Timing of routine vaccinations and the risk of childhood asthma

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Funding

Supported by funds from the Swiss National Science Foundation (Grants No 823B-

046481, 3233-069348 and 3200-069349, Switzerland), R&D Directorates of NHS

Trusts (UK), Children's Research Fund (UK) and Medisearch (Leicester, UK).

Word count: 477

24 **Abbreviations**

25	CI	Confidence interval
26	DPT	Diphtheria, Pertussis, Tetanus
27	OR	Odds ratio
28	SD	Standard deviation
29	UK	United Kingdom

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31 ***To the Editor:***

32 McDonald et al¹ report a decreased risk of childhood asthma in 7 year old children
33 whose first dose of diphtheria, pertussis, tetanus (DPT) vaccination was delayed
34 compared to children with timely vaccinations. Their study assessed both exposure
35 (vaccinations) and outcome (asthma) from health care records. Whether or not a child
36 was classified as asthmatic depended on the parents' tendency to seek health care
37 when their child had symptoms. This is likely to be positively correlated with their
38 tendency to keep to vaccination schedules. We are concerned that this mechanism
39 may have biased the results of the study toward a spurious protective effect of delayed
40 vaccination, as shown by others.^{2,3} The authors attempted to adjust for this by
41 including frequency of physician visits, number of siblings, and socioeconomic status
42 in the analysis, and stated that this did not affect their findings. However, the adjusted
43 result for delays of >2 months and childhood asthma (OR 0.50, 95% CI 0.25-0.97)
44 was weaker than the unadjusted (OR, 0.39, 0.20-0.74) indicating the presence of
45 confounding. Also, the strategy used for selecting confounders might be disputed
46 (covariates were retained in the model if they had an independent effect on asthma
47 ($p < 0.05$), rather than if they changed the effect estimate of vaccinations on asthma).
48 Other factors than those considered by the authors may jointly affect the use of health
49 services and timeliness of immunizations, making it possible that the observed results
50 are due to residual confounding.

51 In 3708 children from a population based prospective cohort study in Leicester, UK,⁴
52 we repeated the analyses proposed in this paper and, did not find a decreased risk of
53 current wheeze in children with delayed DPT vaccination (see Table I). Vaccination
54 records were obtained from the local Health Authority and information on wheeze
55 through parental questionnaires. The first three doses of DPT vaccinations were also

scheduled at 2, 3, and 4 months and timing of the first dose was categorized as in McDonald.¹ We considered a broad range of potential confounders (including those used by McDonald) keeping those in the analysis which 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, 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 UK and the US 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 epidemiological research in this area,⁷ and a single observational study must be treated with much caution. As McDonald et al also state, it is certainly premature to consider changes to vaccination schedules based on their results.

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References

1. McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J Allergy Clin Immunol* 2008; 121:626-31.
2. DeStefano F, Gu D, Kramarz P, Truman BI, Iademarco MF, Mullooly JP, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002; 21:498-504.
3. McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *Am J Public Health* 2004; 94:985-9.
4. 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.
5. Kuehni CE, Brooke AM, Davis A, Silverman M. Vaccinations as risk factors for wheezing disorders. *Lancet* 2001; 358:1186.
6. Enriquez R, Persky V, Hartert T. Trends in Asthma Prevalence and Recommended Number of Childhood Immunizations Are Not Parallel. *Pediatrics* 2008; 119:222-3.
7. 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.

Table I: Age at first vaccination with DPT and corresponding rates and crude and adjusted* ORs for current wheeze at age 5-10 years (mean age 7.3 years) in 3708 children from a population-based cohort study ⁴

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

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

107 [†] Using the same timing categories as used by McDonald et al¹.

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

109 OR: Odds ratio; CI: Confidence interval