Introduction to target trial emulation to improve causal inference in pediatric and perinatal epidemiology

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Road map

+ Overview of target trial emulation
+ Introduce worked exampled:
  -Antibiotics and preterm birth, based Caniglia et al 2023
+ Code demonstration based on simulated data
+ Additional resources on Github:
  -simulated data and R code
  -suggested readings
  -target trial emulation protocol

In reproductive and perinatal epidemiology, we are often interested in interventions to improve health outcomes

- Medication use
  - Anti-depressant or anti-anxiety medications
  - Medication to manage other chronic conditions
- Vaccines
  - Flu vaccine
  - COVID-19 vaccine
- Behavioral strategies
  - Diet and exercise interventions to limit gestational weight gain or manage gestational diabetes

How should we evaluate interventions in pregnancy?

+ Randomized controlled trial

How should we evaluate interventions in pregnancy?

- Randomized controlled trial
- **Challenge**: not all interventions can be safely randomized in pregnancy
- **Challenge**: not all interventions can feasibly be randomized in pregnancy

How should we evaluate interventions in pregnancy?

- Randomized controlled trial
- **Challenge**: not all interventions can be safely randomized in pregnancy
- **Challenge**: not all interventions can feasibly be randomized or studied in pregnancy
- Often, in repro/perinatal epi must **rely on observational data** to evaluate interventions

Target Trial Emulation Framework

- Framework for thinking about how we can try to answer a causal question in observational data
- Not unique to perinatal and pediatric epidemiology, can be applied to any causal question in epidemiology
- Very useful in helping us think explicitly about our question, how best we can answer it in observational data, and avoiding self-inflicted biases common in repro/perinatal epi

Target Trial Emulation Framework

- **Step 1:** Identify a causal question of interest
- **Step 2:** Specify a hypothetical randomized trial to answer that question (the **target trial**)
- **Step 3:** Emulate (as close as possible) that analysis in observational data (the **target trial emulation**)

Specifying a target trial and target trial emulation:

Start with a protocol

Protocol Template			
Protocol Component	**Description**	**Target Randomized Trial**	**Target Trial Emulation**
Eligiblity criteria	Who will be eligible for inclusion in the study?		
Treatment or intervention strat	What intervention or treatment will eligible persons receive?		
Treatement assignment	How will elgible persons be assigned to the intervention or treatment?		
Outcome	What outcome in eligible persons will be compared among intervention or treatment groups?		
Follow-up	When will you start following eligible persons in the study and for how long will they be followed?		
Estimand	What counterfactual contrasts will be estimated using the data?		
Statisticaly Analysis	How will the counterfactual contracts be estiamted?		

How can target trial emulation help us in repro/perinatal epi?

+ Avoid self-inflicted biases due to:

  1. Immortal time bias → example**:** misalignment between exposure ascertainment and the start of follow up

  2. Selection bias → example**:** due to early pregnancy loss

An Example: antibiotic use in pregnancy and preterm birth

- **Worked example paper**: Caniglia et al. Emulating Target Trials to Avoid Immortal Time Bias – An Application to Antibiotic Initiation and Preterm Delivery. Epidemiology, 34:3, 2023.

  -Sample code and data is simulated based on this paper (results will not match exactly)

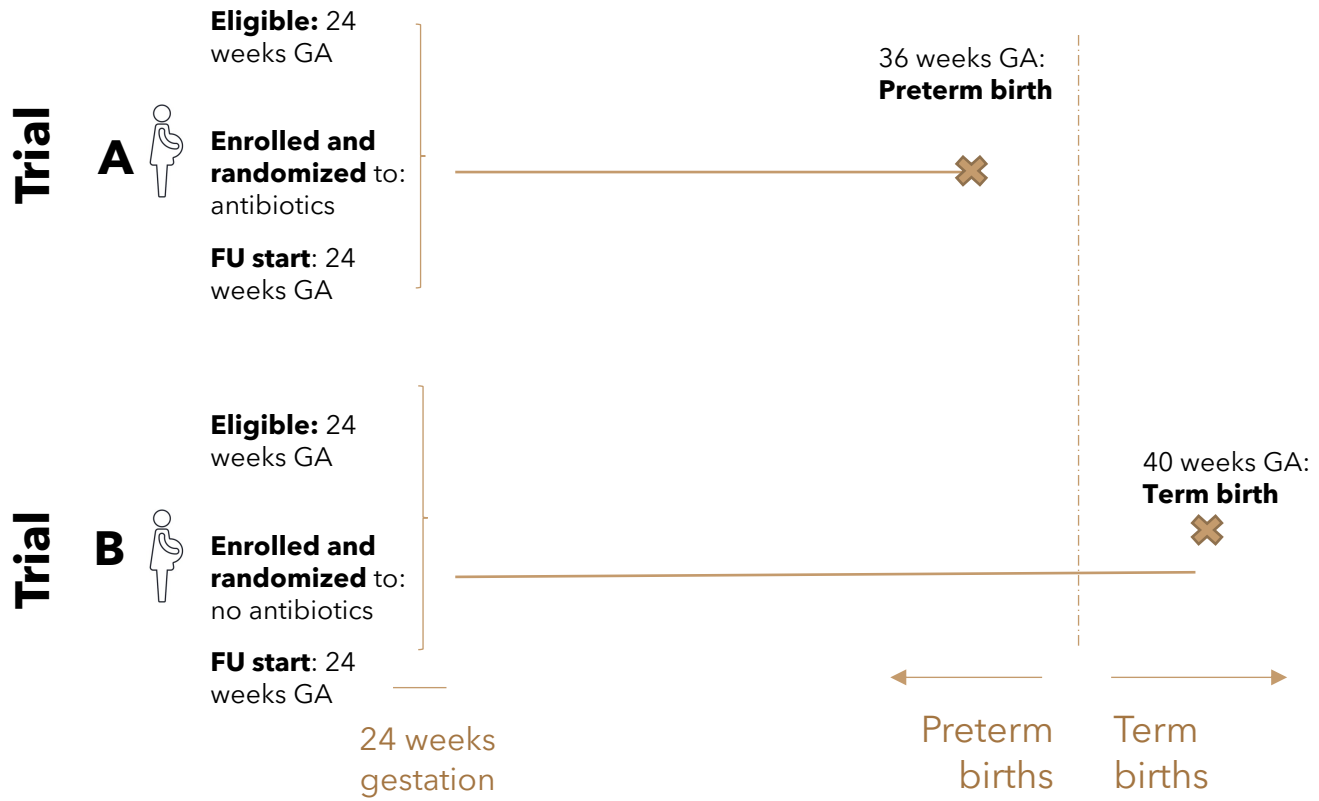
- **Causal question**: What is the effect of antibiotic initiation at 24 weeks gestation on preterm birth?

Let's walk through the specifying the protocol together…

Protocol Component	Description	Target Trial
Eligibility criteria	Who will be eligible for inclusion in the study?	Pregnant people who present to antenatal care before 24 weeks gestation with a singleton pregnancy and who have no used antibiotics before 24 weeks
Treatment strategy	What intervention or treatment will eligible persons receive?	1) Initiate antibiotics between 24- and <25-weeks gestation 2) Do not initiate antibiotics between 24- and <25-weeks gestation
Treatment assignment	How will eligible persons be assigned to the intervention or treatment?	Randomized at 24 weeks gestation
Outcome	What outcome in eligible persons will be compared among intervention or treatment groups?	Preterm birth, delivery <37 weeks gestation
Follow-up	When will you start following eligible persons in the study and for how long will they be followed?	Follow-up from enrollment at 24 weeks gestation to 1) delivery or 2) 37 weeks gestation; whichever comes first
Estimand	What counterfactual contrasts will be estimated using the data?	Intention to treat (effect of being randomized to start antibiotics versus not)
Statical Analysis	How will the counterfactual contracts be estimated?	Log-binomial model to estimate a risk ratio for the effect of treatment strategy on preterm delivery

Based on Caniglia et al. Emulating Target Trials to Avoid Immortal Time Bias – An Application to Antibiotic Initiation and Preterm Delivery. Epidemiology, 34:3. 2023.

Question: What is the effect of antibiotic initiation vs not at 24 weeks gestation on preterm birth?



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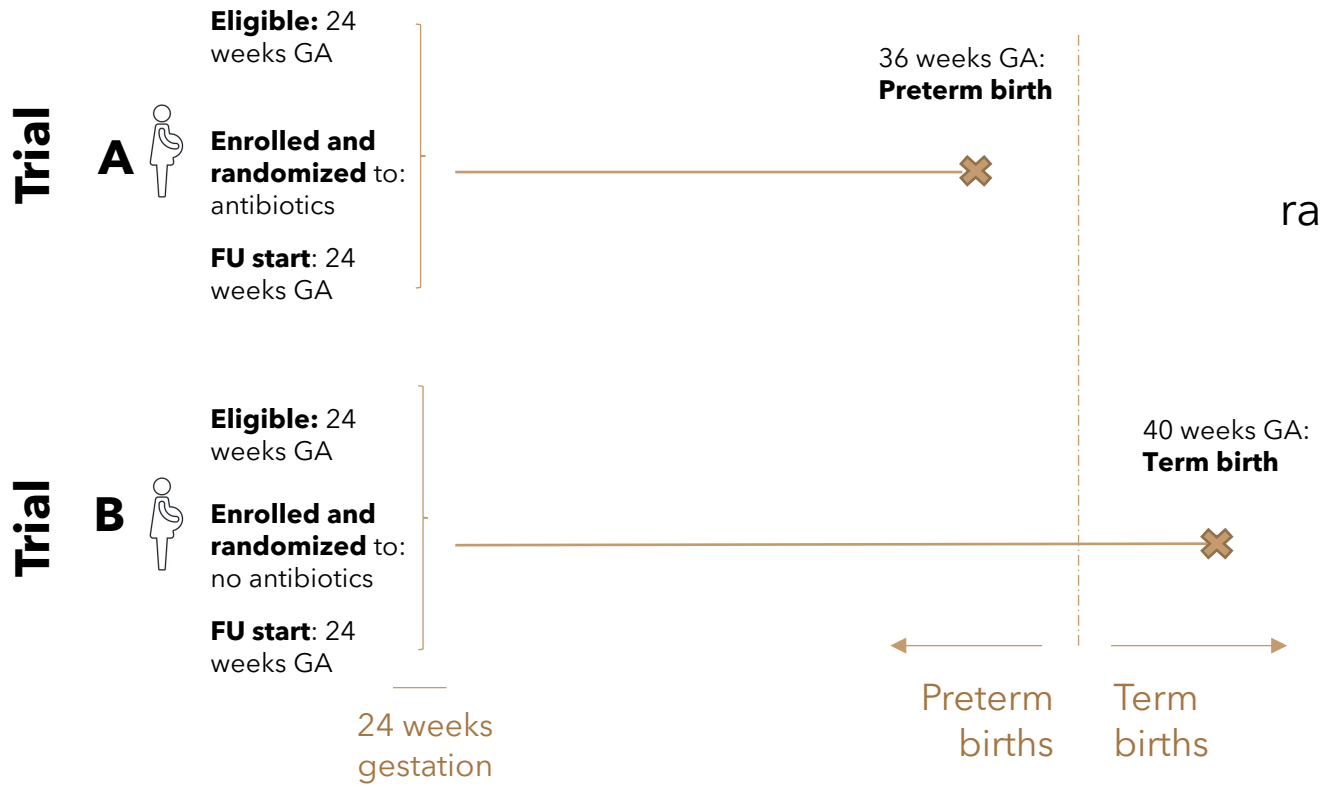


Important:
Eligibility, enrollment & randomization, and start of follow up are all aligned at time zero

*"**As a rule,** in causal analyses of both randomized trials and observational data, each participant's time zero must be the time when they meet the eligibility criteria (enrollment) and are assigned to a treatment strategy. This rule is automatically enforced in randomized trials."*

Hernan, NEJM 2021

We want to emulate this target trial in observational data:

- What is the effect of initiating antibiotic treatment vs not at 24 weeks gestation in an observational cohort?
- We run into a problem: very few people initiate antibiotics at 24 weeks.
- So, we decide to expand our exposure window and change our casual question.

Revised Question 1: What is the effect of antibiotic initiation at any point vs not between 24 and 36 weeks gestation on preterm birth?

Observational

Treatment ascertainment: start antibiotics at 28 weeks GA

FU start: 24 weeks GA

40 weeks GA: **Delivery**

Exposure definition: antibiotic initiation at any point between 24- and 36-weeks gestation

Start of FU: 24 weeks (loss <24 weeks is a miscarriage)

Revised Question 1: What is the effect of antibiotic initiation at any point vs not between 24 and 36 weeks gestation on preterm birth?

Observational

Treatment ascertainment: start antibiotics at 28 weeks GA

FU start: 24 weeks GA

40 weeks GA: **Delivery**

Problem: Start of follow-up and treatment ascertainment are **NOT** aligned

Self-inflicted bias #1: **immortal person time** - we include time before the person was exposed and at risk of a subsequent outcome

Revised Question 1: What is the effect of antibiotic initiation at any point vs not between 24 and 36 weeks gestation on preterm birth?

Observational

Treatment ascertainment: start antibiotics at 28 weeks GA

FU start: 28 weeks GA

40 weeks GA: **Delivery**

Solution: This can be **avoided** by aligning treatment ascertainment and the start of follow-up.

Tradeoff: Participant's start of follow-up will vary depending on when they initiate antibiotic treatment and may not cover the full risk period for preterm birth (from 24 weeks).

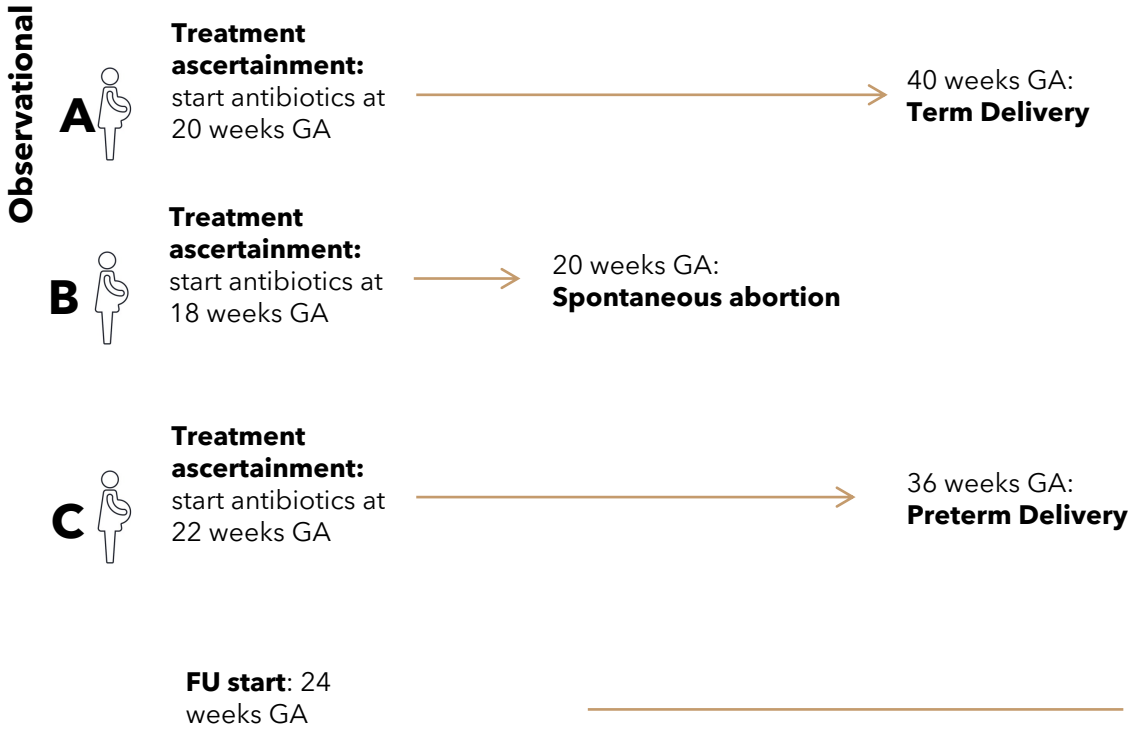
We'd be comparing antibiotic initiators at any time from 24 to 36 weeks gestation to people who did not initiate antibiotics during the entire risk period for preterm birth.

Revised Question 2: What is the effect of antibiotic initiation before 24 weeks gestation on preterm birth?

Exposure definition: antibiotic initiation versus no antibiotic initiation before 24 weeks gestation.

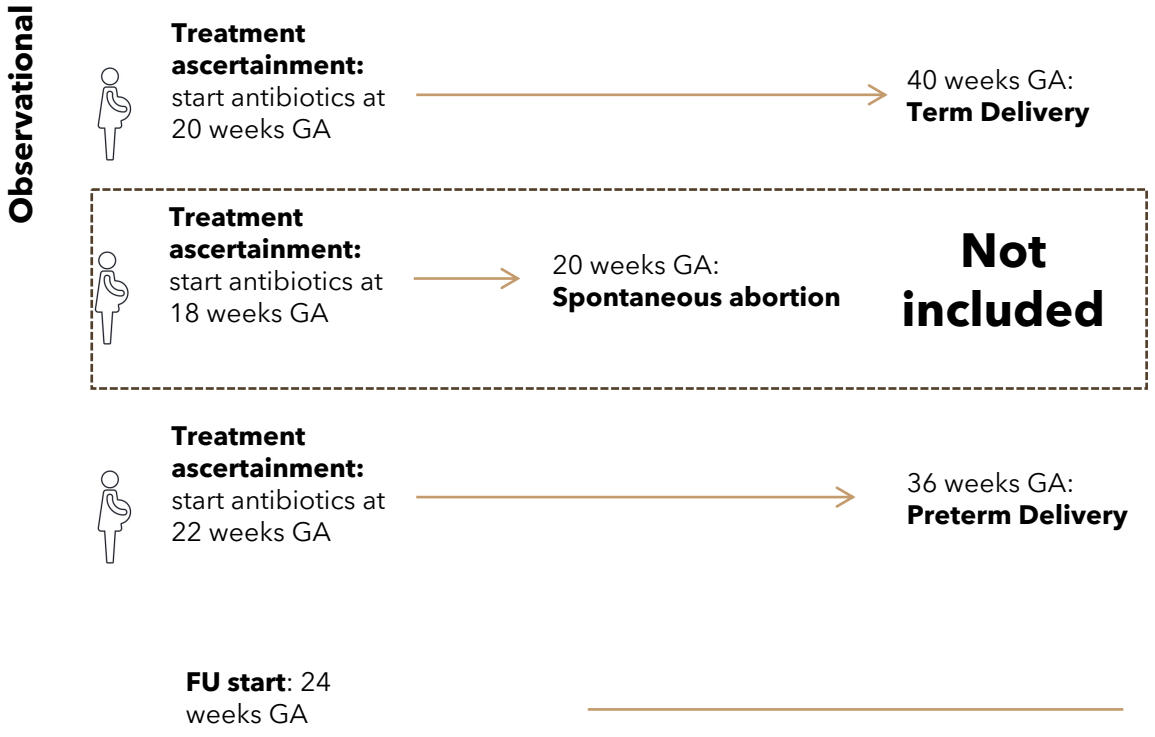
Start of FU: 24 weeks (loss <24 weeks is a miscarriage)

Revised Question 2: What is the effect of antibiotic initiation before 24 weeks gestation on preterm birth?



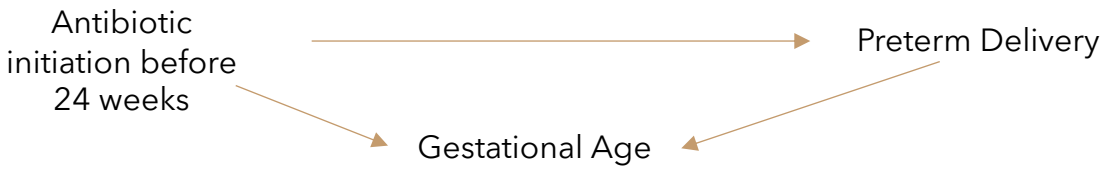
Problem: Start of follow-up and treatment ascertainment are **NOT** aligned.

Revised Question 2: What is the effect of antibiotic initiation before 24 weeks gestation on preterm birth?



Self-inflicted bias #2 - selection bias
due to miscarriage

A simple DAG



An Example: antibiotic use in pregnancy and preterm birth

- **Worked example paper**: Caniglia et al. Emulating Target Trials to Avoid Immortal Time Bias – An Application to Antibiotic Initiation and Preterm Delivery. Epidemiology, 34:3, 2023.

- **Causal question**: What is the effect of antibiotic initiation at 24 weeks gestation on preterm birth?

Target Trial Emulation

Observational Data Source:

+ Tsepamo Study
+ Ongoing birth outcomes surveillance study in Botswana
+ Covers up to 18 government hospitals
+ Includes information on prenatal care and delivery outcomes for live births and stillbirths from 2014-2021

Target Trial Emulation Protocol

Protocol Component	Description	Target Trial	Target Trial Emulation
Eligibility criteria	Who will be eligible for inclusion in the study?	Pregnant people who present to antenatal care before 24 weeks gestation with a singleton pregnancy and who have no used antibiotics before 24 weeks	Same, except individuals without a date of antibiotic initiation are excluded
Treatment strategy	What intervention or treatment will eligible persons receive?	1) Initiate antibiotics between 24- and 25-weeks gestation 2) Do not initiate antibiotics between 24- and 25-weeks gestation	Same
Treatment assignment	How will eligible persons be assigned to the treatment?	Randomized at 24 weeks gestation	Treatment ascertainment based on observed data at 24 weeks gestation
Outcome	What outcome in eligible persons will be compared among treatment groups?	Preterm birth, deliver <37 weeks gestation	Same
Follow-up	When will you start following eligible persons in the study and for how long will they be followed?	Follow-up from enrollment at 24 weeks gestation to 1) delivery or 2) 37 weeks gestation; whichever comes first	Same
Estimand	What counterfactual contrasts will be estimated using the data?	Intention to treat (effect of being randomized to initiate antibiotics versus not)	Observational analogue of intention to treat (effect of initiating antibiotics versus not)
Statical Analysis	How will the counterfactual contracts be estimated?	Log-binomial model to estimate a risk ratio for the effect of treatment strategy on preterm delivery	Log binomial models adjusted for confounders (see paper for list)

Based on Caniglia et al. Emulating Target Trials to Avoid Immortal Time Bias – An Application to Antibiotic Initiation and Preterm Delivery. Epidemiology, 34:3. 2023.

When one target trial isn't enough

- Our trial criteria implies that we will be comparing people initiating antibiotics versus not at 24 weeks gestation.
- In practice, not many people will initiate antibiotics within that narrow window, making our question possibly infeasible and not very generalizable.
- To look at treatment strategies or exposures over time, we can consider multiple target trials.

Sequential target trial emulation

Goal: To estimate the effect of initiating antibiotic treatment from 24-36 weeks gestation (the last week someone is eligible for a preterm birth) on preterm birth

Solution: Emulate a target trial for each eligible week of gestational age (n=13), and then consider pooling the individual estimates

Sequential target trial emulation

For **each** sequential target trial emulation (n=13):

- **Eligible:** individuals are those that have not previously initiated antibiotics and remain pregnant at the start of that week
- **Estimate:** compares those who initiate antibiotics during that week with those who do not initiate antibiotics, followed until delivery or 37 weeks gestation
- **Analysis**: fit a separate log-binomial regression model to estimate the RR for preterm delivery by treatment strategy, adjusted for covariates (13 RRs, 1 for each week of gestation)

Target Trial Emulation Protocol: k=gestational age 24-36

Protocol Component	Description	Target Trial	Target Trial Emulation
Eligibility criteria	Who will be eligible for inclusion in the study?	Pregnant people who present to antenatal care before **k** weeks gestation with a singleton pregnancy and who have no used antibiotics before **k** weeks	Same, except individuals without a date of antibiotic initiation are excluded
Treatment strategy	What intervention or treatment will eligible persons receive?	1) Initiate antibiotics between **k and <k+1** weeks gestation 2) Do not initiate antibiotics between **k and <k+1** weeks gestation	Same
Treatment assignment	How will eligible persons be assigned to the treatment?	Randomized at **k** weeks gestation	Treatment ascertainment based on observed data at **k** weeks gestation
Outcome	What outcome in eligible persons will be compared among treatment groups?	Preterm birth, deliver <37 weeks gestation	Same
Follow-up	When will you start following eligible persons in the study and for how long will they be followed?	Follow-up from enrollment at **k** weeks gestation to 1) delivery or 2) 37 weeks gestation; whichever comes first	Same
Estimand	What counterfactual contrasts will be estimated using the data?	Intention to treat (effect of being randomized to initiate antibiotics versus not)	Observational analogue of intention to treat (effect of initiating antibiotics versus not)
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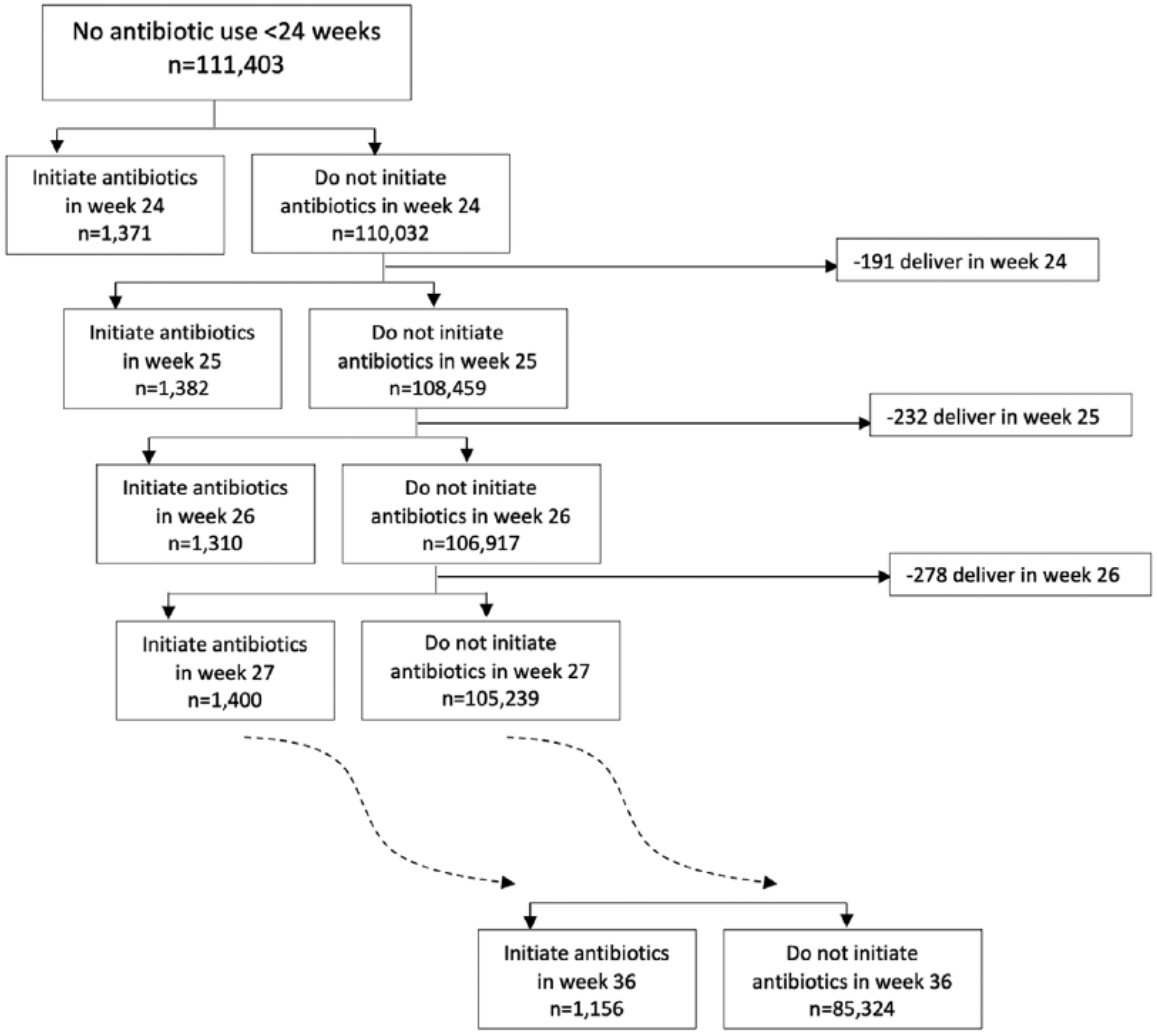

FIGURE 1. Abbreviated flow chart of target trials of antibiotic initiation at each week, 24-36 weeks gestation (complete flow chart is shown in eFigure 1; http://links.lww.com/EDE/C17).

Eligibility for Week 24 trial:
Those that have not previously initiated antibiotics before 24 weeks and remain pregnant at the start of week 24

Eligibility for Week 25 trial:
Those that have not previously initiated antibiotics before 25 weeks and remain pregnant at the start of week 25 (people who delivered in week 24 are excluded)

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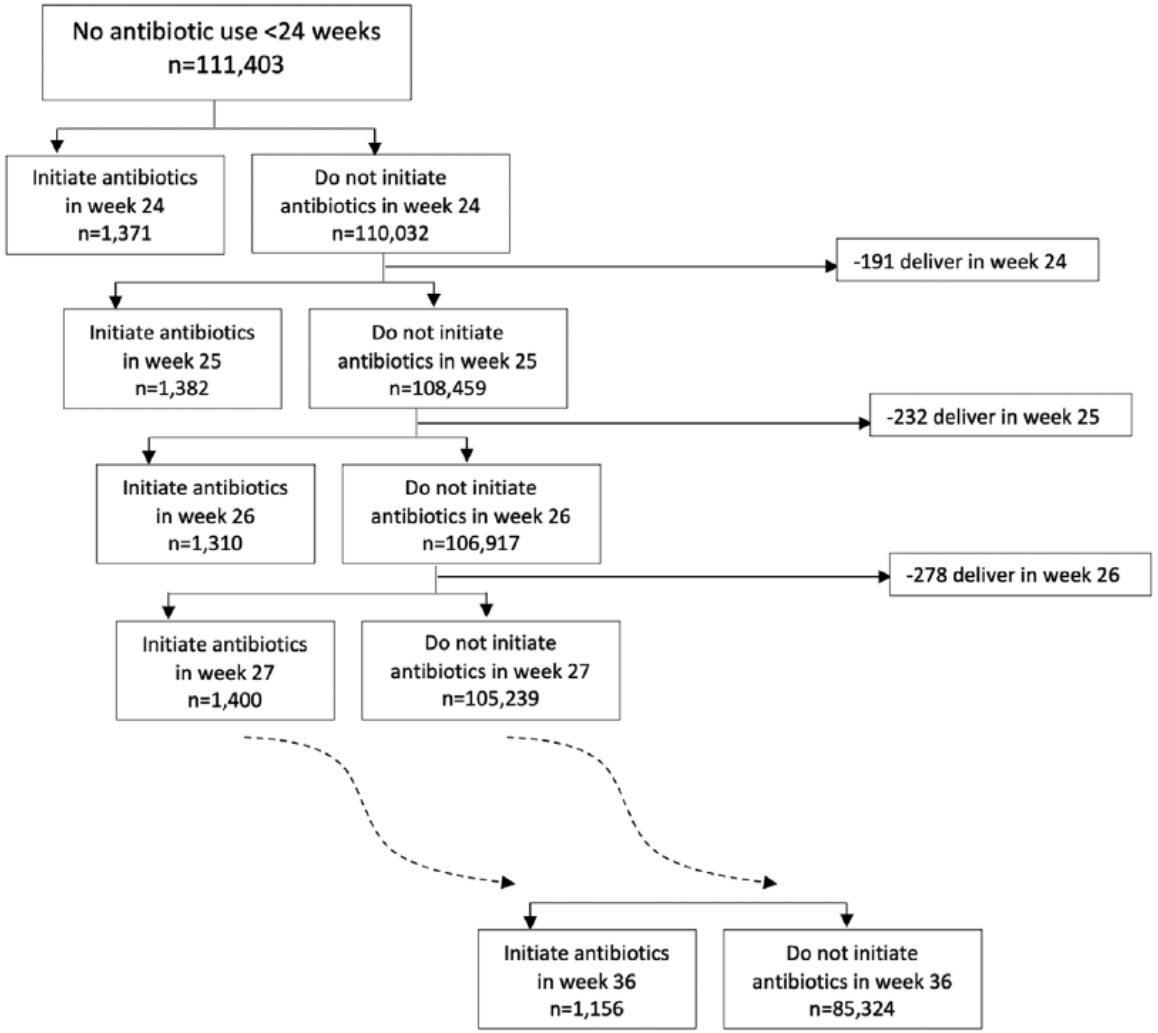

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Those that have not previously initiated antibiotics before 25 weeks and remain pregnant at the start of week 25 (people who delivered in week 24 are excluded)

Participants can contribute data to multiple target trials while they are unexposed and remain pregnant.

Once a person is exposed, that is the last target trial they contribute data to (since they would no longer meet the eligibility criteria for the next target trial).

From Caniglia et al. Emulating Target Trials to Avoid Immortal Time Bias – An Application to Initiation and Preterm Delivery. Epidemiology, 34:3. 2023.

Pooling sequential target trial emulation estimates

We can pool RR and 95% CIs for each of the 13 trials under the **assumption** of no effect modification by gestational age.

Estimand corresponds to a target trial in which pregnant people are identified between 24-36 weeks gestation and assigned to antibiotic initiation that week or not and followed to delivery.

Pooling sequential target trial emulation estimates

Steps to estimate a pooled RR for the 13 individual target trials:

+ Pool data from all 13 target trial emulations into a single dataset
+ Using the pooled dataset:
  - Fit a log binomial model for the effect of treatment strategy on preterm birth
  - Include a variable for trial (taking values 1 to 13, modeled flexibility) as an adjustment variable
  - Include additional covariates included in individual target trial estimates
+ Nonparametric bootstrapping to calculate 95% CIs

Target trial emulation

+ **Can** help us:

  -Thing clearly about our causal question, treatment strategy, and appropriate study design

  -Help us avoid self-inflicted immortal time bias or selection bias

+ **Cannot** help us:

  - Avoid confounding, measurement error, or other forms of information bias which may be inherent to your observational data

Practical considerations

A target trial framework can be applied to any causal question.

+ In repro/perinatal studies it can help us think through issues around pregnancy loss and immortal person time
+ Helpful in ensuring eligibility, treatment ascertainment, and the start of follow-up are aligned
+ Requires large amounts of data, particularly if you want to use a sequential target trial approach
+ Need to think through an exposure window (e.g. antibiotic initiation within 1 gestational week too broad?)

Reading List

Worked example paper: Caniglia et al. Emulating Target Trials to Avoid Immortal Time Bias – An Application to Antibiotic Initiation and Preterm Delivery. Epidemiology, 34:3. 2023.

Additional reading:

+ Hernan et al. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016 November ; 79: 70–75.
+ Hernan and Robins. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758–764.
+ Hernan. Methods of Public Health Research — Strengthening Causal Inference from Observational Data. New England Journal of Medicine. 2021; 385:15.
+ Hernandez-Diaz. Emulating a Target Trial of Interventions Initiated During Pregnancy with Healthcare Databases: The Example of COVID-19 Vaccination. Epidemiology 2023;34: 238–246)

Questions?

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