconsistent. Furthermore, measles vaccine has been associated with the development of allergy in some, but not all, previous studies.

What This Study Adds

This study adds a methodologic aspect to the association between measles vaccination and/or measles infection and allergic disease and atopic sensitization. In this study, we took confounding from disease-related modification of exposure into account.

ABSTRACT

OBJECTIVE. Our aim was to investigate the role of measles vaccination and measles infection in the development of allergic disease and atopic sensitization.

METHODS. A total of 14 893 children were included from the cross-sectional, multicenter Prevention of Allergy–Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle study, conducted in 5 European countries (Austria, Germany, the Netherlands, Sweden, and Switzerland). The children were between 5 and 13 years of age and represented farm children, Steiner-school children, and 2 reference groups. Children attending Steiner schools often have an anthroposophic (holistic) lifestyle in which some immunizations are avoided or postponed. Parental questionnaires provided information on exposure and lifestyle factors as well as symptoms and diagnoses in the children. A sample of the children was invited for additional tests, and 4049 children provided a blood sample for immunoglobulin E analyses. Only children with complete information on measles vaccination and infection were included in the analyses (84%).

RESULTS. In the whole group of children, atopic sensitization was inversely associated with measles infection, and a similar tendency was seen for measles vaccination. To reduce risks of disease-related modification of exposure, children who reported symptoms of wheezing and/or eczema debuting during first year of life were excluded from some analyses. After this exclusion, inverse associations were observed between measles infection and "any allergic symptom" and "any diagnosis of allergy by a physician." However, no associations were found between measles vaccination and allergic disease.

CONCLUSION. Our data suggest that measles infection may protect against allergic disease in children. *Pediatrics* 2009;123:771–778

www.pediatrics.org/cgi/doi/10.1542/peds.2008-0013

doi:10.1542/peds.2008-0013

Key Words
allergic disease, atopic sensitization, measles infection, measles vaccination, Steiner-school children, farm children

Abbreviations
CI—confidence interval
IgE—immunoglobulin E
MMR—measles, mumps, and rubella
OR—odds ratio
PARSIFAL—Prevention of Allergy–Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle

Accepted for publication Jun 16, 2008

Address correspondence to Helen Rosenlund, MSc, Karolinska Institutet, Institute of Environmental Medicine, Department of Environmental Epidemiology, Box 210, SE-171 77 Stockholm, Sweden. E-mail: helen.rosenlund@ki.se.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

The prevalence of immunoglobulin E (IgE)-mediated allergic disease in children has increased during the past decades,[1,2] although recent reports suggest that the occurrence has stabilized.[3,4] Because allergic diseases mostly debut in childhood, it is of great interest to study exposures that occur early in life and could have an effect on the maturation of the immune system.

The occurrence of many types of childhood infections has decreased markedly during past decades because of better hygiene and vaccinations, which has coincided with the increase of allergic disorders.[5] This suggests that certain infections might have a role in the development of allergy. Infection with the measles virus may have an immune-suppressive effect[6] and might affect the development of allergy. However, studies on the impact of measles infection on allergic disease have shown conflicting results.[7–18] The timing of infection,[14] differences in outcome definitions, as well as methodologic limitations might be of importance for the apparently discrepant findings. When measles vaccination was introduced in the 1970s, the incidence of measles infection decreased dramatically.[19] Measles vaccine has been associated with the development of allergic disease, but the evidence seems inconsistent.[5,8–10,13,16,20–23]

In a previous study on Steiner-school children, who have a lower prevalence of allergic disease, we found that measles infection was associated with a lower risk of atopic eczema in sensitized children.[16] Furthermore, measles vaccination was associated with an increased risk of rhinoconjunctivitis. Steiner-school children often have an anthroposophic lifestyle that is characterized by restricted use of antibiotics, antipyretics, and vaccinations, and by high consumption of biodynamic foods.[16,24] Biodynamic farming differs from conventional farming by less use of chemical-synthetic pesticides and fertilizers.

The aim of this study was to investigate the role of measles vaccination and measles infection for allergic disease and atopic sensitization in children of the Prevention of Allergy–Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study, which included farm children, Steiner-school children, and reference children.

MATERIALS AND METHODS

This work was based on the PARSIFAL study, a cross-sectional, multi-center study performed in 5 European countries (Austria, Germany, the Netherlands, Sweden, and Switzerland). The children were 5 to 13 years of age, and born between 1987 and 1996. The study has been described in detail elsewhere.[25] In brief, 4 groups of children were selected for the study: children living on a farm, children attending Steiner schools, as well as 2 reference groups (children from nonfarming households [farm reference children] and children from non–Steiner schools [Steiner reference children]). In total, 14 893 children (69% response rate) participated in the study. Information about environmental exposures, history of vaccinations and infections, lifestyle factors, as well as symptoms and diagnoses of allergic diseases were collected through a parental questionnaire. Most questions were based on the internationally standardized and validated International Study of Asthma and Allergies in Childhood phase II protocol,[3] or derived from previous studies.[24,26,27] Blood samples were provided by 4049 (83% response rate) children invited for blood sampling and required parental consent. Because of a large number of children included in the questionnaire surveys in Germany and Switzerland, a random sample of eligible children was selected in these countries. A total of 3979 samples yielded a sufficient volume for allergen-specific IgE measurements. The study was approved by local ethics committees in the participating countries.

Definition of Exposures and Health Outcomes

Measles vaccination was defined as a positive answer to the question "Has the child been vaccinated against measles?" and in the same way, measles infection was considered if the question "Has the child had measles infection?" was answered positively.

All health outcomes were reported by the parents, except atopic sensitization, which was assessed from blood sampling. Current rhinoconjunctivitis symptoms were defined as sneezing, runny nose, nasal block-up, and itchy eyes in the child during the last 12 months without having a cold at the same time. Children diagnosed with hay fever and who ever had symptoms of hay fever were considered to have a physician's diagnosis of rhinoconjunctivitis. Current wheezing was defined as having wheezing at least once during the last 12 months. Children ever diagnosed with asthma, or obstructive bronchitis more than once, were considered to have a physician's diagnosis of asthma. Current atopic eczema symptoms were present if the child ever had had an itchy rash intermittently for at least 6 months, and if the child had had an itchy rash during the last 12 months. Children diagnosed with atopic eczema and who ever had an itchy rash lasting at least 6 months were considered to have a physician's diagnosis of atopic eczema. If the child had symptoms of at least 1 allergic disease (ie, current rhinoconjunctivitis symptoms, current wheezing, and/or current atopic eczema symptoms), he or she was considered to have "any allergic symptom," and "any diagnosis of allergy by a physician" was defined correspondingly.

Atopic sensitization was indicated if the child had at least 1 allergen-specific serum IgE result of ≥0.35 kU/L against common inhalant allergens (Phadiatop; Pharmacia, Uppsala, Sweden: birch, timothy, mugwort, *Dermatophagoides pteronyssinus* and *farinae*, cat-, dog-, and horse epithelium, and *Cladosporium herbarum*) and/or food allergens (Fx5: egg white, milk, fish, wheat, peanut, and soy) (ImmunoCAP System; Phadia AB, Uppsala, Sweden). In addition, a cutoff value of ≥3.5 kU/L was used in some analyses. All IgE analyses were performed at the Department of Clinical Immunology, Karolinska University Hospital Solna, Stockholm, Sweden.

Statistical Methods

The relation between measles vaccination and/or measles infection and allergic disease or atopic sensitization was calculated by using odds ratios (ORs) and 95% confidence intervals (CIs) computed from logistic regression. Data were analyzed in models adjusted for age (5–6, 7–8, 9, 10–11, or 12–13 years), gender (boy or girl), center (Austria, Germany, the Netherlands, Sweden, or Switzerland), study group (farmer, Steiner, farmer reference, Steiner reference), smoking during pregnancy (yes, no), current environmental smoking (yes, no), mother with asthma and/or rhinoconjunctivi-

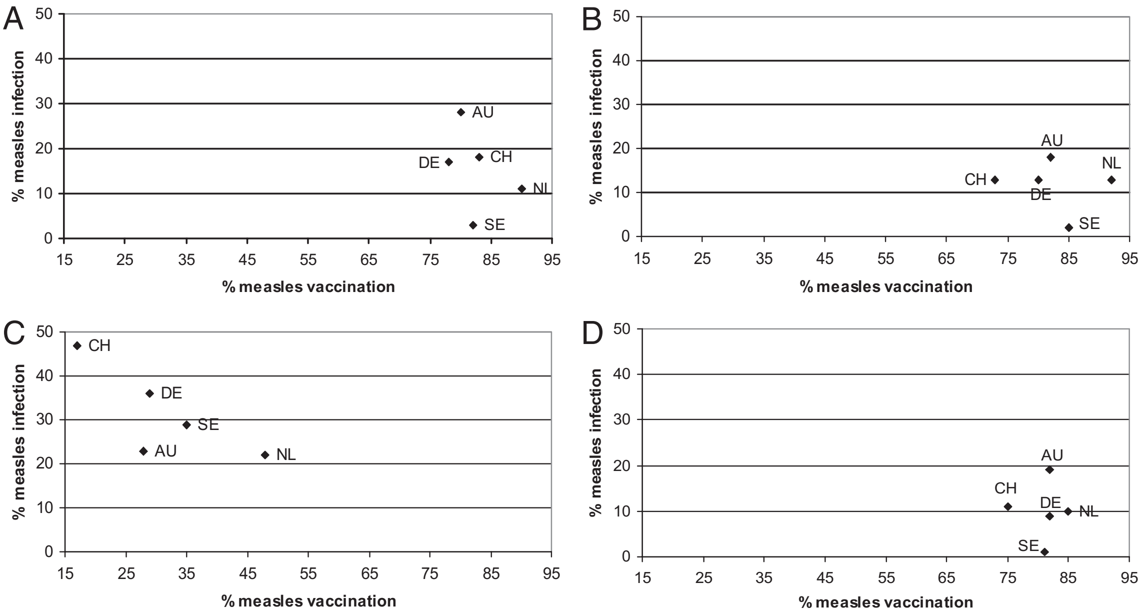

FIGURE 1
Prevalence of measles vaccination and measles infection among children in the PARSIFAL study divided according to group and country. A, Farm children; B, farm reference children; C, Steiner-school children; D, Steiner reference children. AU indicates Austria; CH, Switzerland; DE, Germany; NL, Netherlands; SE, Sweden.

tis (yes or no), father with asthma and/or rhinoconjunctivitis (yes or no), number of older siblings (0, 1, 2, or ≥3), parental education (elementary school, high school, university), and household pets during first year of life (yes, no). First, we analyzed the effect of measles vaccination and infection by using a combined variable with 4 categories (no vaccination or infection, vaccination but no infection, infection but no vaccination, or both vaccination and infection). Second, we performed separate analyses of measles vaccination and infection, 1 adjusted for the other, and vice versa. To reduce bias from disease-related modification of exposure, the data were analyzed in 2 steps. Initially, the effects of measles vaccination and measles infection were analyzed in the whole population, and then after exclusion of children with onset of wheezing and/or eczema during the first year of life ($n = 753$). Finally, analyses were also performed in groups defined by both symptoms/diagnoses and results of the IgE analyses to increase the specificity of the outcome definition in relation to allergy. Stata 8.0 software (Stata Corp, College Station, TX) was used for all statistical analyses. Statistical significance was defined as $P < .05$.

To be included in the analyses the questions on measles vaccination and measles infection had to be answered with "yes" or "no." A total of 2353 children were excluded because of incomplete answers ("do not know" or missing) to any of these questions. Thus, the analyses were based on 12 540 children, including 3378 children with blood samples.

RESULTS

The prevalence of measles vaccination and measles infection varied in the different groups and countries (Fig 1 A–D). In total, 9136 children (73%) were vaccinated against measles, 2561 children (20%) had had measles infection, and 1815 children (14%) were neither vaccinated nor infected with measles. Overall, 11% ($n = 972$) of the children vaccinated against measles reported measles infection, with some variation between the countries (Austria, 13%; Germany, 6%; the Netherlands, 11%; Sweden, 1%; and Switzerland, 9%). Measles vaccination was least common among the Steiner-school children, and there were no significant differences between the other groups. The highest vaccination rate was found in the Netherlands, regardless of group belonging. Steiner-school children reported the highest prevalence of measles infection (33%). The lowest prevalence of measles infection was observed in Sweden, whereas in Austria and Switzerland the prevalence was relatively high. Measles vaccination is generally given in combination with mumps and rubella vaccines. In our data, 8206 (90%) of the children reporting measles vaccination also reported vaccination against mumps and rubella.

Table 1 shows the association between measles vaccination and/or infection and risk of allergic symptoms, physician's diagnoses, and atopic sensitization. We observed a statistically significant positive association between measles vaccination and rhinoconjunctivitis (symptoms and physician's diagnosed) among children who never had measles infection. In the subset of children with blood samples, we observed a trend toward inverse associations between measles vaccination, infection, or both, and atopic sensitization (at allergen-specific IgE level of ≥0.35 and ≥3.5 kU/L). Similar results were observed when inhalant allergens (Phadiatop) and food allergens (Fx5) were analyzed separately. When the analysis was based on measles, mumps, and rubella (MMR) vaccination, instead of measles vaccination, the

TABLE 1 Association Between Measles Vaccination, Measles Infection, or Both and Allergic Disease and Atopic Sensitization Among Children in the PARSIFAL Study

	Adjusted Models[a]							
	No Infection/No Vaccination		Vaccination/No Infection		Infection/No Vaccination		Vaccination and Infection	
	n/*N*[b]	Reference	*n*/*N*[b]	OR (95% CI)	*n*/*N*[b]	OR (95% CI)	*n*/*N*[b]	OR (95% CI)
All children[c]								
Current rhinoconjunctivitis symptoms	116/1670	1.0	569/7390	1.30 (1.02–1.66)	93/1438	0.80 (0.60–1.08)	44/835	1.00 (0.68–1.48)
Physician's diagnosis of rhinoconjunctivitis	59/1667	1.0	329/7356	1.70 (1.23–2.35)	53/1435	0.93 (0.63–1.39)	28/833	1.52 (0.92–2.51)
Current wheezing	134/1667	1.0	530/7395	0.96 (0.76–1.21)	130/1439	1.17 (0.90–1.52)	60/841	1.02 (0.72–1.44)
Physician's diagnosis of asthma	140/1662	1.0	671/7342	1.03 (0.83–1.29)	130/1427	1.04 (0.80–1.35)	60/819	0.84 (0.60–1.18)
Current atopic eczema symptoms	164/1673	1.0	780/7403	1.07 (0.87–1.32)	155/1430	1.12 (0.88–1.42)	73/841	0.95 (0.69–1.29)
Physician's diagnosis of atopic eczema	177/1664	1.0	748/7383	0.94 (0.77–1.15)	159/1425	1.08 (0.85–1.36)	74/842	0.88 (0.64–1.20)
Children with blood samples[c]								
Atopic sensitization (≥0.35 kU/L)	162/467	1.0	597/2042	0.83 (0.63–1.07)	133/409	0.87 (0.65–1.18)	61/219	0.67 (0.45–0.99)
Phadiatop (≥0.35 kU/L)	158/467	1.0	548/2042	0.79 (0.61–1.03)	127/409	0.81 (0.60–1.10)	55/219	0.62 (0.42–0.93)
Fx5 (≥0.35 kU/L)	66/467	1.0	241/2042	0.84 (0.59–1.20)	37/409	0.62 (0.40–0.96)	23/219	0.63 (0.36–1.09)
Atopic sensitization (≥3.5 kU/L)	99/467	1.0	334/2042	0.77 (0.56–1.06)	70/409	0.70 (0.49–1.01)	30/219	0.54 (0.33–0.88)

[a] Adjustments were made for age, gender, center, study group, smoking during pregnancy, current environmental smoking, maternal asthma and/or rhinoconjunctivitis, paternal asthma and/or rhinoconjunctivitis, older siblings, parental education, and household pets during first year of life.
[b] *n* indicates number of children with actual disease; *N*, number of children in the analysis.
[c] All children = 12 540, of which 3378 provided a blood sample.

results remained the same. It should be noted that a majority of unvaccinated children who never had measles (ie, the reference category), as well as those with measles infection, were Steiner-school children (70% and 79%, respectively).

To reduce bias caused by disease-related modification of exposure, mainly regarding vaccination, we excluded children who reported symptoms of wheezing and/or eczema during the first year of life. The numbers in the symptom groups were small and, therefore, we performed analyses of measles vaccination and measles infection, respectively, combining outcomes as any allergic symptom and any diagnosis of allergy by a physician (Table 2). In analyses of all children, we observed inverse associations between measles vaccination and measles infection, respectively, and atopic sensitization, although statistically significant only for measles infection in relation to allergen-specific serum IgE level of ≥3.5 kU/L. There were no significant associations between measles vaccination or infection and any allergic symptom or any diagnosis of allergy by a physician. After excluding children with symptoms of wheezing and/or eczema during the first year of life, measles infection was inversely associated with any allergic symptom and any diagnosis of allergy by a physician, respectively, whereas the association with atopic sensitization was attenuated. There was no clear heterogeneity in results when the 4 study groups were analyzed separately; however, these analyses had low statistical power (data not shown).

To increase the specificity of symptoms/physician's diagnosis in relation to allergic disease, analyses were performed combining these with atopic sensitization (Table 3). Inverse associations were observed between measles vaccination and measles infection, respectively, and having any allergic symptom or any diagnosis of allergy by a physician in combination with atopic sensitization, compared with nonsensitized children free from symptoms/physician's diagnoses, although statistically significant only for measles infection. Measles vaccination was positively associated with having any allergic symptom or a physician's diagnosis without being sensitized. After exclusion of children with symptoms of wheezing and/or eczema during the first year of life, no association remained statistically significant.

DISCUSSION

In our study, including children of farming and anthroposophic families in 5 European countries, inverse associations were indicated between measles infection or vaccination and atopic sensitization in the whole group of children. This association tended to be stronger for an IgE cutoff level of 3.5 kU/L compared with 0.35 kU/L. After exclusion of children with early debuting symptoms of wheezing and/or eczema, this association was attenuated. However, in these analyses, measles infection was inversely associated with any allergic symptom or physician's diagnosis of allergy, whereas there were no associations with measles vaccination. The change in result after exclusion of children with early symptoms may be a result of disease-related modification of exposure (eg, that parents of children with early symptoms of allergy avoided or postponed measles vaccination, and perhaps also measles infection, which might be the case among certain anthroposophic parents).

Disease-related modification of exposure is a potential problem in epidemiologic studies of measles vaccination and measles infection in relation to allergic diseases in children. However, most previous studies do not take

TABLE 2 **Any Allergic Symptom, Any Diagnosis of Allergy by a Physician, or Atopic Sensitization in Relation to Measles Vaccination and Measles Infection Among Children in the PARSIFAL Study**

	Adjusted Models[a]							
	Measles Vaccination				Measles Infection			
	Reference				Reference			
	n/N[b]	Reference	*n/N*[b]	OR (95% CI)	*n/N*[b]	Reference	*n/N*[b]	OR (95% CI)
All children[c]								
Any allergic symptom	647/3197	1.0	1685/8465	1.07 (0.93–1.22)	1858/9234	1.0	448/2325	0.97 (0.85–1.10)
Any diagnosis of allergy by a physician	605/3197	1.0	1588/8465	1.01 (0.88–1.17)	1758/9234	1.0	416/2325	0.94 (0.82–1.40)
Children with blood samples[c]								
Atopic sensitization (≥0.35 kU/L)	303/899	1.0	675/2307	0.83 (0.65–1.05)	763/2536	1.0	195/633	0.85 (0.68–1.06)
Atopic sensitization (≥3.5 kU/L)	175/899	1.0	373/2307	0.78 (0.58–1.04)	434/2536	1.0	100/633	0.70 (0.53–0.92)
Children with early symptoms excluded[c]								
Any allergic symptom	74/2094	1.0	236/5771	1.31 (0.92–1.88)	263/6297	1.0	47/1568	0.69 (0.48–0.99)
Any diagnosis of allergy by a physician	74/2094	1.0	211/5771	0.92 (0.64–1.32)	244/6297	1.0	41/1568	0.65 (0.45–0.95)
Children with blood samples[c]								
Atopic sensitization (≥0.35 kU/L)	153/586	1.0	355/1506	0.88 (0.63–1.22)	392/1662	1.0	116/430	1.05 (0.79–1.38)
Atopic sensitization (≥3.5 kU/L)	61/586	1.0	155/1506	1.04 (0.65–1.66)	171/1662	1.0	45/430	0.87 (0.58–1.31)

[a] Adjustments were made for age, gender, center, study group, smoking during pregnancy, current environmental smoking, maternal asthma and/or rhinoconjunctivitis, paternal asthma and/or rhinoconjunctivitis, older siblings, parental education, household pets during first year of life, and measles infection and measles vaccination, respectively, in the model where it is not the main exposure.

[b] *n* indicates number of cases; *N*, total number of children in the analysis.

[c] In total, 12 540 children were included in the analyses, of which 3378 provided a blood sample. The number of children with early symptoms of wheezing and/or eczema was 753 (211 among children with blood samples).

this into account. We found 6 articles that assessed exposures before outcomes. One study observed an increased risk of asthma after MMR vaccination,[5] whereas another reported an increased risk of atopic dermatitis after either measles vaccination or infection.[9] Some studies found no relation between measles infection and allergic disease,[13,14] or between measles vaccination and allergic disease.[13,20,21] Thus, our result of an inverse association between measles infection and allergic disease seemed to differ from the results of these studies. It is possible that both methodologic issues, such as the way of controlling for disease-related modification of exposure, outcome definitions, and length of follow-up, as well as biological aspects related to timing of exposure and type of vaccine, etc, contribute to explaining the apparently conflicting results. Among studies that did not assess exposure before outcome, measles vaccination was positively,[8,16] inversely,[10,23] or not associated[21,22] with allergic disease or atopic sensitization. The results were more constant for studies on the association between measles infection and allergic disease or atopic sensitization, where inverse associations[7,8,10,12,16,17] dominated, compared with positive[11,18] or no associations.[15] The results seemed inconsistent also considering cohort studies[5,7,21,23,28] and cross-sectional studies[8,10,11,16–18,22] separately.

A major difficulty in studies on measles vaccination and measles infection in relation to allergic disease in children is to assess the time sequence of events, that is, if the exposure precedes the disease or not. This is especially difficult in cross-sectional studies. There are different ways to deal with this problem, and it can be done at different stages of the study, for example, to collect data on vaccination/infection prospectively (design stage), or to group subjects according to age of exposure/outcome if that information is available (analysis stage), or to exclude subjects for whom the information on timing of the exposure/outcome is incomplete (analysis stage). However, even in prospective studies there may be a risk that certain characteristics related to the outcome, eg, allergy among family members, may confound the association between exposure and outcome.

In the PARSIFAL study, 11% of all children vaccinated against measles also reported measles infection, and the prevalence of children who were both vaccinated and infected with measles differed substantially between the countries. This may be explained by differences in vaccination coverage,[29] year of introduction of the vaccine,[19] and recurrent measles epidemics.[29] Some children in our study presumably received only 1 dose, which makes it easier for vaccinated children to get infected.[29] Table 4 presents World Health Organization statistics of MMR vaccination during the study period in 4 countries[30] and data from the Robert-Koch Institute for Germany. The data correspond well with the prevalence of measles vaccination in the PARSIFAL study and contribute to explaining the difference in prevalence of measles infection in the different countries. For example, MMR vaccination was introduced early in Sweden and vaccination coverage has been high, which is in line with the low prevalence of measles infection observed in the Swedish part of the PARSIFAL study. It should be noted that an article on MMR vaccination and autism was published 2 years before the data collection in our

TABLE 3 **Any Allergic Symptom or any Diagnosis of Allergy by a Physician Combined With Atopic Sensitization (0.35 kU/L) in Relation to Measles Vaccination and Infection, Among Children With Blood Samples in the PARSIFAL Study**

	Adjusted Models[a]							
	Measles Vaccination				Measles Infection			
	Reference				Reference			
	n/N[b]		*n/N*[b]	OR (95% CI)	*n/N*[b]		*n/N*[b]	OR (95% CI)
All children[c]								
Any allergic symptom								
No symptoms and no sensitization	510/876	1.0	1347/2261	Reference	1485/2509	1.0	372/628	Reference
Symptoms and no sensitization	65/876	1.0	228/2261	1.42 (0.95–2.13)	217/2509	1.0	55/628	1.05 (0.74–1.51)
No symptoms and sensitization	166/876	1.0	384/2261	0.94 (0.70–1.27)	483/2509	1.0	125/628	1.01 (0.78–1.31)
Symptoms and sensitization	123/876	1.0	264/2261	0.76 (0.54–1.07)	264/2509	1.0	66/628	0.64 (0.46–0.90)
Any diagnosis of allergy by a physician								
No diagnosis and no sensitization	515/876	1.0	1350/2261	Reference	1496/2509	1.0	369/628	Reference
Diagnosis and no sensitization	55/876	1.0	214/2261	1.90 (1.24–2.91)	217/2509	1.0	52/628	1.12 (0.77–1.62)
No diagnosis and sensitization	188/876	1.0	438/2261	1.06 (0.80–1.42)	483/2509	1.0	143/628	1.04 (0.81–1.34)
Diagnosis and sensitization	96/876	1.0	212/2261	0.69 (0.48–1.01)	264/2509	1.0	44/628	0.51 (0.35–0.75)
Children with early symptoms excluded[c]								
Any allergic symptom								
No symptoms and no sensitization	428/586	Reference	1129/1506	Reference	1245/1662	Reference	312/430	Reference
Symptoms and no sensitization	3/586	1.0	15/1506	2.43 (0.53–11.0)	18/1662	1.0	0/430	—
No symptoms and sensitization	135/586	1.0	308/1506	0.86 (0.61–1.22)	338/1662	1.0	105/430	1.06 (0.79–1.41)
Symptoms and sensitization	16/586	1.0	45/1506	1.55 (0.64–3.76)	27/1662	1.0	10/430	0.79 (0.34–1.81)
Any diagnosis of allergy by a physician								
No diagnosis and no sensitization	423/586	Reference	1099/1506	Reference	1219/1662	Reference	303/430	Reference
Diagnosis and no sensitization	5/586	1.0	27/1506	2.57 (0.73–9.11)	28/1662	1.0	4/430	0.56 (0.17–1.77)
No diagnosis and sensitization	138/586	1.0	329/1506	1.01 (0.72–1.43)	358/1662	1.0	109/430	1.06 (0.80–1.42)
Diagnosis and sensitization	9/586	1.0	21/1506	0.51 (0.17–1.55)	27/1662	1.0	3/430	0.46 (0.12–1.79)

[a] Adjusted for age, gender, center, study group, mother with asthma and/or rhinoconjunctivitis, father with asthma and/or rhinoconjunctivitis, older siblings, pets during first year of life, current environmental smoking, mother's smoking during first year of life, parental education, and measles infection or measles vaccination, respectively, in the model where it is not the main exposure.
[b] *n* indicates number of cases; *N*, total number of children in the analysis.
[c] In total, 3378 children provided a blood sample. The number of children with early symptoms of wheezing and/or eczema was 211 among those who provided a blood sample.

study,[31] which may have affected the vaccination rates in some countries.

The strength of the PARSIFAL study is its large size with multinational design, although the cross-sectional design is not optimal for elucidation of the temporal relation between measles vaccination/infection and allergic disease. Another strength of our study is the comparatively high prevalence of children who contracted measles infection (20%), especially because measles usually is now a rare disease in industrialized countries.[6] A limitation of the study is the low prevalence of allergic disease and atopic sensitization in the reference category (unvaccinated children without measles infection), which consisted mostly of Steiner-school children. The positive association between measles vaccination and current rhinoconjunctivitis could be the result of this difference in disease prevalence.

Misclassification of exposure might affect the results. In our material, the child's vaccination status was based on parental recall, which has been associated with both underestimation and overestimation in validity studies.[32,33] The typical symptoms of measles infection, high fever and characteristic skin rash, are often distinct and appear in epidemics, which helps to make parental reports of measles infection reliable. To the extent that the misclassification was nondifferential, it would not change the direction of our observed associations. Un-

TABLE 4 World Health Organization Statistics[30] of Monovalent and Combined Measles Vaccination Between 1988 and 1998

Country	Introduction of Monovalent Measles Vaccine in the Vaccination Program, 1 Dose, Year	Introduction of MMR Vaccination in the Vaccination Program, Year		Mean Vaccination Coverage		Recommended Age for First and Second Dose	
		First Dose	Second Dose	First Dose, %	Second Dose	First Dose, mo	Second Dose, y
Austria	1974	1994	1998	60–90	NI	14	6–7[a]
Germany[b]	1972	1988	1993	47–89	NI	15	6
Netherlands	1976	1987	1987	93–96	NI	14	9
Sweden	1971	1982	1982	94–97	NI	18	12[a]
Switzerland	1976	1985	1996	70–90	NI	15–24	4–7

Relevant comparison period for children in the PARSIFAL study who were born between 1987 and 1996. NI indicates no information.
[a] Since 2006, the second dose is recommended 1 month after the first dose in Austria, or at age 6 in Sweden.
[b] German data were obtained from the Robert-Koch Institute.

fortunately, we did not have information on the child's age at measles infection and, therefore, could not investigate if the allergic symptoms/atopic sensitization or the measles infection came first. Moreover, among Steiner reference children, the prevalence of allergic disease tended to be higher among children who provided a blood sample compared with those who did not.[25] This might bias our results on atopic sensitization or allergic symptoms/diagnoses in combination with atopic sensitization. To assess the magnitude of this potential bias, we adjusted the analyses for symptoms/disease prevalence, which resulted in small effects on the observed ORs, speaking against a major role of selection bias. Furthermore, we cannot exclude that our results are influenced by the other vaccines included in the MMR vaccination, or the different vaccination routines of Steiner-school children, with fewer vaccinations and that are often given later than recommended by the health authorities.[24] Moreover, we can not exclude the possibility that other factors in the anthroposophic lifestyle may influence the observed associations.[16]

CONCLUSIONS

We observed an inverse association between measles infection and any allergic symptoms and any diagnosis of allergy by a physician in children, after excluding children with early symptoms of wheezing and eczema. Most studies on measles vaccination and measles infection in relation to allergic disease have not considered the time sequence of events, and therefore causal associations should be further investigated in prospective cohort studies.

ACKNOWLEDGMENTS

This study was supported by European Union research grant QLRT 1999–01391 and by funding from the Swedish Medical Research Council and the Swedish Foundation for Health Care Science and Allergy Research. The funding sources had no involvement in this work.

The PARSIFAL Study Group included Göran Pershagen, Tobias Alfvén, Johan Alm, Anna Bergström, Lars Engstrand, Helen Rosenlund, Marianne van Hage, Niclas Håkansson, Gunnar Lilja, Fredrik Nyberg, Annika Scheynius, Jackie Swartz, and Magnus Wickman (Sweden); Charlotte Braun-Fahrländer, Marco Waser, Felix Sennhauser, Roger Lauener, Johannes Wildhaber, and Alex Möller (Switzerland); Bert Brunekreef, Dieneke Schram-Bijkerk, Gert Doekes, Mirian Boeve, Jeroen Douwes, Machteld Huber, and Mirjam Matze (the Netherlands); Erika von Mutius, Marcus R. Benz, Jörg Budde, and Markus Ege (Germany); Josef Riedler, Waltraud Eder, Ellen Üblagger, Gertraud Weiss, and Mynda Schreuer (Austria); and Karin B. Michels (United States).

We thank all fieldworkers and other PARSIFAL team members, especially Stina Gustafsson, Eva Hallner, André Lauber, Wiveka Lundberg, Helena Svensson, Anki Wigh, Annika Zettergren, and Anne-Charlotte Öhman-Johansson (Sweden); Susanne Löhliger and Remo Frey (University Children's Hospital Zurich), Marianne Rutschi, Stefan Worminghaus (study center support), and Michaela Glöckler (head of the medical section of the Goetheanum in Dornach) (Switzerland); Anja Strengers, Marieke Siekmans, Patricia Jansen-van Vliet, Janneke Bastiaanssen, Marieke Dijkema, Siegfried de Wind, Jack Spithoven, Griet Terpstra, and Gert Buurman (Netherlands); and Helmut Egger, Martina Burger, Bernadette Burger, and Elisabeth Buchner (Austria). We also thank all the school doctors and teachers and all children and parents who contributed to this study.

REFERENCES

1. Von Hertzen LC, Haahtela T. Asthma and atopy: the price of affluence? *Allergy.* 2004;59(2):124–137
2. Maziak W, Behrens T, Brasky TM, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. *Allergy.* 2003;58(7):572–579
3. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet.* 2006;368(9537):733–743
4. Braun-Fahrländer C, Gassner M, Grize L, et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J.* 2004;23(3):407–413
5. McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *Am J Public Health.* 2004;94(6):985–989
6. Schneider-Schaulies S, ter Meulen V. Measles virus and

immunomodulation: molecular bases and perspectives. *Expert Rev Mol Med.* 2002;4(13):1–18
7. Shaheen SO, Aaby P, Hall AJ, et al. Measles and atopy in Guinea-Bissau. *Lancet.* 1996;347(9018):1792–1796
8. Lewis SA, Britton JR. Measles infection, measles vaccination and the effect of birth order in the aetiology of hay fever. *Clin Exp Allergy.* 1998;28(12):1493–1500
9. Olesen AB, Juul S, Thestrup-Pedersen K. Atopic dermatitis is increased following vaccination for measles, mumps and rubella or measles infection. *Acta Derm Venereol.* 2003;83(6):445–450
10. Roost HP, Gassner M, Grize L, et al. Influence of MMR-vaccinations and diseases on atopic sensitization and allergic symptoms in Swiss school children. *Pediatr Allergy Immunol.* 2004;15(5):401–407
11. Paunio M, Heinonen OP, Virtanen M, et al. Measles history and atopic diseases: a population-based cross-sectional study. *JAMA.* 2000;283(3):343–346
12. Kucukosmanoglu E, Cetinkaya F, Akcay F, Pekun F. Frequency of allergic diseases following measles [in Spanish]. *Allergol Immunopathol (Madr).* 2006;34(4):146–149
13. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax.* 1998;53(11):927–932
14. Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax.* 1998;53(1):28–32
15. Mommers M, Swaen GM, Weishoff-Houben M, et al. Childhood infections and risk of wheezing and allergic sensitisation at age 7–8 years. *Eur J Epidemiol.* 2004;19(10):945–951
16. Flöistrup H, Swartz J, Bergström A, et al. Allergic disease and sensitization in Steiner school children. *J Allergy Clin Immunol.* 2006;117(1):59–66
17. Kuyucu S, Saraclar Y, Tuncer A, et al. Determinants of atopic sensitization in Turkish school children: effects of pre- and post-natal events and maternal atopy. *Pediatr Allergy Immunol.* 2004;15(1):62–71
18. Bernsen RM, van der Wouden JC. Measles, mumps and rubella infections and atopic disorders in MMR-unvaccinated and MMR-vaccinated children. *Pediatr Allergy Immunol.* 2008;19(6):544–551
19. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull World Health Organ.* 1993;71(3–4):421–428
20. Bremner SA, Carey IM, DeWilde S, et al. Timing of routine immunisations and subsequent hay fever risk. *Arch Dis Child.* 2005;90(6):567–573
21. DeStefano F, Gu D, Kramarz P, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J.* 2002;21(6):498–504
22. Anderson HR, Poloniecki JD, Strachan DP, et al. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health.* 2001;91(7):1126–1129
23. Gruber C, Illi S, Lau S, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics.* 2003;111:282–288
24. Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet.* 1999;353(9163):1485–1488
25. Alfvén T, Braun-Fahrlander C, Brunekreef B, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle: the PARSIFAL study. *Allergy.* 2006;61(4):414–421
26. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol.* 2002;13(suppl 15):11–13
27. Riedler J, Braun-Fahrlander C, Eder W, et al. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet.* 2001;358(9288):1129–1133
28. Bager P, Westergaard T, Rostgaard K, Hjalgrim H, Melbye M. Age at childhood infections and risk of atopy. *Thorax.* 2002;57(5):379–382
29. van den Hof S, Conyn-van Spaendonck MA, van Steenbergen JE. Measles epidemic in the Netherlands, 1999–2000. *J Infect Dis.* 2002;186(10):1483–1486
30. World Health Organization. Immunization, vaccines, and biologicals. vaccine-preventable diseases. Available at: www.who.int/immunization_monitoring/data/data_subject/en/index.html. Accessed December 28, 2008
31. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet.* 1998;351(9103):637–641
32. Bolton P, Holt E, Ross A, Hughart N, Guyer B. Estimating vaccination coverage using parental recall, vaccination cards, and medical records. *Public Health Rep.* 1998;113(6):521–526
33. Suarez L, Simpson DM, Smith DR. Errors and correlates in parental recall of child immunizations: effects on vaccination coverage estimates. *Pediatrics.* 1997;99(5). Available at: www.pediatrics.org/cgi/content/full/99/5/e3

Allergic Disease and Atopic Sensitization in Children in Relation to Measles Vaccination and Measles Infection

Helen Rosenlund, Anna Bergström, Johan S. Alm, Jackie Swartz, Annika Scheynius, Marianne van Hage, Kari Johansen, Bert Brunekreef, Erika von Mutius, Markus J. Ege, Josef Riedler, Charlotte Braun-Fahrländer, Marco Waser and Göran Pershagen

Pediatrics 2009;123;771
DOI: 10.1542/peds.2008-0013

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Allergic Disease and Atopic Sensitization in Children in Relation to Measles Vaccination and Measles Infection

Helen Rosenlund, Anna Bergström, Johan S. Alm, Jackie Swartz, Annika Scheynius, Marianne van Hage, Kari Johansen, Bert Brunekreef, Erika von Mutius, Markus J. Ege, Josef Riedler, Charlotte Braun-Fahrländer, Marco Waser and Göran Pershagen

Pediatrics 2009;123;771
DOI: 10.1542/peds.2008-0013