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TITLE PAGE

No association between atopic outcomes and type of pertussis vaccine given in children born on the Isle of Wight 2001-2

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CAPSULE SUMMARY

The increase in food allergy prevalence has coincided with changes in pertussis vaccine used for infant immunization. In a prospective birth cohort study, we report no association between atopic outcomes and type of vaccine used.

Key words- food allergy, sensitization, allergic rhinitis, asthma, eczema, pertussis vaccine

To the Editor,

Pertussis is typically included in most infant vaccination schedules. The development of atopic sensitisation occurs early in infancy, thus the infant vaccine schedule may impact on atopic outcomes. A link between pertussis immunization and risk of atopic disease was first suggested for whole cell pertussis [1,2], although the published data strongly suggest these concerns are unwarranted [3-5].

More recently, many countries have switched from whole cell (wP) to acellular pertussis (aP), a measure instituted to reduce the relative higher rate of adverse events associated with wP immunization. The aP vaccine drives a Th2-like immune response in contrast to the wP vaccine [6,7], which might predispose to atopic disease. Public health bodies in the USA, Australia and Europe have noted that in some countries, the increase in prevalence of food allergy in the last few decades has coincided with the switch from wP to aP. There are no published studies assessing how the risk of atopic disease is affected by type of pertussis immunization, although data suggests that IgE production following a booster with aP appears to be specific for pertussis-related antigens and not for food or environmental allergens [8].

In the United Kingdom, the switch from wP to aP occurred in 2004. However, in 1999-2001, a shortage in supply of wP resulted in the release of aP to meet demand. This period coincided with the establishment of a birth cohort study to assess the epidemiology of atopic disease. As a result, infants included in the birth cohort received a mix of wP and aP almost at random, depending on supply of particular vaccine, avoiding potential biases due to secular trends in the risk of developing atopic disease.

The FAIR (Food Allergy and Intolerance Research) birth cohort included all 1063 babies born on the Isle of Wight (UK) between September 2001 and August 2002. 969 (91%) parents consented to allergy assessments being performed on their child at 1, 2, 3 and 10 years of age [9]. Symptoms of allergic disease were assessed using validated questionnaires [4], in combination with parent interview. Information on family history and history of allergic disease was obtained by questionnaire. Children underwent skin prick tests (SPT) to a standard panel of predefined food (milk, egg, wheat, peanut, sesame, and cod fish) and aeroallergens (house dust mite Dermatophagoides pteronyssinus, cat and grass). A positive SPT was defined as a mean wheal size ≥ 3mm. Children with a history of possible allergic reaction and/or positive SPT to a food were invited to undergo oral food challenge (DBPCFC) [9].

We obtained data relating to vaccine status (type of vaccine, date given) of children included in the FAIR cohort from a centralised register held by Public Health England. A selection of paper child-health records were cross-referenced with this dataset to confirm data integrity. Analysis was limited to children who received their first dose of pertussis vaccine between 6 weeks and 18 weeks of age and in whom the type of vaccine was

recorded. To compare the risks of allergy according to aP and wP exposure, we performed multivariable binomial regression to derive crude relative risks (RR) and RRs adjusted for potential confounders of family history of asthma/hay fever, breast feeding and gender. Ethical approval for the study was obtained from the NRES South Central – Southampton B Research Ethics Committee (REF 10/H0504/11), with data linkage under separate approval granted to Public Health England.

Details regarding the first pertussis vaccine administered were available for 906 children: 71 received their dose after 18 weeks of age, and were therefore excluded, while in 16 children, we were unable to determine the type of pertussis vaccine administered. Thus, 819 children were included in the initial analysis, of whom 224 (27%) received their first vaccine dose containing aP (and the remaining 595 (73%), wP). No significant associations were identified between any outcome measure and type of pertussis vaccine used for the first infant vaccine (Table 1).

To assess whether receipt of any dose of aP was associated with a change in risk, we performed a further analysis in 701 children who received 3 doses of pertussis according to the immunization schedule and in whom data regarding the type of vaccine (aP versus wP) was available. 343 (49%) received at least one dose of aP, while 51% received wP for all three doses. No significant associations were identified between any outcome measure and administration of at least one dose of aP in the first year of life (Table 2). We also assessed for any effect on outcome by dosing trend i.e. which vaccine (aP or wP) was used for each dose: no significant associations were identified (Table 2).

In summary, we did not identify any evidence for an association between type of pertussis vaccine given and allergic/atopic outcomes in this cohort. The strengths of this study include the almost random allocation of vaccine (wP vs aP), prospective data collection, use of objective assessments and high rate of follow-up; however, our analysis is limited by the size of this cohort and we cannot, therefore, exclude a more subtle effect of acellular pertussis on subsequent atopy.

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TABLE 1

Relative risk (RR) of atopic outcomes in those receiving a first dose of acellular pertussis (aP) versus whole cell pertussis (wP), adjusted for potential confounders. The 95% confidence intervals for the RR show the precision of estimates for the different outcomes.

Outcome	First dose aP n/N* (%)	First Dose wC n/N* (%)	RR (95% CI)	Fisher's exact P value	Adjusted RR**	P-value
IgE-mediated food allergy, ever	5/223 (2.2%)	19/591 (3.2%)	0.70 (0.26-1.84)	0.64	0.78 (0.29-2.07)	0.62
Positive SPT to food, ever	5/174 (2.9%)	30/465 (6.5%)	0.45 (0.18-1.13)	0.08	0.46 (0.18-1.17)	0.10
Asthma, by age 3 years	22/204 (10.8%)	54/560 (9.6%)	1.12 (0.70-1.79)	0.68	1.16 (0.71-1.87)	0.55
Asthma, by age 10 years	28/112 (25.0%)	60/336 (17.9%)	1.40 (0.94-2.08)	0.10	1.15 (0.73-1.81)	0.55
Eczema, at 6 months	84/217 (38.7%)	230/568 (40.4%)	0.96 (0.79-1.16)	0.68	0.84 (0.77-1.15)	0.54
Eczema, at 1 year	35/212 (16.5%)	112/564 (19.95)	0.83 (0.59-1.17)	0.31	0.84 (0.59-1.20)	0.35
Eczema at 3 years	40/202 (19.8%)	103/556 (18.5%)	1.07 (0.77-1.48)	0.68	1.06 (0.76-1.47)	0.74
Allergic Rhinitis, by age 10 yrs	54/191 (28.2%)	142/526 (27.0%)	1.05 (0.80-1.37)	0.78	1.05 (0.81-1.38)	0.70
Any positive SPT to aeroallergen, ever	49/202 (24.3%)	99/538 (18.4%)	1.32 (0.97-1.78)	0.08	1.24 (0.90-1.69)	0.19
Sensitised to HDM, ever	30/118 (25.4%)	56/320 (17.5%)	1.45 (0.98-2.14)	0.08	1.30 (0.86-1.98)	0.22
Any atopy	51/203 (25.1%)	106/538 (19.7%)	1.27 (0.95-1.71)	0.11	1.19 (0.88-1.62)	0.25

HDM, house dust mite; SPT, skin prick test. *Where denominators do not add up to 819 this is due to missing data. **Adjusted for family history of asthma/hay fever, breast feeding, gender.

TABLE 2

Relative risk (RR) of atopic outcomes in those receiving any dose of acellular pertussis (aP) versus none (i.e. whole cell pertussis (wP) used for all 3 immunizations), adjusted for potential confounders. We also assessed for any effect on outcome by dosing trend i.e. which vaccine (aP or wP) was used for each dose. The 95% confidence intervals for the RR show the precision of estimates for the different outcomes.

Outcome	Any aP n/N* (%)	No aP (i.e. wP used for all three doses) n/N* (%)	RR (95% CI) (any aP vs none)	Fisher's exact P value	Adjusted RR** (any aP vs none)	P-value	Trend per dose (adjusted RR** per aP dose)
IgE-mediated food allergy, ever	10/340(2.9%)	8/356 (2.2%)	1.30 (0.52-3.28)	0.64	1.16 (0.46-2.97)	0.75	1.17 (0.75-1.80)
Positive SPT to food, ever	13/274 (4.7%)	16/297 (5.4%)	0.88 (0.43-1.79)	0.85	0.76 (0.37-1.58)	0.47	0.87 (0.59-1.27)
Asthma, by age 3 years	37/315 (11.7%)	32/341 (9.4%)	1.25 (0.80-1.96)	0.35	1.13 (0.71-1.80)	0.62	1.12 (0.90-1.38)
Asthma, by age 10 years	41/178 (23.0%)	37/220 (16.8%)	1.37 (0.92-2.04)	0.13	1.21 (0.79-1.87)	0.39	1.04 (0.84-1.29)
Eczema, at 6 months	125/328 (38.1%)	145/346 (41.9%)	0.91 (0.76-1.09)	0.35	0.88 (0.73-1.05)	0.17	0.94 (0.86-1.04)
Eczema, at 1 year	56/325 (17.2%)	73/345 (21.1%)	0.81 (0.60-1.11)	0.20	0.82 (0.59-1.12)	0.21	0.91 (0.78-1.08)
Eczema at 3 years	56/313 (17.9%)	70/338 (20.7%)	0.86 (0.63-1.18)	0.37	0.85 (0.62-1.17)	0.32	0.95 (0.81-1.12)
Allergic Rhinitis, by age 10 yrs	80/301 (26.6%)	98/322 (30.4%)	0.87 (0.68-1.12)	0.33	0.88 (0.68-1.13)	0.31	0.95 (0.84-1.08)
Any positive SPT to aeroallergen, ever	73/311 (23.5%)	60/332 (18.1%)	1.30 (0.96-1.76)	0.10	1.17 (0.86-1.60)	0.31	1.11 (0.96-1.28)
Sensitised to HDM, ever	43/187 (23.0%)	36/217 (16.6%)	1.39 (0.92-2.06)	0.13	1.14 (0.7501,73)	0.54	1.13 (0.94-1.36)
Any atopy	77/312 (24.7%)	64/332 (19.3%)	1.28 (0.95-1.72)	0.11	1.16 (0.86-1.57)	0.32	1.09 (0.95-1.26)

HDM, house dust mite; SPT, skin prick test. * Where denominators do not add up to 701 this is due to missing data. **Adjusted for family history of asthma/hayfever, breast feeding, gender.