

Influence of MMR-vaccinations and diseases on atopic sensitization and allergic symptoms in Swiss schoolchildren

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The prevalence of asthma and allergic disease has increased in many countries. It has been proposed that vaccinations may contribute to the development of allergic disease by reducing clinical infections in infancy or through the direct IgE-inducing effects of the vaccines. Evidence for a potential role of immunizations in the development of allergic disease is scarce. Therefore the objective was to study the associations between vaccinations against measles, mumps and rubella (MMR), natural infections of these diseases and atopic sensitization to indoor and outdoor allergens and allergic symptoms in schoolchildren. The cross-sectional study including 1537 8th grade school children aged 13–15 years living in 10 communities across Switzerland was organized in the framework of an environmental health surveillance program within the School Health Services (Swiss Surveillance Program of Childhood Asthma and Allergies with respect to Air Pollution and Climate, SCARPOL). Main outcome measures were asthma and sneezing during pollen season assessed by parental questionnaires and atopic sensitization determined by IgE concentrations to various allergens. It was found that parents' reported history of measles or mumps was associated with a stronger immune response than two or more vaccinations against the respective infection (measles: geometric mean IgG titers (GMT) IU/ml (95% CI) 2.8 (2.0–3.9) vs. 1.2 (1.0–1.4), mumps: GMT PE/ml (95% CI) 16.3 (13.9–19.1) vs. 8.5 (6.1–11.7). With respect to atopic sensitization similar associations for exposure by natural MMR-infections or MMR-vaccinations were found: measles: OR (95% CI) 1.02 (0.53–1.96) vs. 1.22 (0.69–2.16), mumps: 0.59 (0.38–0.93) vs. 0.79 (0.49–1.27), rubella: 0.93 (0.61–1.43) vs. 0.95 (0.66–1.37), respectively. Inverse relationships were found between the risk of asthma and a positive disease history or vaccination of measles 0.36 (0.14–0.91) vs. 0.45 (0.21–0.98) or a positive serum titer against measles 0.65 (0.35–1.20). From the present study can be concluded that exposure by MMR-vaccinations or natural MMR-infections in childhood does not increase the risk of sensitization to common allergens as well as to allergic respiratory diseases. MMR-vaccinations or natural MMR-infections are therefore an unlikely factor contributing to the increase in atopic disease in developed countries.

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The prevalence of asthma and allergic disease has increased in many countries (1–3), and there has been a great deal of speculation as to the possible causes (4). Environmental factors have a key role

in the genesis of allergic diseases as demonstrated by geographical differences in prevalence rates and by migration from developing to industrialized countries or from rural to urban areas (5).

This may be due to factors associated with a westernized lifestyle including improved hygiene, changes in diet and increased use of antibiotics (6–8). Furthermore, it has been proposed that vaccinations may contribute to the development of allergic disease by reducing clinical infections in infancy, or through the direct immunoglobulin E (IgE)-inducing effects of the vaccines themselves and/or the potentiating adjuvants (9). Based on anthroposophic philosophy it is argued that natural infections such as measles provide a positive opportunity for a child's spiritual and physical development in contrast to vaccinations, which compromise the immune system, resulting in diseases such as asthma, allergies, autism or Crohn's disease (10–12). Measles, mumps and rubella (MMR)-diseases are perceived by some Swiss parents and a publicly active minority of physicians as relatively harmless and beneficial for the natural development of the child's immune system regarding diseases such as allergy or asthma. Whereas, MMR-vaccinations are thought to promote detrimental long-term health effects (13). These views have gained public prominence in a situation where public awareness of the severity of vaccine-preventable illnesses has decreased because of the decline of these diseases, likely prompting greater reluctance to accept vaccinations (14, 15).

In this study, both parental reporting and objective clinical markers of natural MMR-infections and allergic diseases as well as information from vaccination cards were available and provided the opportunity to assess the relation between infectious diseases or vaccinations against these diseases in childhood and the occurrence of allergic sensitization to indoor and outdoor allergens and allergic symptoms in 8th grade Swiss schoolchildren.

Participants and methods

Study population

The Swiss Surveillance Program of Childhood Asthma and Allergies with respect to Air Pollution and Climate (SCARPOL) is a cross-sectional multicenter environmental health monitoring program (16, 17). The aim of SCARPOL is to assess the impact of long-term exposure to air pollution, infectious diseases and vaccinations on respiratory and allergic symptoms and illnesses of schoolchildren (aged 6–15 y) living in 10 different communities in Switzerland. SCARPOL was first conducted during the school year 1992/1993 (SCARPOL I) and repeated with identical methods in 1995/1996 (SCARPOL II) (17). The

study was organized within the framework of the School Health Services, thereby taking advantage of an existing structure of the Health System. The children visit the School Health Services routinely at the age of 6–7 (1st grade), 9–11 (4th grade) and 13–15 yr (8th grade). The present analysis included 8th grade schoolchildren living in Anières (GE), Bern, Biel, Geneva, Rheintal, Langnau i.E., Lugano, Montana, Payerne, Zurich.

A total of 2885 (69.2%) invited parents completed the questionnaire. Of these 2494 (86.4%) provided both the questionnaire and the children's vaccination cards and for 1537 (53.3%) children a completed parental questionnaire, information about the vaccination status and blood samples from their children were available. In order to assess potential participation bias we compared heterogeneity of associations between those who provided questionnaires only, questionnaires and vaccination cards or questionnaires and vaccination cards and blood samples. We found no significant differences across these subgroups with respect to respiratory or allergic symptoms (asthma, sneezing during pollen season past year) and a family history of asthma and/or atopy or parental reporting of measles infection (data not shown).

As there were no systematic differences in prevalence rates of respiratory and allergic symptoms or in atopic sensitization rates between the two surveys, data of both surveys were pooled (17).

The study protocol was approved by the Ethics Committee of the University of Bern.

Statistical analysis

Exposure variables included parental reports of a history of MMR (questionnaire), information about vaccinations against MMR (extracted from vaccination card by school physicians) and serum antibodies (IgG) against MMR (18). The detailed questionnaire completed by the parents included questions on age, sex, respiratory and allergic symptoms, family history of respiratory and allergic diseases, infectious diseases such as MMR, number of siblings, parental education, passive smoking, pet ownership, and study area. The core questions on asthma and allergy of the International Study on Childhood Asthma and Allergy (ISAAC) (19) were incorporated into the questionnaire (20). A history of MMR was defined as a positive response to the question: 'Has your child ever had measles or mumps or rubella'.

Commercially available ELISA kits (Behring [Marburg, Germany] & Sanofi/Pasteur [Chaska,

MN, USA)) were used for the determination of serum IgG titers of MMR from SCARPOL I + II. A positive result was defined as an IgG concentration 0.15 IU/ml for measles, 1.0 PE/ml for mumps and 10 IU/ml for rubella (18).

The exposure information was combined and the following new variables were defined for MMR: history of disease-negative and vaccination-negative, history of disease-positive and vaccination-negative, history of disease-negative and vaccination-positive, history of disease-positive and vaccination-positive. Outcome variables included serum IgE levels to SX1 allergens, parental reports of a history of asthma, and sneezing during pollen season past 12 months (12). The multiscreen test SX1 from Pharmacia (Uppsala, Sweden), screening for the following eight common inhalative allergens was performed with all serum samples from 8th grade children of SCARPOL I + II by CAP-FEIA technology: cat, dog, dust mite, mold, timothy grass, rye grass, mugwort, birch. A positive result was defined as a specific IgE concentration ≥ 0.70 kU/l (CAP class ≥ 2).

Geometric mean IgG titers (GMT) of MMR were calculated according to parents' reported history of MMR and according to the number of vaccine doses against MMR. In order not to lose zero values during logarithmic transformation of IgG titers, a small constant ($c = 0.01$) was added before the logarithm was taken.

To assess a potential dose-response association, positive serum IgG levels were divided into terciles and compared with negative IgG titers. ANOVA models were used to compare geometric mean serum antibody titers across categories of number of vaccine doses. The t-tests compared geometric mean serum antibody titers of subjects with negative or positive history of M/M/R disease.

Separate multivariate logistic regression models were used to examine associations between outcome variables and exposure variables. The models adjusted for age, sex, nationality, study area, social status, number of siblings, breastfeeding, family history of asthma or allergies, current and childhood pet exposure, removal of pets because of allergic diseases, parental smoking, farming as parental occupation, childhood vaccinations against diphtheria, tetanus, pertussis, and polio. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). An OR is statistically significant if the upper and lower limits of the 95% CI are either both below or both above 1. All analyses were carried out in the statistical software program STATA (21).

Results

The mean age of the study population was 14.0 yr (s.d.: ± 0.69), 47.8% were boys ($n = 734/1536$), 80.4% Swiss nationals ($n = 1231/1532$), 51.1% had a positive family history of asthma and/or atopy ($n = 785/1537$). Using a cut-off of 0.70 kU/ml, 36.5% of the children ($n = 561/1537$) had a positive SX1 test, 23.5% were sensitized to any indoor allergens ($n = 360/1530$) and 31.6% to any outdoor allergens ($n = 484/1530$).

The vaccination coverage found in this study for ≥ 1 dose was 81.6% for measles, 65.6% for mumps and 53.7% for rubella. The immunization schedule in Switzerland is comparable with that of other European countries and recommends the administration of the first dose of MMR-vaccine at the age of 12 months and a second dose at the age of 15–24 months (22). The combined MMR-vaccines are used predominantly.

Table 1 shows the geometric mean values of IgG serum antibody titers against MMR according to a history of M/M/R disease and stratified by disease history for the number of vaccine doses. Children with a positive history of disease showed higher IgG titers than children with a negative disease history. A positive association between the number of vaccine doses and the GMT can be demonstrated. Serum IgG titers of non-vaccinated children were significantly lower for children without a history of disease compared to children with a history of disease.

Table 2 shows associations between allergic sensitization to SX1 and exposure to MMR (history of M/M/R disease and/or vaccination). A positive history and/or vaccination against mumps tended to be negatively associated with increased specific IgE to SX1. These negative associations were significant for a positive history of mumps and negative vaccination. For rubella, negative associations of borderline significance with increased specific IgE could be observed for subjects with a positive history of disease and a vaccination compared with subjects with neither a positive anamnesis nor a vaccination. No clear association was observed between a history and/or vaccination to measles and allergic sensitization.

A positive serum IgG response to measles or mumps was associated with a non-significantly reduced risk for an allergic sensitization. For measles and mumps, the negative associations although not statistically significant tended to be stronger for higher IgG titers (highest tercile above cut-off) suggesting a dose-response effect (Fig. 1).

Table 1. Geometric mean of serum antibodies (immunoglobulin G, IgG) against measles, mumps and rubella (MMR) according to history of M/M/R diseases and number of vaccine doses

	Measles		Mumps		Rubella	
	Sample prevalence, N (%)	Geometric mean of serum antibody titer, IU/ml (95% CI)	Sample prevalence, N (%)	Geometric mean of serum antibody titer, PE/ml (95% CI)	Sample prevalence, N (%)	Geometric mean of serum antibody titer, IU/ml (95% CI)
Negative history of M/M/R disease	1102 (71.7)	0.9 (0.8–1.0)**	1102 (72.5)	4.9 (4.4–5.6)**	1199 (78.2)	35.7 (29.2–43.7)**
Vaccinations (number of doses)						
None	126 (11.4)	0.5 (0.3–0.7)*	285 (25.9)	3.3 (2.5–4.2)*	504 (42.0)	11.3 (7.6–16.8)*
1	741 (67.2)	0.9 (0.8–1.0)*	699 (63.4)	5.3 (4.6–6.2)*	601 (50.1)	81.8 (67.8–98.8)*
≥2	235 (21.3)	1.2 (1.0–1.4)*	118 (10.7)	8.5 (6.1–11.7)*	94 (7.8)	84.7 (54.2–132.2)*
Any (≥1)	976 (88.6)	1.0 (0.9–1.0)	817 (74.1)	5.7 (5.0–6.5)	695 (58.0)	82.2 (69.1–97.8)
Positive history of M/M/R disease	434 (28.3)	1.7 (1.4–2.0)**	419 (27.5)	17.6 (15.4–20.1)**	335 (21.8)	116.2 (84.8–159.4)**
Vaccinations (number of doses)						
None	156 (35.9)	2.8 (2.0–3.9)***	238 (56.8)	16.3 (13.9–19.1)***	206 (61.5)	92.8 (58.2–148.0)
1	230 (53.0)	1.2 (1.0–1.5)***	163 (38.9)	17.4 (13.9–21.6)***	118 (35.2)	165.2 (114.5–238.4)
≥2	48 (11.1)	1.6 (1.0–2.5)***	18 (4.3)	52.8 (16.6–167.6)***	11 (3.3)	180.7 (87.3–374.1)
Any (≥1)	278 (64.1)	1.3 (1.0–1.5)	181 (43.2)	19.4 (15.4–24.4)	129 (38.5)	166.5 (118.6–233.7)

*p < 0.05, ANOVA (comparison between categories of number of vaccine doses among children with a negative history of MMR).

**p < 0.05, t-test (comparison between negative and positive history of M/M/R disease).

***p < 0.05, ANOVA (comparison between categories of number of vaccine doses among children with a positive history of MMR).

Table 2. Adjusted odds ratio† of reported allergic symptoms and diseases and exposure to measles, mumps or rubella [MMR, history of M/M/R disease and/or vaccination or a positive serum immunoglobulin G (IgG) titer]

Outcome	Exposure				
	Negative history of disease and negative vaccination	Positive history of disease and negative vaccination	Negative history of disease and positive vaccination	Positive history of disease and positive vaccination	Positive vs. negative serum IgG titer
Measles					
SX1	1.00	1.02 (0.53–1.96)	1.22 (0.69–2.16)	1.17 (0.63–2.17)	0.85 (0.55–1.33)
Asthma ever	1.00	0.36 (0.14–0.91)*	0.45 (0.21–0.98)*	0.47 (0.20–1.12)	0.65 (0.35–1.20)
Sneezing during pollen	1.00	1.15 (0.53–2.53)	0.94 (0.47–1.87)	0.93 (0.44–1.97)	0.62 (0.37–1.03)
Season past year, N/total (%)	104/1384 (7.5)‡	136/1384 (9.8)‡	895/1384 (64.7)‡	249/1384 (18.0)‡	118/1368 (8.6)‡
Mumps					
SX1	1.00	0.59 (0.38–0.93)*	0.79 (0.49–1.27)	0.74 (0.42–1.32)	0.84 (0.56–1.25)
Asthma ever	1.00	1.21 (0.60–2.42)	1.67 (0.79–3.54)	0.99 (0.39–2.57)	0.93 (0.49–1.75)
Sneezing during pollen	1.00	0.92 (0.53–1.60)	0.76 (0.42–1.37)	1.05 (0.52–2.12)	0.90 (0.54–1.50)
Season past year, N/total (%)	255/1384 (18.4)‡	213/1384 (15.4)‡	741/1384 (53.5)‡	175/1384 (12.6)‡	139/1368 (10.2)‡
Rubella					
SX1	1.00	0.93 (0.61–1.43)	0.95 (0.66–1.37)	0.59 (0.34–1.02)	0.97 (0.70–1.35)
Asthma ever	1.00	0.73 (0.38–1.39)	0.95 (0.55–1.63)	0.47 (0.18–1.18)	1.16 (0.71–1.91)
Sneezing during pollen	1.00	0.78 (0.46–1.32)	1.24 (0.78–1.98)	1.09 (0.55–2.17)	1.28 (0.84–1.94)
Season past year, N/total (%)	446/1384 (32.2)‡	188/1384 (13.6)‡	632/1384 (45.7)‡	118/1384 (8.5)‡	241/1368 (17.6)‡

SX1, cat and/or dog and/or dust mite and/or mold and/or timothy grass and/or rye grass and/or mugwort and/or birch.

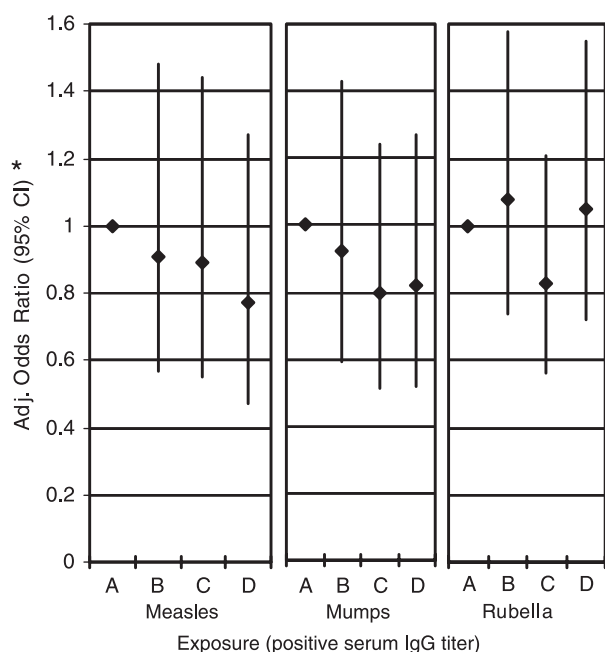
*Significant statistical difference (p < 0.05) compared with reference category (negative history of disease and negative vaccination).

†OR (95% CI) adjusted for age, sex, environmental tobacco smoke exposure, number of siblings, nationality, study area, social status, family history of asthma or allergy, current and childhood pets, removal of pets because of allergic diseases, farming as parental occupation, other childhood vaccination.

‡Total N reduced because of missing information in covariates.

Compared to children without a disease history of measles and no corresponding vaccination (reference group), children with a disease history of measles and/or vaccination against

measles showed a reduced risk for asthma ever. No clear trend was found for sneezing during pollen season past year. Interestingly, stratified analysis of subjects with or without sensitization



A: IgG-titer below cut-off (reference category)
 B: Lowest tertile above cut-off compared to serum IgG titer below cut-off
 C: Medium tertile above cut-off compared to serum IgG titer below cut-off
 D: Highest tertile above cut-off compared to serum IgG titer below cut-off
 Cut-off: measles ≥ 0.15 IU/ml, mumps ≥ 1.0 PE/ml, rubella ≥ 10 IU/ml
 SX1: Cat and/or dog and/or dust mite and/or mould and/or timothy grass and/or rye grass and/or mugwort and/or birch
 * OR (CI 95%) adjusted for age, sex, ETS exposure, number of siblings, nationality, study area, social status, family history of asthma or allergy, current and childhood pets, removal of pets because of allergic diseases, farming as parental occupation, other childhood vaccinations.

Fig. 1. Adjusted odds ratios of the association between allergic sensitization to SX1 and exposure to measles, mumps or rubella [positive serum immunoglobulin G (IgG) titer].

to SX1 exposed to measles disease or vaccination against measles revealed a stronger reduction of the risk for asthma ever in non-atopic subjects (intrinsic asthma): positive history of disease and negative vaccination: OR (95% CI) 0.19 (0.04–0.94), negative history of disease and positive vaccination: 0.21 (0.06–0.76) than in atopic subjects (extrinsic asthma): positive history of disease and negative vaccination: 0.79 (0.22–2.87), negative history of diseases and positive vaccination: 0.61 (0.21–1.77). A positive serum IgG response to measles tended to be associated with a reduced risk for asthma and sneezing during pollen season past year, although statistically not significant.

Discussion

It has been postulated that vaccinations might increase atopic disease either by a direct effect on the immune system or by a reduction of the burden of infection in early childhood (23). This cross-sectional study of immunization rates, natural exposure to MMR and atopic sensitization or symptoms of atopic disease lends no support to

this idea. In line with other studies the results indicate that exposure by measles vaccination and/or natural disease does not increase but rather reduce the risk for atopic diseases (24, 25).

The MMR-vaccine coverage found in this study was relatively low for mumps and rubella. Recent outbreaks of MMR in Switzerland are a consequence of the insufficient and patchy vaccination coverage, observed despite the implementation of routine immunization with one dose in 1976 and with two doses in 1996 (26–28).

Claims that MMR-vaccination might have harmed children by preventing their early exposure (especially to measles) and making them more prone to atopic and allergic diseases have highlighted the fact that levels of antibodies against MMR were shown to persist longer in naturally infected than in immunized individuals and suggested qualitative differences between natural infections and vaccinations (11, 29).

In line with previous studies we found that parents' reported history of MMR was associated with higher antibody concentrations than a vaccination against the respective infection (29, 30).

With respect to atopic sensitization our results document similar associations for exposure by MMR-vaccination or natural MMR-infection suggesting relatedness of induction of immunologic mechanisms between wild-type MMR-viruses and attenuated live MMR-vaccine viruses (30–32). The present study found indications for negative associations with increased specific IgE and a positive history of disease or a vaccination to mumps or rubella but not to measles. Positive serum responses to measles or mumps were non-significantly associated with a reduced risk of allergic sensitization in a dose-dependent manner. Several epidemiologic studies have demonstrated inverse relationships between certain infections such as measles (24, 33–36), mycobacteria (37), hepatitis A, *Toxoplasma gondii*, *Helicobacter pylori* (7) and the risk of atopic sensitization and atopic diseases. Inverse relationships were also found between cumulative vaccine doses received (measles/mumps, pertussis, diphtheria/tetanus) and atopy (25). One theory, known as the 'hygiene hypothesis' states that infections with particular viruses or intracellular organisms may influence the developing immune system toward T-helper cell 1 (Th₁) responses and reduce the risk of allergen sensitization in childhood (4). However, a recent review of the epidemiologic evidence does not provide strong support for this proposition (38).

Our results suggest that exposure to measles either by natural infection and/or vaccination

might modulate immunologic mechanisms and reduce the risk of asthma.

Interestingly, stratified analysis of subjects with or without sensitization to SX1 revealed a stronger reduction of the risk for asthma ever in non-atopic (intrinsic asthma) than in atopic subjects (extrinsic asthma) exposed to measles disease and/or vaccination against measles. These results suggest differences in the regulation of antigen-specific immune functions (e.g., tolerance induction) between atopic and non-atopic individuals and that factors which affect allergic sensitization probably differ from those influencing the onset of asthma (39, 40). Interest in the possibility that measles might be protective against allergy and allergic diseases had previously arisen from the results of several studies (24, 33–36). A recent German birth cohort study demonstrated a trend toward less allergic sensitization, atopic dermatitis or asthma among measles/mumps-vaccinated children in comparison with non-vaccinated children (25). Contrasting with these results a cross-sectional evaluation of computerized medical records of a nationwide Finnish campaign to vaccinate children against MMR found an association between naturally acquired measles infection and increased prevalence of asthma, and trends toward increases in allergic rhinitis and atopic dermatitis (41). Furthermore, results from a national birth cohort study in Denmark demonstrated that measles in the first year of life was associated with a higher risk of atopy than no measles before age 7 yr (42).

A cross-sectional study cannot explain the development of allergy. We have analyzed the long-term outcome of atopy with respect to exposure by MMR-diseases or vaccinations in 8th grade schoolchildren. An analysis of earlier exposition in life was not possible because of sera collection at one time-point only. Although important confounders have been adjusted in the logistic models, the possibility exists that other known (e.g., antibiotics, diet) or unknown factors not adjusted for may have influenced our results.

In our study infections by MMR and allergic diseases were assessed both by parental reporting as well as objective clinical markers (serum IgG against MMR, specific IgE against indoor and outdoor allergens). Parental recall is likely to be incomplete, particularly for non-specific illness, such as fever or respiratory infections, although it is arguably better for the 'once off' viral infections (such as measles, mumps and chickenpox) or severe illness such as asthma. We found that parental reporting of MMR-diseases correlated with the serum IgG antibody responses

against MMR. Hence, a differential reporting bias seems unlikely. Misclassification would most likely have skewed our results toward the null hypothesis. It might also be argued that a selection bias was introduced by the particularity of the reference group used (no history of disease and no vaccination). Parents with a family history of allergy or allergic disease might have different vaccination rates for their children than parents without such diseases. However, no differences in MMR-vaccination rates or reporting of MMR natural infection was found for children with or without a family history of allergy or allergic disease.

In line with previous reports this study indicates that MMR-vaccinations or natural MMR-infections do not increase the risk of atopic sensitization to common allergens as well as allergic respiratory diseases and are therefore unlikely a factor contributing to the increase in atopic disease in developed countries (24, 25). We found that higher levels of antibodies were induced by natural exposure to MMR than by the corresponding vaccinations, emphasizing the need of vaccination programs to monitor and maintain protective antibody levels (43). However, our results do not support claims of qualitative differences of antibodies induced by natural infection or vaccination with respect to the risk of atopic diseases.

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