Emulation of Target Trial on Vaccinations During Pregnancy

CBER BEST Initiative Seminar Series

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HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

DISCLOSURE

- The following personal or financial relationships existed during the past 12 months:
  - SHD consulted for Roche and Moderna
  - SHD participated as investigator in projects funded by Takeda and UCB
  - SHD was the epidemiologist for the North American Antiepileptic Drugs pregnancy registry and advisor for the Antipsychotics Pregnancy Registry, which are funded my multiple companies

Agenda

- Introduction
  - COVID-19 vaccine during pregnancy
  - Target Trial
- Target Trial Emulation to Study Vaccine Effectiveness
- Target Trial Emulation to Study Vaccine Safety
  - Cloning
  - Sequential trials
- Conclusions

Introduction

COVID-19 vaccine in pregnancy

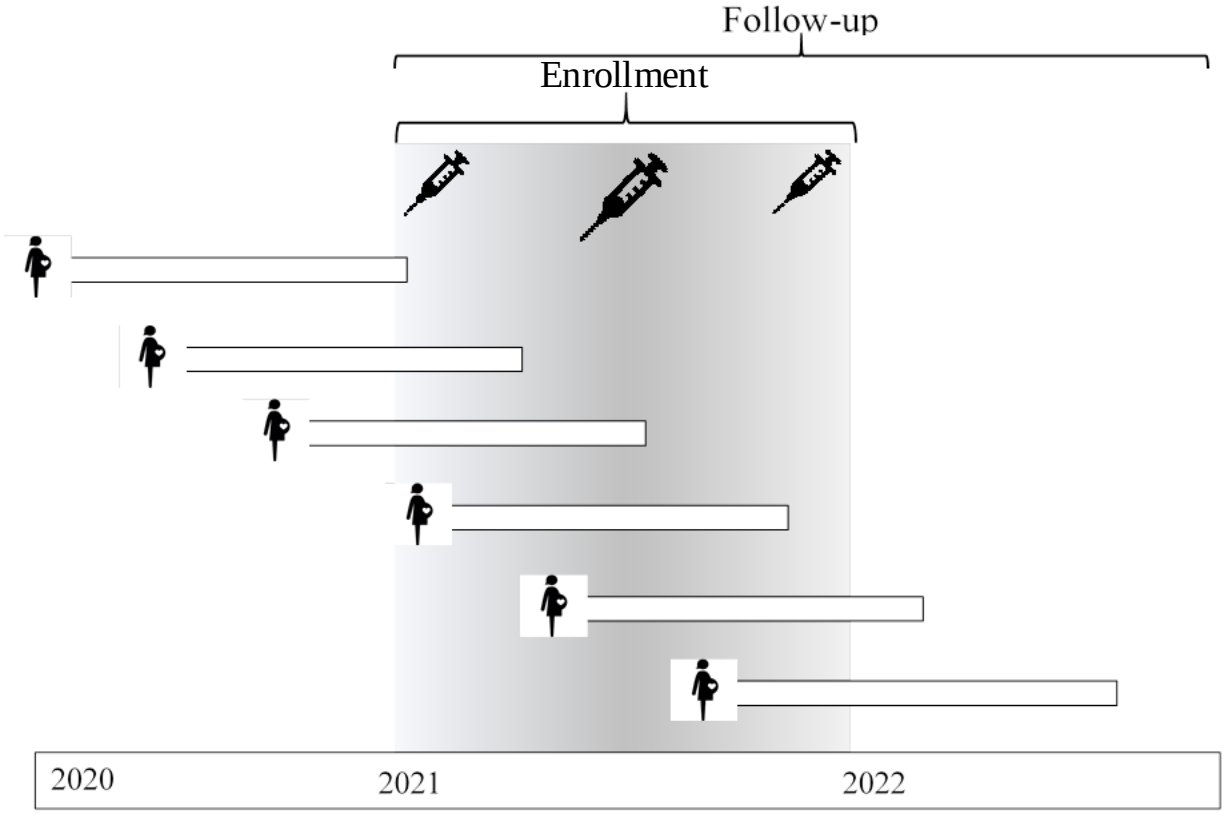
- Coronavirus disease 2019 (COVID-19) vaccines used in pregnant women (human females of any gender identity)
- Need causal knowledge about effectiveness and safety of vaccine in pregnancy
- Phase 3 clinical trials conducted to evaluate the safety and efficacy of COVID-19 vaccines did not include pregnant women
- Inconsistent vaccination guidelines ranging from contraindicated to permitted to recommended in pregnancy

COVID-19 vaccine in pregnancy

- Lack of evidence on vaccine safety main reason for vaccine hesitancy in pregnant women
- When a randomized experiment **(our preferred choice)** is not feasible, decisions must be informed by observational data
- Observational studies are often the main source of evidence for populations typically excluded from clinical trials, e.g., pregnant women

Skjefte M, Ngirbabul M, Akeju O, Escudero D, Hernández-Díaz S, Wyszynski DF, Wu JW. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. Eur J Epidemiol. 2021;36:197-211

Evidence needed in January 2021



RCTs Registries Databases Case control studies

The Target Trial

- Causal inference from observational data can be conceptualized as an attempt to emulate a hypothetical pragmatic randomized trial: the Target Trial
- The randomized trial that we would conduct to answer a causal question if we had no constraints (e.g., funding, time, ethics)

Hernán MA. Methods of Public Health Research - Strengthening Causal Inference from Observational Data. N Engl J Med. 2021;385(15):1345-8

Hernán M, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol 2016;183:758-64

The Target Trial

- The Target Trial framework makes each aspect of the protocol explicit, from the causal question to the analytic approach
  - **Step 1:** Ask a causal question
  - **Step 2:** Design the target trial and describe the protocol
  - **Step 3:** Emulate the target trial using observational data. Must explicitly describe how we emulate each component of the trial protocol
  - **Step 4:** Apply appropriate causal inference analytics
- Designing a **target trial** for observational studies can help identify and avoid biases including confounding, immortal person time bias, and prevalent user bias

Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016:79:70-75

Target Trial Protocol

Protocol Component	Target Trial	Emulation
1. Eligibility criteria		
2. Treatment strategies		
3. Assignment procedures		
4. Follow-up period		
5. Outcome		
6. Causal contrasts of interest		
7. Analysis plan		

Target Trial Protocol

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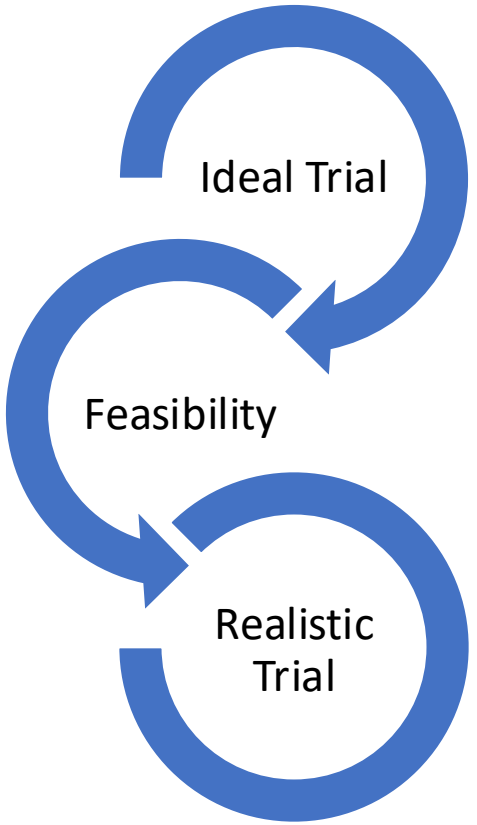


Target Trial Protocol

Protocol Component	Real Trial	Target Trial	Emulation
1. Eligibility criteria	e.g., biologic measures, intentionality		
2. Treatment strategies	e.g., placebo, weight-based dose, do not exist in RWD		
3. Assignment procedures	e.g., blind		No randomization
4. Follow-up period	e.g., longer than observation in data		
5. Outcome	e.g., adjudication, IQ scale	Pragmatic, uses RWD	
6. Causal contrasts of interest	e.g., certain intention to treat situations		
7. Analysis plan			

Summary of Protocol of Target Trial and its Emulation

Eligibility criteria	Population restricted to individuals who met the eligibility criteria of the target trial
Treatment strategies	Treatment strategies as in target trial (e.g., initiation, continuation) No blind assignment, no placebo control
Randomized assignment	This is what "adjustment for confounding" means. Need to adjust for baseline covariates via matching, stratification or regression, standardization or inverse probability (IP) weighting, etc If insufficient data on confounders, then emulation of random assignment fails→ Confounding bias
Start/End follow-up	Starts at randomization and ends at outcome, death, loss to follow-up, or end of follow-up (e.g., delivery, 90 days after vaccine), whichever occurs earlier
Outcome	Outcomes as in target trial Typically, without systematic and blind outcome ascertainment
Causal contrasts	Intention-to-treat effect, per-protocol effect
Analysis plan	Intention-to-treat analysis, per-protocol analysis

Target Trial Emulation

Effectiveness

Causal question: Effectiveness & Safety

- **Effectiveness:**
  - Large numbers required to show differences in healthy young women.

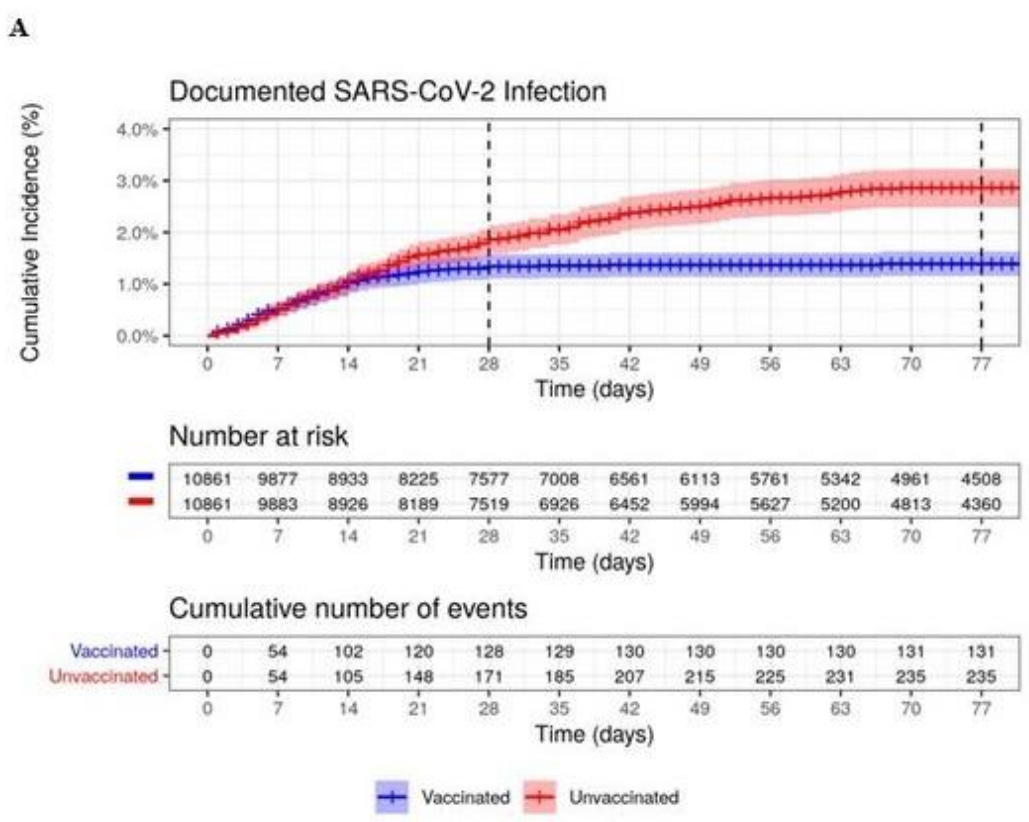
Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy

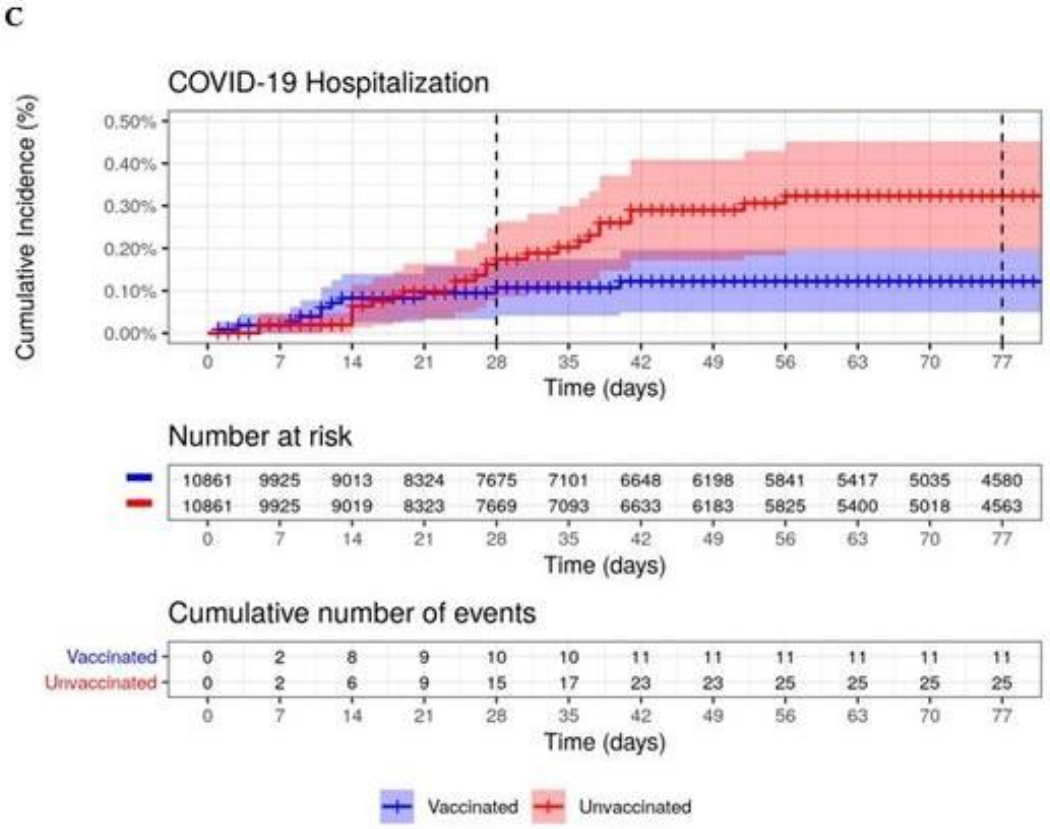
Noa Dagan[1,2,3,4,14], Noam Barda[1,2,3,4,14], Tal Biron-Shental[5,6], Maya Makov-Assif[1], Calanit Key[7], Isaac S. Kohane[3,4], Miguel A. Hernán[8,9], Marc Lipsitch[10], Sonia Hernandez-Diaz[8], Ben Y. Reis[4,11,12] and Ran D. Balicer[1,4,13] ✉

Summary of Protocol of Target Trial Emulation for Vaccine Effectiveness

Eligibility criteria	
Treatment strategies	
Randomized assignment	
Start/End follow-up	
Outcome	
Causal contrasts	
Analysis plan	

Conclusion: Similar to the effectiveness estimated in the general population. Estimated vaccine effectiveness of 97% for symptomatic infection and 89% for COVID-19-related hospitalization from 7 to 56 days after the second dose





Dagan N, Barda N, et al. Effectiveness of the BNT162b2 mRNA COVID-19 Vaccine in Pregnancy. Nature Medicine 2021

Target Trial Emulation

Safety

Causal question: Effectiveness & Safety

- **Pharmacovigilance:** vaccine reactions, we can assume they are similar to other adults, e.g., migraine and local pain after second dose
- **Safety:** Focus on pregnancy-specific outcomes related to the fact that the mother is going through a very special period of gestation, and the fetus is developing. Outcomes of interest include:
  - Pregnancy losses (spontaneous abortions, stillbirths)
  - Malformations
  - Obstetric outcomes (gestational diabetes, preeclampsia, preterm delivery, etc)
  - Neonatal outcomes (small for gestational age, need for NICU, NAS, etc)
  - Childhood outcomes (neurodevelopmental, infections, etc)

Causal question: Effectiveness & Safety

- **Challenge for Evaluation of Effects in Pregnancy**
  - Additional time scale: Gestation
  - Etiologically relevant window varies by outcome
  - Risk of some outcomes vary by week

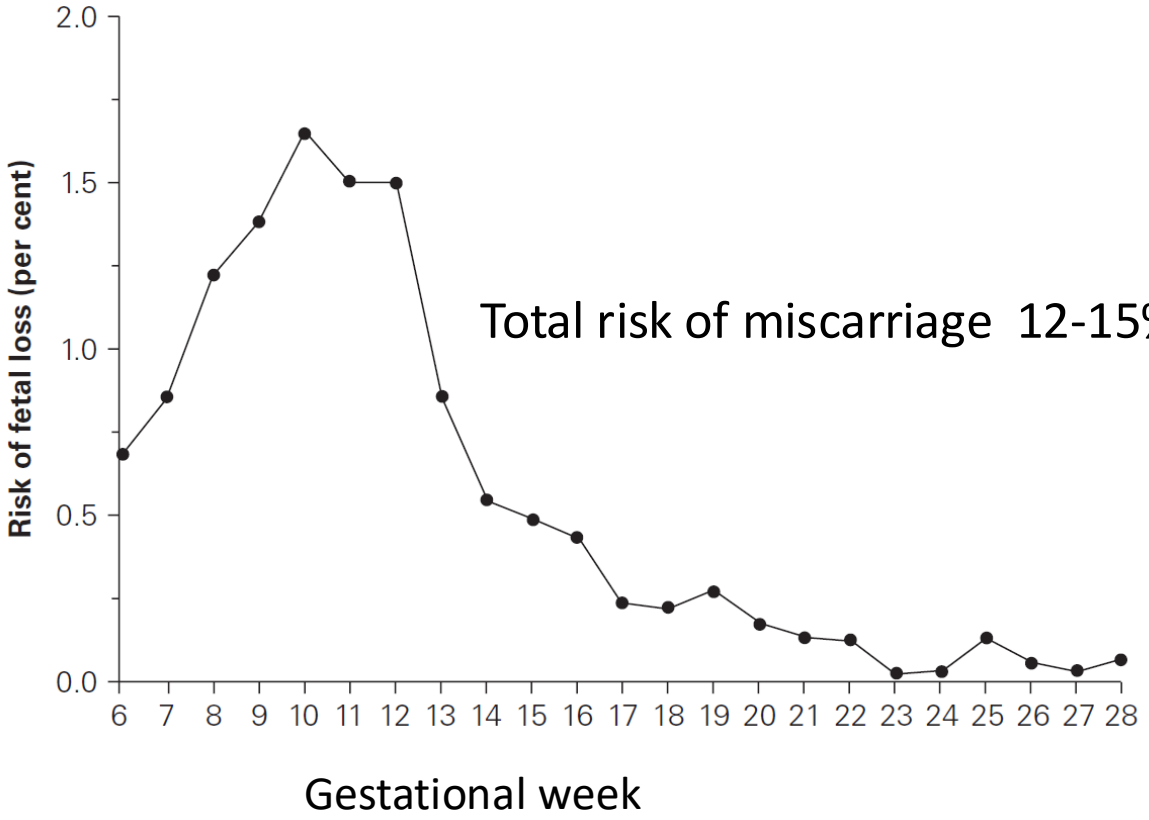
Hernandez-Diaz S, Huybrechts KF, Chiu YH, Yland JJ, Bateman BT, Hernan MA. Emulating a Target Trial of Interventions Initiated During Pregnancy with Healthcare Databases: The Example of COVID-19 Vaccination. Epidemiology 2023;34:238-46.

Huybrechts KF, Bateman BT, Hernandez-Diaz S. Use of real-world evidence from healthcare utilization data to evaluate drug safety during pregnancy. Pharmacoepidemiology and drug safety 2019;28:906-22.

Expected distribution of pregnancy losses by pregnancy week for spontaneous abortions (before 20 weeks)

Wilcox, Weinberg et al. 1988; Mukherjee, Velez Edwards et al. 2013

Clinical Miscarriage Risk by Gestational Week



Total risk of miscarriage 12-15%

Detection under research

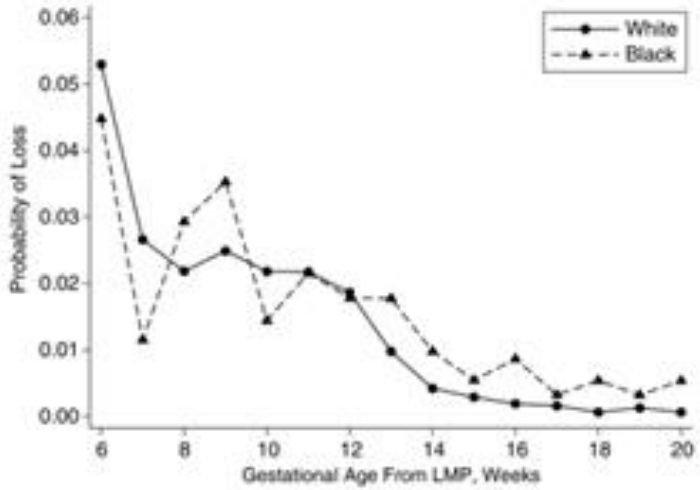
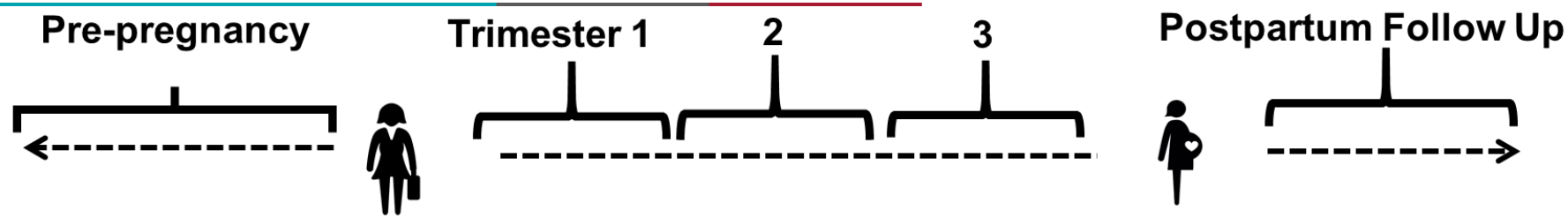


Figure 1. Week-specific probability of pregnancy loss by race among "Right From the Start" participants, 2000–2009. The *x*-axis is gestational age at loss from last menstrual period (LMP); the *y*-axis is probability of pregnancies ending in miscarriage.

Challenges for each phase of pregnancy



- **Phase 0:** Effect of vaccine **pre-conception** on fertility or future outcomes
  - Challenges for post-conception outcomes include defining the intervention "in those planning pregnancy" (?) and the many selection and attrition processes involved
- **Phase 1:** Effect of vaccine **early in pregnancy**
  - Challenge from competing events and survivor cohort. Immortal person time
    - Pregnancy losses (from conception to 20-24 weeks for spontaneous abortion, can ext[illegible] to include stillbirth)
    - Malformations (first trimester)
    - Later outcomes (late exposure or may also be affected by early exposures)
- **Phase 2: Late pregnancy** exposures
  - Challenge from competing events (e.g., prematurity "prevents" preeclampsia), mediators and selection
    - preterm births, NICU… neurodevelopmental outcomes

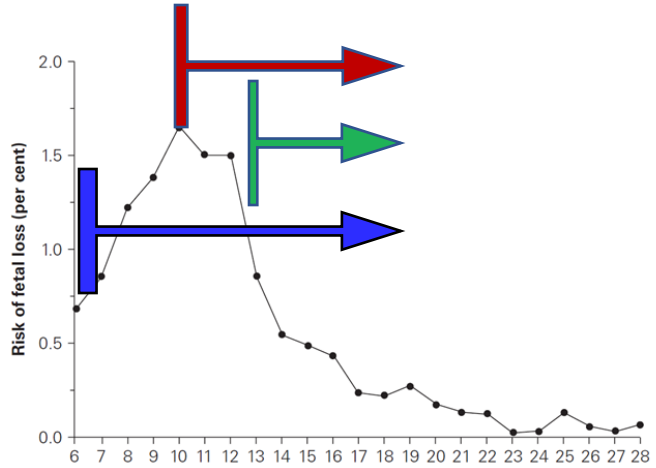
Will focus on this one now

Chiu YH, Stensrud MJ, Dahabreh IJ, Rinaudo P, Diamond MP, Hsu J, Hernandez-Diaz S, Hernan MA. The Effect of Prenatal Treatments on Offspring Events in the Presence of Competing Events: An Application to a Randomized Trial of Fertility Therapies. Epidemiology. 2020;31:636-643

Selection: Enrollment after eligibility (conception)

- **Left truncation**

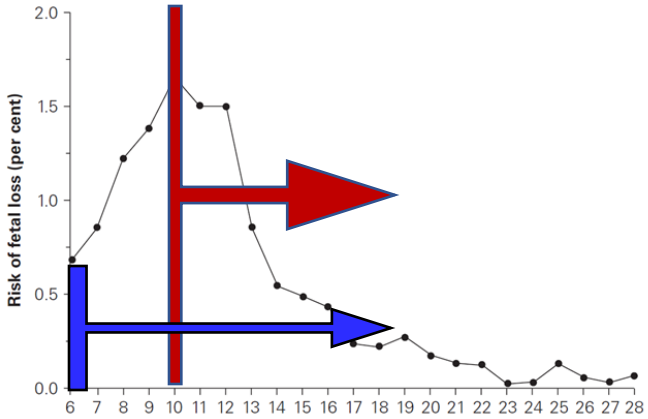
- What would be the relative risk of spontaneous abortions if exposed subjects are enrolled during first trimester and reference group is enrolled…
  - later in pregnancy?
  - at conception ?



Risk of fetal losses

Example: Vaccines and spontaneous abortion

- Among participants in a pregnancy registry receiving a COVID-19 vaccine during pregnancy 13% resulted in **spontaneous abortions** (SAB) relative to about 15% in the general population
  - *Shorter opportunity for vaccination "during pregnancy" in those with SABs*
  - *Shorter opportunity for SAB from vaccination than from conception (until 20 or 24 weeks)*
  - *Time from conception to vaccination "during pregnancy" immortal (no SAB)*



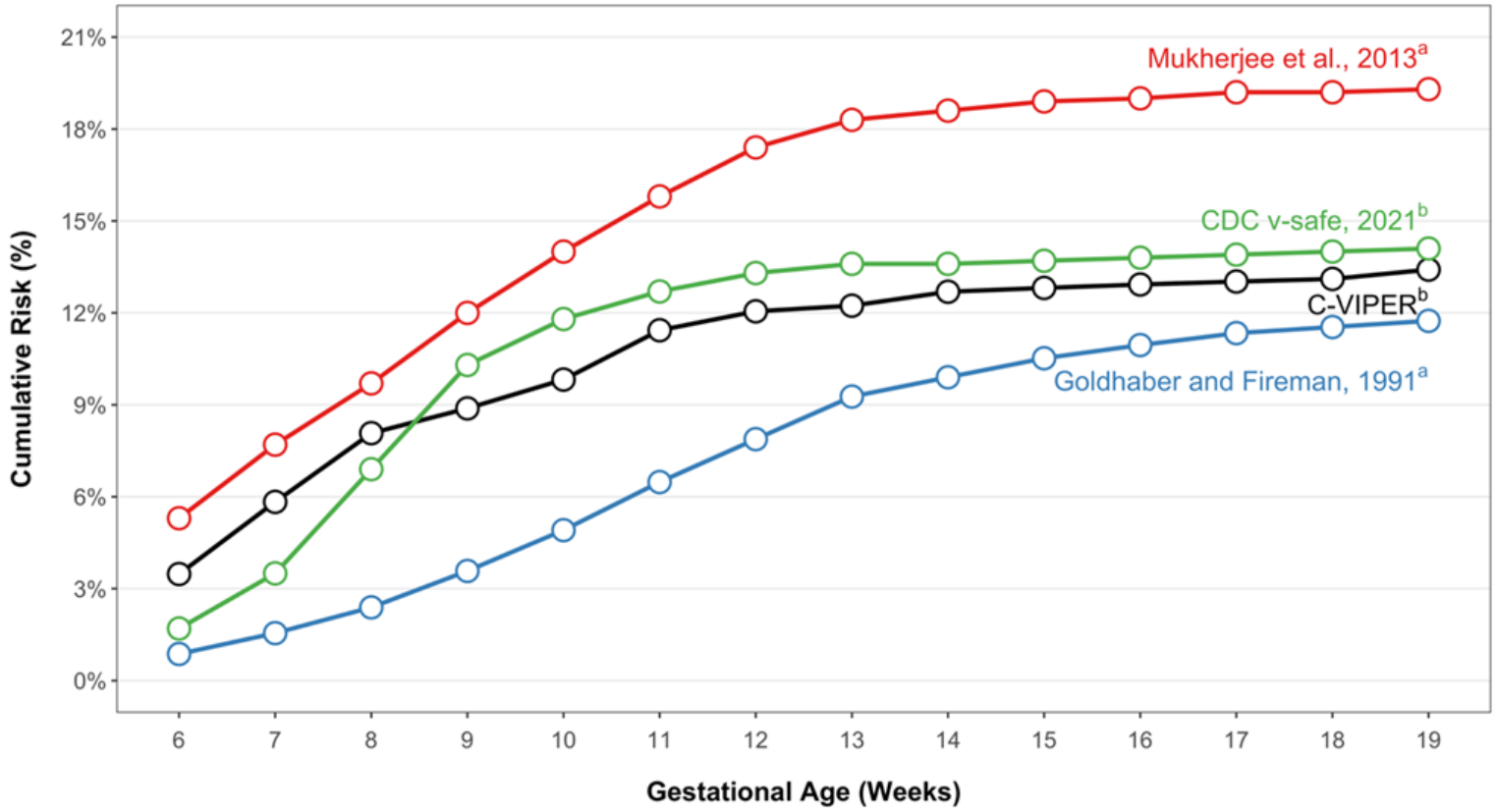
Risk of SAB in the general population

Example: Vaccines and spontaneous abortion

- *Among 3958 participants enrolled in the v-safe pregnancy registry, 827 had a completed pregnancy, of which 115 (13.9%) resulted in a pregnancy loss and 712 (86.1%) resulted in a live birth (mostly among participants with vaccination in the third trimester)* → *Restricted to completed pregnancies, included vaccinations after 20 weeks, shorter opportunity for vaccination in pregnancies with SABs*
- *Among 2,456 pregnant persons who received an mRNA COVID-19 vaccine preconception or prior to 20 weeks' gestation, the age standardized cumulative risk of SAB from 6–19 weeks' gestation was 12.8% (95% CI: 10.8–14.8%).* → **CDC corrected report for final publication**
- Reports regarding *COVID-19* vaccine safety in pregnancy indicate no obvious safety signals

Shimabukuro, T. T. et al. Preliminary findings of mRNA. Covid-19 vaccine safety in pregnant persons. N. Engl. J. Med. 384, 2273–2282 (2021).

Cumulative Risk of Spontaneous Abortion by Gestational Age



a) Population-based cohort: prospective community-based pregnancy cohort (Mukherjee et al., 2013) and U.S. claims (Goldhaber and Fireman, 1991)
b) mRNA vaccine exposed cohorts: CDC v-safe and Pregnancy Registry

Zauche LH et al. Receipt of mRNA Covid-19 Vaccines and Risk of Spontaneous Abortion. New England Journal of Medicine 2021

Mansour O, Hernandez-Diaz S, Wyszynski DF. mRNA COVID-19 vaccination early in pregnancy and the risk of spontaneous abortion in an international pregnancy registry. Pharmacoepidemiol Drug Saf. 2023

Lesson Learned

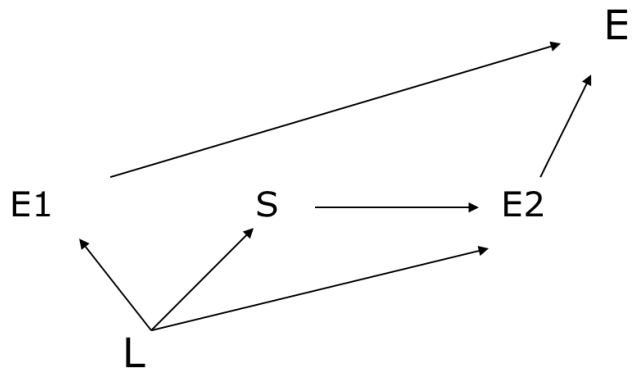
- **Risk of SAB in pregnancies “vaccinated in first 20 weeks”**
  - is not comparable with the expected SAB risk in the general population, or with “non-vaccinated” between conception and 20 weeks
  - **Recommendation**: Don’t

Hernandez-Diaz S, Huybrechts KF, Chiu YH, Yland JJ, Bateman BT, Hernan MA. Emulating a Target Trial of Interventions Initiated During Pregnancy with Healthcare Databases: The Example of COVID-19 Vaccination. Epidemiology 2023;34:238-46.

Immortal time bias

- To be “vaccinated during pregnancy”, pregnancy needs to survive without outcome until vaccination
- Time between conception and vaccination is “immortal”
  - If no outcome (S) exposure can be initiated at E1 or E2
  - If outcome (S) exposure can only be initiated at E1,

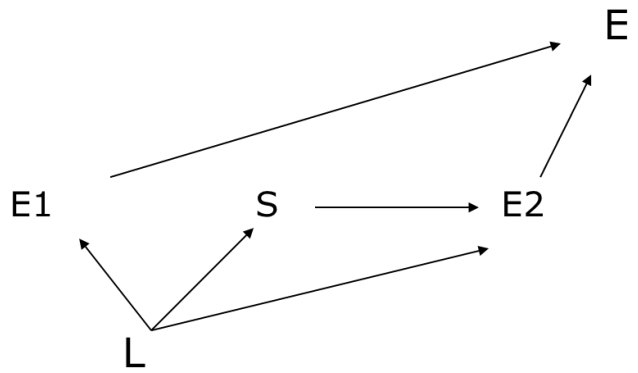
reverse causation S→E2



Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016:79:70-75

Immortal time bias

- Definition of exposure (E) as “any time in first 20 weeks” is affected by feta survival (S). Fetal losses would be inversely associated with the vaccine under the null
- **Avoidable bias.** Target Trial can help



Key components of the emulation of the target trial

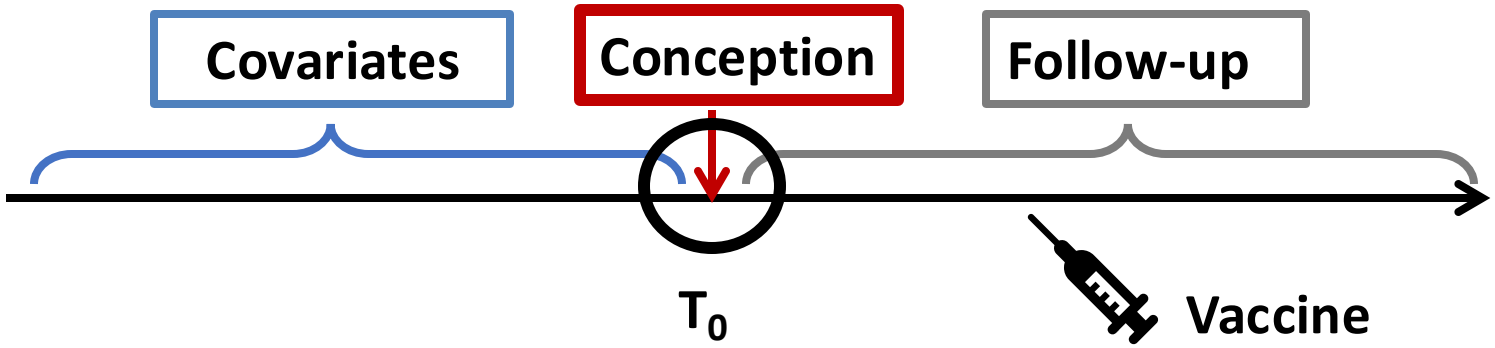
1. Randomized assignment
   - Emulation requires adjustment for confounding
2. Specification of time zero
   - Time zero must be synchronized with determination of eligibility and assignment of treatment strategies

- Lack of randomization is usually blamed for the failings of observational analyses, but…
  - sometimes incorrect specification of time zero is often the actual culprit

Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016:79:70-75

Time zero of follow-up in the Target Trial

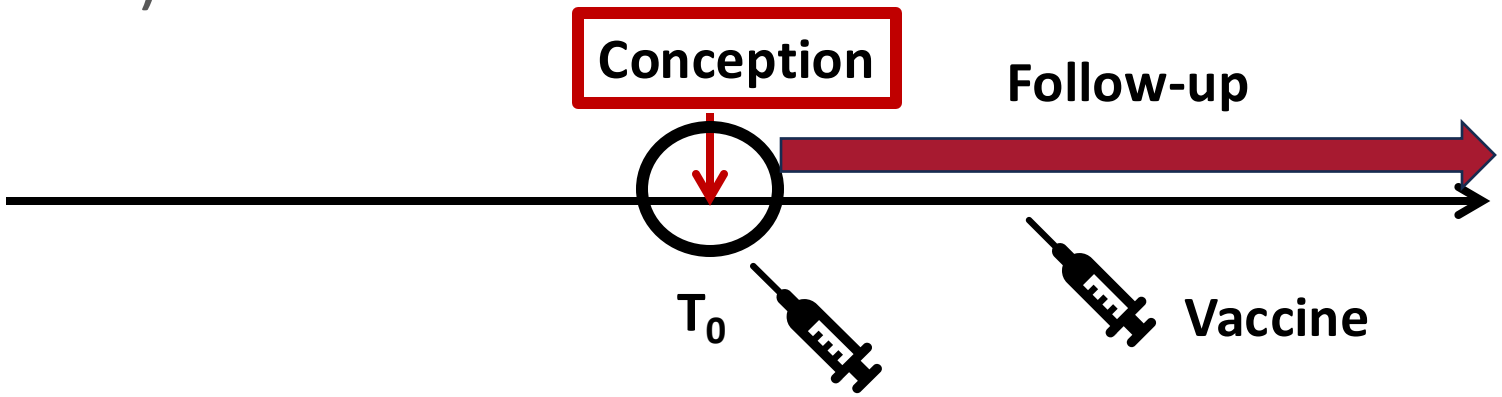
- For each person, the time when 3 things happen
  - eligibility criteria are met (e.g., being pregnant)
  - treatment strategies are assigned (e.g., vaccination)
  - study outcomes begin to be counted (e.g., spontaneous abortion)



- The same applies to observational emulations

Time zero of follow-up in the Target Trial

- Time zero must be synchronized with determination of eligibility (conception) and assignment of treatment strategies (e.g., vaccine)

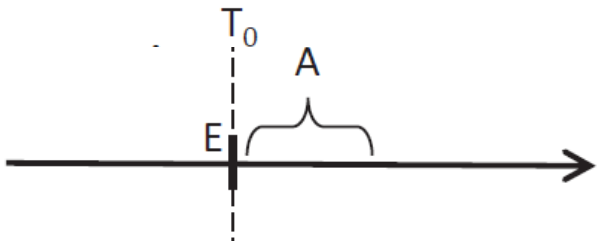


- The challenge with emulating the trial in observational data is that the treatment group (vaccine) may not be known at time zero (conception), it will be revealed after time zero

Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016:79:70-75

Time zero of follow-up in the Target Trial

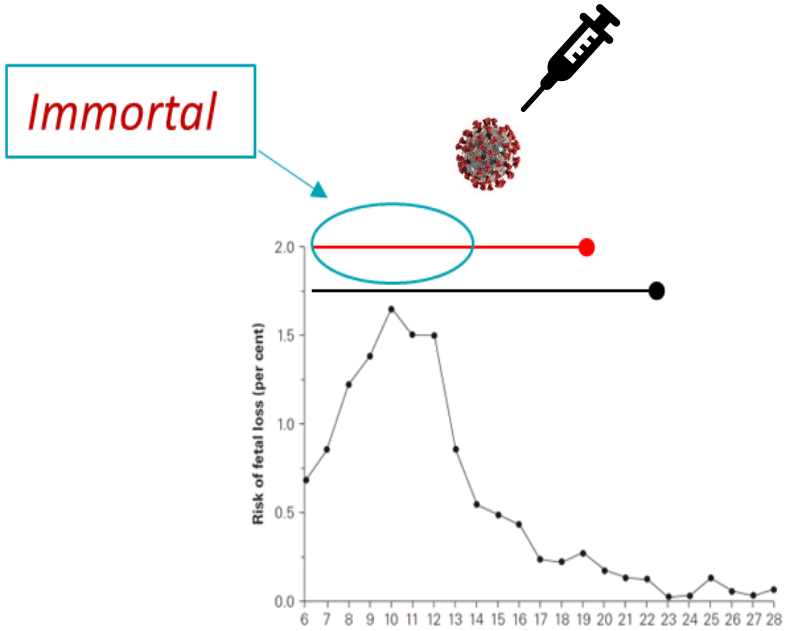
- Misalignment of eligibility criteria (E) and treatment assignment (A) leads to selection bias / immortal time bias

Type of emulation failure		Selection of...	Immortal time
4. T_0 at E but before A		eligible individuals at T_0 who remained under follow-up until completing a treatment strategy	Yes

Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol 2016:79:70-75

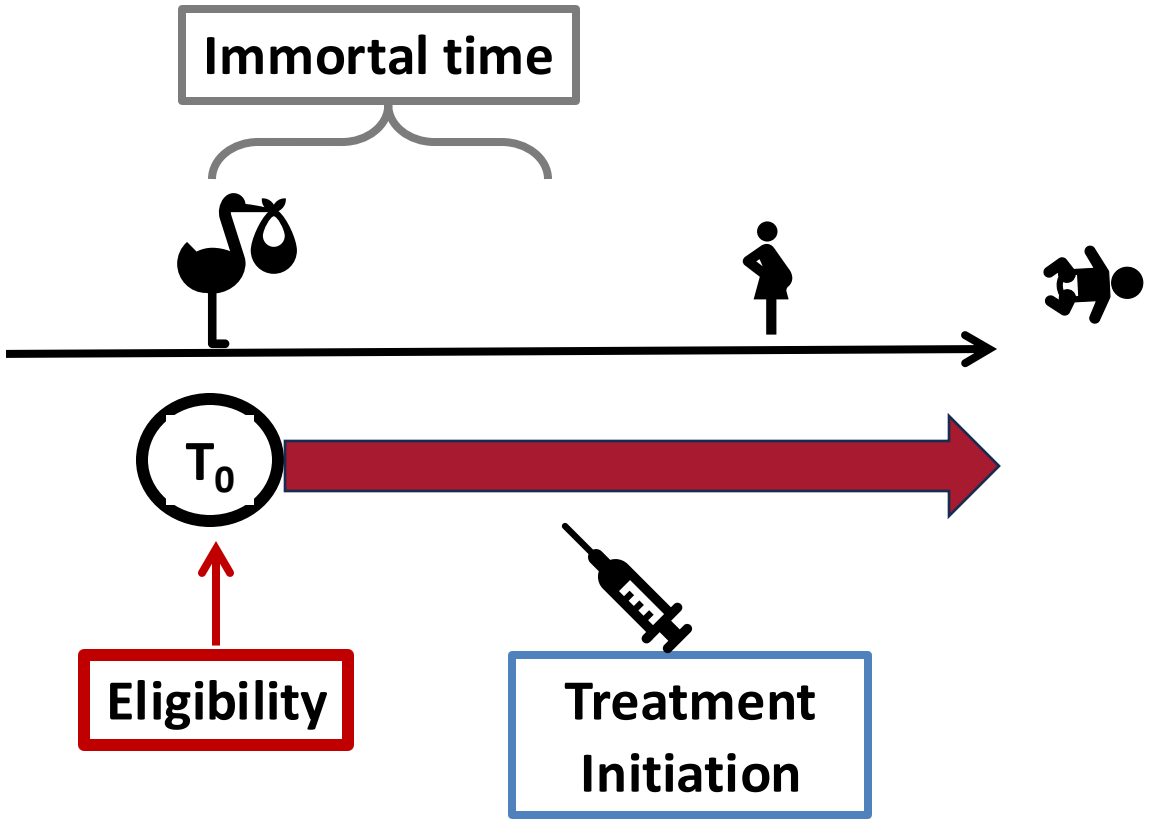
Incorrect emulation #1
Time zero at eligibility and follow to assess exposure

1. Vaccine group: Pregnant (meet the eligibility criteria) that received a vaccine in the 90 days after time zero
   - time zero is their first eligible time (e.g., LMP+5 weeks)
2. No vaccine group: Pregnant (meet the eligibility criteria) that did not receive a vaccine in the 90 days after time zero
   - time zero is their first eligible time



Time zero before treatment initiation (vaccination)

- Misalignment of eligibility criteria and treatment assignment leads to **selection bias** and introduces **immortal time**



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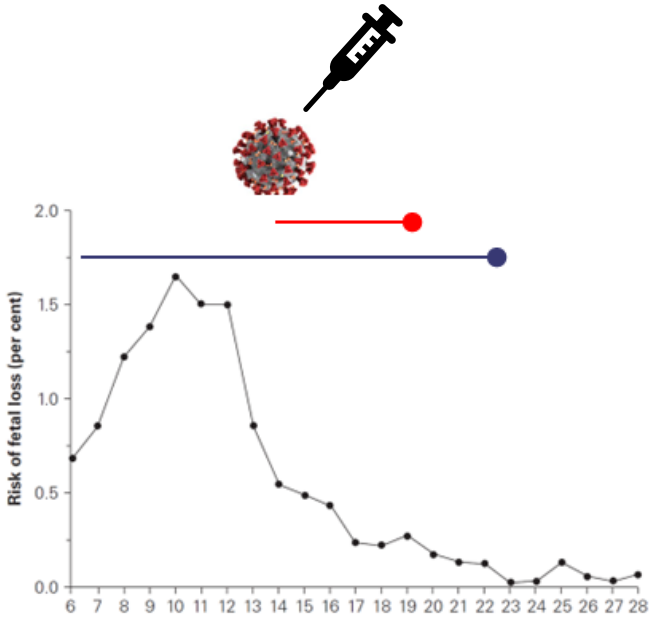
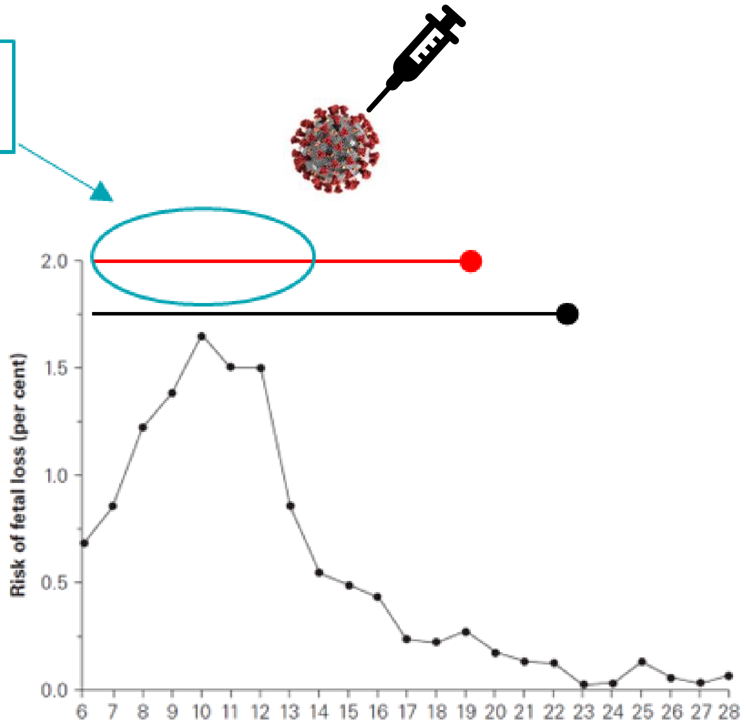
Incorrect emulation #2
Time zero at exposure. And the “No vaccine” group ?

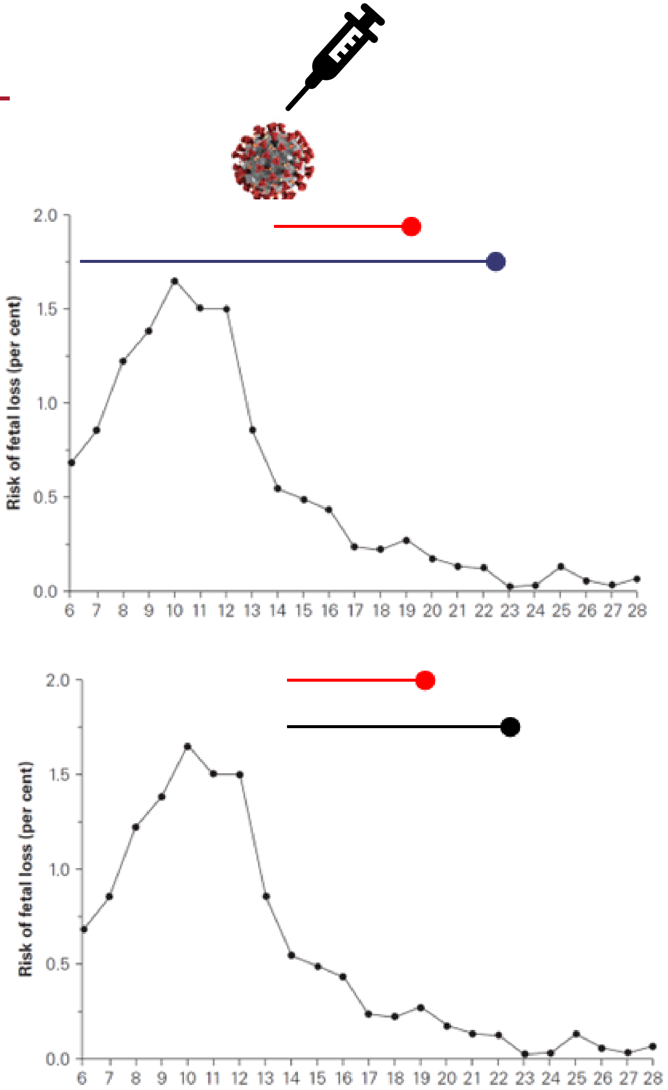
1. Vaccine group: Pregnant (meet the eligibility criteria) and receive a vaccine
   - time zero is the time of the vaccine
2. No vaccine group: Pregnant (meet the eligibility criteria) and did not receive a vaccine in the 90 days after time zero
   - time zero is their first eligible time



Choosing eligible times as time zero

Immortal





Rates (hazards) can be used to accommodate different follow-up

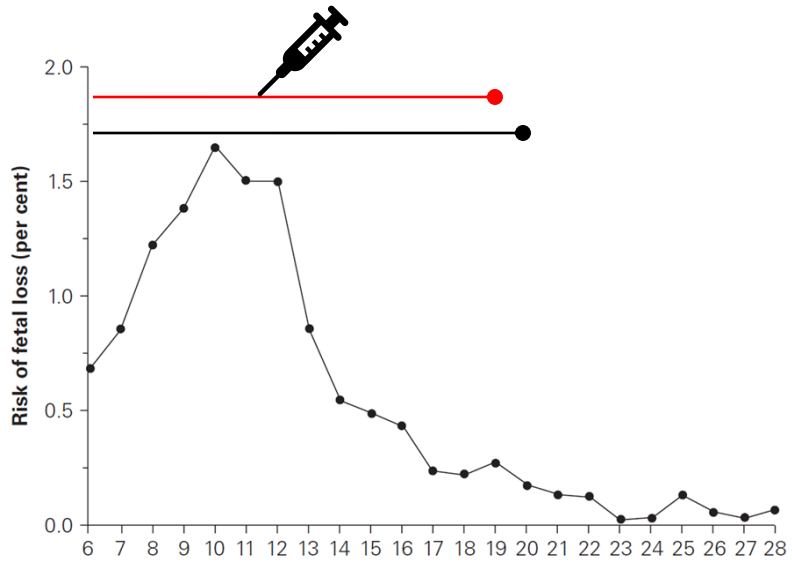
But also non-comparable because daily rate of SAB varies substantially

And would not estimate risks

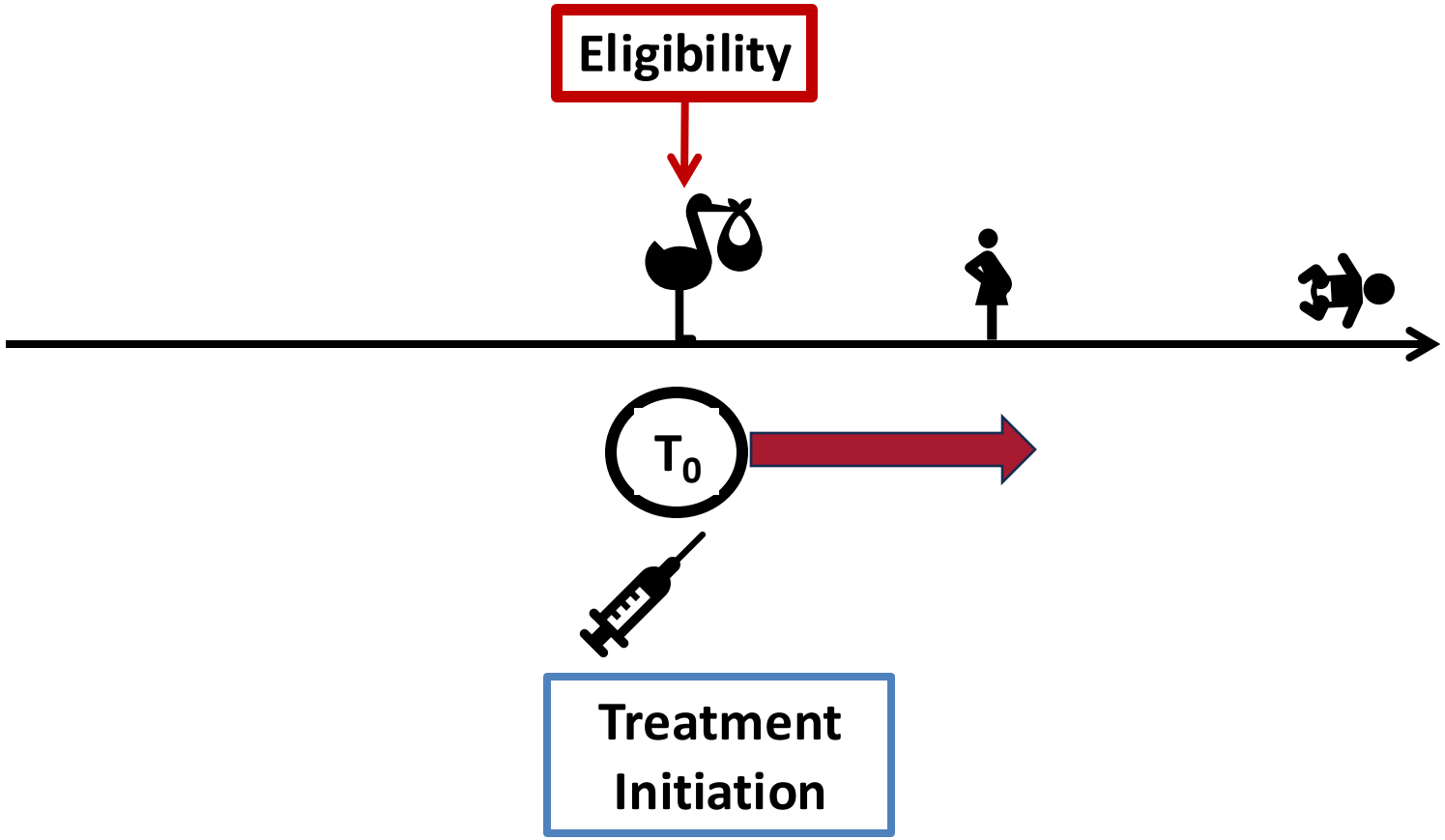
Recommendation: Align time zero of follow-up for exposed and reference

First, the question

- Does vaccine X **during the first 90 days of pregnancy** increase the risk of spontaneous abortions compared to no vaccination during this **grace period**?

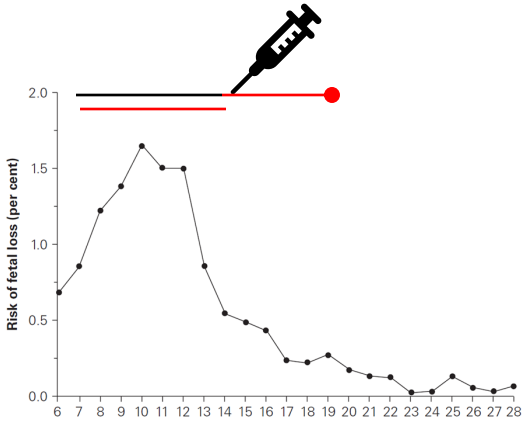


Alignment

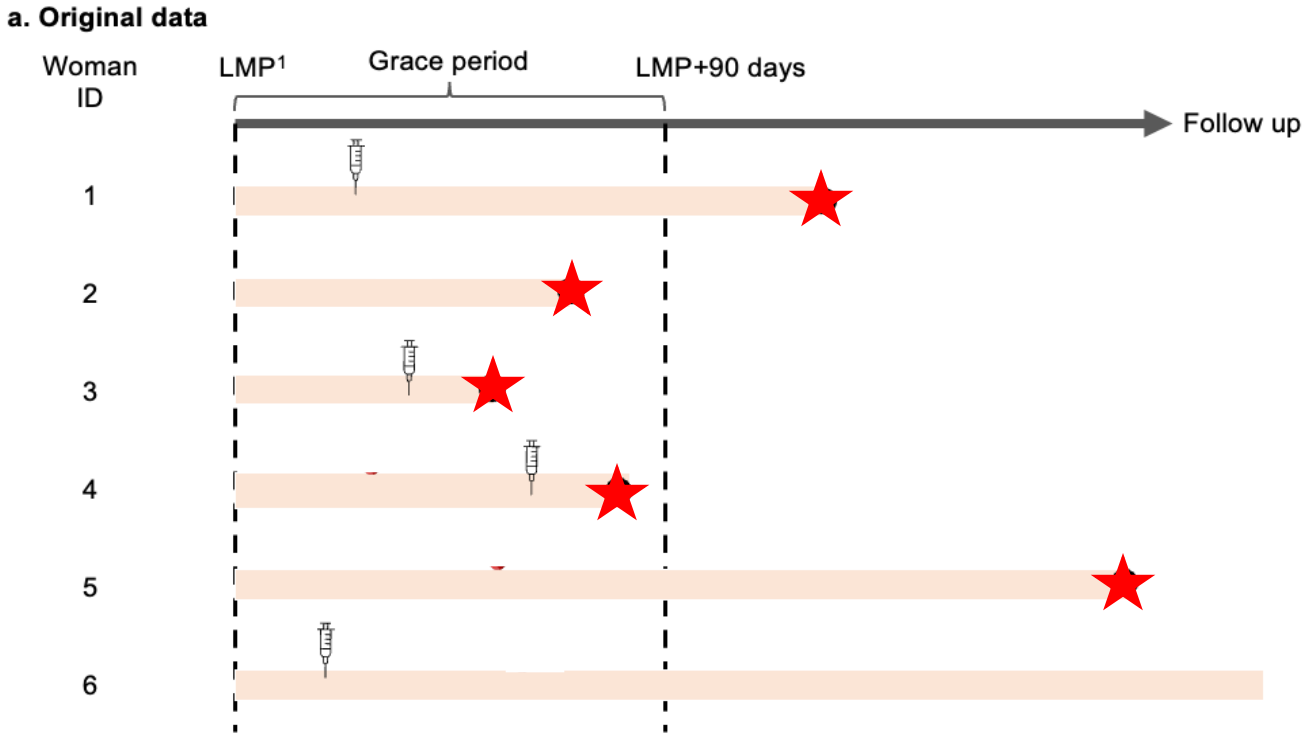


Assigning at conception with grace period
Cloning, Censoring and Weighing

- Emulate a trial **that assigns at conception "vaccination during first 90 days"**
  - Time zero is conception (or week 5 of gestation for example)
- In observational data treatment assignment is not known until vaccination (exposed) or 90 days (unexposed)
- Subjects would be cloned and contribute to both strategies until their treatment is evident, at which point they are censored from the other strategy
- Weighs are applied to adjust for informative censoring
  - Need to consider that individuals are cloned
    - Use a robust variance



Statistical analysis (for emulation)



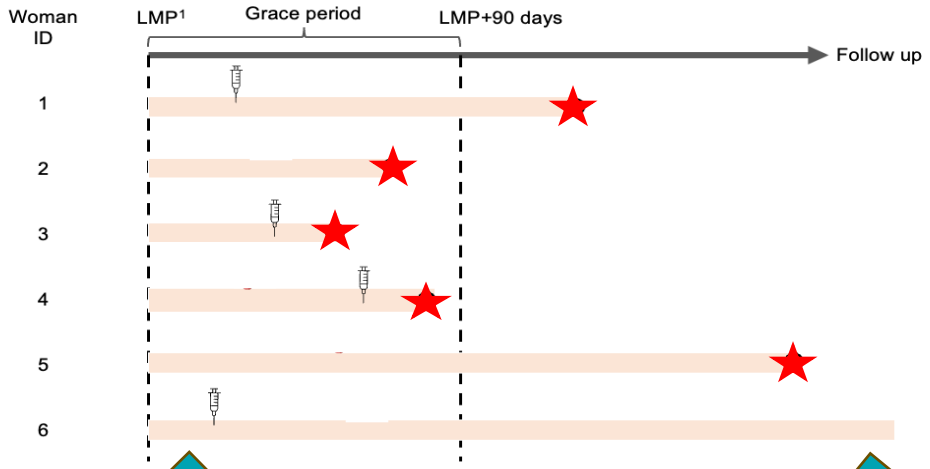
Indicates a vaccination

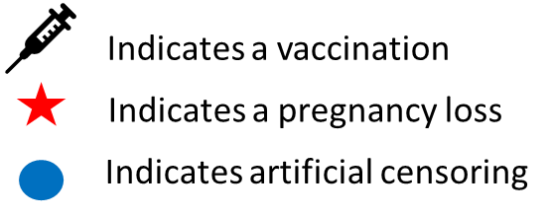
Indicates a pregnancy loss

Indicates artificial censoring

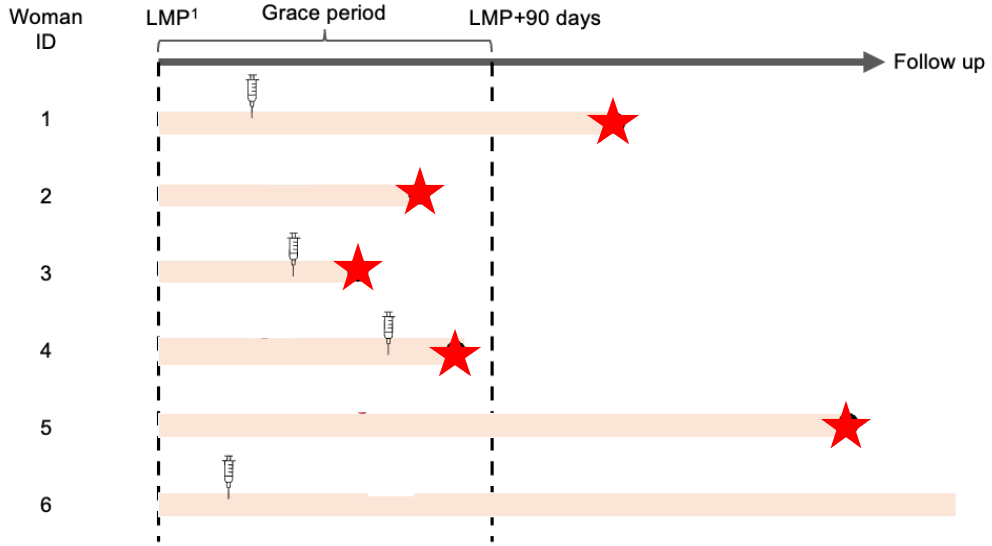
1. Clone

a. Original data

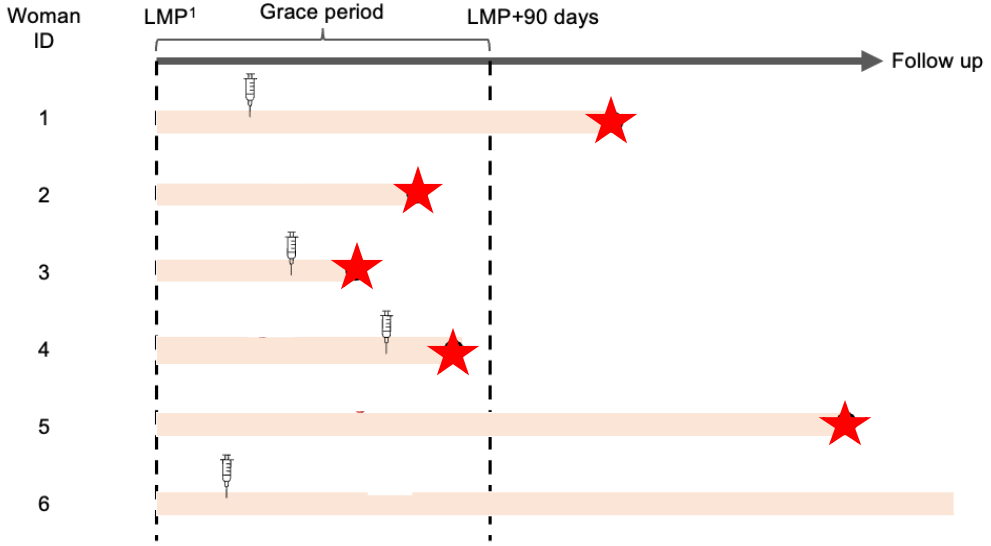




b. Clone assigned to strategy 1: vaccination

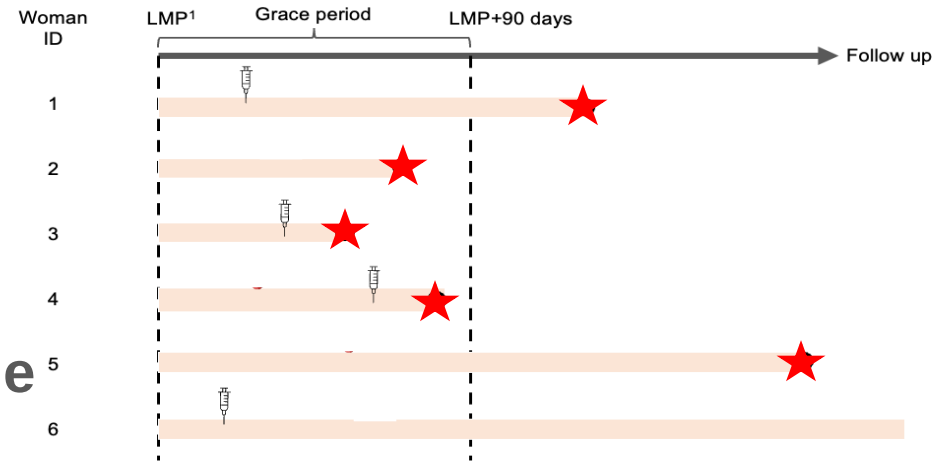


c. Clone assigned to strategy 2: no vaccination



1. **Clone**
2. **Censor when incompatible (●)**
3. **Conduct analyses in the cloned population**

a. Original data

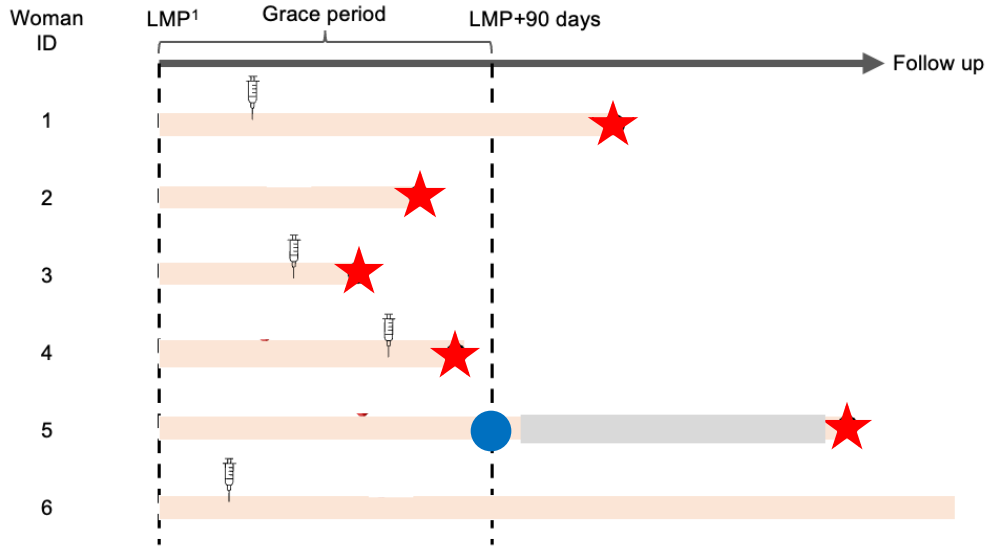


Indicates a vaccination

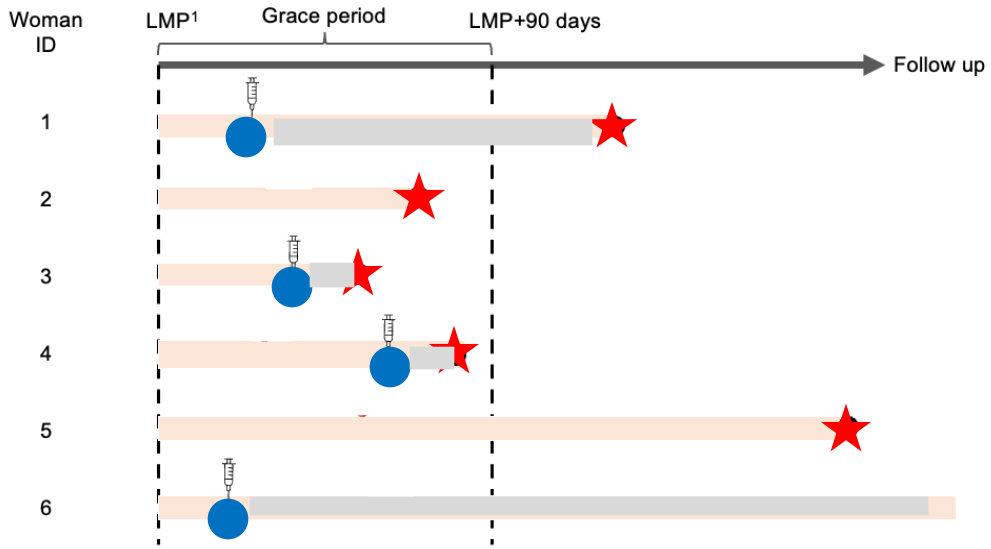
Indicates a pregnancy loss

Indicates artificial censoring

b. Clone assigned to strategy 1: vaccination



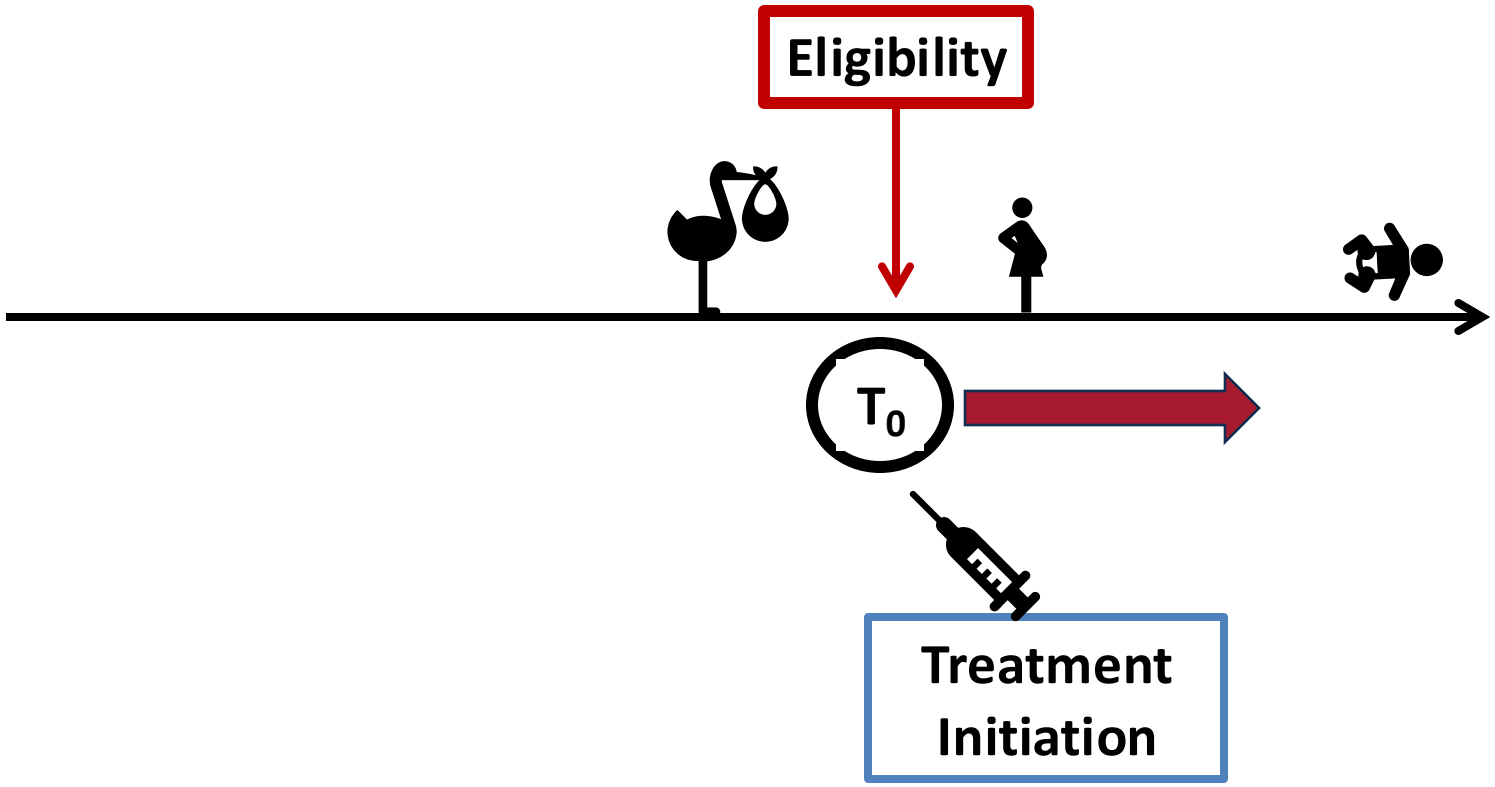
c. Clone assigned to strategy 2: no vaccination



An alternative question → another target trial

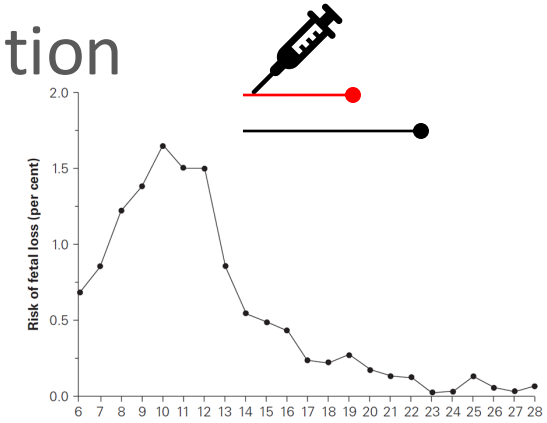
- Does vaccine X at prenatal visit in first 20 weeks of pregnancy increase the risk of spontaneous abortions compared to no vaccination?

Alignment



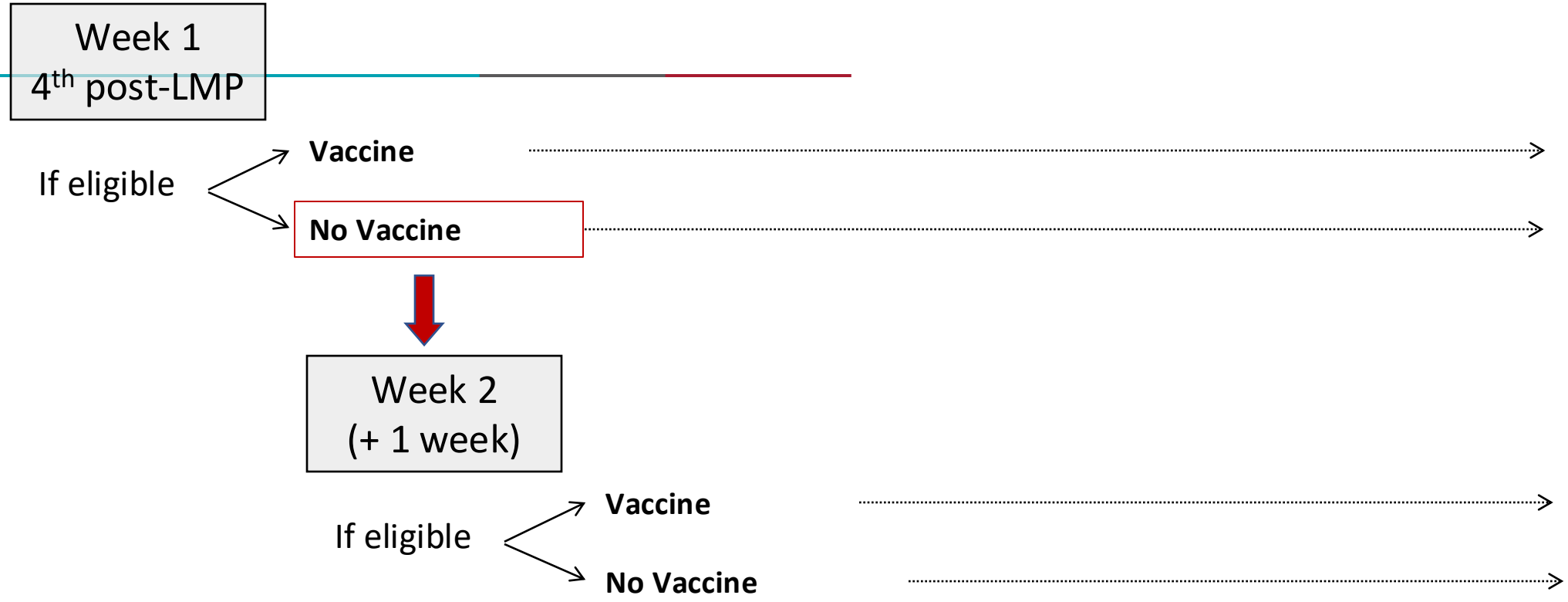
A solution for homogeneous distribution of gestational age at time zero of follow-up

- Sequential trial: Emulate a new target trial each week of follow-up
  - Time zero is different in each trial
- Include in the emulation of each trial all individuals who are eligible (i.e., not previously vaccinated and still pregnant) at its corresponding time zero
- Combine all target trials for a more precise estimation
  - Need to consider that some individuals will contribute to the emulation of several trials
    - Use a robust variance

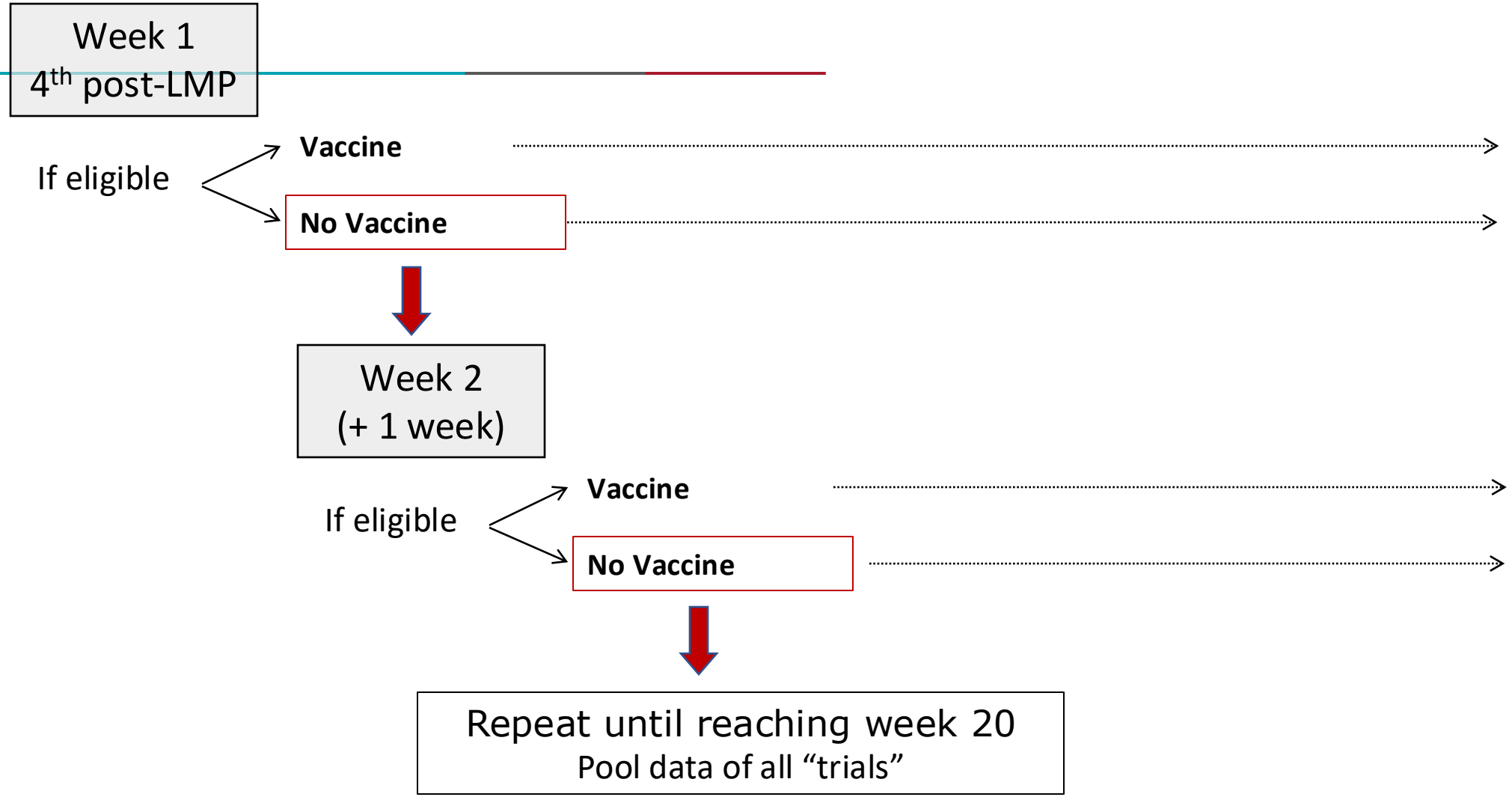


Target trial: sequential emulation

Target trial: sequential emulation

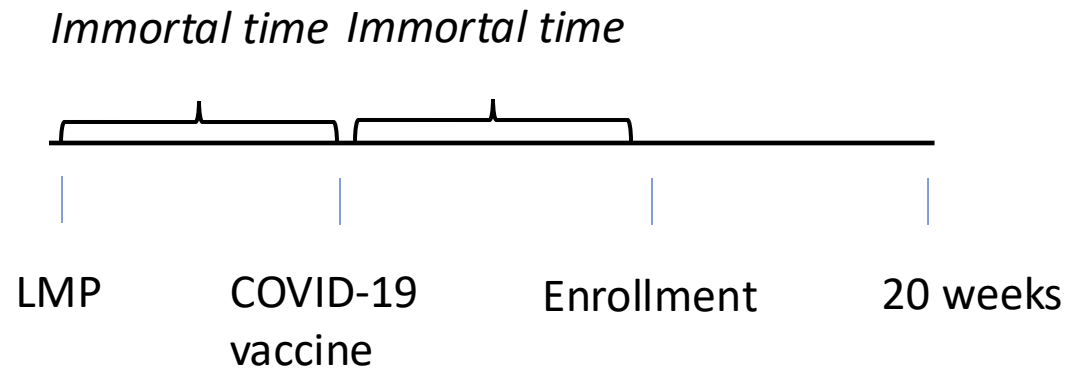


Target trial: sequential emulation



For pregnancy registries

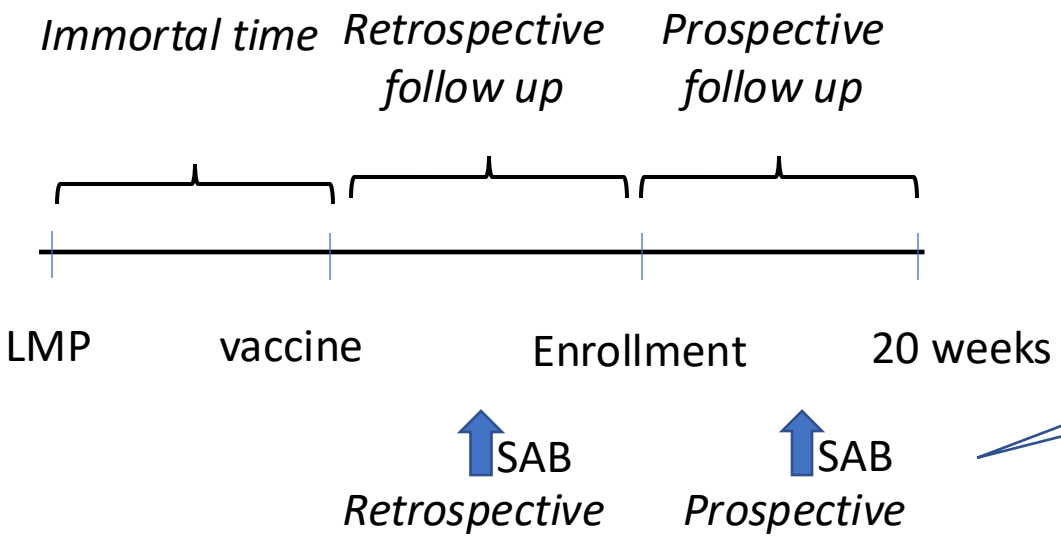
- Time until vaccination is immortal (cannot have SAB and still be pregnant at vaccination)
- IF inclusion criteria “currently pregnant” then time until enrollment also immortal



For pregnancy registries

- Prospective enrollment of pregnancies can miss early abortions (left truncation) and potential early effects on implantation.
- Retrospective enrollment of SAB
  - If included → overestimation if self-selection
  - If excluded → underestimation of SAB cases triggered by SAB

For pregnancy registries



If SAB occurs right after vaccination, SAB cannot be prospective

SAB may trigger enrollment (overestimate risk), particularly among vaccinated (overestimation or RR)

Example

COVID-19 Vaccination

Objective

- Question: Does vaccine X at first visit early in pregnancy increase the risk of spontaneous abortions (pregnancy losses during first 20 or 24 weeks of pregnancy) compared to no vaccination?
  - Propose to emulate a Target Trial using a large healthcare database

Hernández-Díaz S, Huybrechts KF, Chiu YH, Yland JJ, Bateman BT, Hernán MA. Emulating a Target Trial of Interventions Initiated During Pregnancy with Healthcare Databases: The Example of COVID-19 Vaccination. Epidemiology. 2023 Mar 1;34(2):238-246.

Protocol Component	Target Trial	Emulation
Eligibility Criteria	▪ Enrollment period: January to December 2021 ▪ Pregnant: Gestational week 5 to 20 ▪ Aged 18-50 years ▪ Enrolled in insurance with prescription benefits or healthcare system captured in electronic health records at least 6 months before trial initiation ▪ No active COVID-19 infection ▪ No previous coronavirus vaccine	Same. We apply the eligibility criteria by searching for codes in at least 6 months enrollment

Protocol Component	Target Trial	Emulation
Treatment Strategies	1) First dose of vaccine at enrollment, second as indicated 2) Not vaccinated before 20 weeks	Same. We ascertain vaccination, including brand and date, based on pharmacy dispensations and procedure codes for vaccine administration
Assignment Procedures	Individuals are randomly assigned at enrollment to one of the two vaccination strategies and are aware of the strategy to which they have been assigned	Individuals assigned to each vaccination strategy are assumed to be comparable conditional on baseline covariates: gestational week at enrollment, calendar month, age, month, region, chronic conditions, health care utilization, etc

Protocol Component	Target Trial	Emulation
Follow-up Period	▪ Starts at vaccine assignment ▪ Ends at the occurrence of an SAB, 20 weeks after LMP, or loss to follow-up (disenrollment from insurance), whichever occurs earliest	▪ Starts at first vaccine dispensation or procedure ▪ Same except for loss to follow-up. Disenrollment from insurance would be a reason for loss to follow-up. However, pregnancy status is often ascertained by the end-of-pregnancy outcome, which forces a "complete case" approach

Protocol Component	Target Trial	Emulation
Outcome	Clinical spontaneous abortion (SAB)	Same. Diagnoses are identified with algorithms based on combinations of codes identified in claims
Causal Contrasts of Interest	Intention-to-treat effect Per-Protocol effect	Observational analog of per protocol effect

Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-764.

Protocol Component	Target Trial	Emulation
Outcome	Clinical spontaneous abortion (SAB)	Same. Diagnoses are identified with algorithms based on combinations of codes identified in claims
Causal Contrasts of Interest	Intention-to-treat effect Per-Protocol effect	Observational analog of per protocol effect
Analyses	Intention-to-treat analysis: estimate SAB risks in each group and compare them through risk differences and risk ratios (with adjustment for loss to follow-up). Per-protocol analysis: estimate risks in groups defined by adherence to assigned treatment (vaccination or no vaccination) with adjustment for baseline covariates via matching, standardization, etc.	Same per-protocol analysis, except for restriction to pregnancies without loss to follow-up

Conclusions

Lesson learned

- Definition of exposure as “any time during a trimester” can introduce immortal time bias
  - Same applies to other cumulative outcomes (e.g., preterm)
- Solution: Conceptualizing a hypothetical target trial will force us to define a causal question and thus specify population, exposure, time-zero, and outcome
  - May need methods to balance gestational age at time-zero (e.g., cloning, sequential trials emulation)

References - Methods

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References - Examples

- Chiu YH, Stensrud MJ, Dahabreh IJ, Rinaudo P, Diamond MP, Hsu J, Hernández-Díaz S and Hernan MA. The Effect of Prenatal Treatments on Offspring Events in the Presence of Competing Events: An Application to a Randomized Trial of Fertility Therapies. Epidemiology. 2020;31:636-643.
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- Chiu YH, Huybrechts KF, Patorno E, et al. Metformin Use in the First Trimester of Pregnancy and Risk for Nonlive Birth and Congenital Malformations: Emulating a Target Trial Using Real-World Data. Annals of internal medicine 2024;177:862-70.

Take a random sample rather than all eligible
(not as efficient, but computational easier maybe)

- How to choose a time zero in the presence of multiple eligible times?
  - Choose one: time of first eligibility, random time
  - Choose all -> sequence of nested trials with increasing time zero
  - Choose some: all when initiation, random sample when no initiation
- What if treatment strategies are not uniquely defined at time zero? (e.g., grace periods of initiation, duration effect)
  - Randomly assign the individual to one of the strategies
  - Create exact copies of the individual (i.e., clones) in the data and assign each clone to one the strategies (Note: requires variance adjustment)
  - Individuals or clones need to be censored at the time their data stop being consistent with the strategy they were assigned to; adjust for potential selection bias introduced by post-time zero censoring

Hernán et al. J Clin Epidemiol 2016