EMULATING A TARGET TRIAL OF INTERVENTIONS INITIATED DURING PREGNANCY WITH HEALTHCARE DATABASES

The Example of COVID-19 Vaccination

Authors: Hernández-Díaz, Sonia, Krista F. Huybrechts, Yu-Han Chiu, Jennifer J. Yland, Brian T. Bateman, and Miguel A. Hernán. 2022.
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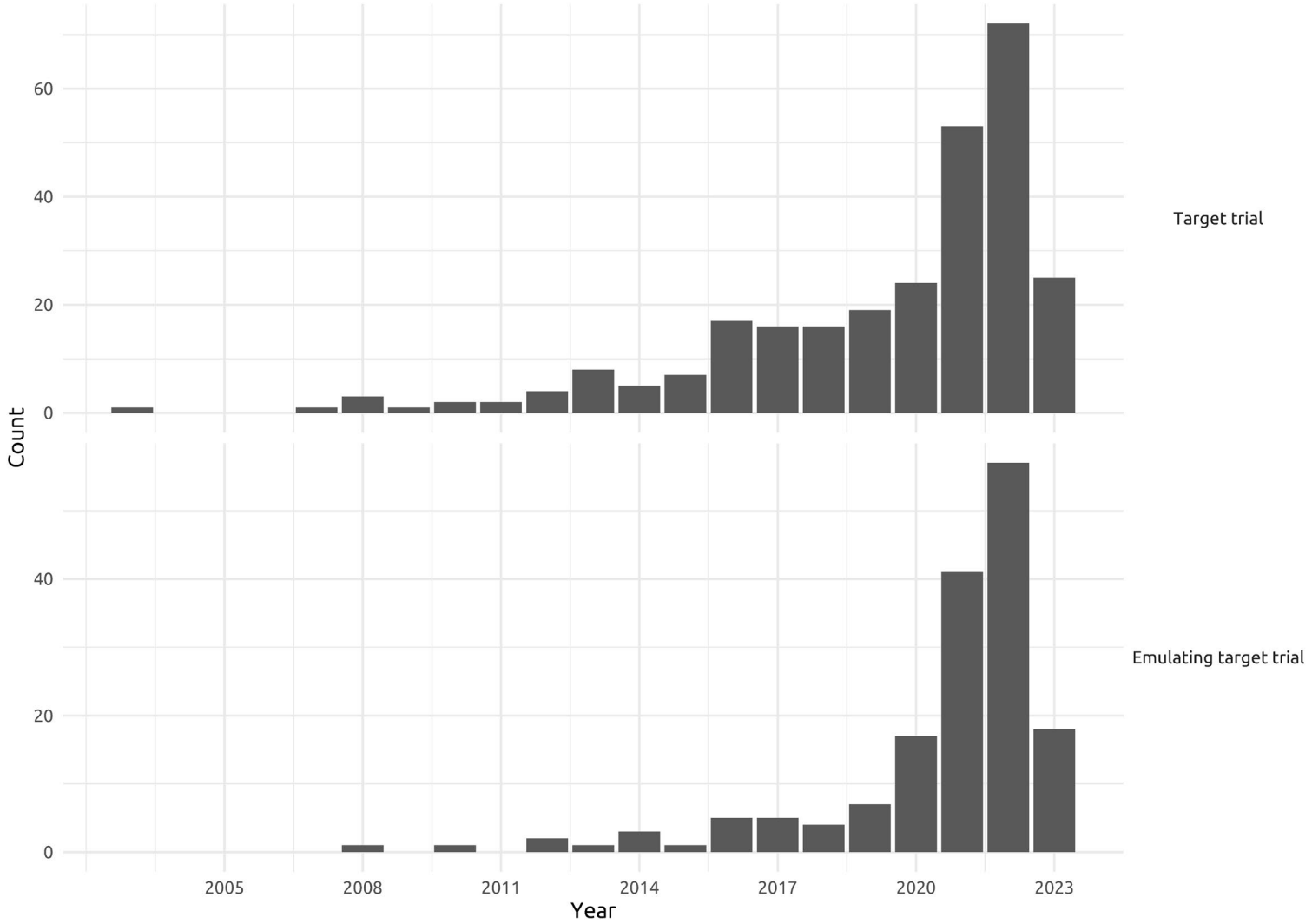
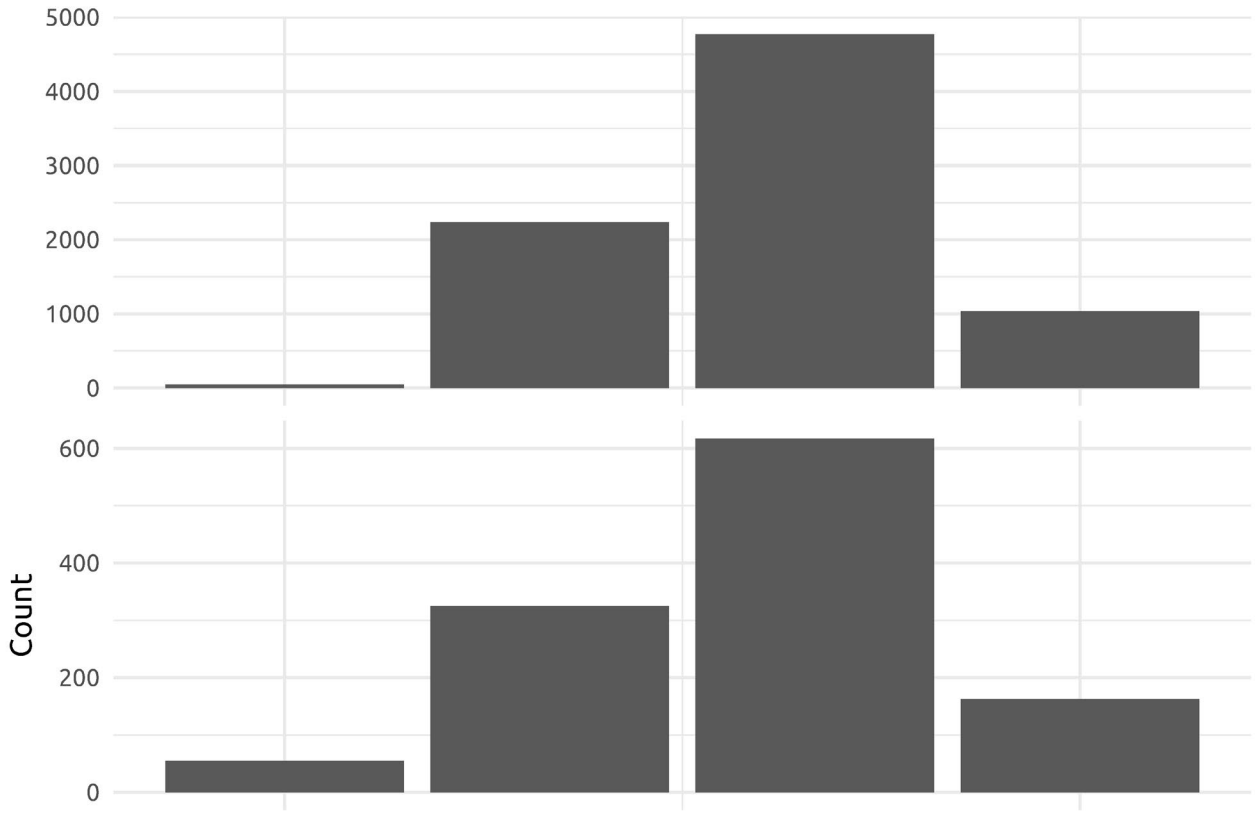
TARGET TRIAL

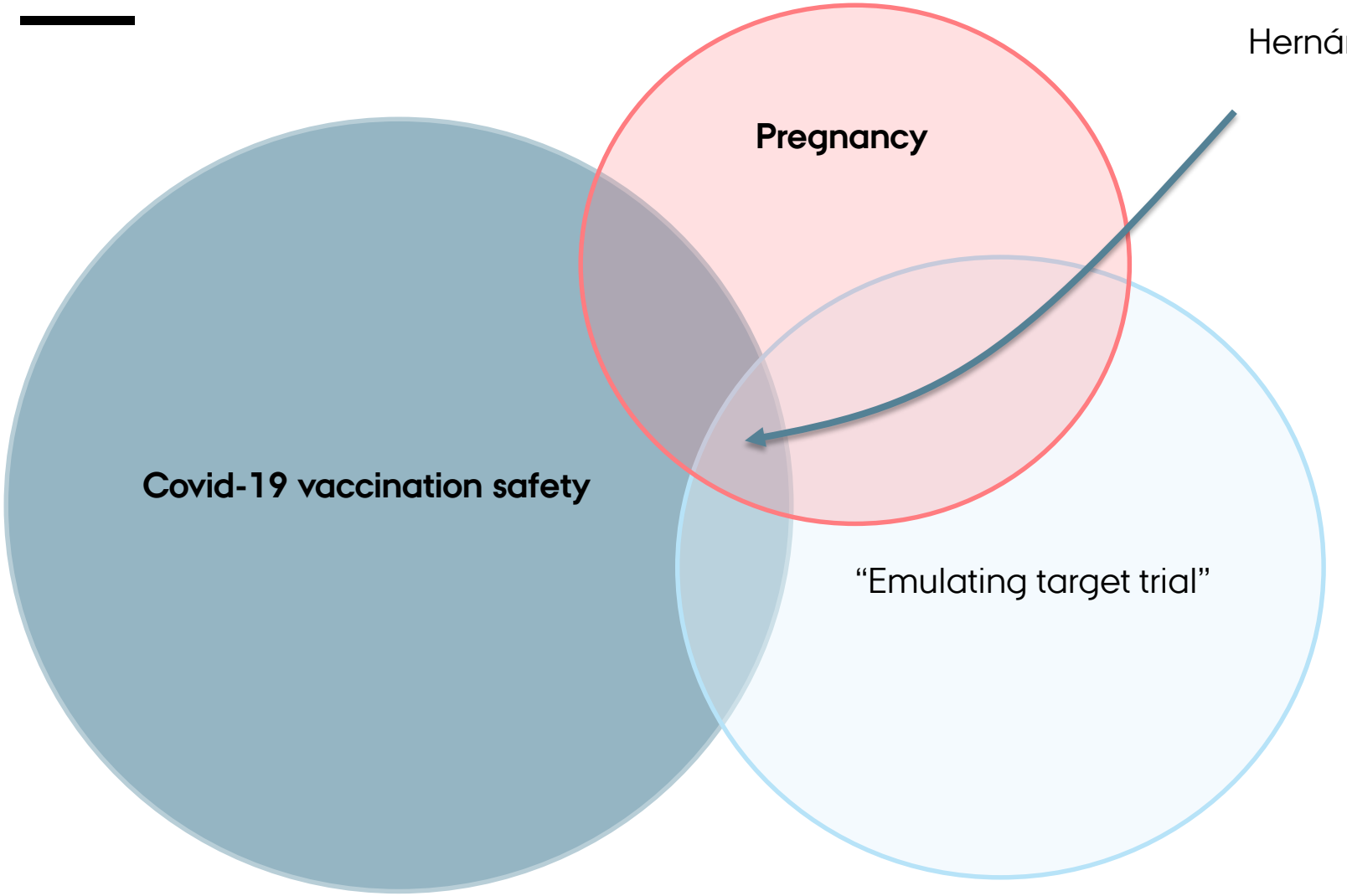


COVID-19 VACCINATION



TODAY'S JOURNAL CLUB

Hernández-Díaz et al. 2022



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RATIONALE

- Observational databases to evaluate interventions during pregnancy
- Randomized trials typically do not exist
- COVID19 vaccine trials in pregnancy:
  - Vaccinations administered only in weeks 24 to 34 of gestation:
    - not the etiologically relevant window for implantation, placentation, and organogenesis
    - too small
    - too short
    - effects of interventions at all gestational ages?

(Hernández-Díaz et al. 2022)

TYPES OF EXPOSURES

- Time-wise
  - Point exposure
  - Sustained exposure strategy

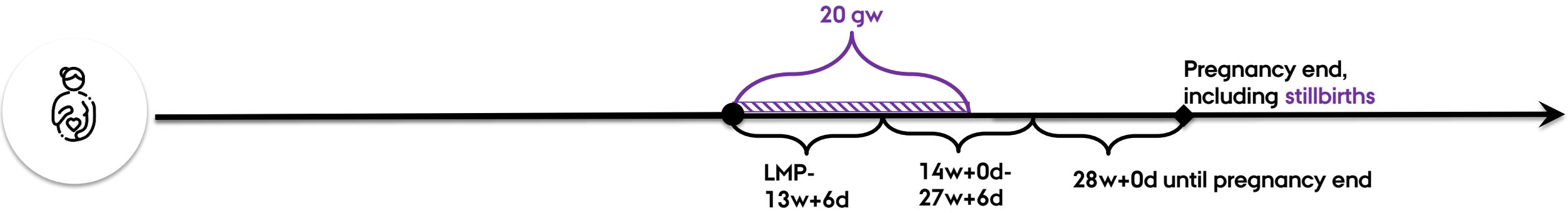
- Pharmacologic and non-pharmacologic interventions

- Causal inference from observational databases:
  - Causal question: hypothetical pragmatic randomized trial (target trial)
  - Emulate each component of the target trial protocol

(Hernández-Díaz et al. 2022)

CHALLENGES

- Gestational age (as an additional implied time scale)
- Pregnancy losses (as a source of potential selection bias)

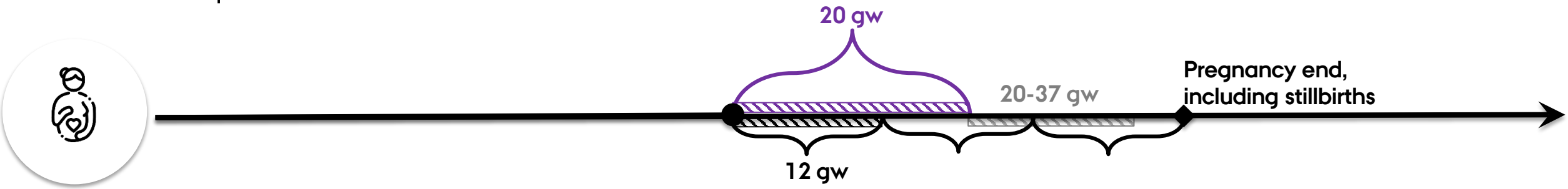


(Hernández-Díaz et al. 2022)

ELEMENTS OF TARGET TRIAL PROTOCOL

Gestational Age at Enrollment when assessing the outcome in a pregnancy/child

- Weeks since LMP (data source sensitive: computed vs ultrasound-based)
- Gestational age at enrollment relevance regarding the outcomes of interest
  - early pregnancy losses
  - congenital malformations
  - preterm birth



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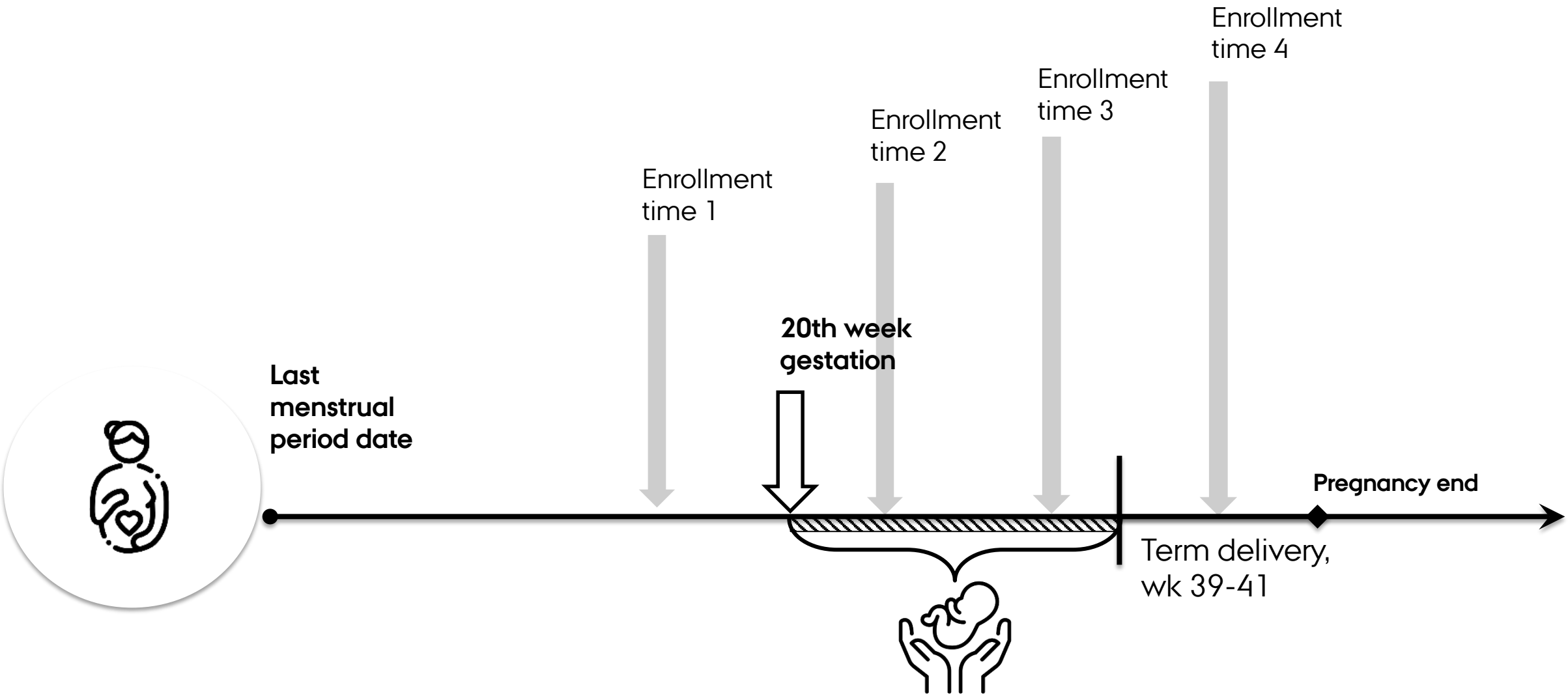
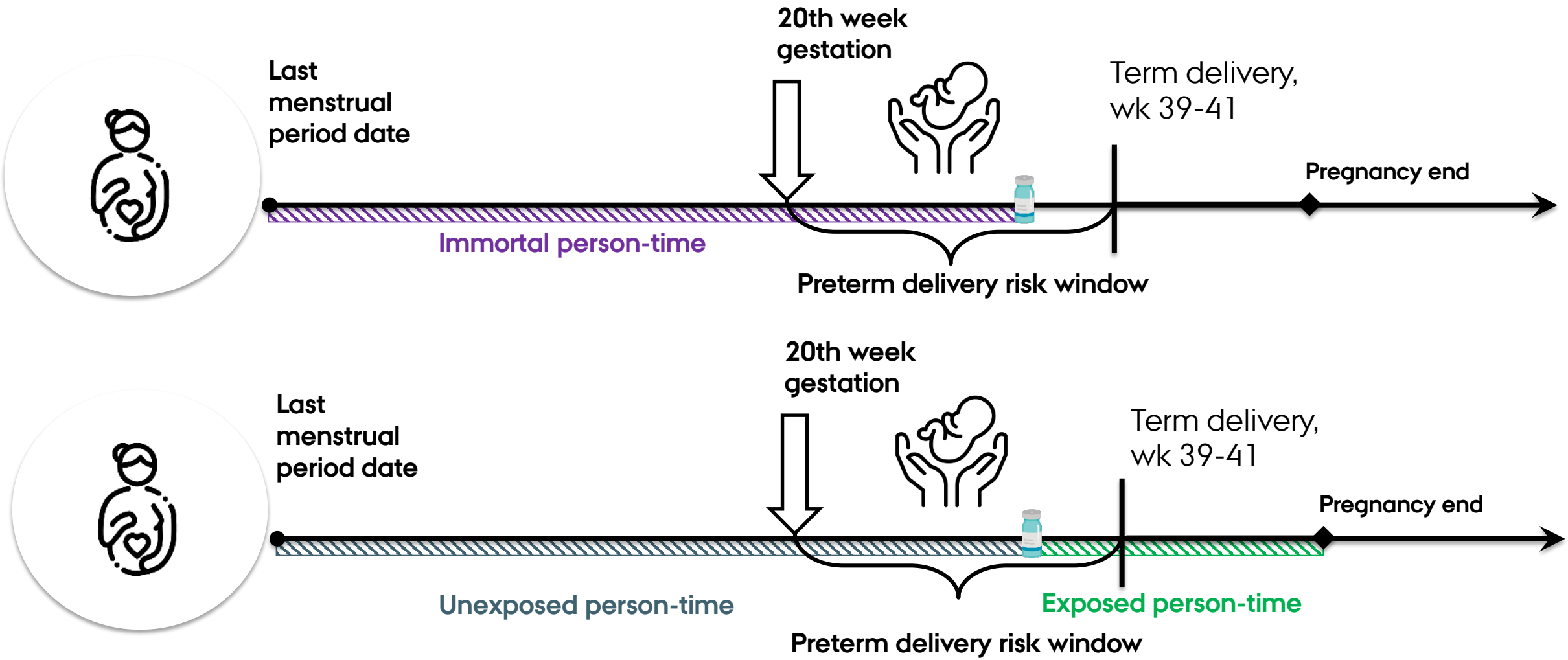
GESTATIONAL AGE IMPORTANCE



(Hernández-Díaz et al. 2022)

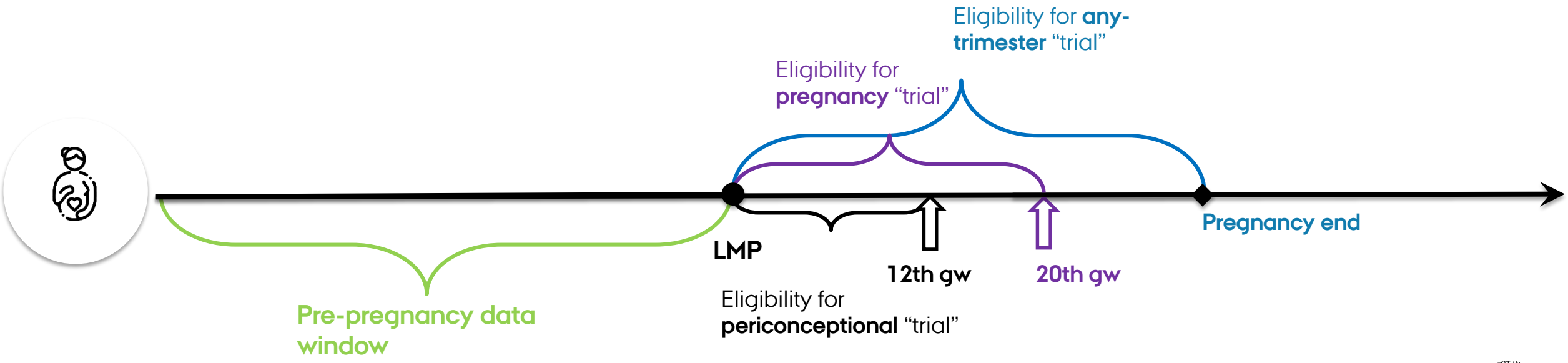
IMMORTAL-TIME



Fell, Deshayne B., Michelle C. Dimitris, Jennifer A. Hutcheon, Justin R. Ortiz, Robert W. Platt, Annette K. Regan, and David A. Savitz. 2021. "Guidance for Design and Analysis of Observational Studies of Fetal and Newborn Outcomes Following COVID-19 Vaccination during Pregnancy." *Vaccine* 39 (14): 1882–86. https://doi.org/10.1016/j.vaccine.2021.02.070.

TYPES OF PREGNANCY "TRIALS" ACCORDING TO GESTATIONAL AGE AT ENROLLMENT

- Periconceptional "trials": malformations
- Early pregnancy "trials": spontaneous abortions
- Late pregnancy "trials": other outcomes
- Any-trimester pregnancy "trials": start at any gestational age (non-pregnancy-specific maternal outcomes, eg, COVID-19 infection)



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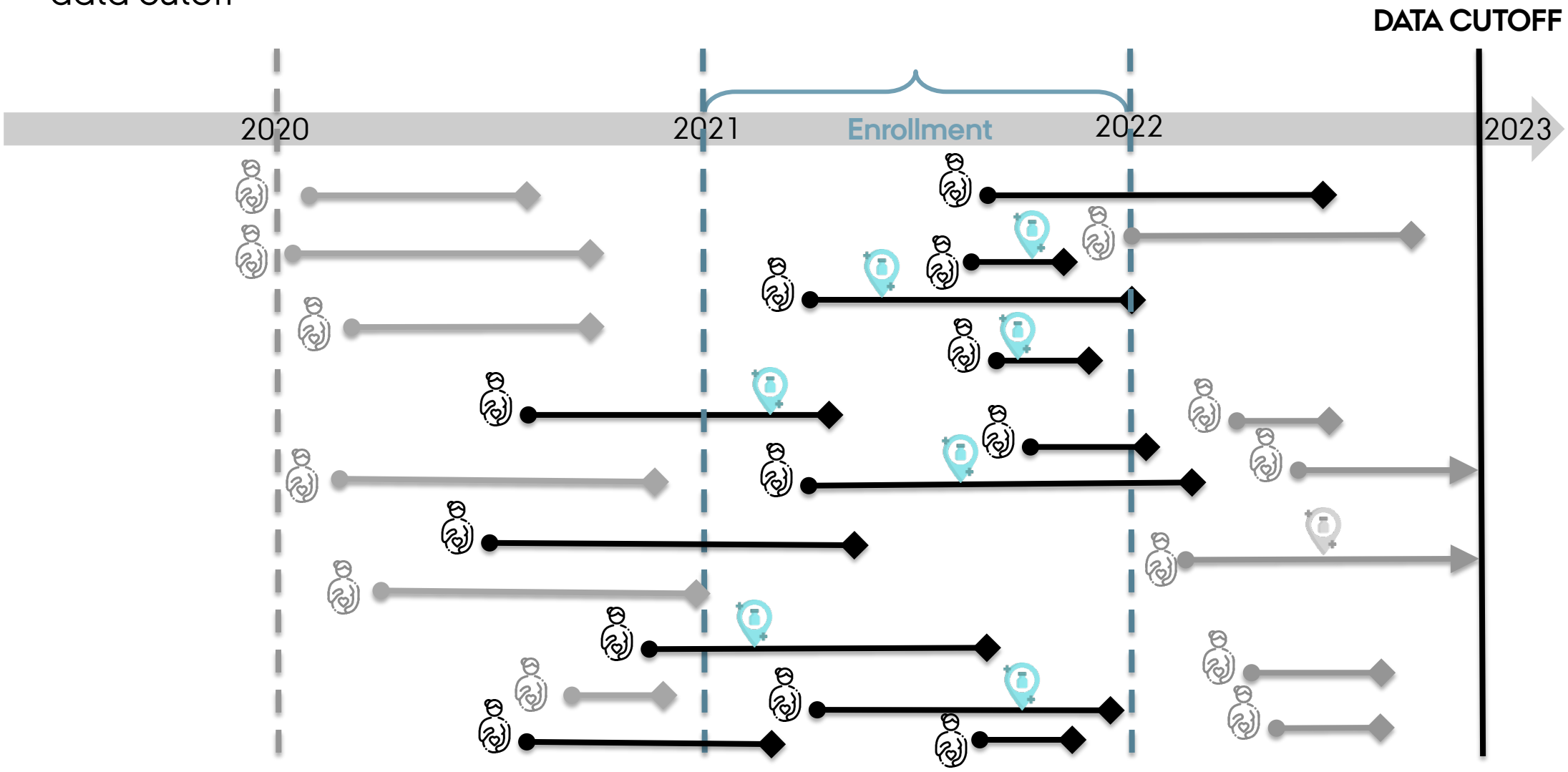
GESTATIONAL AGE AT DATA CUTOFF

- Require that participants are enrolled only if their LMP is at least 12 months before the data cutoff



PREGNANCY LOSSES

- Competing events for later outcomes
- May be caused by earlier outcomes (malformations)
- Interpretation of restriction to livebirths
- Risk bounds; probabilistic bias analyses

(Hernández-Díaz et al. 2022)

TARGET TRIAL DURING PREGNANCY

- 4 target trials to evaluate the effectiveness and safety of a booster of COVID-19 vaccine

1. Eligibility Criteria
2. Treatment Strategy
3. Assignment Procedures
4. Outcomes
5. Follow-up Period
6. Causal Contrast
7. Data Analysis

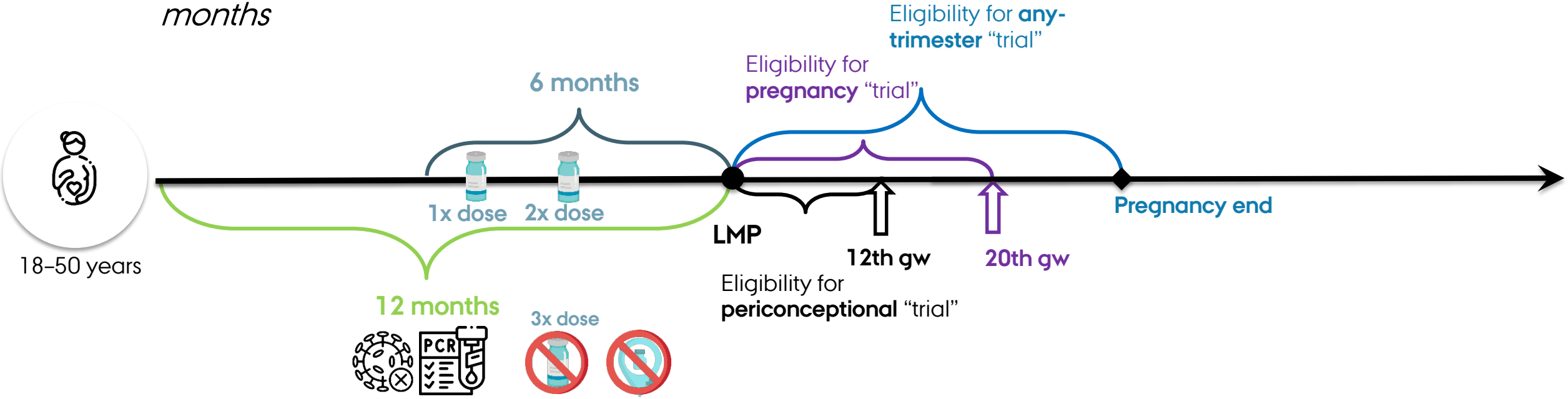
Covid19 booster

- Emulation

(Hernández-Díaz et al. 2022)

1. ELIGIBILITY

- Pregnant women
- Aged 18–50 years in 2021
- With primary vaccination (2 doses) completed at least 6 months ago
- No previous booster dose
- No positive SARS-CoV-2 test and *enrolled in the healthcare system for at least 12 months*



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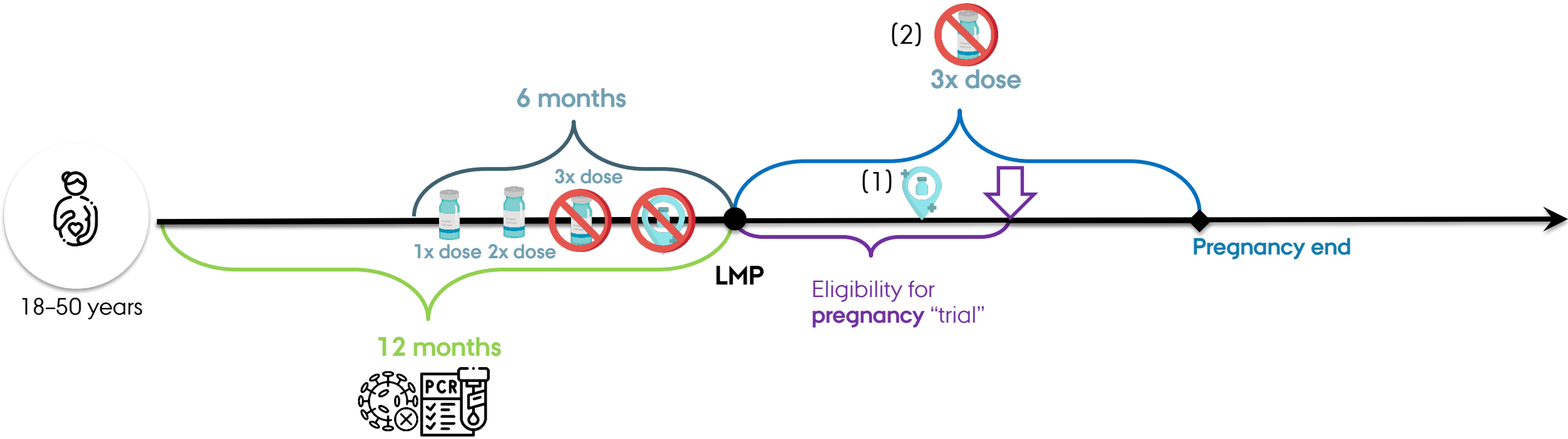
2. TREATMENT STRATEGIES

(1) An mRNA vaccine booster dose at enrollment, and (2) No vaccine doses during pregnancy

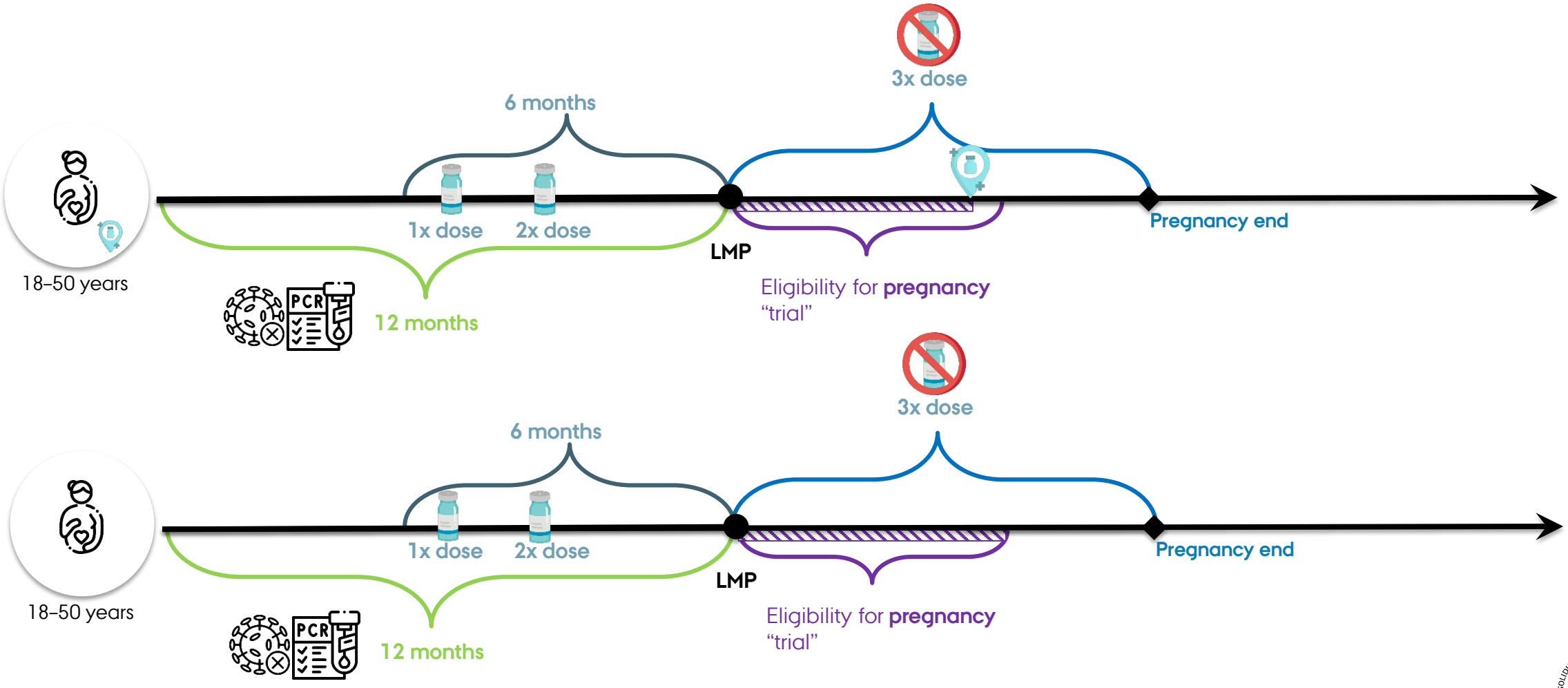


Covid19 booster

(Hernández-Díaz et al. 2022)

3. ASSIGNMENT PROCEDURES

- Individuals are randomly assigned to one strategy and are aware of their assignment



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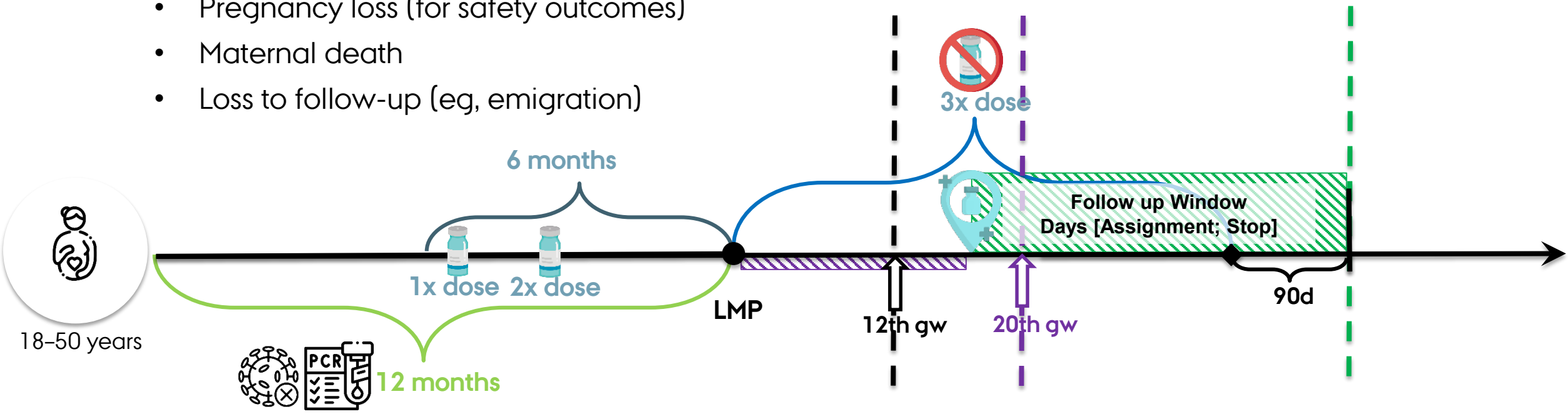
4. OUTCOMES

- Effectiveness
  - Laboratory-confirmed maternal or infant COVID-19 diagnosis
  - Severe COVID-19 requiring hospitalization, ICU admission, or death
- Safety
  - Major congenital malformation → before 12 weeks
  - Spontaneous abortion → before 20 weeks
  - Other maternal or infant complications
    - Elective termination → before 20 weeks
    - Preterm delivery → before 37 weeks
    - Stillbirth → during pregnancy
    - Low birth weight (birth weight) → during pregnancy
    - Small for gestational age → during pregnancy
    - Microcephaly (head circumference) → during pregnancy
    - Gestational diabetes, preeclampsia, postpartum hemorrhage, labor induction, Cesarean section, maternal death → during pregnancy

(Hernández-Díaz et al. 2022)

5. FOLLOW-UP PERIOD

- Starts at assignment
- Stops at the earliest of:
  - Outcome
  - 140 days after LMP (for spontaneous abortions)
  - 90 days after birth (for other outcomes)
  - Pregnancy loss (for safety outcomes)
  - Maternal death
  - Loss to follow-up (eg, emigration)



SETTING UP T0

Ensure that eligibility, start of follow-up, and assignment to a treatment strategy coincide

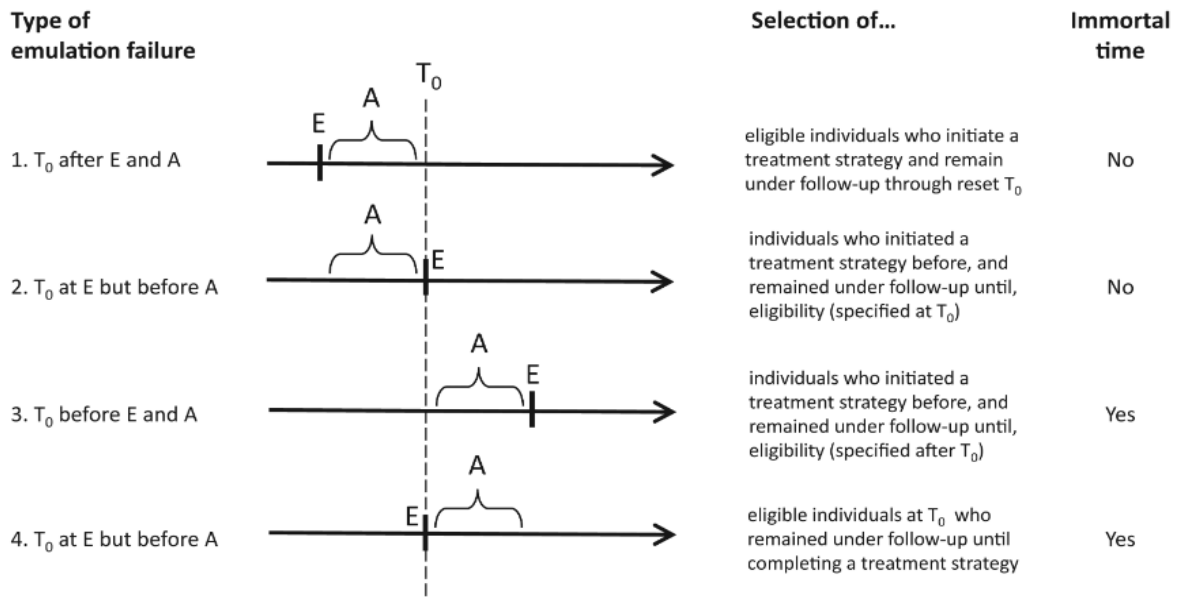


Fig. 1.
Four examples of failures of emulation of a target trial using observational data. T_0, time zero; E, eligibility; A, period during which treatment strategies are assigned.

6. CAUSAL CONTRAST

- Intention-to-treat effect, ITT (as randomized)
- Per-protocol effect (effect of treatment actually received)

(Hernández-Díaz et al. 2022)

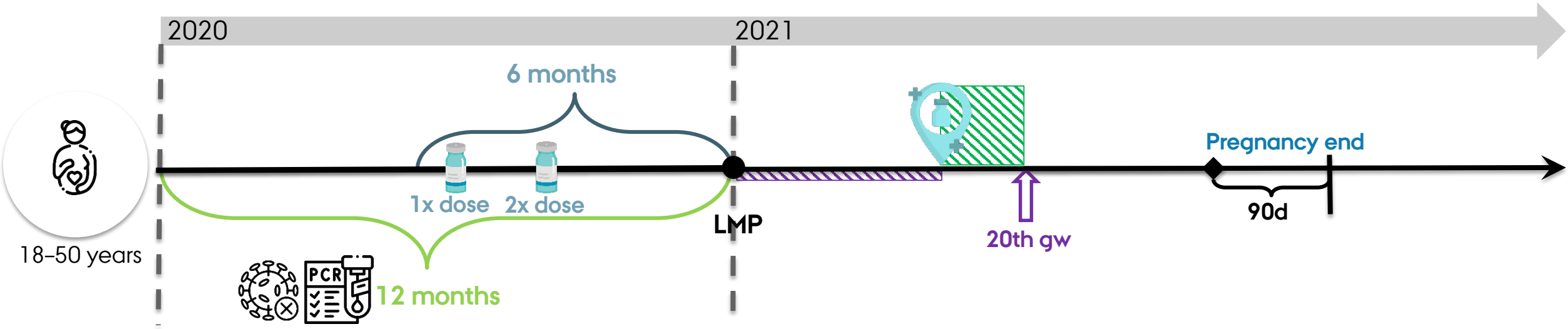
7. DATA ANALYSIS

- For ITT:
  - Compare the risks (cumulative incidences) in each group defined by assignment through differences and ratios
  - Cumulative incidence curves from assignment via the Kaplan–Meier/CI function for competing risks/pooled logistic model
  - Adjust for selection bias due to loss of follow-up
    - Measured variables (at time zero; LMP) include ~all risk factors predicting loss to follow-up
- Per protocol:
  - Individuals are censored if they deviate from the protocol
    - Measured variables (at time zero; LMP) include ~all risk factors predicting loss to follow-up

(Hernández-Díaz et al. 2022)

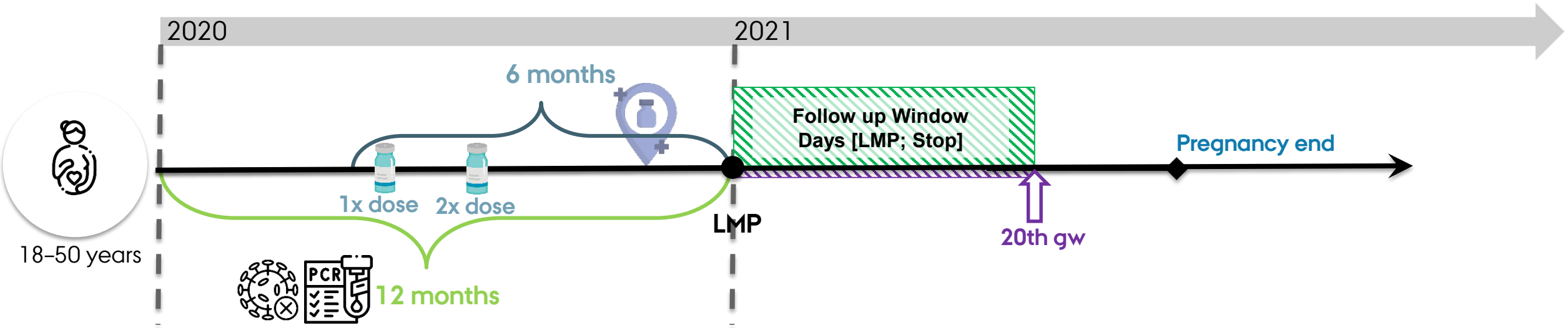
EMULATION OF A TARGET TRIAL DURING PREGNANCY

- Linkage of mother and infant in the database
- Determination of gestational age/LMP
- Algorithms for pregnancy outcomes (data source-specific)
- Eligibility criteria
  - Data from 2020 and 2021 to assess eligibility within the 12 months before the baseline in 2021
  - The absence of codes for a variable (eg, a booster dose) implies no booster was administered



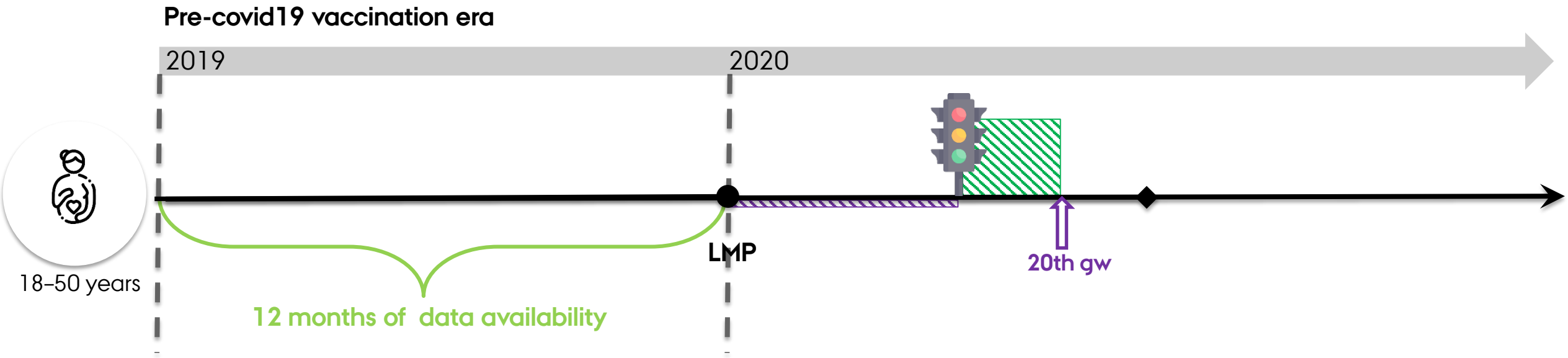
EMULATE TREATMENT STRATEGIES

- Identify pharmacy dispensations for vaccination and procedure codes for vaccine administration
  - Assume that individuals without vaccine codes did not receive the vaccine
- Using multiple comparators:
  - Women who had a record of a booster before pregnancy
  - Assumes pre-pregnancy boosters do not affect the outcome risk



EMULATING TREATMENT STRATEGIES

- Using multiple comparators:
  - Pregnancies in the same month the previous year (when vaccines were not available)
  - Assumes no temporal trends in pregnancy outcomes.



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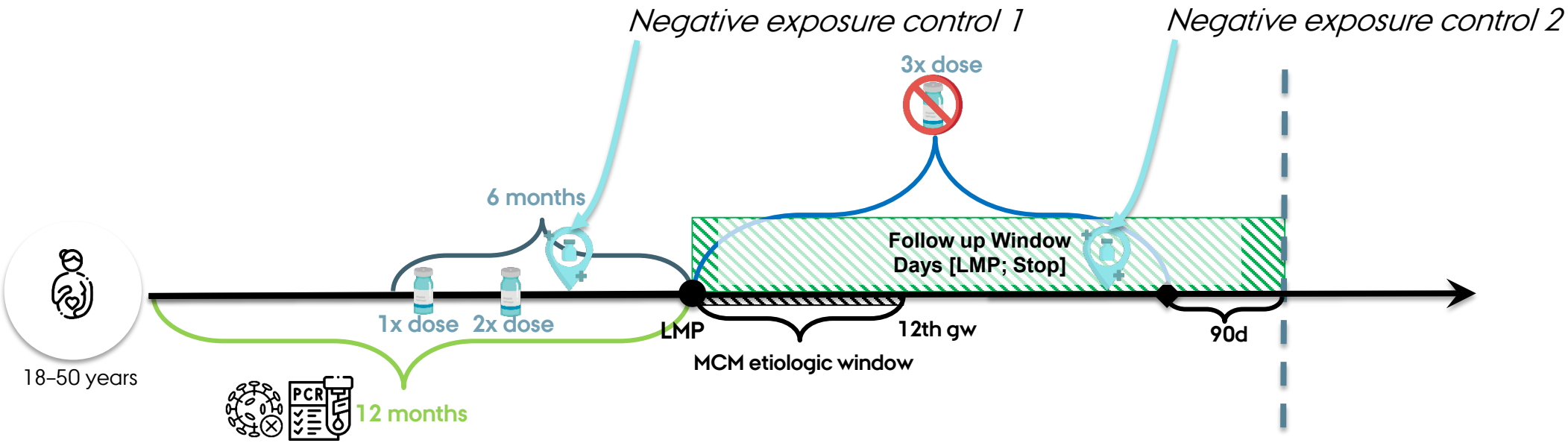
EMULATING TREATMENT ASSIGNMENT

- Assign each eligible woman to the treatment strategy (booster vs no booster) **compatible with their data** under the assumption of **conditional exchangeability** given measured confounding factors:
  - Gestational age
  - Calendar month
  - Geographic region
  - Maternal age at LMP
  - Obstetric characteristics (e.g., multiples, parity)
  - Prior SARS-COV-2 infection
  - Coexisting conditions (e.g., obesity, smoking, pregestational diabetes, hypertension, other cardiovascular conditions, asthma, and their treatments)
  - Proxies for healthcare utilization (e.g., number of hospitalizations and outpatient visits, flu vaccination) in the previous 6 months

(Hernández-Díaz et al. 2022)

EMULATING TREATMENT ASSIGNMENT

- Sensitivity analyses:
  - Negative controls
  - Malformations (MCM) outcome



(Hernández-Díaz et al. 2022)

EMULATING FOLLOW-UP & OUTCOMES

- Outcome misclassification
  - Validity (high specificity)
  - The time of onset vs the time of the record

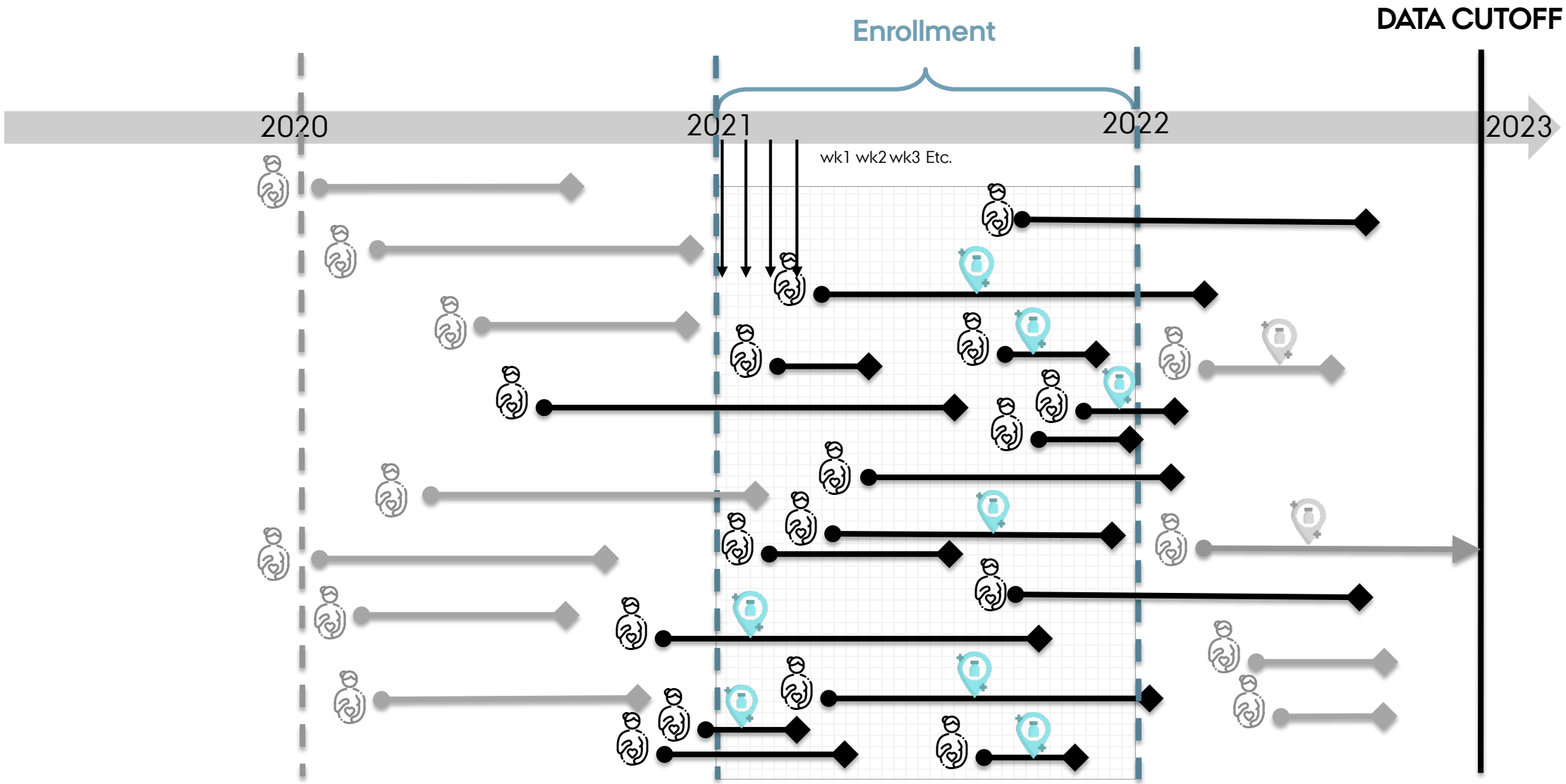
(Hernández-Díaz et al. 2022)

CAUSAL CONTRAST OF INTEREST

- Observational analog of the per-protocol effect (i.e., the effect of receiving the vaccine booster versus receiving no booster during pregnancy)
- No date of assignment to no booster
- To prevent immortal time bias, choose the start of the follow-up (time zero) of each pregnancy in such a way that the **distribution of gestational age at time zero is the same in both groups**
  - Emulation of sequential target trials with weekly recruitment
  - Identify eligible women who received a booster in that week and match each of them with an eligible woman who does not receive a booster in that week (a control)
  - Match on confounding factors

(Hernández-Díaz et al. 2022)

WEEKLY SEQUENTIAL "TRIALS"



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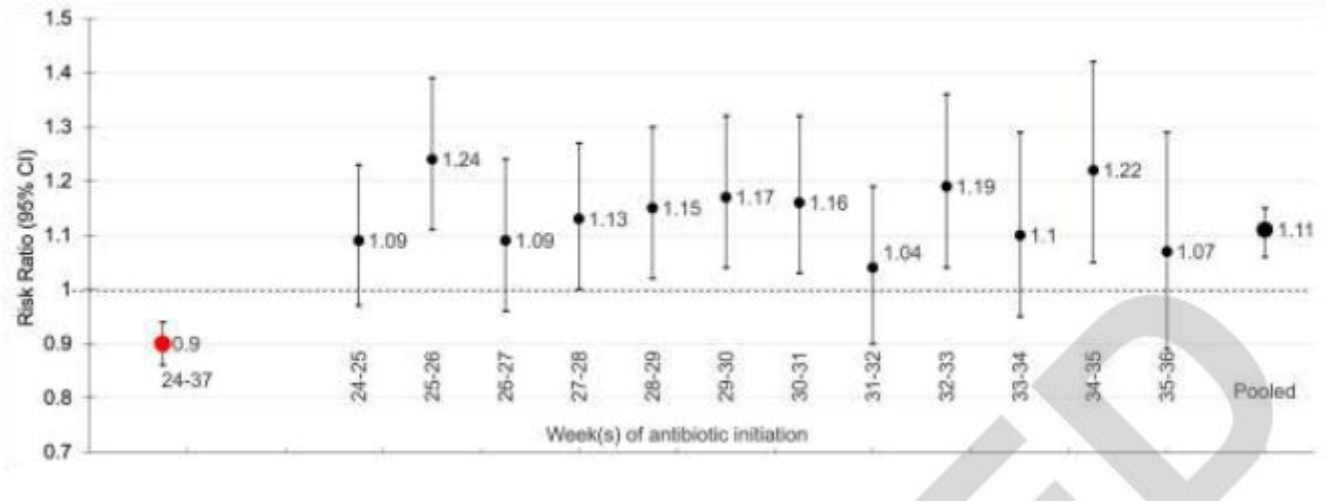
TAKE HOME MESSAGES

- Simple scenario: a point intervention and a sustained strategy
- Emulating target trial:
  - Reduce bias
  - Improves the interpretability of effect estimates
  - Clarifies the nature of the remaining challenges

(Hernández-Díaz et al. 2022)

EXTRA EXAMPLE

- Antibiotic (AB) initiation and preterm delivery
- Emulation of series of weekly target trials for AB initiation in weeks 13:36 vs not initiating AB
- Pooling 13 target trials



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USEFUL LINKS

- Competing events https://pubmed.ncbi.nlm.nih.gov/31985089/
- Pooled logistic regression analysis illustration
- Antibiotic (AB) initiation and preterm delivery paper https://pubmed.ncbi.nlm.nih.gov/36805380/

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