

**Recorded infections and antibiotics in early life; associations with allergy in UK children and their parents**

Jessica M Harris, Pamela Mills, Carol White, Susan Moffat, Anthony J Newman Taylor, Paul Cullinan

Department of Occupational and Environmental Medicine, Imperial College (National Heart and Lung Institute), 1B Manresa Road, London SW3 6LR

Author for correspondence:

*Jessica Harris*

*Occupational and Environmental Medicine*

*Imperial College School of Medicine (NHLI)*

*1B Manresa Road*

*London SW3 6LR, UK*

*tel: +44 (0)20 7351 8307*

*fax: +44 (0)20 7351 8336*

*e-mail: [jessica.harris@imperial.ac.uk](mailto:jessica.harris@imperial.ac.uk)*

Word count: 3713

Key words: birth order, wheeze, atopy, childhood infection, antibiotic

## Abstract

**Background:** It is suggested that the inverse relationship between allergic disease and family size reflects reduced exposure to early life infections; and that antibiotic treatment in childhood diminishes any protective effect of such infection.

**Methods:** Birth cohort study. 642 children were recruited before birth and seen annually until age 8; reported infections and prescribed antibiotics by age 5 years were counted from GP records. Comparisons with a previous study of their parents have been made

**Results:** At age 8, 104 (19%) children were atopic, 79 (13%) were currently wheezy and 124 (21%) had seasonal rhinitis. 577 (97%) children had at least 3 infections recorded by age 5, a figure much higher than that of their parents (69%). By the age of 5 only 11 (2%) children had never received a prescription for antibiotics; the corresponding figure for the parents was 24%. Higher numbers of infections were recorded for firstborn children. After adjusting for parental atopy and birth order, there was no association between infection counts and atopy (odds ratio [OR] 1.01, 95% ci [0.99 to 1.03] *per infection*). Significant positive associations were found for wheeze and seasonal rhinitis. An increased risk of current wheeze was found for each antibiotic prescription (adjusted OR 1.07 [1.03 to 1.10]) but not for atopy. This was primarily explained by prescriptions for respiratory infections. Similar patterns were observed for seasonal rhinitis.

**Conclusions:** Despite very high rates of recorded early life infections and antibiotic prescriptions we have failed to find any plausibly causative relationships with subsequent respiratory allergies.

[252 words]

## Introduction

Observing that allergies were less common among 'native' Canadians than their 'white' counterparts Gerrard *et al.*<sup>1</sup> proposed that "atopic disease is the price paid by some members of the white community...for their relative freedom from diseases due to viruses, bacteria and helminthes". Thirteen years later Strachan *et al.*<sup>2</sup> suggested that the same mechanism might be responsible for the decrease in risk of hay fever with increasing birth order.

Convincing evidence of a general protective effect of infection has, however, remained elusive. In Italy, serological evidence of hepatitis A infection is associated inversely with atopic disease in military recruits<sup>3</sup>, a finding that may also be true for other orally-acquired infections<sup>4</sup>. A similar relationship has been observed in the US<sup>5,6</sup> but not elsewhere<sup>7,8,9</sup>; in any case it is not clear that an association is independent of a separate birth-order effect. Unreplicated studies of infection with measles<sup>10</sup>, mycobacterium tuberculosis<sup>11</sup> or schistosoma<sup>12</sup> may not be relevant to contemporary European populations. Nor is there consistent evidence that treatment with antibiotics in early childhood – which might be expected to diminish any protective effects of infection<sup>13</sup> – is associated with an increase in risk of subsequent allergy<sup>14</sup>.

In 1993 we started to assemble a representative cohort of children born in Ashford, Kent. During this process we observed, among their parents who were born on average 28 years earlier, a strong birth order effect for atopy and allergic respiratory disease. We could not, however, explain this by either documented evidence of common childhood infections or serological evidence of infection with hepatitis A or *H. pylori*<sup>8</sup>. Nor could we measure any association between these outcomes and early life antibiotic prescriptions that was not reasonably explained by reverse causation<sup>15</sup>.

It may be that the relevant experience of the Ashford cohort children was different to that of their parents. Indeed such a criticism was leveled at our findings relating to childhood antibiotic prescriptions, it being argued that any detrimental effect would be apparent only at the much higher contemporary rates of prescription<sup>16</sup>. Here we report the findings from our study of the cohort children, and consider whether changes in infections or antibiotic use across one generation can in any way explain increases in reported allergic disease in the UK.

## Methods

In 1993 we started recruitment to a birth cohort by inviting all newly pregnant women presenting to one of three GP surgeries in Ashford Kent to participate. Details of recruitment and follow up are available elsewhere<sup>17</sup> but, briefly, 658 mothers (93% of those eligible) agreed to take part and subsequently gave birth to 642 babies. Parental atopy was established at recruitment using skin prick tests in all but three mothers and 542 (87%) of their partners; and asthma or hayfever by self-report.

Children were visited annually until they were aged eight at which point allergic outcomes were measured. Using standard questions (ISAAC<sup>18</sup>) administered to parents we collected information – for 92% of the children - on wheeze in the past 12 months and on seasonal rhinitis. Seasonal rhinitis was defined as a positive response to the question "In the past twelve months, has your child ever had a problem with sneezing or a runny or blocked nose when s/he did not have a cold or the flu?" along with a record of this occurring in any of the months from March to September inclusive<sup>19</sup>. Through skin prick tests (85% of children) we established the presence of atopy, defined by the development of  $\geq 1$  positive response (mean wheal 2mm) to three common allergens (pollen mixture, *D.pteronysinus* and cat fur, ALK Abelló, UK). We also collected information on family size, current exposure to cigarette

smoke and other factors including parental occupational details necessary for allocating children to a social class (Registrar General's 1990 classification, Office for National Statistics). Using father's occupation, social class was categorized as I (Professional), II (Managerial and Technical), IIINM and IIIM (Skilled; non-manual and manual), IV (Partly skilled) and V (Unskilled).

Three nurses reviewed general practice medical records for 594 (93%) cohort children to the age of five, recording all visits and those for a pre-determined list of infections and all antibiotic prescriptions. This was done before establishing the child's allergic status. As with our previous, parental analysis we drew up categories of infection: lower respiratory (bronchitis, chest infection, bronchiolitis, pneumonia, cough, wheeze): upper respiratory (upper RTI, croup, tracheitis, laryngitis, pharyngitis, sore or septic throat): ear, eye (conjunctivitis), skin (impetigo), urinary tract and gastro-intestinal infections. Infections were considered separate if recorded at consultations  $\geq 28$  days apart. Dates of antibiotic prescriptions were noted and categorised by indication (respiratory, ear, skin, throat, urinary tract, other). Information was only collected for those children for whom we had access to complete medical records.

In 1998 we conducted a retrospective study of the parents of these cohort children to investigate any associations between infections (measured both serologically and counts from GP records) and antibiotic prescriptions in early life with subsequent respiratory allergy in adulthood. The methodology of collecting infection and antibiotic data from the medical records is described in full elsewhere<sup>8;15</sup> but was essentially identical to that for the children as described above.

The study was approved by the local ethics committee; parents/guardians provided signed, informed consent.

## Statistical analysis

We devised categories of total infection counts ( $<25$  versus  $\geq 25$  by age 5) and prescribed antibiotics ( $<15$  versus  $\geq 15$  by age 5) which approximately isolated the higher 20% of values. Univariate comparisons were undertaken using chi-squared and Mann Whitney tests, and tests for trend using chi-squared or Cuzick's tests. Adjusted logistic regression was used to examine associations between infection or antibiotic counts and allergic outcomes with results presented as odds per infection, or per antibiotic prescription, as appropriate. Identification of confounders was undertaken using a stepwise approach; all factors detailed in Table 1 were considered for inclusion and contributions to the base models were evaluated using changes in log likelihood. Any potential confounder which was significantly associated with any outcome was included in all multivariate models. All analyses were repeated separately for first born children ( $n=270$ ; 42%) in order to minimise any potential behavioural bias. We also repeated the analysis of lower respiratory infections after excluding "cough" and "wheeze". Analyses were completed using SAS (NC, Cary, USA) and Stata (College Station, Texas, USA).

## Results

### ***Infection counts and antibiotic prescriptions: parents vs children.***

Both infection counts and antibiotic prescriptions were higher for the children than their parents, particularly in the first two years of life (Figure). The median number of infections recorded in the medical records up to age 5 was 14 (range 0-71) for the children but just five (0-50) for their parents. By that age, only 3 (0.5%) children - but 7% of parents - had none

recorded. Amongst the children, upper and lower respiratory infections were most common (at least one in the first 5 years, 94% each), followed by ear (80%), eye (65%), gastro-intestinal (63%), urinary tract (15%) and skin infections (15%). The corresponding figures for parents were: upper respiratory (65%), lower respiratory (56%), ear (33%), eye (27%), gastro-intestinal (28%), urinary tract (9%) and skin (45%).

Antibiotics were prescribed more frequently and at an earlier age for the children. The median number of prescriptions up to age 5 was nine (range 0-45) compared to two (0-31) for their parents; and the median age at first prescription 5.0 months (2 days to 4.9 years) *versus* 18.1 months (range 0-5 years) for their parents. By the age of 5, only 11 (2%) children, but 24% of parents, had never received an antibiotic prescription.

### ***Atopy and allergic outcomes: cohort children***

At the age of eight, 104 (19%) children were designated as atopic. Seventy nine (13%) were reported to have had a wheeze in the past 12 months, and 124 (21%) to have seasonal rhinitis.

There were no differences in these proportions by sex (Table 1) or by social class, with the exception of seasonal rhinitis which was less prevalent amongst social class III ( $p=0.04$ ), although this did not follow a linear trend ( $p_{trend}=0.80$ ). Children of atopic mothers or fathers were more likely to be atopic or to have wheeze or seasonal rhinitis. Atopy ( $p_{trend}=0.07$ ) and seasonal rhinitis (0.01), but not current wheeze (0.77) were related inversely to birth order. There were no differences in any outcomes between children registered with different practices.

**Table 1: Sociodemographic associations with allergic outcomes at age 8 in cohort children**

		atopy at age 8			current wheeze at age 8		seasonal rhinitis at age 8	
		n	n (%)	p-value	n (%)	p-value	n (%)	p-value
<b>sex</b>	<b>female</b>	299	44 (17.3%)	0.34	34 (12.6%)	0.61	49 (18.1%)	0.12
	<b>male</b>	342	60 (20.5%)		45 (14.0%)		75 (23.3%)	
<b>maternal atopy</b>	<b>-</b>	423	55 (15.2%)	0.002	48 (12.3%)	0.30	68 (17.4%)	0.004
	<b>+</b>	216	49 (26.5%)		31 (15.4%)		56 (27.7%)	
<b>paternal atopy</b>	<b>-</b>	329	46 (15.7%)	0.01	33 (10.6%)	0.02	63 (20.2%)	0.26
	<b>+</b>	230	51 (25.3%)		39 (17.6%)		54 (24.3%)	
<b>social class<sup>†</sup></b>	<b>I/II</b>	163	28 (19.6%)	0.90*	22 (13.8%)	0.55*	39 (24.4%)	0.80*
	<b>III</b>	274	37 (18.3%)		27 (10.8%)		42 (16.7%)	
	<b>IV/V</b>	126	16 (14.0%)		20 (16.8%)		32 (26.9%)	
<b>birth order</b>	<b>1<sup>st</sup></b>	270	51 (22.0%)	0.07*	35 (13.9%)	0.77*	71 (28.2%)	0.01*
	<b>2<sup>nd</sup></b>	236	37 (18.3%)		28 (12.8%)		30 (13.8%)	
	<b>3<sup>rd</sup>+</b>	136	16 (14.0%)		16 (13.0%)		23 (18.7%)	
<b>smoker in the home</b>	<b>no</b>	373	64 (18.6%)	0.77	39 (10.5%)	0.01	79 (21.2%)	0.86
	<b>yes</b>	219	40 (19.6%)		40 (18.3%)		45 (20.6%)	

<sup>†</sup>social class defined as I (Professional); II (Managerial and Technical); III (Skilled); IV (Partly skilled); V (Unskilled)

\*p-value for trend

### ***Recorded infections: cohort children***

Doctors in one practice recorded higher rates of infection than the other two (median 17 *versus* 12 and 13;  $p < 0.001$ ); they also wrote the highest number of antibiotic prescriptions (median 11 *versus* seven and nine;  $p < 0.001$ ).

Among the children, the median age at first recorded infection was 3.9 months (range 0 days to 4.9 years). Firstborn children were more likely to be older at the point of first recorded infection (median age 4.4 months) than those of higher birth order (3.6 months;  $p = 0.03$ ). This difference was greatest for lower respiratory infections (8.1 vs 5.7 months;  $p < 0.001$ ) and eye infections (14.1 months vs 7.6 months;  $p < 0.001$ ). In contrast first gastro-intestinal infections tended to be reported earlier for firstborns (11.0 months vs 14.1 months;  $p < 0.001$ ).

Children of higher birth order and social class were less likely to have  $\geq 25$  infections by age 5 (Table 2); there were no important differences between children with and without an atopic parent.

**Table 2: Sociodemographic associations with recorded infections, antibiotic prescriptions and total visits to general practitioner (GP) by age 5 years in cohort children.**

			≥25 infections by age 5		≥15 prescriptions by age 5		total visits to GP by age 5	
		total	n (%)	p-value	n (%)	p-value	median (range)	p-value
<b>sex</b>	<b>female</b>	299	44 (16.0%)	0.28	61 (22.2%)	0.94	29 (7-107)	0.02
	<b>male</b>	342	62 (19.4%)		70 (21.9%)		32 (2-151)	
<b>maternal atopy</b>	<b>-</b>	232	66 (16.9%)	0.40	74 (19.0%)	0.02	29 (2-124)	0.004
	<b>+</b>	403	40 (19.7%)		56 (27.6%)		34 (5-151)	
<b>paternal atopy</b>	<b>-</b>	210	54 (17.4%)	0.93	72 (23.2%)	0.44	32 (2-151)	0.33
	<b>+</b>	366	39 (17.7%)		45 (20.4%)		29 (3-124)	
<b>social class</b>	<b>I/II</b>	163	24 (15.3%)	0.06*	33 (21.0%)	0.13*	32 (5-151)	0.86*
	<b>III</b>	274	38 (14.9%)		48 (18.8%)		29 (3-99)	
	<b>IV/V</b>	126	29 (24.4%)		35 (29.4%)		32 (6-82)	
<b>birth order</b>	<b>1<sup>st</sup></b>	270	55 (22.2%)	0.02*	63 (25.4%)	0.43*	34 (4-151)	<0.001*
	<b>2<sup>nd</sup></b>	236	35 (15.9%)		38 (17.3%)		28 (2-91)	
	<b>3<sup>rd</sup>+</b>	136	16 (12.7%)		30 (23.8%)		27 (5-107)	
<b>smoker in the home</b>	<b>no</b>	373	65 (17.8%)	0.98	81 (22.1%)	0.94	31 (3-151)	0.73
	<b>yes</b>	219	38 (17.7%)		47 (21.9%)		31 (2-107)	

<sup>†</sup>social class defined as I (Professional); II (Managerial and Technical); III (Skilled); IV (Partly skilled); V (Unskilled)

\*p-value for trend

On crude analysis, children who had  $\geq 25$  recorded infections by age 5 were more likely to be wheezy or have seasonal rhinitis at age 8 (Table 3). After adjustment – with the single exception of infections between ages of 4 and 5 – there were no relationships between infections of any category and atopy at age 8 (Table 4). In contrast there were positive associations between wheeze and infection counts at all ages; these appear to be confined to lower respiratory and gastro-intestinal infections only ( $p < 0.001$  and  $p = 0.01$  respectively). The patterns were very similar for seasonal rhinitis although there were positive associations also with ear and upper respiratory infections. For both wheeze and seasonal rhinitis, the strength of the associations increased with age of recorded infection. There was some evidence of an overlap between these symptoms; 36 (45.6%) of the children who wheezed also had seasonal rhinitis compared to 88 (17.1%) of the children who were not currently wheezy ( $p < 0.001$ ). However, adjusting the wheezing analyses for presence of seasonal rhinitis and *vice versa* did not have any effect on the final estimates (data not shown).

**Table 3: Associations between infection counts and antibiotic prescriptions by age 5 and outcomes at age 8: cohort children**

		≥25 infections by age 5		≥15 prescriptions by age 5		total visits to GP by age 5		
		total	n (%)	p-value	n (%)	p-value	median (range)	p-value
<b>atopy at age 8</b>	-	444	78 (17.8%)	0.90	94 (21.4%)	0.32	31 (3-151)	0.02
	+	104	19 (18.3%)		27 (26.0%)		35 (2-98)	
<b>current wheeze at age 8</b>	-	514	76 (15.1%)	<0.001	98 (19.4%)	<0.001	29 (11-124)	<0.001
	+	79	27 (35.1%)		30 (39.0%)		39 (2-151)	
<b>seasonal rhinitis at age 8</b>	-	470	67 (14.6%)	<0.001	85 (18.5%)	<0.001	29 (2-124)	<0.001
	+	123	36 (29.5%)		43 (35.3%)		39 (8-151)	

**Table 4: Associations between infection counts by age 5 and outcomes at age 8: cohort children**

		<b>Atopy at age 8</b>		<b>Current wheeze at age 8</b>		<b>Seasonal rhinitis at age 8</b>	
<i>n in model</i>		490		523		523	
	No. of infections	OR* (95% ci)	p-value	OR* (95% ci)	p-value	OR* (95% ci)	p-value
total infections age 0-5	9526	1.01 (0.99, 1.03)	0.28	1.05 (1.03, 1.08)	<0.001	1.05 (1.03, 1.07)	<0.001
total infections age 0-1	2673	0.99 (0.92, 1.05)	0.65	1.09 (1.02, 1.17)	0.01	1.06 (1.00, 1.13)	0.04
total infections age 1-2	2456	0.99 (0.93, 1.06)	0.84	1.10 (1.02, 1.18)	0.01	1.10 (1.04, 1.17)	0.002
total infections age 2-3	1934	1.07 (0.99, 1.15)	0.08	1.11 (1.02, 1.21)	0.02	1.12 (1.05, 1.21)	0.001
total infections age 3-4	1439	1.06 (0.97, 1.16)	0.18	1.20 (1.09, 1.31)	<0.001	1.24 (1.14, 1.35)	<0.001
total infections age 4-5	1122	1.11 (1.01, 1.23)	0.03	1.26 (1.13, 1.39)	<0.001	1.21 (1.10, 1.32)	<0.001
<b>Infection type (age 0-5)</b>							
lower respiratory	3364	1.03 (0.99, 1.07)	0.20	1.14 (1.09, 1.20)	<0.001	1.09 (1.05, 1.14)	<0.001
upper respiratory	3006	0.99 (0.93, 1.06)	0.86	1.05 (0.99, 1.12)	0.13	1.09 (1.03, 1.15)	0.003
ear	1462	1.03 (0.95, 1.12)	0.49	1.07 (0.98, 1.18)	0.16	1.16 (1.07, 1.25)	<0.001
eye	753	1.07 (0.92, 1.23)	0.40	1.17 (1.00, 1.37)	0.06	1.09 (0.95, 1.25)	0.23
gastro-intestinal	695	1.13 (0.96, 1.33)	0.14	1.23 (1.03, 1.47)	0.03	1.36 (1.17, 1.58)	<0.001
urinary tract	132	0.79 (0.52, 1.19)	0.23	0.78 (0.49, 1.25)	0.27	1.01 (0.73, 1.39)	0.96
skin	114	1.30 (0.89, 1.91)	0.18	0.79 (0.45, 1.39)	0.39	1.03 (0.69, 1.54)	0.87

\*adjusted for maternal atopy, paternal atopy, birth order and current exposure to cigarette smoke.

Annual counts of lower respiratory infections were positively associated with current wheeze; adjusted odds ratios increased steadily from 1.16 for infections recorded between birth and age 1, to 1.17, 1.45, 1.66 and 1.86 for infections recorded between ages 1-2, 2-3, 3-4 and 4-5 respectively. Each of these estimates was statistically significant ( $p < 0.05$ ). We found a similar pattern for upper respiratory infections although the trend was weaker; as it was for seasonal rhinitis and both lower and upper respiratory infections (data available). For all outcomes, odds ratios were identical or slightly higher when “wheeze” and “cough” were omitted from the lower respiratory infection categories (data not shown).

### ***Antibiotic prescriptions; cohort children***

Children with an atopic mother were more likely to be prescribed  $\geq 15$  antibiotic courses by age 5 (Table 2). There were small differences by social class ( $p = 0.07$ ) although these differences were not linear ( $p_{trend} = 0.13$ ). No differences were found by birth order. Children with wheeze or seasonal rhinitis at age 8 were significantly more likely to have had more antibiotic prescriptions by age 5 (odds ratio 1.07 and 1.06 respectively per prescription, Table 5); there was no such association with atopy. For both wheeze and rhinitis, the relationship was evident at all ages of prescription above 1 year; and were stronger and statistically significant only (for the most part) for prescriptions provided for respiratory indications. After excluding children who wheezed at age one or two from the analysis ( $n = 257$ ), none of the associations between antibiotic counts and current wheeze were statistically significant and the effect estimates tended towards the null (data not shown). There were no clear associations between age at first prescription and any outcomes (data available).

**Table 5: Associations between antibiotic prescriptions by age 5 and outcomes at age 8: cohort children**

		<b>Atopy at age 8</b>		<b>Current wheeze at age 8</b>		<b>Seasonal rhinitis</b>	
<i>n in model</i>		490		523		523	
	Total no. of prescriptions	OR* (95% ci)	p-value	OR* (95% ci)	p-value	OR* (95% ci)	p-value
Total antibiotics age 0-5	6150	1.00 (0.97, 1.03)	0.86	1.07 (1.03, 1.10)	<0.001	1.06 (1.03, 1.09)	<0.001
Total antibiotics age 0-1	1631	0.96 (0.87, 1.05)	0.37	1.08 (0.98, 1.19)	0.13	1.08 (1.00, 1.17)	0.06
Total antibiotics age 1-2	1596	0.99 (0.91, 1.09)	0.90	1.16 (1.06, 1.27)	0.001	1.10 (1.02, 1.19)	0.02
Total antibiotics age 2-3	1248	1.02 (0.93, 1.13)	0.64	1.15 (1.04, 1.28)	0.01	1.11 (1.02, 1.22)	0.02
Total antibiotics age 3-4	962	1.06 (0.94, 1.19)	0.36	1.27 (1.12, 1.44)	<0.001	1.26 (1.13, 1.40)	<0.001
Total antibiotics age 4-5	776	1.04 (0.92, 1.18)	0.52	1.14 (0.99, 1.30)	0.07	1.18 (1.06, 1.33)	0.004
<b>Respiratory infections</b>							
Total antibiotics age 0-5	2249	1.01 (0.95, 1.07)	0.81	1.15 (1.08, 1.22)	<0.001	1.12 (1.06, 1.18)	<0.001
Total antibiotics age 0-1	731	0.91 (0.77, 1.08)	0.29	1.18 (0.96, 1.32)	0.16	1.15 (1.00, 1.32)	0.06
Total antibiotics age 1-2	608	0.94 (0.79, 1.12)	0.45	1.21 (1.03, 1.42)	0.02	1.19 (1.04, 1.36)	0.01
Total antibiotics age 2-3	431	1.07 (0.88, 1.31)	0.49	1.43 (1.18, 1.74)	0.001	1.25 (1.05, 1.49)	0.02
Total antibiotics age 3-4	315	1.23 (1.00, 1.52)	0.06	1.85 (1.48, 2.32)	<0.001	1.56 (1.27, 1.92)	<0.001
Total antibiotics age 4-5	191	1.14 (0.87, 1.48)	0.35	1.76 (1.32, 2.36)	<0.001	1.54 (1.18, 2.01)	0.001
<b>Non-respiratory infections</b>							
Total antibiotics age 0-5	3901	1.00 (0.96, 1.05)	0.94	1.05 (1.00, 1.10)	0.05	1.06 (1.01, 1.10)	0.01
Total antibiotics age 0-1	900	0.97 (0.85, 1.11)	0.67	1.08 (0.94, 1.25)	0.30	1.07 (0.95, 1.21)	0.26
Total antibiotics age 1-2	988	1.02 (0.91, 1.15)	0.71	1.18 (1.05, 1.33)	0.01	1.08 (0.97, 1.20)	0.16
Total antibiotics age 2-3	817	1.01 (0.89, 1.15)	0.87	1.08 (0.93, 1.24)	0.34	1.09 (0.97, 1.22)	0.15
Total antibiotics age 3-4	647	0.99 (0.84, 1.16)	0.89	1.09 (0.91, 1.30)	0.36	1.21 (1.05, 1.40)	0.01
Total antibiotics age 4-5	585	1.02 (0.87, 1.19)	0.78	0.99 (0.82, 1.18)	0.88	1.13 (0.99, 1.30)	0.09

\*adjusted for maternal atopy, paternal atopy, birth order and current exposure to cigarette smoke.

We found no evidence of effect modification by pet ownership (OR per antibiotic prescription for those with <2 pets in the first year of life was 0.99 [0.95, 1.03] *versus* 1.03 [0.98, 1.08]), maternal asthma (OR 1.06 [0.98, 1.15] present *versus* 0.99 [0.96, 1.03] absent) or breast feeding (OR 1.02 [0.98, 1.06] *versus* 0.98 [0.93, 1.04]).

### ***Infections associated with an antibiotic prescriptions; cohort children***

Almost half of all visits (45.3%) for an infection coincided with an antibiotic prescription for the same reason on the same date. This figure was constant for all ages, but varied by indication; only 2.0% of gastro-intestinal but 86.8% of ear infections resulted in a prescription. Differentiating between infections which were treated by antibiotics and those which were not did not result in any major differences in risk estimates (data not shown).

### ***Number of visits to general practitioner: cohort children***

Children made a median of 31 (range 2-151) visits to their GP between birth and the age of 5 years. Boys had a higher number of total visits than girls (Table 2) as did those who were firstborn; this last relationship was evident only for visits made after the first year of life (data not shown). Children with current wheeze at the age of 8 accrued a higher number of visits than those without wheeze; median 39 (11-124) *versus* 29 (2-151) respectively,  $p < 0.001$ . These figures were very similar for seasonal rhinitis and there were similar but smaller – albeit still statistically significant – differences between children with and without atopy (Table 2).

### ***Stratification by birth order: cohort children***

We repeated all of the above analyses for those children with no older siblings ( $n=270$ ; 42%). Each of the crude and adjusted risk estimates associated with both recorded infections and antibiotic prescriptions were very similar to those derived from the total cohort (data available).

## **Discussion**

The children in this representative contemporary English birth cohort had far higher numbers of recorded infections and far more antibiotic prescriptions than did their parents. Nonetheless we were unable to find any evidence among them of protection from subsequent atopy or allergic disease by infection in early life; indeed children who had either wheeze or seasonal rhinitis at age 8 had a higher number of infections recorded by their general practitioners; the associations were largely limited to respiratory-type infections. Similarly the positive associations with antibiotic prescriptions appeared to be confined to those given for respiratory indications. We also found no evidence of any associations between early antibiotic use and wheeze that started after age 3. In these respects our findings here are very similar to those we observed among the cohort parents; and are best explained, we believe, by reverse causation.

Our population is relatively small but probably representative. Through the goodwill of the cohort families and their general practitioners we have been able to maintain high rates of follow up and the associations we report here are likely to be generalisable to other western European populations. Information from medical records was available for almost all children and was collated prior to ascertainment of allergic status. In the absence of comparable information we do not know how our counts of recorded infections compare with other populations in the UK or elsewhere but the rates of antibiotic prescription may be somewhat higher. In our cohort 81% of children had had at least one antibiotic prescription by the age of one year. Comparable proportions reported by Celedon *et al.* in their

'enriched' cohort<sup>20</sup> and from the UK General Practice Research Database were 71% and 65% respectively<sup>21</sup>. These differences may reflect true variations in medical practice or more accurate ascertainment in our study. In any case it can scarcely still be argued that any detrimental effect of antibiotic use in early life would only be apparent at high rates of prescription.

The role of antibiotics during childhood remains however a contentious issue. Since our earlier summary of the literature<sup>15</sup> there have been four further publications reporting a positive association between antibiotic prescription and childhood allergy. Two large case-control studies using UK general practice databases were reported by Bremner *et al.*<sup>22</sup>. A pooled odds ratio for hayfever of 1.11 (1.03, 1.20) was found for those children exposed to antibiotics in the first year of life, although this reduced to 0.92 (0.85, 1.00) after adjusting for consultation behaviour. In another study<sup>23</sup>, 1584 children who had been notified to state-funded health services with a serious infection at age 0-4 years were compared to 2539 children sampled from the general population. In both groups there was an association between antibiotic use in the first year of life and current wheezing at age 6-7 years (OR 1.78 [1.49, 2.14]) and asthma ever (2.10 [1.79, 2.48]). The authors acknowledged that the possibility of reverse causation cannot be excluded. In a more recent birth cohort, adjusted estimates of the risk of atopy at age 6-7 were elevated (1.48 [0.94-2.34]<sup>24</sup>) although exposures were restricted to any antibiotic exposure in the first six months of life compared to none. To the best of our knowledge this is the only study which has reported a significant association between antibiotic use and atopy where atopy is measured subjectively. We were unable to replicate their findings of heightened risk amongst various subgroups (children with <2 pets in their first year of life, breastfed for ≥4 months, or with maternal asthma). More recently a meta-analysis of eight observational studies investigating the associations between antibiotic exposure in the first year of life and the development of childhood asthma<sup>14</sup> reported a significant pooled risk (OR 2.05 [1.41, 2.99]) although only the "retrospective" studies provided a significant pooled association. The authors also acknowledged that some of the papers relied upon self-reporting and so may be susceptible to bias. No attempt to adjust for indication was made. In addition an ecological comparison of *per capita* antibiotic sales with the prevalence of symptoms of asthma, rhinitis and eczema has been conducted using data from 99 centres in 28 countries<sup>25</sup>. Positive relationships were found, although these generally disappeared after adjustment for gross national product. The investigators concluded that if there was a causal association of antibiotic use with asthma risk it does not appear to explain the international differences in asthma prevalence and that their findings are generally not consistent with the hypothesis that antibiotic use increases the risk of asthma, rhinitis or eczema. An accompanying commentary<sup>26</sup> suggested that the findings give further weight to an explanation of protopathic bias (reverse causation) whereby the increased exposure to antibiotics experienced by individuals with allergic disease is most likely explained by those individuals receiving the antibiotics as treatment for symptoms which were early manifestations of their disease.

For over 20 years it has been widely held that 'infections' are protective against childhood allergies. While this may be true in some settings and for some specific infections it does not appear to be the general case in contemporary English children. In this context our findings – and those from the cohort parents - are very similar to those reported by McKeever<sup>21</sup> although we have used an additional, objective outcome (atopy). Both studies used general practice records of early infection. We recognize the important limitations of this approach and acknowledge the certainty that such measurement will be an incomplete reflection of a child's full infectious experience. In addition there are important and complex variations in health-care seeking behaviour both between and within families; the latter, for example, manifest in our population by the higher number of general practice visits made on behalf of firstborn children – although interestingly only after the first year of life. We also found that firstborn children were more likely to be older at the point of first recorded

infection than those of higher birth order; a difference which was particularly evident for lower respiratory infections. We attempted to account for these differences through multivariate adjustment and by stratification; neither approach made any difference to our findings. Medical behaviour, both in diagnosis and prescription, will also vary - as we found - but there were no accompanying differences between general practices and the rates of atopy or parentally-reported wheeze or rhinitis among the children registered as their patients. While our measures of infection, therefore, are flawed we would nonetheless expect to have detected some signal of protection if such an effect exists. Interestingly, one of two studies<sup>27</sup> to have reported a protective effect of early infection ('runny nose') in a contemporary European population used parentally-remembered - rather than doctor-recorded - information; in this instance it is difficult to exclude a biased recall. The other study<sup>6</sup> reported a reduced risk of atopy ascertained by measurement of specific IgE in serum with increasing number of fevers recorded before age one, although these findings were not replicated for atopy defined by skin test response.

A more recent study<sup>23</sup> reported comparisons between 1584 children notified to state-funded health services with serious infections aged 0-4 and 2539 children sampled from the general population. No difference in the prevalence of current wheezing (23.5% vs 24.3%) between these groups was found and consideration of the major site of the infection had little effect. However, this analysis was restricted to notifiable infections and the authors acknowledge that it may be inappropriate to extent these findings to childhood infections in general. Our findings are similar to those from a ten year follow-up study of the Oslo birth cohort<sup>9</sup> where early respiratory infections did not protect against the development of allergic rhinitis or sensitization and were associated with an increased risk for asthma.

This representative cohort of English children born 10 years ago has had far higher rates of both recorded infections and antibiotic prescriptions than their parents born 35 years earlier. Nonetheless we have failed to find either a convincing protective effect of general infections or detrimental effect of antibiotic prescription on the subsequent development of atopy or associated allergic disease.

### **Acknowledgements**

This study was generously supported by the Colt Foundation. The authors remain grateful to all the families who have participated in the study and to the general practitioners who granted access to their medical records.

### **Licence for publication**

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article to be published in Thorax editions and any other BMJPG Ltd products to exploit all subsidiary rights, as set out in our licence <http://thorax.bmjournals.com/ifora/licence.pdf>.

### **Figure Legend:**

Bars on the left represent proportion of participants with  $\geq 1$  infection recorded by year of age (solid bars: children; hatched bars: parents)

Bars on the right represent proportion of participants with  $\geq 1$  antibiotic prescription by year of age (solid bars: children; hatched bars: parents)

## Reference List

- (1) Gerrard JW, Geddes CA, Reggin PL, Gerrard CD, Horne S. Serum IgE levels in white and metis communities in Saskatchewan. *Ann Allergy* 1976; 37(2):91-100.
- (2) Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299(6710):1259-1260.
- (3) Matricardi PM, Rosmini F, Ferrigno L, Nisini R, Rapicetta M, Chionne P et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997; 314(7086):999-1003.
- (4) Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000; 320(7232):412-417.
- (5) Matricardi PM, Rosmini F, Panetta V, Ferrigno L, Bonini S. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol* 2002; 110(3):381-387.
- (6) Williams LK, Peterson EL, Ownby DR, Johnson CC. The relationship between early fever and allergic sensitization at age 6 to 7 years. *J Allergy Clin Immunol* 2004; 113(2):291-296.
- (7) Bodner C, Anderson WJ, Reid TS, Godden DJ. Childhood exposure to infection and risk of adult onset wheeze and atopy. *Thorax* 2000; 55(5):383-387.
- (8) Cullinan P, Harris JM, Newman Taylor AJ, Jones M, Taylor P, Dave JR et al. Can early infection explain the sibling effect in adult atopy? *Eur Respir J* 2003; 22(6):956-961.
- (9) Nafstad P, Brunekreef B, Skrondal A, Nystad W. Early respiratory infections, asthma, and allergy: 10-year follow-up of the Oslo Birth Cohort. *Pediatrics* 2005; 116(2):e255-e262.
- (10) Shaheen SO, Aaby P, Hall AJ, Barker DJ, Heyes CB, Shiell AW et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996; 347(9018):1792-1796.
- (11) Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; 275(5296):77-79.
- (12) van den Biggelaar AH, van RR, Rodrigues LC, Lell B, Deelder AM, Kremsner PG et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000; 356(9243):1723-1727.
- (13) Bjorksten B. Effects of intestinal microflora and the environment on the development of asthma and allergy. *Springer seminars in immunopathology* 2004; 25(3-4):257-270.
- (14) Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. *Chest* 2006; 129(3):610-618.

- (15) Cullinan P, Harris J, Mills P, Moffat S, White C, Figg J et al. Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. *Thorax* 2004; 59(1):11-15.
- (16) Thomas M. Early life antibiotics and asthma. *Thorax* 2004; 59(6):541.
- (17) Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P et al. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. *Thorax* 2004; 59(10):855-861.
- (18) Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8(3):483-491.
- (19) Braun-Fahrlander C, Wuthrich B, Gassner M, Grize L, Sennhauser FH, Varonier HS et al. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. SCARPOL-team. Swiss Study on Childhood Allergy and Respiratory Symptom with respect to Air Pollution and Climate. *International Study of Asthma and Allergies in Childhood. Pediatr Allergy Immunol* 1997; 8(2):75-82.
- (20) Celedon JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. Lack of association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years. *Am J Respir Crit Care Med* 2002; 166(1):72-75.
- (21) McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, Frischer M et al. Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study with the West Midlands General Practice Research Database. *J Allergy Clin Immunol* 2002; 109(1):43-50.
- (22) Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR et al. Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case-control studies using the General Practice Research Database and the Doctors' Independent Network. *Clin Exp Allergy* 2003; 33(11):1518-1525.
- (23) Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health* 2004; 58(10):852-857.
- (24) Johnson CC, Ownby DR, Alford SH, Havstad SL, Williams LK, Zoratti EM et al. Antibiotic exposure in early infancy and risk for childhood atopy. *J Allergy Clin Immunol* 2005; 115(6):1218-1224.
- (25) Foliaki S, Nielsen SK, Bjorksten B, Von ME, Cheng S, Pearce N. Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: The International Study of Asthma and Allergies in Childhood (ISAAC). *Int J Epidemiol* 2004; 33(3):558-563.
- (26) Pekkanen J. Commentary: use of antibiotics and risk of asthma. *Int J Epidemiol* 2004; 33(3):564-565.
- (27) Illi S, Von ME, Lau S, Bergmann R, Niggemann B, Sommerfeld C et al. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001; 322(7283):390-395.

