Timing of routine vaccinations and the risk of childhood asthma

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DPT</td>
<td>Diphteria, Pertussis, Tetanus</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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To the Editor:

McDonald et al report a decreased risk of childhood asthma in 7 year old children whose first dose of diphtheria, pertussis, tetanus (DPT) vaccination was delayed compared to children with timely vaccinations. Their study assessed both exposure (vaccinations) and outcome (asthma) from health care records. Whether or not a child was classified as asthmatic depended on the parents’ tendency to seek health care when their child had symptoms. This is likely to be positively correlated with their tendency to keep to vaccination schedules. We are concerned that this mechanism may have biased the results of the study toward a spurious protective effect of delayed vaccination, as shown by others. 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 >2 months and childhood asthma (OR 0.50, 95% CI 0.25-0.97) was weaker than the unadjusted (OR, 0.39, 0.20-0.74) indicating the presence of confounding. Also, the strategy used for selecting confounders might be disputed (covariates were retained in the model if they had an independent effect on asthma (p<0.05), rather than if they changed the effect estimate of vaccinations on asthma).

Other factors than those considered by the authors may 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, UK, we repeated the analyses proposed in this paper and, did not find a decreased risk of current wheeze in children with delayed DPT vaccination (see Table I). Vaccination records were obtained from the local Health Authority and information on wheeze 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 Mc Donald, 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


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

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

* 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 al¹.

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

OR: Odds ratio; CI: Confidence interval