ORIGINAL ARTICLE

Association of pertussis and measles infections and immunizations with asthma and allergic sensitization in ISAAC Phase Two

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To cite this article: Nagel G, Weinmayr G, Flohr C, Kleiner A, Strachan DP. Association of pertussis and measles infections and immunizations with asthma and allergic sensitization in ISAAC Phase Two. *Pediatr Allergy Immunol* 2012: **00**.

Keywords
asthma; atopy; bronchial hyperreactivity; International Study of Asthma and Allergies in Childhood; measles; pertussis

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Accepted for publication 21 August 2012

DOI:10.1111/pai.12007

Abstract

Background: Pertussis and measles infection as well as vaccination have been suspected as possible mediating factors of allergic disease in childhood.
Methods: Between 1995 and 2005 cross-sectional studies were performed in 29 centers in 21 countries. Parental questionnaires were used to collect information on allergic diseases and exposures. We analyzed data from 54,943 randomly selected schoolchildren aged 8–12 yr. A subgroup of 31,759 children was also skin prick tested (SPT) to common environmental allergens. Combined odds ratios were calculated by random effect models for meta-analysis.
Results: Pertussis and measles vaccination were not significantly associated with any of the allergy outcomes or SPT positivity. However, pertussis infection was associated with wheeze (OR_{ad} 1.68; 95% CI 1.44–1.97) and rhinoconjunctivitis (OR_{ad} 1.63; 95% 1.33–2.00). Pertussis infection was also significantly associated with a higher prevalence of reported eczema during the past year in non-affluent countries. Measles infection was associated with a higher prevalence of wheeze (OR_{ad} 1.26; 95% 1.10–1.43) and reported eczema (OR_{ad} 1.22; 95% 1.08–1.39). No association with SPT positivity was found, suggesting that these associations are unlikely to be mediated by an allergic component.
Conclusions: Associations of pertussis and measles infection with symptoms of asthma, rhinoconjunctivitis and eczema were found in both affluent and non-affluent countries and are unlikely to be mediated by IgE.

Worldwide differences in the prevalence of asthma and allergic disease in childhood have been observed, and it has been postulated that some of these differences are owing to altered exposure to infections, vaccinations, or differences in sanitation (1–3).

However, the current evidence is conflicting. For instance, a meta-analysis of population-based observational studies on pertussis vaccination and asthma provided no clear evidence for an association, mainly because of methodological heterogeneity (4). In Phase one of the ISAAC Study, Dyptheria-Tetanus-Pertussis immunization was inversely related to rhinoconjunctivitis symptoms in an ecological analysis (5). As for pertussis infection, weak positive associations were observed in relation to asthma in cohort studies and one case–control study (6–9). Similar observations have been made for eczema (10). In one case–control study, the positive associations found between pertussis infection and asthma and hay fever symptoms were confined to children who had also been vaccinated against pertussis (11).

Likewise, conflicting results have been reported on the relationship between measles infection and allergic disease. A protective association for allergic sensitization defined by skin prick test (SPT) was found in Guinea-Bissau after a measles epidemic (12). In a cross-sectional study among children in Switzerland, measles infection protected only against asthma, but not against atopic sensitization (13). Other cross-sectional studies found a positive association between measles vaccination and allergic diseases (eczema, allergic rhinitis, asthma) in Finland and no association with wheeze and allergic sensitization in Germany and the Netherlands (14,

15). Measles vaccination has been positively associated with atopic dermatitis (16).

We investigated the associations of measles and pertussis vaccination and infection with the prevalence of asthma and other allergic diseases as part of the ISAAC Phase Two Study, a cross-sectional survey of children aged 8–12 yr from affluent and non-affluent countries around the world.

Material and methods

Study design

The International Study on Asthma and Allergies in Childhood (ISAAC) Phase Two has already been described elsewhere (17). In brief, random samples of at least 10 schools in a defined geographical area were chosen, and children ($n \geq 1000$ per centre) were invited to participate. Overall, 58,743 schoolchildren (76.4% of those eligible) took part. Parental questionnaires, identical to those used in ISAAC Phase One, were used to collect data on the symptom prevalence of asthma, rhinitis, and eczema between 1995 and 2005 (18). For the present analyses, 44,967 children aged 8–12 yr from 29 centers in 21 countries with parental responses on vaccination or infection were included.

Exposure assessment

Information on measles and pertussis vaccination and infection was collected by parental questionnaire, using the following questions: 'Has your child ever had any of the following diseases? measles (yes/no), whooping cough (pertussis infection) (yes/no)' and 'Has your child been vaccinated against any of the following diseases? measles (yes/no), pertussis (Whooping cough) (yes/no).'

Former ISAAC publication suggested asthma and allergy phenotypes could be different in affluent and non-affluent countries (19, 20). Since also differences in the strength of any association between exposure to vaccination and infection with phenotypes were suspected, we performed by affluence status stratified analyses (21). We classified the study centers into two broad categories on the basis of gross national per capita income (GNI), using the World Bank Atlas method: 'affluent countries' and 'non-affluent countries' (GNI < $9200 per year per capita) (22).

Outcome

The question 'Has your child had wheezing or whistling in the chest in the past 12 months?' was used as the indicator for current asthma symptoms. For symptoms of rhinitis, the parents were asked: 'Has your child ever had a problem with sneezing or a runny or blocked nose, when he/she did not have a cold or flu?' (yes/no = 'rhinitis symptoms ever'), and 'In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?' (yes/no = 'rhinitis symptoms in the past year'). For rhinoconjunctivitis, we used rhinitis symptoms in the past year combined with a positive answer to: 'In the past 12 months, has this nose problem been accompanied by itchy watery eyes?'

For eczema symptoms, the questions were: 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' (yes/no = 'eczema symptoms ever'), 'Has your child had this itchy rash at any time in the past 12 months?' (yes/no = 'eczema symptoms past year'), and 'Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?' (yes/no = 'flexural eczema past year'). In addition, children were physically examined by trained field workers for flexural eczema in five body areas: (i) around the eyes, (ii) the neck, (iii) in front of the elbows, (iv) behind the knees, and (v) in front of the ankles. Participants were categorized as having flexural eczema if they had a typical erythematous rash with surface change (e.g., fine scaling, vesicles, oozing, crusting, or lichenification).

Objective measurements

Spirometry and a test of bronchial hyperreactivity (BHR) to hypertonic saline challenge were performed on 9213 children according to ATS criteria as described elsewhere in detail (17, 23, 24).

In addition, SPTs were performed on 31,759 children using six common aeroallergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat hair, *Alternaria tenuis*, mixed tree and grass pollen (ALK, Hørsholm, Denmark). In addition, allergens of local relevance were used in 15 centers. Any skin prick test with a wheal size ≥ 3 mm after subtraction of the negative control was deemed positive (25).

Statistical analysis

Random effect models for meta-analysis were applied to calculate crude (OR) and adjusted odds ratios (OR_{ad}) with 95% confidence intervals (CI) separately for affluent and non-affluent countries, as well as for all centers combined. In multivariate models, we included as potential confounders sex, age, number of siblings, and bedroom sharing. In addition, the infection models were adjusted for pertussis or measles vaccination and vice versa. If centers had studied stratified subsamples (i.e., approximately 100 children with and 100 children without wheeze in the past year), estimates were calculated applying appropriate sampling weights (26). By calculation of I^2 statistics, no substantial (<50%) heterogeneity between centers according to affluence was detected in the meta-analyses of pertussis and measles infections with asthma and allergies (data not shown) (27). We also stratified the analysis of the association of infections and outcomes by sensitization and vaccination status (yes/no) with differences between strata assessed by *Z*-test, which compares the difference between the stratum specific combined random effects estimate (lnOR) against the standard error of this difference (derived from the variance of each lnOR).

Depending on prevalence and completeness of the variables, the number of subjects and sometimes the number of centers in the models differ. We used SAS release 9.2 (SAS Institute, Cary, N.C., USA) to analyze the data.

Table 1 Characteristics of the study sample in ISAAC Phase Two

Centre	N	Prevalence of wheeze past year %	Prevalence of BHR %	Prevalence of rhinoconjunctivitis %	Prevalence of rhinitis without conjunctivitis %	Prevalence of eczema past year %	Prevalence of eczema by examination %	Prevalence of skin prick test positivity %	Prevalence of pertussis vaccination %	Prevalence of measles vaccination %	Prevalence of pertussis infection %	Prevalence of measles infection %
Albania, Tirana	979	4.4	2.1	6.7	14.6	5.8	2.4	14.7	80.9	72.7	30.3	36.1
Brasil, Uruguaiana	1968	25.6	-	21.0	9.9	11.5	-	13.3	99.1	99.0	2.9	15.7
China, Beijing	3733	3.7	-	7.5	23.2	1.7	1.0	23.9	92.0	89.5	-	-
China, Guangzhou	3290	3.2	-	7.0	29.1	1.3	0.7	32.0	83.9	83.1	1.4	-
China, Hong Kong	2874	5.5	-	12.4	15.2	2.9	3.5	45.3	87.0	89.8	2.4	-
Ecuador, Pichincha	874	0.8	-	1.5	2.7	1.8	4.5	19.7	96.2	96.6	13.2	18.0
Estonia, Tallinn	284	8.4	3.5	5.6	11.4	15.6	4.7	14.6	-	-	10.2	-
France, Creteil	1415	7.6	-	14.6	15.4	12.9	6.6	-	71.0	73.2	0.7	5.3
Georgia, Tbilisi	962	9.2	29.5	7.0	9.6	6.2	14.0	33.0	89.5	86.3	35.3	43.8
Germany, Dresden	2976	7.9	10.5	12.1	9.9	14.1	5.9	25.7	96.8	98.3	1.1	-
Germany, Munich	3220	8.3	17.9	12.8	8.3	9.2	4.1	22.3	58.9	87.5	23.8	-
Ghana, Kintampo	1301	6.4	30.4	-	-	3.5	0.4	1.7	-	-	12.7	37.7
Greece, Athens	985	5.6	13.6	4.8	12.9	7.4	1.3	14.4	94.7	93.2	0.6	0.9
Greece, Thessaloniki	1018	8.4	39.9	7.0	12.7	5.1	1.4	26.8	91.2	90.8	1.5	1.7
India, Mumbai	1649	6.1	47.8	4.9	5.3	4.4	1.1	6.4	86.5	83.9	1.3	36.3
Iceland, Reykjavik	944	9.2	-	11.2	6.3	22.2	8.8	23.5	75.7	75.7	5.5	6.7
Italy, Rome	1311	7.9	33.1	9.6	11.5	6.7	1.6	28.9	78.4	79.5	29.8	19.5
Latvia, Riga	897	6.9	13.5	8.5	15.7	9.5	6.4	19.3	92.6	95.8	10.7	24.0
New Zealand,	1312	21.9	23.9	22.3	12.8	13.8	8.2	34.5	94.9	93.6	5.9	26.9

Table 1. Continued.

Centre	N	Prevalence of wheeze past year %	Prevalence of BHR %	Prevalence of rhinoconjunctivitis %	Prevalence of rhinitis without conjunctivitis %	Prevalence of eczema past year %	Prevalence of eczema by examination %	Prevalence of skin prick test positivity %	Prevalence of pertussis vaccination %	Prevalence of measles vaccination %	Prevalence of pertussis infection %	Prevalence of measles infection %
Hawkes Bay												
Norway, Tromso	3714	14.0	42.7	12.6	7.4	20.8	10.5	32.7	80.4	77.5	3.1	7.9
Palestine, Ramallah	295	8.8	-	6.9	10.1	7.5	2.8	10.3	85.3	77.8	7.9	17.0
Spain, Almeria	1093	15.5	29.7	24.5	13.4	10.0	1.9	43.0	90.3	86.5	5.2	14.4
Spain, Cartagena	1389	11.9	23.7	15.4	9.5	7.1	0.9	23.8	96.7	88.6	3.0	11.1
Spain, Madrid	956	11.6	8.9	18.7	13.4	13.1	3.2	34.5	92.4	92.5	2.3	15.2
Spain, Valencia	1327	9.1	24.4	12.6	10.4	8.7	3.7	14.3	94.1	98.0	2.1	8.6
Sweden, Linkoeping	199	7.9	18.7	13.8	5.1	21.0	8.0	19.8	-	-	41.6	-
Sweden, Oestersund	273	10.2	33.5	12.2	8.9	23.7	14.2	26.5	-	-	45.3	-
Turkey, Ankara	2906	10.9	22.4	11.8	17.7	5.4	1.4	24.6	97.1	97.1	7.2	51.0
UK, West Sussex	823	16.2	41.4	16.2	7.4	14.6	6.7	17.5	93.2	96.2	3.2	9.7

-, no data available; BHR, Bronchial hyperreactivity.

Results

The lifetime prevalences of measles and pertussis vaccination as well as measles and pertussis infection are shown in Table 1. The prevalence of pertussis vaccination ranged between 58.9% in Munich (Germany) and 99.1% in Uruguaiana (Brasil). For pertussis infection, the numbers were between 0.6% in Athens (Greece) and 49.1% in Oestersund (Sweden). Measles vaccination was more prevalent and ranged between 72.7% in Tirana (Albania) and 99.0% in Uruguaiana (Brasil). Prevalence of measles infection ranged between 0.9% in Athens (Greece) and 51.0% in Ankara (Turkey).

Pertussis infection and vaccination

Pertussis infection was associated with 'wheeze in the past year' in both affluent (OR_{ad} 1.56; 95%CI 1.28–1.90) and non-affluent countries (OR_{ad} 1.92; 95%CI 1.48–2.48) (Table 2). Pertussis infection was also less strongly associated with 'rhinoconjunctivitis in the past year' in affluent countries (OR_{ad} 1.28; 95%CI 1.07–1.53) compared with non-affluent countries (OR_{ad} 2.29; 95%CI 1.80–2.92); this difference by affluence being significant (p-value <0.001). Pertussis infection was associated with 'eczema during the past year' only in non-affluent countries (OR_{ad} 1.53; 95%CI 1.13–2.05). No significant associations were present for BHR and SPT positivity.

After stratification by allergic sensitization (Table 3), rhinoconjunctivitis was more prevalent among SPT negative children after pertussis infection (p-value 0.007). Otherwise, the pattern of associations was similar.

Stratification of the analysis by history of pertussis vaccination showed for all disease endpoints no statistically significant differences by vaccination status (Table S1). After adjustment for history of pertussis infection, pertussis vaccination status was not significantly associated with any of the disease endpoints (Table S2). SPT positivity was unrelated to pertussis vaccination status (OR_{ad} 0.92; 95%CI 0.72–1.19).

Measles infection and vaccination

Measles infection was positively related to 'wheeze in the past year' (OR_{ad} 1.26; 95%CI 1.10–1.43) (Table 4) but after

Table 2 Association between pertussis infection, asthma, and allergic diseases according to national GNI per capita*,†

	N	CrudeOR	95% CI		p-value‡	N	AdjOR§	95% CI		p-value‡
Wheeze past year										
All centres	36,016	1.69	1.49	1.91		27,138	1.68	1.44	1.97	
Affluent	23,086	1.58	1.35	1.85		17,490	1.56	1.28	1.90	
Non-affluent	12,930	1.86	1.44	2.41	0.290	9648	1.92	1.48	2.48	0.212
Bronchial hyperreactivity										
All centres	3939	1.11	0.87	1.43		2712	1.07	0.76	1.52	
Affluent	2774	1.25	0.94	1.67		2084	1.15	0.77	1.71	
Non-affluent	1165	0.79	0.48	1.29	0.117	628	0.85	0.39	1.89	0.513
Rhinoconjunctivitis										
All centres	34,451	1.55	1.26	1.90		26,981	1.63	1.33	2.00	
Affluent	22,914	1.22	1.04	1.42		17,425	1.28	1.07	1.53	
Non-affluent	11,537	2.30	1.84	2.87	<0.0001	9556	2.29	1.8	2.92	0.0001
Rhinitis without conjunctivitis										
All centres	32,633	1.15	1.00	1.31		25,047	1.10	0.94	1.29	
Affluent	22,142	1.16	0.97	1.38		16,707	1.13	0.91	1.4	
Non-affluent	10,491	1.13	0.92	1.40	0.885	8340	1.07	0.84	1.36	0.074
Eczema past year										
All centres	36,069	1.30	1.07	1.58		27,240	1.22	1.02	1.45	
Affluent	22,352	1.07	0.88	1.30		16,990	1.07	0.86	1.35	
Non-affluent	13,717	1.83	1.33	2.51	0.005	10,250	1.53	1.13	2.05	0.065
Eczema by examination										
All centres	18,814	1.09	0.85	1.40		10,997	1.21	0.9	1.63	
Affluent	15,054	1.03	0.77	1.38		9019	1.22	0.87	1.72	
Non-affluent	3760	1.30	0.80	2.11	0.430	1978	1.18	0.65	2.15	0.924
Skin prick test										
All centres	20,769	0.99	0.88	1.11		17,055	1.02	0.89	1.18	
Affluent	14,639	0.98	0.85	1.13		11,986	0.96	0.81	1.14	
Non-affluent	6130	1.01	0.79	1.28	0.850	5069	1.17	0.91	1.49	0.205

*Random effect models for meta-analysis.

†Affluent countries (GNI $\geq$ \$9200 per year per capita) and non-affluent countries (GNI < \$9200 per year per capita).

‡*Z*-test for differences between strata.

§Adjusted for age, sex, pertussis vaccination, number of sibs, and bedroom sharing.

Table 3 Association between pertussis infection and allergic disease by skin prick tested (SPT) positivity*

	N	CrudeOR	95% CI		p-value†	N	AdjOR‡	95% CI		p-value†
Wheeze past year										
Atopics	4641	1.92	1.50	2.45		3854	1.59	1.16	2.19	
Non-atopics	13,148	1.83	1.42	2.37	0.792	8972	2.10	1.55	2.85	0.219
Bronchial hyperreactivity										
Atopics	676	0.99	0.59	1.65		424	0.87	0.39	1.92	
Non-atopics	2484	1.22	0.90	1.67	0.485	1638	1.54	0.77	3.08	0.282
Rhinoconjunctivitis										
Atopics	4354	1.12	0.88	1.42		3480	1.24	0.85	1.81	
Non-atopics	14,702	2.09	1.67	2.62	0.0002	12,647	2.30	1.82	2.92	0.007
Rhinitis without conjunctivitis										
Atopics	3236	1.17	0.78	1.75		2561	1.24	0.84	1.83	
Non-atopics	14,946	1.30	1.08	1.56	0.650	11,743	1.26	1.01	1.57	0.939
Eczema past year										
Atopics	3428	1.16	0.83	1.62		2235	1.15	0.76	1.74	
Non-atopics	16,399	1.35	1.03	1.78	0.492	12,881	1.18	0.86	1.62	0.923
Eczema by examination										
Atopics	2479	1.74	1.14	2.67		1767	1.98	1.21	3.22	
Non-atopics	10,401	1.17	0.77	1.78	0.188	5977	1.32	0.70	2.49	0.324

*Random effect models for meta-analysis.

†*Z*-test for differences between strata.

‡Adjusted for age, sex, pertussis vaccination, number of sibs, and bedroom sharing.

stratification by affluence status, this result only reached statistical significance in non-affluent countries (OR_{ad} 1.41; 95%CI 1.20–1.66). The difference between affluent (OR_{ad} 1.12; 95%CI 0.94–1.33) and non-affluent countries failed statistical significance (p-value 0.05). The association between measles infection and BHR was positive and of similar magnitude to that for current wheeze, but was based on smaller numbers of subjects and failed to reach statistical significance.

Measles infection was also associated with 'eczema in the past year' (OR_{ad} 1.22; 95%CI 1.08–1.39) to a similar degree in affluent and non-affluent countries. The magnitude of association was similar with flexural eczema on examination, but this was statistically significant only in affluent countries (OR_{ad} 1.46; 95%CI 1.04–2.05). Associations of measles infection with rhinitis (with and without conjunctivitis) did not differ substantially by affluence.

Pertussis and measles infections were not associated with SPT positivity. Stratification by SPT positivity did not reveal any significant effect modification (Table 5).

Further stratification by measles vaccination status revealed no statistically significant differences for any of the allergic diseases (Table S3). Measles vaccination was not significantly associated with any of the disease outcomes (Table S4), nor with SPT positivity (OR_{ad} 1.08; 95%CI 0.81 –1.44)

Discussion

In this large international study, we found no association between pertussis or measles vaccination and measures of allergic disease. However, after adjustment for prior vaccination history, significant positive associations were found between pertussis and measles infections and symptoms of allergic diseases in mid-childhood. These associations were not explained by atopy, as measured by allergen SPT, were not modified by vaccination status, and were generally consistent between affluent and non-affluent countries.

Strengths and limitations

The retrospective collection of information on history of vaccination and infection may have introduced recall bias. However, infectious diseases, such as measles and pertussis, are likely to be remembered well by parents (28, 29). Reported and observed coverage rate for MMR vaccination were alike (30). Owing to the cross-sectional study design, we could not assess the time sequence of events. Several other potential study limitations need to be considered. Measles vaccination might have been administered in combination with the mumps rubella vaccines (MMR). However, our data show that vaccination is not a strong confounder or effect modifier (Tables S1 and S3), so omission or erroneous recall of vaccination status is unlikely to have introduced significant bias.

Among the strengths of our study are the use of the same standardized ISAAC questionnaires and methodology in all centers and the inclusion of non-affluent countries. In addition, SPT, BHR testing, as well as skin examination for flexural eczema were used as objective markers.

Pertussis infection and vaccination

Our observation of a positive association between pertussis infection and asthma symptoms are in line with the literature

Table 4 Association between measles infection, asthma, and allergic diseases according to national GNI per capita*,†

	N	CrudeOR	95% CI		p-value‡	N	Adj. OR§	95% CI		p-value‡
Wheeze past year										
All centres	23984	1.31	1.16	1.47		18,949	1.26	1.10	1.43	
Affluent	14,022	1.20	1.03	1.40		10,974	1.12	0.94	1.33	
non-affluent	9962	1.41	1.20	1.65	0.150	7975	1.41	1.20	1.66	0.050
Bronchial hyperreactivity										
All centres	2506	1.25	0.83	1.90		1972	1.29	0.79	2.09	
Affluent	1513	1.34	0.87	2.06		1305	1.33	0.84	2.12	
Non-affluent	993	1.23	0.55	2.77	0.856	667	1.26	0.48	3.33	0.922
Rhinoconjunctivitis										
All centres	23,361	1.10	0.99	1.22		19,515	1.12	1.00	1.26	
Affluent	13,934	1.11	0.96	1.28		10,967	1.10	0.93	1.29	
Non-affluent	9427	1.08	0.90	1.30	0.840	8548	1.13	0.93	1.38	0.830
Rhinitis without conjunctivitis										
All centres	24,318	1.12	0.99	1.26		20,474	1.12	1.00	1.27	
Affluent	14,887	1.00	0.82	1.21		11,924	0.97	0.78	1.22	
Non-affluent	9431	1.21	1.05	1.40	0.110	8550	1.22	1.05	1.41	0.100
Eczema past year										
All centres	25,739	1.17	1.04	1.31		20,591	1.22	1.08	1.39	
Affluent	15,012	1.16	0.99	1.36		12,022	1.24	1.04	1.48	
Non-affluent	10,727	1.18	0.94	1.47	0.910	8569	1.20	0.99	1.45	0.790
Eczema by examination										
All centres	15,180	1.15	0.92	1.44		11,154	1.25	0.96	1.63	
Affluent	7641	1.27	0.95	1.69		5503	1.46	1.04	2.05	
Non-affluent	7539	1.01	0.68	1.49	0.360	5651	1.00	0.64	1.55	0.180
Skin prick test										
All centres	18,080	0.91	0.79	1.04		15,104	0.90	0.80	1.01	
Affluent	9659	0.92	0.76	1.13		8559	0.90	0.72	1.11	
Non-affluent	8421	0.89	0.74	1.07	0.800	6545	0.91	0.77	1.08	0.900

*Random effect models for meta-analysis.

†Affluent countries (GNI $\geq$ \$9200 per year per capita) and non-affluent countries (GNI < \$9200 per year per capita).

‡*Z*-test for differences between strata.

§Adjusted for age, sex, measles vaccination, number of sibs, and bedroom sharing.

(6, 7, 11). In addition, we observed positive associations between rhinoconjunctivitis and eczema during the past year. In a large birth cohort study in the UK, the history of having whooping cough (pertussis infection) by the age of 11 yr was associated with increased asthma or wheezing incidence at the age of 8–16 yr (7). Farooqi and Hopkin (6) observed higher prevalence of asthma in children with history of pertussis infection and no associations between pertussis infection and hay fever and eczema. Bernson et al. (11) found positive associations of pertussis infection with hay fever and asthma, but not eczema in a cross-sectional study among Dutch children. We observed a differential association by affluence status between pertussis infection and rhinoconjunctivitis. So far, evidence for an association between pertussis infection and allergic disease comes mainly from affluent countries (6, 7, 11). In non-affluent countries, residual confounding owing to other environmental conditions or health-related events may have contributed to the stronger association between pertussis infection and rhinoconjunctivitis. However, additional adjustment for maternal education or parental atopy did not substantially change the associations (Tables S5 and S6).

When we looked at objective markers, pertussis infection was unrelated to BHR, SPT positivity, and flexural eczema on skin examination. Previous studies did not distinguish between sensitized and non-sensitized individuals, but we found no differential effect for asthma suggesting that allergic sensitization is unlikely to be related to the pertussis infection and asthma relationship; also supported by the absence of an association with allergic sensitization. Nevertheless, allergic sensitization may be an effect modifier as indicated by the differential effect for rhinoconjunctivitis (p-value 0.007). However, in this case, the association was stronger in non-atopic children, again arguing against an underlying allergic mechanism.

In our study, pertussis infection was associated with higher prevalence of eczema symptoms in among children from non-affluent countries. Previous studies showed inconsistent results including positive and no associations (11, 16). After stratification by SPT positivity, the association was somewhat stronger for eczema based on clinical examination among atopic children. However, no effect modification by allergic sensitization was present. Bernsen et al. (11) observed stronger

Table 5 Association between measles infection and allergic diseases according to skin prick tested (SPT) positivity*

	N	CrudeOR	95% CI		p-value†	N	Adj. OR‡	95% CI		p-value†
Wheeze past year										
Atopics	3452	1.43	1.14	1.79		2899	1.31	1.01	1.70	
Non-atopics	11,828	1.38	1.19	1.60	0.790	9485	1.39	1.16	1.66	0.732
Bronchial hyperreactivity										
Atopics	575	1.76	0.90	3.44		414	1.64	0.57	4.74	
Non-atopics	1339	0.99	0.66	1.49	0.152	960	1.12	0.61	2.06	0.542
Rhinoconjunctivitis										
Atopics	3400	1.10	0.88	1.37		3054	1.04	0.81	1.33	
Non-atopics	11,923	1.18	0.96	1.44	0.644	10,254	1.26	1.03	1.55	0.241
Rhinitis without conjunctivitis										
Atopics	3572	1.07	0.83	1.38		3056	1.11	0.81	1.50	
Non-atopics	12,757	1.19	1.03	1.37	0.478	11,490	1.19	1.01	1.39	0.684
Eczema past year										
Atopics	3373	1.24	0.92	1.68		3052	1.19	0.85	1.67	
Non-atopics	13,295	1.28	1.09	1.50	0.866	10,801	1.40	1.16	1.69	0.410
Eczema by examination										
Atopics	2614	1.15	0.75	1.75		2209	1.60	0.83	3.06	
Non-atopics	9718	1.32	0.96	1.82	0.607	7602	1.53	1.10	2.12	0.482

*Random effect models for meta-analysis.

†*Z*-test for differences between strata.

‡Adjusted for age, sex, measles vaccination, number of sibs, and bedroom sharing.

associations of pertussis infection with asthma and hay fever among pertussis vaccinated children aged 8–12 yr. The biological mechanism for a relationship between pertussis infection and allergic disease is not clear (3).

Measles infection and vaccination

Our findings that children after measles infection, had higher prevalence of wheeze in non-affluent countries are in line with previous studies (11, 12, 14). Our observation of an inverse although non-significant association between measles infection and any allergic sensitization is consistent with results from a cross-sectional study among children attending Steiner schools after exclusion of children who reported wheezing and eczema during the first year of life (31). No association has been reported in a small case–control study and a cross-sectional study with allergic sensitization (15, 32). Our observation of a positive although non-significant association between measles infection and rhinitis (with and especially without conjunctivitis) among non-atopic children is in contrast to the overall results from a prospective study on hay fever (33).

We found that eczema (both self-report and on examination) was more prevalent after measles infection. Olesen et al. (34) found an increased incidence of eczema among children with a history of measles infection in Denmark. Other authors reported no relationship between measles infection and eczema (5, 6). In our study, however, measles vaccination did not modify the association between measles infection and allergic disease, nor was it associated directly with allergic disease. Two cross-sectional studies from Scandinavia revealed increased eczema prevalence after MMR vaccination (14, 34). Both studies are based on large samples; however, the availability of information on potential confounders was limited. The improved coverage of measles vaccination world-wide narrows the comparison with unvaccinated children (28).

Conclusion

We found positive associations of pertussis and measles infection with symptoms of several allergic diseases in mid-childhood, but not with SPT positivity. However, the lack of an association of pertussis and measles infection with SPT positivity suggests that non-allergic immunological mechanisms non-IgE mediated should be considered in further studies.

Acknowledgments

We wish to thank all children, parents, teachers, field workers, and lab workers for their enormous contributions to this collaborative study. ALK generously provided reagents for field work in several low-income countries without charge.

The agencies funding the field work are listed elsewhere (17).

The coordination and central laboratory analyses of the European centres were funded by the Fifth Framework Programme of the European Commission, (QLK4-CT-1999-01288).

Conflict of interest

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Association between pertussis infection and allergic disease by pertussis vaccination.

Table S2. Association between pertussis vaccination and allergic disease.

Table S3. Association between measles infection and allergic disease by measles vaccination.

Table S4. Association between measles vaccination and allergic disease.

Table S5. Association between pertussis infection, asthma and allergic diseases according to national GNI per capita.

Table S6. Association between measles infection, asthma and allergic diseases according to national GNI per capita.

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