

DR BRETT GREGORY TOELLE (Orcid ID : 0000-0002-7375-0019)

Article type : Letter to the Editor

Title: **Pertussis vaccination and Allergic illness in Australian children**

Short Running Title: **Pertussis vaccination and Childhood Allergy**

Word count: 1,241

Table count: 2

Figure count: 0

Authors:

Brett G Toelle PhD ^{a, b}

Frances L Garden PhD ^{c, d}

Peter B McIntyre PhD ^{e, f, g}

Nicholas Wood PhD ^{e, f, g}

Guy B Marks PhD ^{a, c, d}

for the Childhood Asthma Prevention Team

Affiliations:

^a Woolcock Institute of Medical Research, The University of Sydney, Sydney, Australia

^b Sydney Local Health District, Sydney, Australia

^c South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

^d Ingham Institute of Applied Medical Research, Sydney, Australia

^e National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Westmead, New South Wales, Australia

^f The Children's Hospital at Westmead, Sydney, New South Wales, Australia

^g The University of Sydney, Sydney, New South Wales, Australia

Corresponding author:

Brett G Toelle, PhD

Woolcock Institute of Medical Research

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/pai.13300](#)

This article is protected by copyright. All rights reserved

Box M77 Missenden Road Post Office

Camperdown, NSW, 2050

Tel: + 61 2 9114-0462

Fax: + 61 2 9114-0011

Email: brett.toelle@woolcock.org.au

Conflict of Interest Statement:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Statement:

National Health and Medical Research Council of Australia, Cooperative Research Centre for Asthma, New South Wales Department of Health, Children's Hospital Westmead, University of Sydney, Faculty of Medicine. Dr Almqvist was funded by the Swedish Heart Lung Foundation and Swedish Society of Medicine. Contributions of goods and services were made by Allergopharma Joachim Ganzer KG Germany, John Sands Australia, Hasbro, Toll refrigerated, AstraZeneca Australia, and Nu-Mega Ingredients Pty Ltd. Goods were provided at reduced cost by Auspharm, Allerssearch and Goodman Fielder Foods. University of Sydney, Faculty of Medicine, Strategic Research Grant 2008.

None of the funding sources had any involvement in analysis and interpretation of data; in the writing of the report nor in the decision to submit the article for publication.

To the Editor,

There has been ongoing interest in the temporal association between the change from whole cell pertussis (wP)-containing to acellular pertussis (aP)-containing vaccines in the routine infant immunization schedule in Australia and increases in childhood food allergies. This is because of the tendency of aP, but not wP, vaccines to promote TH2 immune responses, which are known to predispose children to allergy and allergic disease ¹.

A recent analysis of ICD coded data for anaphylaxis-related hospitalisations in Australia found that observed increases between the years 1998-1999 and 2004-2005 continued between the years 2005-2006 and 2011-20012, especially in older children ².

As the change from wP to aP-containing vaccines between 1997 and 1999 in Australia and coincided with recruitment of a birth cohort into a randomized controlled trial of interventions for the prevention of asthma - the Childhood Asthma Prevention Study (CAPS), we used trial data to conduct a post hoc analysis of the hypothesis that vaccination with wP, rather than aP-containing vaccines, is associated with a decreased prevalence of the atopic markers evaluated in the trial (including skin prick test positivity to peanut and egg) and parent reported diagnosed asthma, rhinitis and eczema ³.

The Childhood Asthma Prevention Study was a randomized controlled trial to test the effectiveness of house dust mite (HDM) avoidance and dietary fatty acid modification during the first 5 years of life as strategies for the primary prevention of asthma and allergy in high-risk children. High risk was defined as a parent or sibling having current asthma or frequent wheeze.. Briefly, between October 1997 and January 2000, 616 high-risk infants were randomized, using a factorial design, to receive an HDM avoidance intervention, a dietary fatty acid modification intervention, both interventions or neither. Clinical assessments were conducted at 18 months, 3, 5, 8, 11.5 and 14 years ⁴⁻⁶. During early life, study nurses collected information about the babies' development, vaccinations, symptoms and home environment. At clinical assessments between 18 months and 14 years, we collected data on respiratory and allergic symptoms and diagnoses and from 5 years of age we measured lung function by spirometry. Skin prick tests were performed with a standardized protocol and classified as positive if the mean wheal size was at least 3mm ⁶.

Although we prospectively collected self-reported data on vaccination, we did not ascertain whether the pertussis vaccine given was wP or aP. To capture this information, we used the Australian Childhood Immunisation Register (ACIR), a national register established in 1996 ⁷. In 2017, we identified cohort members in the ACIR using their name and the address recorded during the first six months of life for each child. Information on the type of pertussis vaccine administered was extracted. This study was approved the Sydney Local Health District RPAH Zone, Human Research Ethics Committee (HREC/08/RPAH/472).

In this analysis, we ascertained pertussis vaccine type for all children who participated in at least the first clinical outcome assessment at 18 months (n=552) and were successful for 524 (94.9%) participants. The analysis was restricted to the 497 children who had their first dose of pertussis vaccine between the ages of six and 18 weeks⁸. Only data on vaccines administered before age 18 months were considered. Exposure to pertussis vaccine was characterized using two binary definitions: 1) first dose was wP vaccine vs first dose was aP vaccine, regardless of subsequent pertussis vaccine type and 2) at least one of the first three doses was wP vaccine vs all of the first three doses were aP. Outcome variables were defined as present at any assessment to age 5, 8 and 11.5 years.

To assess the association between vaccine type and the outcomes, accounting for repeated measurements, we used a hierarchical log-binomial regression model with individuals treated as random intercepts. The results are reported as relative risks (RR) with associated 95% confidence intervals. The longitudinal RR is calculated in a mixed model and use information from all previous assessments. We also present results adjusted for sex and breastfeeding duration (< or ≥ 6 months); and another analyses where we controlled for the CAPS study intervention groups, that is, house dust mite avoidance (active or control) and omega-3 supplementation (active or control) to confirm that the randomized intervention groups did not confound the observed associations.

There were 293 (59%) participants who were recorded on the ACIR with wP as their first dose of pertussis vaccine 204 (41%) with aP as their first dose. A larger proportion (325, 65%) received at least one dose of wP over the three-dose primary course.

The longitudinal relative risk for atopy or allergic illnesses related to exposure to whole cell pertussis vaccine as the first dose is shown in Table 1. wP vaccine was not associated with a reduced risk of allergic illnesses and when relative risk estimates were adjusted for sex and breastfeeding, wP as the first dose was associated with an increased risk of peanut sensitization at 5, 8 and 11.5 years of age. However, none of the associations was significant after adjustment for trial intervention status.

Comparison between children who received any doses of wP vaccine vs children who received aP vaccine for all doses is presented in Table 2. As for the first dose analysis, wP vaccine was associated with an increased risk of peanut sensitization at 5, 8 and 11.5 years of age and additionally this association still reached statistical significance after adjustment for sex, breastfeeding greater than or equal to six months and allocation to the house dust mite (HDM) and diet interventions.

The results were inconsistent for outcomes measured at 18 months, 3 years and 14 years, and because we had fewer positive tests in the earlier years and loss to follow up was greater in the older year we did not want to over interpret statistically significant results(online repository Tables 3 and 4). We also compared a subset of children who received the first 3 doses of wP vs. first three doses of aP (online repository Table 5). The results showed a statistically significant association with peanut across ages, and with any aeroallergen but only in the early ages.

In summary, among children born to families with a strong history of asthma between 1997 and 2000 and prospectively studied for more than 10 years, our post hoc analysis did not support the hypothesis that the move from wP to aP was associated with increased risk of aeroallergen allergy, asthma, eczema or rhinitis. Our findings are similar to those from an unselected birth cohort reported from the Isle of Wight recruited in 2001-2002 and followed to 10 years of age ⁸ and a cohort of Polish children followed to six years of age ⁹. Limitations of our analysis include that the Childhood Asthma Prevention Study was primarily designed to evaluate aeroallergens, did not prospectively collect data on the type of pertussis vaccine received, so we relied on register-recorded data, and sample size was limited. However, skin prick tests for peanut and egg sensitivity were standardized and for all measures examined, the width of the confidence intervals provides some guidance of the magnitude of the effects excluded. Importantly, the direction of effect is at odds with recently published Australian research showing that children who received wP containing vaccines had a lower risk of food allergy ¹⁰. These divergent findings emphasize the importance of the Australian trial currently underway comparing allergic markers among infants randomized to receive their first dose as whole cell or acellular pertussis vaccine ¹¹.

REFERENCES

- Accepted Article
1. Robinson D, Humbert M, Buhl R, et al. Revisiting Type 2-high and Type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy*. 2017;47(2):161-175.
 2. Mullins RJ, Dear KB, Tang ML. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol*. 2015;136(2):367-375.
 3. Garden FL, Toelle BG, Mhrshahi S, et al. Cohort profile: The Childhood Asthma Prevention Study (CAPS). *Int J Epidemiol*. 2018;47(6):1736-1736k.
 4. Marks GB, Mhrshahi S, Kemp AS, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol*. 2006;118(1):53-61.
 5. Toelle BG, Ng KK, Crisafulli D, et al. Eight-year outcomes of the Childhood Asthma Prevention Study. *J Allergy Clin Immunol*. 2010;126(2):388-389, 389 e381-383.
 6. Toelle BG, Garden FL, Ng KK, et al. Outcomes of the Childhood Asthma Prevention Study at 11.5 years. *J Allergy Clin Immunol*. 2013;132(5):1220-1222.
 7. Torvaldsen S, Hull BP, McIntyre PB. Using the Australian Childhood Immunisation Register to track the transition from whole-cell to acellular pertussis vaccines. *Commun Dis Intell*. 2002;26(4):581-583.
 8. Venter C, Stowe J, Andrews NJ, Miller E, Turner PJ. No association between atopic outcomes and type of pertussis vaccine given in children born on the Isle of Wight 2001-2002. *J Allergy Clin Immunol Pract*. 2016;4(6):1248-1250.
 9. Mrozek-Budzyn D, Majewska R, Kieltyka A, Augustyniak M. Whole-cell pertussis vaccine (DTwP) has no influence on allergic diseases and atopic sensitization in children. *Postepy Dermatol Alergol*. 2018;35(4):381-386.

- Accepted Article
10. Estcourt MJ, Campbell DE, Gold MS, et al. Whole cell pertussis vaccination and decreased risk of IgE-mediated food allergy: a nested case-control study. *J Allergy Clin Immunol Pract.* 2019.
 11. Australian New Zealand Clinical Trial Registry.
<https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12617000065392>.
Updated 09/03/2019. Accessed 24/01/2020.

Table 1

Comparison of atopy and allergic illness in children who received first dose of wP vs aP

Outcome	First dose wP n/N (%)	First dose aP n/N (%)	Longitudinal Relative Risk (95% CI)	P value[#]	Adjusted* Relative Risk (95% CI)	P value	Adjusted^s Relative Risk (95%CI)	P value
Positive SPT to any aeroallergen^ to 5 years	107/263 (40.7%)	65/180 (36.1%)	1.39 (0.97, 2.00)	0.07	1.47 (1.02, 2.11)	0.039	1.41 (0.98, 5.56)	0.06
Positive SPT to any aeroallergen^ to 8 years	105/205 (51.2%)	69/159 (43.4%)	1.30 (0.91, 1.85)	0.15	1.37 (0.96, 1.96)	0.085	1.31 (0.92, 1.88)	0.14
Positive SPT to any aeroallergen^ to 11.5 years	106/166 (63.9%)	49/102 (48.0%)	1.38 (0.97, 1.97)	0.07	1.47 (1.03, 2.09)	0.035	1.39 (0.98, 1.98)	0.07
Positive SPT to peanut allergen to 5 years	21/263 (8.0%)	7/180 (3.9%)	2.27 (0.96, 5.38)	0.06	2.44 (1.02, 5.87)	0.046	2.33 (0.98, 5.56)	0.06
Positive SPT to peanut allergen to 8 years	15/202 (7.4%)	11/158 (7.0%)	2.03 (0.95, 4.36)	0.07	2.18 (1.00, 4.76)	0.049	2.05 (0.95, 4.42)	0.07
Positive SPT to peanut allergen to 11.5 years	13/165 (7.9%)	7/96 (7.3%)	2.09 (0.97, 4.51)	0.06	2.22 (1.01, 4.86)	0.047	2.09 (0.96, 4.55)	0.06

Positive SPT to egg allergen to 5 years	19/262 (7.3%)	14/180 (7.8%)	1.12 (0.57, 2.23)	0.74	1.24 (0.61, 2.51)	0.55	3.66 (0.79, 16.96)	0.80
Positive SPT to egg allergen to 8 years	17/204 (8.3%)	12/158 (7.6%)	1.02 (0.85, 1.23)	0.82	1.30 (0.66, 2.58)	0.45	1.12 (0.67, 1.90)	0.65
Positive SPT to egg allergen to 11.5 years	14/167 (8.4%)	6/102 (5.9%)	1.14 (0.59, 2.22)	0.69	1.26 (0.64, 2.50)	0.50	1.11 (0.57, 2.17)	0.75
Current asthma to 5 years	86/278 (30.9%)	58/190 (30.5%)	0.99 (0.66, 1.48)	0.95	0.98 (0.65, 1.48)	0.93	1.00 (0.66, 1.50)	0.99
Current asthma to 8 years	88/234 (37.6%)	58/174 (33.3%)	1.09 (0.74, 1.62)	0.65	1.09 (0.74, 1.63)	0.66	1.10 (0.74, 1.64)	0.62
Current asthma to 11.5 years	86/210 (41.0%)	44/128 (34.4%)	1.10 (0.74, 1.63)	0.64	1.11 (0.75, 1.66)	0.60	1.10 (0.74, 1.64)	0.62
Current eczema to 5 years	128/275 (46.6%)	76/189 (40.2%)	1.43 (1.00, 2.05)	0.051	1.43 (0.99, 2.06)	0.055	1.37 (0.95, 1.97)	0.09
Current eczema to 8 years	105/224 (46.9%)	71/164 (43.3%)	1.33 (0.93, 1.90)	0.12	1.31 (0.91, 1.88)	0.15	1.27 (0.89, 1.82)	0.19
Current eczema to 11.5 years	87/171	46/105	1.27	0.19	1.26	0.22	1.21	0.29

	(50.9%)	(43.8%)	(0.89, 1.83)		(0.87, 1.81)		(0.85, 1.75)	
Current rhinitis to 5 years	209/278 (75.2%)	143/190 (75.3%)	0.84 (0.65, 1.10)	0.21	0.84 (0.64, 1.10)	0.20	0.84 (0.64, 1.10)	0.20
Current rhinitis to 8 years	189/234 (80.8%)	135/172 (78.5%)	0.88 (0.70, 1.12)	0.32	0.87 (0.69, 1.11)	0.28	0.88 (0.69, 1.12)	0.30
Current rhinitis to 11.5 years	179/210 (85.3%)	104/128 (81.3%)	0.96 (0.76, 1.21)	0.73	0.95 (0.76, 1.20)	0.68	0.95 (0.76, 1.20)	0.69
			Mean difference 95%CI		Mean difference 95%CI		Mean difference 95%CI	
Log total IgE at 5 years (mean, SD)	4.2 (1.6)	4.4 (1.3)	-0.191 (-0.439, 0.0574)	0.13	-0.158 (-0.405, 0.089)	0.21	-0.176 (-0.424, 0.072)	0.16
Log total IgE at 8 years (mean, SD)	4.7 (1.6)	4.7 (1.6)	-0.186 (-0.436, 0.063)	0.14	-0.154 (-0.403, 0.095)	0.23	-0.172 (-0.422, 0.078)	0.18
Log total IgE at 11.5 years (mean, SD)	5.1 (1.5)	5.0 (1.5)	-0.156 (-0.407, 0.095)	0.22	-0.124 (-0.375, 0.127)	0.33	-0.143 (-0.394, 0.109)	0.27

* adjusted for sex and breastfeeding ≥ 6 months

^ aeroallergens tested: Dermatophagoides pteronyssinus (HDM), cockroach, cat, Alternaria alternata, rye grass, and grass mix; plus dog and aspergillus at 8 and 11.5 years

P-value from a hierarchical log-binomial regression model with individuals treated as random intercepts.

\$ adjusted for intervention type, HDM and Diet

Mean difference = mean of log total IgE in the first dose wp group - mean of log total IgE in the first dose ap group. Total IgE had a skewed distribution and was log transformed.

Table 2

Comparison of atopy and allergic illness in children who received any dose of wP vs no dose of wP

Outcome	Any dose wP n/N (%)	No dose of wP n/N (%)	Longitudinal Relative Risk (95% CI)	P value[#]	Adjusted* Relative Risk (95% CI)	P value	Adjusted^s Relative Risk (95%CI)	P value
Positive SPT to any aeroallergen [^] to 5 years	117/292 (40.1%)	55/151 (36.4%)	1.34 (0.92, 1.95)	0.13	1.41 (0.97, 2.06)	0.07	1.35 (0.93, 1.98)	0.11
Positive SPT to any aeroallergen [^] to 8 years	112/227 (49.3%)	62/137 (45.3%)	1.20 (0.83, 1.74)	0.33	1.27 (0.88, 1.84)	0.20	1.21 (0.84, 1.76)	0.30
Positive SPT to any aeroallergen [^] to 11.5 years	112/184 (60.9%)	43/84 (51.2%)	1.26 (0.87, 1.81)	0.22	1.34 (0.92, 1.93)	0.12	1.26 (0.87, 1.82)	0.21
Positive SPT to peanut allergen to 5 years	23/292 (7.9%)	5/151 (3.3%)	3.06 (1.14, 8.22)	0.027	3.30 (1.21, 9.01)	0.020	3.22 (1.17, 8.84)	0.023
Positive SPT to peanut allergen to 8 years	18/224 (8.0%)	8/136 (5.9%)	2.69 (1.14, 6.34)	0.024	2.90 (1.21, 6.95)	0.017	2.77 (1.16, 6.61)	0.022
Positive SPT to peanut allergen to 11.5 years	15/183 (8.2%)	5/78 (6.4%)	2.79 (1.17, 6.64)	0.021	2.97 (1.23, 7.18)	0.016	2.86 (1.18, 6.90)	0.020

Positive SPT to egg allergen to 5 years	21/291 (7.2%)	12/151 (8.0%)	1.14 (0.56, 2.32)	0.72	1.25 (0.60, 2.61)	0.54	1.10 (0.53, 2.25)	0.80
Positive SPT to egg allergen to 8 years	18/226 (8.0%)	11/136 (8.1%)	1.17 (0.68, 2.01)	0.57	1.29 (0.63, 2.62)	0.48	1.14 (0.66, 1.96)	0.65
Positive SPT to egg allergen to 11.5 years	15/185 (8.1%)	5/84 (6.0%)	1.14 (0.57, 2.26)	0.72	1.24 (0.61, 2.53)	0.54	1.10 (0.55, 2.19)	0.80
Current asthma to 5 years	96/308 (31.2%)	48/160 (30.0%)	1.01 (0.67, 1.54)	0.95	1.005 (0.66, 1.54)	0.98	1.02 (0.67, 1.56)	0.91
Current asthma to 8 years	96/261 (36.8%)	50/147 (34.0%)	1.08 (0.72, 1.63)	0.70	1.08 (0.71, 1.63)	0.72	1.09 (0.72, 1.65)	0.68
Current asthma to 11.5 years	91/232 (39.2%)	39/106 (36.8%)	1.07 (0.71, 1.61)	0.75	1.08 (0.72, 1.63)	0.71	1.07 (0.71, 1.62)	0.73
Current eczema to 5 years	136/305 (44.6%)	68/159 (42.8%)	1.24 (0.85, 1.80)	0.26	1.24 (0.85, 1.80)	0.27	1.18 (0.81, 1.71)	0.39
Current eczema to 8 years	112/247 (45.3%)	64/141 (45.4%)	1.17 (0.80, 1.69)	0.42	1.15 (0.79, 1.67)	0.47	1.11 (0.77, 1.61)	0.58
Current eczema to 11.5 years	92/189	41/87	1.13	0.53	1.11	0.57	1.07	0.73

	(48.7%)	(47.1%)	(0.78, 1.64)		(0.76, 1.62)		(0.74, 1.55)	
Current rhinitis to 5 years	234/308 (76.0%)	118/160 (73.8%)	0.96 (0.73, 1.27)	0.78	0.96 (0.72, 1.26)	0.75	0.96 (0.73, 1.26)	0.75
Current rhinitis to 8 years	211/261 (80.8%)	113/145 (77.9%)	0.996 (0.78, 1.28)	0.97	0.98 (0.77, 1.26)	0.90	0.99 (0.77, 1.27)	0.94
Current rhinitis to 11.5 years	198/232 (85.34)	85/106 (80.2%)	1.06 (0.84, 1.35)	0.63	1.05 (0.83, 1.34)	0.68	1.05 (0.83, 1.34)	0.67
			Mean Difference 95%CI		Mean Difference 95%CI		Mean Difference 95%CI	
Log total IgE at 5 years (mean, SD)	4.2 (1.6)	4.4 (1.3)	-0.147 (-0.404, 0.111)	0.26	-0.112 (-0.369, 0.144)	0.39	-0.129 (-0.387, 0.129)	0.33
Log total IgE at 8 years (mean, SD)	4.7 (1.6)	4.7 (1.6)	-0.163 (-0.421, 0.096)	0.22	-0.128 (-0.386, 0.130)	0.33	-0.146 (-0.405, 0.113)	0.27
Log total IgE at 11.5 years (mean, SD)	5.0 (1.5)	5.1 (1.6)	-0.12 (-0.38, 0.14)	0.37	-0.085 (-0.345, 0.175)	0.52	-0.105 (-0.365, 0.156)	0.43

* adjusted for sex and breastfeeding ≥ 6 months

^ aeroallergens tested: Dermatophagoides pteronyssinus (HDM), cockroach, cat, Alternaria alternata, rye grass, and grass mix; plus dog and aspergillus at 8 and 11.5 years

P-value from a hierarchical log-binomial regression model with individuals treated as random intercepts.

\$ adjusted for intervention type, HDM and Diet

Mean difference = mean of log total IgE in the any dose of wp group - mean of log total IgE in the no dose of wp group. Total IgE had a skewed distribution and was log transformed.

Table 3

Comparison of atopy and allergic illness in children who received first dose of wP vs aP.
Outcomes for years 1.5, 3 and 14[&] only.

Outcome	First dose wP n/N (%)	First dose aP n/N (%)	Longitudinal Relative Risk (95% CI)	P value[#]	Adjusted* Relative Risk (95% CI)	P value	Adj^s Rel Risk (95%CI)	P value
Positive SPT to any aeroallergen [^] to 1.5 years	24/282 (8.5%)	10/199 (5.0%)	1.76 (0.82, 3.78)	0.1476	1.88 (0.87, 4.07)	0.1106	1.72 (0.80, 3.72)	0.1635
Positive SPT to any aeroallergen [^] to 3 years	70/280 (25.0%)	31/192 (16.2%)	1.73 (1.12, 2.67)	0.0140	1.84 (1.18, 2.86)	0.0069	1.76 (1.13, 2.72)	0.0118
Positive SPT to any aeroallergen [^] to 14 years	78/116 (67.3%)	39/68 (57.4%)	1.42 (1.00, 2.12)	0.0484	1.51 (1.06, 2.16)	0.0220	1.43 (1.00, 2.04)	0.0474
Positive SPT to peanut allergen to 1.5 years	15/282 (5.3%)	5/199 (2.5%)	2.18 (0.78, 6.12)	0.1389	2.33 (0.82, 6.62)	0.1109	2.22 (0.79, 6.27)	0.1308
Positive SPT to peanut allergen to 3 years	16/280 (5.7%)	4/192 (2.1%)	2.40 (0.99, 5.79)	0.0518	2.55 (1.04, 6.25)	0.0410	2.44 (1.00, 5.92)	0.0493
Positive SPT to egg allergen to 1.5 years	18/282 (6.4%)	10/199 (5.0%)	1.29 (0.58, 2.86)	0.5331	1.39 (0.62, 3.14)	0.4240	1.27 (0.57, 2.84)	0.5578
Positive SPT to egg allergen to 3 years	8/280 (2.9%)	6/192 (3.1%)	1.11 (0.55, 2.22)	0.7685	1.22 (0.60, 2.49)	0.5779	1.09 (0.54, 2.20)	0.8008
Positive SPT to egg allergen to 14 years	1/177 (0.9%)	1/68 (1.5%)	1.11 (0.58, 2.15)	0.7497	1.21 (0.61, 2.38)	0.5862	1.08 (0.55, 2.10)	0.8231
Current asthma to 1.5 years	41/293 (14.0%)	23/203 (11.3%)	1.27 (0.74, 2.20)	0.3865	1.29 (0.74, 2.24)	0.3689	1.27 (0.73, 2.21)	0.3896
Current asthma to 3 years	56/284 (19.7%)	41/196 (20.9%)	1.05 (0.68, 1.63)	0.8240	1.05 (0.68, 1.64)	0.8170	1.06 (0.68, 1.65)	0.7949
Current asthma to 14 years	36/188	19/132	1.12	0.5604	1.14	0.5152	1.13	0.5515

	(19.2%)	(14.4%)	(0.76, 1.66)		(0.77, 1.69)		(0.76, 1.67)	
Current eczema to 1.5 years	100/285 (35.1%)	47/200 (23.5%)	1.76 (1.17, 2.65)	0.0069	1.75 (1.15, 2.65)	0.0084	1.71 (1.13, 2.59)	0.0107
Current eczema to 3 years	77/280 (27.5%)	47/195 (24.1%)	1.48 (1.03, 2.12)	0.0327	1.48 (1.03, 2.13)	0.0356	1.43 (0.99, 2.05)	0.0544
Current eczema to 14 years	22/121 (18.2%)	14/73 (19.2%)	1.23 (0.86, 1.78)	0.2603	1.21 (0.84, 1.76)	0.3025	1.18 (0.81, 1.70)	0.3855
Current rhinitis to 1.5 years	154/291 (52.9%)	107/202 (53.0%)	1.00 (1.17, 2.65)	0.9914	0.96 (0.67, 1.39)	0.8355	0.997 (0.69, 1.43)	0.9876
Current rhinitis to 3 years	119/284 (41.9%)	96/196 (49.0%)	0.87 (0.64, 1.16)	0.3344	0.86 (0.64, 1.16)	0.3153	0.86 (0.64, 1.16)	0.3317
Current rhinitis to 14 years	72/188 (38.3%)	45/132 (34.1%)	0.98 (0.78, 1.24)	0.8723	0.97 (0.77, 1.23)	0.8092	0.97 (0.77, 1.23)	0.8065
			Mean difference 95%CI		Mean difference 95%CI		Mean difference 95%CI	
Log total IgE at 1.5 years (mean, SD)	2.92 (1.35)	3.29 (1.31)	-0.37 (-0.66, - 0.08)	0.0126	-0.34 (-0.63, - 0.06)	0.0196	-0.35 (-0.65, - 0.062)	0.0176
Log total IgE at 3 years (mean, SD)	3.58 (1.59)	3.57 (1.44)	-0.19 (-0.46, 0.07)	0.1446	-0.16 (-0.41, 0.10)	0.2369	-0.18 (-0.44, 0.08)	0.1739
Log total IgE at 14 years (mean, SD)	5.17 (1.64)	5.00 (1.46)	-0.13 (-0.38, 0.13)	0.3250	-0.094 (-0.35, 0.16)	0.4684	-0.12 (-0.37, 0.14)	0.3727

* adjusted for sex and breastfeeding ≥ 6 months

^ aeroallergens tested: Dermatophagoides pteronyssinus (HDM), cockroach, cat, Alternaria alternata, rye grass, and grass mix; plus dog and aspergillus at 8 and 11.5 years

P-value from a hierarchical log-binomial regression model with individuals treated as random intercepts.

\$ adjusted for intervention type, HDM and Diet

& Peanut allergy by skin prick test not done at 14 years

Mean difference = mean of log total IgE in the first dose wp group - mean of log total IgE in the first dose ap group. Total IgE had a skewed distribution and was log transformed.

Table 4

Comparison of atopy and allergic illness in children who received any dose of wP vs no dose of wP
Outcomes for: 1.5, 3 and 14[&] years

Outcome	Any dose wP n/N (%)	No dose of wP n/N (%)	Longitudinal Relative Risk (95% CI)	P value[#]	Adjusted* Relative Risk (95% CI)	P value	Adj^{\$} Rel Risk (95%CI)	P value
Positive SPT to any aeroallergen [^] to 1.5 years	26/313 (8.3%)	8/168 (4.8%)	1.81 (0.80, 3.18)	0.1545	1.95 (0.85, 4.47)	0.1135	1.77 (0.78, 4.03)	0.1731
Positive SPT to any aeroallergen [^] to 3 years	79/310 (25.5%)	29/162 (17.9%)	1.62 (1.03, 2.54)	0.0385	1.72 (1.08, 2.73)	0.0205	1.65 (1.04, 2.60)	0.0329
Positive SPT to any aeroallergen [^] to 14 years	82/128 (64.1%)	35/56 (62.5%)	1.27 (0.88, 1.83)	0.1952	1.35 (0.94, 1.96)	0.1047	1.28 (0.88, 1.85)	0.1917
Positive SPT to peanut allergen to 1.5 years	17/313 (5.4%)	3/68 (1.8%)	3.16 (0.91, 10.98)	0.0704	3.42 (0.98, 12.02)	0.0547	3.24 (0.93, 11.33)	0.0654
Positive SPT to peanut allergen to 3 years	23/310 (7.4%)	4/162 (2.5%)	3.46 (1.21, 9.92)	0.0210	3.72 (1.28, 10.84)	0.0160	3.60 (1.24, 10.47)	0.0190
Positive SPT to egg allergen to 1.5 years	20/313 (6.4%)	8/168 (4.8%)	1.37 (0.59, 3.18)	0.4700	1.50 (0.63, 3.55)	0.3546	1.35 (0.58, 3.17)	0.4876
Positive SPT to egg allergen to 3 years	22/310 (7.1%)	12/162 (7.4%)	1.14 (0.55, 2.36)	0.7153	1.26 (0.60, 2.65)	0.5351	1.12 (0.54, 2.33)	0.7547
Positive SPT to egg allergen to 14 years	12/129 (9.3%)	4/56 (7.1%)	1.10 (0.55, 2.18)	0.7904	1.18 (0.58, 2.39)	0.6410	1.06 (0.53, 2.11)	0.8782
Current asthma to 1.5 years	42/324 (13.0%)	22/172 (12.8%)	1.02 (0.58, 1.77)	0.9567	1.02 (0.58, 1.79)	0.9419	1.01 (0.58, 1.77)	0.9682
Current asthma to 3 years	72/315 (22.9%)	36/165 (21.8%)	1.06 (0.67, 1.67)	0.7983	1.06 (0.67, 1.68)	0.8020	1.07 (0.68, 1.69)	0.7685
Current asthma to 14 years	83/208 (39.9%)	46/112 (41.1%)	1.08 (0.74, 1.58)	0.7041	1.09 (0.73, 1.65)	0.6584	1.08 (0.72, 1.63)	0.6970

Current eczema to 1.5 years	103/315 (32.7%)	44/170 (25.9%)	1.39 (0.92, 2.11)	0.1213	1.38 (0.90, 2.11)	0.1374	1.35 (0.88, 2.05)	0.1689
Current eczema to 3 years	126/311 (40.5%)	62/164 (37.8%)	1.21 (0.84, 1.76)	0.3094	1.21 (0.83, 1.76)	0.3258	1.16 (0.80, 1.69)	0.4299
Current eczema to 14 years	63/133 (47.4%)	28/61 (45.9%)	1.08 (0.74, 1.58)	0.6768	1.07 (0.73, 1.56)	0.7393	1.03 (0.70, 1.50)	0.8825
Current rhinitis to 1.5 years	176/322 (54.7%)	85/171 (49.7%)	1.22 (0.84, 1.77)	0.2963	1.18 (0.81, 1.72)	0.3963	1.22 (0.84, 1.78)	0.2959
Current rhinitis to 3 years	214/315 (67.94%)	109/165 (66.1%)	0.99 (0.73, 1.34)	0.9268	0.98 (0.72, 1.33)	0.8977	0.99 (0.73, 1.34)	0.9241
Current rhinitis to 14 years	181/208 (87.0%)	92/112 (82.1%)	1.07 (0.84, 1.36)	0.5916	1.06 (0.83, 1.35)	0.6512	1.06 (0.83, 1.35)	0.6497
			Mean difference 95%CI		Mean difference 95%CI		Mean difference 95%CI	
Log total IgE at 1.5 years (mean, SD)	3.00 (1.38)	3.21 (1.27)	-0.22 (-0.52, 0.09)	0.1622	-0.18 (-0.48, 0.12)	0.2415	-0.19 (-0.50, 0.11)	0.2144
Log total IgE at 3 years (mean, SD)	3.59 (1.57)	3.54 (1.43)	-0.10 (-0.37, 0.17)	0.4538	-0.06 (-0.33, 0.21)	0.6528	-0.088 (-0.36, 0.18)	0.5235
Log total IgE at 14 years (mean, SD)	5.11 (1.63)	5.10 (1.45)	-0.10 (-0.36, 0.16)	0.4580	-0.06 (-0.33, 0.20)	0.6404	-0.086 (-0.35, 0.18)	0.5288

* adjusted for sex and breastfeeding ≥ 6 months

^ aeroallergens tested: Dermatophagoides pteronyssinus (HDM), cockroach, cat, Alternaria alternata, rye grass, and grass mix; plus dog and aspergillus at 8 and 11.5 years

P-value from a hierarchical log-binomial regression model with individuals treated as random intercepts.

\$ adjusted for intervention type, HDM and Diet

& Peanut allergy by skin prick test not done at 14 years

Mean difference = mean of log total IgE in the any dose of wp group - mean of log total IgE in the no dose of wp group. Total IgE had a skewed distribution and was log transformed.

Table 5

Comparison of atopy and allergic illness in children who received the first 3 doses of wP vs. first three doses of aP

Outcome	All doses wP n/N (%)	All doses aP n/N (%)	Longitudinal Relative Risk (95% CI)	P value[#]	Adjusted* Relative Risk (95% CI)	P value	Adjusted^s Relative Risk (95%CI)	P value
Positive SPT to any aeroallergen^ to 1.5 years	20/170 (11.8%)	7/145 (4.8%)	2.63 (1.07, 6.44)	0.0347	2.71 (1.10, 6.71)	0.0311	2.55 (1.04, 6.29)	0.0418
Positive SPT to any aeroallergen^ to 3 years	52/171 (30.4%)	24/140 (17.1%)	2.17 (1.29, 3.66)	0.0037	2.30 (1.36, 3.92)	0.0021	2.24 (1.32, 3.80)	0.0029
Positive SPT to any aeroallergen^ to 5 years	71/160 (44.4%)	47/130 (36.2%)	1.67 (1.08, 2.59)	0.0207	1.77 (1.14, 2.75)	0.0115	1.69 (1.09, 2.62)	0.0195
Positive SPT to any aeroallergen^ to 8 years	62/121 (51.2%)	54/116 (46.6%)	1.40 (0.91, 2.16)	0.1224	1.50 (0.97, 2.31)	0.0695	1.41 (0.91, 2.17)	0.1196
Positive SPT to any aeroallergen^ to 11.5 years	63/99 (63.6%)	39/75 (52.0%)	1.41 (0.92, 2.16)	0.1094	1.52 (0.99, 2.32)	0.0570	1.43 (0.93, 2.19)	0.1026
Positive SPT to any aeroallergen^ to 14 years	47/74 (63.5%)	31/50 (62.0%)	1.43 (0.93, 2.19)	0.1003	1.54 (1.00, 2.36)	0.0492	1.44 (0.94, 2.22)	0.0934
Positive SPT to peanut allergen to 1.5 years	10/170 (5.9%)	3/145 (2.1%)	2.96 (0.79, 11.04)	0.1063	3.17 (0.84, 12.08)	0.0892	3.19 (0.84, 12.08)	0.0873
Positive SPT to peanut allergen to 3 years	13/171 (7.6%)	3/140 (2.1%)	3.64 (1.09, 12.23)	0.0365	4.14 (1.19, 14.44)	0.0260	4.27 (1.21, 15.10)	0.0243
Positive SPT to peanut allergen to 5 years	13/160 (8.1%)	4/130 (3.1%)	2.86 (0.96, 8.49)	0.0580	3.30 (1.07, 10.15)	0.0372	3.49 (1.11, 10.96)	0.0321
Positive SPT to peanut allergen to 8 years	9/120 (7.5%)	6/115 (5.2%)	2.81 (1.08, 7.29)	0.0337	3.24 (1.21, 8.69)	0.0196	3.18 (1.19, 8.50)	0.0210
Positive SPT to peanut allergen to 11.5 years	6/99 (6.1%)	4/70 (5.7%)	2.96 (1.41, 6.22)	0.0043	3.28 (1.20, 8.95)	0.0203	3.26 (1.20, 8.85)	0.0204

Positive SPT to egg allergen to 1.5 years	7/170 (4.1%)	7/145 (4.8%)	0.85 (0.29, 2.49)	0.7617	0.84 (0.28, 2.52)	0.7484	0.88 (0.30, 2.62)	0.8247
Positive SPT to egg allergen to 3 years	8/171 (4.7%)	10/140 (7.1%)	0.73 (0.29, 1.88)	0.5189	0.74 (0.28, 1.94)	0.5364	0.75 (0.29, 1.93)	0.5460
Positive SPT to egg allergen to 5 years	8/160 (5.0%)	10/130 (7.7%)	0.74 (0.29, 1.87)	0.5248	0.73 (0.29, 1.93)	0.5282	0.75 (0.29, 1.92)	0.5509
Positive SPT to egg allergen to 8 years	4/120 (3.3%)	9/116 (7.8%)	0.85 (0.42, 1.72)	0.6536	0.90 (0.35, 2.32)	0.8283	0.85 (0.42, 1.73)	0.6528
Positive SPT to egg allergen to 11.5 years	5/99 (5.1%)	4/75 (5.3%)	0.88 (0.36, 2.17)	0.7799	0.89 (0.35, 2.28)	0.8018	0.89 (0.36, 2.22)	0.8025
Positive SPT to egg allergen to 14 years	4/75 (5.3%)	3/50 (6.0%)	0.88 (0.35, 2.15)	0.7574	0.87 (0.34, 2.23)	0.7678	0.88 (0.35, 2.20)	0.7787
Current asthma to 1.5 years	28/178 (15.7%)	20/149 (13.4%)	1.20 (0.64, 2.25)	0.5590	1.20 (0.64, 2.25)	0.5749	1.18 (0.63, 2.21)	0.6023
Current asthma to 3 years	42/173 (24.3%)	30/143 (21.0%)	1.25 (0.73, 2.16)	0.4127	1.25 (0.72, 2.16)	0.4244	1.24 (0.72, 2.14)	0.4432
Current asthma to 5 years	55/169 (32.5%)	40/138 (29.0%)	1.14 (0.69, 1.89)	0.5996	1.14 (0.68, 1.89)	0.6229	1.12 (0.68, 1.86)	0.6604
Current asthma to 8 years	53/139 (38.1%)	41/126 (32.5%)	1.18 (0.72, 1.92)	0.5140	1.18 (0.72, 1.94)	0.5057	1.15 (0.70, 1.87)	0.5862
Current asthma to 11.5 years	55/128 (43.0%)	35/95 (36.8%)	1.12 (0.69, 1.82)	0.6511	1.14 (0.70, 1.87)	0.5897	1.09 (0.67, 1.78)	0.7187
Current asthma to 14 years	46/115 (40.0%)	39/97 (40.2%)	1.07 (0.70, 1.65)	0.7679	1.10 (0.68, 1.79)	0.6933	1.05 (0.65, 1.70)	0.8372
Current eczema to 1.5 years	60/170 (35.3%)	39/147 (26.5%)	1.51 (0.93, 2.46)	0.0960	1.50 (0.91, 2.45)	0.1086	1.48 (0.90, 2.42)	0.1180
Current eczema to 3 years	72/171 (42.1%)	56/142 (39.4%)	1.29 (0.84, 1.98)	0.2390	1.30 (0.84, 2.02)	0.2314	1.27 (0.82, 1.95)	0.2801
Current eczema to 5 years	76/167	61/137	1.31	0.2135	1.33	0.1895	1.29	0.2473

	(45.5%)	(44.5%)	(0.86, 2.01)		(0.87, 2.06)		(0.84, 1.97)	
Current eczema to 8 years	61/133 (45.9%)	57/120 (47.5%)	1.21 (0.80, 1.83)	0.3748	1.22 (0.80, 1.86)	0.3619	1.19 (0.78, 1.81)	0.4192
Current eczema to 11.5 years	51/102 (50.0%)	39/78 (50.0%)	1.15 (0.75, 1.76)	0.5205	1.16 (0.76, 1.79)	0.4919	1.13 (0.74, 1.74)	0.5716
Current eczema to 14 years	36/76 (47.4%)	27/55 (49.1%)	1.07 (0.70, 1.65)	0.7430	1.08 (0.70, 1.67)	0.7274	1.06 (0.69, 1.63)	0.7948
Current rhinitis to 1.5 years	88/176 (50.0%)	78/148 (52.7%)	0.90 (0.58, 1.39)	0.6292	0.87 (0.56, 1.36)	0.5349	0.91 (0.58, 1.42)	0.6657
Current rhinitis to 3 years	112/173 (64.4%)	98/143 (68.5%)	0.75 (0.53, 1.06)	0.1057	0.74 (0.52, 1.06)	0.1052	0.75 (0.52, 1.06)	0.1046
Current rhinitis to 5 years	127/169 (75.2%)	107/138 (77.5%)	0.75 (0.55, 1.02)	0.0633	0.75 (0.55, 1.01)	0.0607	0.75 (0.55, 1.01)	0.0592
Current rhinitis to 8 years	114/139 (82.0%)	101/124 (81.4%)	0.82 (0.62, 1.07)	0.1466	0.81 (0.61, 1.07)	0.1333	0.81 (0.62, 1.07)	0.1409
Current rhinitis to 11.5 years	111/128 (86.7%)	80/95 (84.2%)	0.88 (0.68, 1.15)	0.3556	0.88 (0.68, 1.15)	0.3518	0.89 (0.68, 1.15)	0.3612
Current rhinitis to 14 years	103/115 (89.6%)	83/97 (85.6%)	0.90 (0.69, 1.18)	0.4415	0.89 (0.68, 1.17)	0.4072	0.90 (0.69, 1.18)	0.4532
			Mean difference 95%CI		Mean difference 95%CI		Mean difference 95%CI	
Log total IgE at 1.5 years (mean, SD)	2.87 (1.40)	3.16 (1.28)	-0.29 (-0.65, 0.08)	0.1202	-0.25 (-0.61, 0.11)	0.1710	-0.26 (-0.62, 0.10)	0.1600
Log total IgE at 3 years (mean, SD)	3.58 (1.63)	3.46 (1.46)	-0.12 (-0.44, 0.21)	0.4850	-0.069 (-0.39, 0.25)	0.6723	-0.10 (-0.43, 0.22)	0.5317
Log total IgE at 5 years (mean, SD)	4.12 (1.62)	4.37 (1.27)	-0.17 (-0.48, 0.14)	0.2888	-0.13 (-0.43, 0.18)	0.4134	-0.15 (-0.46, 0.16)	0.3326
Log total IgE at 8 years (mean, SD)	4.66 (1.63)	4.73 (1.65)	-0.17 (-0.48, 0.14)	0.2756	-0.13 (-0.44, 0.18)	0.3988	-0.16 (-0.47, 0.15)	0.3102
Log total IgE at 11.5 years	5.04 (1.59)	5.10 (1.66)	-0.14	0.3661	-0.10	0.5211	-0.13	0.4051

(mean, SD)			(-0.46, 0.17)		(-0.41, 0.21)		(-0.45, 0.18)	
Log total IgE at 14 years (mean, SD)	5.09 (1.69)	5.17 (1.51)	-0.12 (-0.44, 0.20)	0.4526	-0.078 (-0.3.9, 0.24)	0.6320	-0.11 (-0.43, 0.21)	0.4862

* adjusted for sex and breastfeeding ≥ 6 months

^ aeroallergens tested: Dermatophagoides pteronyssinus (HDM), cockroach, cat, Alternaria alternata, rye grass, and grass mix; plus dog and aspergillus at 8 and 11.5 years

P-value from a hierarchical log-binomial regression model with individuals treated as random intercepts.

\$ adjusted for intervention type, HDM and Diet

Peanut allergy by skin prick test not done at 14 years

Mean difference = mean of log total IgE in the any dose of wp group - mean of log total IgE in the no dose of wp group. Total IgE had a skewed distribution and was log transformed.