

## Is Infant Immunization a Risk Factor for Childhood Asthma or Allergy?

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The Christchurch Health and Development Study comprises 1,265 children born in 1977. The 23 children who received no diphtheria/pertussis/tetanus (DPT) and polio immunizations had no recorded asthma episodes or consultations for asthma or other allergic illness before age 10 years; in the immunized children, 23.1% had asthma episodes, 22.5% asthma consulta-

tions, and 30.0% consultations for other allergic illness. Similar differences were observed at ages 5 and 16 years. These findings do not appear to be due to differential use of health services (although this possibility cannot be excluded) or confounding by ethnicity, socioeconomic status, parental atopy, or parental smoking. (Epidemiology 1997;8:678-680)

**Keywords:** asthma, allergy, immunizations, children.

The prevalence of asthma and allergic disease has increased in many countries,<sup>1-4</sup> and there has been a great deal of speculation as to possible causes,<sup>5-11</sup> including the possible role of immunization in promoting allergic sensitization.<sup>12</sup> For example, pertussis vaccination acts as an adjuvant for antigen-specific responses in laboratory animals<sup>13-15</sup>; a specific immunoglobulin E (IgE) response to pertussis toxin itself has been identified in children receiving pertussis immunization<sup>16</sup>; and vaccination with some other organisms enhances histamine release in laboratory animals.<sup>17,18</sup> In addition, two studies have found that pertussis infection increased the risk of atopy,<sup>19,20</sup> and another study found that aluminum-adsorbed vaccines produce greater IgE responses.<sup>21</sup> It is therefore theoretically possible that immunization may contribute to the development of allergic disease, whether through reducing clinical infections in infancy,<sup>12</sup> or through the

direct IgE-inducing effects of the vaccines themselves and/or the potentiating adjuvants. We have therefore examined data from a New Zealand cohort study to investigate the relation between infant immunization and subsequent allergic disease.

### Methods

The Christchurch Child Development Unit comprises 1,265 children born in 1977.<sup>22</sup> Information on immunizations, asthma, and other allergic disease (collected annually until age 16 years) was obtained from (1) a medical diary supplied to all mothers, (2) direct questioning of the mother about medical contacts, and (3) cross-checking with the family doctor when maternal reports or diary records were vague or inconsistent. Infants were scheduled to receive diphtheria/pertussis/tetanus (DPT) and polio immunizations at ages 3 and 5 months and measles immunization at 12-15 months; we did not consider subsequent immunizations, since our hypothesis focused on infant immunizations. Data on asthma, eczema, and other allergies (including rhinitis, food allergy, and urticaria, but excluding drug allergies) were categorized as to whether children had consultations (reported medical contacts) or episodes (consultations plus reported episodes not medically seen) up to ages 5, 10, and 16 years. A child was assigned to a negative category only if there were complete negative data for that child; a positive category was allocated if any episodes or consultations took place, whether or not the data were complete.

We analyzed the data using the Mantel-Haenszel summary risk ratio<sup>23,24</sup> and Fisher exact methods where appropriate.

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TABLE 1. Characteristics of the Immunized and Nonimmunized Groups

|                       | Immunized<br>(N = 1,184) |      | Nonimmunized<br>(N = 23) |      | Total<br>(N = 1,207*) |      |
|-----------------------|--------------------------|------|--------------------------|------|-----------------------|------|
|                       | Number                   | %    | Number                   | %    | Number                | %    |
| Gender                |                          |      |                          |      |                       |      |
| Female                | 587                      | 49.6 | 12                       | 52.2 | 599                   | 49.6 |
| Male                  | 597                      | 50.4 | 11                       | 47.8 | 608                   | 50.4 |
| Ethnicity             |                          |      |                          |      |                       |      |
| Polynesian            | 164                      | 13.9 | 9                        | 39.1 | 173                   | 14.3 |
| European/other        | 1,020                    | 86.1 | 14                       | 60.1 | 1,034                 | 85.7 |
| Socioeconomic status† |                          |      |                          |      |                       |      |
| Classes 1 and 2       | 248                      | 20.9 | 3                        | 13.0 | 251                   | 20.8 |
| Classes 3 and 4       | 634                      | 53.6 | 6                        | 26.1 | 640                   | 53.0 |
| Classes 5 and 6       | 302                      | 25.5 | 14                       | 60.9 | 316                   | 26.2 |
| Parental history of   |                          |      |                          |      |                       |      |
| Asthma                | 214                      | 18.1 | 5                        | 21.7 | 219                   | 18.1 |
| Eczema                | 253                      | 21.4 | 6                        | 26.1 | 259                   | 21.5 |
| Allergic rhinitis     | 356                      | 30.1 | 5                        | 21.7 | 361                   | 29.9 |
| Parental smoking 0–5  | 650                      | 56.2 | 19                       | 82.6 | 669                   | 56.7 |
| Pet ownership 0–5     | 923                      | 79.8 | 21                       | 91.3 | 944                   | 80.4 |

\* Totals do not sum to 1,207 where data are not complete.

† Elley-Irving socioeconomic index for New Zealand occupations.

## Results

Only 23 (1.8%) children in the cohort were recorded as having received neither of the two scheduled DPT and polio vaccinations due at 3 and 5 months. They were more likely to be in a low socioeconomic group, Polynesian, or exposed to parental smoking, but there was little difference with respect to gender, pet ownership, or parental histories of asthma, eczema, or allergic rhinitis (Table 1).

Table 2 shows the risk ratios (RRs) (with Fisher exact confidence intervals) for various outcomes. The 23 nonimmunized children had no episode or consultation for asthma or consultation for other allergies before age 10

years; between ages 11 and 16 years, some events were recorded, but the risks were still relatively low. There was little association between immunization and eczema (Table 2), or for consultations for gastrointestinal symptoms before age 2 years [RR = 1.3; 95% confidence interval (CI) = 0.6–3.3], reported gastrointestinal symptoms before age 2 years (RR = 1.0; 95% CI = 0.6–1.8), or reported measles, rubella, chicken pox, or mumps (not shown in table).

We were not able to adjust for all potential confounders simultaneously because of the small numbers involved, with some analyses involving no cases in the nonimmunized group. Nevertheless, we did attempt to assess confounding by: (1) assessing whether potential confounders were related to the outcome in the overall dataset, and (2) for the outcomes with some cases in the nonimmunized group, adjusting for each confounder in turn.

Ethnicity, low socioeconomic status, parental smoking, and pet ownership (Table 1) had no association, or a positive association, with the outcome measures [for example, at age 10 years, Polynesian ethnicity was not associated with asthma episodes (RR = 1.0), asthma consultations (RR = 1.0), or allergy consultations (RR = 1.0); the corresponding relative risks were 1.3, 1.4, and 0.9 for socioeconomic groups 5 and 6; 1.1, 1.1, and 1.0 for parental smoking; and 0.8, 0.9, and 1.0 for pet ownership]. There was also little evidence of confounding in the adjusted analyses. For example, to age 16 years, the relative risk for asthma episodes was 2.9 (Table 2); this value became 2.8 when adjusted for ethnicity, 3.0 when adjusted for socioeconomic status, 3.0 when adjusted for parental smoking, and 2.8 when adjusted for pet ownership. The corresponding figures were 2.7, 2.7, 2.9, 2.8, and 2.6 for asthma consultations; and 5.6, 5.7, 5.7, 5.7, and 5.6 for allergy consultations. Thus, there is little evidence that the findings in Table 2 are due to confounding by the factors shown in Table 1.

We also examined associations between infant measles, mumps, rubella, or chicken pox infections, or measles vaccination, and the outcome measures described above, but we found no strong association. For example, for asthma episodes up to the age of 10 years, the relative risk was 1.2 (95% CI = 1.0–1.4) for reported measles infection and 1.0 (95% CI = 0.9–1.1) for measles vaccination.

TABLE 2. Asthma and Allergies in the Immunized and Nonimmunized Groups\*

|                  | Immunized |     | Nonimmunized |    | Risk Ratio | 95% CI   |
|------------------|-----------|-----|--------------|----|------------|----------|
|                  | Yes       | No  | Yes          | No |            |          |
| Ages 0–5 years   |           |     |              |    |            |          |
| Asthma episodes  | 133       | 936 | 0            | 20 | ∞          | 0.7–∞    |
| Asthma consults  | 134       | 935 | 0            | 20 | ∞          | 0.7–∞    |
| Allergy consults | 165       | 899 | 0            | 16 | ∞          | 0.7–∞    |
| Eczema consults  | 283       | 798 | 4            | 16 | 1.3        | 0.5–4.9  |
| Ages 6–10 years  |           |     |              |    |            |          |
| Asthma episodes  | 234       | 777 | 0            | 17 | ∞          | 1.05–∞   |
| Asthma consults  | 227       | 782 | 0            | 17 | ∞          | 1.03–∞   |
| Allergy consults | 302       | 704 | 0            | 13 | ∞          | 1.05–∞   |
| Eczema consults  | 334       | 686 | 5            | 13 | 1.2        | 0.5–3.7  |
| Ages 11–16 years |           |     |              |    |            |          |
| Asthma episodes  | 315       | 625 | 2            | 15 | 2.9        | 0.8–23.6 |
| Asthma consults  | 297       | 641 | 2            | 15 | 2.7        | 0.7–22.3 |
| Allergy consults | 404       | 530 | 1            | 12 | 5.6        | 1.0–22.6 |
| Eczema consults  | 398       | 552 | 7            | 12 | 1.3        | 0.5–2.8  |

\* Totals do not sum to 1,207 where data are not complete.

## Discussion

The findings presented here are consistent with the hypothesis that some component of infant immunization may increase the risk of developing asthma in childhood. An important limitation of our data is the small nonvaccinated group. The vaccinated differed from the nonvaccinated with respect to several factors, including parental smoking,<sup>25</sup> Polynesian ethnicity,<sup>26</sup> and lower socioeconomic status,<sup>27</sup> but these factors have been found in previous New Zealand studies, and in the current study, either to be positively related or to have no association with asthma symptoms or diagnosed asthma.

All the outcome variables used in this analysis have a health service component, and it is possible that health service access or utilization, or recognition of symptoms, was different for the nonvaccinated children. There was little difference, however, between the vaccinated and nonvaccinated groups with respect to consultations for eczema or gastrointestinal symptoms, or for reported measles, rubella, chicken pox, or mumps. Nevertheless, we cannot exclude the possibility that the findings are due to differences in health service access or use.

Three previous studies have examined immunization, and the findings are inconsistent. Butler and Golding<sup>28</sup> found no association between pertussis immunization and wheeze at age 5 years, but a lower risk of eczema. Odent *et al*<sup>29</sup> found that pertussis vaccination increased the risk of diagnosed asthma. Nilsson and Storsaeter<sup>30</sup> conducted a randomized trial of two types of acellular pertussis vaccine, whole cell pertussis vaccine and no pertussis vaccine; they found no differences in a telephone survey of wheeze, itching, and sneezing at age 2 years. These findings are, to some extent, reassuring with regard to pertussis immunization, but not necessarily about all immunizations, since all children in our study also received diphtheria and tetanus immunizations. We have also had the opportunity to re-analyze the Dunedin Multidisciplinary Health and Development Study,<sup>31</sup> involving 1,037 children born in 1972–1973, but only five children were recorded as having no vaccination before the age of 3 years.

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