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Childhood Vaccination and Allergy: A Systematic Review and Meta-analyses

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Some Abbreviations Used:

AD	Atopic Dermatitis	PPD	Purified Protein derivative
BCG	Bacillus Calmette-Guérin	MMR	Measles, Mumps, Rubella

aP	acellular Pertussis	OPV	Oral polio vaccine
wP	whole cell Pertussis	TBE	Tick Borne Encephalitis
DTP	Diphtheria, Tetanus, Pertussis	RCT	Randomised Controlled Trial
DTaP	Diphtheria, Tetanus, acellular Pertussis	SPT	Skin Prick Test
CDT	Combined Diphtheria and Tetanus	DPPT	Diphtheria, Purified Pertussis, and Tetanus
TST	Tuberculin Skin Test	NOS	Newcastle Ottawa Scale
AHRQ	Agency for Health Research and Quality	ARC	Acute Rhino Conjunctivitis
IPV	Injectable Polio Vaccine	re	Random effects
JE	Japanese Encephalitis	HPV	Human Papilloma Virus
SARS	Severe Acute Respiratory Syndrome	MERS	Middle East Respiratory Syndrome
COVID-19	Corona Virus Disease 2019	SARS-CoV-2	Severe Acute Respiratory Syndrome Corona virus 2
N.A.	Not Applicable	IgE	Immunoglobulin E

Abstract:

Background and Objective

As the rise in prevalence of allergic diseases worldwide corresponds in time with increasing infant vaccination, it has been hypothesized that childhood vaccination may increase the risk of allergic disease. We aimed to synthesize the literature on the association between childhood vaccination and allergy.

Design

We searched the electronic databases PubMed and EMBASE (January 1946- January 2018) using vaccination and allergy terms.

Methods

Two authors selected papers according to inclusion criteria. Pooled effects across studies were estimated using random-effects meta-analysis. Due to inadequate number of homogeneous publications on newer and underused vaccines, meta-analysis was limited to allergic outcomes following administration of (Bacillus-Calmette-Guérin) BCG, measles or pertussis vaccination. The review was prospectively registered in the PROSPERO systematic review registry (NO: CRD42017071009).

Results

A total of 35 publications based on cohort studies and 7 publications based on randomized controlled trials (RCTs) met the inclusion criteria. RCTs: From 2 studies, early vaccination with BCG vaccine was associated with a reduced risk of eczema (RR= 0.83; 95% CI= 0.73 – 0.93; I^2 = 0%) but not food allergy or asthma. No association was found between pertussis vaccine and any allergic outcome based on a single RCT.

Cohort studies: Childhood measles vaccination was associated with a reduced risk of eczema (RR= 0.65; 95% CI= 0.47 – 0.90, I²= 0.0%), asthma (RR= 0.78; 95% CI= 0.62 – 0.98, I²= 93.9%) and, with a similar, statistically non-significant reduction in sensitisation (RR= 0.78; 95% CI= 0.61 – 1.01, I²= 19.4%).

Conclusions

We found no evidence that childhood vaccination with commonly administered vaccines were associated with increased risk of later allergic disease. Our results from pooled analysis of both RCTs and cohort studies suggest that vaccination with BCG, and measles vaccines were associated with a reduced risk of eczema.

Introduction

The global epidemic of allergic diseases in children and young adults is a major public health issue that needs urgent attention^{1,2}. In addition to increase in prevalence, the common allergic diseases, (asthma, eczema, allergic rhinitis and food allergy), have a substantial impact on the quality of life of affected individuals and families which often goes unrecognised. Furthermore, they are responsible for a huge economic burden on the health care systems of low and middle-income countries, as well as countries that are more affluent²⁻⁵. According to the Global Asthma Network, currently there are 334 million people living with asthma worldwide⁶, whilst The World Allergy Association estimates that globally: 10 to 30% of people have allergic rhinitis; 20% of children, and 2 – 10% of adults have atopic eczema; and 240-550 million people have food allergies⁷. The increase in prevalence of allergic diseases over the past few decades coincides with a global increase in the practice of mass vaccination; thereby leading to the hypothesis that childhood vaccination may increase the risk of allergic diseases⁸⁻¹⁰.

Allergic diseases are characterised by an increased level of allergen specific Immunoglobulin E (IgE) from a T helper lymphocyte 2 (T_H2) response. The 'hygiene hypothesis' postulates that decreased exposure to infectious diseases in early life due to improved hygiene or vaccination, might cause suppression of the T_H1 immune response (cell mediated immunity) and lead to an over-active antibody-mediated T_H2 immune response (humoral immunity). This T_H2 dominant response may increase the risk of allergen sensitisation and allergic disease¹¹.

Escalation of emerging infectious diseases, particularly zoonotic viral diseases in the last decade has led to introduction of novel vaccines at a rapid pace. Vaccination holds a pivotal role in prevention of viral diseases where other medical options are almost non-existent. Although evidence implicating vaccination in allergic disease is scarce and conflicting, the suggestion that vaccinations increase risk of allergic disease has been used by anti-vaccination lobbying campaigns, jeopardising the sustainability of vaccine programmes. A consequence of these campaigns is reduction in herd immunity, which has the potential to increase the risk of serious outbreaks of previously vaccine-controlled infectious diseases, undermining the work of global, evidence-based public health programmes.

Since the first published report on childhood vaccination and allergic outcomes by Odent et al in 1994¹², several studies using original data and systematic reviews have been conducted on this topic. However, the evidence remains inconsistent^{13,14}. The published systematic reviews on this topic are quite outdated and are limited to studies on exposures of Bacillus-Calmette-Guérin (BCG), Measles-Mumps-Rubella (MMR) and/or Diphtheria-Tetanus-Pertussis (DTP) vaccines¹⁵⁻¹⁹. The relationship between many other commonly used vaccines (e.g. Haemophilus influenza type b (Hib) vaccine, Hepatitis B (Hep B), pneumococcal vaccine, meningococcal vaccine, newer conjugated vaccines and other vaccines recommended for the childhood period) and allergic diseases have not been systematically reviewed. We were unable to find studies with any other vaccines evaluated for allergy development. Furthermore, previous systematic reviews have provided only low-quality evidence as they included study designs such as cross-sectional and case control, which cannot assess temporality of these associations^{20,21}. In addition, the existing systematic reviews are methodologically heterogeneous to the inclusion of several study designs in a single review without reference to the importance of each study design in contributing to the weight of evidence²⁰.

Having recognised the limitations and knowledge gaps of the existing literature, we aimed to conduct a systematic review of the published randomized controlled trials and cohort studies, which investigated the association between childhood vaccination and later development of allergic outcomes.

Methods

Search strategy

We searched PubMed and Embase databases from January 1946 to January 2018. We identified peer reviewed articles of original studies, published in English, using a combination of two sets of search terms for the exposure (childhood vaccine) and the allergic outcomes (Table S1). The search terms were developed by one author (SN) and reviewed by other authors (NW, CL, and SD). The search was last updated on 22nd January 2018. The review was prospectively registered in the PROSPERO systematic review registry (NO: CRD42017071009).

Eligibility criteria

We restricted our review to randomised controlled trials (RCTs), prospective cohort studies and retrospective cohort studies which had measured the exposure and outcome objectively. Studies investigating childhood vaccines as the exposure were considered eligible irrespective of different timings, number of doses or whether they were compared to a placebo, control vaccine or no vaccine. The allergic outcomes could have been reported at any age. Studies where the outcome preceded the exposure were excluded.

Study Selection and Data Extraction

Title and abstract screening of all references identified from the literature search for potentially eligible articles was carried out by two authors independently (SN, ME). Full text article screening was carried out by the same authors and any disagreement was resolved by discussion with a third author (CL).

Data were extracted by one author (SN) into a standardised table format and cross checked by a second author (ME). Any discrepancy was resolved by consensus. The information extracted included: (i) first author, journal, year of publication and study design, (ii) characteristics of study participants (including age, study setting, sex, socio-demographic variables and study population size), (iii) type of exposure (including source of exposure information, age at exposure, dose and frequency, comparator), (iv) allergic outcome measured (and how defined), (v) relevant effect measure and the 95% confidence limits, (vi) confounders considered in the analysis and (vii) author's conclusion.

Study Variables: Exposures and outcomes

The exposure of interest was any vaccine given in childhood (birth-18 years).

The primary outcomes considered were asthma/wheeze, rhinoconjunctivitis/ allergic rhinitis/hay fever, atopic dermatitis/eczema, food allergy and allergic sensitisation. Where outcomes were reported at multiple time points, the most suitable age for diagnosis of each outcome was taken into consideration (e.g. asthma diagnosed after 6 years of age, eczema and food allergy before 1 year)

Quality Assessment

The quality of the included randomised controlled trials studies was appraised using the Cochrane Collaboration Tool for assessing risk of bias, while the Newcastle Ottawa Scale (NOS) was used for cohort studies(carried out by SN and checked by ME). Wherever feasible, published study protocols and previous articles on the same study were sourced for more insight into a particular study methodology. The DAGitty on-line tool was used to create a Directed Acyclic Graph (DAG) to visualise the potential confounders for the relationship between vaccination and allergic disease. Based on this we identified socio-economic status, maternal age, age of the child, family history of allergic diseases, having older siblings, neonatal antibiotic exposures, child care attendance, environment tobacco smoke and period of gestation/ birth weight as confounders. From these a minimal set of confounders was identified and used as part of the study quality assessment (Figure S1). The results of the NOS were converted into Agency for Health Research and Quality (*AHRQ*) standards(good, fair and poor) accordingly²².

Qualitative analysis: In the qualitative synthesis, study characteristics, exposure variability, outcome variability and study quality were the factors taken into consideration.

Meta-analysis: Taking the heterogeneity of the outcome variables/ terms used into consideration, some outcomes were collapsed under one outcome variable/ term. The umbrella terms such as ‘atopic outcomes’ and ‘allergic outcomes’ were analysed based on the definition and on the context in which they were reported by the original authors. Outcome variables defined based on SPT and/ or IgE were first considered separately and then as one variable by amalgamating into one group.

Where the effect measures were reported as odds ratios, the results were converted to risk ratios as described by Zhang et al, the upper and lower limits of the confidence limits for the risk ratio were calculated^{23,24}. Where the vaccine group was analysed as the reference group in the original papers^{25,26}, the effect measure and the respective 95% confidence limits were inverted so that the

control group became the reference group. Similarly, the inverse of the risk estimate was considered where a protective effect was shown by delayed administration of the vaccine²⁷. We meta-analysed studies (2 or more) with similar measures of effect where there was homogeneity of exposures and outcome measurements. Heterogeneity across the studies was evaluated by the I^2 statistic. As described by the original authors. cut off values for low, moderate and high heterogeneity were set arbitrarily at 25%, 50% and 75% respectively²⁸. Studies with similar exposure and outcome variables were pooled using the statistical software Stata version 14²⁹. Random-effect models were used to derive the pooled estimates and the 95% confidence intervals. Possibility of publication bias was assessed by visually inspecting the funnel plots. Data analysis was carried out by SN and was cross checked by CL and SD.

Results

Search Results

Our initial search generated 5622 references. After title and abstract screening, there were 187 potentially relevant articles for full text screening. From these, we identified seven publications based on RCTs and 35 publications based on cohort studies that satisfied our eligibility criteria (Table 1 and Tables S2 and S5), giving 42 full text articles to be included in the review. Of the publications based on cohort studies, 10 were from prospective study designs, 10 from birth cohorts, 2 had a combination of retrospective and prospective study components, and 13 were from retrospective cohort study designs. Seven publications investigated BCG (5 publications based on 3 RCTs; 12 cohort studies), 22 publications investigated pertussis either alone or as DTP/DPPT combined vaccine (3 publications based on 1 RCT; 19 cohort studies), 8 publications (cohort studies) investigated MMR vaccination, 5 publications (cohort studies) investigated measles vaccination, 4 publications investigated Hib vaccination (cohort studies), whilst 2 publications (cohort studies) investigated smallpox vaccination. Even though 2 publications based on a cohort study have mentioned TBE as an exposure whilst 8 publications have mentioned polio (OPV, IPV or as a component of a combined vaccine), the outcomes of these exposures have not been evaluated. Furthermore, we did not identify studies investigating pneumococcal vaccine, yellow fever, Japanese encephalitis, rubella, rota virus, HPV, Varicella, Hepatitis A or B, Typhoid,

Cholera or any other vaccines recommended by the WHO during the childhood period. The Preferred Reporting Items for Systematic Reviews (PRISMA) diagram is shown in Figure 1.

Study characteristics of the articles based on RCTs (Tables 1 and S5)

There were four included RCTs, reported in seven publications for different outcomes. These studies were carried out in Guinea-Bissau³⁰, Sweden^{31,32}, Netherlands³³ and Denmark³⁴⁻³⁶. The numbers of participants in these studies ranged from 121 – 4262. Except for the RCT by Steenhuis et al³³ which was carried out in a population of Caucasian high-risk newborns, all other studies were population based (Tables 1 and S5).

Exposures (Table S2)

A. BCG

As shown in the Table 1, of the seven publications based on four RCTs, five investigated (3 RCTs) the allergic outcomes following BCG vaccination out of which in 2 RCTs the vaccine was given at the age of 6 weeks^{30,33} while in the other RCT the vaccine was given within 7 days of birth³⁴⁻³⁶ (On-line supplement tables S2 and S5).

The trial by Kiraly et al used a two-by-two factorial design, randomising low birth weight infants in Guinea-Bissau to 4 groups based initially on early BCG (intervention) and usual policy BCG timing (control) followed by Vitamin A (intervention) and placebo (control)³⁰. Three of the remaining four publications were based on Danish Calmette Study which had a non-vaccinated control group³⁴⁻³⁶, whilst the other, carried out in the Netherlands, used normal saline as a placebo control³³.

B. Pertussis

Two publications based on the other RCT reported allergic outcomes following pertussis vaccination at 2, 4 and 6 months of age^{31,32}.

Outcomes

There was substantial variability in the outcomes investigated in the seven RCT-based articles. Two articles reported on the relationship between BCG vaccination and developing asthma or wheeze^{33,36} at the age of 4, 18 months³³ and 13 months³⁶; two reported on associations with atopic dermatitis/ eczema^{33,35} at the age of 4, and 18 months³³ and 13 months³⁵; two reported on outcomes of food allergy^{33,34}, at the age of 4, and 18 months³³ and 13 months³⁴; one on the development of rhinoconjunctivitis/ rhinitis/ hay fever³³ at the age of 4 and 18 months, three reported on atopic / allergic outcomes based on SPT³⁰⁻³² at 3-9 years³⁰, 7 months, 2.5 years³¹ and 7 years³². The effect measures were reported as increase in risk³¹, odds ratios^{30,32} and relative risks³³⁻³⁶.

Summary of RCT findings (Tables 1 and S5)

None of the publications from the RCTs found evidence of an association between BCG or pertussis vaccine and allergic manifestations apart from a small reduction in the risk of eczema in the first year of life found in 2 studies following BCG vaccination^{33,35}. Of these, the study by Steenhuis et al³³ was performed in a high-allergy risk population while the study by Thostesen et al³⁴⁻³⁶ was population based. However, Thostesen et al³⁵ carried out a post-hoc analysis on a sample of children with atopic predisposition finding evidence of a further reduction in the risk of developing eczema following BCG vaccination (from RR = 0.9; 95% CI = 0.80-1.00) to RR 0.84; 95% CI = 0.74-0.95).

Study quality (Table S3)

Overall, the quality of the included RCT studies, as assessed by the Cochrane collaboration risk of bias tool revealed one study (three articles)³⁴⁻³⁶ to be of good quality, two studies (three articles)³⁰⁻³² to be of fair quality and one article/ study³³ to be poor quality (Table S3).

Meta- analysis of the RCTs involving BCG (Figure 2)

As shown in Figure 2, BCG vaccination by 7 days – 6 weeks of age was associated with reduced pooled risk of eczema (RR= 0.83; 95% CI= 0.73 – 0.93; I^2 = 0%) There were non-significant reductions in risk of wheeze (RR= 0.93; 95% CI= 0.65 – 1.34; I^2 = 60%), and parent-reported food allergy (RR= 0.93; 95% CI= 0.73 – 1.19; I^2 = 0%).

Study characteristics of the articles based on cohort studies (Tables 1 and S5)

A total of 35 publications based on 29 cohort studies (with multiple publications for some cohorts) met the inclusion criteria. One was a multinational study carried out in Turkey, Thailand and Argentina²⁵. There were 9 studies from the United Kingdom^{19,37-44}, 5 from Australia^{27,45-48}, 4 from Denmark⁴⁹⁻⁵², 3 from Germany⁵³⁻⁵⁵, 2 from Netherlands^{26,56}, 3 from Sweden⁵⁷⁻⁵⁹ and 1 each from New Zealand⁶⁰, Poland⁶¹, Canada⁶², United States of America⁶³, Korea⁶⁴, Brazil⁶⁵, Guinea Bissau⁶⁶, and Taiwan⁶⁷

Exposures (Tables 1, S2 and S5)

Of the 35 publications from a total of 29 cohort studies one prospective cohort²⁵, 2 birth cohorts^{54,55} and 9 retrospective cohorts^{19,44,48,51,58,59,64-66} investigated allergic outcomes following BCG vaccination. Whereas most of the comparison groups in these studies did not receive any vaccine or placebo, 2 publications based on a retrospective cohort had a late BCG (>12 months) control group^{19,44}, whilst another retrospective cohort study compared multiple BCG doses against one BCG dose⁶⁵.

Three publications examined allergic outcomes following a combination of DTP with other vaccines^{26,60,67}, 10 publications looked at the allergic outcomes following DTP vaccination alone^{27,41,43,45,47,53,56,57,62,63}. The study by Matheson et al reported the effect estimate for the risk of developing asthma following pertussis vaccination in addition to DTP combined vaccine⁴⁵. Five other publications based on 5 cohort studies investigated pertussis vaccine alone as the exposure^{37-39,42,46}. Most of the studies except for Kiraly et al and Venter et al compared pertussis vaccine versus no vaccine. In the study by Kiraly et al²⁷, the controls received acellular pertussis vaccine in the form of DTaP later than the accepted schedule. In the study by Venter et al³⁷ the comparison group received a whole cell pertussis vaccine in contrast to the usually scheduled DTaP vaccine and acellular pertussis vaccine received by the cases.

Of the publications based on cohort studies, 7 investigated MMR as the exposure^{41,47,49,50,53,55,63} whilst 4 investigated measles vaccine alone^{40,42,61,66}. Four studies investigated Hib vaccine^{26,53,63,67} out of which in the study by Wang et al⁶⁷, the cases received DTP-Hib-OPV in contrast to the control group that received DTP-OPV. Two articles published on the Tasmanian Longitudinal Health Study^{45,46} and the study by DeStefano et al⁶³ looked at the allergic outcomes following small pox vaccination in childhood.

Outcomes (Table S2)

All cohorts except one prospective cohort²⁵, one birth cohort⁴⁰ and 2 retrospective cohorts^{59,66} investigated either asthma and/or wheezing as an outcome. Similarly, most of the same studies investigated eczema/ atopic dermatitis as another outcome^{19,26,27,37,41,42,46-49,53,56,58,60,67}. In terms of other allergic outcomes, 2 prospective cohorts^{27,46}, 6 birth cohorts^{37,40,42,49,53,54}, and 5 retrospective cohorts^{19,48,51,52,58} investigated rhinoconjunctivitis/ rhinitis/ hay fever as an outcome measure, and 2 prospective cohorts^{27,46}, one birth cohort³⁷, and 2 retrospective cohorts^{58,64} investigated the development of food allergy.

Outcome variables were reported as hazard ratios^{39,41,55}, risk ratios^{19,25,37,38,45,47,48,50,60,63} and odds ratios.

Summary of findings from cohort studies (Tables 1 and S5)

A. BCG

There was conflicting evidence about the effect of BCG vaccination on allergic outcomes. Five studies demonstrated a reduced risk of developing allergic outcomes following BCG vaccination, whilst one study showed an increase in the risk of allergic outcomes⁵⁹ and 6 other studies found no evidence of association^{19,48,51,54,58,65}.

B. Pertussis

In terms of pertussis exposure, the overall evidence contributed by all the cohort studies suggested no strong evidence of association. The study by Bernsen et al⁵⁶ found evidence of a reduced risk of allergic outcomes following whole cell pertussis vaccination. In contrast, the study by Farooqi⁴² found an increased risk of allergic outcomes with the same vaccine. The control group in the former⁵⁶ was very small representing only 2% of the population, compared with 25% in the latter⁴². Four other studies failed to show any significant association between pertussis vaccine and allergic outcomes^{37-39,43}.

C. Measles

Apart from the studies by Farooqi et al⁴² (weak higher risk) , and Mckeever et al ⁴¹ (higher risk estimates for asthma and eczema given as hazard ratios and adjusted hazard ratios), all the other studies showed a protective effect^{47,49,50,53,55,61,63} or a null effect^{40,66} following measles/ MMR

vaccine. It was not possible to ascertain the individual effect of measles vaccination on allergic outcomes in the study by Bernsen et. Al⁵⁶ as the ultimate protective effect represented the combined effect of several vaccines.

Study quality (Table S4)

The results for the quality assessment using the NOS are given in Table S4. Usually, by design the evidence from the prospective cohorts is better than the retrospective cohorts. However, we found that two prospective cohorts were of poor quality^{25,60} whilst 6 of the retrospective cohorts were of good quality^{19,44,56,62,64,66}.

Meta-analysis of the cohort studies

A: BCG (Figure 3)

Pooling the effect estimates of 4 studies^{44,48,51,64} that investigated the relationship between BCG vaccination in the neonatal period and development of asthma at 6 years found no evidence of an association with asthma; re RR=0.92, 95% CI= 0.59 – 1.46. However, the heterogeneity was high ($I^2= 82.9\%$) indicating that the pooled estimate was unreliable.

There was no evidence of a protective effect from BCG vaccination for allergic sensitisation (SPT); re RR=0.97, 95% CI= 0.89 – 1.05, $I^2= 0\%$. Similarly, there was no evidence of association for the risk of hay fever following vaccination with BCG; re RR= 1.08, 95% CI = 0.83 – 1.4, $I^2=42.9\%$.

B1. Acellular pertussis (Figure 4)

There was no evidence of any association for vaccination with acellular pertussis on the development of wheeze/asthma, eczema, or sensitisation. The pooled effect estimate of three studies exploring the association between childhood vaccination with acellular pertussis and development of wheeze/ asthma^{27,37,57} showed no evidence for an association (RR= 0.96, 95% CI= 0.82 – 1.13, $I^2= 26.6\%$). Similarly, three studies^{27,37,66} exploring the association between childhood vaccination with acellular pertussis and development of sensitisation measured as detected by the skin prick test failed to demonstrate a significant association as 95% CI included the null (RR= 1.34, 95% CI=0.83 – 2.17, $I^2= 49.4\%$).

B2. Whole cell pertussis (Figure 5)

We found no evidence for an association between vaccination with whole-cell pertussis vaccine and allergic disease. Pooling effect estimates of 5 cohort studies investigating the effect of childhood whole-cell pertussis vaccine and development of asthma^{38,43,46,56,63} showed no evidence of association: RR= 0.98, 95% CI= 0.88 – 1.08, I^2 = 33.9%.

C. Measles (Figure 6)

There was evidence of a protective effect of measles vaccination for development of all allergic outcomes from all studies except for the study by Farooqi et al⁴² which used ‘allergy’ as the outcome measure. Pooling of the estimates from 4 cohort studies^{49,50,61,63} investigating the association between measles vaccination and development of asthma showed a protective effect; RR= 0.78, 95% CI = 0.62 – 0.98. However, the heterogeneity was unacceptably high for the pooled estimate to be reliable; I^2 = 93.9%. This may be due to the differences in age of outcome measurement which would affect the definitive diagnosis of asthma, and exposure being a multi-component vaccine (MMR) in 3 studies^{49,50,63} in comparison to measles only vaccine in the other⁶¹. In contrast, the pooled estimate from 2 studies (3 risk estimates for different populations^{49,53} investigating the association between measles vaccination and eczema was protective; RR= 0.65; 95% CI= 0.47 – 0.90; I^2 = 0.0%. Pooling of 3 studies^{49,53,66} also showed modest evidence of a reduced risk of allergic sensitisation; RR= 0.78; 95% CI= 0.61 – 1.01, with low heterogeneity; I^2 = 19.4%. However, the confidence interval included the null value.

There was no clear evidence of small study effects, as shown by visual inspection of the funnel plot (Figure S2).

Discussion

Our systematic review and meta-analysis found no evidence of an increase in the risk of allergic outcomes following childhood immunization with commonly administered childhood vaccines.

Pooling estimates from RCTs indicated some evidence for protection from development of eczema but not for asthma or parent-reported food allergy following BCG vaccination in infancy whilst pooling estimates from cohort studies found that childhood vaccination did not significantly influence development of any allergic diseases later in life. However, we found some low quality evidence from cohort studies that measles vaccination may be associated with less risk of development of eczema (low quality of the studies according to NOS), asthma (high heterogeneity of the pooled estimate) and sensitisation (confidence interval included the null value).

Interpretation of the findings in the context of international literature

It has been proposed that an immunogenic agent such as a vaccine administered in infancy to protect against infection might also confer altered risk of later allergic sensitisation or allergic disease. This hypothesis was fuelled by the publication of a non-peer reviewed letter by Odent et al¹² suggesting a possible cross-sectional link between vaccination with whole-cell pertussis vaccine and increased risk of asthma. Further cross-sectional studies from New Zealand⁶⁰ and the UK⁴² added to concerns that early life vaccination might increase the risk of later atopic disease. There was some theoretical support for this proposition with specific IgE antibody to Tetanus and Diphtheria toxoids detected in about 50% of immunised infants,⁶⁸ and that proportion rose to 90% after booster injections⁶⁹. This Th2 mediated response seemed more common in atopic children⁶⁸.

However, other systematic reviews on atopic risk reported contrary results. A systematic review¹⁷ published in 2004 concluded that there was no evidence that infant vaccination resulted in an increase in later atopic disease. However, non-existence of RCTs on the topic at that time limited their review to observational studies of varying quality and heterogeneity.

The evidence uncovered through previous systematic reviews and meta-analyses suggests that BCG vaccination is unlikely to be protective against development of eczema and sensitisation¹⁸, whilst it may offer some protection over development of asthma^{18,19}. Lack of data from RCTs was a limitation identified in those reviews.

Undoubtedly, pooling estimates from RCTs in the current review made way to better synthesis of evidence. We found some evidence for protection from development of eczema following BCG vaccination in infancy. The pooled estimate from two RCTs examining the effect of BCG vaccination on eczema after the first year of life in high-risk populations showed a clinically important and statistically significant 17% risk reduction. One of the trials was of poor quality and the calculated pooled estimate should be regarded with caution³³. Further, the nature of the populations studied renders generalizability of the results doubtful.

Furthermore, contrary to Arnoldssen et al¹⁸ and Linehan et al¹⁹ we did not find any evidence suggesting a protection against development of wheeze/ asthma following BCG vaccination by pooling effect estimates of both RCTs and cohort studies separately through our review. Even though, ages of outcome are not suitable to arrive at a definitive diagnosis of asthma in both RCTs considered for risk of development of asthma following BCG vaccination in this review, the

consistency of the findings made by pooling of the effect estimates from 4 cohort studies in which the age of outcome is suitable for a definitive diagnosis of asthma, adds more weight in this regard.

In all, 35 publications based on 29 cohort studies from 16 individual countries were included in this review and the study quality varied considerably. Only 50% of the studies were rated “good”, 18% were “fair” and 32% were “poor” based on the Newcastle-Ottawa Scale. Common vaccines were studied, often co-administered, inevitably leading to difficulty in teasing out the effect of one vaccine from another.

In the present review, with the exception of a significant reduction in eczema risk with administration of measles vaccine, the cohort studies examining the effect of vaccination on later allergy risk found no evidence for an association between vaccination and common childhood allergies.

The pooled estimate from 2 cohort studies (3 estimates, as one study had risk estimates for high and low risk samples) shown in Figure 6 indicated a clinically important 35% risk reduction for eczema following measles vaccination. The estimate was obtained from studies that were classed as poor quality based on the NOS. Additionally, the pooled estimate was clearly driven by the results from one study performed in a high-risk population so that methodological heterogeneity will have influenced the estimate which must be interpreted with caution. Again, the pooled estimate from 4 cohort studies indicated an important 22% risk reduction for asthma from measles vaccination. While 3 of the 4 studies were classed as good quality, there was strong evidence for heterogeneity with an I^2 exceeding 90%. Three of the said studies^{49,50,63} considered MMR to be the exposure whilst it was measles only in the other study⁶¹. In addition, age of diagnosis of the outcome is an issue here in 2 studies^{50,63} as definitive diagnosis of asthma may not be possible prior to 5 years of age^{70,71}. Consequently, the pooled estimate must be regarded as unreliable.

The pooled estimate from the cohort studies exploring the effect of whole cell pertussis vaccine on eczema is in the same direction as that of measles vaccine. However, it is of interest that the pooled estimates from the cohort studies exploring the effect of acellular and whole-cell vaccines on eczema were in the opposite directions, but these estimates should be regarded with caution given the quality of the studies, high heterogeneity of pooled estimate of whole-cell vaccines and the probable methodological differences in the studies on acellular pertussis vaccines.

Hence, it is noteworthy that the aim of Kiraly et al²⁷ was to examine the effect of the timing of vaccine administration on allergic outcomes, not the effect of acellular pertussis vaccine compared to either whole-cell vaccine or no vaccine. From the same study, it was not possible to attribute the observed reduction in eczema risk to the use of acellular pertussis vaccine which was but one component of a combined DTaP vaccine. Venter et al³⁷ found an 18% reduction in eczema risk when comparing the effect of acellular pertussis which is a component of a combined diphtheria/tetanus/pertussis vaccine to whole cell pertussis vaccine at 1 year of age. In the latter scenario, any effect from the diphtheria and tetanus components should have been common to each multi-component vaccine, lending more weight to the findings on reduced eczema risk. Nonetheless, the methodological differences are important and must cast some doubt on the reliability of the pooled estimate. A reduced risk is biologically plausible in that the lack of some cell wall components in the acellular pertussis vaccine could down-regulate the atopic response⁵³.

Similarly, the pooled estimate from three cohort studies that used a whole-cell pertussis vaccine showed no effect on eczema risk. Bernsen et al⁵⁶ found evidence of a reduced risk of allergic outcomes following whole cell pertussis vaccination. In contrast, Farooqi found an increased risk of allergic outcomes with the same vaccine⁴². These contradictory findings may have arisen from study differences including different populations, and different methods for determining allergic outcomes. The Bernsen study used very sensitive but not highly specific measures as opposed to the Farooqi study where highly specific but not sensitive measures were employed. Perhaps the most important difference is that the control group in the Bernsen study represented only 2% of the study population (compared with 25% in Farooqi) raising the question of the appropriateness of this comparison group that may have differed for a range of other exposures.

Overall, results from the cohort studies in this review did not support the view that early-life vaccination was associated with an increased risk of allergic disease. While not definitive, the pooled estimates from the cohort studies tend towards the opposite view, that is, that early-life vaccination with measles vaccine could be associated with a reduced risk of eczema. However, more methodologically homogeneous studies are needed to conclude on this regard.

Strengths, limitations, and Implications for Policy, Practice and Research

A systematic review with meta-analyses of this nature, offers a strong evaluation of the available evidence, while inherently limited by what evidence is available. The main strengths of this study

are our attempt to encompass all the eligible articles with a systematic search strategy, independent screening of the articles for eligibility and quality by two authors, and inclusion of only randomised controlled trials and cohort studies due to their inherent ability to establish the temporal relationship between exposure and outcome. In contrast all the previous reviews examining the association between childhood vaccination and allergic outcomes were limited to observational studies¹⁵⁻¹⁷ except for Arnolessen et al¹⁸ and Linehan et al¹⁹ which had one single blinded RCT in their review. There is a scarcity of RCTs addressing the issue as it is often unethical to withhold the vaccines from a control arm. In this current review, pooling the effect estimates separately for RCTs and cohort studies and the consistency from both RCTs (BCG) and cohort studies (measles) in finding possible beneficial effects from infant vaccination on the risk of eczema is important in this regard. Similarly, there was consistency of evidence from both RCTs and cohort studies with regards to finding no association between BCG vaccination and wheeze/ asthma outcomes. Even though meta-analysed separately, the heterogeneity in the outcome variables is note-worthy, i.e. allergic outcome in the 2 RCTs is wheezing at 1 – 2 years of age whilst in the 4 cohort studies it was asthma above 6 years of age. However as noted above, in cohort studies where the exposure and outcome were measles vaccination and asthma respectively, even though a statistically significant protective effect was denoted by the pooled estimate, the inappropriate age for a definitive diagnosis of asthma seen in 2 of the meta-analysed studies should be taken into consideration when interpreting the results. Similarly, there were differences in the control groups in the studies where the exposure was acellular pertussis. Hence, methodological heterogeneity and questionable generalizability in many of the included studies is a limitation of the available evidence.

In summary, this review and meta-analysis found no evidence of an adverse effect from common childhood vaccinations on allergic outcomes but showed some evidence of a beneficial effect on eczema risk with BCG and measles vaccines.

Large population-based cohort studies in future may provide additional evidence of an effect, either beneficial or adverse, on allergic outcomes. It would be interesting to further evaluate whether this favourable effect of BCG and measles vaccines on eczema is a specific effect or a more generalized T_H1 effect, pointing to the role of bacteria and viruses towards the pathogenesis of eczema. Given the overwhelming evidence in favour of infant vaccination as a protection against infectious diseases and the voluminous evidence against development of allergy following

childhood vaccinations, it is doubtful that further RCTs using placebo or no vaccination could be justified where BCG, measles and pertussis vaccination and allergic outcomes are concerned. As such, further studies on these vaccines will need to either measure the impact of timing of vaccination or compare the impacts of different forms of vaccines. It is crucial to study the comparatively newer and underused vaccines such as Rota virus, HPV, pneumococcal, meningococcal, influenza, varicella, JE, cholera etc. that may precipitate allergic outcomes. Emergent of novel zoonotic viral diseases in the recent past have led to the rapid development of newer and novel vaccines with newer antigens and/or adjuvants such as SARS, MERS and COVID-19 (SARS-CoV-2). Continuation of research on these novel vaccines is obligatory. Meanwhile, it is imperative to promote the importance of continuing childhood vaccines for prevention of vaccine preventable diseases, maintenance of the herd immunity to protect vulnerable sub-groups, and sustainability of the vaccination programmes.

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Table 1: Characteristics of the publications used for the qualitative synthesis (Details on control group for cohort studies, sources of information etc given in Table S5)

Reference, country	Study sample	Exposure	Outcome	Nature of the association
Randomised controlled Trials				
Kiraly et al. 2013 ³⁰ , Guinea-Bissau (West Africa)	Guinea-Bissau Health Project (N=289) → (N=281) →	BCG & Vit A (2x2 factorial), DTP, Extra measles vaccine vs no extra vaccine	Atopy (based on positive SPT or asthma, eczema or food allergy)	None
Nilsson et al. 1998 ³¹ , Sweden	Infants from the Swedish pertussis vaccine trial (N=669)	Pertussis 2-c, 5-c, WC vs. DT	Any atopic disease	None
Nilsson et al. 2003 ³² , Sweden	Infants from the Swedish pertussis vaccine trial (N=667)	Pertussis Pa2, Pa5, WC vs. DT	Asthma, AD, allergic disease, AR, SPT	None;
Steenhuis et al. 2008 ³³ , Netherlands	Newborns from high risk families (N=121)	BCG vs saline placebo	Asthma, AR, Eczema, Food allergy	Eczema and use of eczema drugs: weak protective effects
Thostesen et al. 2018 ³⁵ , Denmark	Danish Calmette Study, (N=4,262)	BCG vs none	AD	Protective, NNT= 21
Thostesen et al. 2017 ³⁴ , Denmark	Danish Calmette Study, (N=4,262)	BCG vs none	Allergic sensitisation and food allergy	None
Thostesen et al. 2017 ³⁶ , Denmark	Danish Calmette Study, (N=4,262)	BCG vs none	Recurrent wheeze	None
Birth cohorts				
Grabenhenrich et al. 2014 ⁵⁵ , Germany	German atopy risk enhanced sample from MAS-90, 20 year follow up (N=941/1,314)	BCG, TBE vaccine, MMR	Asthma	Protective*
Grüber et al. 2003 ⁵³ , Germany	German atopy risk enhanced sample from MAS-90, 5 years follow up (N=1,131/1,314)	DTP, MMR, OPV, Hib, TBE	AD, Allergic sensitisation, Asthma, allergic rhinitis, total serum IgE	Protective#

Reference, country	Study sample	Exposure	Outcome	Nature of the association
Grüber et al, 2001 ⁵⁴ , Germany	German atopy risk enhanced birth cohort sample from MAS-90, 2 years follow up, (N=1,314)	BCG	AD, recurrent wheezing, allergic rhinitis	None
Kummeling et al.2007 ²⁶ , Netherlands	Infants in the KOALA birth cohort , (N=2,764/ 2,834)	DPPT, Hib	Eczema, recurrent wheeze	None*
Lewis and Britton. 1998 ⁴⁰ , UK	British Birth Cohort (N=6,350)	Measles	Allergic rhinitis	Protective*
McKeever et al. 2004 ⁴¹ , UK	West Midlands General Practice Research Database. (N=20,228)	DPPT, MMR	Eczema, asthma	Higher risk *
Timmermann et al, 2015 ⁴⁹ , Faroe Islands	Faroe Islands Birth cohort, (N=555)	MMR	Asthma hypersensitivity , ARC, Eczema, SPT, Total IgE	Protective*
Venter et al, 2016 ³⁷ , UK	Isle of Wight (FAIR) birth cohort(N=819)	aP vs wP	Food allergy (IgE), SPT	None*
Farooqi et al, 1998 ⁴² , UK	Oxfordshire Family practice Birth Cohort: (N=1,934)	wP , Measles	Atopy, asthma, eczema, allergic rhinitis	Weak higher risk*
Population based prospective cohort studies				
Henderson et al, 1999 ³⁸ , UK	Avon longitudinal study of pregnancy and childhood. N= 13,810/ 13,971	Pertussis	Wheezing illness	None*
Jedrychowski et al, 2004 ⁶¹ , Poland	9 years old School children in 12 primary schools N= 1,005	Measles	Chronic respiratory symptoms, asthma and allergy	Protective*
Kemp et al, 1997 ⁶⁰ , NZ	Christchurch Health and Development Study N=1265	OPV+DTP measles	Asthma , eczema and other allergic disease	Higher risk*
Kiraly et al, 2016 ²⁷ , Australia	HealthNuts study, (N=4856)	DTaP On-time vs late	Food allergy (SPT or IgE), eczema and eczema medication	Delayed DTaP- Protective for eczema*
Maitra et al. 2004 ⁴³ , UK	Avon longitudinal study of pregnancy and childhood. N= 13,810/ 13,971	Pertussis	Asthma, Wheeze, atopy (SPT)	None*
Matheson et al. 2009 ⁴⁵ , Australia	Tasmanian Longitudinal Health Study (TAHS). (N=5,729)	Diphtheria, Tetanus, Pertussis, Polio	Asthma,, eczema,, food allergy, hay fever	None*

Reference, country	Study sample	Exposure	Outcome	Nature of the association
		Smallpox, DTP		
Nakajima et al. 2007 ⁴⁶ , Australia	Tasmanian Longitudinal Health Study (TAHS). (N=8,443)	DTP, Polio, Small pox	Asthma, Eczema, Food allergies Hay fever	None*
Spycher et al. 2009 ³⁹ , United Kingdom	Population based Cohort Study Leicestershire, UK. (N=6,048/ 6,811)	Pertussis vaccine	Asthma	None*
Thomson et al, 2010 ⁴⁷ , Australia	Infants in the Melbourne Atopy Cohort Study (MACS) (N=620)	DTP, CDT, Sabin vaccine, MMR	Asthma, AR, eczema	Sabin- protective for asthma CDT- higher risk for asthma*
Townley et al, 2004 ²⁵ Turkey, Thailand, Argentina	Multinational sample N=1,704	BCG	PPD test, SPT for common allergens, atopy and allergy	Protective
Wang et al, 2012 ⁶⁷ , Taiwan	Taiwan Birth Cohort Study.(N=19,968)	DTP-Hib & OPV DTP-Hib-IPV	AD, recurrent wheezing	Hib combination vaccines: Minimal risk for AD *
Population based cohort studies with prospective and retrospective components				
Destefano et al. 2002 ⁶³ , USA	Children enrolled in HMO from birth to at least 18 months. (N=167, 240)	DTP, OPV, Hib, MMR, Hep B	Asthma	DTP, OPV, MMR- None* Hib, Hep B- higher risk (weak)*
Hviid and Melbye, 2008 ⁵⁰ Denmark	Danish Nation-wide cohort study, (N=871,234)	MMR	In patients with asthma or status asthmaticus, anti-asthma medication	Protective*
Population based retrospective cohort studies				
Aaby et al. 2000 ⁶⁶ Guinea-Bissau (West Africa)	Population based, N=400	BCG, Measles DTP/OPV	Atopy (SPT)	BCG vaccine given early maybe protective*
Alm et al. 1997 ⁵⁸ , Sweden	Nordic children born in 1989-1992 with atopic heredity vs controls N=1,196 (Cases- 216 controls- 980)	BCG	Asthma, AD, rhino conjunctivitis, urticaria, food allergy, SPT, IgE	None
Alm et al. 2002 ⁵⁹ , Sweden	Same cohort of 3-8 years old children with atopic heredity Vs controls N=574 (Cases- 216 Controls- 358)	BCG	SPT, atopic disease, IgE, Genotyping of LC11A1 (formerly NRAMP1) gene	Higher risk

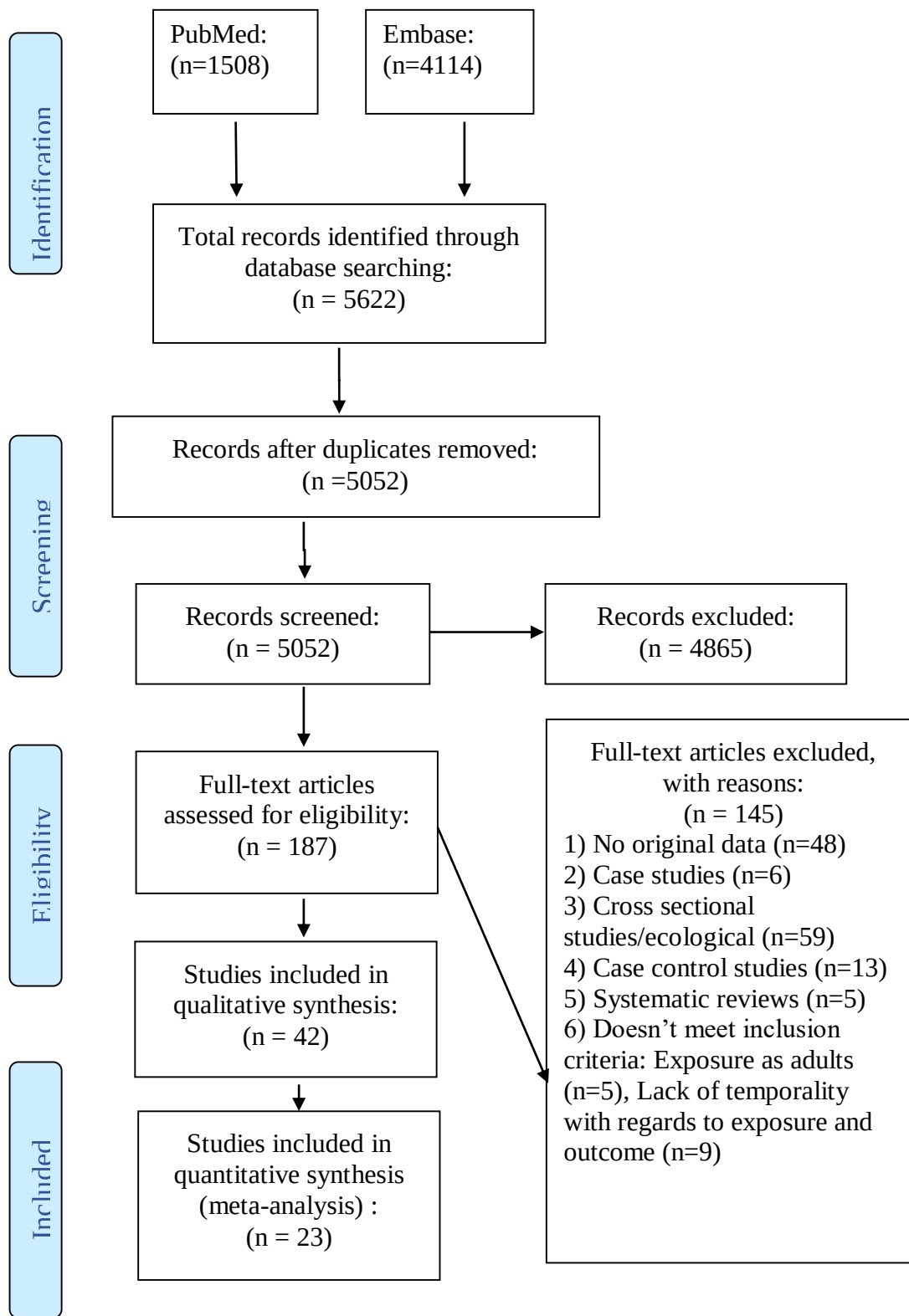
Reference, country	Study sample	Exposure	Outcome	Nature of the association
Bager et al. 2003 ⁵¹ , Denmark	Pregnant women living in Copenhagen, identified through Danish National Birth Cohort; (N=2,176)	BCG	Asthma, allergic rhinitis, IgE	None*
Bager et al. 2003 ⁵² , Denmark	Pregnant women living in Copenhagen identified through Danish National Birth Cohort; (N=2,181)	small pox	Asthma, allergic rhinitis, IgE	Weak higher risk*
Bernsen et al. 2003 ⁵⁶ , Netherlands	Children born in 1988, 1989 or 1990 in Zwijndrecht (N=1,724)	DTP (WC), MMR Booster DT, Polio	any type of allergy, asthma, eczema	Whole cell Pertussis may be protective *
Linehan et al. 2007 ⁴⁴ , UK	Manchester Community asthma study: MANCAS (N= 2,414)	BCG	wheeze	Protective*
Linehan et al. 2014 ¹⁹ , UK	Manchester Community asthma study 2: MANCAS 2 (N= 1,608)	BCG	Wheeze, hay fever, AD	None*
Marks et al. 2003 ⁴⁸ , Australia	Children born to mothers with South Asian origin in Sydney Cases: 309 (locality A) Controls: 442 (locality B)	BCG	Wheeze, hay fever, AD, SPT, IgE, spirometry, TST reaction size, γ IFN to PPD	High risk Subgroup : Protective*
McDonald et al. 2008 ⁶² , Canada	Children born in Manitoba in 1995 N=13,980	DTP whole cell vaccine timing	asthma	Delay in administering 1 st dose- Protective*
Park et al. 2015 ⁶⁴ , Korea	Pulmonology clinic attendees, (N=200)	BCG (scar)	SPT, Lung function tests and methacholine/ mannitol challenge	BCG scar- protective*
Sarinho et al. 2010 ⁶⁵ , Brazil	High socio-economic group with health insurance from Para (N=2,311)	BCG (frequency)	asthma	None
Vogt et al. 2014 ⁵⁷ , Sweden	Cases: N= 79,705- from RCT Controls: N=21,485- from the population (Linköping)	DTaP	Asthma medication	None*

* Adjusted for a minimum set of Confounders

Adjusted only for age and sex

Abbreviations: Vit.- Vitamin; 2-c/ Pa2- two component acellular pertussis vaccine; 5-c/ Pa5- five component acellular pertussis vaccine; γ IFN- γ interferon; Hib- Haemophilus influenza type b; Hep B- Hepatitis

A total of 35 publications based on cohort studies and 7 publications based on randomized controlled trials (RCTs) met the inclusion criteria for this systematic review. We found no evidence that childhood vaccination with commonly administered vaccines were associated with increased risk of later allergic disease. Our results from pooled analysis of both RCTs and cohort studies suggest that vaccination with BCG, and measles vaccines were associated with a reduced risk of eczema. In addition, childhood measles vaccination was associated with a reduced risk of asthma.

Figure 1: PRISMA flow Diagram

BCG and Allergy in Randomised Controlled Trials

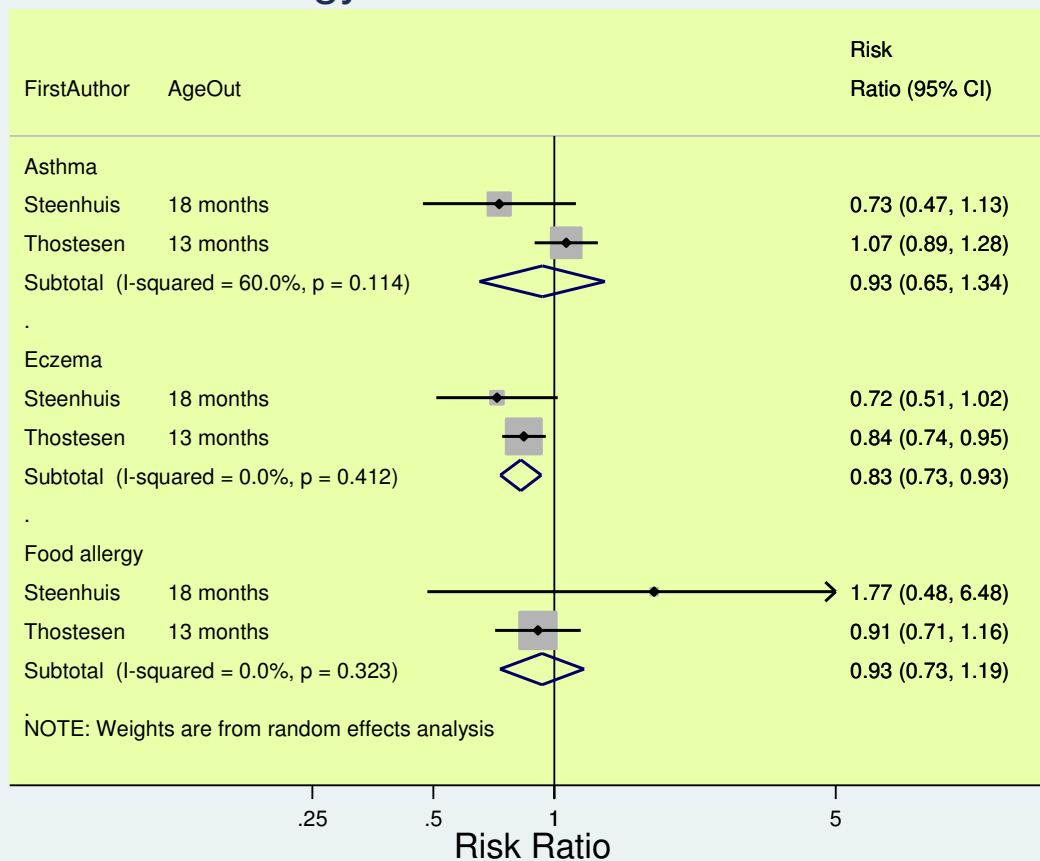


Figure 2: Forest plot showing RRs and 95% CIs for the association between BCG vaccination and Childhood allergy measured as wheeze/asthma, eczema, and food allergy for the Randomised Controlled Trials

BCG and Childhood Allergy

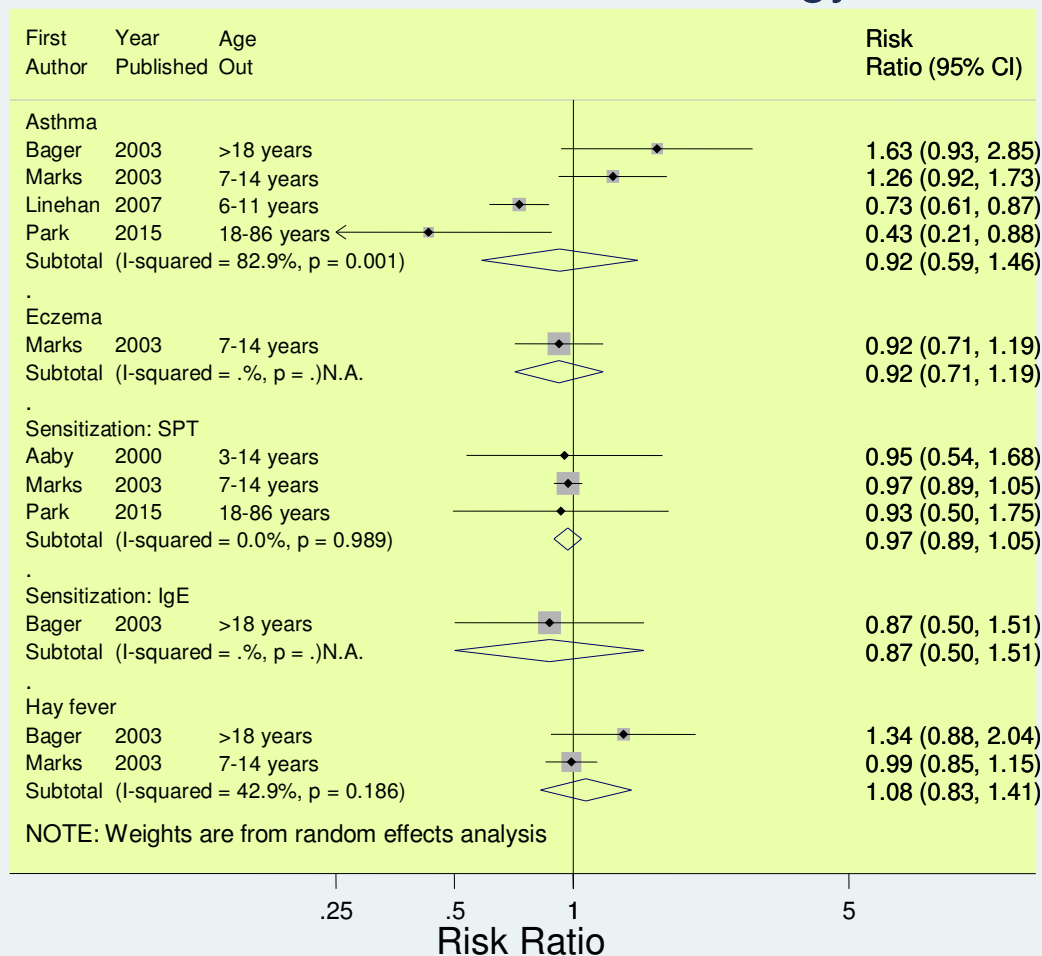


Figure 3: Forest plot showing RRs and 95% CIs for the association between BCG vaccination and childhood allergy measured as asthma, eczema, sensitisation and hay fever for the cohort studies

Accepted Article

Acellular Pertussis and Childhood Allergy

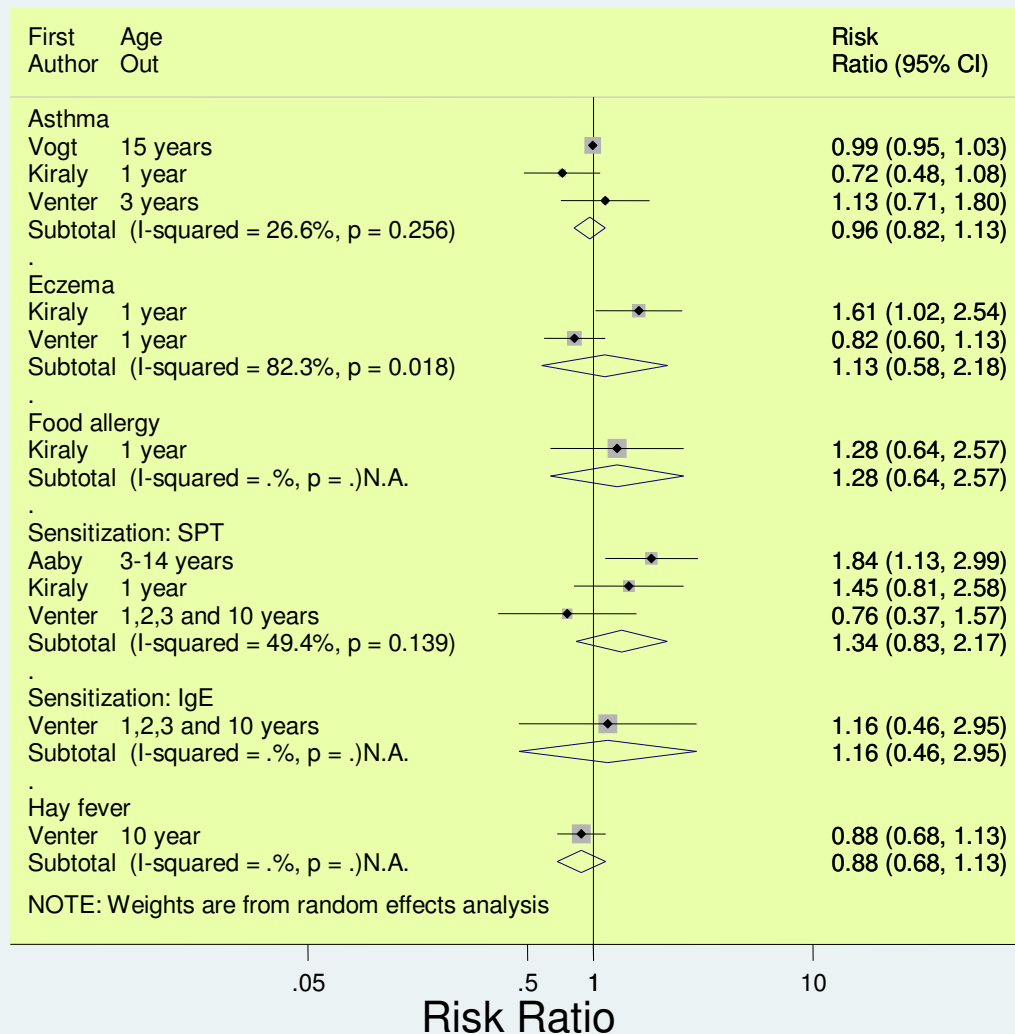


Figure 4: Forest plot showing RRs and 95% CIs for the association between Acellular Pertussis vaccination (Control groups: Kiraly et al- delayed DTaP; Venter et al- whole cell vaccine) and childhood allergy measured as Wheeze/ asthma, eczema, food allergy sensitisation (SPT and IgE) and hay fever for the selected cohort studies

Accepted Article

Whole-cell Pertussis and Childhood Allergy

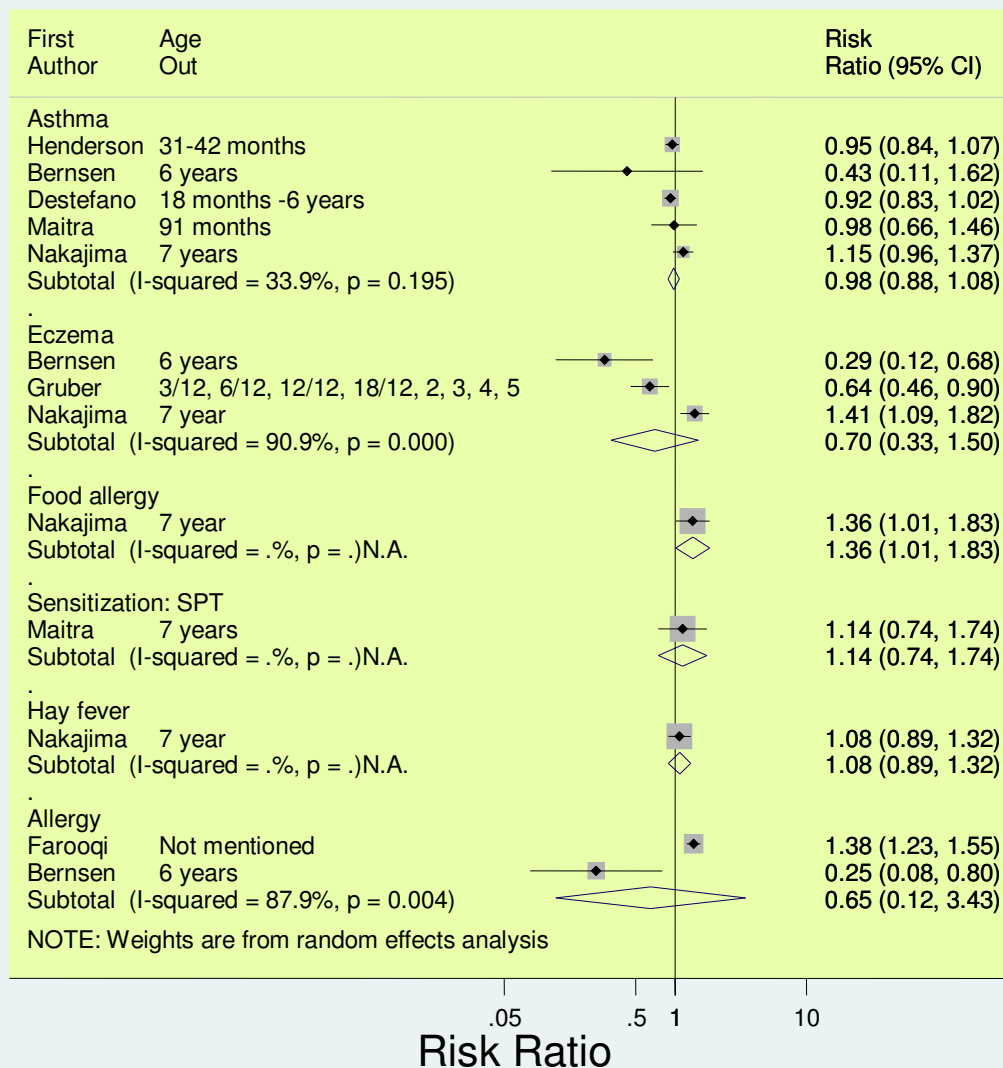


Figure 5: Forest plot showing RRs and 95% CIs for the association between Whole Cell Pertussis vaccination and childhood allergy measured as asthma, eczema, food allergy sensitisation (SPT), hay fever and allergy as an umbrella term for the selected cohort studies

Measles and Childhood Allergy

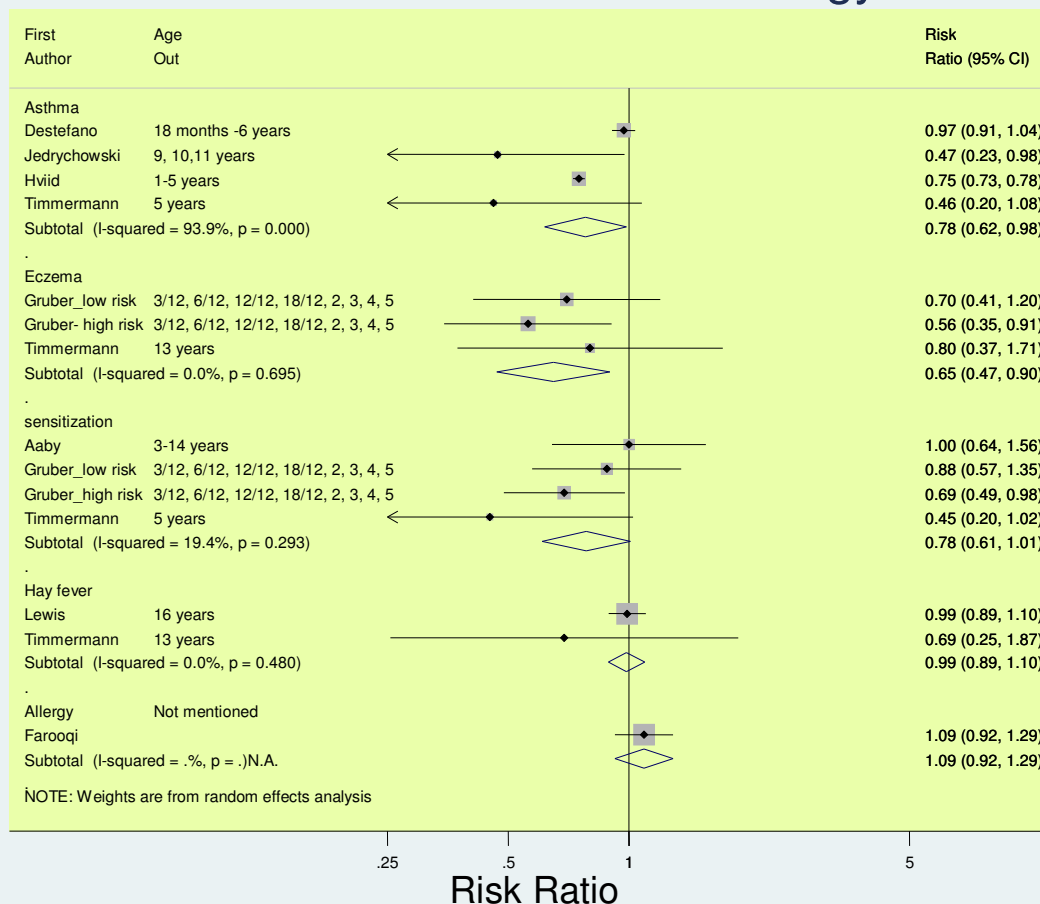
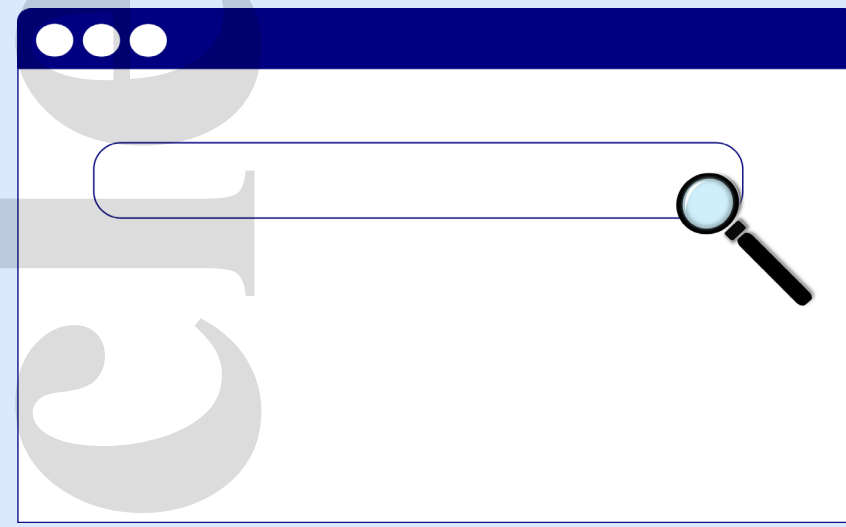


Figure 6: Measles and Allergy Forest plot showing RRs and 95% CIs for the association between Measles vaccination and childhood allergy measured as asthma, eczema, food allergy sensitisation and hay fever for the selected cohort studies

Search



35 publications based on cohort studies and 7 publications based on randomized controlled trials

Protection from Allergy



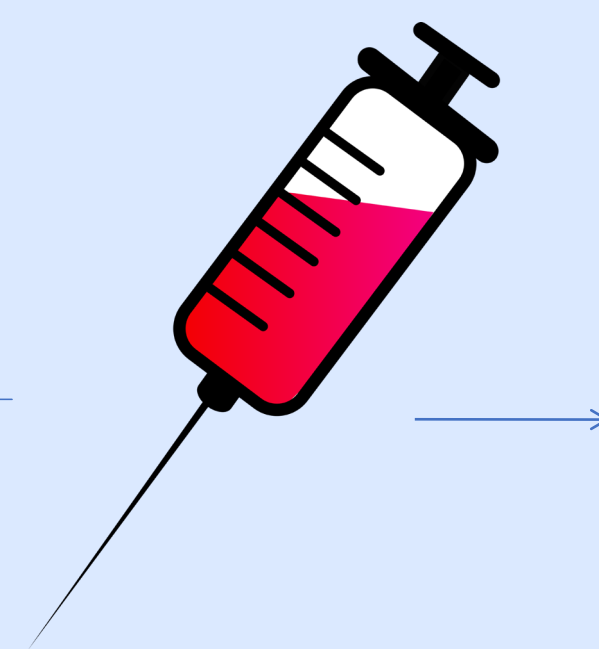
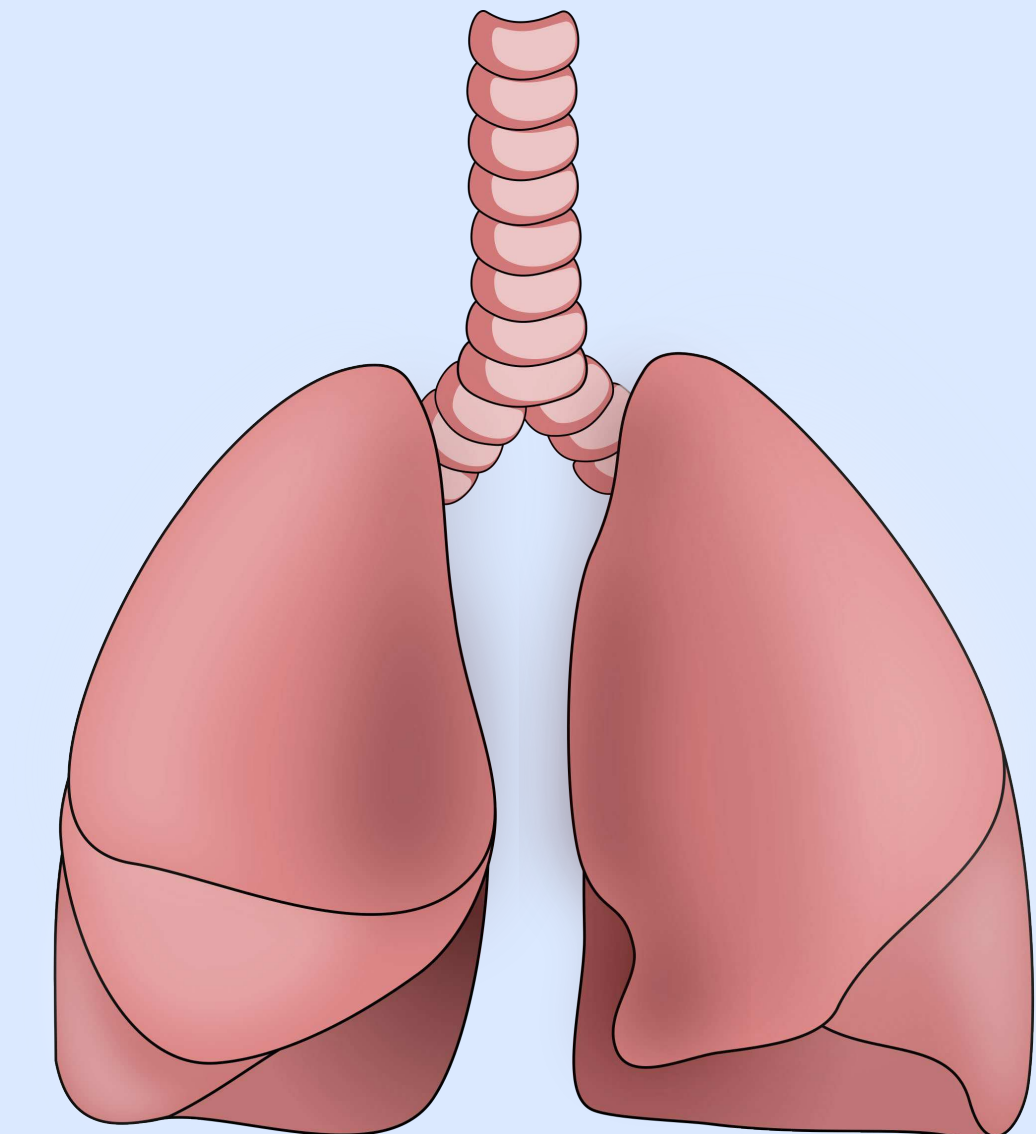
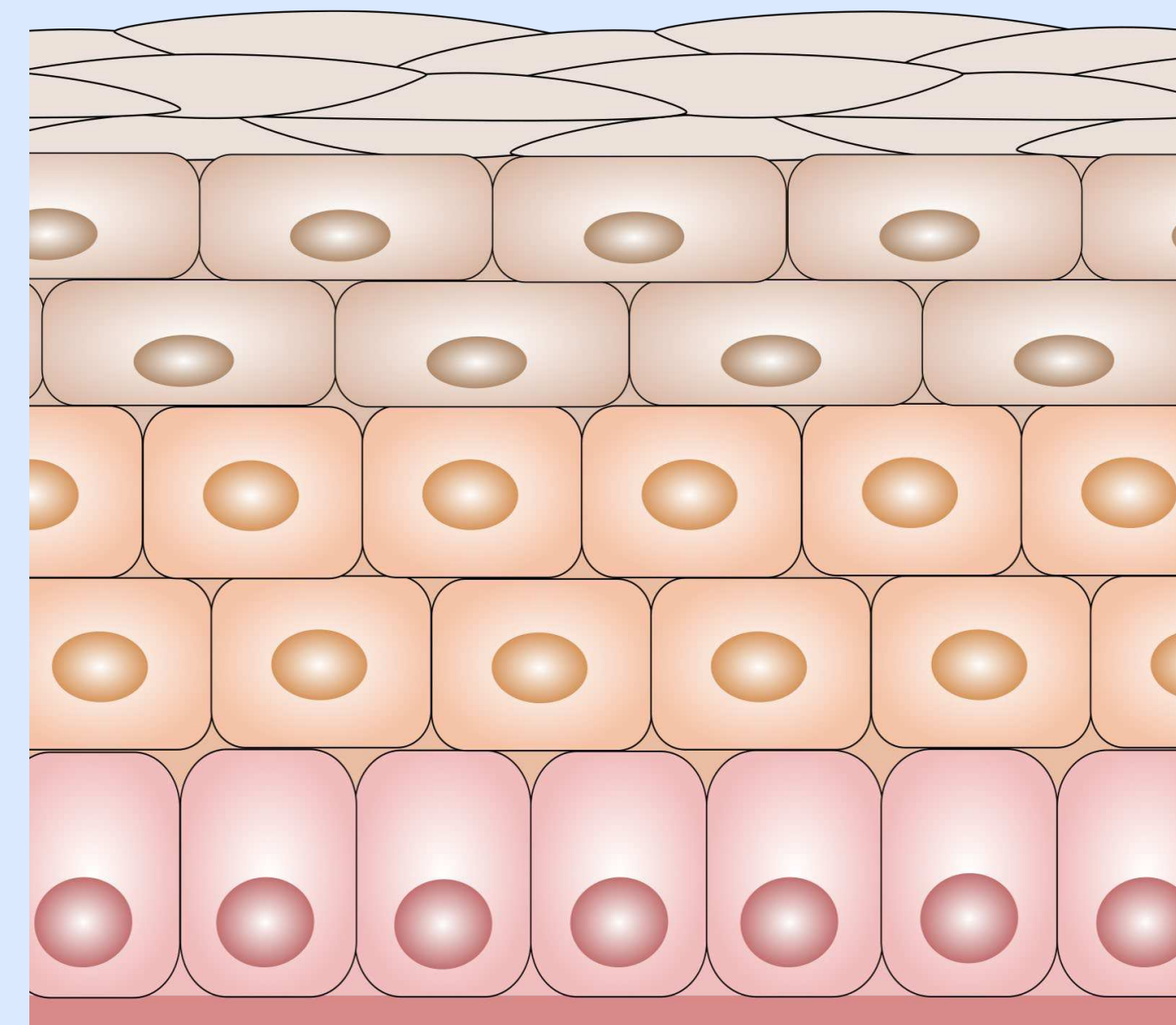
BCG vaccine



Measles vaccine

Reduced risk of eczema

Reduced risk of asthma



No increased risk of later allergic disease

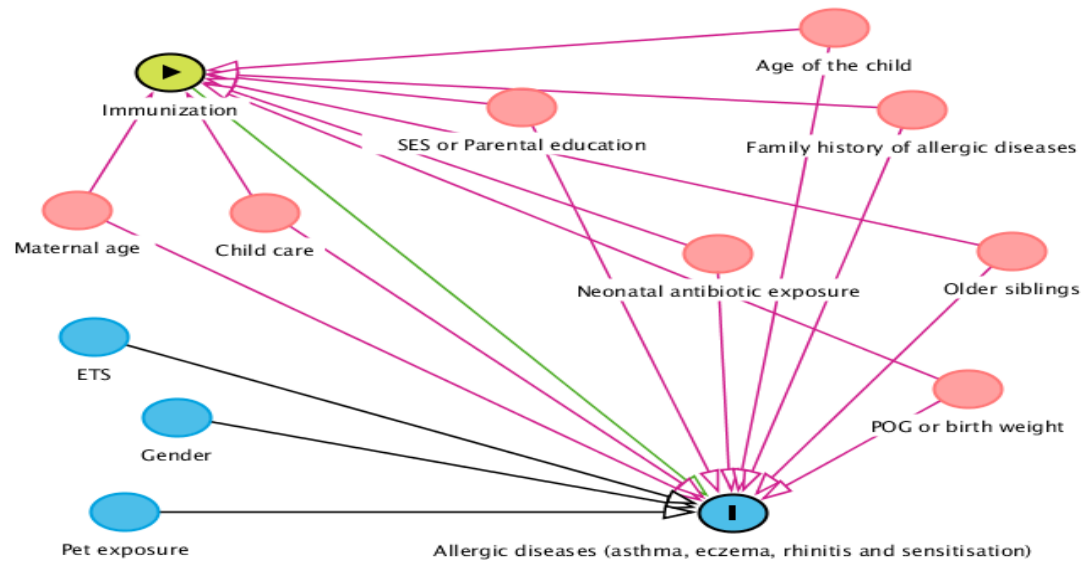
Risk of Allergy

ON-LINE SUPPLEMENT

Table S1. Search Strategy

1. immunization	33. conjunctivitis
2. immuni*	34. Allergic conjunctivitis
3. vaccination	35. conjunctivit*
4. vaccine	36. rhinoconjunctivit*
5. vaccin*	37. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
6. 1 or 2 or 3 or 4 or 5	38. food allergy
7. allerg*	39. food allerg*
8. hypersensitivit*	40. food hypersensitivity
9. atop*	41. food hypersensitivit*
10. react* allerg*	42. food sensit*ation*
11. 7 or 8 or 9 or 10	43. 38 or 39 or 40 or 41 or 42
12. asthma	44. anaphylaxis
13. asthm*	45. anaphyla*
14. night cough*	46. anaphylaxis react*
15. wheez*	47. anaphylactic react*
16. respiratory hypersensitivity	48. anaphylactic shock
17. hyper-responsiveness wheez*	49. anaphylactoid syndrome
18. allergic alveolitis	50. anaphylactoid shock
19. 12 or 13 or 14 or 15 or 16 or 17 or 18	51. idiopathic anaphylaxis
20. eczema	52. acute systemic allergic react*
21. eczem*	53. 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
22. dermatitis, atopic	54. sensiti*ation*
23. neurodermatitis	55. skin prick test
24. dermatiti*	56. RAST
25. urticaria	57. Radioimmunosorbent test
26. pruritis	58. 54 or 55 or 56 or 57
27. prurigo	59. drug allergy
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	60. drug allerg*
29. allergic rhinitis	61. drug hypersensitivit*
30. hay fever	62. 59 or 60 or 61
31. Rhinitis, Allergic, seasonal	63. 11 or 19 or 28 or 37 or 43 or 53 or 58 or 62
32. nasal obstruction	64. 6 and 63
	65. limit 64 to clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or observational study or pragmatic clinical trial or randomized controlled trial

Figure S1: Directed Acyclic Graph



Abbreviation	Description
SES	Socio-economic status
hx	history
POG	Period of gestation
ETS	Environment tobacco smoke

Table S2: Exposures and Outcomes assessed in the chosen studies

Reference	Exposure assessed (Childhood vaccine)															Control s	Outcome assessed (allergic outcome)								Age at which the outcomes were assessed (years)	
	Cases																									
	BCG	Diphtheria	Tetanus	Pertussis (wc/ ac)	Measles	Mumps	Rubella	Pneumococcus	meningococcal	Hepatitis B	Hib	DTP (wc/ ac)	MMR	OPV/IPV	Other		Asthma / wheezing	Atopic dermatitis/ eczema	rhino conjunctivitis Allergic rhinitis Hay fever	Food allergy	Atopic outcomes (umbrella term)	Allergic manifestation/ sensitisation	SPT	IgE		
RCTs																										
Kiraly et al, 2013 ¹	*											*			Vit A						* Based on SPT		*3 house dust mites, and cow’s milk, egg and peanut		3 – 9	
Nilsson et al, 1998 ²												*/ *				DT						*based on SPT	*milk, egg, 2 house dust mites, cat dog, timothy and birch		7/12, 2 – 5	
Nilsson et al, 2003 ³												*/ *				DT						*based on SPT	*cat, birch, timothy, 2 house dust mites		7	
Steenhuis et al, 2008 ⁴	*															Placebo (Normal Saline)	*	*	*	*				*	4/12, 18/12	
Thostesen et al, 2018 ⁵	*															-		*							13/12	
Thostesen et al, 2017 ⁷	*															-				*				*	3/12, 13/12	
Thostesen et al, 2017 ⁸	*															-	*								13/12	
	Prospective Cohort Studies																									
Henderson et al, 1999 ²¹				*												-	*								6/12,18/12,30/12,42/12	
Jedrychowski,et al 2004 ²²					*											-	*					*mother reported			9,10,11	

Reference	Exposure assessed (Childhood vaccine)														Outcome assessed (allergic outcome)								Age at which the outcomes were assessed (years)		
	Cases													Control s											
	BCG	Diphtheria	Tetanus	Pertussis (wc/ ac)	Measles	Mumps	Rubella	Pneumococcus	meningococcal	Hepatitis B	Hib	DTP (wc/ ac)	MMR	OPV/IPV	Other		Asthma / wheezing	Atopic dermatitis/eczema	rhino conjunctivitis Allergic rhinitis Hay fever	Food allergy	Atopic outcomes (umbrella term)	Allergic manifestation/sensitisation	SPT	IgE	
Kemp et al, 1997 ²³					*							*		*			*	*				*based on rhinitis, food allergy, urticaria and drug allergy			5, 10, 15 (followed up annually)
Kiraly et al, 2016 ²⁴												ac				Late DTaP	*	*		*		* based on SPT	*egg, peanut and sesame	*	3 –7
Matheson et al, 2010 ²⁶		*	*	*								*		*	Small pox	-	*								44
Nakajima et al, 2007 ²⁷		*	*	*										*	Small pox		*	*	*	*					7,13,30
Spycher et al, 2009 ²⁸				*												-	*								5 –9 followed up 4 years annually
Thomson et al, 2010 ²⁹												*	*	*	Combi ned DT, infecti on		*	*	*						6
Townley et al, 2004 ³⁰	*															-						*based on SPT, questionn aire	*2 house dust mites, 3 fungi, 2 grass, cockroach, cat, dog, egg, milk, shrimp		9 –12/12

Reference	Exposure assessed (Childhood vaccine)															Outcome assessed (allergic outcome)								Age at which the outcomes were assessed (years)	
	Cases														Control s										
	BCG	Diphtheria	Tetanus	Pertussis (wc/ ac)	Measles	Mumps	Rubella	Pneumococcus	meningococcal	Hepatitis B	Hib	DTP (wc/ac)	MMR	OPV/IPV	Other		Asthma / wheezing	Atopic dermatitis/ eczema	rhino conjunctivitis Allergic rhinitis Hay fever	Food allergy	Atopic outcomes (umbrella term)	Allergic manifestation/ sensitisation	SPT	IgE	
Wang et al, 2012 ³¹											*	*		*/ *		DTP-OPV	*	*							6/12,18/12
	Birth Cohorts																								
Grabenhenrich et al, 2014 ¹²	*												*		TBE	-	*					Allergic asthma#		*	20
Grüber et al, 2003 ¹³											*	*	*	*	TBE		*	*	*					*	3/12,6/12,12/12,18/12,2,3,4,5
Grüber et al, 2001 ¹⁴	*															-	*	*	*					*	3/12,6/12,12/12,18/12,2,3,4,5,6,7
Kummeling et al, 2007 ¹⁵											*	*		*			*	*							7/12, 1
Lewis and Britton, 1998 ¹⁶					*										Measles infection	-			*						5, 10, 16
Maitra et al, 2004 ²⁵												*			DT	-	*				*based on SPT		*3 allergens (not specified)		69 –81/12, 91/12 SPT-7
McKeever et al, 2004 ¹⁷												*	*	*			*	*							?
Timmermann,et al, 2015 ¹⁸													*				*	*	*				* birch, grass, cat, dog and house dust mite	*	5,7,13
Venter et al, 2016 ¹⁹				ac												wc	*	*	*	*			*milk, egg, wheat, peanut, sesame, cod		1,2,3, 10

Reference	Exposure assessed (Childhood vaccine)														Outcome assessed (allergic outcome)							Age at which the outcomes were assessed (years)				
	Cases													Control s												
	BCG	Diphtheria	Tetanus	Pertussis (wc/ ac)	Measles	Mumps	Rubella	Pneumococcus	meningococcal	Hepatitis B	Hib	DTP (wc/ac)	MMR	OPV/IPV	Other		Asthma / wheezing	Atopic dermatitis/ eczema	rhino conjunctivitis Allergic rhinitis Hay fever	Food allergy	Atopic outcomes (umbrella term)	Allergic manifestation/ sensitisation	SPT	IgE		
																							fish, house dust mite, cat and grass			
Farooqi et al, 1998 ²⁰				*	*										infecti on	-	*	*	*		*Based on asthma, eczema and hay fever					Not reported
	Studies with a prospective and a retrospective component																									
Destefano et al, 2002 ³²										*	*	*	*	*			*									>18/12
Hviid and Melbye, 2008 ³³													*			-	*									1-5
	Retrospective Cohorts																									
Aaby et al, 2000 ³⁴	*				*							*		*							* based on SPT		*	2 house dust mites and cockroach mix		3 – 14
Alm et al, 1997 ³⁵	*																*	*	*	*		urticaria	*birch cat, cldosporium,1 house dust mite, dog, horse mugwort, timothy, egg, cow’s milk, peanut, cod fish, soy		3 – 7	
Alm et al, 2002 ³⁶	*																				* based on		*birch cat, cldosporium,1	*	3-8	

Reference	Exposure assessed (Childhood vaccine)															Outcome assessed (allergic outcome)								Age at which the outcomes were assessed (years)	
	Cases														Control s										
	BCG	Diphtheria	Tetanus	Pertussis (wc/ ac)	Measles	Mumps	Rubella	Pneumococcus	meningococcal	Hepatitis B	Hib	DTP (wc/ac)	MMR	OPV/IPV	Other		Asthma / wheezing	Atopic dermatitis/ eczema	rhino conjunctivitis Allergic rhinitis Hay fever	Food allergy	Atopic outcomes (umbrella term)	Allergic manifestation/ sensitisation	SPT	IgE	
																					response s from question naire, SPT and IgE		house dust mite, dog, horse mugwort, timothy, egg, cow’s milk, peanut, cod fish, soy		
Bager et al, 2003 ³⁷	*															-	*		*		* based on IgE			*	POA: 6 – 12/52, 24/52
Bager et al, 2003 ³⁸															Small pox	-	*		*		* based on IgE			*	POA: 6 – 12/52, 24/52
Bernsen et al, 2003 ³⁹												*	*	*	DT	-	*	*			*based on asthma, eczema and allergy	*doctor diagnosed			6
Linehan et al, 2007 ⁴⁰	*															Late BCG (>12 m)	*								Between 6 – 11
Linehan et al 2013 ⁴¹	*															Late BCG (>12 m)	*	*	*						Between 13 – 17
Marks et al, 2003 ⁴²	*															-	*	*	*				*2 house dust mites, 3 fungi, cockroach, cat, rye, grass	*	7 – 14

Reference	Exposure assessed (Childhood vaccine)															Outcome assessed (allergic outcome)	Age at which the outcomes were assessed (years)
	Cases														Control s		
	BCG	Diphtheria	Tetanus	Pertussis (wc/ ac)	Measles	Mumps	Rubella	Pneumococcus	meningococcal	Hepatitis B	Hib	DTP (wc/ac)	MMR	OPV/IPV	Other		
McDonald et al, 2008 ⁴³												*				Timing of DTP	Not mentioned
Park et al, 2015 ⁴⁴	*															BCG scar neg	18 – 86
Sarinho et al, 2010 ⁴⁵	*															One BCG dose	10 – 25
Vogt et al, 2014 ⁴⁶												ac				wc	Up to 15 years

*-Exposures studied; \$-Combined results for all exposures given
7/12- 7 months; 3/12- 3 months, 18/12- 18 months; 12/52- 12 weeks etc.

Table S3: Study Quality of Randomised Controlled Trials by Cochrane collaboration risk of bias tool

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Other bias	Overall quality	Reviewer's comments
Kiraly et al ¹ , 2013 ¹	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk		Fair	The factorial design is on a subset of the initially randomised population. Thus, it is a small sample size
Nilsson et al ² , 1998 ²	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk		Fair	More details on the study extracted from another publication ²
Nilsson et al, 2003 ³	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk		Fair	More details on the study extracted from another publication ²
Steenhuis et al 2007 ⁴	Unclear	Unclear	Unclear	low risk	High risk: Parents were not blinded	Unclear		poor	Single Blind trial: Even though the controls were given a saline injection BCG vaccine cause local inflammation
Thostesen et al, 2018 ⁵	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	good	More information taken from

Reference	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Selective reporting (reporting bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Other bias	Overall quality	Reviewer's comments
									another publication ⁶
Thostesen et al ⁷ , 2017 ⁷	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	good	More information taken from another publication ⁶
Thostesen et al, 2017 ⁸	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	good	More information taken from another publication ⁶

Table S4: Quality assessment of the Cohort Studies Using the Newcastle-Ottawa Scale and conversion into Agency for Health Research and Quality (AHRQ) standards

Reference	Selection				Comparability	Outcome			Reviewer's comments	AHRQ Quality
	Representativeness of the exposed	Selection of non-exposed	Exposure ascertainment	Outcome of interest not present at start of study	Comparability of cohorts based on design or control for confounders	Assessment of Outcome	Sufficient follow-up	Adequate follow-up		
Prospective cohort studies										
Henderson et al, 1999 ²¹	b*	a*	a*	b	a*	c	a*	c		fair
Jedrychowski et al, 2004 ²²	b*	a*	a*	b	a*	c	a*	b*		good
Kemp et al, 1997 ²³	a*	a*	a*	b	c	a*	a*	b*		poor
Kiraly et al, 2016 ²⁴	b*	a*	a*	a*	a*	a*	a*	b*		good
Matheson et al, 2010 ²⁶	b*	a*	a*	b	a*	c	a*	b* (78% at 44 years)		good
Nakajima et al, 2007 ²⁷	a*	a*	c	b	a* b*	c	a*	b*		fair
Spycher et al, 2009 ²⁸	a*	a*	a*	b	a* b*	b*	a*	c		good
Thomson et al, 2010 ²⁹	b*	b*	b*	b	a* b*	c	a*	b*		good
Townley et al, 2004 ³⁰	b*	a*	a*	b	c	c	a*	c		poor

Reference	Selection				Comparability	Outcome			Reviewer's comments	AHRQ Quality
	Representativeness of the exposed	Selection of non-exposed	Exposure ascertainment	Outcome of interest not present at start of study	Comparability of cohorts based on design or control for confounders	Assessment of Outcome	Sufficient follow-up	Adequate follow-up		
Wang et al, 2012 ³¹	a*	a*	a*	b	a* b*	c	a*	b*		good
Birth Cohorts										
Grabenhenrich et al, 2014 ¹²	b*	a*	b*	b	a*	a/b*	a*	c		good
Grüber et al, 2003 ¹³	b*	a*	a*	b	c	a*	a*	71% (checked dropouts)-b*?		poor
Grüber et al, 2001 ¹⁴	b*	a*	a*	b	c	a*	a*	74.4% b*?		poor
Kummeling et al, 2007 ¹⁵	b*	b	b*	b	a* b*	c	a*	b*		fair
Lewis and Britton, 1998 ¹⁶	b*	a*	b*	b	a*	c	a*	c		fair
Farooqi et al, 1998 ²⁰	b*	a*	a*	b	c	b*	a*	a*		poor
Maitra et al, 2004 ²⁵	a*	a*	a*	b	a* b*	c	a*	c/d		
McKeever et al, 2004 ¹⁷	b*	a*	a*	b	a* b*	b*	a*	b*		good
Timmermann et al, 2015 ¹⁸	b*	a*	a*	b	c	a*	a*	b*		poor

Reference	Selection				Comparability	Outcome			Reviewer's comments	AHRQ Quality
	Representativeness of the exposed	Selection of non-exposed	Exposure ascertainment	Outcome of interest not present at start of study	Comparability of cohorts based on design or control for confounders	Assessment of Outcome	Sufficient follow-up	Adequate follow-up		
Venter et al, 2016 ¹⁹	a*	a*	a*	b	a-*	a*	a*	b*		good
Studies with a prospective and a retrospective components										
Destefano et al, 2002 ³²	a*	a*	a*	b	a*	b*	a*	d- no statement-167240 included from more than 500000 initial records?!?		good
Hviid and Melbye, 2008 ³³	a*	a*	a*	b	a*	b*	a*	b*		good
Retrospective cohort studies										
Aaby et al, 2000 ³⁴	b*	a*	a*	b	a*	a*	a*	c	More information on the study taken from another publication on this study ⁹	good
Alm et al, 1997 ³⁵	b*	a*	c	b	c	a *	a*	b*		poor
Alm, 2002 ³⁶	b*	a*	c	b	c	a *	a *	b*		poor

Reference	Selection				Comparability	Outcome			Reviewer's comments	AHRQ Quality
	Representativeness of the exposed	Selection of non-exposed	Exposure ascertainment	Outcome of interest not present at start of study	Comparability of cohorts based on design or control for confounders	Assessment of Outcome	Sufficient follow-up	Adequate follow-up		
Bager et al, 2003 ³⁷	b *	a *	a*	b	c	atopy- a asthma and allergic rhinitis- c star???	a*	b*		poor
Bager et al, 2003 ³⁸	b *	a *	a*	b	c	atopy- a asthma and allergic rhinitis- c star???	a*	b*		poor
Bernsen et al, 2003 ³⁹	a*	a*	a*	b	a* b*	b*	a*	b*		good
Linehan et al, 2007 ⁴⁰	b*	a*	a*	b	a/b*	b*	a*	c		good
Linehan et al, 2013 ⁴¹	b*	a*	a*	b	a/b*	b*	a*	c		good
Marks et al, 2003 ⁴²	b*	b	a*	b	a *	c	a*	b*		fair
McDonald et al, 2008 ⁴³	a*	a*	a*	a*	a* b*	b*	a*	b*		good
Park et al, 2015 ⁴⁴	b*	a*	a*	b	a*	a*	a*	a*		good
Sainho et al, 2010 ⁴⁵	c	a*	a*	b	c	b*	a*	a*		poor
Vogt et al, 2014 ⁴⁶	a*	b	a*	b	b*	b*	a*	a*		fair

a, b, c, *- the appropriate scale item/s in the NOS

**NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (NOS)
COHORT STUDIES**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative of the average _____ (describe) in the community *
 - b) Somewhat representative of the average _____ in the community *
 - c) Selected group of users e.g. nurses, volunteers
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort *
 - b) Drawn from a different source
 - c) No description of the derivation of the non-exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g. surgical records) *
 - b) Structured interview *
 - c) Written self-report
 - d) No description
- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes *
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis*
 - a) Study controls for _____ (select the most important factor) *
 - b) Study controls for any additional factor *(This criterion could be modified to indicate specific control for a second important factor.)

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment *
 - b) Record linkage *
 - c) Self report
 - d) No description
- 2) Was follow-up long enough for outcomes to occur
 - a) Yes (select an adequate follow up period for outcome of interest) *
 - b) No
- 3) Adequacy of follow up of cohorts
 - a) Complete follow up - all subjects accounted for *
 - b) Subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
 - c) Follow up rate < ____% (select an adequate %) and no description of those lost
 - d) No statement

Thresholds for converting NOS to AHRQ standards:

Good- 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair- 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor- 0 or 1 star in selection domain 0 stars in comparability domain AND 0 or 1 star in outcome/exposure domain

Table S5: Detailed Characteristics of the publications used for the qualitative synthesis

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
RCTs					
Kiraly et al. European Journal of Allergy 2013 ¹ , Guinea-Bissau (West Africa)	Guinea-Bissau Health Project (N=289) (N=281) Factorial design (BCG and Vit A) Separate RCTs for extra dose of Measles and DTP	BCG & Vit A (2x2 factorial), DTP, Extra measles vaccine vs no extra vaccine	Atopy (defined as positive SPT, or asthma, eczema, food allergy –By ISAAC questionnaire or Reaction to food)	NR	None
Nilsson et al. Arch Pediatr Adolesc Med 1998 ¹⁰ , Sweden	Infants from the Swedish pertussis vaccine trial (N=669) Double Blind RCT	Pertussis 2-c, 5-c, WC vs. DT	Any atopic disease By questionnaire + medical records + clinical examination	NR	None
Nilsson et al. Arch Pediatr Adolesc Med 2003 ¹¹ , Sweden	Infants from the Swedish pertussis vaccine trial (N=667) Double Blind RCT	Pertussis Pa2, Pa5, WC vs. DT	Asthma, AD, allergic disease, AR, SPT By interviewer administered questionnaire	NR	None;
Steenhuis et al, Clinical and Experimental Allergy 2008 ⁴ Netherlands	Newborns from high risk families (N=121) Single-blind RCT	BCG vs saline placebo	Asthma, AR, Eczema, Food allergy Survey, Physical examination, Lung function tests, Immune parameters in peripheral blood, IgE, Overall statistical score for allergy	NR	Eczema and use of eczema drugs: weak protective effect s
Thostesen et al. Allergy 2018 ⁵ , Denmark	Danish Calmette Study, (N=4262) Double Blind RCT	BCG vs none	AD clinical examination or parental report of a Doctor confirmed diagnosis (telephone interviews)	NR	Protective, NNT= 21
Thostesen et al., Pediatr Allergy Immunol 2017 ⁷ , Denmark	Danish Calmette Study, (N=4262) Double Blind RCT	BCG vs none	Allergic sensitisation and food allergy telephone interviews and clinical ex.	NR	None

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
Thostesen et al. JACI, 2017 ⁸ , Denmark	Danish Calmette Study, (N=4262) Double Blind RCT	BCG vs none	Recurrent wheeze physician-diagnosed, Clinical ex/ auscultation:	NR	None
Birth Cohorts					
Grabenhenrich et al. JACI 2014 ¹² Germany	German atopy risk enhanced sample from MAS-90, 20 year follow up (N=941/1,314)	BCG, TBE vaccine, MMR National data base	Asthma face to face, telephone and online questionnaires	Parent allergic diseases, socio-economic factors, cord blood IgE, sex, smoking during pregnancy, day care	Protective*
Grüber et al. Pediatrics 2003 ¹³ , Germany	German atopy risk enhanced sample from MAS-90, 5 years follow up (N=1314)	DTP, MMR, OPV, Hib, TBE vaccination records	AD, Allergic sensitization, Asthma, allergic rhinitis, total serum IgE questionnaire and structured interview, Physical ex. - physician	Parental education	Protective#
Grüber et al, Pediatrics, 2001 ¹⁴ , Germany	German atopy risk enhanced birth cohort sample from MAS-90, 2 years follow up, (N=1314),	BCG Vaccination documents	AD, recurrent wheezing, allergic rhinitis Physical examination		None
Kummeling et al. Pediatr Allergy Immunol 2007 ¹⁵ , Netherlands	Infants in the KOALA birth cohort, (N=2,764/2,834)	DPTT, Hib Parent reported vaccination history verified in a random sample of 300 by cross checking with the vaccination records	Eczema, recurrent wheeze questionnaire	history of allergy, sibling history of allergy, number of older siblings, breast feeding duration, day care attendance, pets, exposure to ETS, antibiotic exposure through breastfeeding, antibiotic exposure through medication and sub-cohort	None*
Lewis and Britton. Clinical and Experimental Allergy 1998 ¹⁶ , UK	British Birth Cohort (N=6350)	Measles Parental interviews	Allergic rhinitis Parental interviews	Sex, social advantage, BF duration, birth order maternal smoking	Protective*

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
McKeever et al. American Journal of Public Health 2004 ¹⁷ , UK	West Midlands General Practice Research Database. (N=29,238)	DPPT, MMR West Midlands General Practice Data base	Eczema, asthma Oxford Medical Information System (ICD-8)	Consulting frequency	Higher risk *
Timmermann et al Pediatr Allergy Immunol, 2015 ¹⁸ , Faroe Islands	Faroe Islands Birth cohort, (N=555)	MMR Vaccination cards and maternal interview	Asthma hypersensitivity, ARC, Eczema, SPT, Total IgE Parent questionnaire, interview and examination by a paediatrician	Birth weight and family history of chronic bronchitis/asthma	Protective*
Venter et al, JACI 2016 ¹⁹ , UK	Isle of Wight (FAIR) birth cohort(N=819)	aP vs wP	Food allergy (IgE), SPT Questionnaires combined with parent interviews	Family history of asthma/ hay fever, breast feeding and sex	None*
Farooqi et al, BMJ 1998 ²⁰ , UK	Oxfordshire Family practice Birth Cohort: (N=1934)	wP, Measles medical records	Atopy, asthma, eczema, allergic rhinitis medical records	Social class, year of birth, number of visits to the family doctor in early childhood	Weak higher risk*
Prospective Cohort Studies					
Henderson et al, BMJ 1999 ²¹ , UK	Avon longitudinal study of pregnancy and childhood. (N=9,444)	Pertussis Avon computerised record of child immunisations	Wheezing illness structured questionnaire	Highest level of maternal education, ethnic origin of the child, number of children in the household, crowding in the home, damp or mould in the house, presence of cats in the house, financial difficulties reported by the mother, gender, maternal age, duration of breast feeding, maternal smoking during pregnancy, exposure of the child to tobacco smoking, use of day care services, birth weight and the gestation	None*

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
Jedrychowski et al International Journal of Occupational Medicine and Environmental Health , 2004 ²² Poland	9 years old School children in 12 primary schools N= 1005	Measles vaccination records kept with school nurse	Chronic respiratory symptoms, asthma and allergy Mother reported (physician diagnosed?)	Gender, education of parents, outdoors air traffic pollution, exposure to environment tobacco smoking, smoking of mother during pregnancy, and mould on the house walls, ETS, household heating system and moulds/dampness problems, residence in the city area, and the level of traffic pollution.	Protective*
Kemp et al, Epidemiology 1997 ²³ , NZ	Christchurch Health and Development Study N=1265	OPV+DTP measles recorded in the maternal diary provided by the investigators Crosschecking with the family doctor when diary records were vague or inconsistent	Asthma, eczema and other allergic disease medical diary, direct questioning and from the family doctor	ethnicity, socio-economic status, parental smoking, and pet ownership	Higher risk*
Kiraly et al, European Journal of Allergy and Clinical Immunology 2016 ²⁴ , Australia	HealthNuts study, (N=4856)	DTaP On-time vs late From parents, Australian Childhood Immunisation Register (ACIR)	Food allergy (SPT or IgE) reported by parents or diagnosed by doctor/ trained nurse on recruitment, eczema and use of eczema medication	Sex, SEIFA quintile, siblings, antibiotic use, childcare attendance, smokers at the home and parent country of birth	Delayed DTaP- Protective for eczema*
Maitra et al. BMJ 2004 ²⁵ , UK	Avon longitudinal study of pregnancy and childhood. (N=13,810/13 971)	Pertussis Child health surveillance database	Asthma, Wheeze, atopy Parental reporting from questionnaire, physical ex-physician, SPT	Maternal education, maternal smoking during pregnancy, maternal history of asthma, or eczema, maternal financial	None*

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
				difficulties, damp housing, overcrowding, child's ethnicity, number of siblings, contacts with cats in the home, duration of breast feeding and exposure to tobacco smoking Maternal age at delivery, birth weight, sex, gestational age	
Matheson et al. Pediatr Allergy, Immunol 2009 ²⁶ , Australia	Tasmanian Longitudinal Health Study (TAHS). (N=5729)	Diphtheria, Tetanus, Pertussis, Polio Smallpox, DTP school medical records	Asthma, eczema, food allergy, hay fever Postal survey	Sex, history of bacterial infection, birth order and social class	None*
Nakajima et al. Thorax 2007 ²⁷ , Australia	Tasmanian Longitudinal Health Study (TAHS). (N=8,443)	DTP, Polio, Small pox school, medical reports (parent reported)	Asthma, Eczema, Food allergies, Hay fever in 1968 and 1971 parents reported in 1991 pro-bands themselves reported	Sex, birthplace, history of bacterial infection, parental smoking, parental asthma, history of viral infection, birth order and history of pneumonia	None*
Spycher et al Pediatrics.2009 ²⁸ , United Kingdom	Population based Cohort Study Leicestershire, UK. (N=6048/6,811) (5,863 fully vaccinated, 106 partially vaccinated and 79 non-vaccinated)	Pertussis vaccine Specialist Community Child Health Services, Leicester City Primary Care Trust	Asthma	Gender, age, ethnicity, Townsend score, overcrowding, single parenthood, duration of breast feeding, birth weight, maternal smoking during pregnancy and number of smokers at home	None*
Thomson et al, Pediatr Allergy Immunol 2010 ²⁹ , Australia	Infants in the Melbourne Atopy Cohort Study (MACS) (N=620)	DTP, CDT, Sabin vaccine, MMR telephone questionnaire	Asthma, AR, eczema Diagnosis by physician	Otitis media, LRTI, gastrointestinal infections, gender, older siblingss, mother's and father's SE	Sabin- protective for asthma CDT- higher risk for asthma*

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
				characteristics and medical history (education, marital status, smoking, asthma, eczema allergic rhinitis food allergy and drug allergy)	
Townley et al, Annals of Allergy, Asthma and Immunology 2004 ³⁰ Turkey, Thailand, Argentina	Multinational sample N=1704	BCG ISAAC questionnaire, physician/hospital record	PPD test, SPT for common allergens, atopy and allergy ISAAC questionnaire		Protective
Wang et al, Journal of the Formosan Medical Association 2012 ³¹ , Taiwan	Taiwan Birth Cohort Study. (N=19,968)	DTP-Hib & OPV D Child Health Card government computerized Immunization system	AD, recurrent wheezing Home interview using a structured questionnaire Diagnosis by a physician	Gender, maternal education and nationality, maternal history of atopy, family income place of residence, duration of breast feeding, older siblings, fungi on house walls and environmental tobacco smoke exposure	Hib combination vaccines: Minimal risk for AD *
Studies with a prospective and a retrospective component					
Destefano et al. Pediatr Infect Dis J 2002 ³² , USA	Children enrolled in HMO from birth to at least 18 months. (N=167, 240)	DTP, OPV, Hib, MMR, Hep B Computerized immunisation tracking systems maintained by the HMOs	Asthma computerized medical encounter and pharmacy data bases	Stratified by HMO and month and year of birth and adjusted for gender, low birth weight, vaccines in the table	DTP, OPV, MMR- None* Hib, Hep B- higher risk (weak)*
Hviid and Melbye, American Journal of Epidemiology 2008 ³³ Denmark	Danish Nation-wide cohort study, (N=871,234)	MMR National Board of Health register	In patients with asthma or status asthmaticus, anti-asthma medication Danish National Hospital Registry and Danish Prescription Drug Database	Age, calendar period, hospitalization propensity in infancy, birth weight, place of birth, mother's country of birth, infant vaccine compliance, birth order, maternal age at birth, sex	Protective*

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
Retrospective Cohort Studies					
Aaby et al., Clinical and Experimental Allergy 2000 ³⁴ Guinea-Bissau (West Africa)	Population based, N=400	BCG, Measles DTP/OPV Vaccine info: health cards/ project population register	Atopy (SPT) questionnaire	Sex, current age, district, season of testing (dry/ rainy), place of birth (home/hospital, in Bissau, outside Bissau), Mother's schooling, older siblings, measles infection, other vaccination (BCG, DTP/polio, measles)	BCG vaccine given early maybe protective*
Alm et al. Lancet 1997 ³⁵ , Sweden	Nordic children born in 1989-1992 with atopic heredity vs controls N=1196 (Cases-216 controls-980)	BCG child welfare centre records, confirmation of BCG scar	Asthma, AD, rhino conjunctivitis, urticaria, food allergy, SPT, IgE questionnaire	None	None
Alm et al. Genes and Immunity 2002 ³⁶ , Sweden	Same cohort of 3-8 years old children with atopic heredity vs controls N=574 (Cases-216 Controls-358)	BCG child welfare centre records, confirmation of BCG scar	SPT, atopic disease, IgE, Genotyping of <i>LC11A1</i> (formerly <i>NRAMP1</i>) gene	Interactions: <i>SLC11A1</i> GT alleles and <i>D2S1471</i> alleles	Higher risk
Bager et al. Clinical and Experimental Allergy 2003 ³⁷ , Denmark	Pregnant women living in Copenhagen, identified through Danish National Birth Cohort; (N=2176)	BCG school health records telephone calls	Asthma, allergic rhinitis, IgE telephone calls	Birth cohort, sib-ship size, age of the woman's mother at birth, social class in childhood	None*
Bager et al. JACI 2003 ³⁸ , Denmark	Pregnant women living in Copenhagen identified through Danish National Birth Cohort, (N=2181)	small pox school health records	Asthma, allergic rhinitis, IgE telephone calls	Birth cohort, sib-ship size, age of the woman's mother at birth, social class in childhood	Weak higher risk*
Bernsen et al. Eur Respir J 2003 ³⁹ , Netherlands	Children born in 1988, 1989 or 1990 in Zwijndrecht (N=1724)	DTP (WC), MMR Booster DT, Polio preventive health check-up files	any type of allergy, asthma, eczema preventive health check-up files	Birth order, family size, year of birth, atopy of the father, age of mother at birth	Whole cell Pertussis may be protective *

Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
Linehan et al. JACI 2007 ⁴⁰ , UK	Manchester Community asthma study: MANCAS (N= 2414)	BCG ISAAC questionnaire and Immunisation records held by the PCT	Wheeze Parents completed ISAAC questionnaire	Sex, history of hay fever or eczema, family history of asthma	Protective*
Linehan et al. JACI 2014 ⁴¹ , UK	Manchester Community asthma study 2: MANCAS 2 (N= 1608)	BCG health authority records	Wheeze, hay fever, AD Postal questionnaire		None*
Marks et al. JACI 2003 ⁴² , Australia	Children born to mothers with South Asian origin in Sydney Cases: 309 (locality A) Controls: 442 (locality B)	BCG health records And independent examination for BCG scar by two examiners	Wheeze, hay fever, AD, SPT, IgE, spirometry, TST reaction size, γ IFN to PPD, parental questionnaire	Sex, family history of asthma/ allergy, mothers' country of birth, any positive SPT	High risk Subgroup: Protective*
McDonald et al. JACI 2008 ⁴³ , Canada	Children born in Manitoba in 1995 N=13,980	DTP whole cell vaccine timing Manitoba Immunisation Monitoring system data base	Asthma From Health care records, data from the Manitoba Health Services Insurance Program, Records of Physician reimbursement for medical care	Sex, maternal history of asthma, urban/rural location, household income, number of siblings, number of courses of antibiotics and number of health care visits	Delay in administering 1 st dose- Protective*
Park et al. Int. J.Med.Sci 2015 ⁴⁴ , Korea	Pulmonology clinic attendees, (N=200)	BCG (scar) Routinely recorded by an examiner since 2009	SPT, Lung function tests and methacholine/ mannitol challenge	Sex, age	BCG scar- protective*
Sarinho et al. J Bras Pneumol 2010 ⁴⁵ , Brazil	High socio-economic group with health insurance from Para (N=2311)	BCG (frequency) data base	Asthma Diagnosis of asthma made by the physician during 10 years : data base		None
Vogt et al. Pediatrics 2014 ⁴⁶ , Sweden	Cases: N= 79,705- from RCT Controls: N=21485- from the population (Linköping)	DTaP from a RCT	Asthma medication: Swedish medical birth register and	Maternal age, mother's country of birth, gestational age, LSCS,	None*

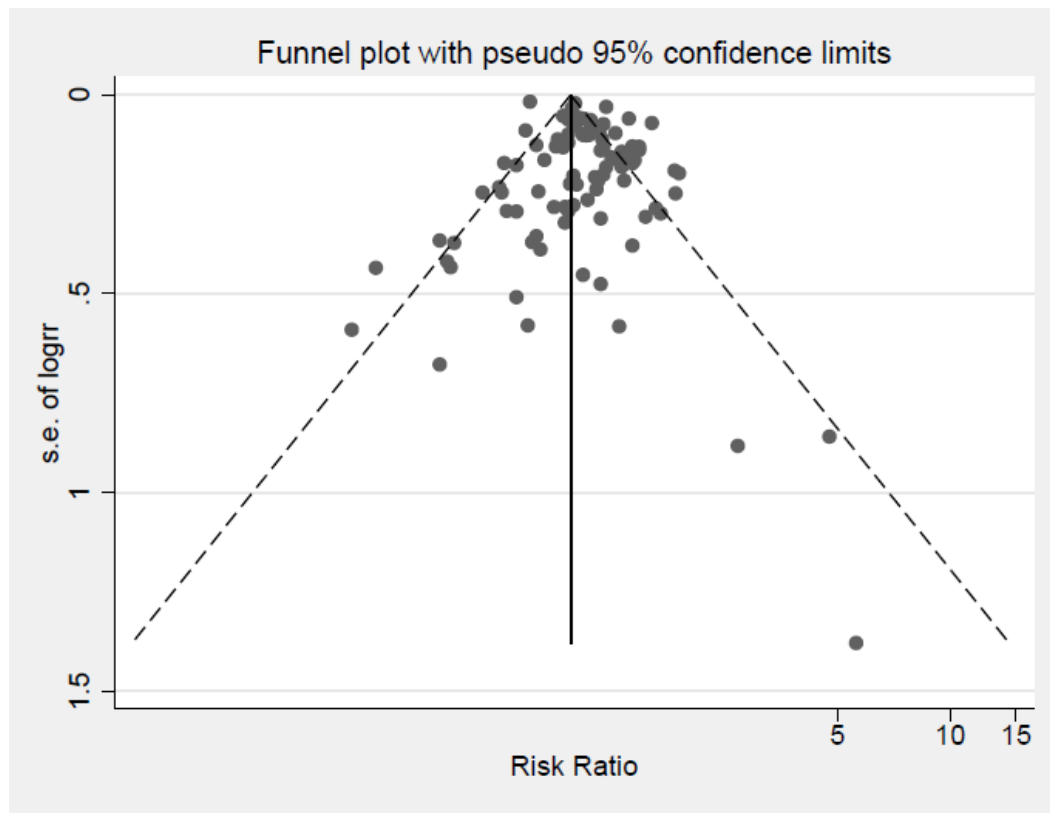
Reference, country	Study sample/ Type	Exposure/ Source	Outcome/ Source	Confounding factors/ interactions included in model	Nature of the association
			Swedish Prescribed drug register	maternal smoking, asphyxia, mother's BMI, parity, mother's asthma medication	

* Adjusted for a minimum set of Confounders

Adjusted only for age and sex

Abbreviations: Vit. - Vitamin; 2-c/ Pa2- two component acellular pertussis vaccine; 5-c/ Pa5- five component acellular pertussis vaccine; γ IFN- γ interferon; Hib- Haemophilus influenza type b; Hep B- Hepatitis

Figure S2: Funnel plot for publication bias for the estimates used in the meta-analysis



s.e.. of logrr- standard error of logarithm relative risk (risk ratio)

Note: The symmetric nature of the funnel plot suggests that publication bias is unlikely

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