

Journal Pre-proof

Timeliness of DTaP-IPV-Hib vaccination and development of atopic dermatitis between 4 months and 1 year of age – Register-based cohort study

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PII: S2213-2198(20)31002-3

DOI: <https://doi.org/10.1016/j.jaip.2020.09.024>

Reference: JAIP 3134

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 18 December 2019

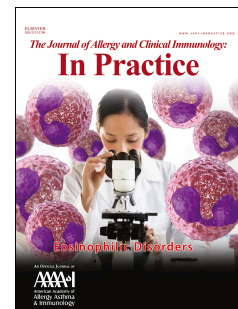
Revised Date: 24 August 2020

Accepted Date: 14 September 2020

Please cite this article as: Gehrt L, Rieckmann A, Kiraly N, Georg Jensen AK, Aaby P, Benn CS, Sørup S, Timeliness of DTaP-IPV-Hib vaccination and development of atopic dermatitis between 4 months and 1 year of age – Register-based cohort study, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.09.024>.

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27 **Funding:** The Danish National Research Foundation [DNRF108]. The Danish Council for
28 Independent Research [DFF – 4183-00316].

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30

31 **Keywords:** atopic dermatitis; eczema; heterologous immunity; non-specific effects of vaccines;
32 Diphtheria, Tetanus, acellular Pertussis – Inactivated Polio vaccine – Haemophilus influenzae type
33 b vaccine

34 **Abbreviations:** Atopic dermatitis (AD); *Diphtheria, Tetanus, acellular Pertussis – Inactivated*
35 *Polio vaccine – Haemophilus influenzae type b* (DTaP); diphtheria, tetanus, and pertussis vaccine
36 (DTP); Bacillus Calmette Guérin (BCG); Pneumococcal conjugate vaccine (PCV); *Diphtheria,*
37 *Tetanus, acellular Pertussis – Inactivated Polio vaccine – Haemophilus influenzae type b –*
38 *hepatitis B* (DTaP-IPV-Hib-HepB); odds ratio (OR); adjusted odds ratio (aOR); relative risk (RR);
39 adjusted relative risk (aRR); confidence interval (CI); Anatomical Therapeutic Chemical
40 classification (ATC); International Classification of Diseases version 10 (ICD-10);

41 **Potential conflicts of interest:** All authors no conflict.

42

43 **Running title:** Timeliness of DTaP and atopic dermatitis

44 **Word count abstract:** 255

45 **Word count text:** 4152

46 **References:** 46

47 Abstract

48 Background

49 An Australian study including 4433 children found that delayed Diphtheria–Tetanus–acellular
50 Pertussis containing vaccination was associated with reduced risk of developing atopic dermatitis
51 (AD) before 1 year of age.

52 Objective

53 We assessed if delayed vaccination against diphtheria, tetanus, acellular pertussis, polio, and
54 *Haemophilus Influenzae* type b (DTaP) was associated with a reduced risk of new cases of AD
55 before 1 year of age in Denmark.

56 Methods

57 We used nationwide registers to follow 883,160 children born in Denmark from 1997 to 2012.
58 Binary regression models adjusting for potential confounding factors were applied to estimate
59 relative risks (aRR) of developing AD among children with delayed DTaP vaccination (defined as
60 given 1 month or more after the recommended age) compared with timely vaccinated children.

61 Results

62 Among 143,429 children with a delayed first dose of DTaP, 4847 (3.4%) developed AD between 4
63 months and 1 year of age, compared with 27,628 (3.7%) among 739,731 children not having
64 delayed DTaP (aRR 0.94 (95% confidence interval (CI): 0.91-0.97)). The aRR was 0.94 (95% CI:
65 0.90-0.99) for children with a delayed second dose, and aRR=0.88 (95% CI: 0.2-0.93) comparing
66 children with delayed first and second dose with all timely vaccinated children.

67 Conclusion

68 The results support the hypothesis that delayed vaccination with DTaP is associated with reduced
69 risk of developing new cases of AD after 4 months of age. The dose-dependent relationship

70 strengthens the evidence of a causal relationship. Some countries are introducing maternal pertussis
71 vaccination and delaying the first dose of DTaP, providing a possibility for further testing the
72 hypothesis.

Highlights:

- 1. What is already known about this topic?
Vaccines can trigger non-antigen specific immune responses. An Australian study of approximately 4000 children, found that delayed vaccination with the non-live DTaP vaccine was associated with reduced risk of atopic dermatitis
- 2. What does this article add to our knowledge?
Delayed vaccination (at least 1 month) with the first dose of DTaP was associated with 6% lower risk of developing new cases of more severe atopic dermatitis between 4 months and 1 year of age in a cohort of nearly 900,000 Danish children.
- 3. How does this study impact current management guidelines?
Many issues should be considered when designing vaccination programmes. Maternal

73 Introduction

74 Atopic dermatitis (AD) is the most common skin disease in high income countries affecting up to
75 25% of children; up to 90 % have onset within the child's first year of life (1, 2). The etiology is
76 largely unknown, but involves skin barrier dysfunction, heritable and environmental factors, and
77 activation of immune responses (3).

78 Epidemiological studies show that vaccines in addition to their disease-specific protection may have
79 so-called *non-specific effects*, altering susceptibility towards diseases other than the vaccine-
80 targeted infections (4-7). In 2014, WHO concluded that the live BCG and measles containing
81 vaccines reduce overall mortality more than would be expected through their effects on the vaccine-
82 targeted diseases (8). In contrast, the non-live diphtheria, tetanus, and pertussis vaccine (DTP) may
83 be associated with an increase in all-cause mortality (8), especially for girls (8, 9). Immunological
84 insights suggest that in addition to the specific adaptive immunity towards the vaccine-targeted
85 pathogen, vaccines also alter the responsiveness of the innate immune system (10, 11). It is likely
86 that vaccines capability to trigger non-antigen-specific responses may affect development of other
87 childhood morbidities – such as allergy and atopy (5, 12).

88 A cohort study, including 4433 children from the HealthNuts Cohort (13) in Australia, scheduled to
89 receive the first dose of the non-live Diphtheria–Tetanus–acellular Pertussis containing vaccine at 2
90 months of age found that delayed vaccination (> 3 compared with < 3 months of age) was
91 associated with an adjusted odds ratio (aOR) of 0.57 (95% confidence interval (CI): 0.34–0.97) for
92 development of eczema (as an indicator of AD) within the child's first year of life (14). Most
93 previous studies on associations between DTP-containing vaccines and subsequent development of
94 AD have not focused on the timing of vaccination (15-18); one study divided DTP vaccinated

95 children into quartiles according to age at vaccination and found no effect of timing of vaccination
96 on development of eczema (19).

97 In the present study, we tested the hypothesis that delayed vaccination with the non-live *Diphtheria*,
98 *Tetanus, acellular Pertussis – Inactivated Polio vaccine – Haemophilus influenzae type b* vaccine
99 (henceforward referred to as DTaP) reduces the risk of developing new cases of AD between 4
100 months and 1 year of age in Danish children.

101 **Methods**

102 This cohort study is based on information from Danish nationwide registers linked by a unique
103 personal identification number (ID) given at birth to all Danish residents (20-25). We included all
104 children born in Denmark from 1997 to 2012 who had received their first dose of DTaP within their
105 first year of life (for further inclusion criteria see Figure 1).

106 **Vaccine information**

107 In Denmark, all children born from 1997 until 2012 were recommended to receive three doses of
108 DTaP at 3, 5, and 12 months of age (26) (Figure E1). In 2007, the Pneumococcal conjugated
109 vaccine (PCV) was introduced in Denmark (27). We investigated the effect of delayed vaccination
110 with DTaP irrespective of simultaneous administration of PCV.

111 In Denmark, the recommended childhood vaccinations are administered free of charge by the
112 general practitioners. For the purpose of reimbursement, general practitioners report vaccinations
113 along with information on the ID of the recipient and the information is available from the Danish
114 National Health Service Register for Primary Care (28). Vaccinations are registered on a weekly
115 basis; we defined the vaccination date as Wednesday of the respective week of vaccination. After
116 1996, registration of childhood vaccinations changed from being registered with the ID of the
117 parent to being registered with the ID of the child (28). However, childhood vaccinations were
118 occasionally reported for adults in the years following 1996. In these rare cases, vaccinations were
119 assigned to that adult's child who was closest to the recommended age for that vaccine, as
120 previously described (29).

121 In our primary analysis, we investigated whether delayed versus not delayed vaccination with the
122 first dose of DTaP reduced the risk of developing AD between 4 months and 1 year of age. We
123 categorized children as timely vaccinated if they received the first dose of DTaP before 4 months of

age and as delayed if they received it at or after 4 months of age. In our second analysis, we investigated if delayed vaccination with the second dose of DTaP reduced the risk of developing AD between 6 months and 1 year of age among children with a timely first dose. We categorized children as timely vaccinated if they received it before 6 months of age and as delayed if they received it at or after 6 months of age. In a *post hoc* analysis we pursued the findings from the above analyses and investigated the combined effect of multiple delayed doses of DTaP (both doses timely; first OR second dose delayed; or first AND second dose delayed) on the risk of developing AD between 6 months and 1 year of age.

Atopic dermatitis

Based on insights from previous studies which use register information to identify AD among children aged 0-17 years (30, 31), we developed an algorithm, which identifies AD using information on Anatomical Therapeutic Chemical classification (ATC) codes of filled prescriptions for treatment of AD registered at the Danish National Prescription Register (23) and International Classification of Diseases version 10 (ICD-10) codes for hospital diagnosed AD from the Danish National Patient Registry (25) (Online Repository Text). The algorithm was adjusted in cooperation with pediatricians with expert knowledge on childhood atopy (see acknowledgements) to better fit the younger population in the present study to whom many of the included contraindications for use of prescription medicines for AD among the older study populations in previous studies (30, 31) do not apply. Data is only available for filled prescriptions and registered on the date of redemption.

Other register based information

We defined inclusion and follow-up with information on births, deaths, and emigration from the Danish Civil Registration System, which also contain information about a child's parents, siblings, and household (24). Information about maternal smoking during pregnancy, maternal age, and birth characteristics was obtained from the Danish Medical Birth Register (20). Information on

household income (21), and maternal education (22) was obtained from Statistics Denmark. We obtained information on antibiotic use from the Danish National Prescription Register (23) and identified chronic diseases based on information from the Danish National Patient Registry (25) as done elsewhere (32).

Statistical analysis

Primary analysis

We estimated the relative risk (RR) of developing AD from 4 months of age until 1 year of age among delayed vaccinated children with the first dose of DTaP compared with timely vaccinated children in a binary regression model using STATA 15.1. The model was adjusted for all predefined potential confounders listed in Table 1 at 4 months of age. We examined effect modification by sex to investigate potential sex differential non-specific effects of delayed DTaP. To investigate potential divergent effects of delayed vaccination across the levels of the included covariates and if the birth cohort was offered PCV, we also performed an exploratory investigation for effect modification as pre-specified in the analysis plan. Wald tests for homogeneity of effects were performed on all stratified analyses.

Sensitivity analyses

Lag-time is expected from actual onset of AD until redemption of prescription medicine or hospital contact; therefore, we performed an analysis where date of onset of AD was set to one month prior to fulfillment of the AD algorithm.

Children with older siblings may use prescription medicines for AD already in the household, which will result in underreported use. We conducted a subgroup analysis only including first-born children.

Finally, we investigated the association between AD prior to 3 months of age and subsequent delayed vaccination to assess the possibility of reverse causation.

172 *Secondary analysis*

173 Among children with a timely first dose of DTaP, we estimated the adjusted RR (aRR) of
174 developing AD from 6 months until 1 year of age among delayed vaccinated children with the
175 second dose of DTaP compared with timely vaccinated. We investigated if the effect differed by
176 sex.

177 *Post hoc analysis*

178 We estimated the aRR of developing AD from 6 months until 1 year of age among children delayed
179 with both the first and second dose of DTaP compared with children delayed with either the first or
180 second dose, and children who received both doses on time. We investigated if the effect differed
181 by sex.

182 Second, we performed a sensitivity analysis using only 1 prescription of corticosteroids for topical
183 use to fulfill criteria 2 in the algorithm for identification of AD.

184 **Ethical aspects and registration**

185 The protocol for this study has been preregistered at ClinicalTrials.gov (identifier: NCT03142139).
186 The study was based on already collected information from nationwide Danish registers and such
187 studies do not require ethical permission in Denmark, but permission was obtained from the Danish
188 Data Protection Agency and the subjects were anonymized according to the requirements from the
189 Danish Health Data Authority.

190

191

Results

From 1 January 1997 to 31 December 2012, 1,027,559 children were born in Denmark. After exclusions, 883,160 children who had not developed AD by 4 months of age were included in the primary investigation of the association between delayed vaccination with the first dose of DTaP and subsequent development of AD from 4 months until 1 year of age (Figure 1). AD before baseline was identified in 12,949 children excluded from the study which corresponds to 24.9 % of all cases of AD before 1 year of age. Background characteristics of included and excluded children are presented in Table E1.

Delayed vaccination

Among the children included for the primary investigation, 739,731 (83.8%) were vaccinated before 4 months of age and 143,429 (16.2%) were delayed vaccinated with the first dose of DTaP. The median age at vaccination with the first dose of DTaP was 96 days (interquartile range, 91-102 days) among timely vaccinated children and 150 days (interquartile range, 133-165 days) among delayed vaccinated children.

There were minor differences in the distribution of some baseline variables between timely and delayed vaccinated children; children with delayed vaccination had higher number of other children in the household, prematurity, low birth weight, chronic disease, maternal smoking during pregnancy, low household income and low maternal education than timely vaccinated children. The analyses were adjusted for all baseline variables presented in Table 1.

Delayed vaccination with the first dose of DTaP and AD before 1 year of age

From 4 months until 1 year of age, 32,475 (3.7%) children were identified with AD mainly by fulfilling the criteria of receipt of ≥ 2 prescription medicines for treatment of AD (91.5%; Table E2).

214 Among children with no AD prior to 4 months of age, children vaccinated with the first dose of
215 DTaP after 4 months of age had an aRR of 0.94 (95% CI: 0.91-0.97; Table 2; Figure E2) of
216 developing AD before 1 year of age compared with children with a timely first dose of DTaP,
217 corresponding to the prevention of 1 case of AD for every 281 delayed vaccinated children. Girls
218 had 7% lower risk of AD following delayed vaccination, compared with 5 % lower risk among boys
219 (test for interaction, $P=0.46$; Table 2).

220 The exploratory investigation for effect modification by other variables showed that the effect of
221 delayed vaccination was more pronounced among children of families from the lowest household
222 income quintile (aRR=0.87; 95% CI: 0.82-0.92; Table E3).

223 *Sensitivity analyses*

224 The association between delayed vaccination and development of AD remained when onset of AD
225 was re-categorized to one month prior to identification by the algorithm (aRR=0.95; 95% CI: 0.92-
226 0.98; Table E4). A similar association between delayed vaccination and development of AD was
227 observed among the 369,884 firstborn children (aRR=0.96; 95% CI: 0.92-1.01; Table E5).

228 There was no association between AD before 3 months of age and subsequent risk of delayed
229 vaccination (aRR=1.01; 95% CI: 0.96-1.06).

230 When using the more sensitive measure of AD only including 1 prescription of topical
231 corticosteroids, the association between delayed vaccination with the first dose of DTaP and
232 development of AD persisted (aRR=0.94 (95% CI: 0.93-0.96; Table E6)).

233 **Delayed vaccination with the second dose of DTaP**

234 Among 701,681 children vaccinated with the first dose of DTaP before 4 months of age and no AD
235 before 6 months of age, delayed vaccination with the second dose (after 6 months of age) was

236 associated with similar reductions in the risk of developing AD before 1 year as for the first dose of
237 DTaP (aRR=0.94; 95% CI: 0.90-0.99; Table 3).

238 **Combined effect of delayed vaccination with the first and/or second dose of DTaP**

239 Among 793,924 children with no AD before 6 months of age, delayed vaccination with both the
240 first and second dose was associated with an aRR of 0.88 (95% CI: 0.82-0.93; Table 4) of
241 developing AD from 6 months until 1 year of age compared with children who were timely
242 vaccinated with both the first and second dose. The association was significantly stronger among
243 girls (aRR=0.83; 95% CI:0.76-0.92) compared with boys (aRR=0.91; 95% CI: 0.84-0.99).

Discussion

Main results

Among children who had not developed AD at 4 months of age, we found that delayed vaccination (after 4 months of age) with the first dose of DTaP was associated with a 6% (95% CI: 3%-9%) reduced risk of developing AD between 4 months and 1 year of age adjusted for potential confounding factors. Delayed vaccination with the second dose of DTaP (after 6 months of age) was associated with similar risk reductions of developing AD from 6 months until 1 year of age. In a *post hoc* analysis, the combination of delayed vaccination with both the first and second dose was associated with 17% (95% CI: 8%-24%) reduced risk of developing AD from 6 months until 1 year of age among girls and 9% (95% CI: 1%-16%) among boys.

Strengths and limitations

Use of nationwide population-based registers allowed for inclusion of the entire Danish population born from 1997 to 2012. This study thus has high statistical power with the ability to detect small differences while adjusting for multiple potential confounding factors. However, the observational nature of the study entails an inherent risk of residual confounding and the large sample size also entails that even minor bias introduced in the estimation can lead to spurious effects being significant.

The algorithm for identifying AD in the registers relies on information on hospital diagnosed AD and redeemed prescription medicines for treatment of AD. The algorithm has not been validated but is derived from validated algorithms from two previous studies which identify AD in children up to 17 years of age (31, 33), and adapted in cooperation with Danish pediatricians to better fit the younger study population of children below 1 year of age in this study.

Including AD cases among children excluded from the study, the algorithm identified AD in 5.1%

of children before 1 year of age, which corresponds well with the incidence observed in a previous Danish register based study (30). Meanwhile, AD is estimated to affect up to 25 % of children in high income countries with up to 90% experiencing onset within the first year of life (1, 2). Concurrently a previous Danish trial diagnosed AD before 13 months of age in 24% of the study population based on clinical examinations (34).

The algorithm relies on information on filled prescription medicines for treatment of AD, however, fatty moisturizers and mild topical corticosteroids are available as over the counter drugs. Hence, the low rates of AD observed in the present study may result from underreporting of mild cases of AD compared with studies which identified AD at clinical examinations, thus the reported associations are likely to represent the potential effect on more severe cases of AD.

Our analyses compare children vaccinated before versus after 4 months of age, whereby we avoid bias related to reasons for non-vaccination. There is, however, still a risk of bias related to reasons for delayed vaccination. Previous studies on timing of vaccination has pointed towards ascertainment bias, where families who consult their physician less often would be less likely to get their children vaccinated on time and less likely to present their child with AD symptoms (35). This bias would result in differential misclassification of AD due to different health care seeking behavior among parents of timely and delayed vaccinated children and thereby an association between delayed DTaP and lower risk of AD as found in the present study. If there was bias related to health care seeking behavior, we would expect higher rates of timely vaccination among children who are diagnosed with AD prior to the date of recommended vaccination. We found no association between AD before 3 months of age and timing of vaccination, which could indicate that bias related to health care seeking behavior should be of lesser concern in this study. Furthermore, we also found reduced risk of AD following delayed vaccination with the second dose of DTaP, if ascertainment bias is an expression of general lower health care seeking behavior, then it is unlikely

that this bias would be as strong in this subgroup of children who all have a timely first dose of the vaccine. We further found evidence of a graded association between number of delayed doses and reduced risk of AD, which strengthens the assumption of a causal relationship. Multiple delayed doses were especially beneficial for girls, which is in line with previous epidemiological studies of non-specific effects of DTP-containing vaccines (9).

Previous studies have raised concern for healthy vaccinee bias (36-39), i.e. the healthiest children receive vaccines first. We adjusted the analyses for chronic illness and receipt of antibiotics prior to baseline as proxies of health status to minimize healthy vaccinee bias. It is important to note that healthy vaccinee bias would affect the estimates in the opposite direction of ascertainment bias i.e. delayed vaccination should be associated with a higher risk of AD, which is opposite to the findings from this study.

Comparisons with other studies

The present study was inspired by an Australian study by Kiraly et al. that reported a 43% (95% CI: 3-66%) reduction in the odds of developing AD following delayed vaccination with DTaP (14), which is considerably stronger than the 6% risk reduction found in the present study. Several factors may explain the different results. First, Kiraly et al. minimize outcome misclassification as AD is identified using doctor diagnosed AD during follow-up, or eczematous rash observed by a trained nurse at end of follow-up (14). In contrast, the register-based definition of AD in the present study may have resulted in unsystematic misclassification of AD, which may have biased our estimates towards the null. Secondly, the children from the Australian HealthNuts Cohort were selected towards higher participation among children with atopy (14), with 29.9% of the children developing AD during follow-up compared with 3.7% among children in the present study, thus the greater effect of delayed vaccination with DTaP-containing vaccines in Australia may be interpreted as effect modification by sensitization towards atopy. Third, the Australian vaccination programme

prescribes vaccination with the first dose of DTaP at 2 months of age compared with vaccination at 3 months of age in Denmark. The timely vaccinated children in Denmark thus receive the vaccine at ages corresponding to the delayed vaccinated children in Australia whereby the lower effect of delayed vaccination observed in Denmark may result from an already lower risk of AD in the timely vaccinated group. However, we also found a beneficial effect of delayed vaccination with the second dose of DTaP, which may indicate a more general beneficial effect of delayed vaccination. Finally, the vaccination program in Australia prescribes DTaP in combination with hepatitis B vaccination (DTaP-IPV-Hib-HepB) as well as Hepatitis B vaccination at birth and the study by Kiraly et al. did not consider co-administration of other vaccines before or during the study period. The rotavirus vaccine was introduced as part of the Australian vaccination program the same year as the study participants were recruited for the HealthNuts cohort, with the first dose recommended between 6-15 weeks of age (40) (Figure E1). In contrast, we excluded children who had received vaccines other than DTaP before one year of age. It is possible that different vaccine combinations affect the association between delayed vaccination with DTaP-containing vaccines and development of AD differently.

Findings from other studies on an association between DTP containing vaccines and development of AD are inconsistent, displaying both higher risk (18, 19), lower risk (15, 16), and no association (17). Important issues may have impacted these observational studies; first they compare vaccinated versus non-vaccinated children and are hereby affected by bias related to reasons for non-vaccination. Second AD was assessed at different ages and sequencing of vaccines was not taken into consideration. It is possible that sequencing of vaccination may explain some of the heterogeneity, as studies which assess AD at older ages may be distorted by a modifying effect of subsequent vaccinations. Furthermore, the results from this and previous studies (14, 35) illustrate that timing of vaccination may explain some of the heterogeneity.

339 Interpretation and biological mechanisms

340 DTaP-IPV-Hib protects against five pathogens and was administered with and without PCV over
341 the course of the study period, thus it is not possible to identify which component or combination of
342 components that is responsible for modifying the risk of developing AD. There was no effect
343 modification by introduction of PCV into the vaccination program (Table E3). Furthermore, as all
344 children eventually receive the vaccine, the results of the analyses only pertain to the modifying
345 effect of *timing* of vaccination, and it is not possible to attribute any risk of AD to vaccination with
346 DTaP-IPV-Hib alone.

347 The non-live DTP vaccine has been found to be associated with sex differential detrimental non-
348 specific effects on infectious disease mortality in epidemiological studies (8, 9). There is no clear
349 biological mechanism that explains why delayed vaccination with DTaP could be related to lower
350 risk of AD. One study randomizing 75 healthy female adult volunteers to receive DTaP in different
351 sequences found that DTaP vaccination resulted in repression of monocyte-derived cytokine
352 responses and T-cell reactivity to unrelated pathogens 3 months later (41). Skin barrier dysfunction
353 and multiple changes of the immune system are involved in the aetiology of AD (42). It is therefore
354 possible that alterations of inflammatory immune responses may affect development of AD (10,
355 43).

356 In comparison vaccination with the live BCG vaccine was associated with reduced risk of
357 developing AD in Danish and Dutch randomised trials (34, 44). Thus, it is possible that vaccines
358 affect the risk of developing AD differently depending on the type of vaccine administered.

359 Finally, we found that the association between delayed vaccination and development of AD was
360 driven by a strong association among children of the lowest household income quintile. It is

possible that low socioeconomic status is associated with health and lifestyle related factors, which may modify the effect of delayed vaccination.

Conclusion and implications

This nationwide register-based cohort study showed that vaccination at or after 4 months of age versus vaccination before 4 months of age with the non-live DTaP vaccine was associated with a slightly reduced risk of developing AD between 4 months and 1 year of age, suggesting prevention of 1 new case of AD between 4 months and 1 year of age for every 281 delayed vaccinated children. The association was stronger with increasing number of delayed doses. Greater protective effects of delayed vaccination with DTaP have been found in previous studies with earlier DTP vaccination and higher degree of atopic sensitization.

The algorithm identified AD in 5.1% of the total study population, considerably less than the up to 25% reported in previous studies (2, 34). The algorithm would tend to miss children with mild AD, and thus the effect estimates should be interpreted as the potential effect of delayed DTaP on the incidence of the more severe AD leading to hospital contacts and prescriptions.

The clinical implications of delayed vaccination with DTaP on development of AD depends on the actual underlying burden of AD as even small risk reductions may be noteworthy in frequent outcomes.

If supported in other settings, the available evidence suggests that these non-live vaccines may be one of many contributing factors in the development of AD. Immunological studies of possible pathways would be important as well as identification of factors which modify the association including identification of risk-groups and whether co-administration with other (live) vaccines can reduce the risk of developing AD.

383 Beneficial effects of delayed vaccination must be seen in relation to the benefits of timely
384 vaccination against serious childhood diseases. As such, the results are particularly interesting as
385 many countries start using pertussis vaccine in pregnancy. Children whose mother has been
386 vaccinated are already protected by maternal antibodies from birth, thus e.g. The Netherlands has
387 accompanied maternal pertussis vaccination with later DTaP vaccinations for their children (45,
388 46). With the high prevalence of AD and the toll it takes on the children, their parents and the health
389 economy, risk reductions by minor modifications of vaccination programs are worth pursuing under
390 appropriate consideration for the effects on the targeted infections.

391 **Contributors:** LG, SS, NK, AKGJ, CSB and AR conceptualized and designed the study. SS
392 acquired the data. LG and AKGJ performed the statistical analyses. LG, AR, NK, AKGJ, PA, CSB
393 and SS analysed and interpreted the data. LG drafted the initial manuscript. AR, NK, AKGJ, PA,
394 CSB and SS critically revised the manuscript for important intellectual content.

395 **Acknowledgements:** We thank Simon Dauding from the University of Copenhagen, and Poul-Erik
396 Lund Kofoed and Signe Vahlkvist from the Department of Paediatrics and Adolescent Medicine at
397 Kolding Sygehus for their indispensable contributions in developing the algorithm for identifying
398 AD using register information.

399 This study was funded by The Danish National Research Foundation [DNRF108] and The Danish
400 Council for Independent Research [DFR – 4183-00316].

References

1. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab.* 2015;66 Suppl 1:8-16.
2. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nature reviews Disease primers.* 2018;4(1):1.
3. Brunner PM, Guttman-Yassky E, Leung DY. The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies. *The Journal of allergy and clinical immunology.* 2017;139(4s):S65-s76.
4. Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. *Trends Immunol.* 2013;34(9):431-9.
5. Flanagan KL, Plebanski M. Sex-differential heterologous (non-specific) effects of vaccines: an emerging public health issue that needs to be understood and exploited. *Expert review of vaccines.* 2017;16(1):5-13.
6. Flanagan KL, van Crevel R, Curtis N, Shann F, Levy O. Heterologous ("nonspecific") and sex-differential effects of vaccines: epidemiology, clinical trials, and emerging immunologic mechanisms. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2013;57(2):283-9.
7. Pollard AJ, Finn A, Curtis N. Non-specific effects of vaccines: plausible and potentially important, but implications uncertain. *Archives of disease in childhood.* 2017;archdischild-2015-310282.
8. Higgins JPT, Soares-Weiser K, López-López JA, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ (Clinical research ed).* 2016;355.
9. Aaby P, Ravn H, Fisker AB, Rodrigues A, Benn CS. Is diphtheria-tetanus-pertussis (DTP) associated with increased female mortality? A meta-analysis testing the hypotheses of sex-differential non-specific effects of DTP vaccine. *Trans R Soc Trop Med Hyg.* 2016;110(10):570-81.
10. Moorlag S, Roring RJ, Joosten LAB, Netea MG. The role of the interleukin-1 family in trained immunity. *Immunol Rev.* 2018;281(1):28-39.
11. Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, et al. Trained immunity: A program of innate immune memory in health and disease. *Science.* 2016;352(6284):aaf1098.
12. Plotkin SA, Orenstein WA, Offit PA. *Vaccine Immunology. Vaccines.* 6th ed: Elsevier 2013. p. 14-32.
13. Koplin JJ, Wake M, Dharmage SC, Matheson M, Tang ML, Gurrin LC, et al. Cohort Profile: The HealthNuts Study: Population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol.* 2015;44(4):1161-71.
14. Kiraly N, Koplin JJ, Crawford NW, Bannister S, Flanagan KL, Holt PG, et al. Timing of routine infant vaccinations and risk of food allergy and eczema at one year of age. *Allergy.* 2016;71(4):541-9.
15. Gruber C, Warner J, Hill D, Bauchau V. Early atopic disease and early childhood immunization--is there a link? *Allergy.* 2008;63(11):1464-72.
16. Martignon G, Oryszczyn MP, Annesi-Maesano I. Does childhood immunization against infectious diseases protect from the development of atopic disease? *Pediatr Allergy Immunol.* 2005;16(3):193-200.
17. Mohrenschlager M, Haberl VM, Kramer U, Behrendt H, Ring J. Early BCG and pertussis vaccination and atopic diseases in 5- to 7-year-old preschool children from Augsburg, Germany: results from the MIRIAM study. *Pediatr Allergy Immunol.* 2007;18(1):5-9.
18. Nakajima K, Dharmage SC, Carlin JB, Wharton CL, Jenkins MA, Giles GG, et al. Is childhood immunisation associated with atopic disease from age 7 to 32 years? *Thorax.* 2007;62(3):270-5.
19. McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *American journal of public health.* 2004;94(6):985-9.

- 449 20. Bliddal M, Broe A, Pottegard A, Olsen J, Langhoff-Roos J. The Danish Medical Birth Register.
450 European journal of epidemiology. 2018.
- 451 21. Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments.
452 Scandinavian journal of public health. 2011;39(7 Suppl):103-5.
- 453 22. Jensen VM, Rasmussen AW. Danish Education Registers. Scandinavian journal of public
454 health. 2011;39(7 Suppl):91-4.
- 455 23. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data
456 Resource Profile: The Danish National Prescription Registry. Int J Epidemiol. 2017;46(3):798-f.
- 457 24. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in
458 epidemiology. European journal of epidemiology. 2014;29(8):541-9.
- 459 25. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish
460 National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol.
461 2015;7:449-90.
- 462 26. Høeg-Jensen L. Vejledning om gratis vaccination mod visse smitsomme sygdomme m.v.
463 <https://www.retsinformation.dk/Forms/R0710.aspx?id=179107>: National Board of Health.; 2016.
- 464 27. Statens Serum Institut. Historisk oversigt over anvendte vacciner www.ssi.dk2017 [updated
465 November 28, 2017; cited 2017 December]. Available from:
466 <https://www.ssi.dk/Vaccination/Boernevaccination/Historisk%20oversigt.aspx>.
- 467 28. Andersen JS, Olivarius NDF, Krasnik A. The Danish National Health Service Register.
468 Scandinavian journal of public health. 2011;39(7 Suppl):34-7.
- 469 29. Sorup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles,
470 mumps, and rubella and the risk of hospital admissions for nontargeted infections. Jama. 2014;311(8):826-
471 35.
- 472 30. Henriksen L, Simonsen J, Haerskjold A, Linder M, Kieler H, Thomsen SF, et al. Incidence rates
473 of atopic dermatitis, asthma, and allergic rhinoconjunctivitis in Danish and Swedish children. The Journal of
474 allergy and clinical immunology. 2015;136(2):360-6 e2.
- 475 31. Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of
476 asthma and eczema in population-based Swedish drug and patient registers. Pharmacoepidemiol Drug Saf.
477 2013;22(8):850-60.
- 478 32. Kristensen K, Hjuler T, Ravn H, Simoes EA, Stensballe LG. Chronic diseases, chromosomal
479 abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a
480 population-based cohort study. Clinical infectious diseases : an official publication of the Infectious Diseases
481 Society of America. 2012;54(6):810-7.
- 482 33. Stensballe LG, Klanso L, Jensen A, Haerskjold A, Thomsen SF, Simonsen J. The validity of
483 register-data to identify children with atopic dermatitis, asthma or allergic rhinoconjunctivitis. Pediatr
484 Allergy Immunol. 2017.
- 485 34. Thostesen LM, Kjaergaard J, Pihl GT, Birk NM, Nissen TN, Aaby P, et al. Neonatal BCG
486 vaccination and atopic dermatitis before 13 months of age: A randomized clinical trial. Allergy.
487 2018;73(2):498-504.
- 488 35. McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus
489 vaccination is associated with a reduced risk of childhood asthma. The Journal of allergy and clinical
490 immunology. 2008;121(3):626-31.
- 491 36. Benn CS, Fisker AB, Rieckmann A, Jensen AKG, Aaby P. How to evaluate potential non-
492 specific effects of vaccines: the quest for randomized trials or time for triangulation? Expert review of
493 vaccines. 2018;17(5):411-20.
- 494 37. Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication
495 and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic
496 review. BMC Infect Dis. 2015;15:429.

38. Sorup S, Stensballe LG, Krause TG, Aaby P, Benn CS, Ravn H. Oral Polio Vaccination and Hospital Admissions With Non-Polio Infections in Denmark: Nationwide Retrospective Cohort Study. *Open Forum Infect Dis*. 2016;3(1):ofv204.
39. Tielemans S, de Melker HE, Hahne SJM, Boef AGC, van der Klis FRM, Sanders EAM, et al. Non-specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: population based cohort study in the Netherlands. *BMJ (Clinical research ed)*. 2017;358:j3862.
40. Hull BP, Menzies R, Macartney K, McIntyre PB. Impact of the introduction of rotavirus vaccine on the timeliness of other scheduled vaccines: the Australian experience. *Vaccine*. 2013;31(15):1964-9.
41. Blok BA, de Bree LCJ, Diavatopoulos DA, Langereis JD, Joosten LAB, Aaby P, et al. INTERACTING NON-SPECIFIC IMMUNOLOGICAL EFFECTS OF BCG AND Tdapf VACCINATIONS: AN EXPLORATIVE RANDOMIZED TRIAL. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2019.
42. Peng W, Novak N. Pathogenesis of atopic dermatitis. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2015;45(3):566-74.
43. Arts RJW, Moorlag SJCFM, Novakovic B, Li Y, Wang S-Y, Oosting M, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell Host & Microbe*. 2018;23(1):89-100.e5.
44. Steenhuis TJ, van Aalderen WM, Bloksma N, Nijkamp FP, van der Laag J, van Loveren H, et al. Bacille-Calmette-Guerin vaccination and the development of allergic disease in children: a randomized, prospective, single-blind study. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2008;38(1):79-85.
45. Barug D, Pronk I, van Houten MA, Versteegh FGA, Knol MJ, van de Kasstelee J, et al. Maternal pertussis vaccination and its effects on the immune response of infants aged up to 12 months in the Netherlands: an open-label, parallel, randomised controlled trial. *The Lancet Infectious diseases*. 2019;19(4):392-401.
46. Health Council of the Netherlands. Vaccination schedule for infants after maternal pertussis vaccination. In: The Hague: Health Council of the Netherlands, editor. publication no. 2018/272018.

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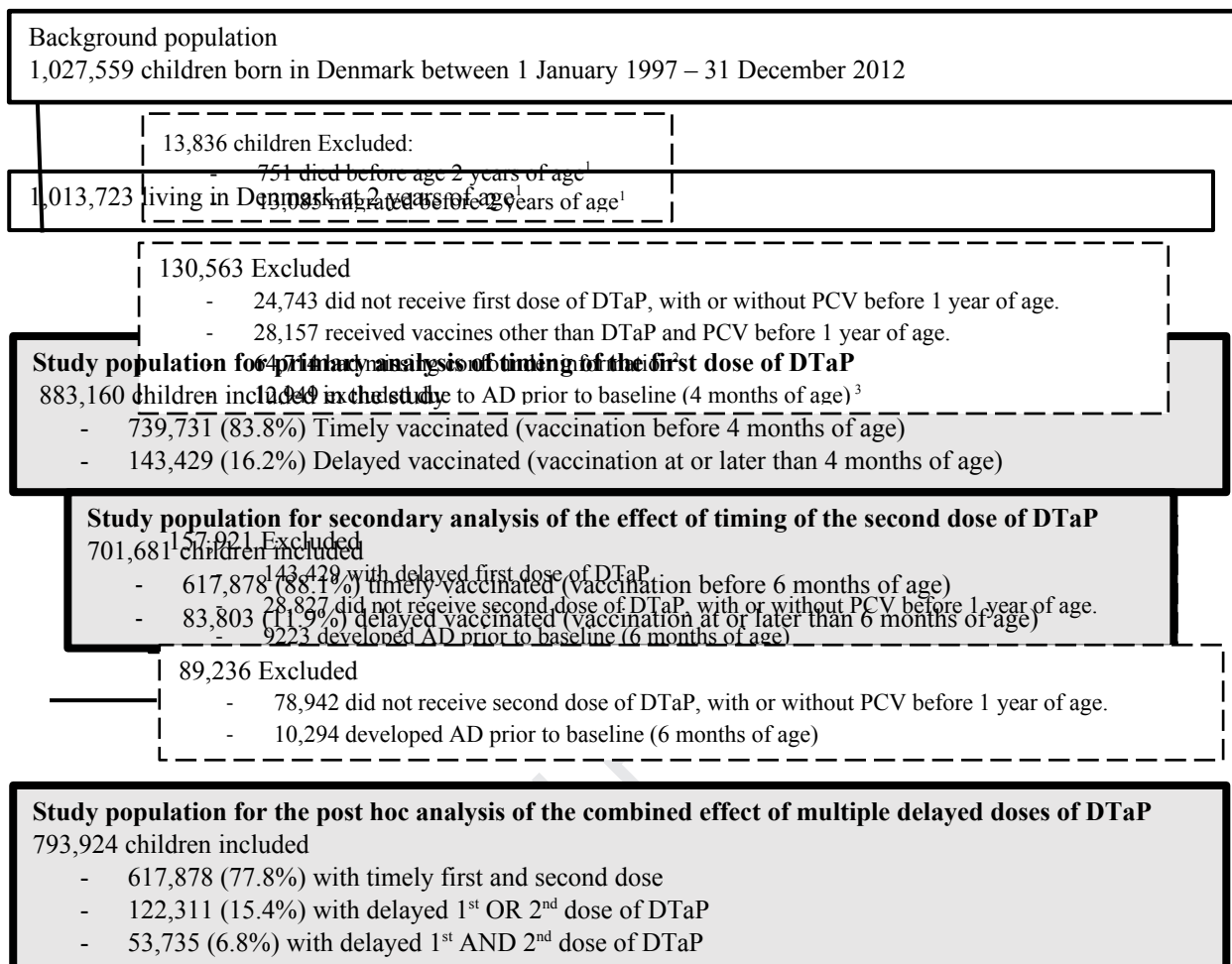
Table E4: Association between delayed vaccination with the first dose of DTaP and development of AD1 before one year of age – Date of AD set one month prior to registration date

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Online Repository Text

Online Repository Text: Algorithm to define children with atopic dermatitis

Figure 1: Flowchart of inclusion in the study

Abbreviations: DTaP=Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; PCV=Pneumococcal Conjugate Vaccine; AD=Atopic Dermatitis¹) The algorithm for identification of AD (sAppendix 2) uses information on prescriptions up until 1 year after the last age of outcome assessment (1 year of age in this study) to confirm a case. Children must therefore be alive and living in Denmark until two years of age, representative of age at end of follow-up plus one year.

²) Missing information on (note one child can have missing information on more variables): maternal smoking during pregnancy (N=31,320); highest attained education for the adult female in household (N=28,412); income quintile (N=537); number of children in the household, population density and area of residence (N=532); single parenthood (N=2372), prematurity (N=10,603), birthweight (N=7301), parents origin at birth (N=16), maternal age at delivery (N=611).

³) AD before 1 year of age was identified in 19,542 of the 144,399 children excluded from the study of which 12,949 were excluded ONLY due to AD before 4 months of age

Table 1: Baseline characteristics of the study population

	Timely ¹ vaccinated with DTaP1		Delayed ² vaccinated with DTaP1	
	N	(%)	N	(%)
Total	739,731		143,429	
Season of birth				
Spring	185,385	(25.1%)	37,243	(26.0%)
Summer	201,084	(27.2%)	35,595	(24.8%)
Fall	182,231	(24.6%)	37,008	(25.8%)
Winter	171,031	(23.1%)	33,583	(23.4%)
Sex				
Male	377,280	(51.0%)	73,698	(51.4%)
Female	362,451	(49.0%)	69,731	(48.6%)
Number of children in household				
1	323,555	(43.7%)	46,329	(32.3%)
2	282,779	(38.2%)	60,230	(42.0%)
3	104,745	(14.2%)	26,891	(18.7%)
4 or more	28,652	(3.9%)	9979	(7.0%)
Delivered by Cesarean section				
No	597,406	(80.8%)	113,645	(79.2%)
Yes	142,325	(19.2%)	29,784	(20.8%)
Gestational age				
≥ 37 weeks	696,819	(94.2%)	130,188	(90.8%)
<37 weeks	42,912	(5.8%)	13,241	(9.2%)
Birth weight (g)				
<2000	10,159	(1.4%)	5722	(4.0%)
2001-2500	23,416	(3.2%)	5700	(4.0%)
2501-3000	91,095	(12.3%)	17,812	(12.4%)
3001-3500	237,568	(32.1%)	43,870	(30.6%)
3501-4000	250,004	(33.8%)	45,860	(32.0%)
4001-4500	104,168	(14.1%)	19,888	(13.9%)
4501+	23,321	(3.2%)	4577	(3.2%)
Maternal smoking during pregnancy				
No	613,136	(82.9%)	114,354	(79.7%)
Yes	126,595	(17.1%)	29,075	(20.3%)
Antibiotic use before baseline				
No	725,081	(98.0%)	139,296	(97.1%)
Yes	14,650	(2.0%)	4133	(2.9%)
Chronic disease³ before baseline				
No	715,790	(96.8 %)	136,031	(94.8 %)
Yes	23,941	(3.2 %)	7398	(5.2 %)
Family history of AD⁴				
No	543,097	(73.4%)	104,300	(72.7%)
Yes	196,634	(26.6%)	39,129	(27.3%)
Single parenthood				
Lives with two adults	691,222	(93.4%)	130,872	(91.2%)
Lives with single parent	48,509	(6.6%)	12,557	(8.8%)
Population density				
<50	47,191	(6.4%)	10,434	(7.3%)
50-499	416,272	(56.3%)	80,940	(56.4%)
500-1999	143,077	(19.3%)	27,088	(18.9%)
2000-4999	32,744	(4.4%)	6395	(4.5%)

>=5000	100,447	(13.6%)	18,572	(12.9%)
Maternal age at delivery				
<=19	9006	(1.2%)	2110	(1.5%)
20-24	83,460	(11.3%)	16,215	(11.3%)
25-29	251,754	(34.0%)	44,990	(31.4%)
30-34	267,608	(36.2%)	51,943	(36.2%)
35-39	110,112	(14.9%)	23,938	(16.7%)
>=40	17,791	(2.4%)	4233	(3.0%)
Parental birth countries				
Denmark	617,319	(83.5%)	116,379	(81.1%)
Denmark and foreign	71,065	(9.6%)	14,910	(10.4%)
Foreign countries	51,347	(6.9%)	12,140	(8.5%)
Household income quintile				
First (lowest)	151,815	(20.5%)	39,285	(27.4%)
Second	170,366	(23.0%)	34,797	(24.3%)
Third	170,706	(23.1%)	30,014	(20.9%)
Fourth	141,498	(19.1%)	22,648	(15.8%)
Fifth (highest)	105,346	(14.2%)	16,685	(11.6%)
Highest educational level adult female				
Primary school	127,666	(17.3%)	31,655	(22.1%)
High school exam	70,877	(9.6%)	13,760	(9.6%)
Vocational training	238,011	(32.2%)	44,396	(31.0%)
Bachelor academy	223,316	(30.2%)	39,981	(27.9%)
Master+	79,861	(10.8%)	13,637	(9.5%)

Abbreviations: DTaP1= First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis

¹⁾ Vaccinated with first dose of DTaP with or without PCV before 4 months of age; ²⁾ Vaccinated with first dose of DTaP with or without PCV at or after 4 months of age; ³⁾ Identified according to algorithm from Kristensen et al. (31); ⁴⁾ Mother, father or sibling with AD identified according to the algorithm in sAppendix 2 before baseline.

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Table 2: Delayed vaccination with the first dose of DTaP and development of atopic dermatitis¹ before 1 year of age

	Cases of AD/N (%)	RR ² (95%CI)	aRR ^{2,3} (95% CI)
All children			
Timely ⁴ DTaP1	27,628/739,731 (3.7 %)	1(ref)	1(ref)
Delayed ⁵ DTaP1	4847/143,429 (3.4%)	0.90 (0.88-0.93)	0.94 (0.91-0.97)
Boys			
Timely ⁴ DTaP1	16,291/377,280 (4.3 %)	1(ref)	1(ref)
Delayed ⁵ DTaP1	2904/73,698 (3.9 %)	0.91 (0.88-0.95)	0.95 (0.91-0.99)
Girls			
Timely ⁴ DTaP1	11,337/362,451 (3.1%)	1(ref)	1(ref)
Delayed ⁵ DTaP1	1943/69,731 (2.8%)	0.89 (0.85-0.93)	0.93 (0.89-0.97)
Test for interaction			P=0.46

Abbreviations: AD=Atopic Dermatitis; DTaP1=First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; RR=Relative Risk; aRR=adjusted Relative Risk

¹⁾ Atopic Dermatitis identified according to the algorithm in sAppendix 2; ²⁾Relative risk estimated using a binary regression model; ³⁾ Adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education; ⁴⁾First dose of DTaP before 4 months of age; ⁵⁾First dose of DTaP at or after 4 months of age.

Table 3: Delayed vaccination with the second dose of DTaP (vaccination at or after 6 months of age) and development of AD before 1 year of age

	Cases of AD ¹ /N (%)	RR ² (95%CI)	aRR ^{2,3} (95% CI)
All children			
Timely⁴ DTaP2	15,498/617,878 (2.5%)	1(ref)	1(ref)
Delayed⁵ DTaP2	1864/83,803 (2.2 %)	0.89 (0.85-0.93)	0.94 (0.90-0.99)
Boys			
Timely⁴ DTaP2	8702/313,008 (2.8 %)	1(ref)	1(ref)
Delayed⁵ DTaP2	1093/43,458 (2.5 %)	0.90 (0.85-0.96)	0.96 (0.90-1.02)
Girls			
Timely⁴ DTaP2	6796/304,870 (2.2 %)	1(ref)	1(ref)
Delayed⁵ DTaP2	771/40,345 (1.9 %)	0.86 (0.80-0.92)	0.91 (0.85-0.98)
Test for interaction			P=0.3

Abbreviations: DTaP2=Second dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis; RR=Relative Risk; aRR=adjusted Relative Risk

¹⁾ Atopic Dermatitis identified according to the algorithm in sAppendix 2; ²⁾Relative risk estimated using a binary regression model; ³⁾ Adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education; ⁴⁾Second dose of DTaP before 6 months of age; ⁵⁾ Second dose of DTaP at or after 6 months of age.

Table 4: Association between number of delayed doses of DTaP (vaccination at or after 1 months after date of recommended vaccination) and development of AD between 6 months of age and 1 year of age

	Cases of AD ¹ /N (%)	RR ² (95%CI)	aRR ^{2,3} (95% CI)
All children			
Timely⁴ DTaP1 and DTaP2	15,498/617,878 (2.5%)	1 (ref)	1 (ref)
Delayed⁵ DTaP1 or DTaP2	2803/122,311 (2.3 %)	0.91 (0.88-0.95)	0.96 (0.92-1.00)
Delayed⁵ DTaP1 and DTaP2	1092/53,735 (2.0 %)	0.81 (0.76-0.86)	0.88 (0.82-0.93)
Boys			
Timely⁴ DTaP1 and DTaP2	8702/313,008 (2.8 %)	1(ref)	1(ref)
Delayed⁵ DTaP1 or DTaP2	1627/63,022 (2.6 %)	0.93 (0.88-0.98)	0.98 (0.93-1.03)
Delayed⁵ DTaP1 and DTaP2	643/27,508 (2.3 %)	0.84 (0.78-0.91)	0.91 (0.84-0.99)
Girls			
Timely⁴ DTaP1 and DTaP2	6796/304,870 (2.2 %)	1(ref)	1(ref)
Delayed⁵ DTaP1 or DTaP2	1176/59,289 (2.0 %)	0.89 (0.84-0.95)	0.94 (0.88-1.00)
Delayed⁵ DTaP1 and DTaP2	449/26,227 (1.7%)	0.77 (0.70-0.84)	0.83 (0.76-0.92)

Test for interaction

P=0.03

Abbreviations: DTaP1=First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; DTaP2=Second dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis; RR=Relative Risk; aRR=adjusted Relative Risk

¹) Atopic Dermatitis identified according to the algorithm in sAppendix 2; ²) Relative risk estimated using a binary regression model; ³) Adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education; ⁴) Second dose of DTaP before 6 months of age; ⁵) Second dose of DTaP-IPV-Hib at or after 6 months of age.

Figure E1

Danish vaccination schedule					Australian vaccination schedule					
Age in months					Age in months					
	3	5	12	15		Birth	2	4	6	12
Jan 97	DTaP-IPV + Hib	DTaP-IPV + Hib	DTaP-IPV + Hib	MMR	Nov 05	Hep B	DTaP-IPV- Hib - HepB + PCV13	DTaP-IPV- Hib - HepB + PCV13	DTaP-IPV+ PCV13	MMR + HepB-Hib + Men C
Jul 02	DTaP-IPV- Hib	DTaP-IPV- Hib	DTaP-IPV- Hib	MMR	Jul 07	Hep B	DTaP-IPV- Hib - HepB + PCV13 + Rotavirus	DTaP-IPV- Hib - HepB + PCV13 + Rotavirus	DTaP-IPV+ PCV13 + Rotavirus	MMR + HepB-Hib + Men C
Oct 07	DTaP-IPV- Hib + PCV7 ¹	DTaP-IPV- Hib + PCV7	DTaP-IPV- Hib + PCV7	MMR	Mar 08	Hep B	DTaP-IPV- Hib - HepB + PCV13 + Rotavirus	DTaP-IPV- Hib - HepB + PCV13 + Rotavirus	DTaP-IPV- Hib - HepB + PCV13 + Rotavirus	MMR + Hib + Men C
Apr 10	DTaP-IPV-Hib + PCV13 ²	DTaP-IPV- Hib + PCV13	DTaP-IPV- Hib + PCV13	MMR						

Abbreviations: D=Diphtheria; T=Tetanus; aP=acellular Pertussis; IPV=Inactivated Polio Vaccine; Hib=Haemophilus influenzae type b; MMR=Measles-Mumps-Rubella; PCV7=seven-valent Pneumococcal Conjugate Vaccine; PCV13=thirteen-valent Pneumococcal Conjugate Vaccine; HepB= Hepatitis B vaccine; Men C= meningococcal type C vaccine. **Red color= non-live vaccines; Green color=live vaccines.**

¹Children born after April 30th 2006 was offered PCV7 in a phase-in program. ²Children who have received PCV7 prior to the introduction of PCV13 could freely shift to PCV13 for future vaccination. PCV13 was gradually phased in as the stock of PCV7 was used first.

E-tables

Table E1: Baseline characteristics of included and excluded children

	Included	(%)	Excluded	(%)
Study population	883,160		144,399	
Season of birth				
Spring	222,628	(25.2%)	35,543	(24.6%)
Summer	236,679	(26.8%)	36,432	(25.2%)
Fall	219,239	(24.8%)	35,966	(24.9%)
Winter	204,614	(23.2%)	36,458	(25.2%)
Missing	0		0	
Sex				
Male	450,978	(51.1%)	75,890	(52.6%)
Female	432,182	(48.9%)	68,509	(47.4%)
Missing	0		0	
Number of children in household				
1	369,884	(41.9%)	60,418	(43.2%)
2	343,009	(38.8%)	49,576	(35.5%)
3	131,636	(14.9%)	20,276	(14.5%)
4 or more	38,631	(4.4%)	9464	(6.8%)
Missing	0		4665	
Delivered by Ceasarean section				
No	711,051	(80.5%)	116,292	(80.5%)
Yes	172,109	(19.5%)	28,107	(19.5%)
Missing	0		0	
Gestational age				
>= 37 weeks	827,007	(93.6%)	120,242	(92.2%)
<37 weeks	56,153	(6.4%)	10,138	(7.8%)
Missing	0		14,019	
Birth weight (g)				
<2000	15,881	(1.8%)	3587	(2.7%)
2001-2500	29,116	(3.3%)	5058	(3.8%)
2501-3000	108,907	(12.3%)	18,023	(13.4%)
3001-3500	281,438	(31.9%)	43,599	(32.5%)
3501-4000	295,864	(33.5%)	42,858	(32.0%)
4001-4500	124,056	(14.0%)	16,958	(12.6%)
4501+	27,898	(3.2%)	4054	(3.0%)
Missing	0		10,262	
Maternal smoking during pregnancy				
No	727,490	(82.4%)	88,769	(82.0%)
Yes	155,670	(17.6%)	19,507	(18.0%)
Missing	0		36,123	
Antibiotic use before baseline				
No	864,377	(97.9%)	140,393	(97.2%)
Yes	18,783	(2.1%)	4006	(2.8%)
Missing	0		0	
Chronic disease¹ before baseline				
No	851,821	(96.5%)	137,452	(95.2%)
Yes	31,339	(3.5%)	6947	(4.8%)
Missing	0		0	
Family history of AD²				
No	647,397	(73.3%)	110,290	(76.4%)
Yes	235,763	(26.7%)	34,109	(23.6%)
Missing	0		0	

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Single parenthood

Lives with two adults	822,094	(93.1%)	120,160	(86.0%)
Lives with single parent	61,066	(6.9%)	17,483	(12.5%)
No parents	0	(0.0%)	2091	(1.5 %)
Missing	0		4665	

Population density

<50	57,625	(6.5%)	7178	(5.1%)
50-499	497,212	(56.3%)	68,616	(49.1%)
500-1999	170,165	(19.3%)	29,274	(20.9%)
2000-4999	39,139	(4.4%)	6954	(5.0%)
>=5000	119,019	(13.5%)	27,712	(19.8%)
Missing	0		4665	

Maternal age at delivery

<=19	11,116	(1.3%)	4285	(3.0%)
20-24	99,675	(11.3%)	19,500	(13.6%)
25-29	296,744	(33.6%)	47,396	(33.0%)
30-34	319,551	(36.2%)	47,328	(33.0%)
35-39	134,050	(15.2%)	20,746	(14.5%)
>=40	22,024	(2.5%)	4092	(2.9%)
Missing	0		1052	

Parental birth countries

Denmark	733,698	(83.1%)	86,993	(60.3%)
Denmark and foreign	85,975	(9.7%)	21,992	(15.2%)
Foreign countries	63,487	(7.2%)	35,378	(24.5%)
Missing	0		36	

Household income quintile

First (lowest)	191,100	(21.6%)	53,349	(38.2%)
Second	205,163	(23.2%)	29,590	(21.2%)
Third	200,720	(22.7%)	22,944	(16.4%)
Fourth	164,146	(18.6%)	18,136	(13.0%)
Fifth (highest)	122,031	(13.8%)	15,706	(11.2%)
Missing	0		4674	

Highest educational level adult female

Primary school	159,321	(18.0%)	24,014	(22.4%)
High school exam	84,637	(9.6%)	12,084	(11.3%)
Vocational training	282,407	(32.0%)	32,164	(30.0%)
Bachelor academy	263,297	(29.8%)	28,263	(26.4%)
Master+	93,498	(10.6%)	10,498	(9.8%)
Missing	0		37,376	

Abbreviations: AD=Atopic Dermatitis

¹⁾ Identified according to algorithm from Kristensen et al. (31); ² Mother, father or sibling with AD identified according to the algorithm in sAppendix 2 before baseline.

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Table E2: Distribution of AD cases by first criteria fulfilled according to the algorithm

Criteria 1:	≥1 prescription with– ATC: D11AH “Agents for dermatitis, excluding corticosteroids”	1646 (5.1 %)
Criteria 2:	≥2 prescription within 12 months with ATC: D07 “Corticosteroids for topical use” or ATC: D11AH “Agents for dermatitis, excluding corticosteroids”	29,725 (91.5 %)
Criteria 3:	Hospital contact with ICD10: L20 “atopic dermatitis”	1104 (3.4 %)

Abbreviations: AD=Atopic Dermatitis; ATC=Anatomical Therapeutic Chemical Classification System, ICD10=International Classification of Disease version 10

E-tables

Table E3: Effect modification by the included baseline variables of the association between delayed vaccination with the first dose of DTaP and development of AD1 before 1 year of age

	aRR ² (95% CI) for development of AD comparing delayed ³ DTaP1 with timely ⁴ DTaP1		Walds test for interaction ⁵
	Delayed DTaP1	Timely DTaP1	
Season of birth			
Spring	0.95(0.90-1.01)	1 (ref)	P=0.63
Summer	0.94(0.88-0.99)	1 (ref)	
Fall	0.92(0.86-0.97)	1 (ref)	
Winter	0.97(0.91-1.03)	1 (ref)	
Sex			
Male	0.95(0.91-0.99)	1 (ref)	P=0.46
Female	0.93(0.89-0.97)	1 (ref)	
Number of children in household			
1	0.96(0.91-1.00)	1 (ref)	P=0.32
2	0.95(0.90-0.99)	1 (ref)	
3	0.92(0.85-1.00)	1 (ref)	
4 or more	0.84(0.73-0.96)	1 (ref)	
Delivered by caesarean section			
No	0.93 (0.90-0.96)	1 (ref)	P=0.17
Yes	0.98 (0.92-1.05)	1 (ref)	
Gastational age			
≥37 weeks	0.95 (0.92-0.98)	1 (ref)	P=0.24
<37 weeks	0.88 (0.79-0.99)	1 (ref)	
Birth weight			
≤2000g	0.94(0.78-1.14)	1 (ref)	P=0.97
2001-2500g	0.99(0.85-1.16)	1 (ref)	
2501-3000g	0.94(0.86-1.03)	1 (ref)	
3001-3500g	0.93(0.88-0.98)	1 (ref)	
3501-4000g	0.96(0.91-1.01)	1 (ref)	
4001-4500g	0.94(0.87-1.02)	1 (ref)	
4501g or more	0.91(0.77-1.06)	1 (ref)	
Maternal smoking during pregnancy			
No	0.95 (0.92-0.98)	1 (ref)	P=0.48
Yes	0.92 (0.86-0.99)	1 (ref)	
Antibiotic use before baseline			
0	0.94 (0.91-0.97)	1 (ref)	P=0.83
1	0.93 (0.79-1.09)	1 (ref)	
Chronic disease⁶ before baseline			
No	0.94 (0.91-0.97)	1 (ref)	P=0.68
Yes	0.92 (0.80-1.05)	1 (ref)	
Family history of AD⁷			
No	0.93(0.90-0.97)	1 (ref)	P=0.45
Yes	0.96(0.91-1.01)	1 (ref)	
Single parenthood			
Lives with two adults	0.95 (0.92-0.98)	1 (ref)	P=0.08
Lives with single parent	0.86 (0.78-0.96)	1 (ref)	
Population density			
< 50	0.92 (0.82-1.03)	1 (ref)	P=0.03
50-499	0.94 (0.90-0.98)	1 (ref)	

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500-1999	1.02 (0.96-1.09)	1 (ref)	
2000-4999	0.86 (0.74-1.00)	1 (ref)	
>=5000	0.88 (0.80-0.96)	1 (ref)	
Maternal age at birth of the child			
<=19	0.84(0.66-1.07)	1 (ref)	P=0.05
20-24	0.88(0.81-0.95)	1 (ref)	
25-29	0.99(0.94-1.04)	1 (ref)	
30-34	0.96(0.92-1.01)	1 (ref)	
35-39	0.87(0.80-0.95)	1 (ref)	
>=40	0.95(0.79-1.15)	1 (ref)	
Parental birth countries			
Denmark	0.95(0.92-0.98)	1 (ref)	P=0.53
Denmark and foreign country	0.90(0.82-0.99)	1 (ref)	
Foreign countries	0.93(0.86-1.01)	1 (ref)	
Household income quintile			
First (lowest)	0.87(0.82-0.92)	1 (ref)	P=0.03
Second	0.97(0.91-1.03)	1 (ref)	
Third	0.96(0.90-1.03)	1 (ref)	
Fourth	0.98(0.91-1.05)	1 (ref)	
Fifth (highest)	0.98(0.90-1.07)	1 (ref)	
Highest educational level adult female			
Primary school	0.89(0.84-0.95)	1 (ref)	P=0.21
High School exam	0.91(0.83-1.01)	1 (ref)	
Vocational training	0.95(0.90-1.00)	1 (ref)	
Bachelor academy	0.99(0.93-1.05)	1 (ref)	
Master +	0.94(0.85-1.05)	1 (ref)	
PCV recommended at 3 months of age			
No PCV ⁸⁾ recommended	0.94 (0.90-0.97)	1 (ref)	P=0.44
PCV7 ⁹⁾ recommended	0.92 (0.85-0.99)	1 (ref)	
PCV13 ¹⁰⁾ recommended	0.98 (0.91-1.07)	1 (ref)	

Abbreviations: DTaP1=First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis; aRR=adjusted Relative Risk; PCV=Pneumococcal Conjugate Vaccine.

¹⁾Atopic Dermatitis identified according to the algorithm in sAppendix 2; ²⁾ Relative risk calculated using a binary regression model, adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education; ³⁾ First dose of DTaP at or after 4 months of age; ⁴⁾ First dose of DTaP before 4 months of age; ⁵⁾ P-value (Wald test for homogeneity); ⁶⁾ Identified according to algorithm from Kristensen et al. (31); ⁷⁾ Mother, father or sibling with AD identified according to the algorithm in sAppendix 2 before baseline. ⁸⁾ Children recommended to receive the first dose of DTaP before October 1st 2007. ⁹⁾ Children recommended to receive the first dose of PCV7 Oct 1st 2007, ¹⁰⁾PCV13 recommended from April 1st 2010

E-tables

Table E4: Association between delayed vaccination with the first dose of DTaP and development of AD¹ before one year of age – Date of AD set one month prior to registration date²

All Children	Cases of AD/N (%)	RR ³ (95%CI)	aRR ^{3,4} (95% CI)
Timely ⁵ DTaP1	25,653/734,828 (3.5%)	1(ref)	1(ref)
Delayed ⁶ DTaP1	4,542/142,568 (3.2%)	0.91(0.88-0.94)	0.95 (0.92-0.98)
Boys			
Timely ⁵ DTaP1	14,693/374,142 (3.9%)	1(ref)	1(ref)
Delayed ⁶ DTaP1	2,634/73,132 (3.6%)	0.92(0.88-0.96)	0.96 (0.92-1.00)
Girls			
Timely ⁵ DTaP1	10,960/360,686 (3.0%)	1(ref)	1(ref)
Delayed ⁶ DTaP1	1,908/69,436 (2.8%)	0.90(0.86-0.95)	0.94 (0.90-0.99)

Test of interaction**P=0.68**

Abbreviations: DTaP1=First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis; RR=Relative Risk; aRR=adjusted Relative Risk

¹⁾ Atopic Dermatitis identified according to the algorithm in sAppendix 2; ²⁾ 5764 less children included compared to the primary investigation, as more children are registered with AD prior to baseline; ³⁾ Relative risk estimated using a binary regression model;

⁴⁾ Adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education. ⁵⁾ First dose of DTaP before 4 months of age; ⁶⁾ First dose of DTaP at or after 4 months of age.

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Table E5: Association between delayed vaccination with the first dose of DTaP and development of AD before 1 year of age among firstborn children only¹

All Children	Cases of AD ²	RR ³ (95%CI)	aRR ^{3,4} (95% CI)
Timely ⁵ DTaP1	14,103/323,555 (4.4 %)	1(ref)	1(ref)
Delayed ⁶ DTaP1	1940/46,329 (4.2 %)	0.96(0.92-1.01)	0.96 (0.92-1.01)
Boys			
Timely ⁵ DTaP1	8160/165,260 (4.9 %)	1(ref)	1(ref)
Delayed ⁶ DTaP1	1152/23,822 (4.8 %)	0.98 (0.92-1.04)	0.98 (0.92-1.04)
Girls			
Timely ⁵ DTaP1	5943/158,295 (3.8 %)	1(ref)	1(ref)
Delayed ⁶ DTaP1	788/22,507 (3.5 %)	0.93(0.87-1.00)	0.93 (0.87-1.01)

Test for interaction**P=0.33**

Abbreviations: DTaP1=First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis; RR=Relative Risk; aRR=adjusted Relative Risk

¹ Of the 883,160 children included for the primary investigation, 369,884 (41.9 %) children are firstborn; ² Atopic Dermatitis identified according to the algorithm in sAppendix 2; ³Relative risk estimated using a binary regression model; ⁴ Adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education; ⁵First dose of DTaP before 4 months of age; ⁶ First dose of DTaP at or after 4 months of age.

Table E6: Association between delayed vaccination with the first dose of DTaP and development of AD before 1 year of age – sensitive AD identification¹

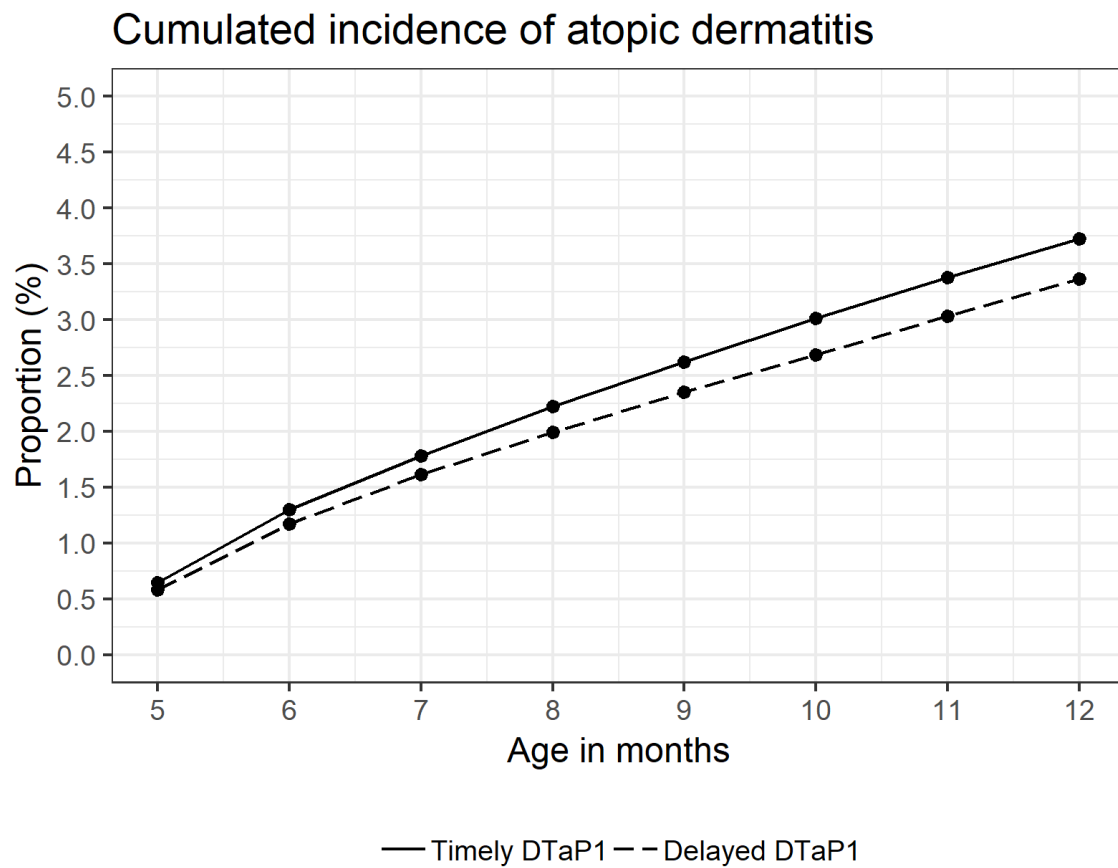
All Children	Cases of AD ¹	RR ² (95%CI)	aRR ^{2,3} (95% CI)
Timely ⁴ DTaP1	69,189/725,252 (9.5 %)	1(ref)	1(ref)
Delayed ⁵ DTaP1	12,217/141,011 (8.7 %)	0.91 (0.89-0.93)	0.94 (0.93-0.96)
Boys			
Timely ⁴ DTaP1	39,164/369,907 (10.6 %)	1(ref)	1(ref)
Delayed ⁵ DTaP1	7023/72,400 (9.7 %)	0.92 (0.89-0.94)	0.95 (0.93-0.98)
Girls			
Timely ⁴ DTaP1	30,025/356,345 (8.4 %)	1(ref)	1(ref)
Delayed ⁵ DTaP1	5194/68,611 (7.6 %)	0.90 (0.87-0.92)	0.93 (0.91-0.96)

Test for interaction**P=0.32**

Abbreviations: DTaP1=First dose of Diphtheria, Tetanus, acellular Pertussis - Inactivated Polio Vaccine - Haemophilus influenzae type b vaccine; AD=Atopic Dermatitis; RR=Relative Risk; aRR=adjusted Relative Risk

¹ Atopic Dermatitis identified according to the algorithm in sAppendix 2, but using only 1 prescription of corticosteroids for topical use to fulfill criteria 2; ²Relative risk estimated using a binary regression model; ³ Adjusted for season of birth, sex, number of children in the household, caesarean section, preterm birth, birthweight, maternal smoking during pregnancy, antibiotic use, chronic disease, family history of AD, single parenthood, population density, maternal age, parents origin at birth, income quintile, maternal education; ⁴First dose of DTaP before 4 months of age; ⁵ First dose of DTaP at or after 4 months of age.

Figure E2



Timely DTaP1: vaccination with first dose of DTaP-IPV-Hib before 4 months of age
Delayed DTaP1: vaccination with first dose of DTaP-IPV-Hib at or after 4 months of age

Online Repository Text – Algorithm to define children with atopic dermatitis

A child is defined as having atopic dermatitis from the first date¹ when any of the below criteria are fulfilled:

Criteria 1:

≥1 redeemed prescription with Tacrolimus/picremolimus: **D11AH01, D11AH02**

Criteria 2:

≥2 redeemed prescriptions, with at least two weeks between redemption of prescriptions and a maximum of 12 months-between redemption of prescriptions with below ATC-codes: _

- Glucocorticoids for external use, weak, moderately potent, potent or very potent (group 1, 2, 3 and 4): **D07AA, D07AB, D07AC, D07AD**
- Glucocorticoids for external use with antiseptics, weak, moderately potent, or potent (group 1, 2, 3, and 4): **D07BA, D07BB, D07BC, D07BD**
- Glucocorticoids for external use with antibiotics, weak, moderately potent, or potent (group 1, 2, 3, and 4): **D07CA, D07CB, D07CC, D07CD**
- Tacrolimus/picremolimus: **D11AH01, D11AH02**

(The criteria is fulfilled both if two prescriptions with the same ATC-code are redeemed and if two prescriptions with different ATC-codes are redeemed. The date of atopic dermatitis diagnosis will be defined as the date when the first prescription is redeemed in the series defining atopic dermatitis)

Criteria 3:

≥1 hospital contact² with a diagnosis³ of ICD10-codes: L20 (atopic dermatitis) including all sublevels

¹: For prescriptions, the date is the date of redemption of the prescription (not the date the prescription was made).

²: Any hospital contact will be included irrespective of whether it is coded as inpatient, outpatient, day patient or emergency room patients.

³: Any diagnosis will be included irrespective of the ordering of the diagnosis, e.g. both main diagnosis and all other diagnoses will be used to define atopic dermatitis.