# The PCORnet Antibiotics and Childhood Growth Study: Toward PCORnet Research Readiness

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*NIH Health Care Systems Research Collaboratory Grand Rounds*
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# Talk Overview

- Taking PCORnet for a Test Drive
- Challenges of Working in a New Network
- Results of the PCORnet Antibiotics and Childhood Growth Study
- PCORnet Future Directions

# PCORnet® Common Data Model domains

- Based on FDA Sentinel Common Data Model
- Licensed under Creative Commons (open-access, use, and share)
- Designed to promote multi-site, patient-centered research
- Allows for interoperability

## PCORnet Common Data Model Domains, v3.0 and v3.1

**DEMOGRAPHIC** v1.0
Demographics record the direct attributes of individual patients.

**ENROLLMENT** v1.0
Enrollment is a concept that defines a period of time during which a person is expected to have complete data capture. This concept is often insurance-based, but other methods of defining enrollment are possible.

**ENCOUNTER** v1.0
Encounters are interactions between patients and providers within the context of healthcare delivery.

**DIAGNOSIS** v1.0
Diagnosis codes indicate the results of diagnostic processes and medical coding within healthcare delivery.
Data in this table are expected to be from healthcare-mediated processes and reimbursement drivers.

**PROCEDURES** v1.0
Procedure codes indicate the discreet medical interventions and diagnostic testing, such as surgical procedures and lab orders, delivered within a healthcare context.

**VITAL** v1.0
Vital signs (such as height, weight, and blood pressure) directly measure an individual's current state of attributes.

**LAB_RESULT_CM** v2.0
Laboratory result Common Measures (CM) use specific types of quantitative and qualitative measurements from blood and other body specimens. The common measures are defined in the same way across all PCORnet networks, but this table can also include other types of lab results.

**CONDITION** v2.0
A condition represents a patient's diagnosed and self-reported health conditions and diseases. The patient's medical history and current state may both be represented.

**PRO_CM** v2.0
Patient-Reported Outcome (PRO) Common Measures (CM) are standardized measures that are defined in the same way across all PCORnet networks. Each measure is recorded at the individual item level: an individual question/statement, paired with its standardized response options.

**DISPENSING** v2.0
Outpatient pharmacy dispensing, such as prescriptions filled through a neighborhood pharmacy with a claim paid by an insurer. Outpatient dispensing may not be directly captured within healthcare systems.

**PRESCRIBING** v3.0
Provider orders for medication dispensing and/or administration. These orders may take place in any setting, including the inpatient or outpatient basis.

**PCORNET_TRIAL** v3.0
Patients who are enrolled in PCORnet clinical trials.

**DEATH** v3.0
Reported mortality information for patients.

**DEATH_CAUSE** v3.0
The individual causes associated with a reported death.

**HARVEST** v3.0
Attributes associated with the specific PCORnet datamart implementation, including data refreshes.

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# Antibiotics and Weight in Childhood

- Biological premise related to alterations in microbiome affecting metabolism and direct growth promoting effects of antibiotics
- Prior studies done in varied environments have been mixed
- Meta-analysis of 15 studies
  - Mean BMI z-score: 0.07 (0.05, 0.09) higher with antibiotic exposure; significant higher association in 5 of 8 studies
  - Overweight/obesity: RR of 1.23 (1.13, 1.35); significantly higher RR in 6 of 9 studies

**Corpella, et al., 2016; Moore, et al., 1946; Shao, et al., 2017**

# PCORnet Antibiotics Study

- Aims: to assess the association between antibiotic use before age 2 and childhood weight outcomes:
  - Antibiotics use & weight outcomes at age 5 and 10
  - Antibiotics use & childhood weight trajectories
  - Incorporation of maternal variables in 7 DataMarts
- Qualitative Aim:
  - Parent focus groups and provider interviews focusing on association between antibiotics and childhood obesity
- Study setting and team
  - 36 healthcare institutions participating, 10 CDRNs

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# Site Selection Process

- Data characterization to assess data quality and availability of vitals and prescribing data; counts of frequencies of outcomes and covariates
- 7 sites removed at this stage
  - 5 – data quality issues
  - 2 – unwilling to share individual-level data
- Sites with any available data included
  - N range – 34 to 187,226
  - 14/36 institutions contributed 83% of data

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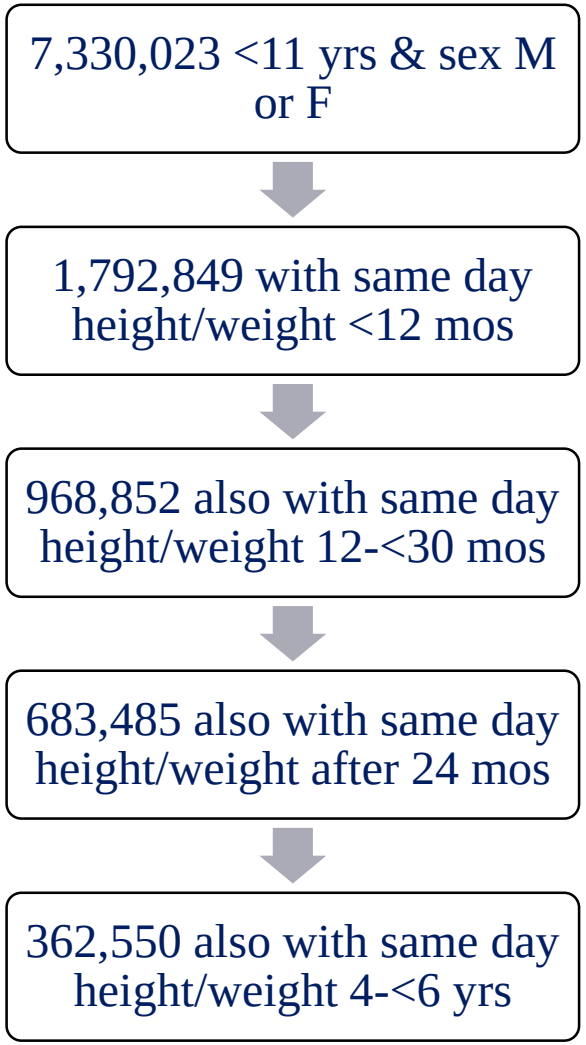
# Cohort Inclusion Flow Diagram




Block, et al., 2018.

# Key Challenges

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# It’s Hard to Do Research on a Network While Building

- PCORnet provided extensive guidance to networks, but it takes some time (and frequent assessments) for all to implement
- Many source medication codes mapped to RxNorm codes, but use of codes varied, esp. specificity of codes
- Cannot always get details on medications, such as days supply
- Varied models of PCORnet Network Partners create different levels of transparency

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# Tracking Issues Encountered and Addressed

- 28 NPs of an initial 33 planned had some issues; 5 had to be removed
- 29 separate issues identified with prescribing tables – most resolved
- 6 issues with vitals tables, specifically height and weight – again, most resolved

# **Aim 1 Analysis:** Antibiotics Use <24 Months & Weight Outcomes at Age 4 to <6

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# Primary Outcome/Aim Analysis

- Outcome – Chose height/weight value closest to 60 months of age and calculated BMI z-score and weight status
- Exposure – Antibiotics ≤24 months of age, yes v. no
- Covariates
  - Demographics: gender, race, Hispanic
  - Clinical: # of visits, asthma diagnosis, prematurity diagnosis, corticosteroid use, # of infections (mediator)

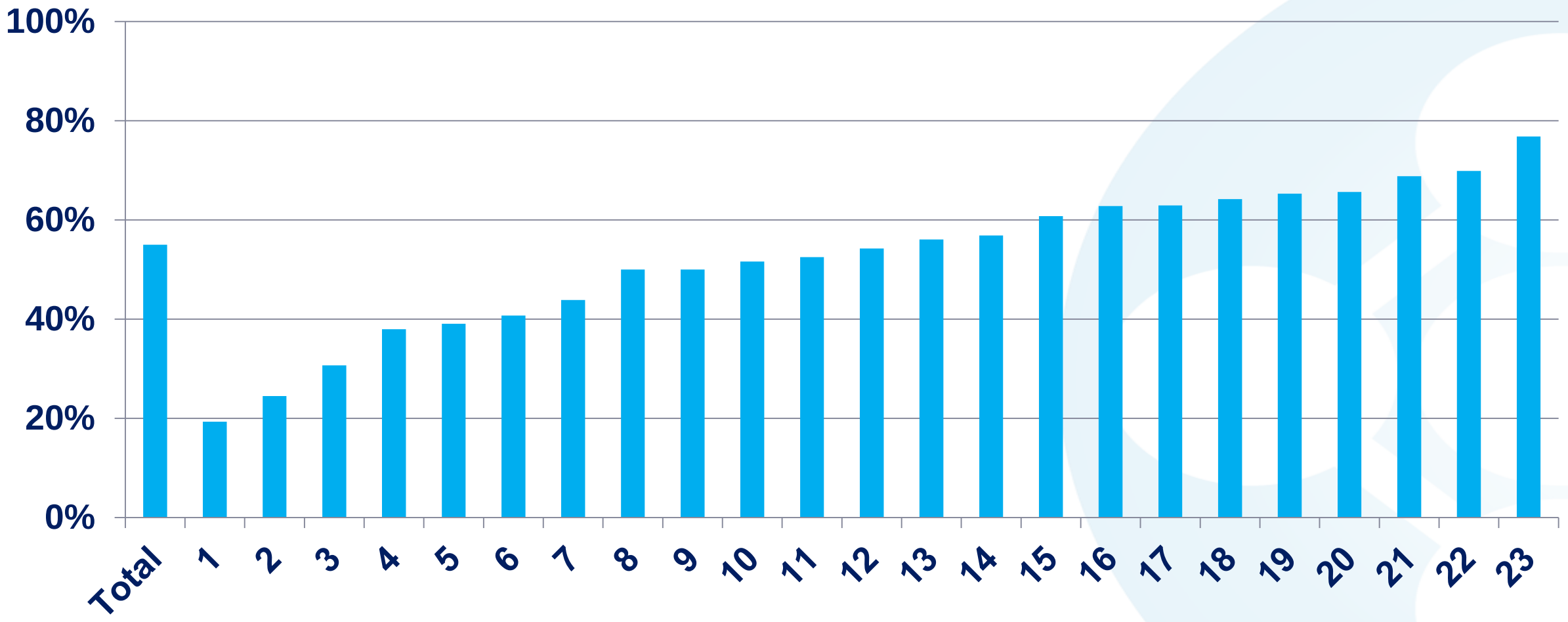
# Secondary and Sensitivity Analyses

- Secondary analyses
  - Narrow (amoxicillin, penicillin) and broad
  - Age-specific exposure (0-<6 mos, 6-<12 mos, 12-<24 mos)
  - Dose response from 0 to 4+
- Sensitivity analyses
  - Prescriptions only for less severe infections
  - Children with at least one well-child visit documented
  - Data Partners with over 40% antibiotics prescribing

# Results: Table 1

| | | |
|---|---|---|
| Gender | Male | 52% |
| | Female | 48% |
| Race | White | 53% |
| | Black, African American | 27% |
| | Refuse/Unknown/No info | 8% |
| | Other/Multiple Race | 8% |
| | Asian | 4% |
| Hispanic | No/Unknown | 82% |
| | Yes | 18% |
| Diagnoses | Complex Chronic Condition | 14% |
| | Asthma | 13% |
| | Prematurity | 7% |

# Antibiotic Prescribing Rate Differed by Network Partner

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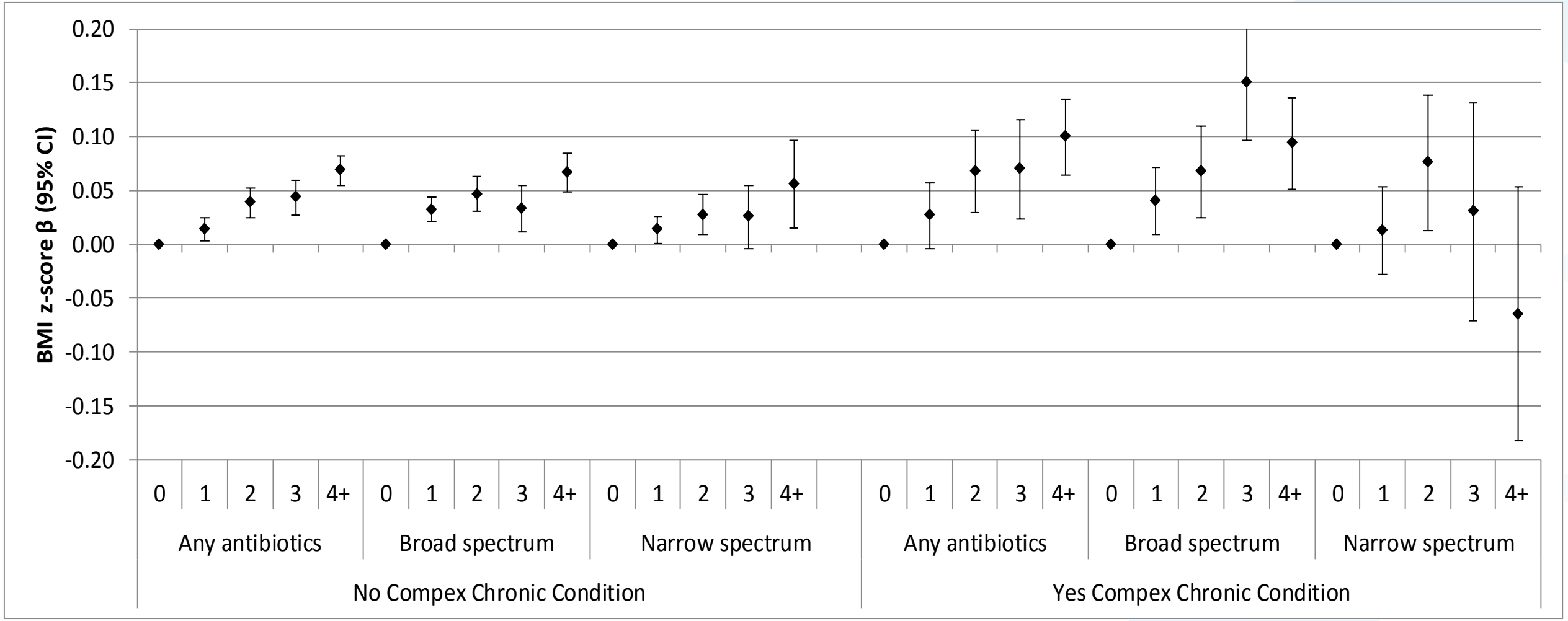
# Results: Multivariable Regression, Any Antibiotics <24 months and BMI z-score Parameter Estimates

| Type of Antibiotic | No Complex Condition | Complex Condition |
|---|---|---|
| All | 0.05 (0.04, 0.06) | 0.07 (0.05, 0.10) |
| Broad | 0.05 (0.04, 0.06) | 0.08 (0.06, 0.10) |
| Narrow | 0.03 (0.02, 0.04) | 0.04 (0.00, 0.07) |

*Adjusted for sex, race, ethnicity, # clinical encounters, steroid use, asthma, prematurity

# Results: Multivariable Regression, Dose Response



# Conclusions

- Limited association between antibiotics in early life and weight outcomes at age 4 to <6 years
- Clinical implication of this likely negligible; population effect uncertain

# Workflow in Aim 1 Aggregate Analysis

**Patient-level analytic dataset stored locally at each data mart**

| Main analysis | Aggregate Analysis |
| --- | --- |
| DataMarts return patient-level analytic dataset above to study team | DataMarts execute a distributed program locally against its analytic data set above |
| Study team pools all the patient-level analytic datasets | DataMarts return requested aggregate output to the study team |
| Study team executes a program against the pooled patient-level dataset to generate effect estimates and 95% CIs | Study team executes a program centrally against the returned aggregate output to generate effect estimates and 95% CIs |

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# Results: Main Analysis vs. Aggregate Analysis – Model 1*

* No complex chronic conditions, binary exposure (any antibiotics <24 months vs. none)

| Select variables | Parameter estimate | | Standard error | | t-value | |
|---|---|---|---|---|---|---|
| | Main | | Main | | Main | |
| Variable 1 | 0.17399 | | 0.04962 | | 3.51 | |
| Variable 2 | 0.04280 | | 0.00496 | | 8.62 | |
| Variable 3 | 0.02114 | | 0.00435 | | 4.86 | |
| Variable 4 | -0.22029 | | 0.00940 | | -23.45 | |

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| Variable 4 | -0.22029 | -0.22029 | 0.00940 | 0.00940 | -23.45 | -23.45 |

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| Variable 4 | -0.22029 | -0.22029 | 0.00940 | 0.00940 | -23.45 | -23.45 |

**Maximum difference in all 39 variables in the model: 3.8906E-10**

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# Summary of Findings from the Other 11 Models

- Results are highly comparable
- Estimates from aggregate analysis differed from estimates in the main analysis at the 10$^{th}$ decimal place or further

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# **Aim 2 Analysis:** Antibiotics Use & childhood weight trajectories

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# Trajectory Analysis Objectives

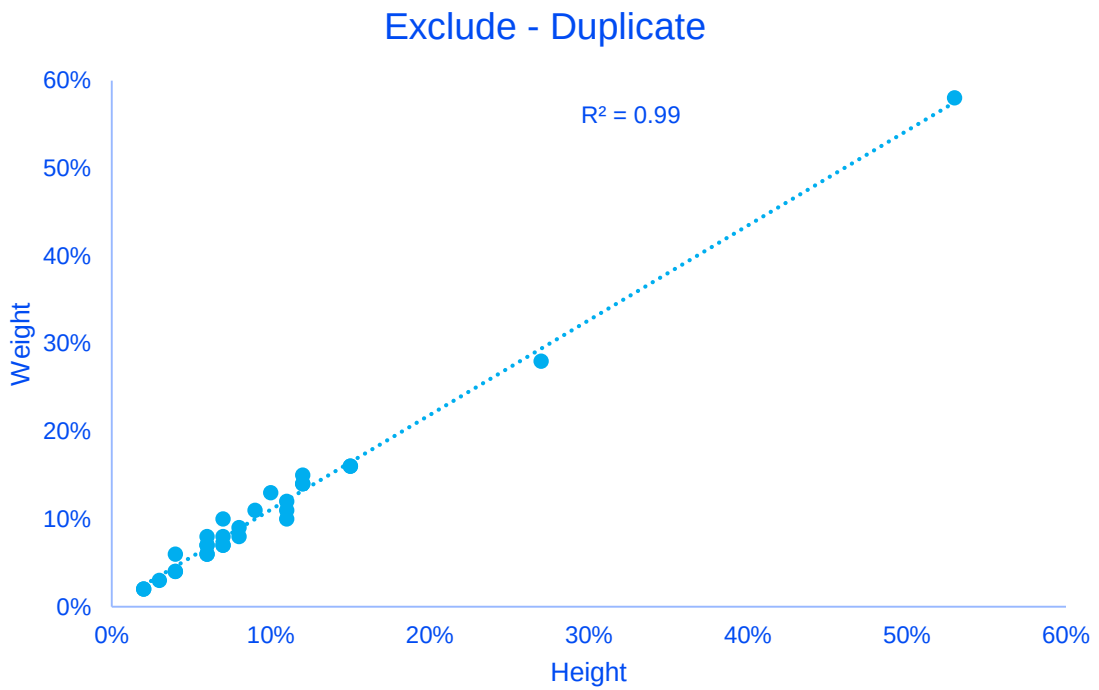
- Assess age-sex-height standardized weight trajectory over several years following antibiotic exposure ≤2 years

- Examine age-sex-height standardized weight trajectory immediately following antibiotic administration

# Ht/Wt Data Quality Assessment

- CDC thresholds for Biologically Implausible Values (identical to Aim 1)
  - Retained 96% (ht) / 99% (wt) as plausible measurements
- Longitudinal (within-person) errors – Daymont *et al*. 2017
  - Probable unit conversion errors
  - Probable reuse of existing values
  - Outliers within an individual's trajectory
  - Inconsistency between height and weight

# Error Correlation by Data Source





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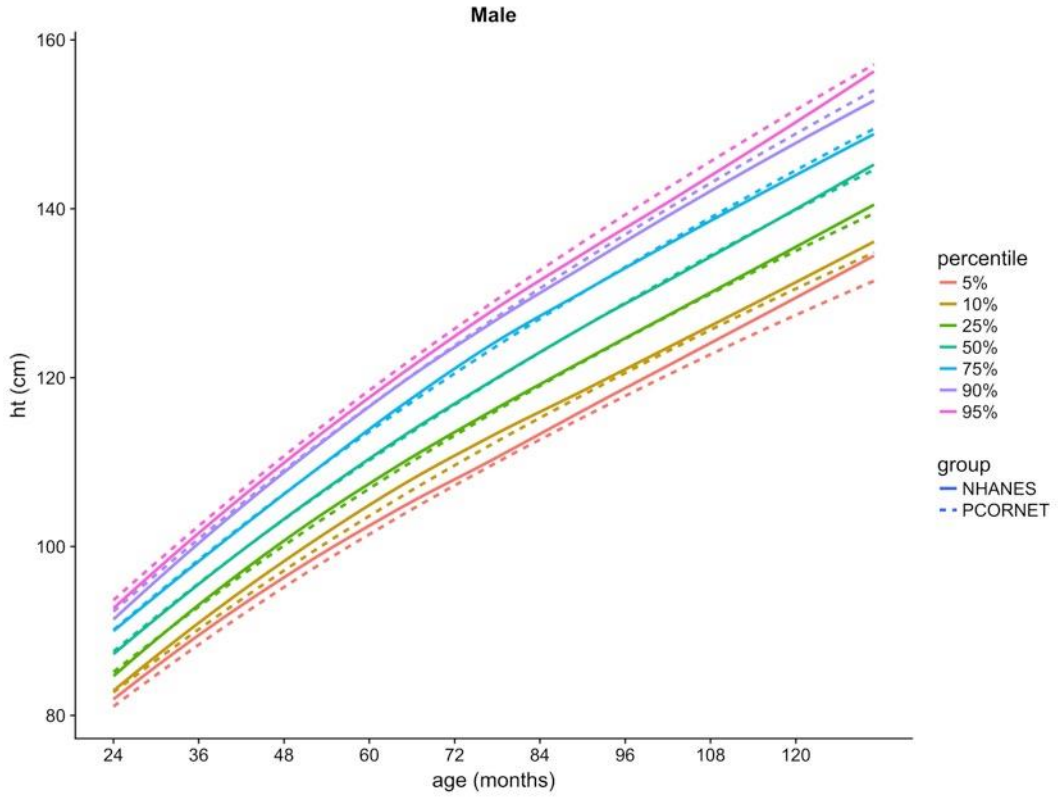
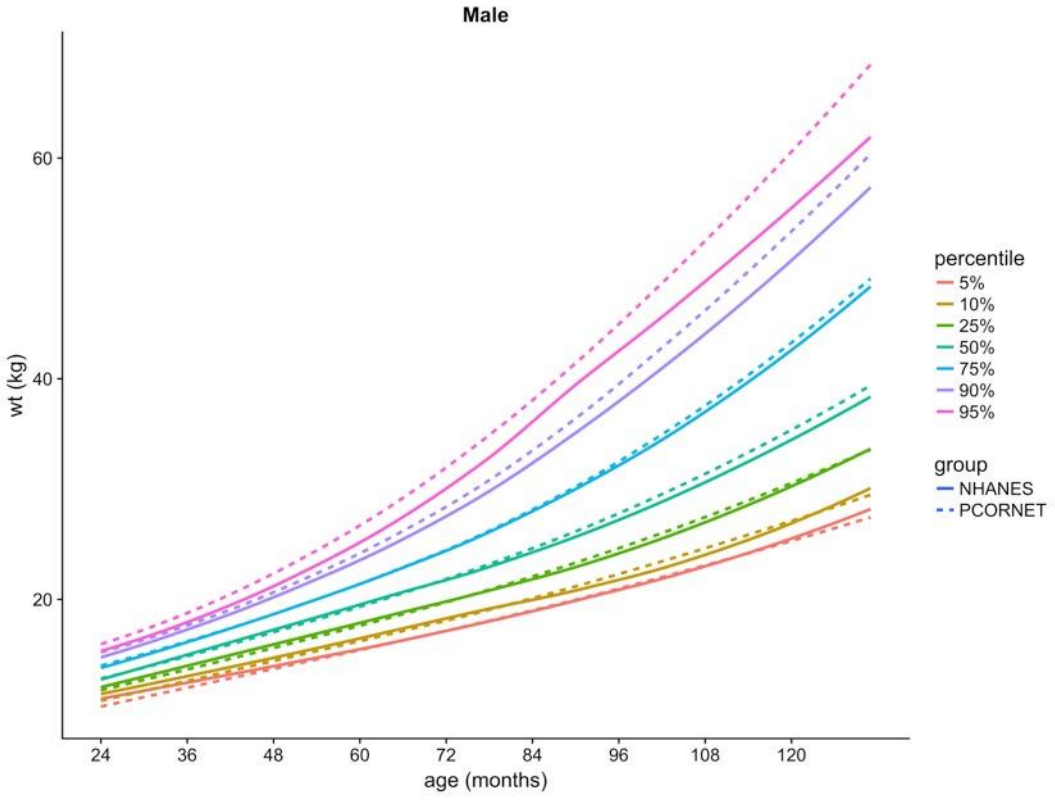
# NHANES 2009-14 Comparison

## Height




## Weight

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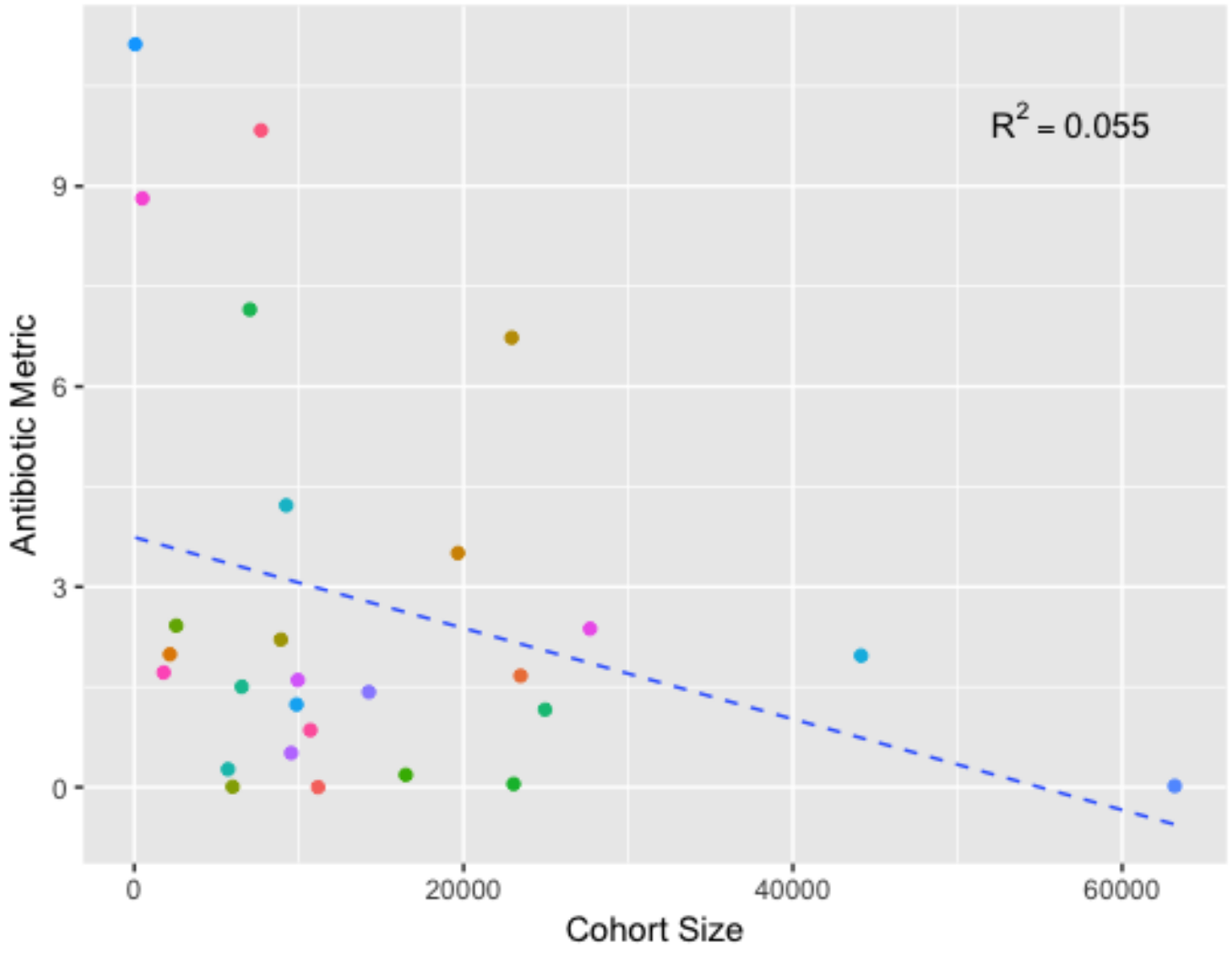
# Drug Exposure DQA

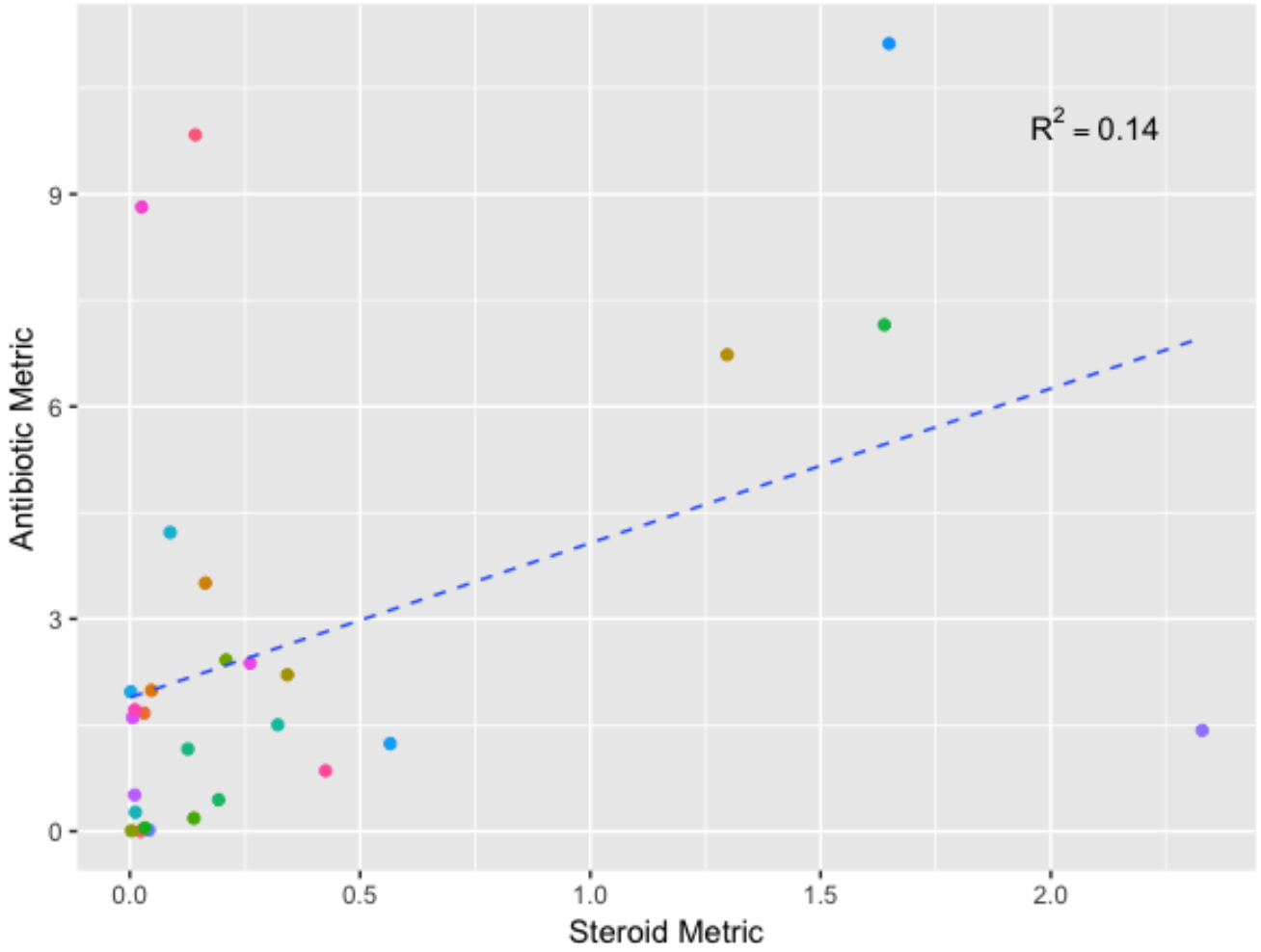
- Average abx rate for population (51%) has face validity
  - Small variations likely represent practice patterns
  - Large variations more likely to represent data collection problem or non-representative population

- Measure data quality as distance from the mean

# Drug Exposure DQA



# Drug Exposure DQA



| Aim 2 Cohort Selection | n | Loss | Retained % |
|---|---|---|---|
| # of unique patients in PCORnet dataset | 683,485 | – | – |
| 2 + plausible height and weight > 24 mos with Height/ Weight <30 days apart | 682,162 | 1,323 | 99.1 |
| >=2 Height/ Weight >=6 mos apart in outcome window | 497,324 | 186,161 | 72.76 |
| Longitudinal Data Cleaning | 489,792 | 193,693 | 71.66 |
| Data Quality Assessment | **445,700** | 237,785 | 65.21 |

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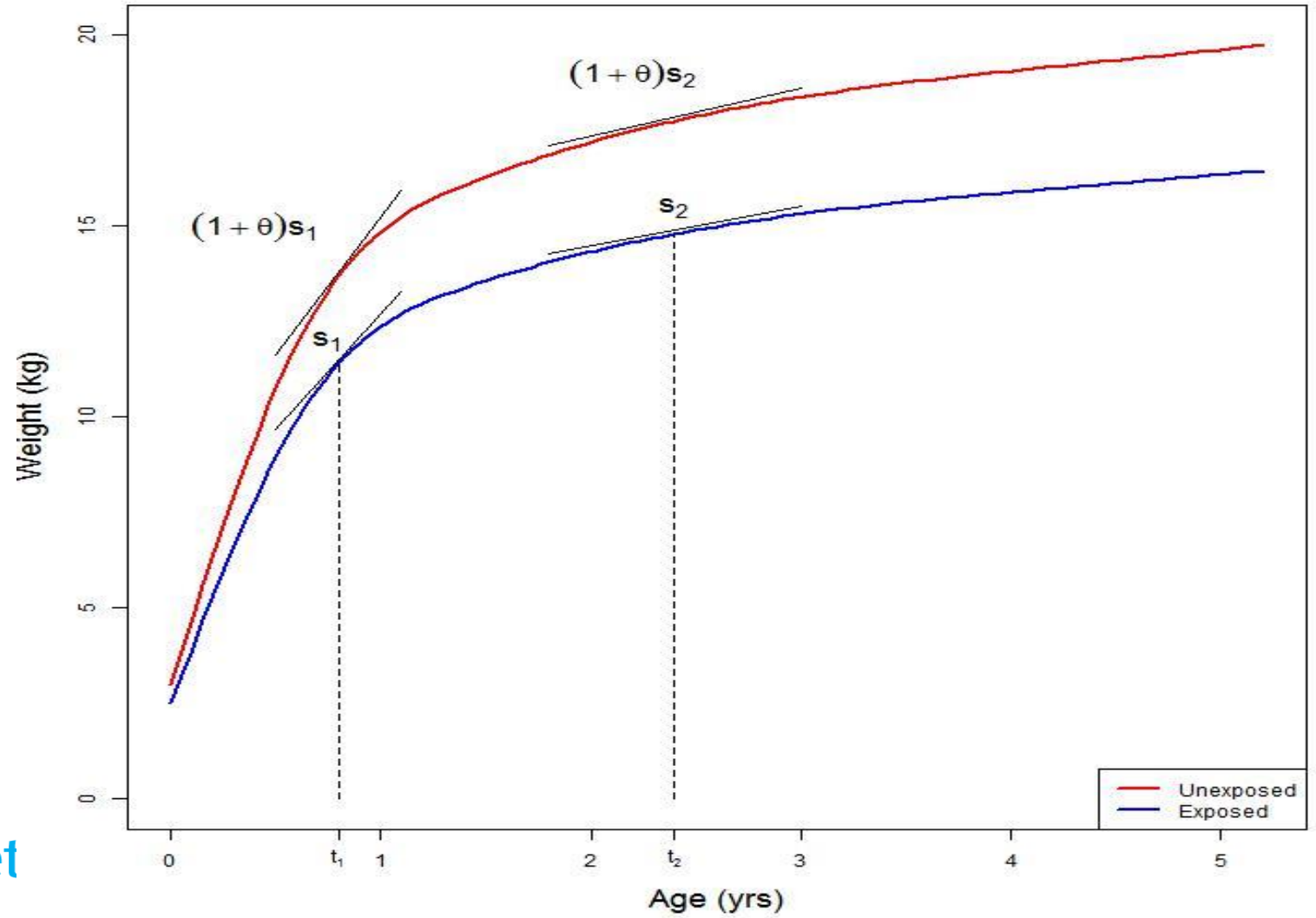
# Approach

- Longitudinal Rate Regression (LRR)
  - Non-linear model
    - General function for longitudinal trajectories e.g. regression splines
  - Proportional Rate Assumption
    - Characterizes differences in rates of change as a percentage relative to a reference group
  - Account for confounders
    - Mean Level
    - Rate Level

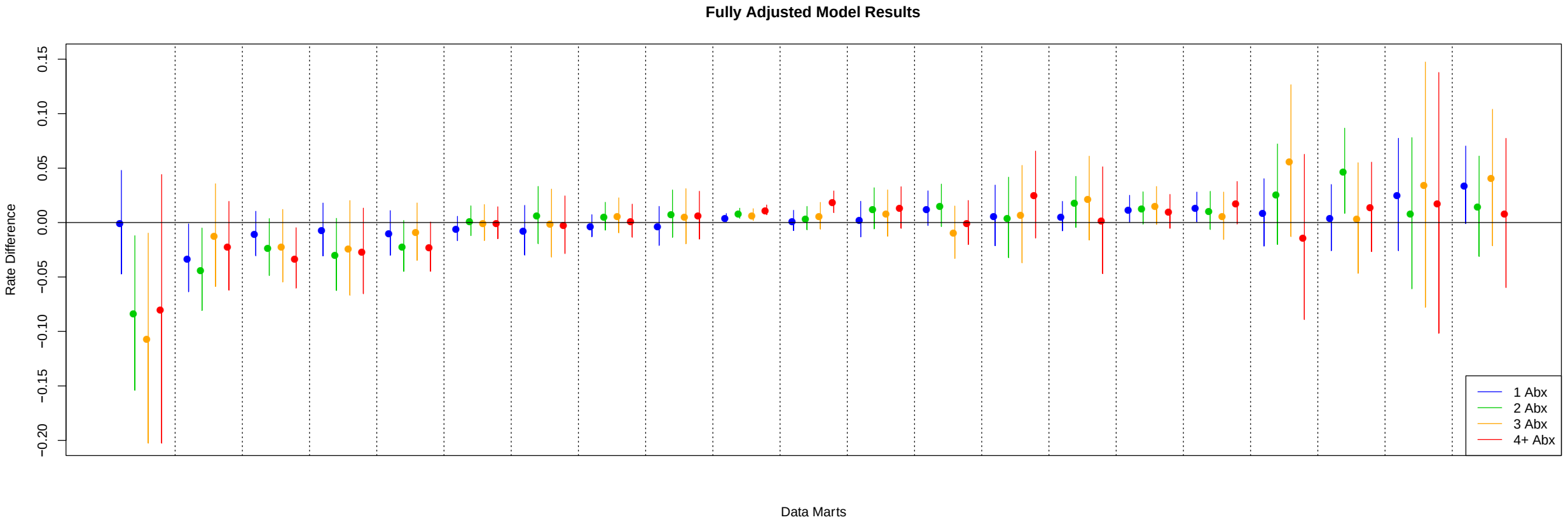
# Proportional Rate Assumption



# Fully adjusted models controlled for:

- Sex
- Height
- Race/Ethnicity
- Asthma
- Oral Steroids (0,1,2,3,4+)
- Anti-Reflux Medications (0,1,2,3,4+)
- Infectious Visits (0,1,2,3,4+)
- Chronic Condition
- Preterm

# Rate Δ – Count of Antibiotic Episodes



# Conclusions

- Significant variability across network partners in data quality
- Impact of any antibiotic exposure small, though detectable
- Adjustment for clinical covariates centers variation, but does not change range
- Analysis incorporating degree of exposure ongoing
- Follow-on analyses for short-term effects

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# Aim 3: Maternal-Child Linkage Analysis

*Led by Bill Heerman (Vanderbilt), Jason Block (HPHC), Matt Daley (PORTAL), Janne Boone-Heinonen (ADVANCE)*

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# Maternal-Child Linkage Aim

- Examine association of maternal antibiotics during pregnancy and child weight outcomes at age 4 to <6 yrs
- Re-examine child antibiotics and weight association, incorporating specified maternal covariates
  - Pre-pregnancy BMI and gestational weight gain
  - Diabetes and gestational diabetes
  - Maternal smoking status
- 7 sites participating

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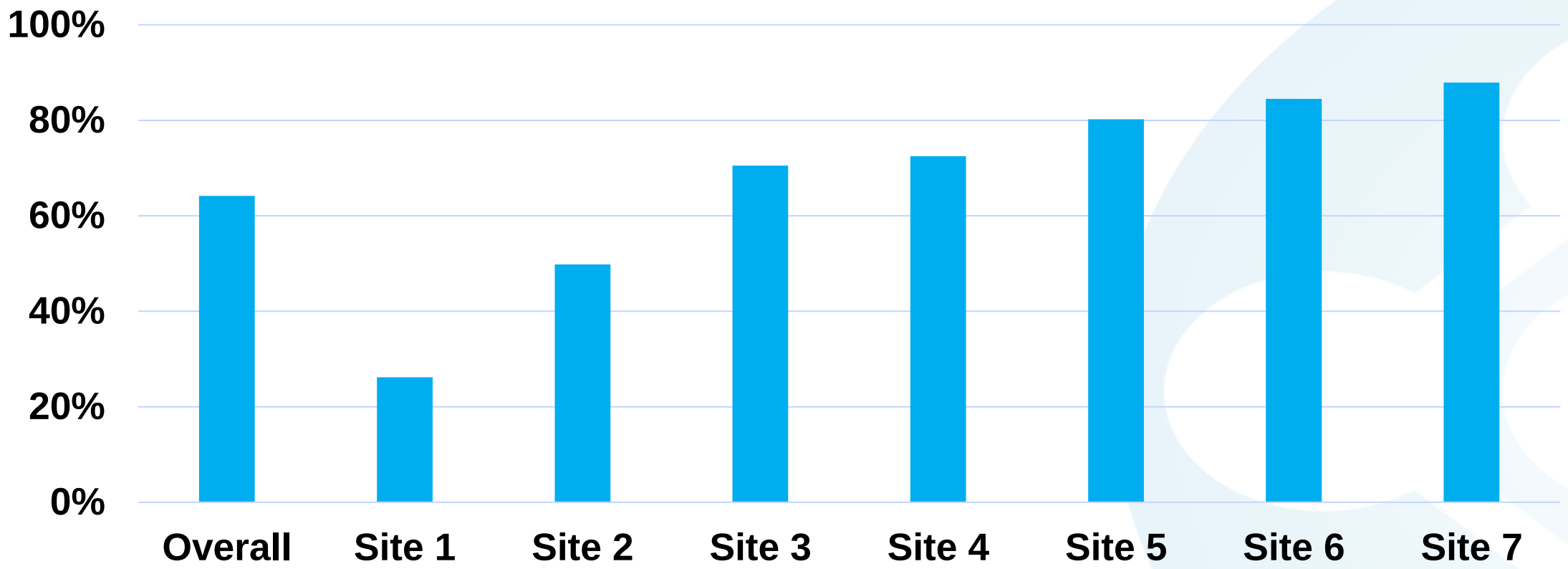
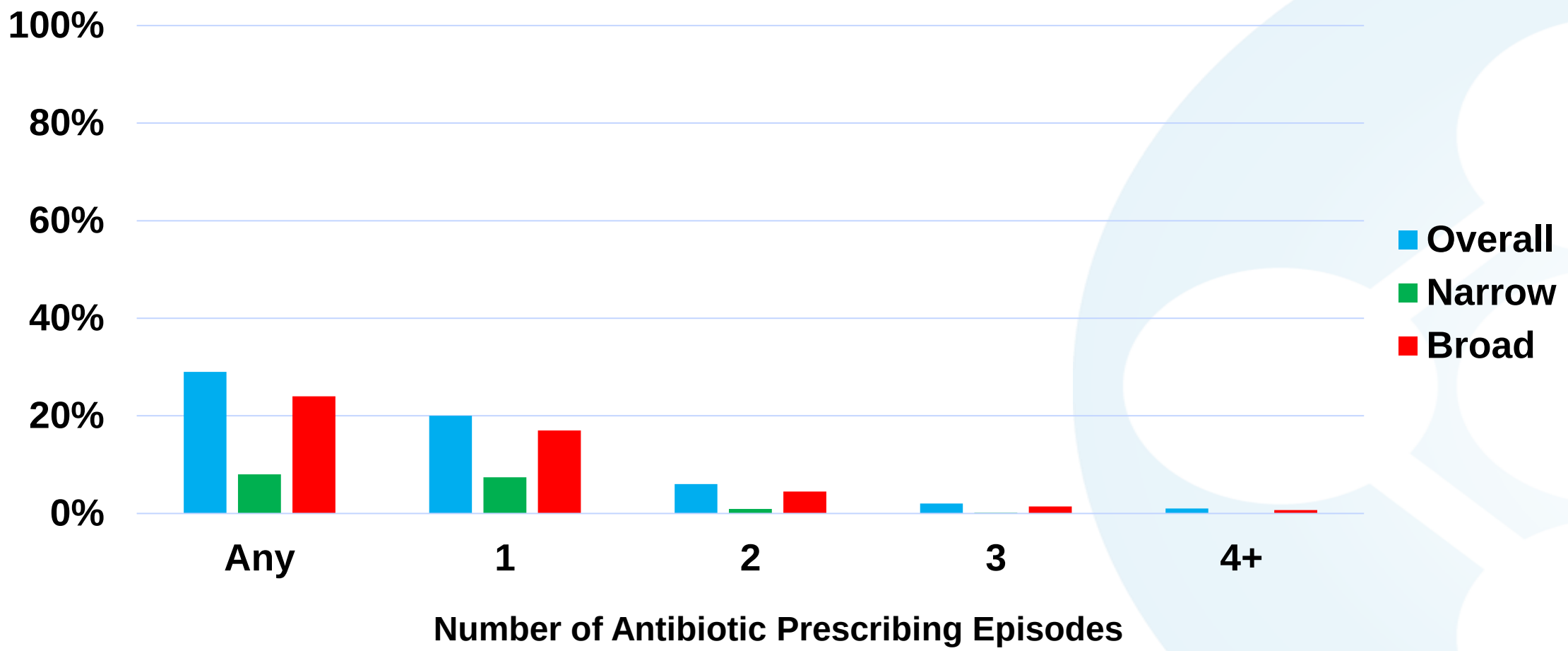
# Ancillary Table Elements Captured During Linkage

| All Sites | Most but Not All Sites |
|---|---|
| Pre-pregnancy BMI | Type of delivery |
| Gestational weight gain | Smoking during pregnancy |
| Gestational diabetes | Infant birth weight* |
| Antibiotics during pregnancy | Gestational age at birth* |

# Percentage of Linked Mother-Child Pairs



# Maternal Antibiotics During Pregnancy

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# Results: Abx During Pregnancy on Child BMI z-score at 4 to <6 years

| | Parameter Est. | 95% CI |
|---|---|---|
| Any Antibiotics | 0.00 | -0.03, 0.03 |
| 1 course | 0.00 | -0.03, 0.04 |
| 2 courses | -0.02 | -0.08, 0.03 |
| 3 courses | -0.06 | -0.14, 0.03 |
| 4+ courses | 0.03 | -0.09, 0.14 |
| Any Broad | 0.00 | -0.03, 0.03 |
| Any Narrow | -0.01 | -0.07, 0.05 |

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**Fully adjusted models, controlling for all maternal and child covariates

# **Qualitative Aim:** Parent and Provider Assessments of Antibiotics and Obesity Risk

*Research and analysis completed by: Ellen A. Lipstein, MD MPH; Bill Heerman, MD, MPH; Cassandra Dodds; J. Kiely Law; Douglas Lunsford; Paula Winkler; Jonathan A. Finkelstein, MD, MPH*

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# Study Purpose

- Understand parents' and providers' beliefs about risks and benefits of antibiotic use
- Explore how a potential risk of future obesity would be perceived and integrated into parents' and providers' decision making

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# Summary of Qualitative Findings

- In setting of acute illness for their children, the long-term impact of obesity is not a major factor in parent or physician decision making.
- Parents/providers are pretty skeptical about an abx-weight association; would need to see huge effects to consider it.
- Differences in assessments of risk and benefit are wide – maybe hard to overcome for any small risk factor.

# PCORnet Opportunities

- Data quality improved in short time – still relatively early days but felt confident in final data (as did bariatric team)
- Need to assess data on a study-by-study basis, perhaps before grants go in, to decide which sites to include
- Opportunities for important studies moving forward - Patient-Centered Research Foundation will drive research focus and sustainability
- Academic model creates complexity – how to pay on soft money model and give academic recognition for multi-institutional research

# Thanks to the 28 Participating Network Partners, 36 Healthcare Institutions

Boston Medical (ARCH)
Wake Forest (ARCH)
ADVANCE
OneFlorida
Greenway (Mid-South)
UNC (Mid-South)
Vanderbilt (Mid-South)
Baylor Univ (REACHnet)
Ochsner Clinic (REACHnet)
Tulane (REACHnet)

PEDSnet (PEDSnet)
Cincinnati Childrens (PEDSnet)
Denver Health (PORTAL)
KP Washington (PORTAL)
Health Partners (PORTAL)
KP Colorado (PORTAL)
KP Mid-Atlantic (PORTAL)
KP Northwest (PORTAL)
NYC-CDRN

Marshfield Clinic (GPC)
Medical College of WI (GPC)
Univ of Iowa (GPC)
UT San Antonio (GPC)
Loyola Medicine (CAPriCORN)
Lurie Childrens (CAPriCORN)
North Shore (CAPriCORN)
Rush Univ (CAPriCORN)
Univ of Chicago (CAPriCORN)

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# Thank You!

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