

Measles, mumps and rubella infections and atopic disorders in MMR-unvaccinated and MMR-vaccinated children

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Vaccinations have been incriminated in the increase of atopic disorders. Especially the measles-mumps-rubella (MMR) vaccination is often refused by people having a notion that these infectious diseases are beneficial for a healthy development of a child's immune system. This practice endangers herd immunity and is the cause of repeated outbreaks. As the clinical course of infections and also its possible impact on the development of atopy may be different in vaccinated and unvaccinated individuals, we explored in vaccinated and unvaccinated children associations of MMR infection with atopic disorders. Using data from a previously conducted study on the relationship between the diphtheria-tetanus-pertussis-(inactivated) poliomyelitis vaccination in the first year of life and atopic disorders, the study population of 1872 8–12-yr-old was divided as children MMR-unvaccinated and children MMR-vaccinated in the first year of life. Within each group the association between MMR infections and atopic disorders (both as reported by the parents) was assessed. We found a statistically significant positive association between measles infection and 'any atopic disorder' [adjusted odds ratio, OR (95% confidence interval, CI): 1.77 (1.20–2.61)] in the MMR-vaccinated group, mainly because of the relationship with eczema. For rubella there was a negative association with eczema and food allergy in the unvaccinated group: adjusted OR (95% CI): 0.57 (0.38–0.85) and 0.23 (0.07–0.76), respectively. All other associations were not statistically significant. We found a positive relationship between measles infection and any atopy in a group of MMR-vaccinated children and a negative association between rubella infection and eczema and food allergy in unvaccinated children. However, we cannot conclude that these relationships are causal. The negative association with rubella may be an artefact. This study shows no evidence for any protective effects from MMR diseases for the development of atopy and therefore supports conclusions found elsewhere that childhood vaccinations do not cause atopy.

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The prevalence of atopic disorders has increased dramatically during the second half of the previous century, but explanations for this epidemic are still being sought. After the launch of the hygiene hypothesis in 1989 (1), there have been numerous studies on the association

between infections and atopic disorders, leading to conflicting results and considerable controversy. In this respect, also the issue of vaccinations was drawn into the discussions, related not only to the question whether they could directly cause atopic disease, but also to the fact that

vaccinations prevent infectious diseases and could therefore possibly inhibit the supposedly beneficial effect (on the development of atopy) of early life infections postulated by the hygiene hypothesis. This hypothesized effect of infections in childhood is often interpreted as a beneficial effect of even serious infections by people with an anthroposophic lifestyle and these people are consequently generally reluctant to take childhood vaccinations, thus endangering herd immunity. Especially the measles-mumps-rubella (MMR) vaccination, considered preventing less serious diseases than the diphtheria-tetanus-pertussis (DTP) vaccination, is often refused (2). However, recent studies concluded that childhood vaccinations very unlikely cause atopy (3, 4).

Measles infection and atopy

Studies investigating the association between measles infection and atopy show conflicting results. After a measles epidemic in Guinea-Bissau, Shaheen et al. (5) found that children who had been infected had a prevalence of atopy that was about half of that in children who had not been infected and were vaccinated after the epidemic. However, conclusions drawn from this study were invalidated by the fact that there was a substantial loss to follow-up (mainly due to the high mortality rate) (6). A cross-sectional study in Switzerland among 13–15-yr-old children found a protective effect only for asthma, not for atopic sensitization (7), while a multicenter (five countries) cross-sectional study in Steiner school children (with a reference sample from the general population) found that measles infection was protective for immunoglobulin E (IgE)-mediated eczema (8). A cross-sectional study conducted in the 1980s in Finland (9) found a positive association between measles infection and asthma, rhinitis and eczema, while a retrospective case-control study in Italy (10), a cross-sectional study in Germany and the Netherlands (11) and an ecological study in Brazil (12) found no important associations.

Mumps infection and atopy

A few studies investigating the association between measles and atopy also looked at other MMR infections: recently published data from the Finnish population-based cross-sectional study showed positive associations of mumps infection with asthma, rhinoconjunctivitis and eczema (13), the Italian and the German–Dutch study found no associations

(10, 11), whereas the Swiss study (7) found a negative association between mumps infection and atopic sensitization.

Rubella infection and atopy

The Finnish study found positive associations between rubella infection and asthma, rhinoconjunctivitis and eczema (13), while the Italian, the German–Dutch study and the Swiss study found no important associations between rubella infection and atopy (7, 10, 11).

Rationale for the study

Even in populations with high vaccination coverage, outbreaks of measles occur, especially if there are clusters of unvaccinated people (14). During these outbreaks, also vaccinated cases may get infected, because in about 5% of the vaccinated children no seroconversion takes place (15). In most studies of the association between infections and atopy no distinction is made between vaccinated and unvaccinated children, although the association between infection and atopy may be modified by vaccination status as a previous study on the association between pertussis infection and atopy has shown (16). Therefore, we attempted to assess the association between MMR diseases and atopy in vaccinated and unvaccinated children in data collected in a previous study on the relationship between the DTP-(inactivated) poliomyelitis vaccination (IPV) in the first year of life and reported atopic disorders at 8–12 yr of age (4).

Patients and methods

Study area, population and design

The present study was conducted in the framework of a previous study designed to assess the relationship between the DTP-IPV vaccination and reported atopic diseases (4). Briefly, in 2003 and 2004, we sent questionnaires to 4480 children (aged 8–12 yr) of 38 orthodox reformed (Protestant) primary schools in the Netherlands. Many parents of children attending these schools refuse vaccinations for religious reasons. A total of 1872 questionnaires (42%) were returned and suitable for analysis of which 671 pertained to reportedly DTP-IPV-unvaccinated children. A subsequent non-responder investigation found no evidence of any selection bias (4). Of the 1201 DTP-IPV-vaccinated children 1077 were also MMR-vaccinated and of the 671 DTP-IPV-unvaccinated children, only one was

MMR-vaccinated (4). The MMR vaccination is part of the Dutch National Vaccination Program and is offered at 14 months of age with a booster at 9 yr of age. For the present study we divided the population into two groups:

I. MMR-unvaccinated children (i.e. no MMR vaccination at 14 months of age) and II. MMR-vaccinated children (MMR vaccination at 14 months of age).

Data collection

The questionnaire asked for symptoms (or ever having had the disease) of asthma, hay fever and eczema [Dutch translation of the ISAAC questionnaire (17, 18)], physician-diagnosed food allergy ever, childhood vaccinations, gender, passive smoking history, date of birth, perinatal data, birth order, ZIP code, year of birth of the mother, any atopic disorders of parents or siblings, family composition, education, income, living conditions (current and during the first year of life), day-care attendance, breast feeding, nutrition during the past month, frequency of exercise, body length and weight and having had common infectious diseases preventable by vaccinations (measles, mumps, rubella and pertussis).

Reliability of vaccination status

Comparison of reported vaccination status with official registration data in a random subgroup of 120 children yielded 100% agreement for the MMR vaccination status (4).

Statistical analysis

We planned to carry out analyses for measles, mumps and rubella infection separately. However, the skewness of the distribution of the exposure variable (i.e. reported lifetime infection) was a major determinant of the power of our tests. We decided to carry out the following analyses only if the actual size of the subgroup was sufficient to detect an odds ratio (OR) for atopy of 2 with a power of 0.80, significance level of 0.05, assuming a prevalence of atopy of 15% in the group unexposed to infection and a distribution of infection as found in the data. In other cases we just presented the prevalence of atopic disorders stratified for exposure to infection.

The relationship between infection as independent variable and (current symptoms or ever had) asthma (current symptoms or ever had), hay fever, asthma and/or hay fever (current symptoms or ever had), eczema, physician-diagnosed food allergy ever and 'any atopic disorder'

Table 1. Distribution of participants (n = 1872) according to measles-mumps-rubella (MMR) vaccination at 14 months and attrition as a result of unknown MMR vaccination status and unknown MMR infection

MMR vaccination	No (769)	Yes (1078)	Unknown (25)
Measles infection			
Unknown	27	61	
Known	742	1017	
Mumps infection			
Unknown	119	54	
Known	650	1024	
Rubella infection			
Unknown	180	91	
Known	589	987	

Numbers in bold are the resulting group sizes for measles, mumps and rubella infection, respectively.

(anyone of these disorders) as dependent variable, was estimated by means of series of logistic regression. We computed adjusted associations only if the univariate association was significant ($p < 0.05$). As a first approach to multivariate modeling we fitted multivariate models (i.e. models including potential confounders as independent variables) and included only variables (confounders) which changed the univariate point estimate (log OR) by at least 10% (19). These potential confounders are listed elsewhere (4) and included, apart from the characteristics shown in Table 2, perinatal data, data on day-care attendance, nutrition, physical exercise, housing, family history of atopic disease and socioeconomic data. If a potential confounder turned out to be a candidate for a multivariate model in either of the two groups (vaccinated or unvaccinated), we also included it in the corresponding multivariate model for the other group. As a second approach we adjusted the univariate models for sib-ship size and a family history of atopy as these two characteristics could obviously be related to both MMR infection and atopic status of the child. Additionally, we performed sensitivity analyses by exploring the effect of assuming that participants with uncertain infection history (this was 5% for measles, 9% for mumps and 15% for rubella) all had either a negative history or a positive history of infection. Finally, as the vaccinated group and the unvaccinated group differ considerably in sib-ship size, we looked at sib-ship size as an effect modifier in both groups separately in order to try to explain different results in the two groups. SPSS version 14.0 was used for all analyses.

Results

The original study population consisted of 1872 children with usable questionnaires: 769 (41%)

Table 2. Characteristics of 1847 children with known measles-mumps-rubella (MMR) vaccination status

	Unvaccinated* n = 769	Vaccinated† n = 1078
	Median (min–max)	Median (min–max)
Age (yr)	10.2 (7.3–13.7)	10.3 (7.3–13.4)
Number of children in the family	5 (1–13)	4 (1–11)
Gender (%)		
Male	51.2	50.9
Asthma (%)		
Yes	12.8	15.0
Hay fever (%)		
Yes	16.2	18.1
Asthma and/or hay fever (%)		
Yes	22.7	26.3
Eczema (%)		
Yes	31.5	34.5
Food allergy (%)		
Yes	6.9	7.7
Any atopic disorder (%)		
Yes	44.2	49.2
Atopic disorders in parents and/or siblings (%)		
Yes	62.8	65.2
Highest education of parents (%)		
Lower professional or less	36.2	21.7
Medium professional	27.1	30.7
Higher secondary	9.9	15.8
High professional and university	26.7	31.9
Measles infection (%)		
Yes	88.5	13.0
Mumps infection (%)		
Yes	9.4	2.1
Rubella infection (%)		
Yes	29.7	5.0

*Unvaccinated means: no MMR vaccination was received at 14 months of age.

†Vaccinated means: MMR vaccination was received at 14 months of age.

of these were reportedly MMR-unvaccinated at 14 months, 1078 (58%) were MMR-vaccinated and 25 (1%) did not answer this question. Table 1 shows the numbers of missing values for MMR vaccination and infection and the resulting group sizes for measles, mumps and rubella infection, respectively. Table 2 shows history of MMR infections, prevalence of atopy and other characteristics for the 1847 children with known MMR vaccination status.

Measles

Prevalence of atopic disorders for the unvaccinated and the vaccinated groups, with and without reported measles infection, and p-values where applicable, are presented in Table 3a. The actual group size of the unvaccinated group was less than the minimum group size needed as explained in the 'Methods'

section. For the vaccinated group the size was sufficient: all prevalences of atopic disorders were slightly higher in the measles-infected group, but only the association between measles infection and 'any atopic disorder' was statistically significant. The adjusted OR (95% confidence interval, CI) was 1.77 (1.20–2.61) (Table 3b). Our second approach of multivariate modeling yielded similar results (not shown). The sensitivity analyses did not substantially change the results, only when we classified participants with an unknown history of measles as positive, the adjusted OR for any atopic disorder in the vaccinated group slightly attenuated, but remained significant (results not shown).

Mumps

Prevalence of atopic disorders for the two groups, with and without mumps infection, is shown in Table 4. Neither the group size of the unvaccinated group nor that of the vaccinated group was sufficient to perform any further analyses according to the criteria outlined in the 'Methods' section.

Rubella

Prevalence of atopic disorders for the two groups, with and without rubella infection, is shown in Table 5a. The group size of the unvaccinated group was sufficiently large to perform further statistical analyses, while the size of the vaccinated group was too small. In the unvaccinated children, the associations with rubella infection were significant only for eczema, food allergy and any atopic disorder. Crude and adjusted OR and 95% CI are shown in Table 5b. The adjusted OR (95% CI) for eczema and food allergy were 0.57 (0.38–0.85) and 0.23 (0.07–0.76), respectively suggesting that rubella infection could be protective for food allergy and eczema.

The second approach of multivariate modeling as well as the sensitivity analyses yielded results that were close to the results shown here, except for food allergy and any atopic disorder, where classification of participants with unknown history of rubella as positive, yielded an insignificant OR somewhat closer to the null value.

Sib-ship size as effect modifier

For all of the relationships studied, there was no evidence that sib-ship size was an effect modifier.

Table 3a. Prevalence of reported atopic disorders by measles infection and measles-mumps-rubella (MMR) vaccination status

Measles infection?	Unvaccinated* n = 742			Vaccinated† n = 1017		
	No (11%) n = 85	Yes (89%) n = 657	p-value	No (87%) n = 885	Yes (13%) n = 132	p-value
Asthma	10.6	13.2	Not tested	14.6	15.6	0.87
Hay fever	11.9	16.7	Not tested	17.6	19.2	0.75
Asthma and/or hay fever	19.0	23.2	Not tested	25.8	27.9	0.69
Eczema	32.9	31.8	Not tested	33.5	41.7	0.08
Food allergy	7.1	6.9	Not tested	7.2	9.2	0.53
Any atopic disorder	42.4	44.9	Not tested	48.1	58.5	0.03

Values are in percentage (%).

*Unvaccinated means: no MMR vaccination was received at 14 months of age.

†Vaccinated means: MMR vaccination was received at 14 months of age.

Table 3b. Crude and adjusted odds ratio (OR) with 95% confidence intervals (CI) for the association between measles infection and any atopic disorder in the measles-mumps-rubella (MMR)-vaccinated group

	Crude		Adjusted	
	OR	95% CI	OR	95% CI
Any atopic disorder	1.52	1.05–2.21	1.77†	1.20–2.61

†Adjusted for family history of atopy and education.

Discussion

We found a positive association between reported measles infection and atopic disorders (mainly eczema) in a group of MMR-vaccinated children attending orthodox reformed (Protestant) primary schools, a population where about one-third of the children do not receive vaccinations for religious reasons. This association is not necessarily causal as it is not unlikely that children who fail to seroconvert have a higher risk of atopic disease (compared with children who do seroconvert). Causality is also not supported by the findings in the unvaccinated

group (although the size of this group was considered by us to be too small to perform any statistical tests), where one would expect an effect of infection at least as large as in the vaccinated group. For rubella infection, the association with eczema and food allergy was negative in unvaccinated children.

Limitations

Our study has several limitations. First, data were collected by cross-sectional means and we therefore cannot establish the sequence of MMR infections and the onset of atopic symptoms. Second, MMR infections were reported by the parents and no laboratory tests were performed to confirm the diagnoses. Also, parents were sometimes uncertain about whether their child had experienced an MMR infection or not. For measles, there was doubt in only 5% of the participants, but for mumps it was 9% and for rubella 15%. However, this uncertainty was not related to having any atopic disorders and our sensitivity analyses showed that reclassifying these participants either as 'infection' or 'no

Table 4. Prevalences of reported atopic disorders by mumps infection and measles-mumps-rubella (MMR) vaccination status

Mumps infection?	Unvaccinated* n = 650			Vaccinated† n = 1024		
	No (91%) n = 589	Yes (9%) n = 61	p-value	No (98%) n = 1002	Yes (2%) n = 22	p-value
Asthma	12.3	18.0	Not tested	14.6	22.7	Not tested
Hay fever	14.6	16.4	Not tested	17.9	19.0	Not tested
Asthma and/or hay fever	21.1	29.5	Not tested	25.8	36.4	Not tested
Eczema	32.1	31.1	Not tested	34.1	40.9	Not tested
Food allergy	7.2	4.9	Not tested	7.1	13.6	Not tested
Any atopic disorder	43.8	44.9	Not tested	48.8	54.5	Not tested

Values are in percentage (%).

*Unvaccinated means: no MMR vaccination was received at 14 months of age.

†Vaccinated means: MMR vaccination was received at 14 months of age.

Table 5a. Prevalence of reported atopic disorders by rubella infection and measles-mumps-rubella (MMR) vaccination status

Rubella infection?	Unvaccinated* n = 589			Vaccinated† n = 987		
	No (70%) n = 414	Yes (30%) n = 175	p-value	No (95%) n = 938	Yes (5%) n = 49	p-value
Asthma	12.9	10.9	0.60	15.1	8.3	Not tested
Hay fever	15.2	16.0	0.89	17.6	20.8	Not tested
Asthma and/or hay fever	22.3	21.1	0.84	25.9	25.0	Not tested
Eczema	35.7	25.3	0.02	34.7	28.6	Not tested
Food allergy‡	8.7	1.7	0.004	7.3	8.2	Not tested
Any atopic disorder	47.1	37.4	0.04	49.0	45.8	Not tested

Values are in percentage (%).

*Unvaccinated means: no MMR vaccination was received at 14 months of age.

†Vaccinated means: MMR vaccination was received at 14 months of age.

‡Physician diagnosed.

Table 5b. Crude and adjusted odds ratio (OR) with 95% confidence intervals (CI) for the association between rubella infection and eczema, food allergy and any atopic disorder in the measles-mumps-rubella (MMR)-Unvaccinated group

	Crude		Adjusted	
	OR	95% CI	OR	95% CI
Eczema	0.61	0.41–0.91	0.57†	0.38–0.85
Food allergy	0.19	0.06–0.61	0.23‡	0.07–0.76
Any atopic disorder	0.67	0.47–0.97	0.66§	0.45–0.96

†Adjusted for family history of atopy.

‡Adjusted for family history of atopy, birth order and sib-ship size.

§Adjusted for family history of atopy and sib-ship size.

infection' did not substantially change the results. Third, because of the skewed distribution of infection in most groups, subgroup sizes were often too small to perform statistical tests with sufficient power. Only for measles in vaccinated children and for rubella in unvaccinated children were the subgroup sizes sufficiently large to carry out the complete analyses.

Comparison of our prevalence of life-time atopy with other studies

We found prevalence of life-time atopic disorders in 8–12-yr-old children between 44% and 49% (Table 2), with an overall prevalence of 47%. This apparently somewhat high prevalence agrees well with another study conducted in the Netherlands in 13–14-yr-old children in the same year as our study (2003) that found a prevalence of life-time atopic disorders of 52.6% using (like we did) the ISAAC questionnaire (20). Our high prevalence of family history of atopy of around 65% (Table 1) is probably because of the large family size in this population.

Life-time prevalence of MMR diseases: comparison with surveillance data

Measles. The life-time prevalence of 88.5% in the unvaccinated group in our study population is very close to the figure (85.4%) found in a serosurveillance study for the age group 0–24 yr in the same religious population (21). As there are regular outbreaks of measles in this community (about every 6 yr) (22) and protection provided by the vaccine is not 100%, a fraction of the vaccinated part of the population is still expected to get the disease. According to van den Hof et al. (14), with the present vaccination schedule, about 1.5% of the lifetime is spent susceptible, mainly under the age of 10, and the probability for a susceptible vaccine acceptor under the age of 10 to become a reported case during an epidemic is roughly 0.06 (14). If we combine these figures with the assumption that each reported case represents at least 40 real cases (23) and the fact that our study population experienced on average 1.5 epidemics, we would expect a prevalence of measles in vaccine acceptors of about 35%, which is higher than our figure of 13%. This might suggest that measles infection in vaccinated children is often subclinical or not serious enough to be remembered and retrospectively reported. However, in contrast to this estimated prevalence of 35% is the fact that during the 1999–2000 epidemics in the Netherlands none of the 25 vaccinated pupils of the orthodox reformed primary school where the epidemic started had clinical symptoms (24).

Mumps. A serosurveillance study in the Netherlands showed that in the religious, low-vaccine coverage population the seroprevalence in 1–4-yr-old children (this population involves both unvaccinated and vaccinated individuals) was

about 30% (lower than in the general population), while in the age group of 5 yr and older it was 97% (25). This indicates that the majority of the children older than 4 yr in this religious population got a natural infection. Therefore our prevalence of 9.4% seems very low, probably because a considerable part of the infections are subclinical or mild and are seldom brought to the attention of a physician (26).

Rubella. Seroprevalence was assessed in the Netherlands in a national sample and in a sample of the orthodox reformed population by de Haas et al. (27). This 1999 study shows that the Dutch population has high levels of antibodies from about 14 months of age onwards. This shows that the vaccine offers good protection and it agrees well with our lifetime prevalence of disease of 5% in the vaccinated group. de Haas et al. (27) found that the orthodox reformed population has a high seroprevalence (almost 100%) from about 10 yr of age (although the authors state that this figure may be biased because of selective non-response), while in our study the unvaccinated group had a lifetime prevalence of almost 30%. This seems rather low and might be explained by the fact that in children the symptoms are usually mild.

Comparison of our findings with other studies

Measles. Our finding of a positive association between measles infection and any atopic disorder (mainly eczema) is in agreement with the Finnish study by Paunio et al. (9). Other studies found no associations (10–12) or a negative association with asthma (7) or eczema (8). There can be different explanations for these discrepancies: first, our result for measles infection pertains to a group of MMR-vaccinated children whereas this may not be the case for the other studies; second, measles infection has been measured retrospectively in these studies and therefore the sequence of the infection and the development of atopic symptoms cannot be assessed; third, infection was self-reported in some studies and assessed by antibodies in others and fourth, an ecological association (12) does not automatically imply an association on an individual level.

Rubella. The Finnish study (9) found again positive associations contrary to our findings of negative associations with eczema and food allergy and no associations with asthma and hay fever. Our results were not contradicting

those of the Swiss study (7) and the Dutch–German study (11), which neither found important associations for asthma and atopic sensitization (these studies did not consider eczema as outcome). This negative relationship found in the present study in the unvaccinated group must be viewed with caution as in this religious group almost all 10-yr-old children are seropositive (27) and therefore our reported cases were probably only a fraction of the real number of (mostly mild or subclinical) cases.

The role of sib-ship size

The number of siblings differed considerably between the vaccinated and the unvaccinated groups. The difference in prevalence of atopy, which was not a hypothesis in the present study, was explained by this difference in sib-ship size (4). We found no evidence that sib-ship size was modifying the effect of infection.

Conclusion

We found a positive relationship between measles infection and any atopy in a group of MMR-vaccinated children and a negative association between rubella infection and eczema and food allergy in unvaccinated children. However, as the rubella cases reported in this study probably represent only a fraction of the real number of cases, it is not clear whether this association is an artifact. By no means can we conclude that any relationships are causal. Follow-up studies measuring seroconversion and symptoms of infection and atopy could yield more insight into these relationships. We conclude that this study shows no evidence for any protective effects from MMR diseases for the development of atopy. This is supporting the conclusions found elsewhere that childhood vaccinations do not cause atopy.

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