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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, I^2= 0.0%), asthma (RR= 0.78; 95% CI= 0.62 – 0.98, I^2= 93.9%) and, with a similar, statistically non-significant reduction in sensitisation (RR= 0.78; 95% CI= 0.61 – 1.01, I^2= 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 affluent[2-5]. According to the Global Asthma Network, currently there are 334 million people living with asthma worldwide[6], 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 allergies[7]. 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 diseases[8-10].

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 disease[11].

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 1994[12], 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) vaccines[15-19]. 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 vaccinesand 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 evidence[20].

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 smokeand 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) accordingly[22]**.**

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 vaccine[27]. 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% respectively[28]. Studies with similar exposure and outcome variables were pooled using the statistical software Stata version14[29]. 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 one RCTs; 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-Bissau[30], Sweden[31,32], Netherlands[33] and Denmark[34-36]. The numbers of participants in these studies ranged from 121 – 4262. Except for the RCT by

Steenhuis et al[33] 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 birth[34-36] (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 group[34-36], whilst the other, carried out in the Netherlands, used normal saline as a placebo control[33].

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 months[33] and 13 months[36]; two reported on associations with atopic dermatitis/ eczema[33,35] at the age of 4, and 18 months[33] and 13 months[35]; two reported on outcomes of food allergy[33,34], at the age of 4, and 18 months[33] and 13 months[34]; one on the development of rhinoconjunctivitis/ rhinitis/ hay fever[33] at the age of 4 and 18 months, three reported on atopic / allergic outcomes based on SPT[30-32] at 3-9

years[30], 7 months, 2.5 years[31] and 7 years[32]. The effect measures were reported as increase in risk[31], odds ratios[30,32] and relative risks[33-36].

Summary of RCT findings (Tables1 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 al[33] was performed in a high-allergy risk population while the study by Thostesen et al[34-36] was population based. However, Thostesen et al[35] 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/ study[33] 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 Argentina[25]. There were 9 studies from the United Kingdom[19,37-44], 5 from Australia[27,45-48], 4 from Denmark[49-52], 3 from Germany[53-55], 2 from Netherlands[26,56], 3 from Sweden[57-59] and 1 each from New Zealand[60], Poland[61], Canada[62], United States of America[63], Korea[64], Brazil[65], Guinea Bissau[66], and Taiwan[67]

Exposures (Tables 1, S2 and S5)

Of the 35 publications from a total of 29 cohort studies one prospective cohort[25], 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 dose[65].

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 vaccine[45]. 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 al[27], the controls received acellular pertussis vaccine in the form of DTaP later than the accepted schedule. In the study by Venter et al[37] 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 al[67], 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 al[63] looked at the allergic outcomes following small pox vaccination in childhood.

Outcomes (Table S2)

All cohorts except one prospective cohort[25], one birth cohort[40] 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 cohort[37], 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 outcomes[59] 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 al[56] found evidence of a reduced risk of allergic outcomes following whole cell pertussis vaccination. In contrast, the study by Farooqi[42] found an increased risk of allergic outcomes with the same vaccine. The control group in the former[56] was very small representing only 2% of the population, compared with 25% in the latter[42]. 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 al[42] (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. Al [,56] 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 al[42] 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 other[61]. 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 al[12] suggesting a possible cross-sectional link between vaccination with whole-cell pertussis vaccine and increased risk of asthma. Further cross-sectional studies from New Zealand[60] and the UK[42]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 injections[69]. This Th2 mediated response seemed more common in atopic children[68].

However, other systematic reviews on atopic risk reported contrary results. A systematic review[17]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 sensitisation[18], 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 caution[33]. Further, the nature of the populations studied renders generalizability of the results doubtful.

Furthermore, contrary to Arnoldssen et al[18] and Linehan et al[19] 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 study[61]. 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 al[27]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 al[37] 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 response[53].

Similarly, the pooled estimate from three cohort studies that used a whole-cell pertussis vaccine showed no effect on eczema risk. Bernsen et al[56]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 vaccine[42]. 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 studies[15-17] except for Arnolessen et al[18] and Linehan et al[19] 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 noteworthy, 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, asthma, eczema, 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#
Grüber et al, 2001[54], Germany	German atopy risk enhanced birth cohort sample	BCG	AD, recurrent wheezing, allergic	None

Reference, country	Study sample	Exposure	Outcome	Nature of the association
	from MAS-90, 2 years follow up, (N=1,314)		rhinitis	
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=29,238)	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=9,444	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 Smallpox, DTP	Asthma, eczema, food allergy, hay fever	None*

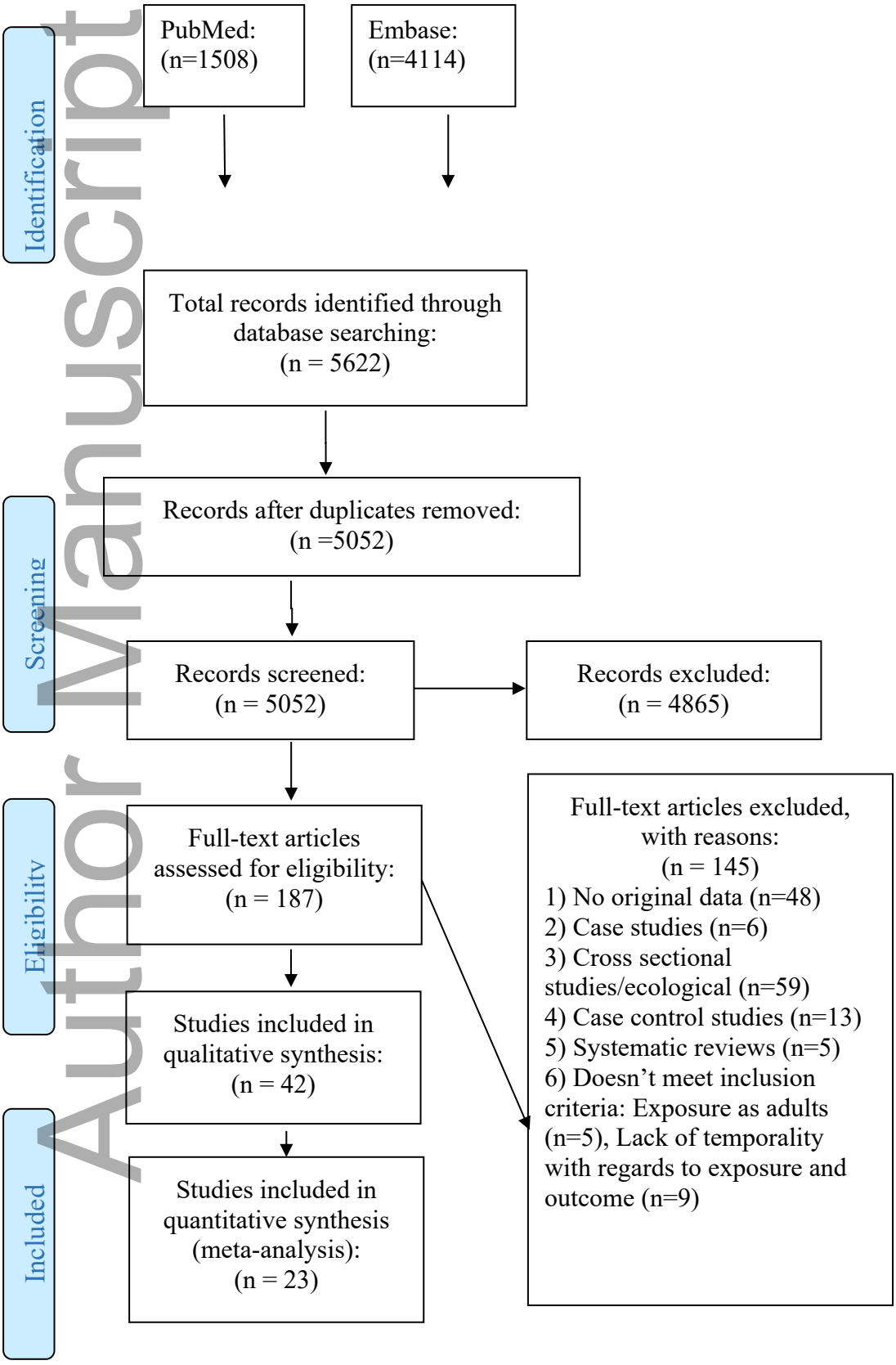
Reference, country	Study sample	Exposure	Outcome	Nature of the association
Nakajima et al. 2007[46], Australia	Tasmanian Longitudinal Health Study (TAHS). (N=8,443)	DTP, Polio, Small pox	Asthma, Eczema, Food allergies Hay fever	None*
Spycher et al.2009[39], United Kingdom	Population based Cohort Study 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 *LC*11A1 (formerly NRAMP1) gene	Higher risk
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*

Reference, country	Study sample	Exposure	Outcome	Nature of the association
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, ɤIFN to PPD	High risk Subgroup: Protective*
McDonald et al. 2008[62], Canada	Children born in Manitoba in 1995 N=13,980	DPT whole cell vaccine timing	asthma	Delay in administering 1st 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; ɤIFN- ɤ interferon; Hib- Haemophilus influenza type b; Hep B- Hepatitis

Figure 1: PRISMA flow Diagram



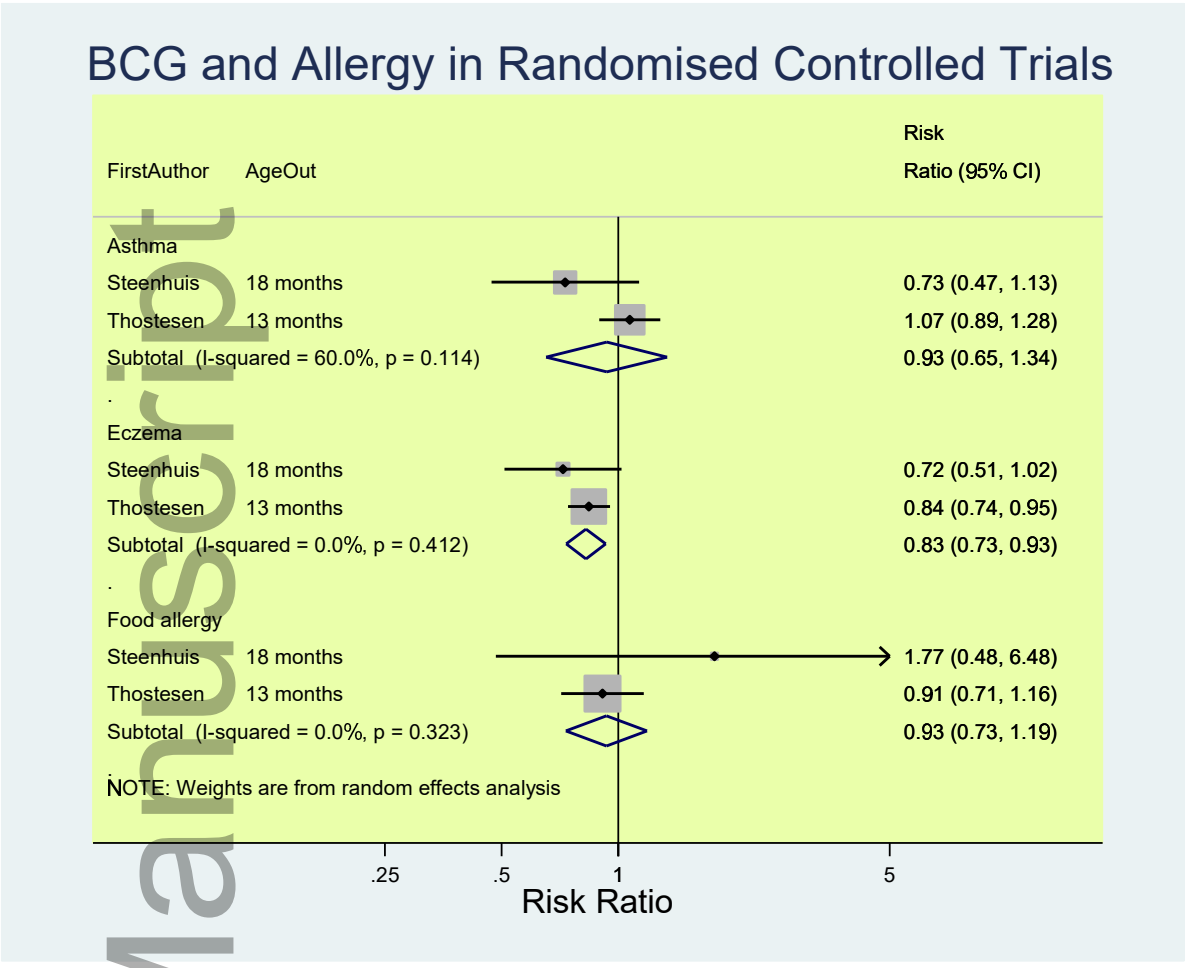


Figure 2: Forest plot showing RRs and 95% CIs for the association between BCG vaccination and Childhood allergy measured as wheeze/asthma, eczema, and food allergy for the Randomised Controlled Trials

T

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

T

Figure 4: Forest plot showing RRs and 95% CIs for the association between Acellular Pertussis vaccination (Control groups: Kiraly et al- delayed DTaP; Venter at 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

T

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

T

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

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=29,238)	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=9,444	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

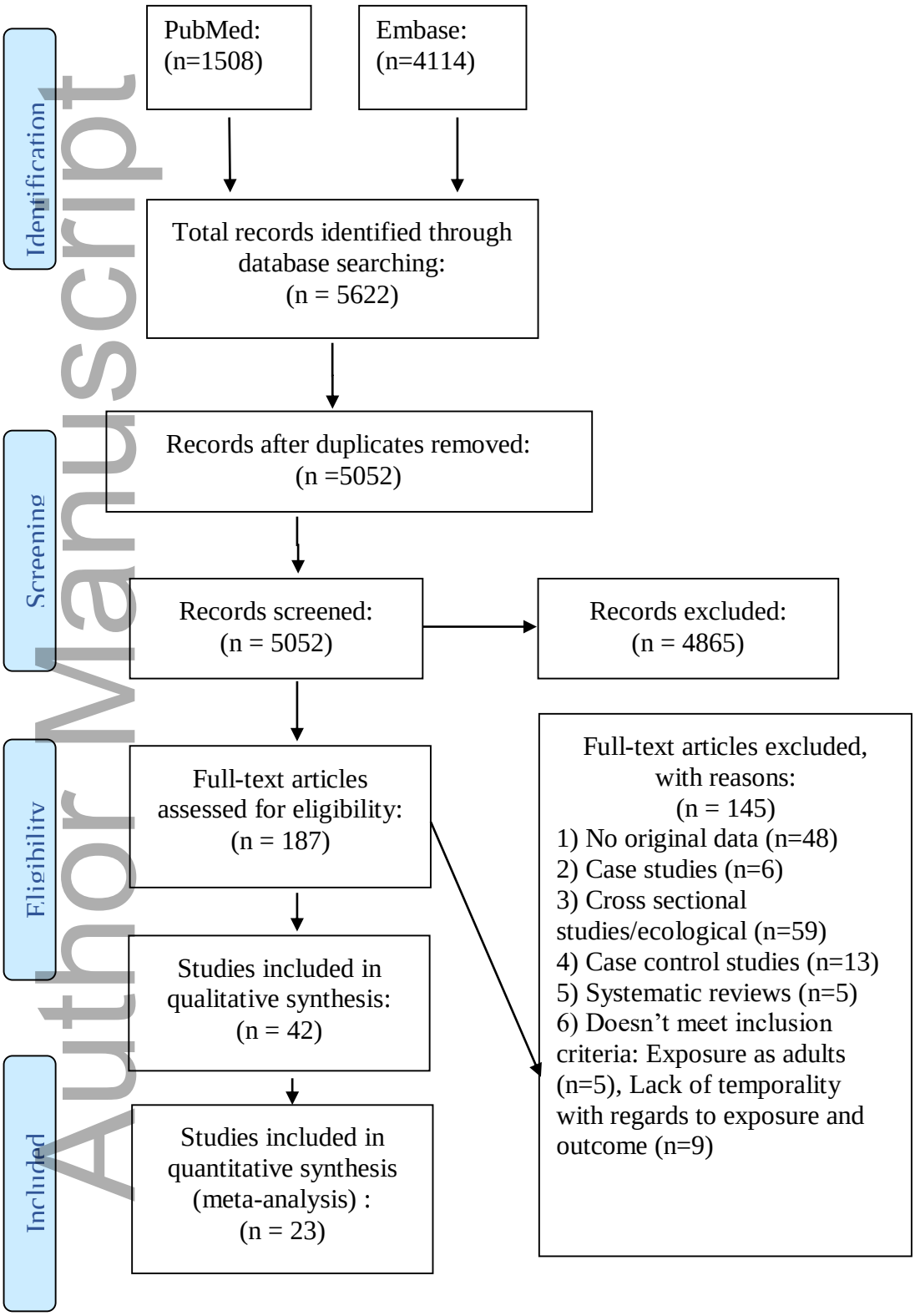
Reference, country	Study sample	Exposure	Outcome	Nature of the association
Bager et al. 2003[51], Denmark	Pregnant women living in Copenhagen, identified through Danish National Birth Cohort; (N=2,176)	BCG	Asthma, allergic rhinitis, IgE	None*
Bager et al. 2003[52], Denmark	Pregnant women living in Copenhagen 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, ɤIFN 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 1st 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; ɤIFN- ɤ 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



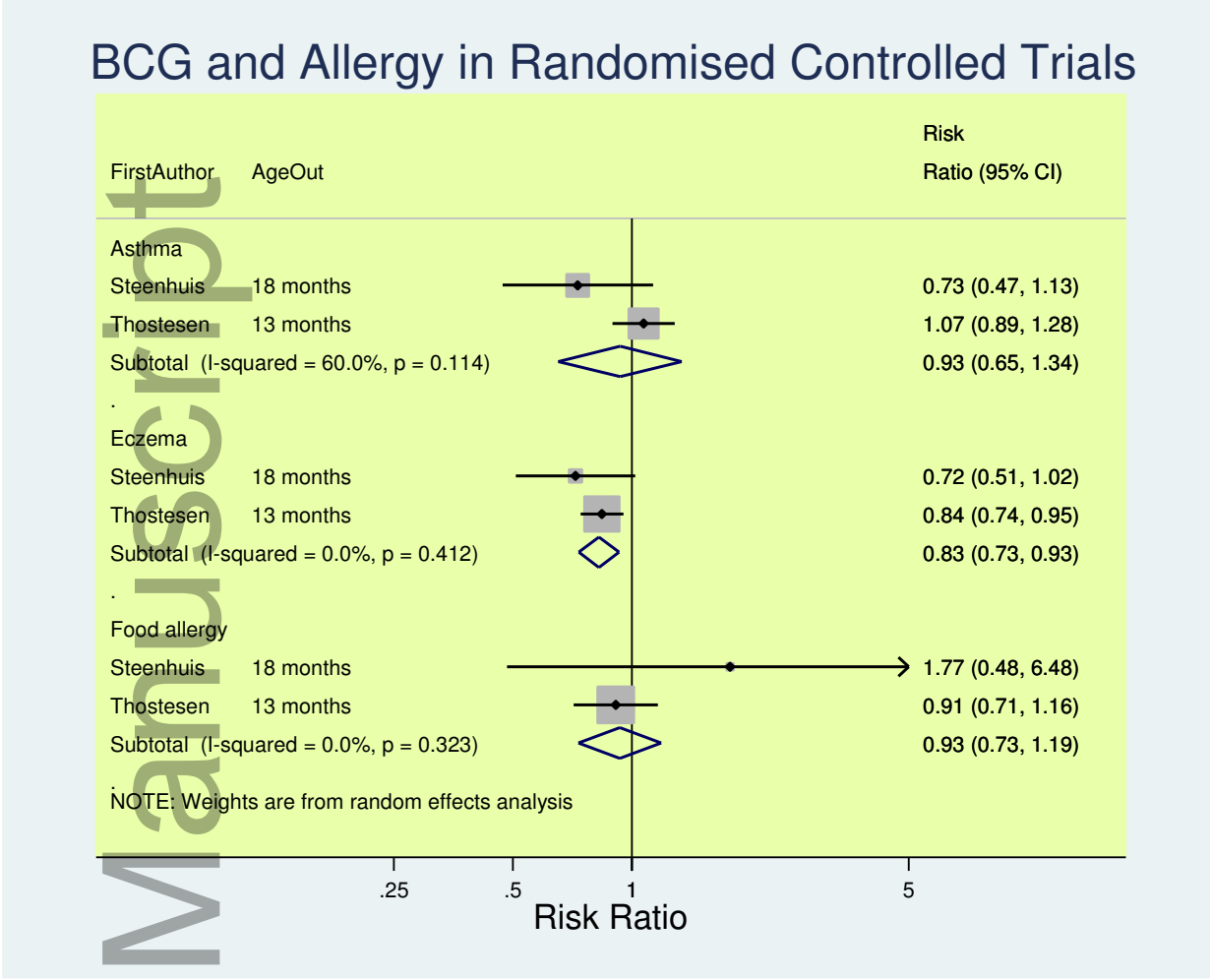
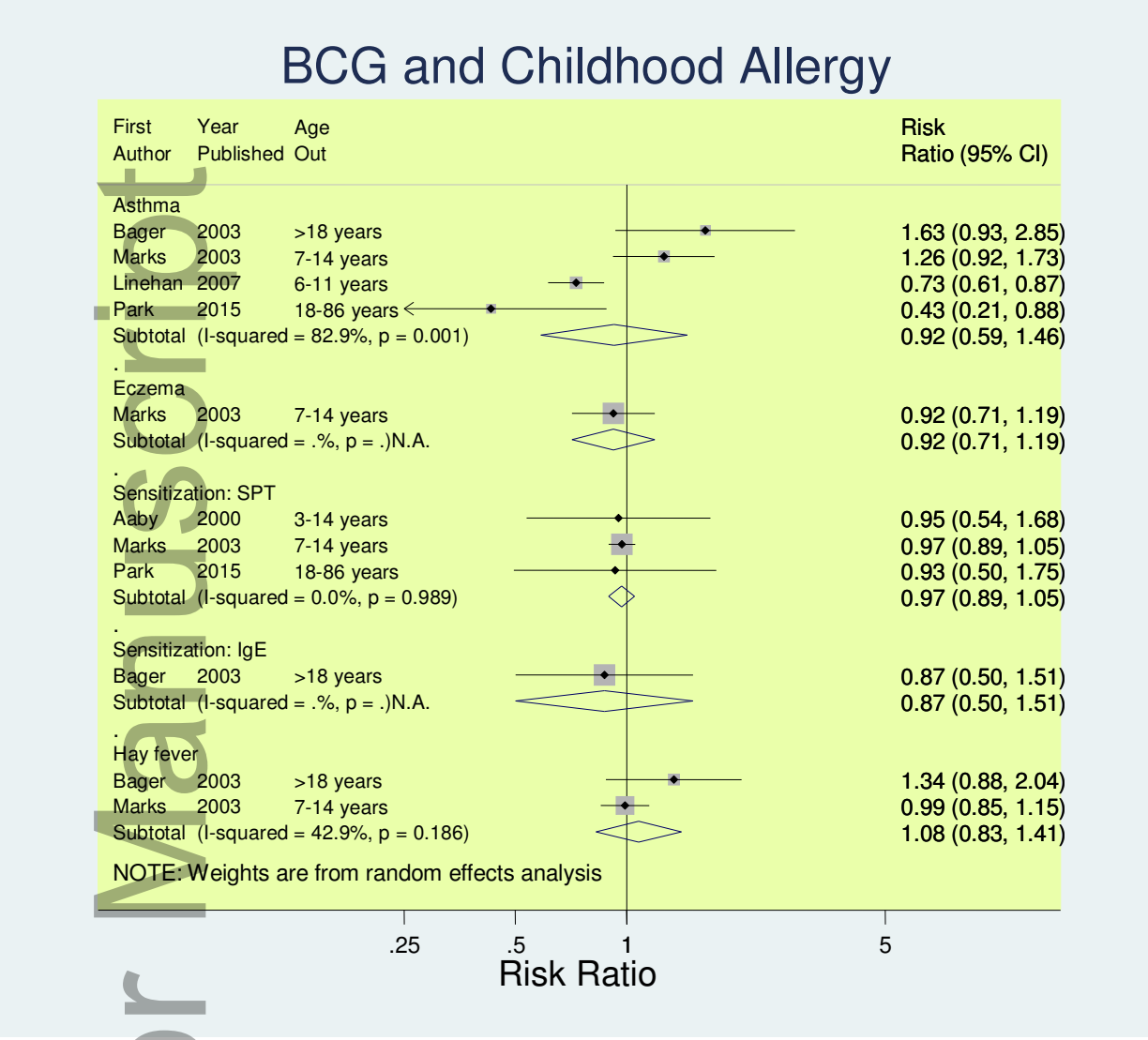


Figure 2: Forest plot showing RRs and 95% CIs for the association between BCG vaccination and Childhood allergy measured as wheeze/asthma, eczema, and food allergy for the Randomised Controlled Trials



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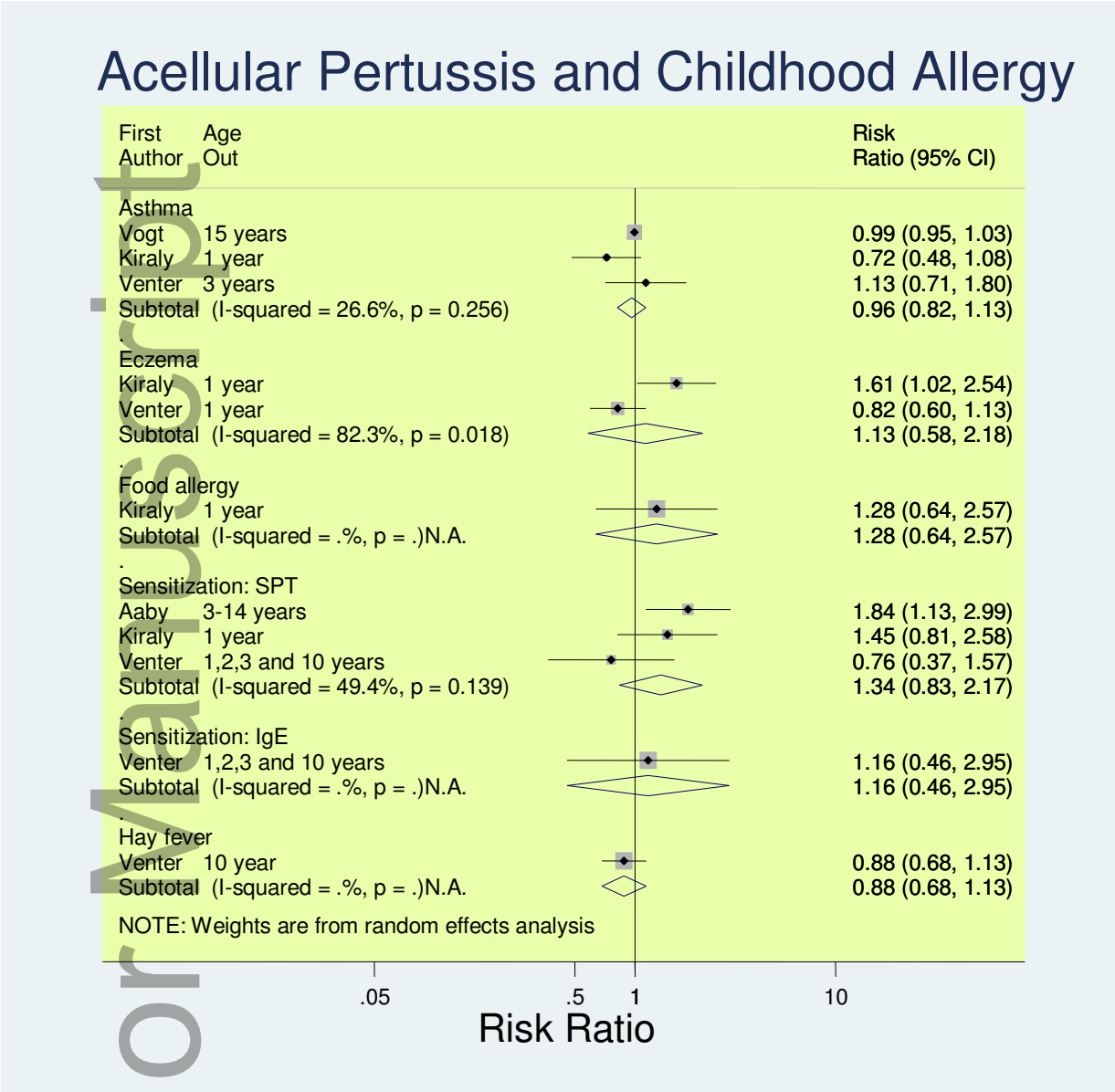

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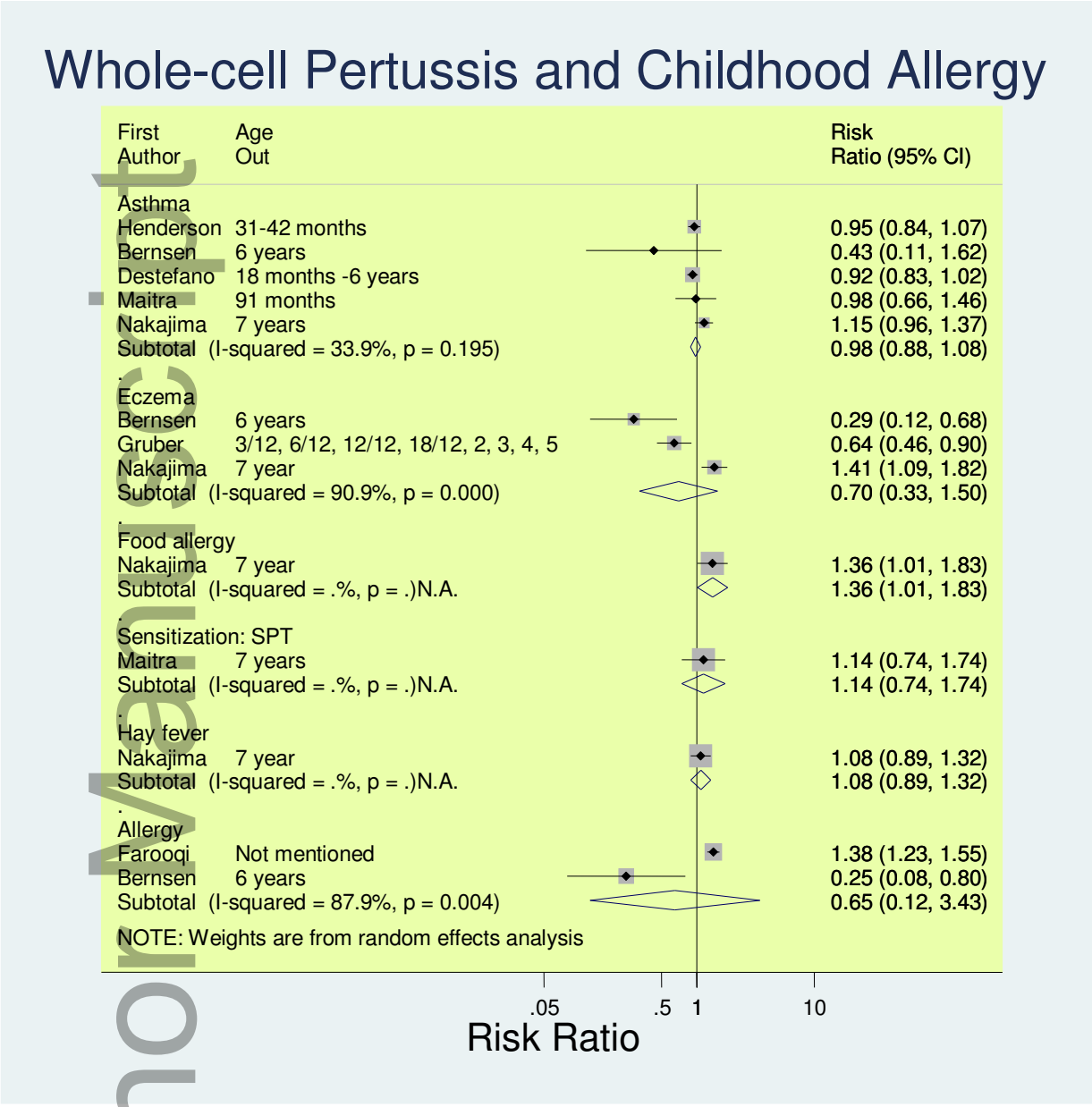

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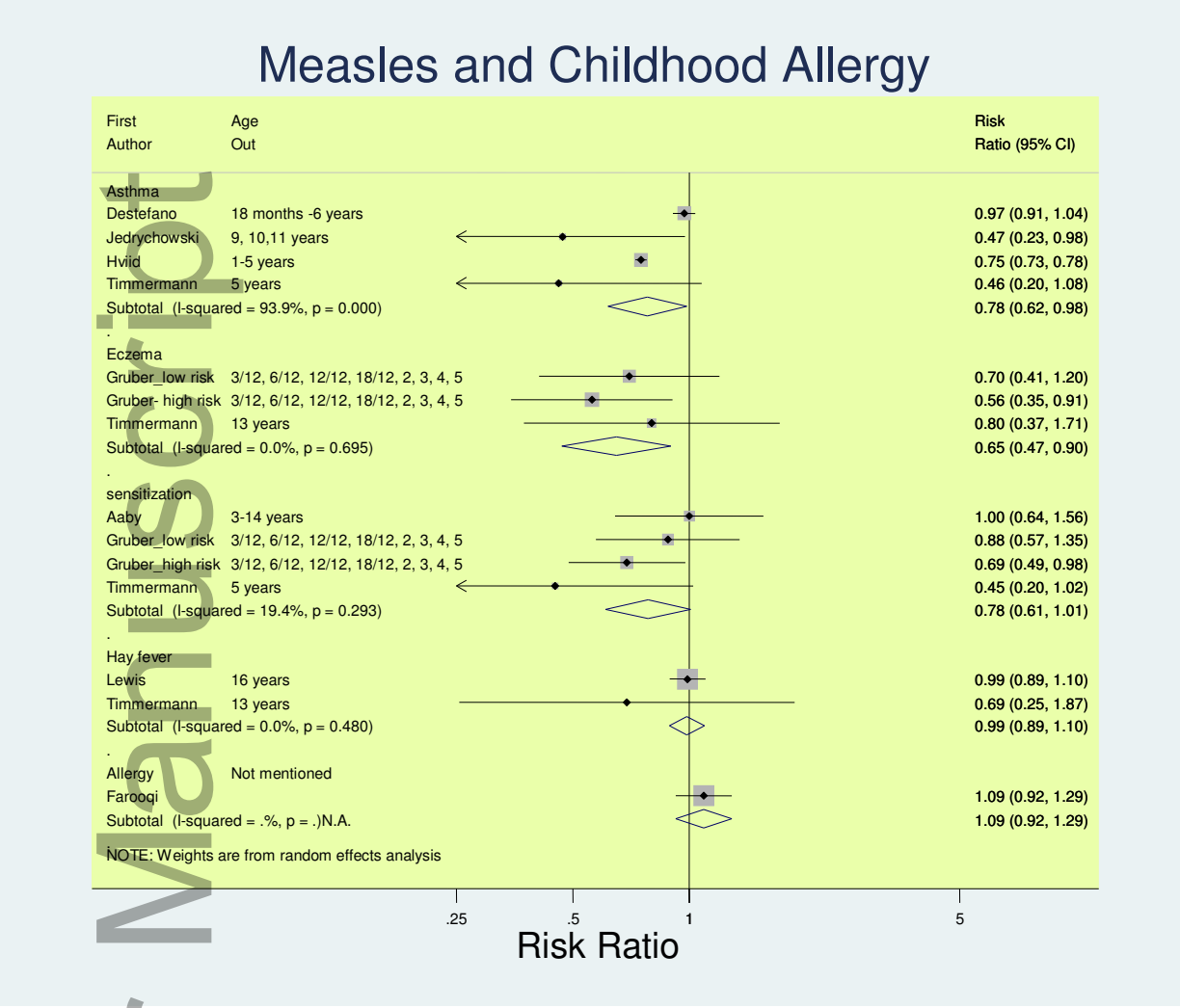

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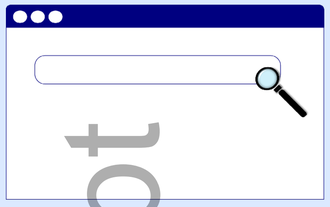
Search

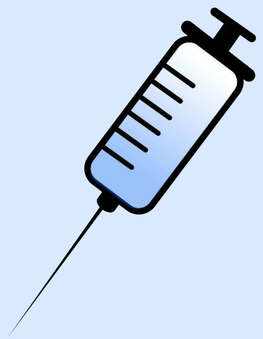


35 publications based on cohort studies and 7 publications based on randomized controlled trials

Risk of Allergy

No increased risk of later allergic disease

Protection from Allergy

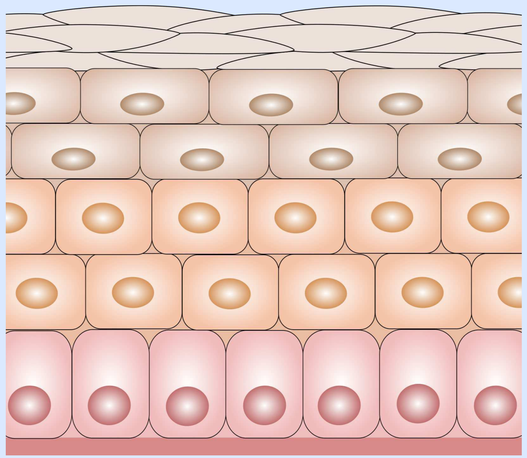


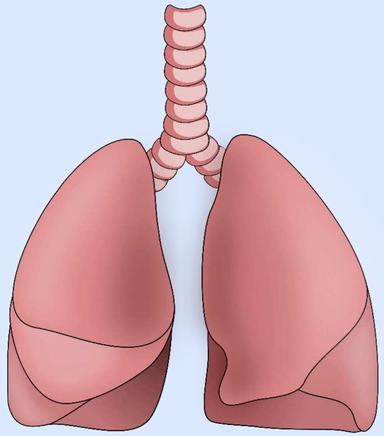
BCG vaccine

Measles vaccine

Reduced risk of eczema

Reduced risk of asthma





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Childhood vaccination and allergy: A systematic review and meta-analysis

Date:
2021-07

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