

Correspondence

Timing of routine vaccinations and the risk of childhood asthma

To the Editor:

McDonald et al¹ report a decreased risk of childhood asthma in 7-year-old children whose first dose of diphtheria, pertussis, tetanus (DPT) vaccine was delayed compared with the risk seen in children receiving timely vaccinations. Their study assessed both exposure (vaccinations) and outcome (asthma) from health care records. Whether a child was classified as asthmatic depended on the parents' tendency to seek health care when their children had symptoms. This is likely to be positively correlated with their tendency to keep to vaccination schedules. We are concerned that this mechanism might have biased the results of the study toward a spurious protective effect of delayed vaccination, as suggested by others.^{2,3} The authors attempted to adjust for this by including frequency of physician visits, number of siblings, and socioeconomic status in the analysis and stated that this did not affect their findings. However, the adjusted result for delays of more than 2 months and childhood asthma (odds ratio [OR], 0.50; 95% CI, 0.25-0.97) was weaker than the unadjusted result (OR, 0.39; 95% CI, 0.20-0.74) (own computations based on published figures), indicating the presence of confounding. Also, the strategy used for selecting confounders can be disputed: covariates were retained in the model if they had an independent effect on asthma ($P < .05$) rather than if they changed the effect estimate of vaccinations on asthma. Other factors than those considered by the authors can jointly affect the use of health services and timeliness of immunizations, making it possible that the observed results are due to residual confounding.

In 3708 children from a population-based prospective cohort study in Leicester, United Kingdom,⁴ we repeated the analyses done by McDonald et al¹ and did not find a decreased risk of current wheeze in children with delayed DPT vaccination (Table I). Vaccination records were obtained from the local health authority, and information on wheeze was obtained through parental questionnaires. The first 3 doses of DPT vaccine were also scheduled at 2, 3, and 4 months, and the timing of the first dose was categorized as in the study by McDonald et al.¹ We considered a broad range of potential confounders (including most of those used by McDonald et al and more), keeping those in the analysis that altered the estimates for vaccination delay. A sensitivity analysis restricted to children with

complete follow-up (participation in all of 4 surveys) did not indicate the presence of participation bias.

Overall, the conclusion of McDonald et al,¹ and particularly the reference to parallel time trends in change of asthma prevalence and vaccination schedules in Japan, does overemphasize a potential protective effect of late vaccinations. Studies from the United Kingdom and the United States do not confirm an association between vaccination schedules and increased asthma prevalence in children.^{5,6} The heterogeneity of published results on vaccinations and asthma reflects the many potential biases affecting epidemiologic research in this area,⁷ and a single observational study must be treated with much caution. As McDonald et al¹ also state, it is certainly premature to consider changes to vaccination schedules based on their results.

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REFERENCES

- McDonald KL, Huq SI, Lix LM, Becker AB, Kozyskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J Allergy Clin Immunol* 2008;121:626-31.
- DeStefano F, Gu D, Kramarz P, Truman BI, Iademaro MF, Mullooly JP, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002;21:498-504.
- McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *Am J Public Health* 2004;94:985-9.
- Kuehni CE, Brooke AM, Strippoli M-PF, Spycher BD, Davis A, Silverman M. Cohort profile: the Leicester Respiratory Cohorts. *Int J Epidemiol* 2007;36:977-85.
- Kuehni CE, Brooke AM, Davis A, Silverman M. Vaccinations as risk factors for wheezing disorders. *Lancet* 2001;358:1186.
- Enriquez R, Persky V, Hartert T. Trends in asthma prevalence and recommended number of childhood immunizations are not parallel. *Pediatrics* 2008;119:222-3.
- Balicer RD, Grotto I, Mimouni M, Mimouni D. Is childhood vaccination associated with asthma? A meta-analysis of observational studies. *Pediatrics* 2007;120:e1269-77.

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TABLE I. Age at first vaccination with DPT and corresponding rates and crude and adjusted* ORs for current wheeze at age 5 to 10 years (mean age, 7.3 years) in 3708 children from a population-based cohort study⁴

Age at first DPT dose†	Total no. of children	No. with current wheeze	Rate of current wheeze	Crude OR	95% CI	Adjusted OR	95% CI
0-2 mo (<62 d)	1008	147	14.6	Reference‡		Reference‡	
2-3 mo (63-93 d)	2529	339	13.4	0.91	0.74-1.12	0.93	0.75-1.16
3-4 mo (94-124 d)	156	21	13.5	0.91	0.56-1.49	0.93	0.56-1.55
>4 mo (>124 d)	15	4	26.7	2.13	0.67-6.78	2.03	0.61-6.76

*Adjusted for sex, ethnicity (white or south Asian), birth year, maternal history of asthma and hay fever, birth weight, duration of breast-feeding, crowding, Townsend score (an area-based deprivation score), and central heating.

†Using the same timing categories as used by McDonald et al.¹

‡The reference group consists of children receiving the first DPT vaccine dose according to schedule.