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# Antibiotic Use in Children Is Associated With Increased Risk of Asthma

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## What's Known on This Subject

Studies evaluating the association between the use of antibiotics in early childhood and the development of asthma have shown conflicting results.

## What This Study Adds

This is the largest study to date which shows that use of antibiotics in the first year of life is associated with a small risk of asthma and that this risk is associated with the number of antibiotic courses administered.

## ABSTRACT

**BACKGROUND.** Antibiotic exposure in early childhood is a possible contributor to the increasing asthma prevalence in industrialized countries. Although a number of published studies have tested this hypothesis, the results have been conflicting.

**OBJECTIVE.** To explore the association between antibiotic exposure before 1 year of age and development of childhood asthma.

**METHODS.** Using administrative data, birth cohorts from 1997 to 2003 were evaluated (N = 251 817). Antibiotic exposure was determined for the first year of life. After the first 24 months of life, the incidence of asthma was determined in both those exposed and not exposed to antibiotics in the first 12 months of life. Cox proportional hazards models were used to adjust for potential confounders and determine the hazard ratios associated with antibiotic exposure for the development of asthma.

**RESULTS.** Antibiotic exposure in the first year of life was associated with a small risk of developing asthma in early childhood after adjusting for gender, socioeconomic status at birth, urban or rural address at birth, birth weight, gestational age, delivery method, frequency of physician visits, hospital visit involving surgery, visits to an allergist, respirologist, or immunologist, congenital anomalies, and presence of otitis media, acute, or chronic bronchitis, and upper and lower respiratory tract infections during the first year of life. As the number of courses of antibiotics increased, this was associated with increased asthma risk, with the highest risk being in children who received >4 courses. All antibiotics were associated with an increased risk of developing asthma, with the exception of sulfonamides.

**CONCLUSIONS.** This study provides evidence that the use of antibiotics in the first year of life is associated with a small risk of developing asthma, and this risk increases with the number of courses of antibiotics prescribed. *Pediatrics* 2009;123:1003–1010

ASTHMA IS THE most common chronic disease of childhood. Almost 1 in 8 school-aged children are affected by asthma, and ~10% of children (compared with 5% of adults) take medication for it.<sup>1,2</sup> Numerous studies performed in different countries and varying populations over the last 30 years have indicated that the prevalence of asthma has increased significantly.<sup>3</sup> A 1980 survey showed the overall prevalence of self-reported asthma in the 12 months before the survey was 3% and that there was a twofold increase in this figure when the survey was repeated in 1999.<sup>4</sup>

Antibiotics are commonly used to treat infections during early childhood, and their use in children increased significantly in the late 1980s and early 1990s.<sup>5</sup> Given that this increase in antibiotic use has been accompanied by an increase in the prevalence of asthma, scientists have hypothesized that a causal association exists. This postulate is consistent with the “hygiene hypothesis,” which suggests that growing up in a more hygienic

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### Key Words

asthma, antibiotics, epidemiology, children, pediatrics

### Abbreviations

HR—hazard ratio  
CI—confidence interval  
BC—British Columbia  
SES—socioeconomic status  
ATC—Anatomical Therapeutic Chemical Classification System  
ICD-9—*International Classification of Diseases, Ninth Revision*  
URTI—upper respiratory tract infection  
LRTI—lower respiratory tract infection  
MSP—medical services plan  
PY—person-years  
OR—odds ratio

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environment with less microbial exposure may increase atopic (T-helper cell type 2) immune responses and, thus, the development of asthma.<sup>6,7</sup> Although a number of studies have evaluated this association, the epidemiologic evidence is conflicting.<sup>8–17</sup>

The objective of this study was to explore the association between exposure to antibiotics in the first year of life and the subsequent development of asthma using a large, population-based cohort. Specifically, we sought to evaluate the association between antibiotics prescribed within the first year of life and the development of asthma, and to evaluate a potential dose-response relationship between the number of courses of antibiotics received and the development of asthma.

## METHODS

### Study Population

The longitudinal study cohort consisted of all live births in British Columbia (BC), Canada, from January 1997 through December 2003. To be included in the analysis, at least 2 years of follow-up had to be available from the time of birth. Those who died or left the province were right censored. Follow-up information was available from all data files up to December 2005.

Births between 1997 and 2003 and deaths until 2005 were extracted. In addition to gender, birth-related data were also extracted and classified as follows: (1) gestational age, classified as <37, 37, 38, 39, 40, or >40 completed weeks; (2) birth weight, classified as <1500, 1501 to 2500, 2501 to 3500, 3501 to 4500, or >4500 g; and (3) mode of delivery, classified as spontaneous vertex, cesarean (first, second, or third), breech, forceps extraction, vacuum extraction, or unknown.

### Data Sources

We used linked administrative health data that contained information on all physician services, hospital admissions, and all outpatient dispensing episodes of prescription drugs to assess potential antibiotic exposures, potential confounders, and outcomes. We further linked vital status information from the provincial vital statistics bureau. Linkages among the various data files were achieved through the use of a personal health number unique to every BC resident. Family socioeconomic status (SES) was determined according to neighborhood income per person from the Canadian census and reported in quintiles. Similarly, the urban or rural area based on the home address at birth was determined according to postal code information. In our data set, all traceable personal identifiers were removed to protect patient confidentiality. Ethics approval was obtained from the University of British Columbia Behavioral Research Ethics Board.

Information on dispensed asthma drugs and antibiotics between 1997 and 2005 was extracted based on the Anatomic Therapeutic Chemical Classification System (ATC) codes. Asthma medications (ATC codes: R03A–D) consisted of short-acting  $\beta$ -agonists, inhaled corticosteroids, ipratropium, ketotifen, or leukotriene receptor antagonists. Antibiotics (ATC code: J01) were classified as

penicillins, cephalosporins, macrolides, sulfonamide, or other classes.

Physician visits in the database were classified according to the 3-digit diagnostic code (*International Classification of Diseases, Ninth Revision* [ICD-9]) associated with that claim, the type of physician (eg, general practitioner versus specialist), unique physician identifier, fee service codes, and the professional fees paid for each service claim. Information on physician billings for asthma occurring between 1997 and 2005 was obtained by using ICD-9 code 493. Information on physician billings for other diseases salient to this analysis within the first year of life were obtained by using ICD-9 codes 034 or 461–5 (upper respiratory tract infection [URTI]), 481–6 (lower respiratory tract infection [LRTI]), 381–2 (otitis media), 466 or 490–1 (bronchitis), and 740–59 (congenital anomalies). All physician billings during the first year of life were extracted to estimate the frequency of physician visits. In addition, any billing for an allergist, respirologist, or immunologist visit during the first year of life was obtained. Similar codes were used to classify hospitalizations.

### Asthma Definition

The date of asthma diagnosis was defined as the first of: (1) a hospital discharge for asthma (ICD-9 code: 493); or (2) 2 medical fee-for-service claims coded ICD-9 493 within a moving 12-month period; or (3) 2 prescriptions for a known asthma medication within a moving 12-month period.

This definition of asthma was used because it had the highest positive predictive value when compared with other definitions. Previous research comparing various database asthma definitions to a gold standard of an allergist's diagnosis of childhood asthma found that this definition of asthma had a positive predictive value of 92%, which was higher than other definitions that require fewer visits and prescriptions.<sup>18</sup>

### Statistical Analysis

The primary hypothesis was to explore the association between antibiotic exposure before 1 year of age and development of childhood asthma. For the purposes of our primary analysis, we excluded children if they were followed-up for <2 years ( $n = 8014$ ) or if they met the definition of having asthma during the first 2 years of life ( $n = 22\,736$ ), realizing that these children may have exhibited symptoms of asthma in infancy, which could have led to an antibiotic prescription. Hence, incident cases of asthma were identified prospectively as the children were followed from age 2 years until the earliest of: December 31, 2005, death, or departure from BC. This enabled a maximum follow-up period of 7 years (until a maximum age of 9). For children not registered with the medical services plan (MSP) on December 31, 2005, the date of departure from BC was defined as the later of: the end of last period of MSP coverage, the last MSP billing, the last hospital separation, or the last PharmaNet record.

Potential confounders included gender, SES at birth,

**TABLE 1 Incident Asthma Rates According to Age at Diagnosis**

| Age at Diagnosis, y | Incident Asthma Cases | PY        | Incidence Cases per 100 PY |           |
|---------------------|-----------------------|-----------|----------------------------|-----------|
|                     |                       |           | Rate                       | 95% CI    |
| 2–3                 | 6239                  | 229 683.5 | 2.72                       | 2.71–2.72 |
| 3–5                 | 8133                  | 337 868.4 | 2.41                       | 2.40–2.41 |
| 5–9                 | 4492                  | 257 756.8 | 1.74                       | 1.74–1.75 |
| Overall (2–9)       | 18 864                | 825 308.7 | 2.29                       | 2.28–2.29 |

urban or rural address at birth, birth weight, gestational age, delivery method, frequency of physician visits, allergist/respirologist/immunologist visit, hospital visit involving surgery, congenital anomalies, and related diseases (otitis media, bronchitis, URTI, and LRTI). Cox proportional hazards regression analysis was used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the association between exposure to antibiotics in the first year of life and subsequent development of childhood asthma, while adjusting for potential confounders. Exposure to antibiotics in the first year was measured in 3 ways: ever dispensed antibiotics versus never dispensed, the number of antibiotic prescriptions dispensed (0, 1–2, 3–4, >4), and by type of antibiotic dispensed.

To assess the validity of the Cox proportional hazards assumption, a piecewise proportional hazards model was fit. The follow-up time was split into 3 periods to predict asthma diagnosis at different ages (2–3, 3–5, and 5–9 years). For each variable, this allowed the HR to follow a step function across time that varied across the 3 periods. The proportional hazards assumption was then tested by using a method proposed by Moreau et al,<sup>19</sup> whereby the hypothesis that the HR remain constant across the 3 periods is tested. For those variables that violated the proportional hazards assumption, the variable was replaced by a piecewise variable (ie, allowed to vary across the 3 periods). Modeling of the piecewise variable was aided by observing the Schoenfeld residuals.<sup>20</sup> A non-parametric smoothed plot of the hazard function was

obtained to observe how the rate of asthma diagnoses changed over time. The incidence rate of asthma diagnoses was also calculated overall and across each of the 3 time periods. Multicollinearity was tested for by observing the standard errors when variables were added and removed from the model. Also, correlations and scatterplots were observed between all variables in the model.

To evaluate the potential for protopathic bias (a spurious association if the antibiotics were being used to treat early symptoms of asthma), 2 sensitivity analyses were performed where we restricted the definition of antibiotics exposure in the first year of life to only those antibiotics not dispensed for LRTI, URTI, bronchitis, or otitis media and where we restricted the analysis only to those children who did not have a diagnosis of LRTI, URTI, bronchitis, or otitis media (irrespective of antibiotic exposure) in the first year of life.

Statistical significance in this study was defined as  $P < .05$ . SAS 9 (SAS Institute, Inc, Cary, NC) and R 2.3.1 (R Foundation for Statistical Computing, Vienna, Austria [www.R-project.org]) were used for all statistical analyses.

## RESULTS

There were 251 817 live births included in the study cohort (223 were excluded because of database linkage problems). Fifty percent were male, 85% were born in urban areas, and there was an even distribution across socioeconomic quintiles. Ninety-three percent of infants

**TABLE 2 Association Between Antibiotic Exposure During the First Year of Life and Development of Asthma According to Age at Diagnosis**

| Antibiotic Exposure Variable    | n<br>(N = 251 817) | %    | Unadjusted Risk According to Year of Diagnosis |           |        |       |           |        |       |           |        |
|---------------------------------|--------------------|------|------------------------------------------------|-----------|--------|-------|-----------|--------|-------|-----------|--------|
|                                 |                    |      | 2–3 y                                          |           |        | 3–5 y |           |        | 5–9 y |           |        |
|                                 |                    |      | HR                                             | 95% CI    | P      | HR    | 95% CI    | P      | HR    | 95% CI    | P      |
| Antibiotic exposure             | 108 958            | 43.3 | 1.60                                           | 1.52–1.68 | <.0001 | 1.45  | 1.39–1.52 | <.0001 | 1.35  | 1.28–1.44 | <.0001 |
| No. of antibiotic prescriptions |                    |      |                                                |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| 0 (reference)                   | 142 859            | 56.7 | 1.00                                           | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 1–2                             | 83 541             | 33.2 | 1.46                                           | 1.39–1.55 | <.0001 | 1.36  | 1.30–1.43 | <.0001 | 1.26  | 1.19–1.35 | <.0001 |
| 3–4                             | 18 495             | 7.3  | 1.91                                           | 1.75–2.07 | <.0001 | 1.60  | 1.48–1.72 | <.0001 | 1.56  | 1.41–1.71 | <.0001 |
| >4                              | 7016               | 2.8  | 2.44                                           | 2.18–2.73 | <.0001 | 2.08  | 1.88–2.30 | <.0001 | 1.76  | 1.53–2.02 | <.0001 |
| Exposure by type of antibiotic  |                    |      |                                                |           |        |       |           |        |       |           |        |
| Amoxicillin                     | 84 922             | 33.7 | 1.35                                           | 1.28–1.42 | <.0001 | 1.24  | 1.19–1.30 | <.0001 | 1.20  | 1.13–1.27 | <.0001 |
| Penicillin                      | 6488               | 2.6  | 1.20                                           | 1.12–1.30 | <.0001 | 1.20  | 1.12–1.30 | <.0001 | 1.20  | 1.12–1.30 | <.0001 |
| Cephalosporin                   | 20 731             | 8.2  | 1.27                                           | 1.21–1.33 | <.0001 | 1.27  | 1.21–1.33 | <.0001 | 1.27  | 1.21–1.33 | <.0001 |
| Sulfonamide                     | 20 041             | 8.0  | 1.12                                           | 1.07–1.17 | <.0001 | 1.12  | 1.07–1.17 | <.0001 | 1.12  | 1.07–1.17 | <.0001 |
| Macrolide                       | 23 298             | 9.3  | 1.43                                           | 1.33–1.54 | <.0001 | 1.28  | 1.20–1.37 | <.0001 | 1.19  | 1.08–1.31 | .0003  |
| Other antibiotic in first year  | 350                | 0.1  | 1.11                                           | 0.82–1.50 | .49    | 1.11  | 0.82–1.50 | .49    | 1.11  | 0.82–1.50 | .49    |

**TABLE 3 Full Model (Exposure to Antibiotics)/Adjusted Risks Associated With Development of Asthma According to Age at Diagnosis**

| Variable                                                     | n<br>(N = 251 817) | %    | Adjusted Risk According to Year of Diagnosis |           |        |       |           |        |       |           |        |
|--------------------------------------------------------------|--------------------|------|----------------------------------------------|-----------|--------|-------|-----------|--------|-------|-----------|--------|
|                                                              |                    |      | 2–3 y                                        |           |        | 3–5 y |           |        | 5–9 y |           |        |
|                                                              |                    |      | HR                                           | 95% CI    | P      | HR    | 95% CI    | P      | HR    | 95% CI    | P      |
| Antibiotic exposure                                          | 108 958            | 43.3 | 1.12                                         | 1.08–1.16 | <.0001 | 1.12  | 1.08–1.16 | <.0001 | 1.12  | 1.08–1.16 | <.0001 |
| Male gender                                                  | 126 000            | 50.0 | 1.46                                         | 1.38–1.53 | <.0001 | 1.40  | 1.34–1.46 | <.0001 | 1.31  | 1.24–1.39 | <.0001 |
| Area type at birth                                           |                    |      |                                              |           | .0001  |       |           | .0001  |       |           | .0001  |
| Rural (reference)                                            | 31 971             | 12.7 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| Urban                                                        | 212 993            | 84.6 | 1.10                                         | 1.05–1.16 | <.0001 | 1.10  | 1.05–1.16 | <.0001 | 1.10  | 1.05–1.16 | <.0001 |
| Unknown                                                      | 6853               | 2.7  | 1.16                                         | 1.03–1.29 | .01    | 1.16  | 1.03–1.29 | .01    | 1.16  | 1.03–1.29 | .01    |
| SES at birth, quintiles                                      |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| First (reference)                                            | 53 612             | 21.3 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| Second                                                       | 51 919             | 20.6 | 1.01                                         | 0.97–1.06 | .57    | 1.01  | 0.97–1.06 | .57    | 1.01  | 0.97–1.06 | .57    |
| Third                                                        | 48 323             | 19.2 | 0.95                                         | 0.91–0.99 | .02    | 0.95  | 0.91–0.99 | .02    | 0.95  | 0.91–0.99 | .02    |
| Fourth                                                       | 46 971             | 18.7 | 0.90                                         | 0.86–0.95 | <.0001 | 0.90  | 0.86–0.95 | <.0001 | 0.90  | 0.86–0.95 | <.0001 |
| Fifth                                                        | 40 450             | 16.1 | 0.86                                         | 0.82–0.90 | <.0001 | 0.86  | 0.82–0.90 | <.0001 | 0.86  | 0.82–0.90 | <.0001 |
| Unknown                                                      | 10 542             | 4.2  | 0.97                                         | 0.88–1.07 | .56    | 0.97  | 0.88–1.07 | .56    | 0.97  | 0.88–1.07 | .56    |
| Birth weight, kg                                             |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| <1.5 (reference)                                             | 1222               | 0.5  | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 1.5–2.5                                                      | 10 100             | 4.0  | 0.78                                         | 0.66–0.92 | .003   | 0.78  | 0.66–0.92 | .003   | 0.78  | 0.66–0.92 | .003   |
| 2.5–3.5                                                      | 122 894            | 48.8 | 0.77                                         | 0.66–0.90 | .002   | 0.77  | 0.66–0.90 | .002   | 0.77  | 0.66–0.90 | .002   |
| 3.5–4.5                                                      | 111 611            | 44.3 | 0.70                                         | 0.60–0.83 | <.0001 | 0.70  | 0.60–0.83 | <.0001 | 0.70  | 0.60–0.83 | <.0001 |
| >4.5                                                         | 5657               | 2.3  | 0.69                                         | 0.57–0.83 | .0001  | 0.69  | 0.57–0.83 | .0001  | 0.69  | 0.57–0.83 | .0001  |
| Unknown                                                      | 333                | 0.1  | 0.92                                         | 0.52–1.64 | .78    | 0.92  | 0.52–1.64 | .78    | 0.92  | 0.52–1.64 | .78    |
| Gestational age, wk                                          |                    |      |                                              |           | .01    |       |           | .01    |       |           | .01    |
| <37 (reference)                                              | 15 147             | 6.0  | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 37                                                           | 14 292             | 5.7  | 1.00                                         | 0.92–1.08 | .95    | 1.00  | 0.92–1.08 | .95    | 1.00  | 0.92–1.08 | .95    |
| 38                                                           | 37 804             | 15.0 | 0.95                                         | 0.88–1.03 | .20    | 0.95  | 0.88–1.03 | .20    | 0.95  | 0.88–1.03 | .20    |
| 39                                                           | 56 174             | 22.4 | 0.95                                         | 0.88–1.02 | .14    | 0.95  | 0.88–1.02 | .14    | 0.95  | 0.88–1.02 | .14    |
| 40                                                           | 83 490             | 33.2 | 0.91                                         | 0.84–0.98 | .01    | 0.91  | 0.84–0.98 | .01    | 0.91  | 0.84–0.98 | .01    |
| >40                                                          | 44 479             | 17.7 | 0.90                                         | 0.83–0.97 | .01    | 0.90  | 0.83–0.97 | .01    | 0.90  | 0.83–0.97 | .01    |
| Unknown                                                      | 431                | 0.2  | 0.78                                         | 0.48–1.27 | .31    | 0.78  | 0.48–1.27 | .31    | 0.78  | 0.48–1.27 | .31    |
| Delivery method                                              |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| Spontaneous vertex (reference)                               | 163 308            | 64.9 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| Cesarean                                                     |                    |      |                                              |           |        |       |           |        |       |           |        |
| First                                                        | 38 859             | 15.4 | 1.15                                         | 1.10–1.19 | <.0001 | 1.15  | 1.10–1.19 | <.0001 | 1.15  | 1.10–1.19 | <.0001 |
| Second                                                       | 16 941             | 6.7  | 0.99                                         | 0.93–1.05 | .82    | 0.99  | 0.93–1.05 | .82    | 0.99  | 0.93–1.05 | .82    |
| Third                                                        | 4368               | 1.7  | 0.90                                         | 0.80–1.01 | .08    | 0.90  | 0.80–1.01 | .08    | 0.90  | 0.80–1.01 | .08    |
| Breech delivery                                              | 1274               | 0.5  | 0.83                                         | 0.68–1.02 | .07    | 0.83  | 0.68–1.02 | .07    | 0.83  | 0.68–1.02 | .07    |
| Forceps extraction                                           | 14 604             | 5.8  | 1.14                                         | 1.08–1.21 | <.0001 | 1.14  | 1.08–1.21 | <.0001 | 1.14  | 1.08–1.21 | <.0001 |
| Vacuum extraction                                            | 11 681             | 4.6  | 1.12                                         | 1.04–1.20 | .003   | 1.12  | 1.04–1.20 | .003   | 1.12  | 1.04–1.20 | .003   |
| Unknown                                                      | 782                | 0.3  | 1.00                                         | 0.78–1.28 | .98    | 1.00  | 0.78–1.28 | .98    | 1.00  | 0.78–1.28 | .98    |
| No. of physician visits in first year (quintiles)            |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| 0–6 (reference)                                              | 46 199             | 18.4 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 7–9                                                          | 49 587             | 19.7 | 1.36                                         | 1.22–1.52 | <.0001 | 1.28  | 1.16–1.40 | <.0001 | 1.19  | 1.07–1.33 | .002   |
| 10–12                                                        | 51 323             | 20.4 | 1.59                                         | 1.43–1.76 | <.0001 | 1.48  | 1.35–1.61 | <.0001 | 1.41  | 1.27–1.57 | <.0001 |
| 13–16                                                        | 50 349             | 20.0 | 2.14                                         | 1.94–2.37 | <.0001 | 1.93  | 1.77–2.10 | <.0001 | 1.60  | 1.44–1.78 | <.0001 |
| >16                                                          | 54 359             | 21.6 | 2.88                                         | 2.61–3.17 | <.0001 | 2.72  | 2.50–2.96 | <.0001 | 2.10  | 1.89–2.32 | <.0001 |
| Allergist, respirologist, or immunologist visit <sup>a</sup> | 350                | 0.1  | 1.95                                         | 1.26–3.02 | .003   | 1.95  | 1.26–3.02 | .003   | 1.95  | 1.26–3.02 | .003   |
| Surgery                                                      | 3076               | 1.2  | 0.95                                         | 0.85–1.07 | .41    | 0.95  | 0.85–1.07 | .41    | 0.95  | 0.85–1.07 | .41    |
| Congenital anomalies                                         | 22 564             | 9.0  | 0.95                                         | 0.90–1.00 | .05    | 0.95  | 0.90–1.00 | .05    | 0.95  | 0.90–1.00 | .05    |
| No. of otitis media diagnoses                                |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| 0 (reference)                                                | 194 897            | 77.4 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 1–2                                                          | 45 442             | 18.1 | 0.91                                         | 0.88–0.95 | <.0001 | 0.91  | 0.88–0.95 | <.0001 | 0.91  | 0.88–0.95 | <.0001 |
| 3–4                                                          | 8139               | 3.2  | 0.87                                         | 0.81–0.94 | .0002  | 0.87  | 0.81–0.94 | .0002  | 0.87  | 0.81–0.94 | .0002  |
| >4                                                           | 3339               | 1.3  | 0.75                                         | 0.67–0.84 | <.0001 | 0.75  | 0.67–0.84 | <.0001 | 0.75  | 0.67–0.84 | <.0001 |
| No. of bronchitis diagnoses                                  |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | .0006  |
| 0 (reference)                                                | 214 666            | 85.3 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 1–2                                                          | 31 807             | 12.6 | 1.29                                         | 1.21–1.38 | <.0001 | 1.17  | 1.11–1.24 | <.0001 | 1.07  | 0.98–1.16 | .11    |
| 3–4                                                          | 4155               | 1.7  | 1.67                                         | 1.46–1.90 | <.0001 | 1.24  | 1.11–1.38 | .0001  | 1.24  | 1.11–1.38 | .0001  |
| >4                                                           | 1189               | 0.5  | 1.91                                         | 1.54–2.37 | <.0001 | 1.26  | 1.00–1.59 | .05    | 0.91  | 0.63–1.31 | .61    |

**TABLE 3 Continued**

| Variable              | n<br>(N = 251 817) | %    | Adjusted Risk According to Year of Diagnosis |           |        |       |           |        |       |           |        |
|-----------------------|--------------------|------|----------------------------------------------|-----------|--------|-------|-----------|--------|-------|-----------|--------|
|                       |                    |      | 2–3 y                                        |           |        | 3–5 y |           |        | 5–9 y |           |        |
|                       |                    |      | HR                                           | 95% CI    | P      | HR    | 95% CI    | P      | HR    | 95% CI    | P      |
| No. of URTI diagnoses |                    |      |                                              |           | <.0001 |       |           | <.0001 |       |           | <.0001 |
| 0 (reference)         | 138 435            | 55.0 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 1–2                   | 85 788             | 34.1 | 1.09                                         | 1.06–1.13 | <.0001 | 1.09  | 1.06–1.13 | <.0001 | 1.09  | 1.06–1.13 | <.0001 |
| 3–4                   | 19 850             | 7.9  | 1.20                                         | 1.15–1.26 | <.0001 | 1.20  | 1.15–1.26 | <.0001 | 1.20  | 1.15–1.26 | <.0001 |
| >4                    | 7744               | 3.1  | 1.22                                         | 1.14–1.30 | <.0001 | 1.22  | 1.14–1.30 | <.0001 | 1.22  | 1.14–1.30 | <.0001 |
| No. of LRTI diagnoses |                    |      |                                              |           | .01    |       |           | .64    |       |           | .64    |
| 0 (reference)         | 259 518            | 97.3 | 1.00                                         | —         |        | 1.00  | —         |        | 1.00  | —         |        |
| 1–2                   | 5774               | 2.29 | 1.17                                         | 1.02–1.33 | .02    | 0.99  | 0.89–1.10 | .81    | 0.99  | 0.89–1.10 | .81    |
| >2                    | 768                | 0.30 | 1.34                                         | 0.99–1.81 | .06    | 0.88  | 0.67–1.16 | .36    | 0.88  | 0.67–1.16 | .36    |

Data missing for years 1997–2001. All variables were assessed during the first year of life only.

weighed between 2.5 kg and 4.5 kg and 65% were delivered naturally, although cesarean section accounted for 24% of births; 108 958 (43%) children were prescribed at least 1 antibiotic in their first year of life. The mean follow-up time was 5.5 years (SD: 2.0) with a range of 2 to 9 years. Seven percent of children ( $n = 18\,864$ ) developed asthma over the follow-up period, and the overall incidence of asthma was 2.3 per 100 person-years (PY) of follow-up; however, the rate ranged from 2.7 per 100 PY for diagnoses at 2 to 3 years to 1.7 per 100 PY for diagnosis at 5 to 9 years (Table 1). Additional demographic and antibiotic treatment details are shown in Tables 2 and 3.

The unadjusted HRs for the association between antibiotic exposure and asthma were not constant over time. The association between antibiotic prescription in the first year of life and asthma was stronger for diagnoses earlier in the follow-up period (Table 2). There also seemed to be a dose-response relationship in the unadjusted results, with a monotonically increasing relationship between the number of course of antibiotics in the first year of life and the development of asthma. In addition, all antibiotic classes seemed to be associated with asthma development.

When the results were adjusted for potential confounders, exposure to antibiotics in the first year of life

was positively associated with asthma (adjusted HR: 1.12 [95% CI: 1.08–1.16]) (Tables 3 and 4). There was an increased risk of asthma associated with being male, living in an urban location, having lower SES, lower birth weight, lower gestational age, first cesarean (but not for later cesareans), forceps or vacuum extraction, no congenital anomalies, specialist visit, increased frequent physician visits in the first year, increased bronchitis, URTI, or LRTI diagnoses, and fewer otitis media diagnoses (Table 3). The risk of developing asthma also increased with the number of courses of antibiotics taken during the first year of life (adjusted HR for > 4 courses: 1.30 [95% CI: 1.20–1.41]) (Table 4). The association with asthma varied according to type of antibiotic dispensed with macrolide exposure exhibiting the strongest association with asthma (adjusted HR: 1.11 [95% CI: 1.06–1.17]).

The results of the sensitivity analyses are shown in Table 5. There was a continued association with respect to antibiotic use and development of asthma, and the strength of the association was slightly larger in these groups than in the primary analysis.

## DISCUSSION

We evaluated the association between antibiotic exposure in the first year of life and subsequent development

**TABLE 4 Adjusted Risks Associated With Exposure to Antibiotics and Development of Asthma**

| Antibiotic Exposure Variable    | n<br>(N = 251 817) | %    | HR   | 95% CI    | P      |
|---------------------------------|--------------------|------|------|-----------|--------|
| Antibiotic exposure             | 108 958            | 43.3 | 1.12 | 1.08–1.16 | <.0001 |
| No. of antibiotic prescriptions |                    |      |      |           | <.0001 |
| 0 (reference)                   | 142 859            | 56.7 | 1.00 | —         |        |
| 1–2                             | 83 541             | 33.2 | 1.11 | 1.07–1.15 | <.0001 |
| 3–4                             | 18 495             | 7.3  | 1.15 | 1.09–1.22 | <.0001 |
| >4                              | 7016               | 2.8  | 1.30 | 1.20–1.41 | <.0001 |
| Exposure by type of antibiotic  |                    |      |      |           |        |
| Amoxicillin                     | 84 922             | 33.7 | 1.05 | 1.02–1.09 | .005   |
| Penicillin                      | 6488               | 2.6  | 1.10 | 1.02–1.19 | .01    |
| Cephalosporin                   | 20 731             | 8.2  | 1.08 | 1.03–1.13 | .001   |
| Sulfonamide                     | 20 041             | 8.0  | 1.03 | 0.98–1.08 | .31    |
| Macrolide                       | 23 298             | 9.3  | 1.11 | 1.06–1.17 | <.0001 |
| Other antibiotic in first year  | 350                | 0.1  | 0.93 | 0.69–1.26 | .64    |

Risks were adjusted for the confounding variables in shown Table 3.

**TABLE 5** Sensitivity Analyses Examining Exposure to Antibiotics in the First Year Not Dispensed for URTI, LRTI, Bronchitis, or Otitis Media (Sensitivity Analysis 1) and Excluding Children Who Were Diagnosed With URTI, LRTI, Bronchitis, or Otitis Media in the First Year of Life (Sensitivity Analysis 2)

| Variable                                                            | No. Exposed to Antibiotic | Total Cohort | Percentage Exposed to Antibiotic | 2–9 y           |           |        |
|---------------------------------------------------------------------|---------------------------|--------------|----------------------------------|-----------------|-----------|--------|
|                                                                     |                           |              |                                  | HR <sup>a</sup> | 95% CI    | P      |
| Primary analysis                                                    |                           |              |                                  |                 |           |        |
| Any antibiotic in first year                                        | 108 958                   | 251 817      | 43.3                             | 1.12            | 1.08–1.16 | <.0001 |
| Sensitivity analysis 1                                              |                           |              |                                  |                 |           |        |
| Any antibiotic (not dispensed for RI or otitis media) in first year | 56 998                    | 251 817      | 22.6                             | 1.13            | 1.09–1.16 | <.0001 |
| Sensitivity analysis 2                                              |                           |              |                                  |                 |           |        |
| Excluding children diagnosed with RI or otitis media in first year  | 16 387                    | 102 789      | 15.9                             | 1.17            | 1.10–1.25 | <.0001 |

RI indicates URTI/LRTI/bronchitis.

<sup>a</sup> Adjusted for all confounding variables in Table 3.

of asthma in the largest cohort study to date. The results of our analysis show a small but significant association between antibiotic use and the subsequent development of asthma. In addition, we found a positive dose response between the number of courses of antibiotics in the first year of life and the risk of asthma, but we did not find that the increased risk was associated with any particular type or class of antibiotics. Although we conducted extensive adjustment for potential confounding factors, the possibility for residual confounding of our results was plausible. Therefore, we conducted sensitivity analyses where we excluded antibiotics prescribed for a URTI, LRTI, bronchitis, or otitis media, and, in another analysis, we excluded all children with a diagnosis for these conditions. In these analyses, we found that the association remained and was in fact larger than in the primary analysis. As such, we conclude that there is an increased risk of asthma associated with antibiotic exposure in the first year of life.

There have now been numerous studies evaluating this question with divergent results.<sup>17–19</sup> The findings from our study were very much in line with the association observed in our meta-analysis, which showed a small effect in prospective studies (odds ratio [OR]: 1.12 [95% CI: 0.88–1.42]) but a greater effect in retrospective studies (OR: 2.82 [95% CI: 2.07–3.85]).<sup>8</sup> In general, retrospective studies have not been able to adjust for reverse causation, whereas the prospective studies, including ours, adjusted for multiple factors and showed either no or small but positive associations between antibiotic use in early life and development of asthma.

The 3 largest prospective cohort studies (including ours) that adequately adjusted for confounders have all found small, positive associations between antibiotic exposure in the first year of life and the subsequent development of asthma.<sup>12,17</sup> The study by McKeever et al<sup>12</sup> is most comparable to ours in design and analysis. This study examined 21 129 children between birth and 11 years of age in the United Kingdom's West Midlands General Practice Research Database who were registered with their primary care physician within 3 months of birth and whose medical history showed at least 1 consultation. In their Cox regression model, the investiga-

tors found that the association between >4 courses of antibiotics in the first year of life and asthma was an adjusted HR of 1.99 (95% CI: 1.72–2.31). Similarly, Kozyrskyj et al,<sup>17</sup> who conducted a similar study in a smaller Canadian cohort from Manitoba, found their adjusted HR for exposure to >4 courses of antibiotics in the first year of life to be (OR: 1.46 [95% CI: 1.14–1.88]). These results are very similar to ours in that we found an adjusted HR of 1.30 (95% CI: 1.20–1.41) in those who received >4 courses of antibiotics. Both of these studies used the same criteria for diagnosis of asthma; however, the age of asthma development differed between the 2 studies. We applied our definition of asthma after the age of 2, whereas in the study by Kozyrskyj et al,<sup>17</sup> the diagnostic criteria were applied only at the age of 7. Another important similarity between the 2 studies was the results of our sensitivity analyses and Kozyrskyj and colleagues' analysis restricted to antibiotic use for nonrespiratory tract infections as both showed stronger associations in these subgroups than in the main analysis.

Our study has several strengths and limitations, which must be noted. This is the largest population-based study to examine this question with almost a quarter of a million children followed for up to 7 years. We were able to adjust for many potential confounding factors that have not been previously examined including method of delivery, surgery during the first year, and the presence of birth complications. Because of the very large number of children and the comprehensiveness of British Columbia linked health data, we were adequately powered to examine whether the association occurred even when we excluded antibiotics prescribed (first analysis) or those with a diagnosis (second analysis) for an episode of URTI and LRTI or otitis media. In addition, our birth cohorts were large enough to adequately examine the impact of multiple courses of antibiotics and the type of antibiotic on the risk of developing asthma.

As with any study based on administrative records, the data were not collected for the purposes of research. As such, there are often problems with the data and inconsistencies with coding. However, we carefully

cleaned the data before analysis and removed any records likely to have implausible results (for example, those with death dates before birth dates). These records comprised <0.1% of the data. There is no reason to believe that there was differential misclassification of individuals in the 2 groups (those receiving antibiotics before 1 year of age and those who did not); therefore, any bias because of this is likely limited. In addition, although we adjusted for many variables thought to be associated with the development of asthma, we were unable to adjust for all variables that have been shown to be associated with childhood asthma such as maternal asthma. Although positive family history of asthma predicts an increased risk of asthma,<sup>21</sup> it identifies a minority of children at risk for asthma. In addition, Kozyrskyj et al<sup>17</sup> found the association between antibiotic use and asthma to be present only among children with no maternal history of asthma. Other potential confounders that we could not adjust for included parental smoking and the presence of mites. Although we believe that our SES variable would have controlled somewhat for these factors, we cannot rule out residual confounding.

Finally, in consideration of these findings, it might be helpful to assess them in light of Hill's criteria for causality.<sup>22</sup> The first criterion, the strength of the association, can act as a clue to causation (assuming that no confounding remains); however, the finding of a weak or strong association is neither necessary nor sufficient to deny or affirm causality. From our results, we found that the observed association between antibiotic exposure in the first year of life and subsequent asthma was somewhat weak, although statistically significant. The second criterion, consistency of results from different studies, has been satisfied in that our results tend to agree with other large, well-designed studies.<sup>12,17</sup> In terms of specificity, which "stems from old beliefs related to a 1 disease, 1-outcome model of illness," this criterion does not hold for our current study and likely has little validity for most studies in epidemiology.<sup>23</sup> However, there is strong evidence of the next criterion (temporality) in that we ensured that the exposure to antibiotics preceded the onset of asthma symptoms by excluding any diagnoses in the second year of life. Clearly, we found a dose-effect relationship with the risk of asthma increasing with the number of course of antibiotics in the first year of life, and this effect was also shown by previous studies.<sup>9,11,12,14,16</sup> The next criterion, biologic plausibility, depends on one's acceptance of the hygiene hypothesis as a mechanism in the development of asthma.<sup>7</sup> For coherence, there seems to be growing evidence in support of the hygiene hypothesis from a range of studies examining exposure to endotoxin levels and the subsequent development of atopic conditions and asthma.<sup>7</sup> In terms of analogous evidence, this criterion seems to have been satisfied as there is agreement with other studies that have examined the association between other atopic conditions and exposure to antibiotics early in life.<sup>9,10,12-17</sup> For experimental evidence, the most compelling evidence of causation, this has not yet been fully satisfied in this area. Because of the large sample size required and the requirement to

withhold antibiotics from children who would require them in a control arm, it would not be feasible or ethical to conduct a randomized, controlled trial to examine this question. As such, we have to continue to formulate our evidence base from well-designed pharmacoepidemiologic studies and observational, prospective cohort studies.

## CONCLUSIONS

We have shown that in a large, population-based cohort, after careful conducted analyses adjusting for many potential confounders and with multiple sensitivity analyses, the association between antibiotic exposure and the subsequent development of asthma remains.

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#### SURGEON SHORTAGE PUSHES HOSPITALS TO HIRE TEMPS

“The shift toward temporary assignments comes as the traditional way of practicing general surgery is fading in many parts of the country. For decades, general surgeons have been the backbone and economic engine of the community hospital. While maintaining their own private practices, they staff trauma and critical-care units and perform most common abdominal procedures. Without them, hospitals couldn’t provide many emergency-room services. In rural areas, their backup is necessary for everything from complicated births to inserting chest tubes. But the increasingly grueling schedules, shrinking payments and the temptation of more profitable surgical niches have made the field less attractive. Over the past 25 years, the number of general surgeons per capita has declined 25%, according to a study published in the *Archives of Surgery* earlier this year. Staffing agencies estimate that at least 1 in 20 of America’s 17 000 general surgeons now works on a temporary basis some or all of the time. Full-time temporary surgeons can earn \$250 000 or more a year, in some cases nearly twice as much as in private practice. That’s largely because they don’t have to pay overhead costs anymore. The American College of Surgeons has long condemned the practice of ‘itinerant surgery,’ where doctors operate on patients and leave follow-up care to a family physician. But it has refrained from issuing guidelines on locum tenens. Paul Collicott, a director of the ACS, says it’s ‘a necessary part of surgical practice today,’ given the overall shortage in the field.”

Fuhrmans V. *Wall Street Journal*. January 13, 2009

Noted by JFL, MD

## Antibiotic Use in Children Is Associated With Increased Risk of Asthma

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