

# Antibiotic use in infancy and the risk of asthma in Mexican American children

Kamal M. Eldeirawi, PhD; Colin Kunzweiler, MS; Abdulkarim Atek, BS; Victoria W. Persky, MD

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## Abstract

**Objective:** This study examined the associations of antibiotic use in infancy with lifetime doctor-diagnosed asthma and current wheeze among Mexican American children. **Methods:** In a population-based, cross-sectional investigation, parents of 2,023 children 4-18 years of age completed a questionnaire/interview addressing respiratory conditions, antibiotic use, and covariates. **Results:** In adjusted analyses, among children without history of ear infections in infancy, children who used antibiotics  $\geq 3$  times and 1-2 times were more likely to report doctor-diagnosed asthma compared with their peers who did not use antibiotics in infancy [adjusted odds ratio (aOR) = 5.14, 95% confidence interval (CI): 2.88-9.17, and aOR = 2.15, 95% CI: 1.26-3.69, respectively,  $p$  trend < 0.0001]. The respective

aORs for current wheeze were 3.67 (95% CI: 1.95-6.89) and 1.63 (95% CI: 0.91-2.95). Antibiotic use in infancy was not associated with asthma or current wheeze in children who had ear infections in infancy. In additional analyses, antibiotic use in infancy was associated with asthma in children without parental history of asthma or allergies (aOR = 2.73, 95% CI: 1.70-4.39) but not in those with parental history of asthma or allergies. Among Mexico-born participants born in rural areas, antibiotic use in infancy was associated with a 7-fold increase in risk of asthma (aOR = 7.21, 95% CI: 1.46-35.65), while the association was non-significant in Mexico-born children born in urban areas in Mexico. **Conclusions:** Antibiotic use in infancy may increase the risk of asthma and wheezing, but these associations were limited to subgroups of children.



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## Abstract

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## Introduction

Studies have linked antibiotic use early in life with an increased risk of asthma and respiratory symptoms [1-7]. It has been suggested that antibiotic use early in life may increase the risk of asthma by decreasing microbial diversity and disrupting normal gut microflora [2, 4, 8]. However, the evidence remains controversial with several studies [9-13] showing weak or no associations between antibiotic use and asthma. Nonetheless, some of these studies reporting no associations [9, 12, 13] included genetically predisposed children suggesting that the negative effect of antibiotics use on asthma might be more prominent in children with no predisposition to atopic conditions. In addition, other studies demonstrated an increased risk of asthma or atopy from antibiotics only in subgroups of the children such as children without parental history of asthma [4], children without respiratory tract infections in infancy [4], and rural children [6]. These findings suggest that the impact of antibiotics use in early life might not be uniform in all children.

In the US, the prevalence of asthma is lower, but not negligible, among Mexican Americans (MAs), especially those born in Mexico, relative to other racial/ethnic groups [14-16]. However, there is limited research on asthma risk factors in MAs. Previous studies addressing the associations of antibiotics and asthma in the US were conducted with high-risk, white, or English speaking populations and therefore excluded MAs living in inner city communities with environmental and lifestyle factors that might differ from other populations. The purpose of the current study was to investigate the associations of antibiotic use in infancy with the risk of asthma in a sample of MA children. Because otitis media is one of the main causes for antibiotics use in infancy [17] and it has been linked with asthma in some studies [18] including our analysis of data from the current study population [19], we also examined how the associations of antibiotics with asthma are moderated and modified by history of ear infections in infancy.

## Methods

### *Design and data collection*

This study, Study of Asthma in Children of Mexican Descent (SACMD) was a population-based, cross-sectional study. A description of the study can be found elsewhere [20].

The study was conducted on a sample of children whose parents responded to the screening survey of the Chicago Asthma School Study (CASS) [21] which screened selected schools in Chicago to identify students who had asthma and/or asthma-related symptoms and facilitated their referral to a mobile asthma clinic and/or the school nurse. Between January and May of 2004, CASS screened 15 public schools in Chicago. Surveys were sent through the schools to the parents of the 13,462 enrolled students. A total of 9,895 completed surveys were received, a response rate of 74%. Of respondents, 6,896 indicated that they were of Mexican descent and were born either in the US or in Mexico. For SACMD, parents of all Mexico-born students (1,366) and a random sample of US-born students (1,485) were invited to complete a questionnaire or a telephone interview. Of those, parents of 2,023 completed the study questionnaire/interview, of which almost 91% were completed in Spanish. Data collection lasted for almost 8 months, from August, 2004 to April, 2005. All the study materials were in English and Spanish. Phone interviews were conducted by trained bilingual research assistants following standardized procedures and scripts. Both studies were approved by the University of Illinois at Chicago's Institutional Review Board.

### *Definition of variables*

Data on doctor-diagnosed asthma was derived from the question, "Has a doctor ever said that your child had asthma?" The questions on wheezing and other respiratory conditions were similar to those used in the standardized core questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) (available at <http://isaac.auckland.ac.nz>). Current wheeze refers to history of wheezing or whistling in the chest in the last 12 months. Antibiotic use in infancy was assessed by the question: "In his/her first year of life, did your child receive

antibiotics (including not prescribed) to treat an infection?” We did not collect data on the indication/s for antibiotic use in infancy. History of ear infections in infancy was assessed by the question “In his/her first year of life, did your child have an ear infection diagnosed by a health care provider?” Participants were also asked to indicate if their children had other infections diagnosed by a doctor or other health care provider in the first year of life. We combined variables on chicken pox, mumps or measles, rubella, and varicella into “viral infections” ( $n=373$ ); and tuberculosis, whooping cough, worm infections/parasites, and tonsillitis into “bacterial infections” ( $n = 32$ ). Four participants indicated that their children had croup, pneumonia, bronchitis, or sinusitis in infancy and were included in the bivariate analyses but were later excluded from logistic regression analyses. Of the 523 participants who received antibiotics but did not have ear infections in infancy, 128 (24.5%) had a viral ( $n = 123$ ) or bacterial ( $n = 10$ ) infection, while 395 (75.5%) reported neither in infancy. We also collected information on other covariates that were considered in the final multiple logistic regression models including parental history of asthma or allergies; Tylenol (acetaminophen) use in infancy; exposures to animals/pets in utero, in infancy, or at the time of the survey; number of siblings; daycare or pre-school attendance, maternal smoking during pregnancy, exposure to environmental tobacco smoke in the home when the child was born; and current exposure to environmental tobacco smoke at the time of the survey. Place of birth was categorized as rural (farm/ranch, rural area, or village) or urban (town, urban, or suburban).

### *Statistical analysis*

Statistical analyses were done using SAS for Windows Version 9.3 (SAS Institute, Cary, NC). Statistical significance was set at  $p < 0.05$ . We conducted multiple logistic regression analyses to account for covariates. A change of more than 10% of the ORs obtained in logistic regression models was

considered evidence for confounding. Adjusting the models for viral and/or bacterial infections in infancy, Tylenol use in the first year, presence of a smoker in the house at child birth, and daycare or preschool attendance did not appreciably change the associations of antibiotic use in infancy with asthma or current wheeze and therefore were excluded from the multiple logistic regression models. Although child age and having a regular access to a doctor or clinic did not appreciably change the association between antibiotic use and asthma or wheeze, we included them in the final models because they are important demographic variables. The final analyses were stratified by history of ear infections in infancy. We also performed the analyses after excluding participants who were diagnosed as having asthma in infancy. Dose response associations were assessed by including the three antibiotic use categories ( $\geq 3$  times, 1-2 times, none) as an ordinal variable in logistic regression models.

## Results

The characteristics of the sample and their associations with antibiotic use in infancy are shown in Table 1. The prevalence of doctor diagnosed asthma was 7.36% and 6.5% reported current wheeze. Of the 2,011 children with complete answers to the question on antibiotic use in infancy, 40% used it, 49.2% did not use it, and 10.8% ( $n = 217$ ) were not sure and were excluded in bivariate and logistic regression analyses. Approximately one-fifth (20.4%) of the children had history of ear infections in infancy.

Antibiotic consumption in infancy was significantly more common in males than in females ( $p = 0.020$ ), and in US-born than in Mexico-born children [ $p = 0.007$  (Table 1)]. Antibiotic use in infancy was significantly associated with parental history of asthma or allergies, daycare or preschool attendance, having a smoker in the house when the child was born, and history of ear infections in infancy (Table 1). The prevalence of asthma as well as current wheeze was associated with antibiotic use in infancy and increased significantly when the frequency of antibiotic use in infancy increased ( $p$  values for trend were  $<0.0001$  and  $0.0002$  for

asthma and wheezing, respectively; Table 2 and Figure 1). Antibiotic use in infancy was also associated with other respiratory conditions such as ever wheeze, ever rhinitis, exercise induced wheeze in the past year, and dry cough at night in the past year (Table 2).

Use of antibiotics in infancy (yes vs. no) was associated with an increased risk of asthma after adjusting for age, sex, country of birth, history of ear infections in infancy, having a regular doctor or clinic, and parental history of asthma or allergies. The adjusted ORs for antibiotics use of  $\geq 3$ , and 1-2 times were 3.43 (95% CI: 2.06-5.73) and 1.81 (95% CI: 1.13-2.88), respectively, with a significant dose-response relationship (Table 3). We found no evidence suggesting interaction between antibiotic use in infancy and parental history of asthma or allergies, age, and country of birth. However, we found a statistically significant interaction between antibiotic use in infancy and ear infections in infancy ( $p = 0.044$ ). As shown in Table 4, among children who had no history of ear infections in infancy, participants who used antibiotics  $\geq 3$  times were 5.14 times (95% CI: 2.88-9.17) and those using antibiotics 1-2 times were 2.15 times (95% CI: 1.26-3.69) as likely to report doctor diagnosed asthma compared with their peers who did not use antibiotics in infancy, after adjusting for age, sex, country of birth, having a regular doctor or clinic, and parental history of asthma or allergies with a significant dose response relationship ( $p$  for trend  $< 0.0001$ ). These associations persisted with a significant dose response relationship but the ORs were reduced when we excluded children who were diagnosed as having asthma in infancy. In this subgroup analysis, children who used antibiotics  $\geq 3$  times were 3.53 times (95% CI: 1.80-6.94) and those using antibiotics 1-2 times were 1.92 times (95% CI: 1.04-3.53) as likely to report doctor diagnosed asthma compared with their peers who did not use antibiotics in infancy. In children who had a history of ear infections in infancy, antibiotic use in infancy was not associated with doctor diagnosed asthma.

When the analyses were repeated for current wheeze, children who used antibiotics  $\geq 3$  times in infancy had a significantly elevated odds of current wheeze after adjusting for covariates [aOR = 2.47, 95% CI: 1.39-4.38 (Table 5)]. However, we found no statistically significant association of antibiotic use for 1-2 times in infancy with the odds of current wheeze (Table 5).

We found evidence for a statistically significant interaction between antibiotic use in infancy and history of ear infections in infancy ( $p = 0.023$ ). Among participants with no history of ear infections in infancy, antibiotic use for  $\geq 3$  times in infancy increased the odds of current wheeze (aOR = 3.67, 95% CI: 1.95-6.89) while antibiotic use 1-2 times in infancy was associated with an elevated odds of wheezing, but the relationship was not statistically significant (Table 6). Nonetheless, the dose dependent association between the frequency of antibiotic use and current wheeze was statistically significant. Associations among children with no history of ear infections in infancy did not change appreciably when we excluded children who were diagnosed as having asthma in infancy and the test for trend remained statistically significant ( $p$  for trend 0.002). There was no association between antibiotic use in infancy and the risk of current wheeze in children with a prior history of ear infections in infancy.

Although we did not find a statistically significant interaction between antibiotic use and parental history of asthma or allergies, the association of antibiotic use in infancy (yes vs. no) with asthma was stronger, and significant, among children with no parental history of asthma or allergies (aOR = 2.73, 95% CI: 1.70-4.39) but was weaker, and non-significant, among children with parental history of asthma or allergies (Table 7). With regard to current wheeze, the magnitude of the ORs did not vary appreciably by parental history of asthma or allergies (Table 7). We also found the association of antibiotic use in infancy (yes vs. no) with asthma to be stronger in Mexico-born children (aOR = 2.7, 95% CI: 1.27-5.74) than in their US-born peers [aOR = 2.21, 95% CI: 1.32-3.69 (data not shown)]. Of the Mexico-born participants, approximately 44% were born in a rural area. Interestingly, among this subgroup, antibiotic use in infancy (yes vs. no) was associated with over a 7-fold increase in the risk of asthma (aOR = 7.21, 95% CI: 1.46-35.65), albeit the estimate was imprecise, while the association was weaker and non-significant in their Mexico-born peers who were born in urban areas in Mexico (Table 7). With regard to current wheeze, a similar trend was observed but the associations were not statistically significant. Mexican children born in rural areas were more likely to be exposed to animals (cats/dogs, poultry, birds,

sheep/goats, pigs, and cattle) in pregnancy, have viral infections, and were less likely to attend day care or preschool than their Mexican peers born in more urban areas (not shown). However, controlling for these variables did not change the ORs for the association of antibiotic use in infancy with asthma and current wheeze appreciably.

## Discussion

We found that use of antibiotics in infancy was associated with an increased risk of asthma, with a significant dose-response relationship, after adjusting for covariates. However, this relationship persisted only among children without history of ear infections in infancy. In this subgroup, children who used antibiotics  $\geq 3$  times in infancy were over five times as likely and those who used antibiotics 1-2 times were over twice as likely to report asthma compared with those who did not use antibiotics in infancy. In additional subgroup analyses, we found the associations of antibiotic use with asthma to hold only among children without parental history of asthma or allergies. In addition, among Mexican born children, the effect of antibiotic use in infancy on the risk of asthma was particularly high in those born in rural Mexico as compared to their peers born in more urban areas of Mexico.

Our findings add to the ongoing discussion arguing that antibiotic use early in life is associated with asthma and asthma related conditions. Our results are consistent with those from several cross-sectional studies [1, 22-27], some retrospective cohort studies [3, 6, 28, 29], and some prospective investigations [4]. Previous studies have also found dose response associations of antibiotic use in infancy and the risk of asthma [2-4, 6, 11, 22, 26-28, 30] or wheezing [5, 22, 27]. However, other studies, especially prospective studies, did not find significant associations of antibiotic use and the risk of asthma [9, 12, 13]. Several of those reporting no associations were in high-risk populations. Celedon et al. [9] studied a sample of mostly white high risk

children. Kusel et al. [13] investigated a small sample of 198 high-risk children as well. The birth cohort of Su et al. [30] was limited to English speaking participants. In contrast, our study included a population-based sample of children of Mexican descent of whom 45% were born in Mexico and of those 44% were born in rural areas in Mexico. Most parents responded in Spanish and only 8.2% of the children reported a parental history of asthma or allergies.

In our study, we found that antibiotics use in infancy was significantly associated with an increased risk of asthma only in children with no history of ear infections in infancy. This finding is consistent to a certain degree with other studies [3, 4, 6]. In a US based birth cohort study [4], antibiotic use in the first 6 months of life was associated with an increased risk of asthma assessed at age 6 years in children without but not in those with lower respiratory tract infections in infancy. In a longitudinal study [6], antibiotic use for non-respiratory tract infections was associated with almost a 2-fold increase in the risk of asthma compared to those not using antibiotics in infancy. Marra et al. [3] found that the positive association of antibiotic use in infancy and the incidence of asthma became stronger when excluding children taking antibiotics for respiratory infections or otitis media. In the current study, controlling for viral and/or bacterial infections in infancy did not change the results appreciably and we excluded the four participants reporting respiratory tract infections. In fact, almost 75% of the children who used antibiotics but did not have an ear infection in infancy did not report any of the viral or bacterial infections assessed in the current study. Therefore, reverse causation remains a possible explanation to our results because it is still possible that those without history of ear infections in infancy had other respiratory conditions that might have led to antibiotic prescriptions. Previous studies have documented that bronchial and pulmonary disease is one of the main causes of antibiotic use in infancy in addition to otitis media [6, 9, 27]. Nonetheless, Kummeling and Thijs [31] reviewed evidence from several prospective investigations and concluded that the observed association of antibiotic use and asthma is not likely due to reverse causation. In the current study, we did not collect data on the indications for antibiotic use and therefore we cannot fully investigate the potential issue of confounding by indication.

Our finding showing strong associations among Mexican children born in rural areas is congruent with a previous study documenting that taking > 4 courses of antibiotics in infancy was associated with the risk of asthma only in rural children [6]. In our study, rural Mexican children were more likely than their more urbanized Mexican peers to be exposed to animals during pregnancy or early in life and therefore may have more diverse gut microbiota [32] which might be reduced by early exposure to antibiotics early in life [33, 34]. Similar to our conclusion, Risnes et al. [4] showed that antibiotic use in the first six months of life significantly increased the risk of asthma in children without parental history of asthma and the relationship was not statistically significant in those with a parental history of asthma. These results are also consistent with studies conducted with genetically pre-disposed children that do not find associations of antibiotic use with asthma.

The lack of association of antibiotic use and asthma or wheezing we observed might be due, in part, to the large overlap between ear infections in infancy and antibiotic use observed in the current study as well as other investigations. In the current study, over two-thirds of the children with asthma and 59% of those who had current wheeze used antibiotics in infancy.

Our study has several limitations that should be considered when interpreting our results. Data collection relied on parental recall of information and therefore our findings might be subject to recall bias. Parental report of asthma and asthma symptoms has been used extensively to determine the burden of asthma and its risk factors in population studies. Our questions on asthma and respiratory symptoms were based on the ISAAC questionnaire which has been widely used and validated in several parts of the world [35, 36]. In another study, parental report of atopic diseases was found to be valid [37]. Although we were not able to formally assess the presence of recall bias with regards to the study main exposure variables, the prevalence of antibiotic use in infancy observed in the current study was similar or lower than that observed in other studies [23, 26]. However, Catalano et al [38] found that parental report of antibiotics use

was found to be reliable only when the parents reported antibiotic use by their children. Parental report of recent acute otitis media was also found to correlate well with medical records (Kappa 0.88) [39]. In the current study, we did not collect data on duration of or indications for antibiotic use nor on the specific types of antibiotics used. In addition, our questionnaire might not have captured all upper or lower respiratory tract infections. Almost 75% of the children who used antibiotics but did not have ear infections in infancy did not report other infections in infancy and the indication of antibiotic use was unknown. Rather than assessing wheezing in infancy, this study assessed wheezing only for the 12 months prior to the study.

Our study has several strengths. The study was conducted with parents of a large population-based sample of understudied population, children of Mexican origin living in inner city Chicago. Most parents were Spanish speaking, often excluded in research studies in the US, and 45% of the children were born in Mexico, and of those, approximately 44% were born in rural areas. Other studies conducted in the US included mainly white [4, 9] or English speaking subjects [40]. We achieved a high response rate, therefore limiting non-response bias. We also controlled for or considered the confounding effects of a wide variety of variables including viral and bacterial infections as well as exposure to animals in pregnancy. Overall, our findings suggest that antibiotic use in infancy may increase the risk of asthma and wheezing but the associations were limited to subgroups of children. Additional prospective studies are needed to further determine the effect of early life exposure to antibiotics on the development of asthma.

#### **Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Characteristics of the study population and prevalence of antibiotic use in infancy by covariates and respiratory conditions

| Variable                                | N (overall) | %    | Antibiotic use<br>% (n/N) | p Value  |
|-----------------------------------------|-------------|------|---------------------------|----------|
| Doctor diagnosed asthma                 |             |      |                           | < 0.0001 |
| Yes                                     | 148         | 7.36 | 69.2 (92/133)             |          |
| No                                      | 1864        | 92.6 | 42.8 (707/1,653)          |          |
| Wheeze in past year                     |             |      |                           | 0.003    |
| Yes                                     | 131         | 6.5  | 58.9 (63/107)             |          |
| No                                      | 1884        | 93.5 | 44 (740/1,682)            |          |
| Antibiotic use in infancy               |             |      |                           |          |
| ≥ 3 times                               | 302         | 15.0 | -                         |          |
| 1-2 times                               | 503         | 25.0 | -                         |          |
| None                                    | 989         | 49.2 | -                         |          |
| Not sure                                | 217         | 10.8 | -                         |          |
| Ear infection in 1 <sup>st</sup> year   |             |      |                           | < 0.0001 |
| Yes                                     | 410         | 20.4 | 73.2 (279/381)            |          |
| No                                      | 1601        | 79.6 | 37.1 (523/1,409)          |          |
| Gender                                  |             |      |                           | 0.020    |
| Male                                    | 992         | 49.1 | 47.6 (422/886)            |          |
| Female                                  | 1030        | 50.9 | 42.2 (383/908)            |          |
| Place of birth                          |             |      |                           | 0.007    |
| US (except Puerto Rico)                 | 1101        | 54.5 | 47.7 (470/985)            |          |
| Mexico                                  | 919         | 45.5 | 41.3 (334/808)            |          |
| Parental history of asthma or allergies |             |      |                           | 0.036    |
| Yes                                     | 164         | 8.2  | 53.1 (78/147)             |          |
| No                                      | 1,841       | 91.8 | 44.06 (720/1,634)         |          |
| Daycare or preschool attendance         |             |      |                           | 0.022    |
| Yes                                     | 1004        | 49.9 | 47.7 (428/897)            |          |
| No                                      | 1008        | 50.1 | 42.3 (377/891)            |          |
| Smoker in house at child birth          |             |      |                           | 0.003    |
| Yes                                     | 307         | 15.5 | 53.2 (143/269)            |          |
| No                                      | 1671        | 84.5 | 43.2 (643/1,488)          |          |
| Age in years (Mean, SD)                 | 9.93        | 2.78 |                           | 0.813    |
| < 8                                     | 471         | 23.3 | 44.9 (190/423)            |          |
| 8-11                                    | 900         | 44.5 | 45.6 (358/785)            |          |
| ≥ 12                                    | 652         | 32.2 | 43.9 (257/586)            |          |
| Tylenol use in 1 <sup>st</sup> year     |             |      |                           | < 0.0001 |
| Yes                                     | 1056        | 52.5 | 54.8 (538/981)            |          |
| No                                      | 957         | 47.5 | 32.9 (267/812)            |          |
| Regular access to a doctor or clinic    |             |      |                           | 0.399    |
| Yes                                     | 1629        | 80.7 | 45.3 (657/1,449)          |          |
| No                                      | 389         | 19.3 | 42.8 (146/341)            |          |

Table 2. Prevalence of asthma and respiratory conditions by antibiotic use in infancy

| Characteristic          | Used antibiotics |         | Did not use antibiotics |         | p Value  |
|-------------------------|------------------|---------|-------------------------|---------|----------|
|                         | %                | n/N     | %                       | n/N     |          |
| Doctor diagnosed asthma | 11.51            | 92/799  | 4.15                    | 41/987  | < 0.0001 |
| Ever wheeze             | 25.53            | 188/799 | 11.98                   | 118/985 | < 0.0001 |
| Wheeze past year        | 7.85             | 63/803  | 4.46                    | 44/986  | 0.003    |

|                                              |       |        |      |        |          |
|----------------------------------------------|-------|--------|------|--------|----------|
| Wheeze past year after exercise              | 4.52  | 36/797 | 2.53 | 25/987 | 0.022    |
| Ever ER visit due to asthma or wheezing      | 6.46  | 52/805 | 2.63 | 26/989 | < 0.0001 |
| Ever hospitalization due to asthma or wheeze | 2.49  | 20/804 | 1.01 | 10/988 | 0.016    |
| Ever rhinitis                                | 7.47  | 60/803 | 4.46 | 44/986 | 0.007    |
| Dry cough at night past year                 | 10.59 | 85/803 | 5.57 | 55/988 | < 0.0001 |

Table 3. Crude and adjusted associations of antibiotic use in infancy with doctor diagnosed asthma ( $n = 1,757$ )

| Frequency of use of antibiotics in infancy | Crude OR (95% CI) | $p$ Value | $p$ Trend <sup>†</sup> | Adjusted <sup>†</sup> OR (95% CI) | $p$ Value | $p$ Trend <sup>†</sup> |
|--------------------------------------------|-------------------|-----------|------------------------|-----------------------------------|-----------|------------------------|
| ≥ 1                                        | 2.75 (1.87-4.02)  | < 0.0001  |                        | 2.33 (1.53-3.55)                  | < 0.0001  |                        |
| None                                       | 1                 |           |                        | 1                                 |           |                        |
| ≥ 3                                        | 3.96 (2.53-6.21)  | < 0.0001  | < 0.0001               | 3.43 (2.06-5.73)                  | < 0.0001  | < 0.0001               |
| 1-2                                        | 2.07 (1.33-3.22)  | 0.001     |                        | 1.81 (1.13-2.88)                  | 0.013     |                        |
| None                                       | 1                 |           |                        | 1                                 |           |                        |

<sup>†</sup> Based on logistic regression analysis with the frequency of antibiotic use treated as an ordinal variable.

<sup>‡</sup> Adjusted for age (continuous), sex, country of birth (US vs. Mexico), history of ear infections in infancy (any vs. none), having a regular doctor or clinic (yes vs. no), and parental history of asthma or allergies (yes vs. no).

Table 4. Associations of antibiotic use in infancy with doctor diagnosed asthma with or without including children diagnosed as having asthma in the 1<sup>st</sup> year of life stratified by history of ear infections in infancy<sup>†</sup>

| Frequency of Use of Antibiotics in Infancy | Including children who were diagnosed as having asthma in the first year of life |                                                              | Excluding children who were diagnosed with asthma in the first year of life |                                                              |
|--------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|
|                                            | In children without ear infections ( $n = 1390$ )<br>OR (95% CI)                 | In children with ear infections ( $n = 367$ )<br>OR (95% CI) | In children without ear infections ( $n = 1370$ )<br>OR (95% CI)            | In children with ear infections ( $n = 359$ )<br>OR (95% CI) |
| ≥1                                         | 2.98 (1.87-4.75)                                                                 | 1.14 (0.55-2.39)                                             | 2.37 (1.39-4.02)                                                            | 0.97 (0.47-1.98)                                             |
| None                                       | 1                                                                                | 1                                                            | 1                                                                           | 1                                                            |
| ≥ 3                                        | 5.14 (2.88-9.17)*                                                                | 1.33 (0.60-2.96)                                             | 3.53 (1.80-6.94)**                                                          | 1.02 (0.49-2.14)                                             |
| 1-2                                        | 2.15 (1.26-3.69)                                                                 | 0.98 (0.42-2.27)                                             | 1.92 (1.04-3.53)                                                            | 0.91 (0.41-1.99)                                             |
| None                                       | 1                                                                                | 1                                                            | 1                                                                           | 1                                                            |

<sup>†</sup> Adjusted for age (continuous), sex, country of birth (US vs. Mexico), having a regular doctor or clinic (yes vs. no), and parental history of asthma or allergies (yes vs. no).

\*  $p$  trend < 0.0001; \*\*  $p$  trend = 0.0002

Table 5. Associations of antibiotic use in infancy with current wheeze ( $n = 1,760$ )

| Frequency of use of antibiotics in infancy | Crude OR (95% CI) | $p$ Value | $P$ Trend <sup>†</sup> | Adjusted <sup>†</sup> OR (95% CI) | $p$ Value | $p$ Trend <sup>†</sup> |
|--------------------------------------------|-------------------|-----------|------------------------|-----------------------------------|-----------|------------------------|
| ≥ 1                                        | 1.97 (1.30-3.00)  | 0.002     |                        | 1.64 (1.02-2.63)                  | 0.039     |                        |
| None                                       | 1                 |           |                        | 1                                 |           |                        |

|      |                  |          |          |                  |       |       |
|------|------------------|----------|----------|------------------|-------|-------|
| ≥ 3  | 2.90 (1.78-4.74) | < 0.0001 | < 0.0001 | 2.47 (1.39-4.38) | 0.002 | 0.004 |
| 1-2  | 1.45 (0.88-2.38) | 0.146    |          | 1.24 (0.73-2.12) | 0.420 |       |
| None | 1                |          |          | 1                |       |       |

† Based on logistic regression analysis with the frequency of antibiotic use treated as an ordinal variable.

‡ Adjusted for age (continuous), sex, country of birth (US vs. Mexico), history of ear infections in infancy (any vs. none), having a regular doctor or clinic (yes vs. no), and parental history of asthma or allergies (yes vs. no).

Table 6. Associations of antibiotic use in infancy with current wheeze with or without including children diagnosed as having asthma in the 1<sup>st</sup> year of life stratified by history of ear infections in infancy<sup>†</sup>

| Frequency of use of antibiotics in infancy | Including children who were diagnosed as having asthma in the first year of life. |                                           | Excluding children who were diagnosed with asthma in the first year of life. |                                           |
|--------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------|
|                                            | In children without ear infections (n = 1393)                                     | In children with ear infections (n = 367) | In children without ear infections (n = 1373)                                | In children with ear infections (n = 359) |
|                                            | OR (95% CI)                                                                       | OR (95% CI)                               | OR (95% CI)                                                                  | OR (95% CI)                               |
| ≥ 1                                        | 2.19 (1.32-3.62)                                                                  | 0.90 (0.25-3.23)                          | 1.96 (1.15-3.34)                                                             | 0.75 (0.34-1.63)                          |
| None                                       | 1                                                                                 | 1                                         | 1                                                                            | 1                                         |
| ≥ 3                                        | 3.67 (1.95-6.89)*                                                                 | 1.06 (0.36-3.10)                          | 3.1 (1.56-6.14)**                                                            | 1.14 (0.49-2.63)                          |
| 1-2                                        | 1.63 (0.91-2.95)                                                                  | 0.52 (0.18-1.51)                          | 1.54 (0.83-2.87)                                                             | 0.45 (0.16-1.23)                          |
| None                                       | 1                                                                                 | 1                                         | 1                                                                            | 1                                         |

† Adjusted for age (continuous), sex, country of birth (US vs. Mexico), having a regular doctor or clinic (yes vs. no), and parental history of asthma or allergies (yes vs. no).

\* *p* trend = 0.0001, \*\* *p* trend = 0.002

Table 7. Adjusted stratified associations of antibiotic use and asthma and current wheeze

|                              | Asthma            |            | Current wheeze    |           |
|------------------------------|-------------------|------------|-------------------|-----------|
|                              | OR                | 95% CI     | OR                | 95% CI    |
| Parental asthma <sup>†</sup> |                   |            |                   |           |
| Yes                          | 1.22              | 0.45-3.34  | 1.59              | 0.53-4.76 |
| No                           | 2.73              | 1.70-4.39  | 1.67              | 0.99-2.83 |
| Place of birth <sup>‡§</sup> |                   |            |                   |           |
| Rural area                   | 7.21 <sup>†</sup> | 1.46-35.65 | 1.68 <sup>†</sup> | 0.51-5.49 |
| Urban area                   | 1.80 <sup>†</sup> | 0.74-4.35  | 1.00 <sup>†</sup> | 0.27-3.71 |

† Adjusted for age (continuous), sex, country of birth (US vs. Mexico), history of ear infections in infancy (any vs. none), and having a regular doctor or clinic (yes vs. no)

‡ Among only children born in Mexico

§ Adjusted for age (continuous), sex, history of ear infections in infancy (any vs. none), having a regular doctor or clinic (yes vs. no), and parental history of asthma or allergies (yes vs. no)

Fig. 1. Prevalence of asthma and current wheeze by antibiotic use in infancy (p values for trend were <0.0001 and 0.0002 for asthma and wheezing, respectively). Dark = asthma; Light = wheezing.

