PCORnet: Weight-Related Observational Use Case
Topic Brief

Long-term Effects of Antibiotics on Childhood Growth:
The Antibiotics and Childhood Growth Study

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§1 Overview/Definition of Topic

1A. Purpose and Aims: The goal of the proposed study is to improve shared decision-making regarding use and choice of antibiotics during the first two years of life. The specific aims are: Aim1: To evaluate the comparative effects of alternative antibiotics used during the first two years of life on body mass index and risk of overweight and obesity during the third to fifth years of life; Aim2: To assess the comparative effects of alternative antibiotics used during the first two years of life on the rates and patterns of childhood growth during the first five years of life; and, Aim3: To explore how the effects of alternative antibiotics on childhood obesity risk and growth vary by patient demographic and clinical characteristics and maternal factors, such as receipt of antibiotics and comorbidities. The proposed study will be done using data exclusively from PCORnet research network databases, and will not require any new data collection in the form of surveys, patient-reported outcomes, or biospecimens. We hope, however, that the results of this initial study will inform future work within PCORnet that will include those data elements.

1B. Background
Antibiotics are the most frequently prescribed medication for children. They are used during a period of heightened vulnerability for families: when children are ill, and parents are worried about their children’s well-being. Deciding whether and which antibiotics to use is usually based on efficacy and short-term risks; e.g., some cause nausea, others diarrhea, and others a rash within a few days of administration. But what if some, but not all, antibiotics had long-term effects on children’s growth and risk of obesity? Growing evidence suggests that this may be the case [1-10]. (See the Appendix for a short discussion on the biological plausibility of this association.) The availability of many years of electronic health record data, which contain both antibiotic exposure information and children’s long-term growth data, coupled with harmonization of those data from disparate research networks to a common data model provide a unique opportunity for PCORnet: to conduct a long-term safety study on the comparative effects of alternative antibiotics given during the first two years of life on longer term growth and risk of obesity.

§2 Patient Centeredness

2A. To what extent is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians?
Antibiotics are the most commonly prescribed drug class for children. Parents seek appropriate treatment of bacterial infections with antibiotics, but also worry about untoward effects of these agents, particularly in settings where they are unnecessary. Clinicians often experience parental pressure to prescribe antibiotics, even if the child’s illness could be viral in nature. The clinical community has identified overuse of antibiotics as one of the most important quality improvement opportunities for young children. Clinicians, public health officials and the public are concerned that overuse of antibiotics is creating drug-resistant bacteria, but this is an abstract notion for most parents and probably does not drive decision making as much as an elevated risk of childhood obesity, whose high prevalence and comorbidities are now fixed in the mind of most Americans. Some scientists have hypothesized that one of the many causes of the obesity epidemic is chronic low-dose exposure to antibiotics [11]. Thus, there is a multi-stakeholder convergence of interest in both ensuring judicious use of antibiotics and identifying modifiable factors that reduce the risk of childhood obesity.

2B. Parent Input
During the preparation of this proposal, parents from PEDSnet provided important input into how they would use information from a long-term study on antibiotics and growth. Illustrative feedback is provided here.

*How would you respond to information that found that certain antibiotics alter the ways in which some children gain weight? How would you use such information?*

- “I would definitely want to know if there were alternative medicines and/or treatments available that would be less likely to promote obesity than the prescribed medication. I would also want to know what the likelihood (percentage chance) would be that the medication originally prescribed might lead to an increased chance for weight gain, and if so how severe might the weight gain be.”
- “If multiple treatments and/or medications were available, I would want to choose the treatment and/or medication that had the greatest chance for success in dealing with the current condition being treated.”
- “If I had an option, I would definitely consider requesting the treatment/medication that did not lead to an
increased chance of obesity."

- "It would help me to decide which antibiotics I’d want my child to take. With my son in particular, he had 11 ear infections in 6 months. I wonder how that affected his weight. With my daughter, she had chronic sinus infections at least twice a year. I wonder how antibiotics were affecting her."

**Let's assume that avoiding certain antibiotics could reduce a child's risk of obesity from 1 in 6 children to 1 in 7 children. Is that a big enough reduction to affect how you would make decisions about antibiotics for your children?**

- “I would want to make sure the current condition is treated. I would, however, weigh many factors, including effectiveness of the different medications/treatments, side effects (including obesity), and cost.”
- “All other factors being relatively equal, the reduction in chances of childhood obesity from 1 in 6 to 1 in 7 would influence my decision.”
- “If I could keep them from having this—not even so much the obesity, but the things that come with it—diabetes, cholesterol… I would do anything I had to keep my kids from dealing with that. We have so much of this in the family (diabetes, heart disease).”
- “I would want to know is getting an antibiotic shot the same as the 10-day antibiotic that I’m given? Is that not as much medicine is going in to your body, or is the 10 days just as much? It would matter, and I would deliberate about this. This is important information for the parent to have. If I have the information, I can make the best informed decision for my child.”

2C. Stakeholder Engagement Plan

As this proposal moves forward into protocol development and study conduct, the team should include parents of young children (a suggestion made by parents involved in study concept preparation), parents of children in early-middle childhood who are overweight or obese, primary care and specialty clinicians, and scientists. The engagement plan, though, should also specify how diverse stakeholder groups could contribute to the study. These representatives might be drawn from the American Academy of Pediatrics, American Academy of Family Physicians, other clinical societies involved in the care of children, as well as health plan and pharmacy benefit management company thought leaders who can help interpret findings and disseminate results.

§3 Burden on Society

Childhood obesity is a major public health problem, with 1 in 3 children and adolescents in the United States either overweight or obese [12]. The frequency of antibiotic use in young children can lead to long-term side-effects and might contribute to emerging obesity patterns in children. Despite research investigating determinants of childhood obesity, additional work is needed to identify modifiable risk factors in order to mitigate its impact. Childhood obesity is associated with cardio-metabolic outcomes such as type 2 diabetes, hyperlipidemia, hypertension, premature adult mortality, and consequences that affect children’s health, such as asthma, orthopedic conditions, and psychological problems. Obese children have higher health care utilization and costs of care and their self-reported global health and well-being is lower than their counterparts.

§4 Assessment of Current Options

4A. Based on recent literature, what is known about the topic?

As early as 1955, the first report that showed that antibiotic administration increased the weight of humans was published [13]. Well before this report, it was recognized that antibiotics given to farm animals increased their size, a practice still in use today. In a birth cohort study of approximately 11,500 children born in the United Kingdom in 1991-1992, parents reported on antibiotic exposure. Infants receiving antibiotics in the first six months of life, but not later, had a greater risk of being obese at 38 months of age (odds ratio 1.22) [14]. A Danish birth cohort study done among 28,354 infants found using questionnaire data that antibiotic exposure during the first six months of life increased the risk of obesity by 7 years of age for children born to mothers with normal weight (OR 1.54 95CI 1.09-2.17) and a decreased risk among those who mothers were obese (OR 0.54 95CI 0.30-0.98)[4]. A cross-national retrospective survey done in 18 countries asked parents of children 5-8 years to record current height and weight and exposure to antibiotics in the first year of life. The study of 74,946 participants found a small effect, for boys but not girls, of antibiotic exposure on body mass index, after controlling for breastfeeding, parental smoking, and current presence of asthma [15].
A recent study from PEDSnet using electronic health record data from the Children’s Hospital of Philadelphia involved extracting EHR data from 2001–2013 for 64,580 children; treatment episodes for prescribed antibiotics were ascertained up to 23 months of age [10]. Obesity outcomes were determined directly from anthropometric measurements, using NHANES 2000 BMI norms. Cumulative exposure to broad-spectrum antibiotics was found to be associated with later obesity (RR 1.16, 95CI 1.06-1.29). Narrow-spectrum antibiotics were not associated with later obesity [10]. The PEDSnet study was not sufficiently powered to examine the effects of specific classes of or individual antibiotics, to examine the combined effect of early exposure and higher number of doses, or to evaluate how antibiotics affect growth trajectories. The proposed study will address these limitations. Results are expected to augment information on the short-term safety of antibiotics by providing information to parents and clinicians on long-term effects on growth. The findings of this study hold the potential for influencing shared decision-making for an event, antibiotic prescribing during the first two years of life, that affects 70% of children [10].

4B. What are the limitations of current literature for which new research could contribute to achieving better patient-centered outcomes?
The opportunities presented by a PCORnet study include:
1. Ability to evaluate specific medications and patterns of medications given during the first two years of life, extending prior work that addressed narrow versus broad spectrum antibiotics, which will aid shared decision-making about use and choice of antibiotics;
2. Evaluation of the effect of antibiotics on growth velocity and growth trajectories, which are likely mediators of the effects of antibiotics on childhood obesity;
3. Assessment of patient sub-class analyses that have not been done (e.g., effects for premature or low birth weight infants, differences by race/ethnicity, etc.);
4. Examination of effect modification by other medications--for example, the effects of antibiotics may be potentiated in the presence of corticosteroids;
5. Replication of findings across diverse settings, strengthening the argument for causality;
6. Modeling the effect on a continuous measure of body mass index rather than the dichotomous outcome of obesity, which should increase power to detect differences;
7. Ability to examine the effects of antibiotics on development of other outcomes, such as asthma and atopy, adding to the growing literature on long-term effects of these medications;
8. Determine if there are sensitive periods of infancy when exposure to antibiotics has its largest effect;
9. Contrast the effect sizes for prescribed (from EHRs) versus dispensed (from retail pharmacy claims) medications; and,
10. Capacity to test the complex query functionality of the distributed research network and processes for generating a patient-level data set within PCORnet.

4C. What recent innovations made research on this topic especially compelling?
EHR data accumulated across diverse settings over a 5+ year interval and standardization of those data to the PCORnet data model.

4D. What is the added value of performing this research in PCORnet over doing it in more limited settings, eg a single CDRN?
Please see limitations section above, points 1-12.

§5 Potential for New Information to Improve Care and Patient-Centered Outcomes
5A. How likely is it that new CER on this topic would provide better information to guide clinical decision-making? The proposed study will examine the long-term relationships between antibiotics and childhood growth. Elucidating these associations will add new information to the safety profile of antimicrobial medicines. Findings from the proposed study will provide novel and important information to support shared decision-making regarding use and choice of antimicrobial therapy, the most common medical decision in pediatrics, during the early years of life.

5B. How likely is it that the results of new research on this topic would be implemented in practice right away? We think that the parents’ comments, provided above, give a cogent assessment of how information from the proposed study would be used to inform parental decision-making. Clinicians and parents would use the long-term risk of obesity associated with specific antibiotics information when making a decision about use and choice of antibiotic. This would augment existing short-term efficacy and safety information
gleaned from clinical trials. Furthermore, a study done in PCORnet that shows a relationship between antibiotics and obesity would find immediate application in antibiotic stewardship initiatives across the nation, and probably internationally as well.

5C. How would findings be disseminated? Should this study go forward, investigators should work with pediatric and family medicine professional societies, PCORI, and media outlets to publicize these results as quickly as possible. The team would publish articles in peer-reviewed journals, and would leverage existing relationships among all PCORnet networks with patients and clinicians to rapidly disseminate results. Because of the frequency of use of antibiotics in young children, we are confident that the study’s findings would be of interest to a wide range of media outlets (which was the case for the PEDSnet-CHOP study).

§6 Feasibility of the Study within Health Systems

6A. Does this study meet the requisite technical, governance and regulatory constraints described below? This study will be done in two parts: a set of complex queries in which statistical code is distributed to networks and results analyzed centrally, and the creation of a deidentified, patient-level database. The complex queries could be implemented once PCORnet’s distributed data network is functional. PCORnet has to work out the details of data sharing across networks for patient-level observational studies.

§7 Study Design

7A. Conceptual Model

We base the biological plausibility of the association between antibiotics and growth on the work of Cox and Blaser, who elaborated the molecular pathways that result from antibiotic exposure [16]: Antibiotics → Alter Intestinal Microbiome → Affects Infant Energetics → Excess Weight Gain → Obesity

7B. Aims and Hypotheses

The goal of the proposed study is to improve shared decision-making regarding use and choice of antibiotics during the first two years of life. The specific aims are:

Aim1: To evaluate the comparative effects of alternative antibiotics used during the first two years of life on body mass index and risk of overweight and obesity during the third to fifth years of life.

Hypothesis: Our hypothesis is that there will be a dose-response relationship between the number of antibiotic courses given during the first two years of life and the development of obesity during the 3rd-5th year of life. This relationship will be strongest for broad-spectrum antibiotics, particularly those with a spectrum of activity that covers intestinal microflora.

Aim2: To assess the comparative effects of alternative antibiotics used during the first two years of life on the rates and patterns of childhood growth during the first five years of life.

Hypothesis: Administration of broad spectrum antibiotics will influence the subsequent growth trajectories of children. These alterations in growth will increase children’s risk of later overweight obesity during the third through fifth years of life. This effect will not be seen for narrow spectrum antibiotics.

Aim3: To explore how the effects of alternative antibiotics on childhood obesity risk and growth vary by patient demographic and clinical characteristics and maternal factors, such as receipt of antibiotics and comorbidities.

Hypotheses:
- The antibiotic effect will not vary by patient or clinical characteristics.
- Long-term corticosteroid use will potentiate the effect of antibiotics on childhood obesity.
- Antibiotic exposure during infancy will be associated with other health conditions, such as asthma, atopy, and other allergic-related conditions.
- There will be no difference in effect sizes when prescribed or dispensed medications are used to characterize the independent variable.

7C. Selection Criteria: Patients with at least one encounter in the exposure windows, which for will be either
0-11 months and 0-23 months; at least one additional encounter for routine care between 24 and 59 months for which a BMI can be computed.

7D. Variables

**Exposures:** antibiotic exposure will be assessed using outpatient or inpatient prescriptions (or dispensed medications) between birth and 23 months of age; we will explore the quality of the data and determine whether sufficient information is available to compute mean daily dosage in addition to computing the number of courses of treatment; antibiotic exposures will comprise systemic medications with primarily antibacterial activity; drugs with primarily antiviral or antifungal activity will be excluded; and, a single episode of antibiotic exposure will be defined as all days from the start of a course through the beginning of a 14-day antibiotic-free interval.

**Outcomes: Growth:** Obesity, yes/no; Overweight, yes/no; Normal weight, Overweight, Obesity as a categorical outcome; Obesity class, categorized by % of the 95th age-sex percentile for BMI (Level 1: 100-119%, Level 2: 120-139%; Level 3: 140% and higher); body mass index, age-sex percentile; and, growth trajectories, using body mass index.

**Covariates:** Demographics, including residence; medications; co-morbidities; primary care practice identifier; year of visit; birth weight; prematurity; if available, maternal factors such as receipt of antibiotics, gestational diabetes, and comorbidities; if available, route of delivery. We will explore the ability in PCORnet research networks to link data from mothers with their infants. This may be possible in a subset of networks, so analyses using maternal data, at best, will be a subset of the full study sample.

7E. Which current and future CDM elements are required (list based on CDM 2.0)? The following tables would be used: Demographic; Enrollment; Dispensing; Vital; Condition; Encounter; Diagnosis; Procedure.

7F. Analytic Approach

The analysis will be done in two phases: complex query analysis using the distributed data network and a patient-level dataset that would involve data sharing across the networks. Statistical analysis will be done within each participating network using Cox proportional hazards models when modeling binary outcomes. This work can be done using privacy-protecting methods implemented by the DRN. We will also model growth trajectories using the SITAR method developed by Cole and colleagues [17]. This approach uses a spline curve and non-linear random effects model to estimate an average growth curve for BMI, length, and weight for the entire sample as well as each individual's deviation from the average on size, velocity, and timing of peak velocity. This methodology will allow us to determine whether exposure to antibiotics influences the dynamics of infant growth which then predisposes a child to obesity.

7G. Limitations

Our model connects antibiotic exposure to changes in the dynamics of growth, and subsequent obesity. In prior work, only the exposure and outcome variable were assessed. In this study, we will replicate what has been done in the past at a more granular level (assessing individual antibiotics and patterns of antibiotics received) and add analyses of growth dynamics. Future research will be required to ascertain how antibiotics affect the microbiome and how those changes in turn influence growth. Because this study will be based on the CDM only, some covariates, such as diet, breastfeeding, and other potential confounders will not be collected.
Appendix. Biological Basis of the Association between Antibiotics and Growth.

Early childhood obesity has been associated with several factors, including maternal pre-pregnancy body mass index (BMI), nutritional intake, physical activity, and sleep time [1]. One novel factor noted by the Institute of Medicine Committee on Obesity Prevention Policies for Young Children is the role of microbial populations in the intestine [1]. Recent evidence suggests bacteria differ in their ability to extract energy, and colonization patterns can influence growth in both animals and humans [2-5]. The intestinal microbiome plays an important role in host energy metabolism through several pathways, including the expression of genes influencing energy available from short chain fatty acids and for processing otherwise indigestible polysaccharides [2]. Recent research has suggested intestinal microflora are associated with risk of obesity [3-6] and that antibiotic exposure influences microbial diversity and composition [7-9]. Given the modifiable nature of the intestinal microflora, the national burden of obesity, and ample opportunity for improved antimicrobial use, there is a need to determine the influence of antibiotic use on early childhood obesity.
References


