

Reply

To the Editor:

We are appreciative that Spycher et al¹ were able to implement our methods in a similar population-based cohort, because this is not often possible. We would like to first respond to their critique and then offer an explanation for the discrepancy between their results and our findings from a cohort of 11,531 Manitoba children immunized with at least 4 doses of cellular diphtheria, pertussis, tetanus (DPT) vaccine.²

As cited by Spycher et al,¹ a recent meta-analysis of 7 studies showed no difference in asthma prevalence between children immunized and not immunized with cellular pertussis DPT vaccine.³ Findings of an increased risk in individual studies are attributed to ascertainment bias, whereby less frequent health care (real-life or from missing records) reduces the likelihood of ever vaccination and asthma.⁴ Less frequent health care, as well as larger family size and low socioeconomic status, are also associated with delayed immunization of children. For certain, when we adjusted our models for these factors, they reduced the magnitude of the odds ratios (ORs) for asthma from 0.39 to 0.50.² The statement in our Discussion section questioned by Spycher et al¹ was intended to communicate that our results remained statistically significant, despite adjustment for the above confounding factors.

Few studies have investigated the timing of vaccine administration. In an earlier study of the Leicester cohorts, Kuehni et al⁵ reported a doubling of preschool wheeze from 1990 to 1998, times over which the immunization schedule had changed from 3, 5, and 7 months to 2, 3, and 4 months. The risk of wheeze in 1998 increased after adjustment for immunization against pertussis, but without controlling for ascertainment bias, these results are difficult to interpret. After the recent application of our methods to the Leicester cohort, Spycher et al¹ reported an adjusted OR of 2.03 for wheeze in a total of 15 schoolchildren with a 2-month or greater delay in vaccination with the first dose of DPT vaccine. The OR was not statistically significant, but it was bounded by a wide 95% CI. Although these findings are discrepant with the reduced likelihood we observed, the small number of children in the analysis precludes a definitive conclusion.

Our results are, however, consistent with the study by Bremner et al⁶ (a nested case-control study of the General Practice Research Database [GPRD]), which documented a lower risk of hay fever at school age (OR, 0.80; 95% CI, 0.64-0.99) with 2-month and greater delays in the third dose of DPT vaccine after adjustment for health care use and sibship structure. In our study 86% of children with delays in the first dose had delays in all 3 doses.² We found that the reduced risk of asthma was no longer apparent with postponement of the third DPT vaccine dose when the first dose was given on time, relegating an "effect" to the first dose. Unfortunately, data on the first 2 doses of DPT vaccine were incompletely recorded in the GPRD and thus not analyzed by Bremner et al.⁶ Also accessing data from the GPRD, McKeever et al⁷ reported no relation between age at first DPT vaccine dose and childhood asthma, but we wonder whether incomplete data records might have influenced these nil findings.

There remain many unanswered questions regarding the association between DPT immunization and atopic disease. The meta-analysis by Balicer et al³ reported a positive association with cellular DPT vaccine and asthma (OR, 1.26; 95% CI, 1.04-1.54) in high-quality studies. These studies were more rigorously conducted but also included a larger proportion of unvaccinated

children who might have environmental exposures that decrease the risk of asthma. Unvaccinated children might also be at higher risk for asthma because of lower endotoxin exposure in their homes⁷; grouping children with disparate types of environmental exposures into the unvaccinated category has the potential to produce null findings. Bremner et al⁶ found no difference in hay fever prevalence between unvaccinated children and children vaccinated on time, despite a lower risk in children with substantial delays in DPT vaccination.

Although this was not made clear by Spycher et al,¹ it is likely that both cellular and acellular pertussis vaccine were administered in the Leicester 1990 and 1998 cohorts. Cellular pertussis elicits a strong fever response, which we propose as a mechanism for protection against asthma.⁸ Fever stimulates the immune system to mount a T_H1 response against the invading pathogen, and fevers in early life have been shown to protect against asthma development.^{9,10} An indirect mechanism is also plausible subsequent to the presence of fever in the child as a reason for the postponement of DPT vaccine administration; this mechanism would also apply to acellular pertussis vaccine. To date, comparisons of the cellular and acellular pertussis vaccine on immune system responses in infants show a greater T_H2 response for the latter.¹¹

We advocate for further research on the association between timing of acellular pertussis DPT vaccine administration and the development of atopic disease, which includes detailed information on the reasons for delay in vaccine administration. Until all questions have satisfactorily been answered, no recommendations can be made to change immunization schedules because the repercussions of doing so are well known.

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α_1 -Antitrypsin deficiency and Pi typing

To the Editor:

We read with interest the recent article by Drs Rachelefsky and Hogarth¹ regarding the diagnosis of α_1 -antitrypsin (AAT) deficiency. Our recent findings shed light on the issue of the cutoff level of AAT, below which samples should be sent for Pi genotyping, and have important financial and clinical implications.

During a period of 1 year, our laboratory analyzed AAT levels in 1780 patient samples using an immunoturbidimetric assay run in an Abbott Architect Ci8200 (Abbott Laboratories, Chicago, Ill). Of these, 215 (12.1%) had results <1.3 g/L and therefore were sent for Pi typing. The lowest AAT with a clinically significant Pi type was 1.11 g/L (Pi type SS). The typical between-run SD of the assay across the concentration range was 0.025 g/L (25 mg/L). The 95% CI at 1.2 g/L, based on a method SD of 0.025 g/L, would be 1.15 to 1.25; therefore, we are assured that using this cutoff will not compromise clinical sensitivity. Our former cutoff level was 1.3 g/L, so reducing the cutoff by 0.1 g/L to 1.2 g/L results (in our laboratory) in doing 96 fewer Pi types over a 14-month period. Our Pi typing costs approximately \$61, so adopting this new cutoff level saves approximately \$5800 per year.

The authors¹ rightly point out that there are significant method differences between radial immunodiffusion (RID) and turbidimetric assays, with RID methods overestimating AAT

concentration by 35-40%.² However, it is worth noting that comparison of our current immunoturbidimetric assay, run in an Abbot Architect Ci8200 analyzer, showed excellent correlation ($r^2 = 0.977$, with a slope and intercept of 1.07 and -0.01 , respectively) with our previous results in an Olympus AU640 system (Olympus Diagnostic Systems, Middlesex, United Kingdom). This suggests that a Pi-typing cutoff of 1.20 g/L might be applicable in similar assay systems but should be determined by individual laboratories, as the choice of cutoff level has financial implications and also potentially causes unnecessary concerns to the patient if inappropriate follow-up Pi testing is undertaken. However, AAT cutoff values do not apply when Pi typing samples are part of family studies or pediatric cases, where Pi typing should be done irrespective of the AAT concentration.

Another aspect of investigating patients with suspected AAT deficiency worth emphasizing is that we believe it is vital that all patients being investigated for possible AAT deficiency have liver function tests performed. Moreover, affected patients, particularly homozygous ZZ, should be advised to avoid (if possible) hepatotoxic drugs and alcohol.

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