

Antibiotic use in the first year of life and asthma in early childhood

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Summary

Background An association between antibiotic use in early life and asthma in childhood has been reported in five retrospective studies and one longitudinal study.

Objective To examine the relation between the use of oral antibiotics in the first year of life and asthma in early childhood.

Methods Longitudinal follow-up of 4408 children enrolled in a health maintenance organization (HMO) from birth to the age of 5 years.

Results After adjusting for sex and illnesses of the lower respiratory tract (LRIs), we found a significant association between antibiotic use in the first year of life and asthma between the ages of 1 and 2 years (odds ratio (OR) for 1–2 vs. no courses of antibiotics = 1.9, 95% confidence interval (CI) = 1.3–2.7; OR for 3–4 vs. no courses of antibiotics = 1.6, 95% CI = 1.1–2.4; OR for at least 5 vs. no courses of antibiotics = 2.1, 95% CI = 1.5–3.2). After adjustment for sex and LRIs in the first year of life, there was no significant association between antibiotic use in the first year of life and asthma that was initially diagnosed between the ages of 2 and 5 years and that persisted up to the age of 5 years (OR for 1–2 vs. no courses of antibiotics = 1.1, 95% CI = 0.8–1.4; OR for 3–4 vs. no courses of antibiotics = 1.3, 95% CI = 0.9–1.8; OR for at least 5 vs. no courses of antibiotics = 1.0, 95% CI = 0.7–1.4).

Conclusions Our findings do not support the hypothesis that antibiotic use in early life is associated with the subsequent development of asthma in childhood but rather suggest that frequent antibiotic use in early life is more common among asthmatic children.

Keywords antibiotic use, asthma, early life

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Introduction

Asthma is a significant public health problem and the most common chronic disease of childhood in the US [1, 2]. Reduced exposure to infections [3] and the use of oral antibiotics in early life [4] have been proposed as factors that may have contributed to the increase in the prevalence of asthma in the US and other industrialized countries over the last three decades [5–7].

To date, findings from epidemiologic studies have supported [4, 8–12] and refuted [13, 14] an association between antibiotic use in early childhood and asthma. The administration of antibiotics to infant mice leads to alterations of the intestinal flora and impaired T-helper type 1 (Th1) immune responses [15], and it has been hypothesized that frequent use of antibiotics in young children may lead to a Th2 polarized immune deviation and to allergic diseases such as asthma [4, 8]. Since oral antibiotics are frequently prescribed for children

with illnesses of the upper and lower respiratory tract [16, 17], an understanding of the relation between antibiotic use in early life and asthma is critical to public health practitioners and clinicians worldwide. Previous attempts to assess whether there is a causal association between antibiotic use in early childhood and asthma have been hampered by a cross-sectional or retrospective study design [4, 8–11], a lack of adequate data on respiratory illnesses in early life [8–12], a lack of information on antibiotic use in early life [13], and a relatively small sample size [14]. We have examined the association between the use of oral antibiotics in the first year of life and asthma at ages 2 and 5 years in a cohort of children followed from birth at a health maintenance organization (HMO) in Boston, MA.

Methods

We reviewed medical record data for a cohort of children born between 1 January 1992 and 31 December 1993 who were enrolled within 90 days of their day of birth and were continuous members for 5 years in a staff-model HMO with

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14 health centres (Harvard Pilgrim Health Care, now Harvard Vanguard Medical Associates). Of 4672 identified children, 241 were excluded from the study because of either the absence of ambulatory visits during their first 2 years of life ($n = 23$) or having an asthma diagnosis before the age of 1 year ($n = 208$). Thus, 4408 children were included in the current study. The study was approved by the Human Subjects Committee of Harvard Pilgrim Health Care.

The health plan maintains an automated medical record system for ambulatory care, a separate automated pharmacy system, and a claims system for hospitalizations and visits to the emergency departments. All diagnoses associated with outpatient encounters were entered into the automated medical record system with the use of computerized stored ambulatory record (COSTAR) codes [18]. Claims related to hospitalizations and emergency department visits contained standard International Classification of Diseases (ICD)-9 codes. The automated pharmacy records included information on all prescriptions dispensed at outpatient pharmacies in each of the clinical centres.

After a review of its distribution, the number of courses of oral antibiotics in the first year of life was categorized as follows: 0, 1–2, 3–4, and at least 5 courses of antibiotics. Children who were prescribed any oral antibiotics in their first year of life were also categorized as receiving (1) amoxicillin, penicillin, or dicloxacillin only; (2) at least 1 course of erythromycin but no antibiotics other than those in the first category; (3) at least 1 course of either trimethoprim/sulphamethoxazole or acetyl sulphisoxazole but no antibiotics other than those in the first two categories; (4) at least 1 course of amoxicillin/clavulanate acid but no antibiotics other than those in the first three categories; and (5) at least 1 course of cephalosporins. After the diagnostic codes for each patient–physician encounter in the first year of life were reviewed, respiratory illnesses were divided into illnesses of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis) and the upper respiratory tract (otitis, sinusitis/allergic rhinitis (AR), and cough/upper respiratory illness (URI)). The number of URIs, the number of lower respiratory illnesses (LRIs), and the number of visits to a physician's office in the first year of life were categorized at appropriate cut points after a review of their distributions.

Every year starting at age 1 year, asthma was considered present if the child had at least two ambulatory visits or at least one emergency department visit or at least one hospitalization for asthma (ICD-9 codes: 493.*), or if he/she had received at least two dispensings of any asthma medication (inhaled β -agonists, inhaled steroids, cromolyn, nedocromyl, or leukotriene modifiers) in the previous 12 months. Every year starting at age 1 year, severe asthma was considered present if the child had at least five ambulatory visits or at least two emergency department visits for asthma or at least one hospitalization for asthma, or if he/she had at least six dispensings of any asthma medications in the previous 12 months. Asthma was considered present at age 2 years if our diagnostic criteria for asthma were met at age 2 years. Because children with asthma before age 1 year had been excluded from the analysis, children with asthma at age 2 years had to be diagnosed with asthma between the ages of 1 and 2 years. Asthma was considered present at age 5 years if our diagnostic criteria for asthma were met at age 5 years but

not before the age of 2 years. Thus, children with asthma at age 5 years had to be initially diagnosed between the ages of 2 and 5 years and had to have evidence of 'active' asthma between the ages of 4 and 5 years. The same algorithm was used to define severe asthma at age 2 years and severe asthma at age 5 years.

SAS software (SAS Institute, Cary, NC, USA) was used for the statistical analysis. The bivariate analysis of the relation between antibiotic use in the first year of life and asthma at ages 2 and 5 years was conducted with χ^2 tests. Multivariate logistic regression models were used to examine the relation between antibiotic use in the first year of life and asthma at ages 2 and 5 years while adjusting for potential confounders such as respiratory illnesses in the first year of life. All of the multivariate models were adjusted for sex.

Results

Of the 4408 identified children, 2222 (50.4%) were girls. The median number of antibiotic courses dispensed to participating subjects in the first year of life was 2 (range, 0–23). Figure 1 shows the frequency of children receiving a particular class of antibiotic in the first year of life. Of 3292 children who were prescribed any antibiotics in the first year of life, 1168 (35.5%) received only amoxicillin, penicillin, or dicloxacillin, and 798 (24.2%) received at least 1 course of cephalosporins.

Table 1 shows the number of URIs, LRIs, office visits, and frequency of antibiotic use in the first year of life in children with and without asthma at ages 2 and 5 years. Children who had asthma at age 2 years were more likely to have LRIs, to have URIs, to have visited a physician's office, and to have received antibiotics in the first year of life than were children without asthma at age 2 years. Children who had asthma at age 5 years were more likely to have LRIs and to have visited a physician's office in the first year of life than were children without asthma at age 5 years. There was no significant difference in antibiotic use in the first year of life between children with and without asthma at age 5 years. On the basis of the results shown in Table 1, LRIs, URIs, and office visits in the first year of life were classified as continuous variables for the multivariate analysis.

Table 2 shows the results of the multivariate analysis of the relation between antibiotic use in the first year of life and asthma at age 2 years. After adjustment for sex (model 1), antibiotic use in the first year of life was significantly associated with increased odds of having asthma at age 2 years. After adjustment for either the number of office visits to a health-care practitioner (model 2) or the number of illnesses of the respiratory tract in the first year of life (models 3 and 4), there was still a significant association between antibiotic use in the first year of life and asthma at age 2 years. However, the strength of this association was reduced.

We repeated all of the analyses shown in Table 2 to examine whether the use of a particular class of antibiotic in the first year of life could be more or less strongly associated with asthma at age 2 years. We found that children receiving any class of antibiotics in the first year of life had similarly increased odds of asthma at age 2 years (data not shown).

Table 3 shows the results of the multivariate analysis of the association between antibiotic use in the first year of life and

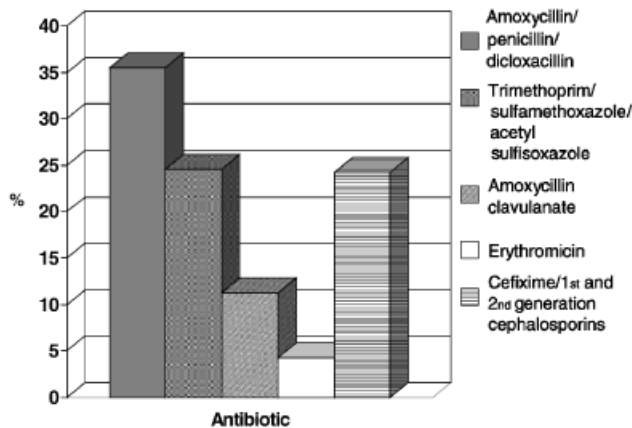


Fig. 1. Frequency of children receiving the following classes of antibiotics in their first year of life: (1) amoxycillin, penicillin, or dicloxacillin only, (2) at least 1 course of erythromycin but no antibiotics other than those in the first category, (3) at least 1 course of either trimethoprim/sulphamethoxazole or acetyl sulphisoxazole but no antibiotics other than those listed in the first two categories, (4) at least 1 course of amoxycillin/clavulanate acid but no antibiotics other than those listed in the first three categories, and (5) at least 1 course of cephalosporins.

Table 1. Antibiotic use, respiratory illnesses, and office visits in the first year of life and asthma among participating children

	Number (%)			
	Asthma at age 2 years		Asthma at age 5 years	
	No (N = 4085)	Yes (N = 323)	No (N = 3864)	Yes (N = 314)
Lower respiratory illnesses				
0	3449 (94.4)	203 (5.6)	3275 (93.0)	248 (7.0)
1	409 (88.2)	55 (11.8)	372 (90.7)	38 (9.3)
2	144 (82.8)	30 (17.2)	140 (89.2)	17 (10.8)
3	56 (77.8)	16 (22.2)	55 (91.7)	5 (8.3)
>3	27 (58.7)	19 (41.3)*	22 (78.6)	6 (21.4)*
Upper respiratory illnesses				
0	754 (96.4)	28 (3.6)	717 (94.0)	46 (6.0)
1–2	1189 (93.2)	87 (6.2)	1136 (93.8)	75 (6.2)
3–4	807 (92.4)	66 (7.6)	752 (91.3)	72 (8.7)
5–7	700 (92.0)	61 (8.0)	652 (91.1)	64 (8.9)
8–12	475 (89.1)	58 (10.9)	453 (91.3)	43 (8.7)
>12	160 (87.4)	23 (13.0)*	154 (91.7)	14 (8.3)†
Number of courses of antibiotics				
0	1073 (96.2)	43 (3.8)	1013 (93.3)	73 (6.7)
1–2	1349 (92.4)	111 (7.6)	1276 (92.6)	102 (7.4)
3–4	756 (92.8)	59 (7.2)	702 (90.9)	70 (9.1)
>4	907 (89.2)	110 (10.8)	873 (92.7)	69 (7.3)‡
Number of office visits				
1–8	923 (95.2)	47 (4.8)	898 (95.9)	38 (4.1)
9–12	1327 (94.4)	79 (5.6)	1250 (92.8)	97 (7.2)
13–16	945 (93.0)	71 (7.0)	890 (91.7)	81 (8.3)
>16	890 (87.6)	126 (12.4)*	826 (89.4)	98 (31.2)*

**P* for linear trend <0.01; †*P*-value for linear trend = 0.06; ‡*P*-value for linear trend = 0.30.

asthma at age 5 years. After adjustment for sex (model 1), there was no significant association between antibiotic use in the first year of life and asthma at age 5 years. These negative results were not appreciably changed after adjustment for LRIs or URIs in the first year of life (models 3 and 4). In a multivariate analysis adjusting for sex and office visits in the

first year of life (model 2), there was an inverse association between having at least 5 courses of antibiotics in the first year of life and asthma at age 5 years. We found no association between the use of any particular class of antibiotic in the first year of life and asthma at age 5 years. As an example, there was no association between the use of any cephalosporins in the first year of life and asthma at age 5 years after adjustment for sex and LRIs in the first year of life (OR for ≥ 1 course of cephalosporins vs. no antibiotics = 0.9%, 95% CI = 0.4–1.9, *P* = 0.65).

To examine whether antibiotic use in the first year of life was associated with severe asthma at age 5 years (*n* = 118), we repeated the multivariate analyses shown in Table 3 with severe asthma as the dependent variable, obtaining similar results (data not shown). To assess whether atopy could influence the relation between antibiotic use in the first year of life and asthma at age 5 years, we also repeated the analyses among 630 children who were diagnosed with eczema before the age of 1 year. We found no significant association between antibiotic use in the first year of life and asthma at age 5 years among children with physician-diagnosed eczema in the first year of life.

Discussion

We analysed automated records for children followed from birth to the age of 5 years and found a significant association between antibiotic use in the first year of life and asthma between the ages of 1 and 2 years. We found no significant association between antibiotic use in the first year of life and asthma that was initially diagnosed between the ages of 2 and 5 years and that was active between the ages of 4 and 5 years.

Figure 2 summarizes the results of published studies of the relation between antibiotic use in early life and asthma. Five retrospective studies found an association between antibiotic use in early life and asthma [4, 8–11]. Because of their assessment of exposure to antibiotics in early childhood, none of these retrospective studies could adequately exclude reverse causation and recall bias as an explanation for their findings. Two of these studies found no association between antibiotic use in early childhood and atopy or atopic diseases other than asthma [8, 10], and a third study found an association between early antibiotic use and asthma only among children with a parental history of hayfever [11]. A recent longitudinal study found an association between antibiotic use in the first year of life and the subsequent development of asthma that became weaker after adjustment for consulting behaviour in the first year of life [12]. In that study, the analysis of the association between antibiotic use and asthma was neither adjusted for respiratory illnesses nor restricted to children who did not receive antibiotics for LRIs in early life.

A prospective birth cohort study of German children showed no association between the use of antibiotics in the first 3 years of life for reasons other than LRIs and asthma, bronchial hyper-reactivity, or atopy at age 7 years [13]. More recently, a longitudinal study of children with a parental history of atopy found no association between antibiotic use in the first year of life and asthma, allergic rhinitis, or eczema at age 5 years [14]. These studies were limited by a lack of description of the relation between antibiotic use in the first

Table 2. Antibiotic use, respiratory illnesses, and number of office visits in the first year of life and asthma between ages 1 and 2 years*

Variable (reference group)	Odds ratio (95% CI), <i>P</i> -value for Wald test†			
	Model 1	Model 2	Model 3	Model 4
Courses of antibiotics (none)				
1–2	2.0 (1.4–2.9), <0.01	1.8 (1.3–2.6), <0.01	1.9 (1.3–2.7), <0.01	1.2 (1.1–1.3), <0.01
3–4	1.9 (1.3–2.9), <0.01	1.5 (1.0–2.3), 0.06	1.6 (1.1–2.4), 0.03	1.7 (1.1–2.5), 0.01
>4	3.0 (2.1–4.3), <0.01	1.9 (1.2–2.8), <0.01	2.1 (1.5–3.2), <0.01	2.5 (1.7–3.6), <0.01
Each office visit (e.g. 1 vs. 0, 2 vs. 1)		1.05 (1.03–1.07), <0.01		
Each illness of the lower respiratory tract (e.g. 1 vs. 0, 2 vs. 1)			1.6 (1.5–1.8), <0.01	
Each illness of the upper respiratory tract (e.g. 1 vs. 0, 2 vs. 1)				1.2 (1.1–1.3), <0.01

*All models were adjusted for sex, in addition to the variables listed in each column. †*P*-value for linear trend for the association between antibiotic use in early life and asthma = <0.01 in all models.

Table 3. Antibiotic use, respiratory illnesses, and number of office visits in the first year of life and asthma between ages 2 and 5 years*

Variable (reference group)	Odds ratio (95% CI), <i>P</i> -value for the Wald test (<i>P</i> -value for linear trend)			
	Model 1	Model 2	Model 3	Model 4
Courses of antibiotics (none)				
1–2	1.1 (0.8–1.5), 0.54	0.9 (0.7–1.3), 0.72	1.1 (0.8–1.4), 0.72	1.0 (0.8–1.4), 0.84
3–4	1.4 (1.0–1.9), 0.07	1.0 (0.7–1.4), 0.99	1.3 (0.9–1.8), 0.14	1.2 (0.9–1.7), 0.27
>4	1.1 (0.8–1.5), 0.75 (0.30)	0.6 (0.4–0.9), <0.01 (0.01)	1.0 (0.7–1.4), 0.87 (0.35)	0.9 (0.6–1.3), 0.62 (0.44)
Each office visit (e.g. 1 vs. 0, 2 vs. 1)		1.06 (1.04–1.08), <0.01		
Each illness of the lower respiratory tract (e.g. 1 vs. 0, 2 vs. 1)			1.2 (1.0–1.4), 0.01	
Each illness of the upper respiratory tract (e.g. 1 vs. 0, 2 vs. 1)				1.2 (1.1–1.3), <0.01

*All models were adjusted for sex, in addition to the variables listed in each column.

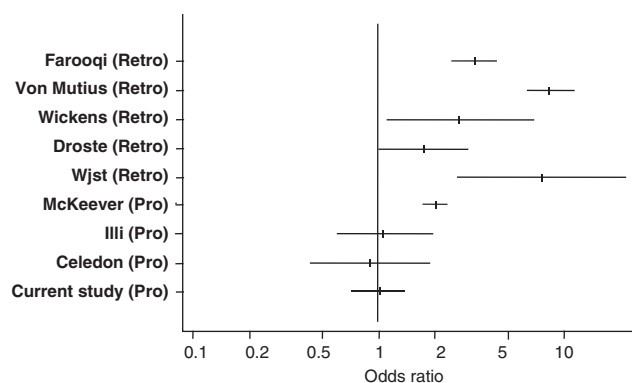


Fig. 2. Estimates of the association between antibiotic use in early life and childhood asthma in previously published studies and in the current study. Odds ratios (OR) and 95% confidence intervals (CI) for the association between antibiotic use in early life and the outcomes of interest are presented for the following categories of exposure: at least 1 course of antibiotics [4, 10, 11], at least 2 courses of antibiotics [13, 14], at least 5 courses of antibiotics (reference [12] and current study), and at least 6 courses of antibiotics [8, 9]. Retro = retrospective study design, pro = prospective study design.

year of life and asthma [13], uncertainty about the generalizability of the results to children without a parental history of atopy [14], and a lack of adequate statistical power to exclude a weak-to-moderate association between antibiotic use in early life and asthma [14].

Wheezing is a common problem in early life that may or may not be related to the subsequent development of asthma

or allergies [19]. In most cases, wheezing that starts in the first 3 years of life is transient and presumed to be related to viral infections in children with reduced airway calibre but not related to allergen sensitization or an elevated total serum IgE level later in childhood. In a minority of infants, wheezing that starts early in life persists up to the age of 6 years. Our finding of an association between antibiotic use in the first year of life and asthma between the ages of 1 and 2 years is consistent with previous findings of an association between antibiotic use in early life and transient wheezing in an analysis that did not account for confounding by indication (e.g. use of antibiotics for wheezing-related respiratory illnesses) [14]. Because we lacked information on the indication for antibiotic use, we could not adjust for confounding by indication in our multivariate analysis. However, we observed that the association between antibiotic use in the first year of life and asthma at age 2 years was reduced after adjustment for either LRIs or health-care utilization (number of office visits) in the first year of life, suggesting 'reverse causation' (e.g. children who wheezed early in life received more antibiotics than children who did not wheeze during the same period) as a likely explanation for our results.

None of the epidemiologic studies published to date found an association between antibiotic use in early childhood and objective markers of allergy (e.g. skin test reactivity to allergens, total serum IgE, or IgE to specific allergens) [4, 8–14]. We did not find an association between antibiotic use in the first year of life and asthma that was initially diagnosed

after age 2 years and that persisted up to age 5 years. Because children with asthma at age 5 years are likely to have asthma related to an allergic predisposition, our findings further refute the hypothesis that antibiotic use in early life leads to Th2 polarized immune deviation and, ultimately, to allergic diseases such as asthma.

In our study, there was an association between respiratory illnesses in the first year of life and asthma at age 5 years. Because we assessed the presence of URIs and LRIs through a physician's diagnosis, we do not know whether they were due to infection or allergy. Our findings could thus be due to a higher risk among asthmatic children for respiratory diseases related to infection and atopy in early childhood and/or to a subset of respiratory illnesses being caused by infections associated with childhood wheezing (e.g. respiratory syncytial virus) [20].

We recognize additional limitations to our findings. First, although our results were not significantly changed after the analysis was stratified by early eczema, we had no information on parental history of asthma and allergies and other risk factors for childhood asthma. Although we cannot completely exclude confounding as an explanation for the lack of association between antibiotic use in early life and asthma at age 5 years, it is an unlikely explanation for our results. For an unidentified factor to be a negative confounder, it would have to be positively associated with antibiotic use in the first year of life and negatively associated with asthma at age 5 years (or vice versa). Second, although children who were diagnosed with asthma by a physician and who were actively utilizing health-care resources for asthma at age 5 years are likely 'true asthmatics', it is possible that some of these children did have respiratory conditions other than asthma. However, our results were not appreciably changed when we used a more stringent diagnosis of asthma ('severe asthma') at age 5 years. In addition, a validation study among individuals enrolled in the same health maintenance of study participants found that an asthma diagnosis based on both automated medical records and automated pharmacy records had a positive predictive value for asthma of at least 86% [21]. Third, adjustment for consulting behaviour may lead to over-adjustment of the analysis of the relation between antibiotic use in early life and asthma, perhaps explaining our finding of an apparent protective effect of antibiotic use against asthma at age 5 years after adjustment for office visits in the first year of life (Table 3) [12]. This inverse association between antibiotic use in the first year of life and asthma at age 5 years was not observed in multivariate models adjusting for respiratory illnesses in the first year of life (Table 3).

In summary, the use of oral antibiotics in the first year of life was not associated with an increased risk of asthma at age 5 years. Our findings do not support the hypothesis that antibiotic use in early life is associated with the subsequent development of asthma but rather suggest that frequent antibiotic use in early life is more common among asthmatic children.

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