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Antibiotics Prior to Age Two Years Have Limited Association with Preschool Growth Trajectory

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Author Contributions

LCB, MB, JPB, DL, and CBF conceived the study. LCB, MM, CEH, JER, JLS and RT contributed to study data acquisition and preparation. MB, MM, LCB, RT, and CBF conducted the analyses. LCB drafted the manuscript, and MB, MM, and CBF contributed detailed revisions. JPB, DL, and CBF supervised the Antibiotics and Childhood Growth study. All authors contributed to critical assessment of results and provided critical review of the manuscript

Competing Interests

All statements in this manuscript are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors, or Methodology Committee.

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Abstract

Background: Prior studies of early antibiotic use and growth have shown mixed results, primarily on cross-sectional outcomes. This study examined the effect of oral antibiotics before age 24 months on growth trajectory at age 2–5 years.

Methods: We captured oral antibiotic prescriptions and anthropometrics from electronic health records through PCORnet, for children with ≥1 height and weight at 0–12 months of age, ≥1 at 12–30 months, and ≥2 between 25 and 72 months. Prescriptions were grouped into episodes by time and by antimicrobial spectrum. Longitudinal rate regression was used to assess differences in growth rate from 25 to 72 months of age. Models were adjusted for sex, race/ethnicity, steroid use, diagnosed asthma, complex chronic conditions, and infections.

Results: 430,376 children from 29 health U.S. systems were included, with 58% receiving antibiotics before 24 months. Exposure to any antibiotic was associated with an average 0.7% (95% CI 0.5, 0.9, $p < 0.0001$) greater rate of weight gain, corresponding to 0.05 kg additional weight. The estimated effect was slightly greater for narrow-spectrum (0.8% [0.6, 1.1]) than broad-spectrum (0.6% [0.3, 0.8], $p < 0.0001$) drugs. There was a small dose response relationship between the number of antibiotic episodes and weight gain.

Conclusion: Oral antibiotic use prior to 24 months of age was associated with very small changes in average growth rate at ages 2–5 years. The small effect size is unlikely to affect individual prescribing decisions, though it may reflect a biologic effect that can combine with others.

Introduction

Antibiotics are the most commonly prescribed medications in early childhood (1–3), and their overuse continues notwithstanding evidence-based clinical guidelines for their judicious use in the treatment of common infections. Studies in animal models (4, 5) and humans (6) have documented short-term increases in body weight following antibiotic exposure. Alteration of the gut microbiome is the most common mechanism hypothesized regarding how antibiotic use might impact energy storage and weight gain. Because early infancy is a critical period for establishment of gut microflora, alterations early in life may be particularly impactful, and may exert a prolonged effect on energy homeostasis. Though little randomized data are available, prospective observational studies have shown both short-term disruption of the microbiome by antibiotics, and short-term alterations in weight following modification of the microbiome by fecal transplant (7). Given that childhood obesity continues to rise in US children age 2 to 5 years – reaching 15% in 2015–2016 (8)– and that up to half of antibiotic prescriptions may be inappropriate (9), antibiotic use may be a modifiable risk factor for childhood obesity (10).

Retrospective studies using different outcomes and methods of ascertainment and follow-up have reported differing estimated effects of antibiotic exposure in early childhood on subsequent risk for obesity (3, 11–15), with small effect sizes but generally favoring increased weight gain. Two recent meta-analyses of 8 (16) and 15 (17) studies, respectively

estimated ORs of 1.11and 1.23 for overweight + obesity in exposed vs. unexposed children. However, analysis of outcomes at 4 – 6 years of age in the recent PCORnet Antibiotics and Childhood Growth Study, the population utilized for this study, yielded much smaller effect estimates (OR for overweight or obesity 1.05, 95% CI 1.03, 1.07) (18).

Because obesity risk in childhood is superimposed on typical physiologic increases in height and weight, investigation of longitudinal effects must account for these expected changes. This is most often done via normalization to the average age- and sex-adjusted endpoints by use of Z-scores based on a standard such as the NHANES 2000 (19) or WHO (20) growth surveys. However, this cross-sectional analysis has limited ability to incorporate intervening events. Additional information may be contained in the trajectory through which children's growth passes to reach an observed endpoint. In an analysis of infant feeding, three distinct growth trajectories were identified, with differing impact on BMI at age 5 (21). Schwartz *et al.* noted in a regional study of 163,000 children several different links between antibiotic exposure in older children and growth trajectory (22). Despite compensation in BMI over time, even reversible alterations may reflect important changes in underlying biological processes. For this reason, it is useful extend our prior analysis of early antibiotic exposure in a larger U.S. national cohort of children to growth trajectory in addition to fixed endpoints.

In order to examine association between antibiotic exposure and longitudinal growth, this study makes use of infrastructure created by the National Patient-Centered Clinical Research Network (PCORnet) (23). Because trajectory analysis requires multiple anthropometric measurements over time, it may be difficult to accomplish in large cohorts. Through its health system network members, PCORnet provides both prescribing and anthropometric data obtained from clinical encounters, with multiple outpatient encounters typically available before age 6. Prior work has shown that data from electronic health records (EHRs) provides anthropometric estimates comparable to well-controlled national survey data (24). In this manuscript, we select children from this larger data-set in order to conduct the growth trajectory modeling.

Methods

Data Collection.

PCORnet is a broad collaborative network that includes over 100 healthcare institutions in the United States, designed to accelerate clinical research with significant impact and importance to patients. Data from EHRs at member health systems are extracted and transformed to a common data model (CDM) to support data interoperability for research. Thirty-six of the healthcare institutions that participate in PCORnet, referred to as *network partners*, contributed initial data for the study of childhood antibiotic exposure and growth (Table S1), with data from 29 ultimately carried forward to trajectory modeling after data quality analysis. Institutional Review Board review was obtained at all participating institutions, and data sharing agreements were established to allow for the transfer of patient-level data, deidentified to the HIPAA Privacy Rule's Safe Harbor standard, to the Children's Hospital of Philadelphia's study team.

Construction of the study cohort and of analytic variables has been described in detail elsewhere (18, 25). Brief summaries, with detailed description of variations specific to this analysis, are provided below.

Data Quality Assessment.

To examine deviations from expected drug usage, we compared per-patient prescribing rates for study medications across network partners and with previously reported national estimates. We assessed anthropometric measurements for biologically implausible values using the CDC 2000 age/sex norms for height and weight. In addition, to detect intra-patient inconsistencies, multiple measurements for an individual were screened using the exponentially weighted moving average method of Daymont *et al* (26). Data from 7 network partners with the most atypical prescribing rates and the highest rates of likely errors in heights and weights were removed from the analysis prior to cohort formation, in order to reduce misclassification of exposure and outcome (data not shown). These accounted for 5.6% of available individuals. In the remaining data, anthropometric measurements that were implausible for a given patient (<1% of all measurements) or likely duplication (11%) or carry-forward (9%) of prior values were excluded.

Cohort Formation.

To be included in the cohort, children required a valid birthdate and sex of male or female. In order to improve likelihood of obtaining accurate exposure data, we selected patients with recurring health system contact by requiring plausible same-day height and weight measurement between birth and prior to 12 months of age, and between 12 months and 30 months. As the primary objective of this study was to examine the effects of antibiotic use on the changes in growth patterns, we also required 2 concurrently measured height and weight measurements, spaced at least 6 months apart, between 24 and 72 months of age.

Antibiotic exposure.

A codeset comprising RxNorm terms for oral antibiotics was constructed; intramuscular ceftriaxone and penicillin were added as these medications are used in ambulatory settings to treat some common childhood infections. Given the typical antibiotic duration of 5–14 days, we accounted for duplicated prescriptions, rapid changes in antibiotic due to adverse reactions, or changes due to poor initial response by grouping all antibiotic prescriptions within 14 days of each other into a single episode of exposure, coded using the broadest spectrum drug included. Since antibiotics are typically prescribed for short duration, this approach allowed aggregation of medications prescribed for a single infection into one exposure. Based on recommended first-line antibiotics for common childhood infections, narrow-spectrum drugs were defined as penicillin, amoxicillin, and dicloxacillin, and all other antibacterials (*e.g.* azithromycin, amoxicillin/clavulanate, cephalosporins) were considered broad-spectrum. The overall extent of exposure was summarized as 0, 1, 2, 3, or 4+ episodes before 24 months of age.

Covariates.

We chose covariates *a priori* based on prior studies showing associations with childhood growth and antibiotic use and availability of data in the EHR. Age was calculated based on timing of encounters in relation to date of birth at each network partner and rounded to the nearest month before data was returned for analysis. Sex, race, and Hispanic ethnicity were recorded by network partners using local conventions and in accordance with CDM specifications. Oral corticosteroids, which are known to promote weight gain (28, 29), were used as a positive control; no minimum duration of exposure was required. Asthma was defined as the presence of 2 or more International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes at 25–72 months of age, given the low usage of asthma diagnosis codes prior to 24 months of age. Prematurity was defined as the presence of any diagnosis code for preterm birth recorded prior to 24 months of age. The presence of a complex chronic condition was determined using the list of conditions and corresponding codes as reported by Feudtner *et al.* (30). Asthma was excluded, as it was represented separately, as was presence congenital diagnosis with known severe effects on growth, such as hypothyroidism and pituitary disorders, since these children were excluded from the cohort. Health care utilization was defined by a count of all clinical encounters prior to 24 months of age. Diagnoses of infections were grouped using the approach of Fleming-Dutra *et al.* (31), yielding episodes labelled as Tier 1 (strong indication for antibiotics, e.g, pneumonia), Tier 2 (possible improvement with antibiotics, e.g., suppurative otitis media, pharyngitis) and Tier 3 (unlikely to benefit from antibiotics, e.g., non-suppurative otitis media).

Outcome.

We used weight (primary outcome) or height (secondary outcome) measured between 24 and 72 months of age as the outcome variable, with age and sex included as covariates in all analyses. For the primary analysis, weight was adjusted for the nearest height measured within 30 days of the weight measurement; we excluded weights that did not have a paired height measured within this 30-day window. All measurements of stature were considered to be standing heights (i.e. were considered the same quantity as measurements after 36 months of age).

Regression analysis.

Longitudinal rate regression (LRR) was used to examine the difference in rates of weight change (32). The LRR method is a non-linear modeling approach that examines differences in rates of change for a given outcome over time across covariates, characterized in two ways: as overall differences in the mean of the outcome at 24 months of age (mean level differences or main effect, used as baseline for the longitudinal assessments) and differences in the rate of change of the outcome (rate level differences).

All models for this study used regression splines with a cubic B-spline base with knots spaced at 36, 48, and 60 months for the reference time function in order to generate a general smooth trajectory for estimating differences in rates of change. Each antibiotic exposure variable for a given model was included at both the mean and rate level; the rate level estimate was the parameter of interest because it captured growth change over time as

a function of the exposure variable. Covariates were included at the mean and rate level with all continuous rate level covariates centered at their sample mean so that the parameter of interest applies to a *typical* child in the cohort. Estimates of the parameter of interest are presented with an estimated 95% confidence interval (CI).

The greater or lesser amount of weight gained over a fixed time period for an exposed child relative to an unexposed child was calculated. The estimated weight gain for a typical unexposed child between 24 and 72 months was based on the reference time function from the LRR model. This was multiplied by the estimated rate parameter for each antibiotic exposure group to estimate the amount of additional weight that was gained or lost between 24 and 72 months due to the estimated effect on the rate of growth. This alternative interpretation of model results will be referred to as the Attributable Weight Difference of exposure across this age interval.

Models were fit using the cohort as a whole, as well as separately at each network partner to assess variability in the estimated association across network partners. For the primary models, height was included as a time-varying covariate by centering each height measure on estimated baseline height for each individual. Baseline height was estimated by linear extrapolation of standardized length measurements taken prior to age 2. The estimated baseline height variable was included as a linear and quadratic term to account for baseline differences due to height. Time-varying height was accounted for by including linear and quadratic terms in the reference time function. Correlation between repeated measures on each patient were accounted for through inclusion of random effects at the mean and rate level.

Software.

Construction of Safe Harbor deidentified analytic datasets at network partners was done using SAS (SAS Corporation, Cary, NC) version 9.3–9.4, via the PCORnet query infrastructure. Aggregated query results and derived analytic variables were stored at the principal site using the Postgres (https://www.postgresql.org) relational database management system, versions 9.5–10.0. Data quality analysis, numerical computation and modeling were done using R, versions 3.3–3.4.

Code Availability.

R code developed for the analyses reported here are available at https://github.com/PEDSnet/pcornet_abx_growth_study/tree/main/lt_trajectory_analysis. Additionally, Daymont *et al.* have made an implementation of their anthropometric data evaluation algorithm available at https://github.com/carriedaymont/growthcleanr.

Results

Analytic Cohort.

For the primary analysis of weight trajectories adjusted for age, sex, and height, 430,376 children met inclusion criteria (Table 1). The contribution from a single network partner, some of which included several health systems, ranged from 0.3% to 48.9% of all

participants (median 2.6%; Supplemental Table S1). Characteristics (Table 2) of the current study cohort were similar to the overall PCORnet Antibiotics Study Entry Cohort of 683,485 children, details of which have been published elsewhere (25). The prevalence of asthma before 72 months was 12%, preterm birth 8%, and complex chronic conditions 14%. Antibiotic use was common before 24 months of age, with 58% of children receiving at least one prescription. The majority of prescriptions were for narrow-spectrum antibiotics, but 35% of children received at least one broad-spectrum antibiotic, with the most common being amoxicillin/clavulanate (33%), azithromycin (28%), and cefdinir (25%). Exposure to systemic steroids and anti-reflux medications were less common, with 13% of the cohort exposed to each. Median follow-up was to slightly less than 5 years of age, and median number of paired height-weight measurements per person was 4 (IQR 3–5). The mean Z score for height or weight measurements from 24 through 71 months, computed using NHANES survey data from 2008–2014, was 0.3 for each, with SD of 1.1 and 1.2, respectively.

Longitudinal Rate Regression Models.

Estimated differences in rates of change due to antibiotic exposure are presented in Table 3. Overall, children with any exposure to antibiotic had an estimated 0.7% (95% CI 0.5%, 0.9%) increase in the rate of change in weight across the observation period compared to unexposed children. This corresponded to an attributable weight difference of 0.05 kg (95% CI 0.04, 0.07). We observed similar degrees of association for narrow- and broad-spectrum antibiotics. There was a small dose response with increasing antibiotic episodes; the estimated difference in rate change in weight was the highest for 4 or more episodes of antibiotics (1.1%, 95% CI 0.7%, 1.4%). Similarly, the largest attributable weight difference was associated with 4 or more narrow spectrum antibiotic episodes (0.08 kg, 95% CI 0.05, 0.12). Similar effect sizes were observed in models using weight only as the outcome of interest, while height-only models showed smaller effects.

There was moderate variation in estimated rate effects across network partners (Figure 1 & S1), with estimated rate difference ranging from −3.2% to 2.8% across network partners. Most network partners showed effect estimates in the positive direction. Four of the network partners had statistically significant results, and those that contributed greater than 10,000 patients showed effect estimates with smaller variation.

Estimated mean effect and rate effect differences for all covariates included in the fully adjusted models for each antibiotic exposure type are presented in Table 4. Both the estimated baseline differences and rate effects were largely consistent across each model. The former estimated significant mean differences at age 24 months for each of the covariates included in the fully adjusted models. Covariates which contributed most substantial differences in rates of change were male sex, diagnosis of asthma, whether a child was preterm, non-Asian race, Hispanic ethnicity, and presence of a chronic condition (Table 3). Overall, the estimated baseline differences and rate effects for each covariates were consistent across models.

Discussion

Using the PCORnet infrastructure, we have assembled a cohort of over 400,000 children with available antibiotic prescription data before the age of 24 months of age, and anthropometric data from 24 to 72 months. Using longitudinal rate regression, we identified a very small change in average growth trajectory up to 5 years of age associated with antibiotic exposure before 24 months of age. These differences, while potentially of some importance at the population level are unlikely to affect clinical decision-making. Our findings are consistent with the analysis of obesity risk using a fixed-end point in the same cohort (18), which showed that receiving antibiotics before 24 months of age was associated with slightly higher BMI z-score (+0.04, 95% CI 0.03, 0.5) and overweight and obesity prevalence (OR 1.05, 95% CI 1.03, 1.07) at 48 to <72 months of age.

Other studies of early childhood growth trajectory have reported small effects of early exposure to antibiotics, similar in magnitude to those found in this study. Gerber *et al.* studied weight trajectories of children in the Children's Hospital of Philadelphia network using electronic health records (15) and found a 2% increase in the rate of growth for children exposed to antibiotics in the first 2 years of life. Schwartz *et al.* examined BMI trajectories based on EHR data and estimated excess weight gains between 0.73 and 1.50 kg through age 18 (22).

It is important to note several limitations of the current analysis. First, exposure data were collected only for outpatient prescribing at ambulatory, ED, or inpatient visits. Although we observed >90% fill rates for antibiotics in the subset of network partners with comprehensive dispensing data available (33), some prescriptions may represent "safety net" practice for equivocal infections, or may not have been given for a full course if symptoms improved. As a result, prescribing data may overestimate true exposure. More importantly, intravenous antibiotic exposure, more common in the neonatal period, coinciding with a potential critical period in establishment of the gut microbiome, was unavailable. For both these reasons, the current analysis may underestimate effects of very early antibiotic exposure. Second, information about other risk factors (e.g., parental weight, diet, income) for altered growth are not directly accounted for, as this information is often absent or unstructured in EHRs. Finally, the LRR method estimates average change in growth rate over the interval examined, and use of a multi-year outcome period may not have adequate resolution in the model to fully reveal short-term effects of antibiotics on growth, as have been observed in some prior studies. Further analyses will be needed to determine whether there is evidence of such short-term effects in the current cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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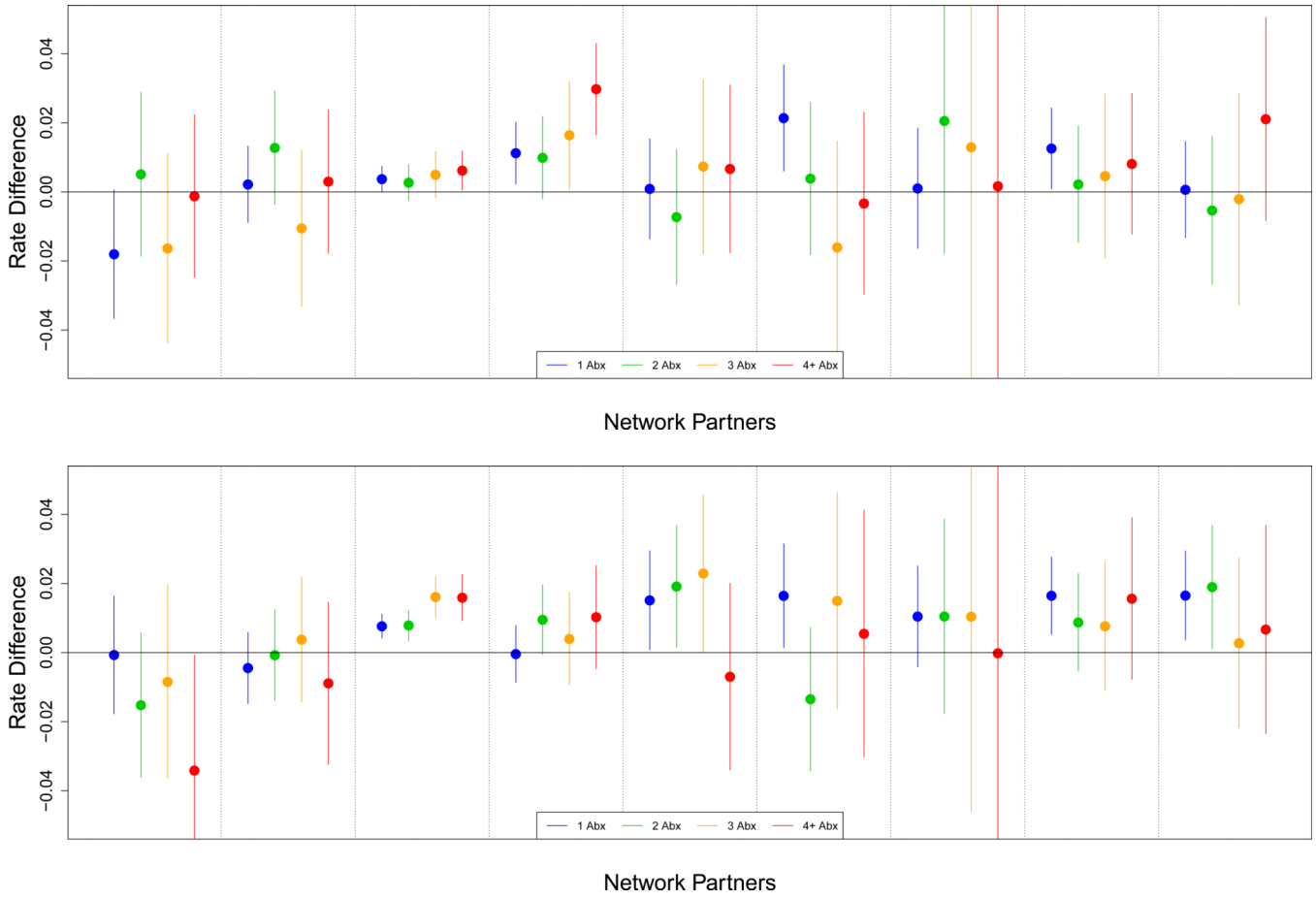

Figure 1.

Estimated effect of antibiotic exposure on growth trajectory for large network partners. Estimates are shown for network partners with ≥10,000 children, based on fully adjusted models using episodes containing at least one narrow- (A) or broad-spectrum (B) antibiotic. Vertical bars denote 95% confidence intervals for each estimate, which correlate with the cohort size for that network partner (*cf.* Table S1).

Table 1.

Formation of Study Cohort

	N	Difference	Percent Remaining of Total
PCORnet Antibiotics Study Entry Cohort [a]	683,485		
At least 2 same-day height and weight measurements between 24 and < 72 months of age	539,650	143,835	79.0%
At least 2 same-day height and weight measurement 6 months apart after exposure	538,552	1,098	78.8%
Valid height and weight measurements			
- Biologically Implausible Value Exclusion	528,844	9,708	77.4%
- EWMA Inconsistent Value Exclusion[b]	468,393	60,451	68.5%
Data quality exclusion	448,614	19,779	65.6%
Valid race or ethnicity	430,636	17,978	63.0%
Valid height measurement before 24 months of age	430,376	260	63.0%

[a] Encounter <11 years of age, valid sex, at least one same day height and weight measurement between 0 and 11 months, 12 and 30 months, and after 24 months] {Block, 2018 #934}

[b] Duplicated or carried-forward values, as identified by the method of Daymont *et al.* {Daymont, 2017 #935}

Table 2.

Characteristics of Analytic Cohort

Characteristic	Overall (%)
Total Population, N	430,376
Age in months during at last follow-up, mean (SD)	42 (14)
Age by year of life	
2 years (24–35 months)	393,592 (91)
3 years (36–47 months)	354,687 (82)
4 years (48–59 months)	284,753 (66)
5 years (60–71 months)	205,402 (48)
Female, n (%)	205,992 (48)
Race/Ethnicity	
Hispanic	79,461 (18)
Asian, Non-Hispanic	18,215 (4)
Black, Non-Hispanic	114,931 (27)
White, Non-Hispanic	197,475 (46)
Other, Non-Hispanic	20,294 (5)
Preterm[a], n (%)	32,623 (8)
Asthma[b], n(%)	52,274 (12)
Complex chronic condition[c], n (%)	58,453 (14)
Systemic corticosteroid episodes[d] **<24 months of age**	
0	373,403 (87)
1	38,525 (9)
2	10,665 (2)
3	4,042 (1)
4+	3,741 (1)
Episodes of presumed infectious illnesses[e] **<24 months of age**, n (%)	
0	58,257 (13)
1	33,802 (8)
2	39,079 (9)
3	41,021 (10)
4+	258,217 (60)
Number of encounters[f] **<24 months of age**, median (IQR)	16 (10–24)
Systemic antibiotic prescribing episodes[g] **<24 months of age**, n (%)	

Characteristic	Overall (%)
0	182,123 (42)
1	94,806 (22)
2	56,462 (13)
3	34,972 (8)
4+	62,013 (14)
Systemic broad spectrum antibiotic prescribing episodes[g] <24 months of age, n (%)	
0	280,865 (65)
1	75,848 (18)
2	32,270 (7)
3	17,035 (4)
4+	24,358 (6)
Systemic narrow spectrum antibiotic prescribing episodes[g] <24 months of age, n (%)	
0	227,087 (53)
1	107,877 (25)
2	53,674 (12)
3	24,761 (6)
4+	16,977 (4)
Systemic anti-reflux medication prescribing episodes[h] <24 months of age, n (%)	
0	374,409(87)
1	26,249 (6)
2	11,980 (3)
3	6,789 (2)
4+	10,949 (2)
Weight z-score during follow-up period (24–71 months of age), mean (SD)	0.3 (1.2)
Height z-score during follow-up period (24–71 months of age), mean (SD)	0.3 (1.1)
Patients with at least 1 valid height/weight pair in	
24–35 months	393, 592 (91%)
36–47 months	354, 682 (82%)
48–59 months	284,753 (66 %)
60–71 months	205,402 (48%)

Abbreviations: IQR, interquartile range

[a] One or more diagnosis codes for prematurity <24 months of age.

[b] Two or more diagnosis codes for asthma <72 months of age.

[c] Two or more diagnosis codes for a complex chronic condition <72 months of age

[d] Multiple corticosteroids given on the same day or within 10 days of each other were considered a single prescribing episode.

[e] Defined by diagnosis codes, with multiple diagnosis codes assigned on the same day or within 14 days of each other considered a single infectious episode of care.

[f] Included all encounters in the inpatient, emergency department, urgent care, and outpatient settings. A subset of network partners include telephone and similar encounters in outpatient counts.

[g] Multiple antibiotics given on the same day or within 14 days of each other were considered a single prescribing episode.

[h] Multiple anti-reflux medications given on the same day or within 10 days of each other were considered a single prescribing episode.

Table 3.

Estimated Differences in Rates of Growth and Attributable Weight Difference in Weight adjusted for Height due to Antibiotic Exposure

	Rate Difference	Attributable Weight Difference[a]
Any Abx	0.7% (0.5%, 0.9%)	0.05 (0.04, 0.07)
Number of Abx		
1 Episode	0.5% (0.2%, 0.7%)	0.03 (0.01, 0.05)
2 Episodes	0.9% (0.6%, 1.2%)	0.06 (0.04, 0.08)
3 Episodes	0.8% (0.4%, 1.2%)	0.05 (0.03, 0.08)
4 or More Episodes	1.1% (0.7%, 1.4%)	0.07 (0.05, 0.10)
Broad Abx	0.6% (0.3%, 0.8%)	0.04 (0.02, 0.06)
Narrow Abx	0.8% (0.6%, 1.1%)	0.06 (0.04, 0.07)
Number of Broad Abx		
1 Course	0.6% (0.3%, 0.8%)	0.04 (0.02, 0.06)
2 Courses	0.5% (0.1%, 0.9%)	0.03 (0.01, 0.06)
3 Courses	0.5% (0.0%, 1.0%)	0.03 (0.00, 0.07)
4 or More Courses	0.7% (0.3%, 1.2%)	0.05 (0.02, 0.08)
Number of Narrow Abx		
1 Course	0.8% (0.5%, 1.0%)	0.05 (0.04, 0.07)
2 Courses	0.8% (0.5%, 1.1%)	0.06 (0.03, 0.08)
3 Courses	1.1% (0.7%, 1.6%)	0.08 (0.05, 0.11)
4 or More Courses	1.2% (0.7%, 1.7%)	0.08 (0.05, 0.12)
Any Abx, Weight Only	0.9% (0.6%, 1.2%)	0.06 (0.05, 0.08)
Any Abx, Height Only	0.1% (0.0%, 0.2%)	0.03[b] (0.01, 0.05)

95% confidence intervals are presented for each estimate.

[a] Estimated additional weight in kg gained (or lost) due to exposure between 24 and 72 months of age.

[b] Estimated additional height in cm gained (or lost) due to exposure between 24 and 72 months of age.

Table 4.

Main Effect and Rate Effect Estimates for Adjusted Covariates in the Longitudinal Rate Regression Model for Weight Adjusted for Height

	Main Effects (Weight Differences at 24 Months)		
Primary Antibiotic Exposure	**Any**	**Broad-Spectrum**	**Narrow-Spectrum**
Male	0.22 (0.21, 0.23)	0.22 (0.21, 0.23)	0.22 (0.21, 0.23)
Has Asthma	0.26 (0.25, 0.28)	0.26 (0.25, 0.28)	0.26 (0.25, 0.28)
Oral Steroids (ref=0)			
1	0.14 (0.12, 0.15)	0.14 (0.12, 0.15)	0.14 (0.13, 0.16)
2	0.23 (0.20, 0.26)	0.24 (0.21, 0.27)	0.24 (0.21, 0.27)
3	0.30 (0.26, 0.35)	0.31 (0.26, 0.35)	0.32 (0.27, 0.36)
4+	0.44 (0.39, 0.49)	0.44 (0.39, 0.49)	0.45 (0.41, 0.5)
Number of Infections (ref=0)			
1	−0.03 (−0.05, −0.01)	−0.03 (−0.05, −0.01)	−0.04 (−0.06, −0.02)
2	−0.03 (−0.05, −0.01)	−0.03 (−0.05, −0.01)	−0.03 (−0.05, −0.01)
3	0.00 (−0.02, 0.02)	0 (−0.02, 0.02)	0 (−0.02, 0.02)
4+	0.03 (0.02, 0.05)	0.04 (0.02, 0.05)	0.04 (0.03, 0.06)
Preterm	0.05 (0.03, 0.06)	0.05 (0.03, 0.06)	0.04 (0.03, 0.06)
Race/Ethnicity (ref=Asian)			
Black, Non-Hispanic	0.55 (0.52, 0.57)	0.55 (0.53, 0.57)	0.55 (0.52, 0.57)
Other, Non-Hispanic	0.41 (0.38, 0.44)	0.41 (0.38, 0.44)	0.41 (0.38, 0.44)
White, Non-Hispanic	0.29 (0.27, 0.31)	0.29 (0.27, 0.31)	0.29 (0.27, 0.32)
Hispanic	0.67 (0.64, 0.69)	0.67 (0.64, 0.69)	0.67 (0.64, 0.69)
Chronic Condition	0.06 (0.05, 0.07)	0.06 (0.04, 0.07)	0.06 (0.05, 0.07)
	Rate Effects (Weight Gain Differences 24–72 Months)		
Primary Antibiotic Exposure	**Any Abx Count**	**Broad Abx Count**	**Narrow Abx Count**
Male	−3% (−3%, −3%)	−3% (−3%, −3%)	−3% (−3%, −3%)
Has Asthma	2% (2%, 3%)	2% (2%, 3%)	2% (2%, 3%)
Oral Steroids (ref=0)			
1	0% (0%, 0%)	0% (0%, 1%)	0% (0%, 0%)
2	0% (−1%, 1%)	0% (0%, 1%)	0% (0%, 1%)
3	0% (−1%, 1%)	0% (−1%, 1%)	0% (−1%, 1%)
4+	1% (0%, 2%)	1% (0%, 2%)	1% (0%, 2%)
Number of Infections (ref=0)			
1	−1% (−1%, 0%)	−1% (−1%, 0%)	−1% (−1%, 0%)

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	Main Effects (Weight Differences at 24 Months)		
Primary Antibiotic Exposure	**Any**	**Broad-Spectrum**	**Narrow-Spectrum**
2	0% (−1%, 0%)	0% (−1%, 0%)	0% (−1%, 0%)
3	0% (0%, 0%)	0% (0%, 1%)	0% (0%, 0%)
4+	1% (0%, 1%)	1% (0%, 1%)	1% (0%, 1%)
Preterm	−6% (−7%, −6%)	−6% (−7%, −6%)	−6% (−7%, −6%)
Race/Ethnicity (ref=Asian)			
Black, Non-Hispanic	8% (7%, 8%)	8% (7%, 8%)	8% (7%, 8%)
Other, Non-Hispanic	5% (5%, 6%)	5% (5%, 6%)	5% (5%, 6%)
White, Non-Hispanic	3% (3%, 4%)	3% (3%, 4%)	3% (3%, 4%)
Hispanic	10% (9%, 10%)	10% (9%, 10%)	10% (9%, 10%)
Chronic Condition	−2% (−2%, −2%)	−2% (−2%, −2%)	−2% (−2%, −2%)