

Vaccinations in the first year of life and risk of atopic disease – Results from the KiGGS study



Martin Schlaud*, Roma Schmitz, Christina Poethko-Müller, Ronny Kuhnert

Robert Koch Institute, Dept. of Epidemiology and Health Monitoring, Berlin, Germany

ARTICLE INFO

Article history:

Received 10 March 2017

Received in revised form 27 July 2017

Accepted 31 July 2017

Available online 8 August 2017

Keywords:

Vaccination

Immunisation

Risk of atopic disease

Children

Paediatrics

ABSTRACT

Background: The study focused on the question of whether and – if so – to what direction and extent immunisations in the 1st year may be associated with the risk of being diagnosed with atopic diseases after the 1st year of life.

Methods: Data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS, 2003–2006) were analysed. For analyses of potential associations between vaccination status and risk of hay fever, atopic dermatitis or asthma, sample sizes of 15254, 14297, and 15262, respectively, were available.

Results: Children with a sufficient TDPHiHeP vaccination at the end of the 1st year of life had a lower risk of being diagnosed with hay fever after the 1st year of life (adjusted prevalence ratio 0.85, 95% confidence interval 0.76–0.96). Analyses for associations between TDPHiHeP vaccination and risk of atopic dermatitis or asthma, or between age at onset of vaccination or of the number of antigens vaccinated in the 1st year of life and risk of atopic disease failed to yield statistical significance.

Conclusions: Our results provide no evidence that immunisations in the 1st year of life may increase the risk of atopic disease. If any association exists at all, our results may be interpreted as weakly supportive of the hypothesis that immunisations may slightly decrease the risk of atopy in later life.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

For the past 30 years, the prevalence of atopic diseases (hay fever, atopic dermatitis and asthma) has increased substantially, not only in most western countries, but almost worldwide [1]. Most remarkably, shortly after German reunification, the prevalence of atopic diseases in Eastern Germany was considerably lower than in the West [2,3]. However, the prevalence of atopic diseases gradually increased in Eastern Germany over time [4,5], before finally equalling the higher prevalence in the West [6]. It has been hypothesised that certain changes in lifestyle, also referred to as ‘westernisation’, may have played a major role in this increase. In general, less close contact to other children early in life (smaller families, less time spent in nursery), less contact with animals, dirt and harmless germs; and less infections with endoparasites seem to be associated with a higher risk of atopic diseases. According to the ‘hygiene hypothesis’ [7–11], non-pathogenic microbial stimuli of a chronic or recurrent nature early in life

may lower the risk of atopic diseases later in life by means of a complex modulation of the immune system.

Following the hygiene hypothesis, there may be an association between atopic diseases and vaccines. On the one hand, immunisations may be associated with a higher risk of atopic diseases because vaccinations prevent the clinical onset of certain communicable diseases and, thus, may also prevent the hypothesised beneficial stimulation and modulation of the immune system. On the other hand, however, vaccinations may be associated with a lower risk of atopy because they contain antigens that are intended to stimulate the immune system similar to pathogens and, therefore, may also modulate the immune system in the hypothesised positive manner. However, it has also been hypothesised that vaccines may stimulate the immune system in a way that promotes atopic disease independent of the effect on infections.

The question as to whether and – if so – to what direction and extent immunisations may be associated with the risk of atopic diseases has been subject to an increasing number of epidemiological studies in recent years. The results, however, have been inconsistent [12,13], which may – at least in part – be attributed to various sorts of bias potentially inherent in some studies [14]. In order to provide a scientific contribution to the debate on potential

* Corresponding author at: Robert Koch Institute, Dept. of Epidemiology and Health Monitoring, PO Box 65 02 61, 13302 Berlin, Germany.

E-mail address: m.schlaud@rki.de (M. Schlaud).

associations of vaccinations and risk of atopic disease, this question was addressed in the framework of a recent nationwide interview and examination survey into health issues in children and adolescents in Germany.

Since only few surveyed children were unvaccinated by the end of the first year of life and unvaccinated children tend to be different from vaccinated children with respect to various health and lifestyle factors, results of comparisons between vaccinated and unvaccinated children would be underpowered and difficult to interpret. Moreover, vaccinated children differ in their exposure to vaccines from having received just 1 dose to having completed the whole vaccination schedule. Thus, a classification as “vaccinated” would be a considerable simplification or even misclassification of their exposure to vaccines. This is why we decided to use 3 different measures of vaccination status as the exposures under study to test the following hypotheses:

1. Age at onset of immunisation may be associated with risk of atopic disease after the 1st year of life.
2. The number of antigens vaccinated in the 1st year of life may be associated with risk of atopic disease after the 1st year of life.
3. Whether or not immunisation against TDPHiHeP is sufficient or insufficient at the end of the 1st year of life may be associated with risk of atopic disease after the 1st year of life.

2. Materials and methods

The methodology of KiGGS, the German Health Interview and Examination Survey for Children and Adolescents, has been described in detail elsewhere [15,16]. In brief, study subjects, aged 0–17 years were sampled from 167 communities in Germany between May 2003 and May 2006. The sampling frame of this cross-sectional study followed a complex, multi-stage, probability-clustered design with intentional oversampling of children and adolescents in Eastern Germany and of non-German nationality. The survey involved questionnaires filled in by parents and parallel questionnaires for children/adolescents aged 11 years or older, physical examinations and tests, and a computer-assisted personal interview (CAPI) with a parent or guardian (preferably the mother) performed by the physicians involved in the study. A wide range of blood and urine testing was carried out at central laboratories. A representative sample of 17641 children and adolescents was surveyed (8985 boys and 8656 girls); informed consent was gained from their parents or guardians and additionally from participants aged 14 years or older. The proportion of sample-neutral dropouts was 5.3%; the response proportion 66.6%. The study was approved by the ethics committee of *Charité – Universitätsmedizin Berlin* (reference number 101/2000) and by the German Federal Office for the Protection of Data. The KiGGS survey obtained data on a broad spectrum of health issues, including physical, mental and social well-being, behavioural risk factors and health care utilisation.

Data on atopic diseases (hay fever, atopic dermatitis and asthma) were obtained by CAPI. The accompanying parent or guardian was asked whether and when the respective condition had ever been diagnosed by a doctor. Information on socio-economic status (SES), migration background, birth order, parental atopic diseases and smoking was obtained by parental questionnaire. The SES was constructed using both parents' educational and professional status as well as the total income available to the household [15].

Data on the type and date of each administered dose of vaccination were extracted from vaccination cards, which parents had been asked to bring to the study centre. Study subjects were excluded from further analyses in the following cases: (a) if a child's parent or guardian was unable to present a vaccination card

but stated that their child had been vaccinated; (b) if they stated that some vaccinations were missing from the card; or, (c) if the card was unreadable or marked as a replacement or was a follow-up to the original vaccination card and the original was no longer available.

For the purpose of this study, a child's vaccination status at the end of his or her first year of life was considered as the relevant exposure. Vaccination status was assessed by 3 different measures: (1) The total number of antigen-doses was calculated by adding all vaccinations together after having multiplied each vaccination by the number of different antigens in the administered vaccine; (2) the age at first vaccination against tetanus was calculated as an indicator for age at onset of immunization because tetanus is recommended as the first vaccination in Germany; and (3) a complex assessment of all vaccinations administered in the 1st year of life was made as to whether immunisation against tetanus, diphtheria, poliomyelitis, haemophilus influenzae type B, hepatitis B and pertussis (TDPHiHeP) was sufficient or insufficient in accordance with the recommendations made by the German Standing Committee on Vaccination (STIKO) at the time of study (2003–2006). These recommendations stated that a one-year-old child should have received 3 doses of pertussis vaccine and 3 doses of a vaccine against tetanus, diphtheria, poliomyelitis, haemophilus influenzae B and hepatitis B if administered as multivalent vaccination including the pertussis component. Two doses were rated as sufficient if the respective vaccines did not include pertussis. As the last dose of the full primary immunisation was scheduled to be administered at age 11–14 months, this study's definition of a sufficient TDPHiHeP vaccination was not equivalent to a full primary immunisation, which required an additional dose in the second year of life.

Children included in these analyses were born between 1985 and 2005. During this time, the national recommendations on vaccination in the first year of life were amended by vaccinations against pertussis (introduced in 1991), haemophilus influenzae B (1990) and hepatitis B (1996). Recommendations on vaccination against poliomyelitis changed from oral vaccination towards IPV in 1998. The first measles, mumps and rubella vaccination (MMR) was initially scheduled for the second year of life and then changed to start at age 11 months in 1997. A second dose of MMR was introduced in 1991, initially scheduled for the 6th year of life and then changed to the second year of life in 2001. A booster vaccination against tetanus and diphtheria was scheduled for age 5–6 years. The outcomes under study were a diagnosis of asthma or hay fever or atopic dermatitis after the first year of life.

Data analyses were performed using the package *Statistical Analysis Software* Version 9.4 (SAS Institute, Cary, NC, USA). In order to ensure that estimates derived from the KiGGS data are representative at the national level, survey weights were applied throughout the statistical analyses. Furthermore, the data were analysed in a manner that took into account the stratified and clustered sample design implemented for KiGGS, using the survey procedures and cluster statements provided by SAS. Statistical significance testing of categorical data was conducted by the Rao Scott chi-square test (Proc Surveyfreq), with testing of metric data was performed by *t*-test (Proc GLM). Prevalence ratios and their 95% confidence intervals were calculated by Proc Genmod.

Covariates were included in multivariable models when they were potential confounders for the associations of exposures and outcomes under study. Final models were adjusted for the dichotomous variables sex (male/female), regional provenance (East/West Germany), socio-economic status (lower/middle/upper), background of migration (none, one-sided, two-sided), birth order (born last, middle/first, as part of multiples or without siblings), whether or not the mother and/or father smoked, and parental atopic disease (yes, no). Both age at time of study and age at the beginning of nursery were entered as continuous variables.

Any p-value of 0.05 or below was considered statistically significant, as were 95% confidence intervals that did not include the value 1.

3. Results

A total of 17641 children and adolescents participated in the KiGGS study. For the purpose of this investigation, 2258 subjects had to be excluded either because they were younger than 1 year at time of study or because of missing/incomplete data on vaccination. Further study subjects had to be excluded due to missing CAPI data on the atopic diseases under study (Fig. 1). For analyses of potential associations between vaccinations and hay fever, atopic dermatitis or asthma, sample sizes of 15254, 14297, and 15262 were available, respectively.

Basic characteristics of the study population, broken down by measures of vaccination status, are shown in Table 1. In the full study population, the average age was 9.3 years (SD – standard deviation, 4.9), 51.3% were boys, 26.4% lived in families of low socio-economic status, and 15.3% had a two-sided background of migration. The mother or father was a smoker in 48.7% and 44.8% of study subjects had at least one parent with an atopic disease. The TDPHiHeP vaccination status at the end of the first year of life was rated as “sufficient” in 7468 and “insufficient” in 7968 study subjects. Both groups were comparable in most characteristics. In the “insufficient” group, however, there were slightly more children with a two-sided background of migration or from former West Germany. The first tetanus vaccination had been administered by the 90th day of life in 3260 and thereafter in 11786 children. Again, both groups were comparable with regard to most

characteristics, whilst the latter group comprised of slightly more children from former West Germany. The mean number of antigens vaccinated in the first year of life was 12.4 (5.2) in the study population and in most subgroups. There were only slight differences in subgroups defined by background of migration and by regional provenance.

Hay fever had been diagnosed in 10.8%, atopic dermatitis in 7.7% and asthma in 4.3% of study subjects after the 1st year of life. Males were more likely to be diagnosed with hay fever (12.8% vs 8.9%) or asthma (5.0% vs 3.7%), whilst atopic dermatitis was more common among females (9.1% vs 7.6%). Children of atopic parents were about twofold more likely to be diagnosed with an atopic disease. A diagnosis of hay fever or atopic dermatitis was reported more often in children from high SES families or in families with two-sided background of migration. Having older siblings was associated with a lower risk of being diagnosed with hay fever (9.1% vs 12.8%) or asthma (3.9% vs 4.7%).

Table 2 shows crude comparisons between the 3 measures of vaccination status and diagnoses of atopic diseases after the 1st year of life. The mean number of vaccinated antigens in the 1st year of life was lower in study subjects who were later diagnosed with hay fever (10.6 vs 12.6; $p \leq 0.0001$), atopic dermatitis (11.8 vs 12.4; $p \leq 0.0001$) or asthma (10.7 vs 12.4; $p \leq 0.0001$). Among those with a diagnosis of hay fever or asthma, more children had had a first tetanus vaccination after the 90th day of life (hay fever 11.3 vs 9.5%, $p = 0.0335$; atopic dermatitis 8.5 vs 7.5%, $p = 0.1610$; asthma 4.5 vs 3.3%, $p = 0.0160$). The TDPHiHeP vaccination status by the end of the 1st year of life was more often “insufficient” in children who were diagnosed with hay fever, atopic dermatitis or asthma after the 1st year (hay fever 12.6 vs 8.7%, $p \leq 0.0001$; atopic dermatitis 8.8 vs 7.6%, $p = 0.0206$; asthma 5.0 vs 3.5%, $p \leq 0.0001$).

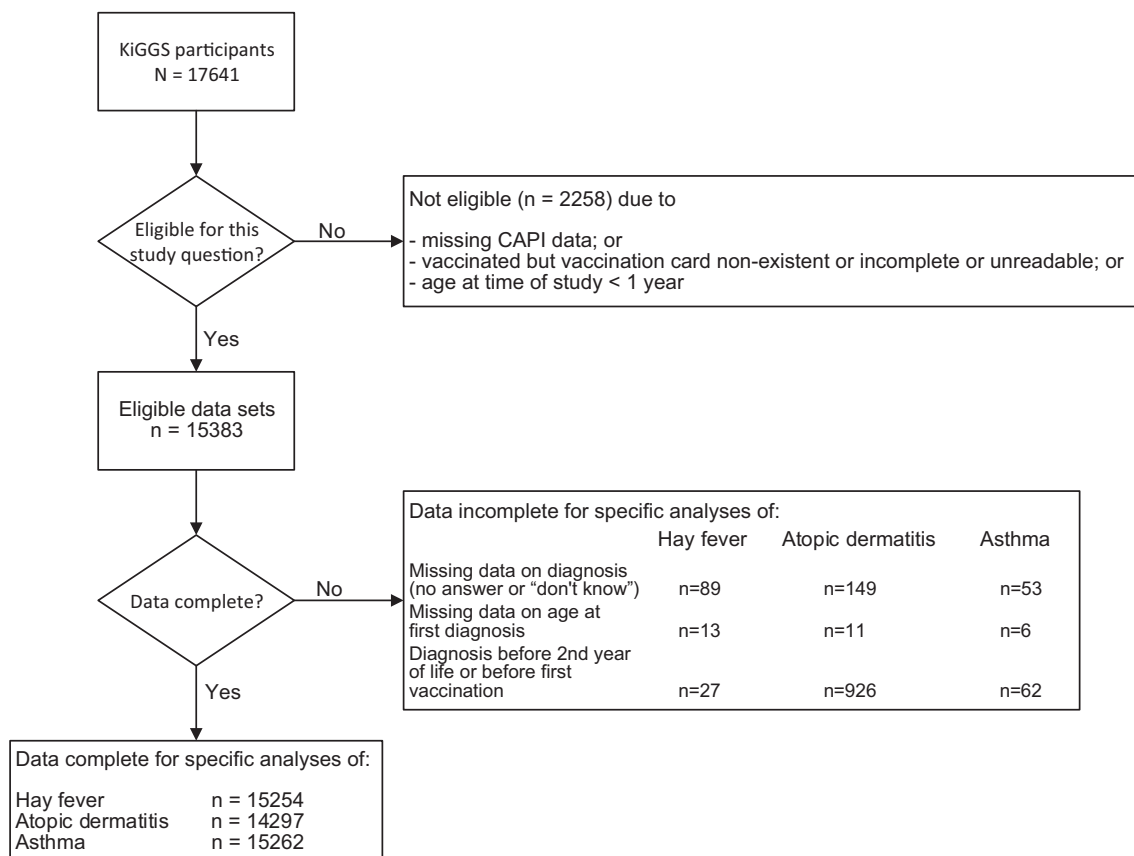


Fig. 1. Selection of study subjects for this data analysis. KiGGS, German Health Interview and Examination Survey for Children and Adolescents; CAPI, Computer Assisted Personal Interview.

Table 1

Basic characteristics of the study population, broken down by 3 different measures of vaccination status.

	Total	TDPHiHeP vaccination status by the end of the 1st year of life ^a (n)		First vaccination (tetanus)		Mean number of antigens vaccinated in the 1st year of life (SD)
		Sufficient	Insufficient	By the 90th day of life ^a (n)	After the 90th day of life ^a (n)	
Study population	n = 15383	n = 7468	n = 7915	n = 3260	n = 11786	n = 15383
Mean age/no. of antigens (SD)	9.3y (4.9)	7.9y (5.0)	10.3y (4.6)	7.7y (4.8)	9.6y (4.9)	12.4a (5.2)
Age group						
≤6 years	33.4% (5491)	48.6% (3687)	21.5% (1804)	50.5% (1704)	29.8% (3679)	16.2a (4.7)
7–13 years	40.6% (6611)	30.5% (2448)	48.4% (4163)	28.1% (978)	43.5% (5513)	11.7a (3.9)
14–17 years	26.0% (3281)	20.9% (1333)	30.1% (1948)	21.4% (578)	26.7% (2594)	8.5a (4.0)
Sex (n)						
Male	51.3% (7809)	50.7% (3731)	51.7% (4078)	51.9% (1659)	51.1% (5980)	12.3a (5.3)
Female	48.7% (7574)	49.3% (3737)	48.3% (3837)	48.1% (1601)	48.9% (5806)	12.4a (5.1)
Socio-economic status						
Lower	26.4% (4055)	25.9% (1938)	26.8% (2117)	25.4% (839)	26.6% (3118)	12.3a (5.3)
Middle	46.1% (7118)	47.8% (3602)	44.7% (3516)	47.4% (1563)	45.8% (5410)	12.5a (4.9)
Upper	27.5% (3940)	26.3% (1815)	28.4% (2125)	27.3% (810)	27.6% (3048)	12.3a (5.4)
Background of migration						
None	76.4% (12175)	77.7% (6100)	75.3% (6075)	75.6% (2671)	76.7% (9256)	12.4a (4.9)
One-sided	8.3% (1114)	8.4% (523)	8.2% (591)	8.7% (209)	8.2% (880)	12.9a (5.7)
Two-sided	15.3% (2030)	13.9% (813)	16.5% (1217)	15.6% (367)	15.1% (1601)	11.8a (6.4)
Regional provenance						
Former East Germany	17.0% (5178)	23.8% (3234)	11.6% (1944)	32.6% (1764)	13.5% (3296)	13.7a (3.2)
Former West Germany	83.0% (10205)	76.2% (4234)	88.4% (5971)	67.4% (1496)	86.5% (8490)	12.1a (5.9)
Smoking mother or father						
No	51.3% (7631)	51.8% (3735)	50.9% (3896)	51.8% (1626)	51.2% (5841)	12.4a (5.3)
Yes	48.7% (7573)	48.2% (3648)	49.1% (3925)	48.2% (1605)	48.8% (5805)	12.3a (5.1)
Parental atopy						
No	55.2% (8538)	54.9% (4153)	55.4% (4385)	55.3% (1855)	55.1% (6502)	12.3a (5.1)
Yes	44.8% (6581)	45.1% (3203)	44.6% (3378)	44.7% (1357)	44.9% (5086)	12.5a (5.2)

SD standard deviation; y years; a antigens.

TDPHiHeP: vaccination against tetanus, diphtheria, poliomyelitis, haemophilus influenzae type B, hepatitis B and pertussis.

Table 2

Crude comparisons of vaccination status in the 1st year of life and diagnosis of atopic diseases after the 1st year of life.

Exposure	Hay fever diagnosed after the 1st year of life		Atopic dermatitis diagnosed after the 1st year of life		Asthma diagnosed after the 1st year of life	
	Yes (n = 1548)	No (n = 13706)	Yes (n = 1200)	No (n = 13097)	Yes (n = 642)	No (n = 14620)
Mean number of antigens vaccinated in the 1st year of life (SD)	10.6 (4.5)	12.6 (5.2)	11.8 (4.8)	12.4 (5.2)	10.7 (4.4)	12.4 (5.2)
P value	≤0.0001		≤0.0001		≤0.0001	
First vaccination (tetanus) in % (n)						
By the 90th day of life	9.5 (275)	90.5 (2963)	7.5 (228)	92.5 (2787)	3.3 (101)	96.7 (3134)
After the 90th day of life	11.3 (1242)	88.7 (10441)	8.5 (946)	91.5 (10020)	4.5 (522)	95.5 (11172)
P value	0.0335		0.1610		0.0160	
Vaccination status of TDPHiHeP ^a by end of the 1st year of life in % (n)						
Sufficient	8.7 (629)	91.3 (6785)	7.6 (552)	92.4 (6410)	3.5 (262)	96.5 (7158)
Insufficient	12.6 (919)	87.4 (6921)	8.8 (648)	91.2 (6687)	5.0 (380)	95.0 (7462)
P value	≤0.0001		0.0206		≤0.0001	

SD: standard deviation.

TDPHiHeP: vaccination against tetanus, diphtheria, poliomyelitis, haemophilus influenzae type B, hepatitis B and pertussis.

^a According to recommendations made by the German Standing Committee on Vaccination (STIKO) at the time.

Adjusted prevalence ratios of associations between the 3 measures of vaccination status and risk of being diagnosed with any of the 3 atopic diseases after the 1st year of life are depicted in Table 3. After adjustment for sex, regional provenance (East/West Germany), socio-economic status, background of migration, birth order, mother or father smoked, parental atopy, age at beginning of nursery and age at time of study, only one statistically significant result remained. Children with sufficient TDPHiHeP vaccination by the end of the 1st year of life were less likely to be diagnosed with hay fever after the 1st year of life (prevalence ratio 0.85, 95% confidence interval 0.76–0.96) than were children with insufficient TDPHiHeP vaccination. Prevalence ratios of all other analyses were 1.0 or slightly below and failed to yield statistical

significance. Further adjustments for vaccinations against tuberculosis (bacillus Calmette–Guérin vaccine; BCG) and against measles, mumps and rubella (MMR), which were described to be potential confounders in some studies [14,17], did not alter the results.

4. Discussion

4.1. Methods

The data for this paper were taken from the KiGGS study, a nationally representative health interview and examination survey in Germany with high participation. Between 81% and 86% of study

Table 3
Adjusted^{*} prevalence ratios (and 95% confidence intervals) of associations between vaccination status in the 1st year of life and risk of being diagnosed with hay fever, atopic dermatitis, or asthma after the 1st year of life.

Exposure	Outcome		
	Hay fever diagnosed after the 1st year of life	Atopic dermatitis diagnosed after the 1st year of life	Asthma diagnosed after the 1st year of life
Number of antigens vaccinated in the 1st year of life (increment for any additional antigen)	0.99 (0.98–1.01)	1.00 (0.98–1.01)	1.00 (0.98–1.02)
First vaccination (tetanus) by the 90th day of life	0.97 (0.82–1.15)	0.96 (0.79–1.15)	0.95 (0.73–1.24)
Sufficient TDPHiHeP vaccination by the end of the 1st year of life	0.85 (0.76–0.96)	0.93 (0.81–1.06)	0.91 (0.78–1.07)

TDPHiHeP: vaccination against tetanus, diphtheria, poliomyelitis, haemophilus influenzae type B, hepatitis B and pertussis.

^{*} Adjusted for sex, regional provenance (East/West Germany), socio-economic status, background of migration, birth order, mother or father smoked, parental atopy, age at beginning of nursery and age at time of study.

subjects met the inclusion criteria of these data analyses and had all the necessary data. Most data were obtained from standardized physician interviews of parents (atopic diseases) or parent-administered questionnaires (SES, migration, smoking and siblings). Data on vaccinations were taken from vaccination cards, which are official documents filled in by doctors after administering vaccinations. Therefore, it is unlikely that there was a major selection or information bias that could have affected the results.

However, since the information on diagnoses of atopic diseases had to be provided through parental recollection during interviews rather than through extraction from medical records, there may be some degree of misclassification. In particular, some level of differential recall by SES, migration background or with increasing age of the child cannot fully be ruled out, but it is unlikely to explain the findings fully.

This paper addresses a secondary study question that was not a focus of the original KiGGS study. However, the available data justify this secondary analysis, even if a tailored study would allow for more detailed analyses of the potential associations between vaccination and the risk of atopy. For example, whilst it was possible to calculate the number of different antigens administered by vaccinations from entries on vaccination cards, it was not possible to determine the amount of each antigen that had been administered.

With 3 measures of vaccination status as exposures and 3 atopic diseases as outcomes, there were multiple statistical comparisons that increase the likelihood of chance findings. This should be considered when interpreting the single statistically significant result of this paper. On the other hand, the lack of statistical significance in some of our results with prevalence ratios below 1 may be due to the combination of low magnitudes of effect and sample size. Therefore these analyses should be repeated in larger studies.

Since the data from this cross-sectional study allow for a clear timing of exposure and outcome, there is no doubt that the vaccinations took place before a doctor had diagnosed atopic diseases. Thus, reverse causality is highly unlikely to have influenced the results.

4.2. Results

Our results suggest that a sufficient TDPHiHeP vaccination status by the end of the 1st year may be associated with a lower risk of hay fever diagnosed after the 1st year of life. If this is not a chance finding, it may be regarded as weakly supportive of the hypothesis that vaccination may be negatively associated with risk of atopy, i.e. that vaccinations may lower the risk of atopic disease in later in life. The German risk-enhanced birth cohort study MAS came to similar conclusions: the cumulative dose of vaccines was inversely related to the risk of atopic dermatitis and asthma later in life [18].

In our data analyses, not a single result was found that could suggest any positive association between degree of immunisation and risk of atopy. This can be regarded as strongly supportive of the hypothesis that there is no association between vaccination and risk of atopy at all, i.e. that vaccinations do not increase or decrease the risk of atopic disease later in life.

Numerous studies have also revealed no or slightly negative associations between vaccination and the risk of atopic diseases. In a French population sample of 718 adolescents, those who had been vaccinated had a significantly lower risk of suffering from asthma or atopic diseases than non-vaccinated study subjects [19]. In a cross-sectional study of 14,893 children in 5 European countries, atopic sensitization was inversely associated with measles infection, and a similar tendency was seen for measles vaccination [20]. A follow-up study with 23,201 person-years at risk in the UK provided no evidence of an association between vaccination against pertussis in infancy and an increased risk of wheeze or asthma in later life [21]. In a follow-up study of 80,000 Swedish children who had been immunized against pertussis as part of a vaccination trial, and 100,000 non-vaccinated control children, no difference was found in the odds of being prescribed asthma medication [22]. In a retrospective study of 700 families in the Netherlands, whole cell pertussis vaccination turned out to be associated with a lower risk of atopic disorders [23]. In another study of 1,875 children attending Orthodox Reformed (Protestant) primary schools in the Netherlands, the same author found an adjusted odds ratio of any atopic disorder (vaccinated/unvaccinated) of 1.00 (CI 95%: 0.80–1.24) [24]. In a follow-up study of 1778 full-term infants, childhood asthma was not significantly associated with having received hepatitis B vaccine or age at first hepatitis B vaccine; number of whole-cell pertussis, haemophilus influenzae type B or oral polio vaccine doses; having received measles, mumps, rubella vaccine; or total number of vaccine doses combined. The only statistically significant predictor of childhood asthma was the number of infant wheezing episodes [25]. In a birth cohort study, McKeever et al. found no association between the age at first injection of either DPPT or MMR and the risk of asthma or eczema [26].

Some studies came to different conclusions concerning the potential associations of immunisation and risk of atopic diseases. A Danish follow-up study found an increased risk of atopic dermatitis after MMR vaccination and measles infection [27]. Results from a Chinese animal study were interpreted in a way that programmed vaccination in China may possibly be responsible for the increasing prevalence of asthma and atopic diseases by inducing T-helper 2 cytokine expression [28]. McDonald et al. found that a delay in scheduled DPT vaccination was associated with a reduced risk of childhood asthma [29]. Bremner et al. came to the conclusion that a late completion of DTP or MMR immunisation may be associated with reduced hay fever risk [30]. Similar

results were found by Kiraly et al. suggesting that delayed DTaP vaccination was associated with reduced risk of eczema and eczema medication use [31].

Literature reviews and meta-analyses provide the most comprehensive assessments of whether or not immunisations may be associated with a risk of atopy in later life. In a literature review, Rottem et al. [32] found no evidence that the BCG; pertussis; influenza; measles, mumps and rubella; or smallpox vaccine have an effect on the risk of atopy in later life. Another review came to the conclusion that the majority of studies have not found an increased risk of asthma and atopies after immunisation [33]. In a systematic review of 7 studies of pertussis vaccination (with a total of 186,663 patients) and 5 studies of BCG vaccination (with a total of 41,479 patients) that directly compared vaccinated and unvaccinated children, and that validated vaccination status using medical charts, and applied current criteria to define asthma, no statistically significant association was detected between either whole-cell pertussis or BCG vaccination and incidence rates of asthma during childhood and adolescence [13].

5. Conclusions

In conclusion, our results provide no evidence that immunisations in the 1st year of life may increase the risk of atopic disease. If any association exists at all, our results may be interpreted as weakly supportive of the hypothesis that immunisations may slightly decrease the risk of atopy. This is reassuring for parents and paediatricians alike who can continue immunising children as recommended by national expert groups.

Our results add to the current evidence and are in line with the majority of similar studies in this field. However, given the limitations of our observational cross-sectional study, future research should address in more detail the potential effects of timing of vaccination and of the number of antigens administered by vaccination on the risk of atopic diseases.

Acknowledgement

The authors wish to thank all participants of the KiGGS study for their invaluable contribution to these analyses.

Author contributions

MS designed this data analysis and wrote the manuscript. RS performed the statistical analyses. CPM designed the 3 different measures of vaccination status. RK designed the algorithms for these assessments. All authors contributed to the interpretation of the results.

Potential conflicts of interest

MS was the PI of an epidemiological study on deaths in children aged 2–24 months, conducted from 2004 to 2009; the study was jointly funded by the German Federal Ministry of Health, the Paul Ehrlich Institute, Sanofi Pasteur and GlaxoSmithKline. CPM was responsible for coordinating that study. RS and RK declare that they have no conflicts of interest.

Ethics approval

This observational epidemiological study was approved by the Ethics Committee of *Charité – Universitätsmedizin Berlin* (reference number 101/2000).

Funding

The KiGGS Study was funded equally by the German Federal Ministry of Health, the German Federal Ministry of Education and Research (reference number 01ED9401) and the Robert Koch Institute.

References

- [1] Pawankar R, Holgate ST, Canonica GW, Lockey RF, Blaiss MS. WAO White Book on Allergy, 2013 Update. Milwaukee, WI (USA): World Allergy Organization; 2013.
- [2] von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994;149(2 Pt 1):358–64.
- [3] Weiland SK, von Mutius E, Hirsch T, Duhme H, Fritzsche C, Werner B, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999;14(4):862–70.
- [4] Schafer T, Kramer U, Dockery D, Vieluf D, Behrendt H, Ring J. What makes a child allergic? Analysis of risk factors for allergic sensitization in preschool children from East and West Germany. *Allergy Asthma Proc* 1999;20(1):23–7.
- [5] Heinrich J, Frye C, Holscher B, Meyer I, Pitz M, Cyrys J, et al. Environmental surveys in the areas of Bitterfeld, Hettstedt and a comparative area in 1992–2000. *Gesundheitswes* 2002;64(12):675–82.
- [6] Schlaud M, Atzpodien K, Thierfelder W. Allergic diseases. Results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Bundesgesundheitsbl* 2007;50(5–6):701–10.
- [7] Martinez FD. The coming-of-age of the hygiene hypothesis. *Respir Res* 2001;2(3):129–32.
- [8] Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 2002;296(5567):490–4.
- [9] Flohr C. Dirt, worms and atopic dermatitis. *Br J Dermatol* 2003;148(5):871–7.
- [10] Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': too clean to be true? *Brit J Dermatol* 2005;152(2):202–16.
- [11] Bresciani M, Parisi C, Menghi G, Bonini S. The hygiene hypothesis: does it function worldwide? *Curr Opin Allergy Clin Immunol* 2005;5(2):147–51.
- [12] Gruber C. Childhood immunisations and the development of atopic disease. *Arch Dis Child* 2005;90(6):553–5.
- [13] Balicer RD, Grotto I, Mimouni M, Mimouni D. Is childhood vaccination associated with asthma? A meta-analysis of observational studies. *Pediatrics* 2007;120(5):e1269–1277.
- [14] Aaby P, Ravn H, Benn CS. The WHO review of the possible nonspecific effects of diphtheria-tetanus-pertussis vaccine. *Pediatr Infect Dis J* 2016;35(11):1247–57.
- [15] Kurth BM, Kamtsiuris P, Holling H, Schlaud M, Dolle R, Ellert U, et al. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. *BMC Public Health* 2008;8:196.
- [16] Kohse KP. KiGGS – the German survey on children's health as data base for reference intervals and beyond. *Clin Biochem* 2014;47(9):742–3.
- [17] Aaby P, Shaheen SO, Heyes CB, Goudiaby A, Hall AJ, Shiell AW, et al. Early BCG vaccination and reduction in atopy in Guinea-Bissau. *Clin Exp Allergy* 2000;30(5):644–50.
- [18] Grüber C, Illi S, Lau S, Nickel R, Forster J, Kamin W, et al. Transient suppression of atopy in early childhood is associated with high vaccination coverage. *Pediatrics* 2003;111(3).
- [19] Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? *Pediatr Allergy Immunol* 2005;16(3):193–200.
- [20] Rosenlund H, Bergstrom A, Alm JS, Swartz J, Scheynius A, van Hage M, et al. Allergic disease and atopic sensitization in children in relation to measles vaccination and measles infection. *Pediatrics* 2009;123(3):771–8.
- [21] Spycher BD, Silverman M, Egger M, Zwahlen M, Kuehni CE. Routine vaccination against pertussis and the risk of childhood asthma: a population-based cohort study. *Pediatrics* 2009;123(3):944–50.
- [22] Vogt H, Braback L, Kling AM, Grunewald M, Nilsson L. Pertussis immunization in infancy and adolescent asthma medication. *Pediatrics* 2014;134(4):721–8.
- [23] Bernsen RM, de Jongste JC, van der Wouden JC. Lower risk of atopic disorders in whole cell pertussis-vaccinated children. *Eur Respir J* 2003;22(6):962–4.
- [24] Bernsen RMD, De Jongste JC, Koes BW, Aardoom HA, Van Der Wouden JC. Diphtheria tetanus pertussis poliomyelitis vaccination and reported atopic disorders in 8–12-year-old children. *Vaccine* 2006;24(12):2035–42.
- [25] Maher JE, Mullooly JP, Drew L, DeStefano F. Infant vaccinations and childhood asthma among full-term infants. *Pharmacoepidemiol Dr S* 2004;13(1):1–9.
- [26] McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *Am J Public Health* 2004;94(6):985–9.
- [27] 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):445–50.
- [28] Zhang JL, Ma Z, Sun WW, Cao JP, Wang ZH, Cui HY. Programmed vaccination may increase the prevalence of asthma and allergic diseases. *Am J Rhinol Allergy* 2016;30(4):113–7.
- [29] McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J Allergy Clin Immunol* 2008;121(3):626–31.

- [30] Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR, et al. Timing of routine immunisations and subsequent hay fever risk. *Arch Dis Child* 2005;90(6):567–73.
- [31] Kiraly N, Koplin JJ, Crawford NW, Bannister S, Flanagan KL, Holt PG, et al. Timing of routine infant vaccinations and risk of food allergy and eczema at one year of age. *Allergy* 2016;71(4):541–9.
- [32] Rottem M, Shoenfeld Y. Vaccination and allergy. *Curr Opin Otolaryngol Head Neck Surg* 2004;12(3):223–31.
- [33] Sanchez-Solis M, Garcia-Marcos L. Do vaccines modify the prevalence of asthma and allergies? *Expert Rev Vaccines* 2006;5(5):631–40.