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Early Life Antibiotic Use and Subsequent Diagnosis of Food Allergy and Allergic Diseases

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Abstract

Background—Antibiotic use in early life has been linked to disruptions in the microbiome. Such changes can disturb immune system development. Differences have been observed in the microbiota of children with and without allergies, but there have been few studies on antibiotic use and allergic disease.

Objective—We evaluated associations of early-life antibiotic use with subsequent occurrence of food allergy and other allergies in childhood using electronic health record data.

Methods—We used longitudinal data on 30,060 children up to age 7 years from Geisinger Clinic's electronic health record to conduct a sex and age matched case-control study to evaluate the association between antibiotic use and milk allergy, non-milk food allergies, and other allergies. For each outcome, we estimated conditional logistic regression models adjusting for race/ethnicity, history of Medical Assistance, and mode of birth delivery. Models were repeated separately for penicillins, cephalosporins, and macrolides.

Results—There were 484 milk allergy cases, 598 non-milk food allergy cases, and 3652 other allergy cases. Children with three or more antibiotic orders had a greater odds of milk allergy (odds ratio; 95% confidence interval) (1.78; 1.28–2.48), non-milk food allergy (1.65; 1.27–2.14), and other allergies (3.07; 2.72–3.46) compared to children with no antibiotic orders. Associations were strongest at younger ages and differed by antibiotic class.

Conclusions and Clinical Relevance—We observed associations between antibiotic orders and allergic diseases, providing evidence of a potentially modifiable clinical practice associated

with pediatric allergic disease. Differences by antibiotic class should be further explored, as this knowledge could inform pediatric treatment decisions.

Keywords

allergic rhinitis; allergy; antibiotics; food allergy; milk allergy

INTRODUCTION

Allergic diseases are among the most common medical conditions affecting children in the United States. [1–3] Respiratory allergy impacts 17% of U.S. children and the prevalence of other allergies is rapidly increasing. [1] Between 1997 and 2011 the prevalence of food allergies in children increased 50% and the prevalence of skin allergies increased nearly 70%. [1,4] The hygiene hypothesis attributes such growth, in part, to an increasingly sanitized Western lifestyle that disrupts the gut microbiota, disturbing normal immune system development. [5–7]

Antibiotic use in early life has been linked to disruptions in the microbiome. [8–10] In the last decade, prescriptions of broad spectrum antibiotics went up 49% in children up to five years of age and doubled in children 5 to 17 years of age, concomitant with the increasing prevalence of allergies. [11] Differences in the gut microbiota have been observed between children with allergic conditions and non-allergic children, though these studies have not evaluated whether these differences could be due to earlier disparities in antibiotic use. [8–10,12–14] Literature demonstrates an association between antibiotic use and asthma [15–19], but few studies have examined early life antibiotic use and other atopic diseases. These studies, based largely on self-report, have produced conflicting results, with some studies reporting a positive association and others reporting no association between antibiotic use and allergic disease. [19–22]

The objective of the current study was to evaluate associations of early-life antibiotic use with subsequent occurrence of food allergy and other allergies in childhood.

METHODS

Study setting and population

We conducted a case-control study among children up to age 7 years using electronic health record (EHR) data on antibiotic use and allergic disease from a large integrated health system. The source population for this study has been previously described [23]. Data were obtained from Geisinger Clinic (GC), a health system serving a 45-county region of Pennsylvania. Age and sex distributions of the GC population are similar to that of the general population of the region. [24] We used EHR data from 2001 to 2012 on 257,729 children to identify primary care patients who had at least two outpatient encounters in the first 3 months of life and who were born between 2001 and 2011. A total of 30,060 patients met these eligibility criteria. Institutional Review Boards at GC and Johns Hopkins Bloomberg School of Public Health approved this study.

Identification of cases of allergic disease and controls

We identified three case groups: milk allergy, non-milk food allergy, and other allergies (allergic rhinitis and unspecified allergy) using International Classification of Diseases 9th edition (ICD-9) codes associated with an outpatient, inpatient, or emergency department encounter or medication order. Milk allergy cases were defined as patients who had at least one milk allergy ICD-9 code (V15.02, 995.67) after two months of age. Non-milk food allergy cases (e.g., nuts, seafood) were defined as patients who had at least one non-milk food allergy ICD-9 code (V15.01, V15.03, V15.04, V15.05, 693.1, 995.60, 995.61, 995.62, 995.63, 995.64, 995.65, 995.66, 995.68, 995.69, 995.7, 447.1) after three months of age. Other allergy cases were defined as patients who had at least two allergy ICD-9 codes (995.3, 477.0, 477.2, 477.8, 477.9) after three months of age or a single inpatient admission with the code. The age window for milk allergy started at two months due to earlier onset of milk allergies. Case groups were not mutually exclusive.

We used incidence density sampling to identify five controls for every case individually matched on sex and age. Controls were observed up to the age of the case's first allergy diagnosis. We used sampling with replacement, allowing controls to be selected multiple times in the same analysis. Patients who became cases before age 7 years could be classified as controls up to the time of diagnosis. In a sub-analysis to evaluate associations of birth delivery mode we restricted the analysis to children born at GC with information on delivery mode and selected new controls.

Defining antibiotic exposure

We used Medi-Span Generic Product Identifier Therapeutic Classification System to identify antibiotic orders. [25] We counted antibiotic orders in total and separately for the most commonly prescribed antibiotic classes (penicillins, cephalosporins, macrolides). To minimize protopathic bias, antibiotic orders within 30 to 60 days of the date of diagnosis or the associated censoring date for controls were excluded, as these may have been prescribed to treat the allergic condition.

Additional variable creation

Covariates included age, sex, race/ethnicity (non-white vs. white), history of using a Medical Assistance program to pay for a healthcare encounter at GC (yes vs. no) [23], delivery mode (cesarean section, vaginal delivery), and inpatient admissions. Age was calculated as the number of days between date of birth and diagnosis or the associated date of censoring for controls. A history of at least one inpatient admission before the diagnosis of allergy was used as a surrogate for overall health status. [26]

Statistical analysis

The goal of the analysis was to determine whether antibiotic orders were associated with a diagnosis of each of three classes of allergic disease. For each outcome, we estimated a conditional logistic regression model. Base models included overall antibiotic order count (for all classes, 1–2 and 3+ vs. 0), race/ethnicity, and history of Medical Assistance. For each model we then added inpatient admissions (1 or more vs. 0). We evaluated whether age at which antibiotic orders were received influenced associations by separately counting and

modeling antibiotic orders in three separate windows (0–12 months, 0–24 months, and up to 60 days prior to diagnosis). The majority of children with milk allergies were diagnosed in infancy, so orders were counted only in the 30 days prior to diagnosis. Models were then repeated separately for each of the three most common antibiotic classes. To understand whether associations differ with age, all models were next stratified by the mean age of allergy diagnosis. We repeated all modeling in the subpopulation of patients on whom we had delivery mode information, adding an indicator for cesarean section (yes vs. no). Given that case groups were not mutually exclusive, we repeated models including children only with one of the three allergy diagnoses per model.

RESULTS

Milk allergy

A total of 484 children met the eligibility criteria for milk allergy and were matched to 2420 controls. The average age at diagnosis was between 10 and 11 months of age (Table 1). Among cases, 43.4% had at least one antibiotic order up to age of diagnosis, compared to 35.7% of controls ($p=0.0011$). In adjusted analysis, both one or two and three antibiotic orders (vs. none) were associated (OR [95% CI]) with milk allergy diagnosis (1.49 [1.15–1.96] and 2.39 [1.25–4.59]), respectively (Table 2).

In adjusted analysis, a history of one or more inpatient admissions was associated with milk allergy diagnosis (1.76 [1.27–2.44]). Adjusting for inpatient admissions strengthened the association between three or more antibiotic orders (vs. none) and milk allergy diagnosed in the first 300 days of life (3.47 [1.38–8.74]). Adjusting for inpatient admissions to the model did not substantively change associations with one to two antibiotic orders or in children diagnosed after 300 days of age (results not shown).

Of the 484 milk allergy cases, 170 children also met the criteria for non-milk food allergy and/or other allergy. These 170 cases included 28% of cases (79/279) diagnosed in the first 300 days of life and 44% of cases (91/205) diagnosed at later ages. After excluding these 170 cases, antibiotic orders were still predictive of milk allergy diagnosis in children diagnosed in the first 300 days of life, but not in children diagnosed at later ages. Of the 484 children with a milk allergy diagnosis, 279 had information on delivery mode. The addition of delivery mode to models did not substantively change associations. Cesarean section was associated with milk allergy only among children diagnosed before 300 days of age (1.51 [1.05–2.16]).

Non-milk food allergy

There were 598 children diagnosed with a non-milk food allergy; these children were matched to 2990 controls. The mean age at diagnosis was a little over two years. By the age of diagnosis, 74.4% of cases and 68.6% of controls had at least one antibiotic order ($p=0.004$). One to two antibiotic orders (vs. none) was associated with non-milk food allergy diagnosis (1.38 [1.08–1.77]) (Table 3). This association was modified by age of diagnosis: among children diagnosed in the first 700 days (1.92 years) of life, antibiotic orders was associated with a two-fold increased odds of a non-milk food allergy diagnosis. There was

no association when non-milk food allergy was diagnosed later in life. Associations were similar across the three antibiotic exposure windows examined. Inpatient admission was not associated with non-milk food allergy and did not substantively change associations between antibiotics and non-milk food allergy.

Of the 598 non-milk food allergy cases, 305 children also met the criteria for milk and/or other allergy. After excluding these 305 cases, there was no longer an association of antibiotic orders with non-milk food allergy diagnosis. When analysis was confined to the 373 non-milk food allergy cases with information on delivery mode, cesarean section was not associated with non-milk food allergy and did not substantively change antibiotic associations.

Other allergy

There were 3652 patients with other allergy diagnosis. The majority of these cases (n=3495) had allergic rhinitis and the remaining 154 cases had unspecified allergy. The average age of diagnosis was approximately 3 years. Among cases, 86.2% of other allergy cases had at least one antibiotic order compared to 75.7% of matched controls ($p < 0.0001$). In adjusted analysis, antibiotic orders (vs. none) was associated with other allergy diagnosis (Table 4). There was a trend of increasing odds ratios across increasing antibiotic order categories ($p < 0.001$). Associations of antibiotic orders with other allergy were modified by age at diagnosis, with stronger associations among children diagnosed before 1000 days (2.74 years) of age. In that age group, three or more antibiotic orders (vs. none) was associated with a nearly four-fold increase in odds of other allergy diagnosis. Although antibiotic orders was associated with other allergy diagnosis in all windows examined, associations were weakest for antibiotics ordered in the first 12 months of life and strongest for orders prescribed up to 60 days before diagnosis. Inpatient admission was not associated with other allergy diagnosis and did not substantively change associations between antibiotic orders and other allergy.

Of the 3652 other allergy cases, 354 children also met the criteria for milk and/or non-milk food allergy. Even after excluding these 354 cases, antibiotic orders was still associated with other allergy diagnosis. When analysis was confined to the 1678 cases with information on delivery mode, cesarean section was neither associated with other allergy nor substantively changed associations of antibiotic orders with other allergy.

Antibiotic classes

Associations differed by antibiotic class (Table 5). Penicillin was most consistently associated with allergy diagnoses. Associations between macrolides and food allergies were only found in children at older ages of diagnosis. Cephalosporin orders were not associated with milk allergy, but were associated with non-milk food allergy diagnosed before 700 days (1.92 years) of age and other allergy diagnoses at all ages.

DISCUSSION

We observed strong and consistent associations of antibiotic orders with milk allergy, non-milk food allergy, and other allergies up to seven years of age. The strength of these

associations increased with the number of antibiotic orders, associations were strongest among children diagnosed at younger ages, and associations differed by antibiotic class. These findings are an important contribution to the evidence linking antibiotic use to allergic disease. Prior studies have been largely dependent on self-reported antibiotic and allergy histories and small sample sizes.

Our findings are generally consistent with the only other study to investigate associations of antibiotics with milk allergy. Similar to our findings, Metsala and colleagues [19] reported that outpatient antibiotic orders in early life were associated with an increased risk of milk allergy and that mode of birth delivery did not confound this association. While we found associations were weakest for cephalosporin orders, Metsala reported strong associations for this medication class. [19] This divergence in our findings could be due to differences in how antibiotic orders were ascertained. We included antibiotic orders from outpatient, inpatient, and emergency departments, while Metsala considered only outpatient orders. [19]

This is the first study of antibiotics and food allergy to use physician diagnosis and a large sample of food allergy cases. In contrast to our findings, two prior studies that examined antibiotic orders and food allergies found no association, [13,27] though one of the studies was not sufficiently powered to detect such an association.[13] As in the asthma literature, [21] we found that associations between food allergies and antibiotic use differed by age group, existing only in children diagnosed under 2 years of age. Ours is also the first study to examine specific antibiotic classes. We found that penicillin and cephalosporin orders were only associated in children diagnosed under two years of age, while macrolides were associated with food allergy diagnosed later in childhood.

Our findings help clarify the association between antibiotic use and other allergic diseases, particularly allergic rhinitis, for which prior studies have reported inconsistent results. [18,20–22,28–31] Our findings are similar to those of the only other study of allergic rhinitis and antibiotic use that did not depend on self-report. [21] As with our food allergy findings, associations were stronger in children diagnosed at a younger age. Similar to the asthma literature [21], we found evidence of a dose-response relation.

We hypothesize that the associations we observed between antibiotic orders and allergic disease are due to changes to the gut microbiome. There is increasing evidence that changes in the gut microbiome are associated with risk of allergic disease. [5–7] For example, several key bacterial phylotypes in the gut have been implicated in the development of IgE-mediated food allergy. [32] Antibiotics modify the composition of the gut microbiome, potentially leading to functional changes that promote the development of allergic disease. [8–10] The differential impact of antibiotics on milk and non-milk food allergies by antibiotic class is consistent with prior reports of class-specific effects of antibiotics on microbiota function. [33–35] Additionally, differences in our associations by age of diagnosis may mirror known differences, by class, in the time it takes the microbiome to recover from an antibiotic exposure. [35]

We found that antibiotic orders was associated with both milk allergy and other allergic diagnoses, independent of additional allergy diagnoses. However, antibiotic orders was not

associated with non-milk food allergies when children with other allergic diseases were excluded. Similarly, antibiotics orders were not associated with children diagnosed with milk allergies at later ages when other allergic disease were excluded. It may be that these other allergy diagnoses account for the association of antibiotic orders with non-milk food allergy that we observed. However, by excluding cases with other allergies it is possible that we systematically excluded children with IgE-mediated allergy, as IgE-mediated food allergies are associated with co-morbid allergic disease. [36,37] As noted above, evidence suggests that one potential pathway between antibiotic use and allergic disease is through the disruption of the intestinal bacteria that downregulate the level of IgE production. [38] The associations observed by our team between antibiotic use and three different allergic diseases lend additional support to this proposed mechanism linking antibiotics to allergic disease as over-production of IgE is a common causal pathway of these distinct conditions. Thus, excluding a group potentially dominated by IgE-mediated allergies could bias our findings to the null.

Prior reports of associations between antibiotic use and allergic disease have been called into question due to concerns about protopathic bias and consultation bias. Protopathic bias results from antibiotics ordered to treat the outcome of interest (i.e., allergy) before it is diagnosed. Consultation bias results because children prescribed antibiotics have an increased opportunity to engage with a physician and, thereby, receive a diagnosis. Both biases are more likely when the antibiotic order and the diagnosis occur close in time. In fact, we did find that associations weakened as the time between antibiotic order and diagnosis increased. However, associations, though weaker, remained significant despite two to three year gaps between antibiotic and diagnosis. Therefore, our study findings indicate that while bias may have resulted in some over-estimation of the magnitude of associations, it does not fully account for these associations.

The study had several limitations. First we did not require that the diagnosis be confirmed with laboratory testing. It is unlikely that case misclassification is correlated with antibiotic use, so such misclassification would bias our results towards the null. Second, we could not confirm whether children filled their prescription orders, nor can we confirm that patients did not obtain an antibiotic from outside of the GC system. We think that this exposure misclassification is likely to be non-differential with regard to diagnosis, so again, would bias our results towards the null. Third, we did not have access to accurate or reliable information on family history of allergic disease, siblings, or asthma/wheeze status. Sibling order and asthma could be common causes of both antibiotic orders and allergy and potentially confound our reported associations.

We observed associations between antibiotic orders and several independent allergy diagnoses, providing evidence of a potentially modifiable clinical practice associated with pediatric allergic disease. Differences by antibiotic class should be further explored, as this knowledge could inform pediatric treatment decisions.

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Characteristics of allergy cases and sex- and age-matched controls

sd = standard deviation

d Not applicable, cases and controls were individually matched on sex and age.

Table 2

Adjusted* associations of antibiotic orders with milk allergy at different ages of diagnosis up to age 7 years

	Antibiotic order count	Age at milk allergy diagnosis**					
		Diagnosed up to 300 days (0.82 years)			Diagnosed after 300 days (0.82 years)		
		Odds ratio	95% confidence interval		Odds ratio	95% confidence interval	
Milk allergy cases, with or without other allergy diagnoses [†]	1-2 vs. none	1.43	0.97	2.09	1.51	1.04	2.21
	3+ vs. none	2.39	1.25	4.59	1.66	1.11	2.49
Milk allergy cases excluding cases with another allergy diagnosis [‡]	1-2 vs. none	1.35	0.84	2.17	0.98	0.59	1.64
	3+ vs. none	3.65	1.75	7.60	1.03	0.61	1.74
					1.54	1.01	2.37

* Adjusted for Medical Assistance and race/ethnicity.

[†] Includes milk allergy cases with and without diagnoses of other allergies: < 301 days includes 279 cases vs. 1395 controls; >300 days includes 205 cases vs. 1025 controls; diagnosed up to 7 years includes 484 cases vs. 2420 controls.

[‡] Excludes cases with a diagnosis of another allergy: < 301 days includes 200 cases vs. 1000 controls; >300 days includes 114 cases vs. 570 controls; diagnosed up to 7 years includes 314 cases vs. 1570 controls.

Table 3

Adjusted* associations of antibiotic orders with non-milk food allergies at different ages of diagnosis up to age 7 years

	Period of antibiotic assessment	Antibiotic order count	Diagnosed up to 700 days (1.92 years) 319 cases vs. 1595 controls		Diagnosed after 700 days (1.92 years) 279 cases vs. 1395 controls		Diagnosed up to 7 years 598 cases vs. 2990 controls	
			Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Non-milk food allergy cases with or without other allergy diagnoses [†]	Model 1: 0–12 months of age	1–2 vs. none	1.27	0.96	0.96	0.72	1.10	0.90
		3+ vs. none	1.95	1.38	0.93	0.66	1.33	1.04
	Model 2: 0–24 months of age	1–2 vs. none	1.35	1.00	1.00	0.69	1.22	0.97
		3+ vs. none	2.14	1.53	1.02	0.73	1.47	1.15
	Model 3: Until 60 days prior to diagnosis	1–2 vs. none	1.35	1.00	1.32	0.82	1.38	1.08
		3+ vs. none	2.14	1.53	1.26	0.82	1.65	1.27
Non-milk food allergy cases excluding cases with another allergy diagnosis [‡]	Model 1: 0–12 months of age	1–2 vs. none	1.01	0.66	0.74	0.49	0.56	0.64
		3+ vs. none	1.40	0.85	0.72	0.45	0.98	0.69
	Model 2: 0–24 months of age	1–2 vs. none	1.24	0.80	1.09	0.66	1.19	0.85
		3+ vs. none	1.57	0.95	0.80	0.50	1.06	0.75
	Model 3: Until 60 days prior to diagnosis	1–2 vs. none	1.24	0.80	1.34	0.63	1.24	0.87
		3+ vs. none	1.57	0.95	0.81	0.46	1.08	0.75

* Adjusted for Medical Assistance and race/ethnicity

[†] Includes non-milk allergy cases with and without diagnoses of other allergies: < 701 days includes 319 cases vs. 1595 controls; > 700 days includes 279 cases vs. 1395 controls; diagnosed up to 7 years includes 598 cases vs. 2990 controls.

[‡] Excludes cases with a diagnosis of another allergy: < 701 days includes 148 cases vs. 740 controls; > 700 days includes 145 cases vs. 725 controls; diagnosed up to 7 years includes 293 cases vs. 1465 controls.

Table 4
Adjusted associations between antibiotic orders and other allergies at different age of diagnosis up to 7 years of age

			Allergy diagnosed up to 1000 days of age (2.74 years)		Allergy diagnosed after 1000 days of age (2.74 years)		All allergy diagnosed at any age up to 7 years	
	Period of antibiotic assessment	Antibiotic order count	Odds ratio	95% confidence interval	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval
Allergy cases with or without a diagnosis of a food allergy. [†]	Model 1: 0–12 months of age	1–2 vs. none	1.67	1.48	1.11	0.99	1.35	1.24
		3+ vs. none	2.49	2.17	1.27	1.11	1.75	1.59
	Model 2: 0–24 months of age	1–2 vs. none	1.85	1.60	1.10	0.95	1.46	1.31
		3+ vs. none	3.35	2.89	1.51	1.31	2.22	2.01
Allergy cases excluding cases with a diagnosis of a food allergy. [‡]	Model 3: Until 60 days prior to diagnosis	1–2 vs. none	1.90	1.64	1.22	0.97	1.69	1.50
		3+ vs. none	3.54	3.04	2.23	1.82	3.07	2.72
	Model 1: 0–12 months of age	1–2 vs. none	1.68	1.48	1.08	0.95	1.32	1.21
		3+ vs. none	2.54	2.19	1.29	1.13	1.76	1.60
	Model 2: 0–24 months of age	1–2 vs. none	1.91	1.64	1.09	0.93	1.46	1.61
		3+ vs. none	3.50	2.98	1.49	1.29	2.22	2.00
	Model 3: Until 60 days prior to diagnosis	1–2 vs. none	1.96	1.67	1.19	0.94	1.71	1.50
		3+ vs. none	3.72	3.16	2.17	1.76	3.12	2.74

* Adjusted for Medical Assistance and race/ethnicity

[†] Includes allergy cases with and without diagnoses of food allergies: < 1001 days includes 1817 cases vs. 9085 controls; > 1000 days includes 1835 cases vs. 9175 controls; diagnosed up to 7 years includes 3652 cases vs. 18260 controls.

[‡] Excludes cases with a diagnosis of a food allergy: < 1001 days includes 1594 cases vs. 7970 controls; > 1000 days includes 1704 cases vs. 8520 controls; diagnosed up to 7 years includes 3298 cases vs. 16490 controls.

Table 5

Association between antibiotic orders by class and other allergies up to 7 years of age by time of diagnosis, adjusted for Medical Assistance and race/ethnicity

Antibiotic classes	Milk allergy diagnosed up to 300 days of age and younger (0.82 years)		Milk allergy diagnosed after 300 days of age (0.82 years)		All milk allergy diagnosed at any age up to 7 years	
	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval
All antibiotics (ever vs. never) ^a	1.58	1.11 2.25	1.58	1.12 2.22	1.58	1.24 2.02
Penicillin (ever vs. never) ^a	1.59	1.10 2.28	1.58	1.13 2.19	1.58	1.24 2.02
Cephalosporins (ever vs. never) ^a	1.77	0.97 3.26	1.30	0.89 1.88	1.40	1.02 1.93
Macrolides (ever vs. never) ^a	1.51	0.60 3.82	1.72	1.19 2.51	1.68	1.19 2.37
	Non-milk food allergy diagnosed up to 700 days of age (1.92 years)		Non-milk food allergy diagnosed after 700 days of age (1.92 years)		Non-milk food allergy diagnosed at any age up to 7 years	
	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval
All antibiotics (ever vs. never) ^a	1.58	1.21 2.07	1.28	0.84 1.96	1.49	1.18 1.87
Penicillin (ever vs. never) ^a	1.58	1.21 2.07	0.90	0.64 1.26	1.29	1.04 1.59
Cephalosporins (ever vs. never) ^a	2.06	1.54 2.76	1.28	0.98 1.68	1.57	1.29 1.93
Macrolides (ever vs. never) ^a	1.36	0.95 1.95	1.72	1.32 2.25	1.58	1.28 1.96
	Other allergy diagnosed up to 1000 days of age (2.74 years)		Other allergy diagnosed after 1000 days of age (2.74 years)		Other allergy diagnosed at any age up to 7 years	
	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval	Odds Ratio	95% Confidence interval
All antibiotics (ever vs. never) ^a	2.49	2.18 2.84	1.94	1.59 2.38	2.32	2.07 2.59
Penicillin (ever vs. never) ^a	2.49	2.19 2.82	1.93	1.62 2.29	2.28	2.06 2.53
Cephalosporins (ever vs. never) ^a	1.95	1.73 2.18	1.52	1.37 1.69	1.70	1.57 1.83

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Macrolides (ever vs. never) ^a	2.21	1.95	2.50	1.84	1.66	2.04	1.98	1.83	2.15
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^aFor milk allergy: antibiotics were included from birth to 30 days before diagnosis or matched date in controls. Non-milk food allergy and other allergies, antibiotics were included from birth to 60 days before diagnosis or matched date in controls. Antibiotic classes were modeled in separate models, adjusted for Medical Assistance and race/ethnicity.