Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood

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BACKGROUND

The “hygiene hypothesis” postulates that infections during infancy may protect against asthma and atopy by down-regulating production of IgE. This hypothesis was first suggested by the striking associations between small family size and hay fever, atopy, and in some instances asthma. Subsequent studies have observed that infections early in life may protect against the development of asthma, but the evidence is far from consistent. Furthermore, the effect of infections may differ with the type (viral, parasitic, or bacterial) and location (respiratory versus gastrointestinal) of infection. A related issue is that antibiotic use may increase the risk of asthma by affecting immunological responses to bacteria through preventing infections or causing major disruptions to the gut bacterial flora. However, the evidence has also been conflicting. Paracetamol use has also been suggested to increase the risk of asthma.

We have therefore investigated the association between infections at age 0–4 years, medication use (antibiotics and paracetamol) early in life, and the subsequent risk of childhood asthma at age 6–7 years. This study was based on data from the New Zealand National Notifiable Diseases Database (EpiSurv), which includes confirmed cases of serious childhood infections identified through a national compulsory notification system. We compared the findings in this “childhood infections group” with the data from phase III of the international study of asthma and allergies in childhood (ISAAC), which was conducted in Wellington in the same age group during the same period.

METHODS

Study populations

The “childhood infections group” consisted of children with notifiable infectious diseases reported to public health services and recorded on the EpiSurv database. Health professionals are required to inform their local medical officer of health of any notifiable disease that they suspect or diagnose. Notification data are recorded in a computerised database (EpiSurv) installed in each public health service. The database included 4838 infections in children aged 0–4 years who were born during 1994–1995; we excluded 19 children for whom the infection was fatal, 8 who were found to have subsequently died from another cause, 632 with incomplete names or addresses, and 45 duplications (different episodes of infections for the same child), leaving 4134 children. The database included the names and addresses of the parents at the time of the notification to the EpiSurv database. We only included in the survey children who were still living at the same address as they were at the time of the notification; if they were confirmed to have moved, they were excluded (1372 children); this left 2762 children eligible for inclusion. The survey was conducted in the first half of 2002.

The “general population group” comprised the participants in the Wellington survey for 6–7-year-olds that was conducted during April–October 2002. Thus, the general population group (which covered the Wellington region) involved a smaller catchment area than the childhood infections group (which was national). We approached all 153 primary schools in the greater Wellington region (Wellington, the Hutt Valley, and Porirua), of which 85 agreed to participate; these included 5375 children in the 6–7 year age group.

Data collection

For both groups, the parents were mailed the ISAAC phase III questionnaire on asthma symptoms and environmental exposures in children aged 6–7 years. The basic questions on symptoms of asthma, rhinitis, and eczema are the same as for the ISAAC phase I survey, but the phase III...
questionnaire includes additional questions on environmental exposures. For the childhood infections group, the parents received three mailings, and then if there was still no response the parents were called and asked to answer the questionnaire over the telephone. Most children in the general population group only received one mailing because the schools were not willing to permit further mailings to be sent through their offices or to provide the contact details of parents.

Data analysis
The analyses involved the key questions on the prevalence of symptoms of asthma, rhinitis, and eczema from the ISAAC questionnaire.41 43 44 For the symptom questions, we followed the standard practice for ISAAC questionnaires and divided the respondents into those with a positive response and those with either a negative or missing response14 (whereas for the questions on environmental exposures, missing values were treated as “missing” in the analysis). The key asthma questions used were those on “wheeze in the past 12 months” (“current wheezing”) and “asthma ever”; the key hay fever questions were those on “problems with sneezing, or a runny, or a blocked nose when not having a cold or the flu in the past 12 months” (when these problems were “accompanied by itchy-watery eyes”) (“allergic rhinoconjunctivitis”) and “hay fever ever”;41 and the key eczema question used was “eczema ever”.44

We examined the overall prevalences in the two surveys, and also conducted sub-analyses of the childhood infections group. For the analysis by major site of infection, the first categories used were: (a) gastrointestinal infections (1216) including campylobacteriosis (640), cryptosporidiosis (98), food poisoning (3), giardiasis (237), salmonellosis (175), shigellosis (9), verotoxin producing Escherichia coli (VTEC) infection (4) and yersiniosis (43); (b) invasive infections (118) such as septicaemia and meningitis caused by Haemophilus influenzae type B (Hib) (2) and meningococcal disease (116); (c) respiratory tract infections (128) including pertussis (106), new cases of tuberculosis disease (9) and tuberculosis infection in chemotherapy treated children (13); and (d) childhood viral infections (122) including measles (88), mumps (8) and rubella (26).

The data were analysed using standard methods for asthma prevalence studies.47 The associations of specific exposures with symptom prevalence were estimated using prevalence odds ratios, with adjustment for confounding using the Mantel-Haenszel method48 and logistic regression.49 The data were analysed using Stata (Stata Statistical Software, Release 7.0; Stata Corporation, College Station, TX, USA, 2001). After conducting the separate analyses of the general population group and the childhood infections group, we found that the key findings were very similar within

Table 1  Prevalence of symptoms of asthma, rhinitis, and eczema in children aged 6–7 years in the general population survey and the infections survey, by major site of infection and pathogen type

<table>
<thead>
<tr>
<th></th>
<th>General population*</th>
<th>Infections group†</th>
<th>Major site of infection</th>
<th>Pathogen type</th>
<th>Childhood viral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2539</td>
<td>N=1584</td>
<td>N=1216</td>
<td>N=118</td>
<td>N=122</td>
</tr>
<tr>
<td><strong>Asthma symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezing ever</td>
<td>44.5 [1130]</td>
<td>46.1 [730]</td>
<td>46.4 [564]</td>
<td>46.6 [55]</td>
<td>49.2 [63]</td>
</tr>
<tr>
<td>months</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rhinitis symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nose symptoms ever</td>
<td>29.5 [748]</td>
<td>31.3 [495]</td>
<td>31.7 [385]</td>
<td>34.8 [41]</td>
<td>29.7 [38]</td>
</tr>
<tr>
<td>12 months</td>
<td>39.9 [1013]</td>
<td>37.9 [601]</td>
<td>38.2 [464]</td>
<td>34.8 [41]</td>
<td>37.3 [417]</td>
</tr>
</tbody>
</table>

*The “general population group” comprises the participants in the Wellington survey for 6–7 year olds. †The “childhood infections group” comprises children with notifiable infectious diseases reported to public health services and recorded on the EpiSurv database.
Table 2: Prevalence of symptoms of asthma, rhinitis, and eczema in children aged 6-7 years, and odds ratios for environmental factors that are relevant to infections (adjusted for dataset, sex, family size, paracetamol, and antibiotics use)

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Current wheezing</th>
<th>Asthma ever</th>
<th>Current allergic rhinoconjunctivitis</th>
<th>Hay fever ever</th>
<th>Eczema ever</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>OR 95% CI</td>
<td>% OR 95% CI</td>
<td>% OR 95% CI</td>
<td>% OR 95% CI</td>
</tr>
<tr>
<td><strong>Dataset</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population*</td>
<td>2539</td>
<td>24.3</td>
<td>1.00</td>
<td>32.8</td>
<td>1.00</td>
<td>17.3</td>
</tr>
<tr>
<td>Infections†</td>
<td>1584</td>
<td>23.5</td>
<td>0.86 0.74 to 1.00</td>
<td>31.9 0.86 0.75 to 0.99</td>
<td>14.0 1.10 0.91 to 1.33</td>
<td>18.2 1.02 0.87 to 1.21</td>
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<tr>
<td><strong>Paracetamol in the first year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>411</td>
<td>15.2</td>
<td>1.00</td>
<td>33.0</td>
<td>1.00</td>
<td>17.3</td>
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<tr>
<td>Yes</td>
<td>3628</td>
<td>25.1</td>
<td>1.38 1.04 to 1.83</td>
<td>34.3 1.72 1.32 to 2.23</td>
<td>13.0 0.97 0.68 to 1.37</td>
<td>18.2 1.25 0.92 to 1.70</td>
</tr>
<tr>
<td><strong>Paracetamol in the past year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Less than once per month</td>
<td>3172</td>
<td>20.6</td>
<td>1.00</td>
<td>30.0</td>
<td>1.00</td>
<td>17.3</td>
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<tr>
<td>At least once per month</td>
<td>840</td>
<td>36.2</td>
<td>1.78 2.10 to 2.49</td>
<td>41.9 1.57 1.34 to 1.84</td>
<td>19.0 1.77 1.43 to 2.18</td>
<td>23.1 1.47 1.22 to 1.78</td>
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<tr>
<td><strong>Antibiotics in the first year</strong></td>
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<td>1243</td>
<td>16.1</td>
<td>1.00</td>
<td>20.7</td>
<td>1.00</td>
<td>17.3</td>
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<td>2684</td>
<td>25.1</td>
<td>1.00</td>
<td>34.1</td>
<td>1.00</td>
<td>17.3</td>
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<td><strong>Older siblings:</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1216</td>
<td>24.0</td>
<td>1.00</td>
<td>30.0</td>
<td>1.00</td>
<td>17.3</td>
</tr>
<tr>
<td>1</td>
<td>1442</td>
<td>22.9</td>
<td>0.83 0.68 to 1.00</td>
<td>30.0 0.78 0.66 to 0.93</td>
<td>12.8 0.90 0.71 to 1.14</td>
<td>17.4 0.73 0.59 to 0.90</td>
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<tr>
<td>2+</td>
<td>1077</td>
<td>24.7</td>
<td>0.92 0.75 to 1.14</td>
<td>33.3 0.94 0.77 to 1.13</td>
<td>11.0 0.78 0.59 to 1.02</td>
<td>13.8 0.56 0.44 to 0.71</td>
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<tr>
<td><strong>Younger siblings:</strong></td>
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<td>31.7</td>
<td>1.00</td>
<td>17.3</td>
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<tr>
<td>1</td>
<td>1585</td>
<td>24.1</td>
<td>0.86 0.72 to 1.03</td>
<td>32.7 0.96 0.82 to 1.13</td>
<td>13.9 1.10 0.87 to 1.38</td>
<td>18.2 0.82 0.67 to 1.00</td>
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<td>2+</td>
<td>816</td>
<td>20.3</td>
<td>0.66 0.51 to 0.84</td>
<td>33.7 0.97 0.78 to 1.21</td>
<td>12.0 0.90 0.66 to 1.23</td>
<td>15.3 0.64 0.49 to 0.85</td>
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<td><strong>Cat in the first year</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2183</td>
<td>25.2</td>
<td>1.00</td>
<td>34.3</td>
<td>1.00</td>
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<td>Yes</td>
<td>1886</td>
<td>22.8</td>
<td>0.83 0.72 to 0.97</td>
<td>30.4 0.79 0.69 to 0.91</td>
<td>11.5 0.75 0.62 to 0.92</td>
<td>15.8 0.74 0.63 to 0.87</td>
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<tr>
<td><strong>Cat now:</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2213</td>
<td>23.6</td>
<td>0.91 0.78 to 1.05</td>
<td>31.0 0.83 0.72 to 0.95</td>
<td>11.8 0.79 0.65 to 0.95</td>
<td>16.4 0.77 0.66 to 0.91</td>
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<tr>
<td>Yes</td>
<td>1863</td>
<td>24.7</td>
<td>1.00</td>
<td>34.3</td>
<td>1.00</td>
<td>17.3</td>
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<tr>
<td><strong>Dog in the first year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2934</td>
<td>23.9</td>
<td>1.00</td>
<td>31.9</td>
<td>1.00</td>
<td>17.3</td>
</tr>
<tr>
<td>Yes</td>
<td>1131</td>
<td>24.4</td>
<td>0.98 0.83 to 1.16</td>
<td>34.0 1.05 0.90 to 1.22</td>
<td>12.3 0.90 0.73 to 1.11</td>
<td>17.9 0.98 0.81 to 1.17</td>
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<td><strong>Dog now:</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>2896</td>
<td>23.1</td>
<td>1.00</td>
<td>31.3</td>
<td>1.00</td>
<td>17.3</td>
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<tr>
<td>Yes</td>
<td>1168</td>
<td>26.4</td>
<td>1.13 0.96 to 1.33</td>
<td>35.5 1.15 0.99 to 1.33</td>
<td>13.1 0.98 0.80 to 1.21</td>
<td>18.0 0.99 0.82 to 1.18</td>
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<td><strong>Farm animals in the first year</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>8552</td>
<td>24.4</td>
<td>1.00</td>
<td>33.0</td>
<td>1.00</td>
<td>17.3</td>
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<td>Yes</td>
<td>518</td>
<td>22.4</td>
<td>0.88 0.69 to 1.11</td>
<td>29.3 0.83 0.67 to 1.03</td>
<td>12.5 0.90 0.67 to 1.21</td>
<td>17.0 0.94 0.73 to 1.22</td>
</tr>
<tr>
<td><strong>Mother had contact with farm animals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>3566</td>
<td>24.3</td>
<td>1.00</td>
<td>32.6</td>
<td>1.00</td>
<td>17.3</td>
</tr>
</tbody>
</table>

*The "general population group" comprises the participants in the Wellington survey for 6-7 year olds. †The "childhood infections group" comprises children with notifiable infectious diseases reported to public health services and recorded on the EpiSurv database.*
the two groups so we combined the two groups and adjusted for “dataset” in the final analyses.

Ethics
The study was approved by the Massey University Human Ethics Committee (protocol 00/154) and conformed to the principles embodied in the Declaration of Helsinki.

RESULTS
The response rates were low, but similar in the two surveys: 1584 (57%) of parents responded to the survey of the childhood infections group; and 2539 (47%) of parents responded to the survey of the general population group.

Childhood infections
There were no significant differences in prevalences of reported symptoms of asthma, rhinitis, and eczema between the two groups (for example, the prevalence of current wheezing was 23.3% in the childhood infections group and 24.3% in the general population group), or between the various subgroups of the childhood infections group (table 1). Also, there was little difference according to the age at which infection occurred (not shown in table): the prevalences of current wheezing were 23.1% in those with infections in the first year of life (n = 242), 20.5% in those with infections at age 1–2 years (n = 536), and 25.6% in those with infections at age 3–4 years (n = 806).

Table 2 shows the adjusted prevalence odds ratios for infections and other relevant exposures. For current wheezing there was a weak protective effect (OR = 0.86, 95% CI 0.74 to 1.00) of serious childhood infections (defined as being in the childhood infections dataset rather than in the general population dataset). When we restricted the analysis to children who had not been reported as using antibiotics in the first year of life (not shown in table) there was a slightly stronger (non-statistically significant) protective effect of infections (OR = 0.78, 95% CI 0.55 to 1.10), whereas there was less evidence of a protective effect in children who had been reported as using antibiotics early in life (OR = 0.95, 95% CI 0.54 to 1.65).

Factors related to infections
With regard to other factors related to infections (table 2), there was a reduced prevalence of reported hay fever in children with two or more older siblings (OR = 0.56, 95% CI 0.44 to 0.71), and in children with one older sibling (OR = 0.73, 95% CI 0.59 to 0.90), when compared with children with no older siblings. The associations for older siblings were weaker for the other symptoms and outcomes considered (table 2). On the other hand, for younger siblings, the strongest associations were for current wheezing (OR = 0.66, 95% CI 0.51 to 0.84 for two or more compared with no younger siblings).

Having a cat in the home during the first year of life was protective against current wheezing (OR = 0.83, 95% CI 0.72 to 0.97), asthma (OR = 0.79, 95% CI 0.69 to 0.91), allergic rhinoconjunctivitis (OR = 0.76, 95% CI 0.62 to 0.92), hay fever (OR = 0.74, 95% CI 0.63 to 0.87) but not eczema (OR = 0.96, 95% CI 0.84 to 1.09); similar results were found for current cat ownership. No effect of contact with dogs was observed, although currently living with a dog was negatively associated with eczema (OR = 0.83, 95% CI 0.72 to 0.96). Contact with farm animals in the first 12 months of life was weakly (non-significantly) protective against subsequent asthma, as was the mother’s exposure to farm animals during pregnancy.

DISCUSSION
The primary reason for conducting this study was to investigate the potential protective effect of notifiable childhood infections for the subsequent development of asthma. We found at most a weak protective effect, although it should be emphasised that the study was confined to infections that were notified to public health authorities, and the findings cannot be extrapolated to childhood infections in general. On the other hand, we found an increased risk of asthma from the use of antibiotics and/or paracetamol in the first year of life, and also for recent paracetamol use.

Both surveys had low response rates. However, it is unlikely that these will have seriously biased our findings

Paracetamol and antibiotics
Table 2 also shows the adjusted prevalence odds ratios for paracetamol and antibiotic use. The use of paracetamol during the first year of life was weakly associated with current wheezing (OR = 1.38, 95% CI 1.04 to 1.83), asthma (OR = 1.72, 95% CI 1.32 to 2.23), hay fever (OR = 1.25, 95% CI 0.92 to 1.70), and eczema 1.27 (95% CI 1.02 to 1.58), but not rhinoconjunctivitis (OR = 0.97, 95% CI 0.68 to 1.37). Recent use of paracetamol at least once per month was associated with current wheezing (OR = 2.10, 95% CI 1.78 to 2.49), asthma (OR = 1.57, 95% CI 1.34 to 1.84), rhinoconjunctivitis (OR = 1.77, 95% CI 1.43 to 2.18), and hay fever (OR = 1.47, 95% CI 1.22 to 1.78) but not eczema (OR = 1.05, 95% CI 0.90 to 1.23). Stronger associations were observed with the use of antibiotics in the first year of life with current wheezing (OR = 1.78, 95% CI 1.49 to 2.14), asthma (OR = 2.10, 95% CI 1.79 to 2.48), rhinoconjunctivitis (OR = 2.04, 95% CI 1.60 to 2.61), hay fever (OR = 1.52, 95% CI 1.25 to 1.85), and eczema (OR = 1.40, 95% CI 1.21 to 1.62). We found similar odds ratios for antibiotics when we restricted the analysis to the childhood infections group or to the general population group (not shown in tables).

We conducted analyses for paracetamol and/or antibiotic use stratified by type of infection but these generally yielded findings similar to the overall analyses (results not shown in tables). However, the risk of current wheezing in association with the use of paracetamol in the first year of life was higher in those with salmonellosis (OR = 9.21 95% CI 1.15 to 73.84).

Policy implications
These findings should be regarded as provisional and preliminary and there are therefore no immediate policy implications.

However, if these findings are confirmed in further research then they would indicate the need for greater caution in the use of both antibiotics and paracetamol early in life.

Key points
- Antibiotic use early in life may increase the subsequent risk of asthma.
- The use of paracetamol early in life, or recent paracetamol use, may also increase the risk of asthma.
- There is at most a weak protective effect of notifiable childhood infections on the subsequent risk of developing asthma.

Infections, paracetamol, antibiotics, and childhood asthma

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increased risk of wheeze.\textsuperscript{16} We found only a weak protective
viral infections (in particular RSV), are associated with an
weak, and they are unlikely to have biased the findings for
and childhood infection groups), but any bias is likely to be
response rates may have biased the findings for childhood
infections (which entailed comparing the general population and
childhood infection groups), but any bias is likely to be
within the childhood infections groups and/or within the general population group and we obtained
similar odds ratio estimates in each group. Thus, the low
response rates may have biased the findings for childhood
infections (which entailed comparing the general population and
childhood infection groups), but any bias is likely to be
same population in the ISAAC phase I survey conducted eight
years previously that had a response rate of 92%\textsuperscript{50}; (c) the
population group were very similar to those obtained in the
surveys; (b) the prevalence estimates obtained in the general
population group were very similar to those obtained in the
broad range of infectious agents (including respiratory
infections) may protect against atopy and atopic disease
such as allergic asthma and hay fever.\textsuperscript{6–11, 18, 26–28} However,
however, this would not explain the reported findings
infections group survey was restricted to children who had
not moved since their original notification to the EpiSurv
database. This could introduce a bias, but this would occur
only if the prevalence of asthma was considerably different in
children who had moved than in children who had not.
A second limitation of the data is that the childhood
infection group survey was national, whereas the general
population survey was in the Wellington region. Once again,
this may have biased the findings for childhood infections,
but could not have biased the findings for medication use as
they involved analyses that were internal to each group.
Furthermore, the bias in the findings for infections is likely to
be small because in the previous ISAAC phase I survey, the
asthma prevalence in Wellington children was found to be
very close to that in the overall ISAAC data for New Zealand
(a prevalence of 25.1% in Wellington and 24.5% nationally
for current wheezing\textsuperscript{21}). A related issue is that the childhood
infections group survey was restricted to children who had
not moved since their original notification to the EpiSurv
database. This could introduce a bias, but this would occur
only if the prevalence of asthma was considerably different in
children who had moved than in children who had not.
A third limitation of the data is that information on
environmental exposures (other than notifiable childhood
infections) was obtained retrospectively. Thus, there are
different issues involved in assessing the validity of the
findings for infections, and those for other exposures; since
the latter could be subject to recall bias. However, this would
only occur if the recall of particular exposures (for example,
paracetamol use early in life) was different in parents of
children with asthma than in parents of children without
asthma. Parents of children from the childhood infections
group might also recall better medication use early in life
than parents of children in the general population group;
however, this would not explain the reported findings
because the observed associations of paracetamol and anti-
biotic use early in life with subsequent childhood asthma
were similar within the childhood infections group and
within the general population group.
Currently the role of infections in the aetiology of asthma is
not clear; results of several studies suggest that exposure to a
broad range of infectious agents (including respiratory
infections) may protect against atopy and atopic disease
such as allergic asthma and hay fever.\textsuperscript{6–11, 18, 26–28} However,
other studies have shown that some, for example, respiratory
infectious agents (in particular RSV), are associated with an
increased risk of wheeze.\textsuperscript{25, 51} We found only a weak protective
effect of childhood infections that appeared to be confined to
children who had not used antibiotics in the first year of life.
This is puzzling to some extent because it is perhaps more
likely that these children experienced viral infections that are
considered risk factors for asthma. Thus, the reason for this
comparatively modest protective effect may be because the
EpiSurv database included a wide range of infections,
potentially including infections that are positively associated
with asthma symptoms. In fact, we found little difference
when we studied the site and type of infection independently,
but these still represent rather broad categories and although
they have all been termed “serious” they actually include a
wider spectrum. At one end, they are largely self limiting
diseases such as campylobacteriosis with a very low case-
fatality rate. At the other is meningococcal disease, which
causes serious invasive disease in the form of septicaemia
and/or meningitis, almost invariably results in hospitalisation
(the hospitalisation rate for campylobacteriosis is about 7%,
compared with about 97% for meningococcal disease, which
carries a case-fatality rate in New Zealand of 4.5%\textsuperscript{52}).
Presumably the immune response to these infections is
similarly different in its form and intensity that may have
different and potentially opposite effects on the TH\textsubscript{1}/TH\textsubscript{2}
balance and the development of atopy and asthma. A further
differentiation was unfortunately not possible because of the
low numbers for specific infectious diseases.
While we found at most a weak protective effect of
childhood infections, we found an approximately twofold
increased risk of asthma, and to a lesser extent hay fever and
eczema, at age 6–7 years in children whose parents reported
that they had used antibiotics in the first year of life. Our
findings are generally consistent with other evidence that
antibiotic use in the first year of life increases the subse-
quent risk of asthma,\textsuperscript{20–26} although a number of authors have
commented on the possibility that these associations may be
attributable to reverse causation in that frequent upper
respiratory infections, often and early symptom of asthma,
are usually treated with antibiotics.\textsuperscript{21} The association was
stronger for asthma and hay fever than for eczema, and it
was observed both within the general population group, and
within the childhood infections group.
We also found an association of paracetamol use in the
first year of life, and also recent paracetamol use, with
asthma at age 6–7 years. The latter finding is consistent with
previous studies.\textsuperscript{37–40} One possibility is simply that health
professionals encourage their asthmatic patients to take
paracetamol rather than aspirin because the latter may
worsen asthma severity, but Shaheen \textit{et al.}\textsuperscript{37} argued that this
was unlikely to explain their findings. Possible underlying
mechanisms involve increased oxidative stress due to the
ability of paracetamol to reduce levels of the anti-oxidant
glutathione in immune cells, thus depleting anti-oxidant
defences and promoting TH\textsubscript{2} allergic inflammation\textsuperscript{27} as well
as increased viral loads as a side-effect of paracetamol use,
possibly leading to asthma.\textsuperscript{29} Thus, there is some preliminary
evidence linking paracetamol use to current asthma in both
children and adults but, to our knowledge, this is the first
report associating paracetamol use early in life with sub-
sequent asthma risk in children. As with adults, the possi-
bility cannot be excluded that the association is due to
reverse causation. Furthermore, it may not necessarily
involve the same mechanisms as the association of more
recent paracetamol use with asthma.
In summary, the findings reported here are consistent
with other evidence that the use of antibiotics and/or para-
cetamol early in life may increase the risk of asthma. They
are also consistent with preliminary evidence associating
recent paracetamol use with an increased risk of asthma.
Any protective effect of notifiable childhood infections was
weak

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