Emulating target trials of post-exposure vaccines using observational data

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ISPE Vaccine SIG

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My research interests

Goal: to better align empirical studies with the real-world clinical and scientific questions that matter most to researchers and patients.

Interests:

- Pragmatic randomized trial design
- Using observational data to estimate causal effects
- Counterfactual prediction

Overview

- Motivation
  - Target trial framework
  - Challenges of evaluating post-exposure vaccines
- Potential trial designs
- Application: JYNNEOS vaccine for Mpox
- Conclusions
- Future work

Motivation

Randomized trials are great but not always feasible, ethical, or timely. Nor can they answer the vast array of questions we'd like to study.

When trials are not possible often we must rely on observational data, but they often yield discordant results.

A common conception is that it is *primarily* the lack of random assignment (confounding) that drives the differences.

💡 Insight: At least some of the differences are due to ill-defined protocols in observational studies, i.e. not explicitly mimicking the design of the randomized trial (apples to oranges).

Background

ORIGINAL ARTICLE

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] *Alvaro Alonso,*[c] *Roger Logan,*[a] *Francine Grodstein,*[a,d] *Karin B. Michels,*[a,d,e] *Walter C. Willett,*[a,d,f] *JoAnn E. Manson,*[a,d,g] *and James M. Robins*[a,h]

What is a target trial?

Imagine the hypothetical trial we would like to conduct, but can't. Specifying the protocol for this ideal trial can help us:

- Unambiguously formulate the causal question that we're interested in.
- Properly define eligibility, treatment strategies to compare, and adherence.
- Figure out the appropriate time zero and the correct sequence of follow up.

This is what is meant by a ***target trial.***

Claim: Many of most egregious discrepancies between observational studies and randomized trials are due to improper or ill-conceived setup rather than confounding per se.

What is an emulation?

Once the target trial is identified, we can use established causal inference approaches to **emulate** the trial using observational data.

1. Define eligibility and time zero
2. Define treatment strategies and adherence
    - Can be complex dynamic or static regimes
3. Manipulate data to mimic trial
    - Clone, censor, weight
    - Sequential nested trials
4. Estimate causal effects
    - Inverse probability weighting
    - G-formula
    - Doubly robust

Advantages

- Can consider more treatment strategies or regimes.
  - Head to head comparisons.
  - Off-label use.
  - Dosing or alternative regimens.
  - Safety/long-term use.
- Can get treatment utilization under “real-world” conditions.
- Can consider subgroups not included in original trial.
- Can get quick(er) insights as disease or treatment landscape evolves.
- Useful for organizing the chaos of claims or electronic medical record data.

Example Target Trials for SARS-CoV-2 vaccines

The NEW ENGLAND JOURNAL of MEDICINE

12 studies that impacted the practice of medicine

IMAGES IN CLINICAL MEDICINE
Cerebral Alveolar Echinococcosis

ORIGINAL ARTICLE
Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A

PERSPECTIVE
The Promise

EDITORIAL
Another Victory Hemophilia

Editor's Note: This article was published on December 1, 2021, at NEJM.org.

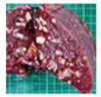
ORIGINAL ARTICLE

Comparative Effectiveness of BNT162b2 and mRNA-1273 Vaccines in U.S. Veterans

Barbra A. Dickerman, Ph.D., Hanna Gerlovin, Ph.D., Arin L. Madenci, M.D., Ph.D., Katherine E. Kurgansky, M.P.H., Brian R. Ferolito, M.Sc., Michael J. Figueroa Muñiz, B.Sc., David R. Gagnon, M.D., Ph.D., M.P.H., J. Michael Gaziano, M.D., M.P.H., Kelly Cho, Ph.D., Juan P. Casas, M.D., Ph.D., and Miguel A. Hernán, M.D., Dr.P.H.

Example Target Trials for SARS-CoV-2 vaccines

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE
Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A

IMAGES IN CLINICAL MEDICINE
Cerebral Alveolar Echinococcosis

PERSPECTIVE
The Promise

Editor's Note: This article was published on April 13, 2022, at NEJM.org.

ORIGINAL ARTICLE

Fourth Dose of BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Ori Magen, M.D., Jacob G. Waxman, M.D., Maya Makov-Assif, M.D., Roni Vered, M.D., Dror Dicker, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Y. Reis, Ph.D., Ran D. Balicer, M.D., and Noa Dagan, M.D.

Article Figures/Media Metrics

27 References 28 Citing Articles Letters

April 28, 2022
N Engl J Med 2022; 386:1603-1614
DOI: 10.1056/NEJMoa2201688

Example Target Trials for SARS-CoV-2 vaccines

The NEW ENGLAND JOURNAL of MEDICINE

PERSPECTIVE
The Promise

REVIEW ARTICLE
Antiretroviral Therapy and Adverse Pregnancy Outcomes in People Living with HIV

PERSPECTIVE
Regulating Reproductive Medicine in a World without Roe

ORIGINAL ARTICLE

BNT162b2 Vaccine Effectiveness against Omicron in Children 5 to 11 Years of Age

Chandra J. Cohen-Stavi, Ph.D., Ori Magen, M.D., Noam Barda, M.D., Ph.D., Shlomit Yaron, M.D., Alon Peretz, M.D., Doron Netzer, M.D., Carlo Giaquinto, M.D., Ali Judd, Ph.D., Leonard Leibovici, M.D., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Ben Y. Reis, Ph.D., et al.

Article Figures/Media Metrics

July 21, 2022
N Engl J Med 2022; 387:227-236
DOI: 10.1056/NEJMoa2205011

20 References 3 Citing Articles

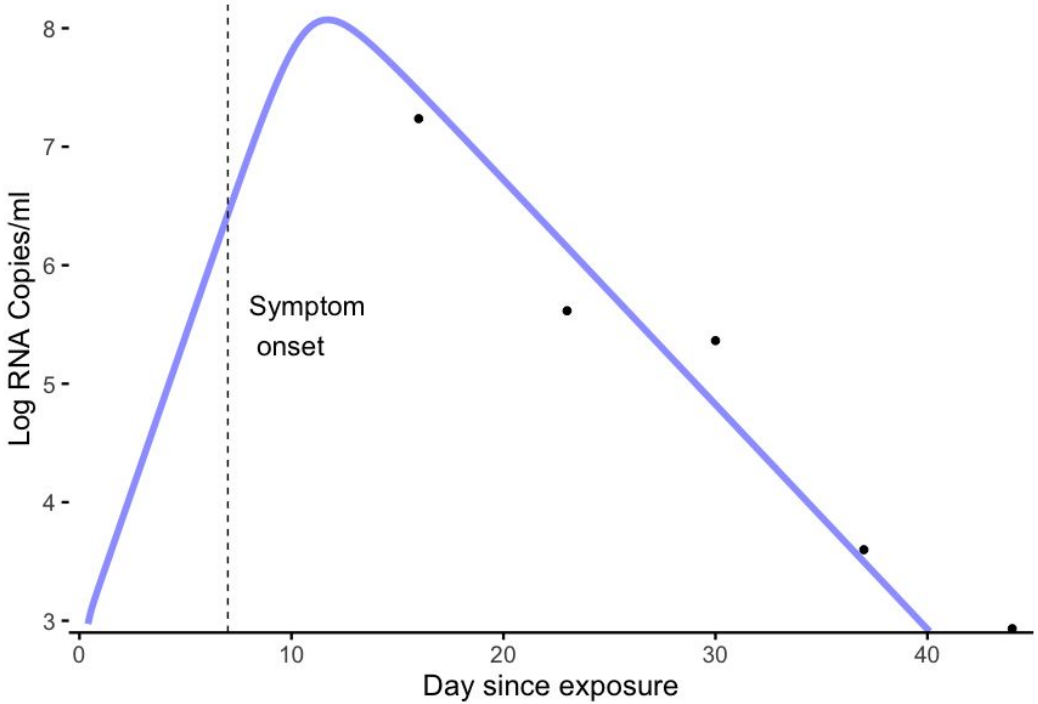
Limitations

- Just because you've specified the target trial and used a proper method to emulate it **doesn't** mean that you will succeed.
  - Need to still think carefully about confounding control (requires subject matter expertise).
  - Be wary of passive measurement.
  - Follow up and the observation process.
- Options to increase confidence:
  - Benchmarking to existing trial evidence.
  - Negative control variables.

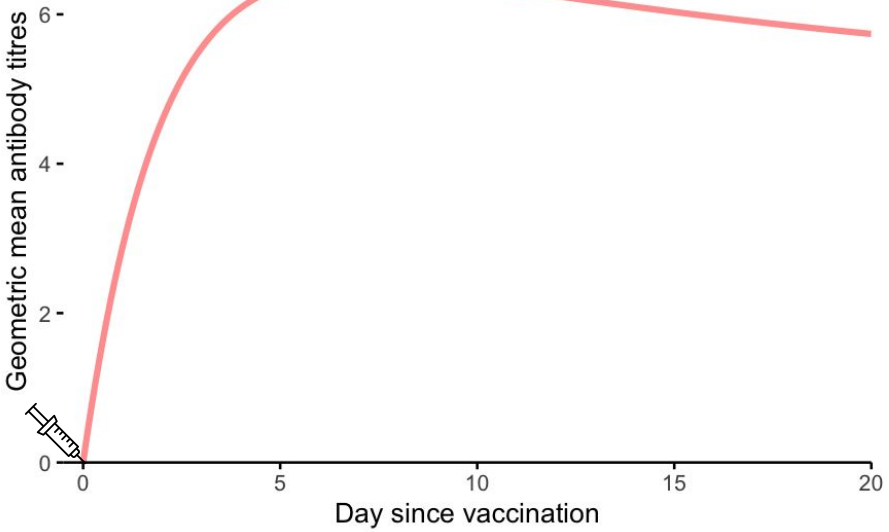
Postexposure vaccination

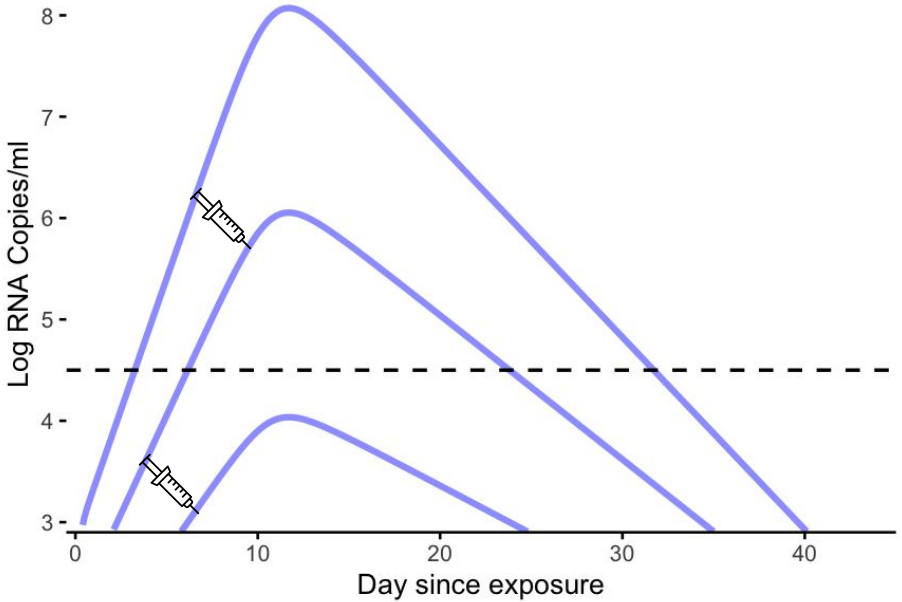
- If a vaccine can induce an immune response **faster or more specific** than that produced by natural infection, **post-exposure administration** could reduce chance of disease onset or severity.
- However, post-exposure vaccine trials are rare:
  - Depending on pathogen, window between exposure and onset may be short.
  - Equipoise, pre-exposure and immunogenicity data, and emergency use.
- In the absence of trials, effectiveness is assessed using **observational data.**
- Thus, they are ideal candidates for **target trial emulation**.

The biology of an acute infection

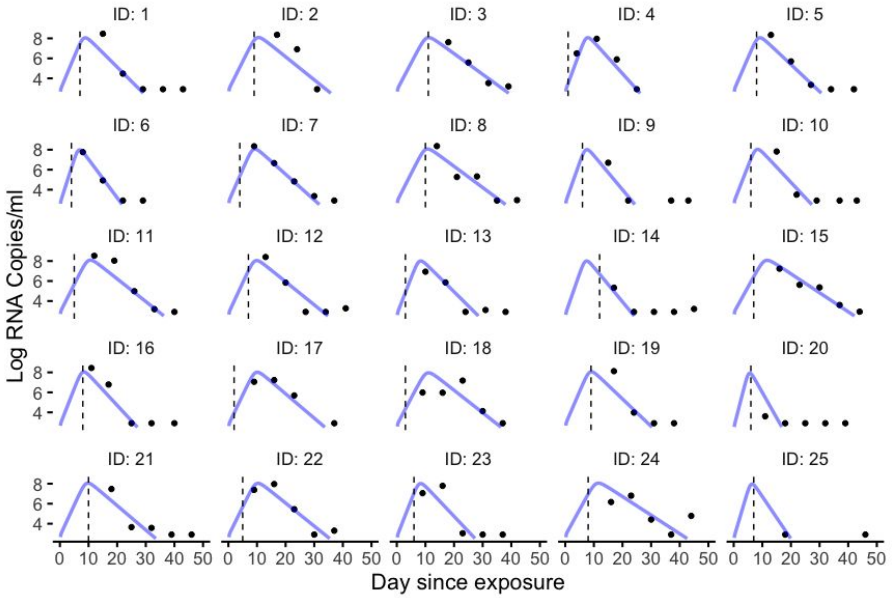


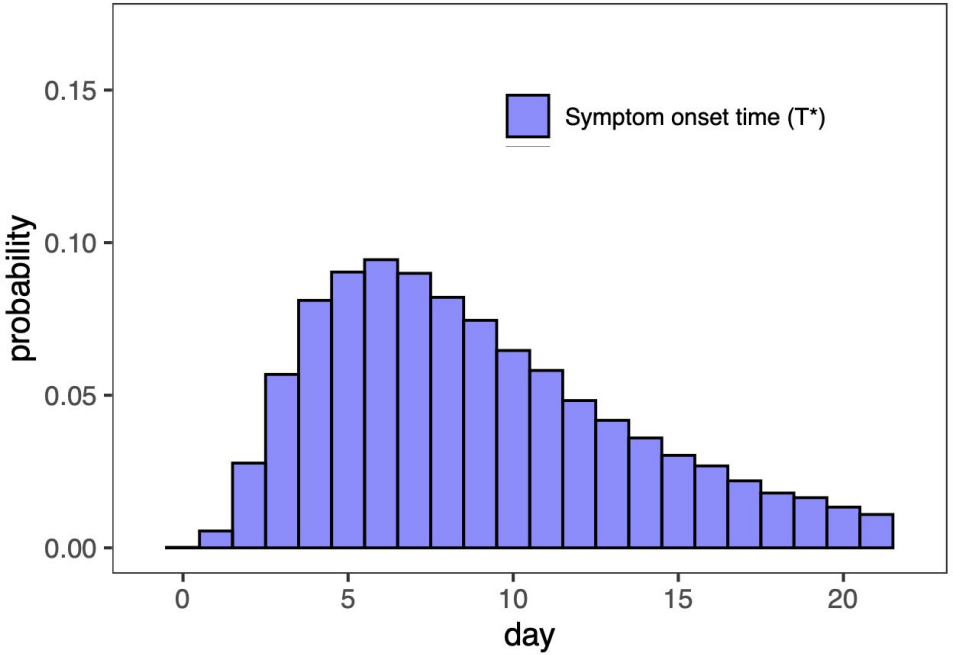
The theory of postexposure prophylaxis



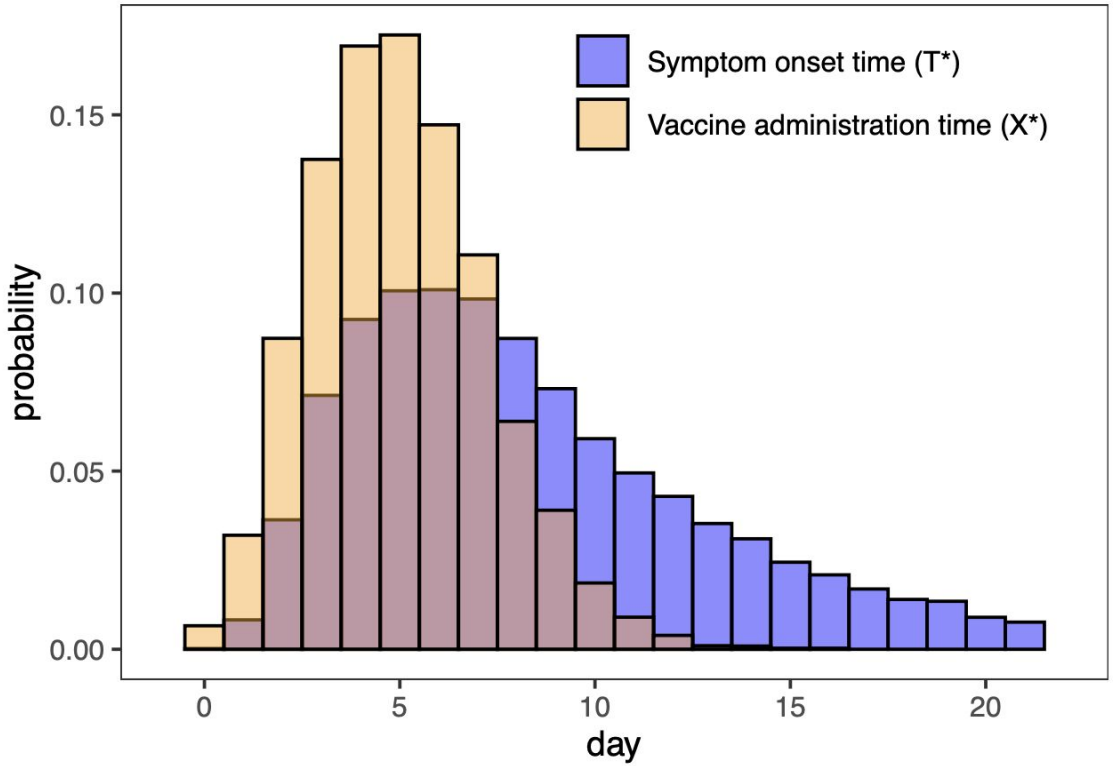


Adding heterogeneity





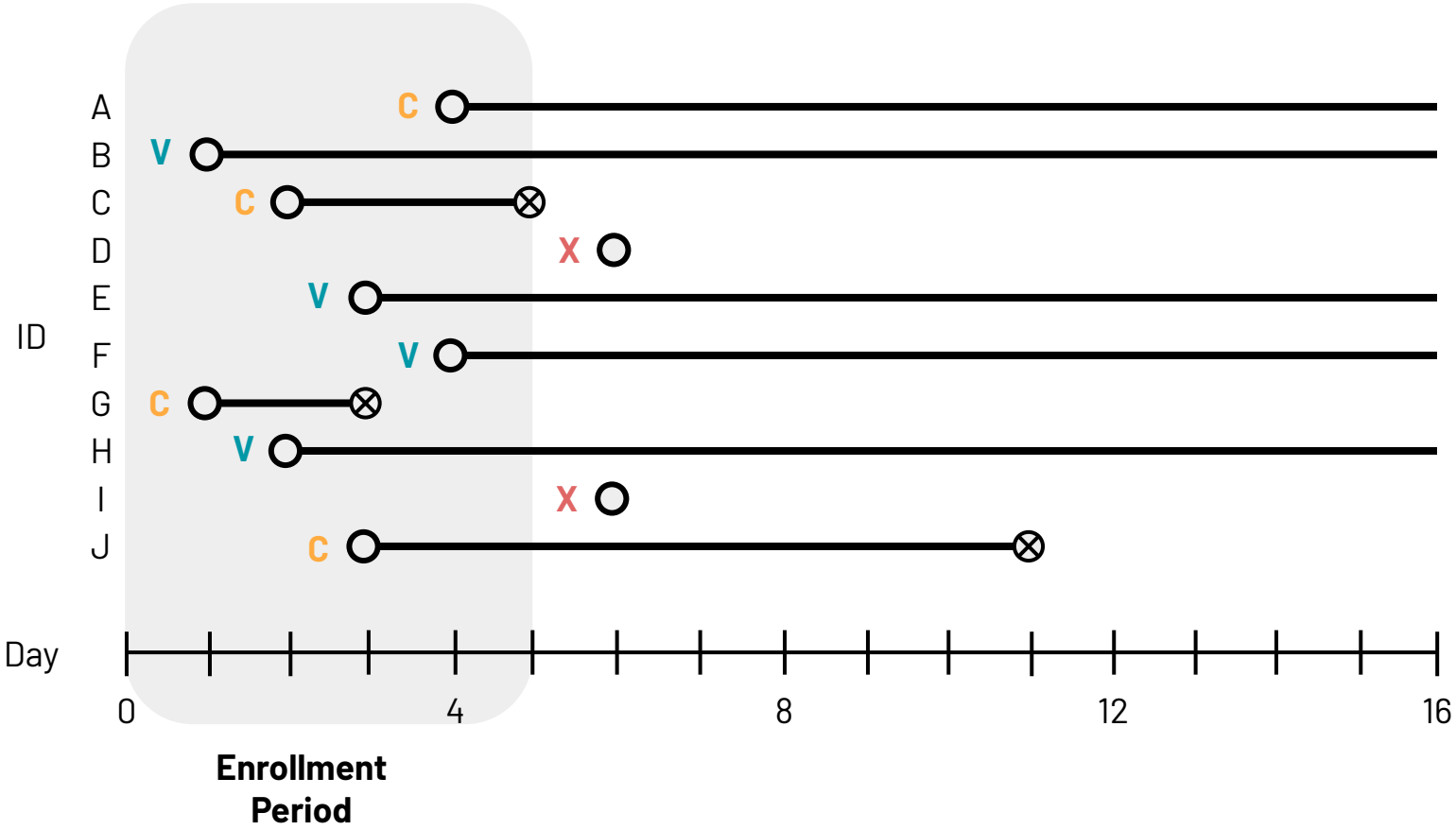
The challenge



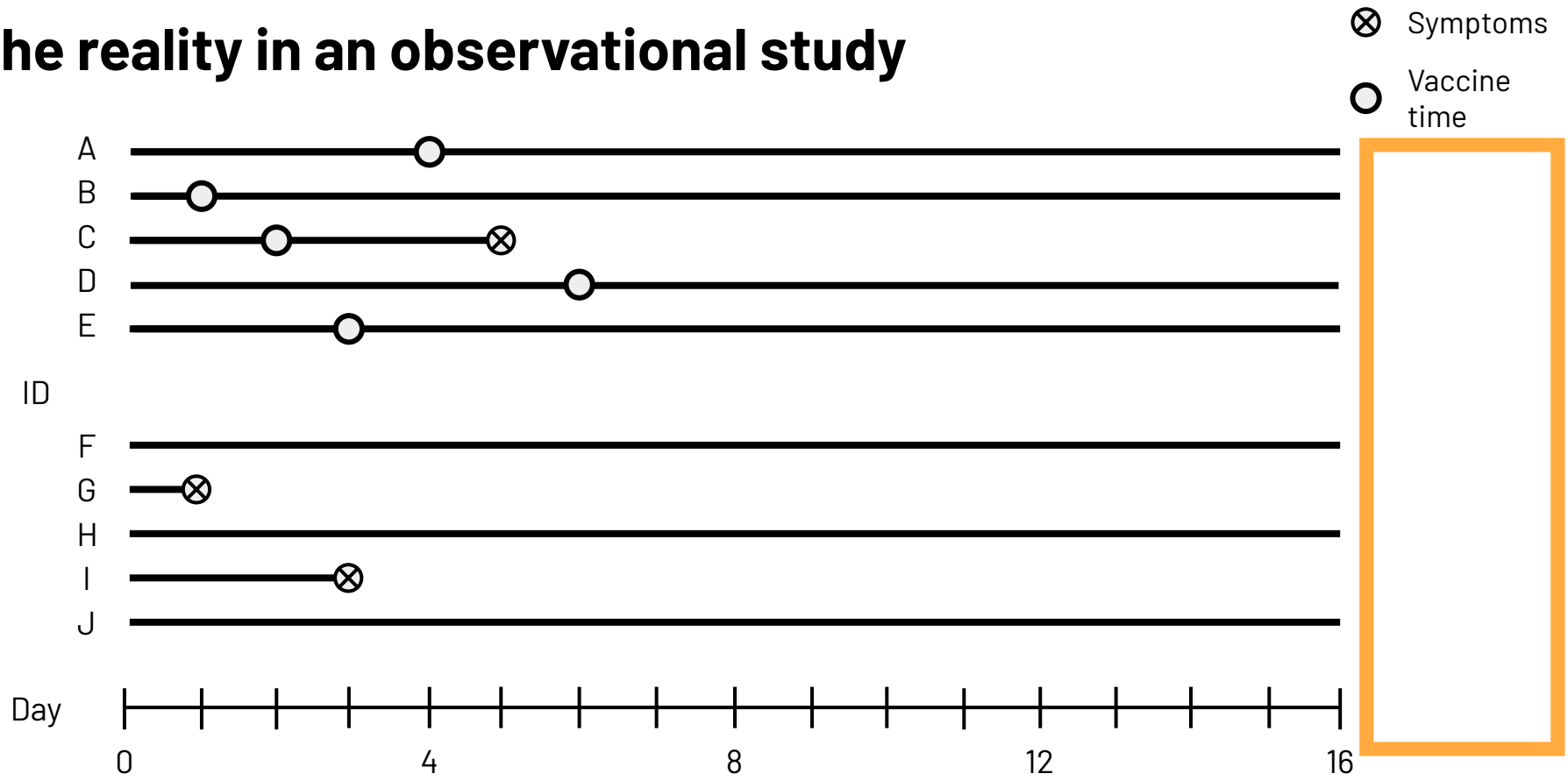
How would this work in a trial?

- The trialist would specify a **protocol** that includes:
  - The window of time postexposure that people are eligible to receive a vaccine.
  - The precise vaccination strategies under consideration.
  - How to handle those who have symptoms prior to enrollment.
- The protocol would have to balance between demonstrating **efficacy under ideal conditions** and **real world effectiveness** of a feasible vaccination policy.
- By design, assignment, enrollment, and the start of follow up would all be aligned.

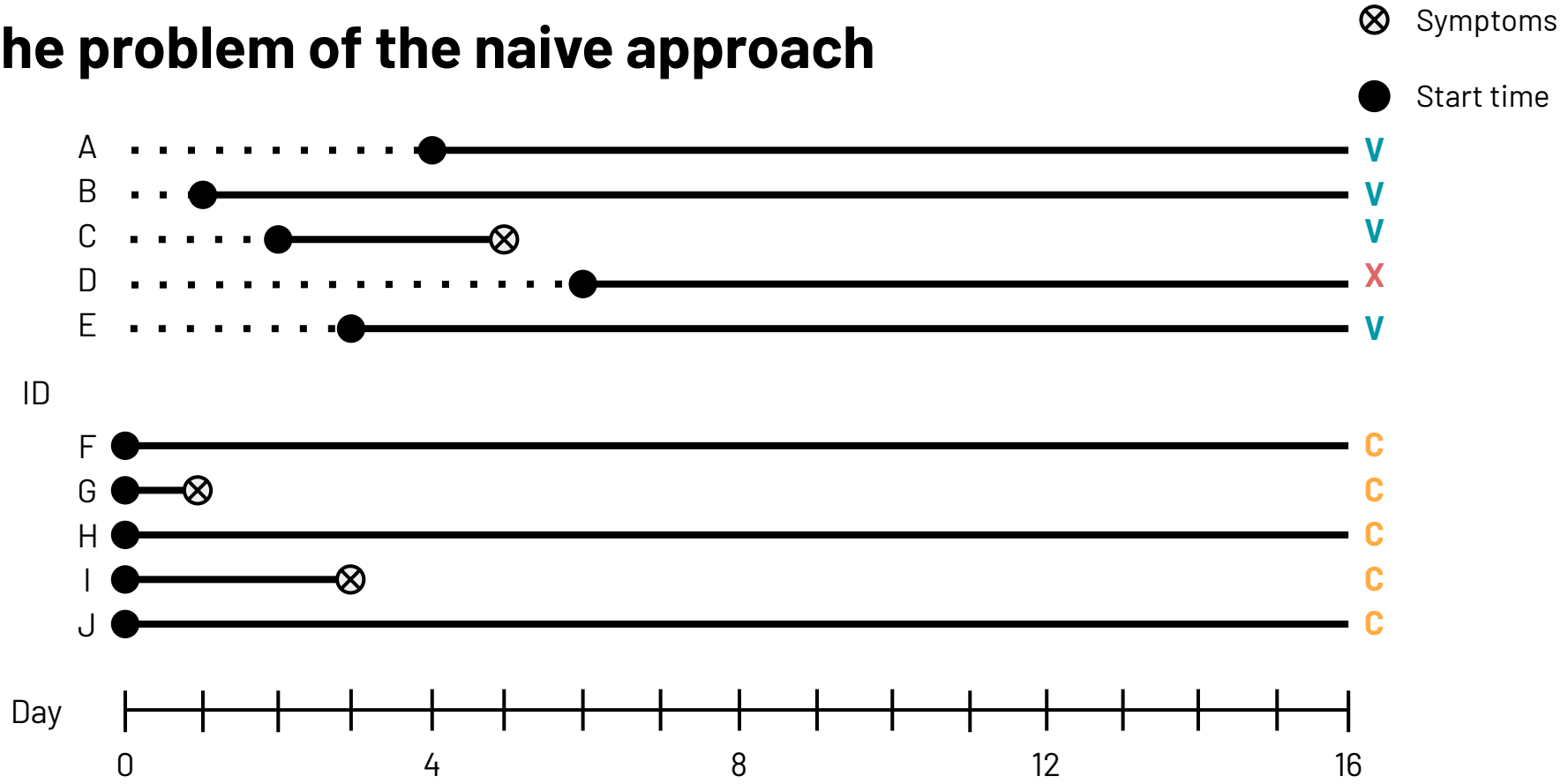
How would this work in a trial?



The reality in an observational study



The problem of the naive approach



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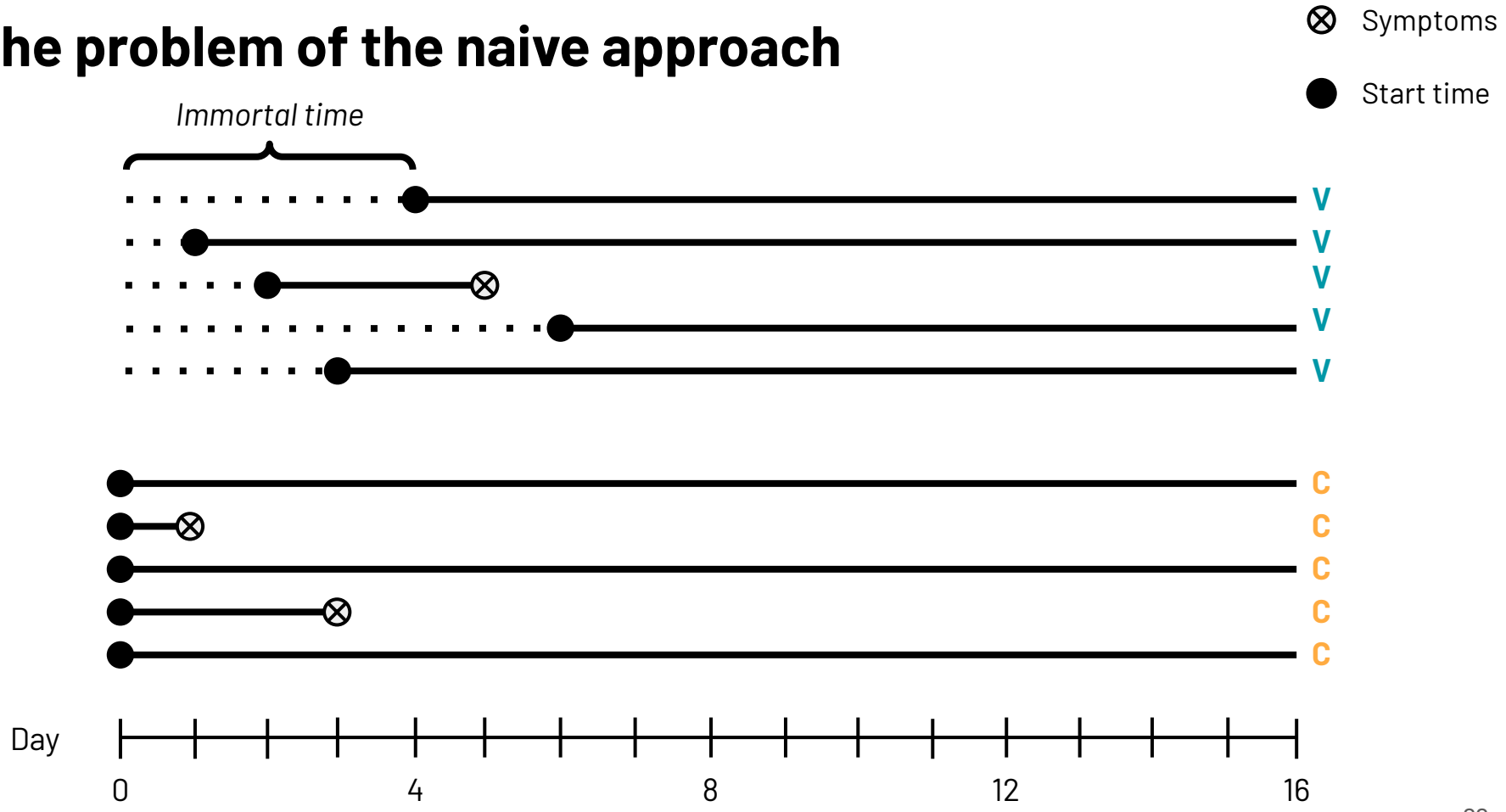


Applying the target trial framework post-exposure

- Previous work on target trials for **pre-exposure** vaccination strategies.
  - However, these studies often compared rather simple vaccination strategies.
- By contrast, there are a range of more **complex post-exposure strategies** that are potentially of interest.
- Our contributions:
  - Identify the potential magnitude of bias of conventional approaches.
  - Define the universe of hypothetical trials or vaccination strategies that might be of interest.
  - Provide guidance on the data sources and observational design elements necessary for trial emulation.
  - Provide guidance on the specific data manipulation and analysis steps.
  - Simulate and apply this to real data! (more to come)

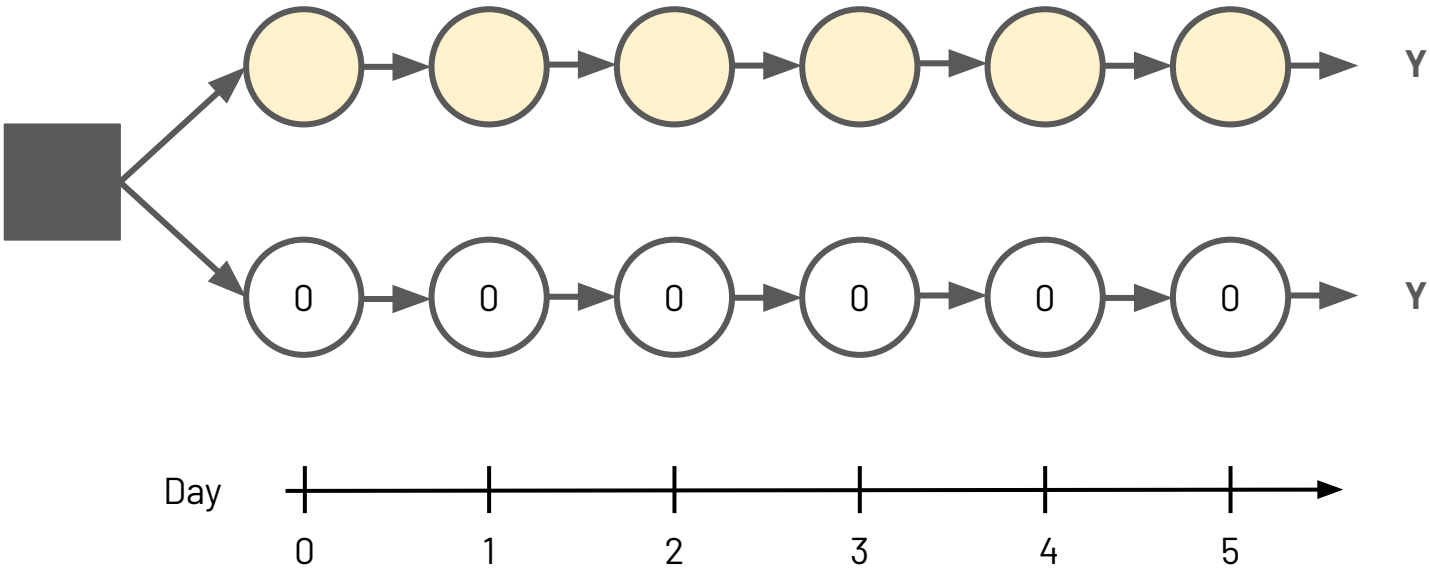
Potential advantages

- **Resolves immortal time bias** by defining unified time zero for strategies under comparison.
- Forces us to formulate a specific **scientific or clinical question**.
    - Encourages specificity in what the ideal trial is that we're attempting to emulate, including the actual vaccination strategy or strategies of interest.
    - Also helps with eligibility criteria, when they are assessed, and making sure they are applied equally.
- Because there's real-world variability we can **consider a range of strategies simultaneously**, which would not be feasible in a trial.

Possible trial designs

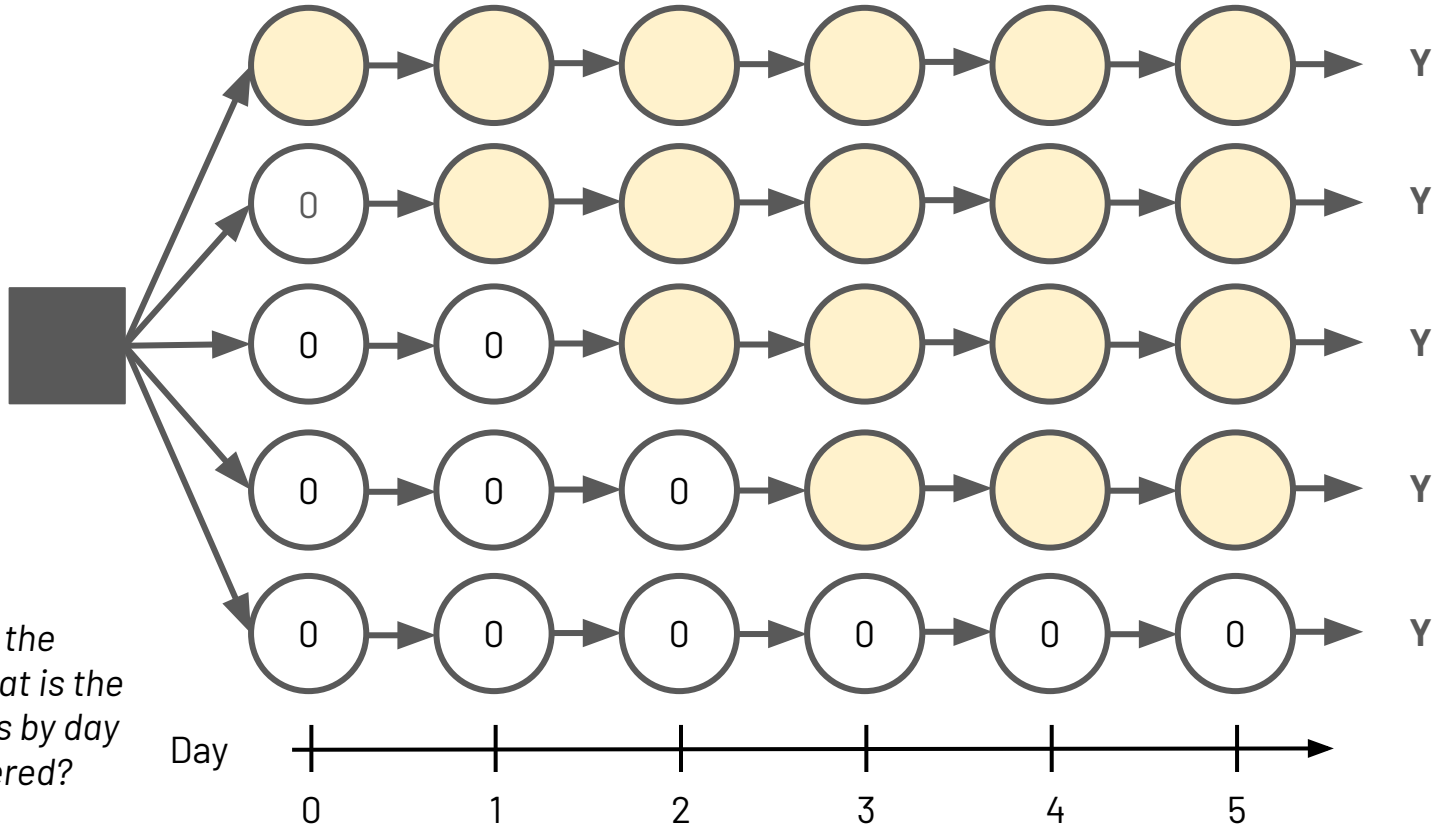
1. Enroll eligible participants on exposure day 0 and ***immediately*** randomize them to vaccine or no vaccine.
2. Enroll eligible participants on exposure day 0, randomize them to vaccine or no vaccine, and then ***additionally randomize*** the day they will receive vaccine.
3. Allow participants to present within a defined window (e.g. 3 days), ***randomize them within strata*** defined by the day they enroll.

1. Enroll eligible participants on exposure day 0 and ***immediately*** randomize them to vaccine or no vaccine.



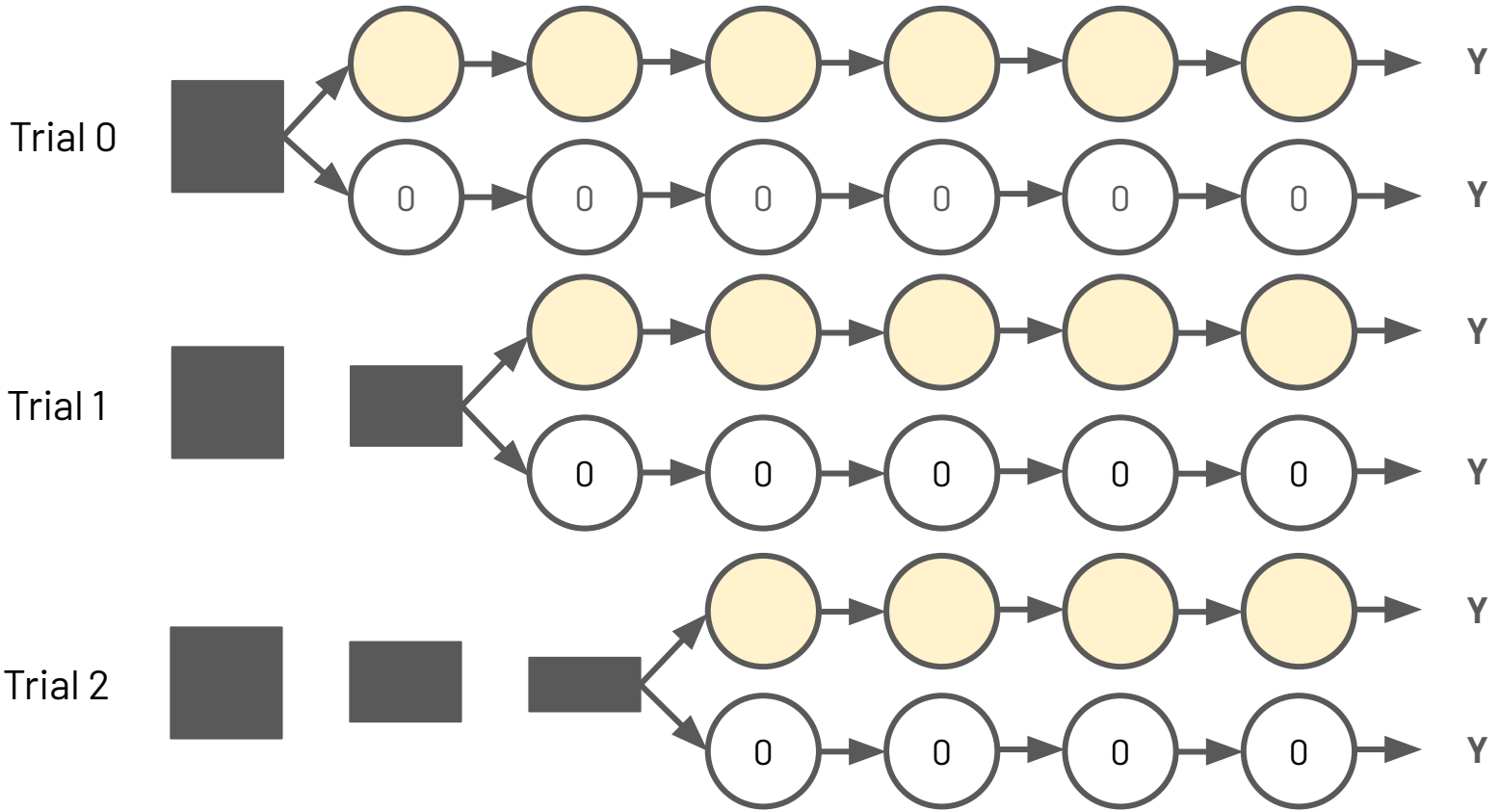
Answers the question: Does vaccination work in, presumably, the most ideal setting?

2. Enroll eligible participants on exposure day 0, randomize them to vaccine or no vaccine, and then ***additionally randomize*** the day they will receive vaccine.



Answers the question: what is the effectiveness by day administered?

3. Allow participants to present within a defined window (e.g. 3 days), ***randomize them within strata*** defined by the day they enroll.



Answers the question: given that I survived to day X is vaccine still effective?

Data manipulation and analysis steps

For designs 1 and 2, we can use the **clone, censor, weight** approach, i.e. for each strategy of interest

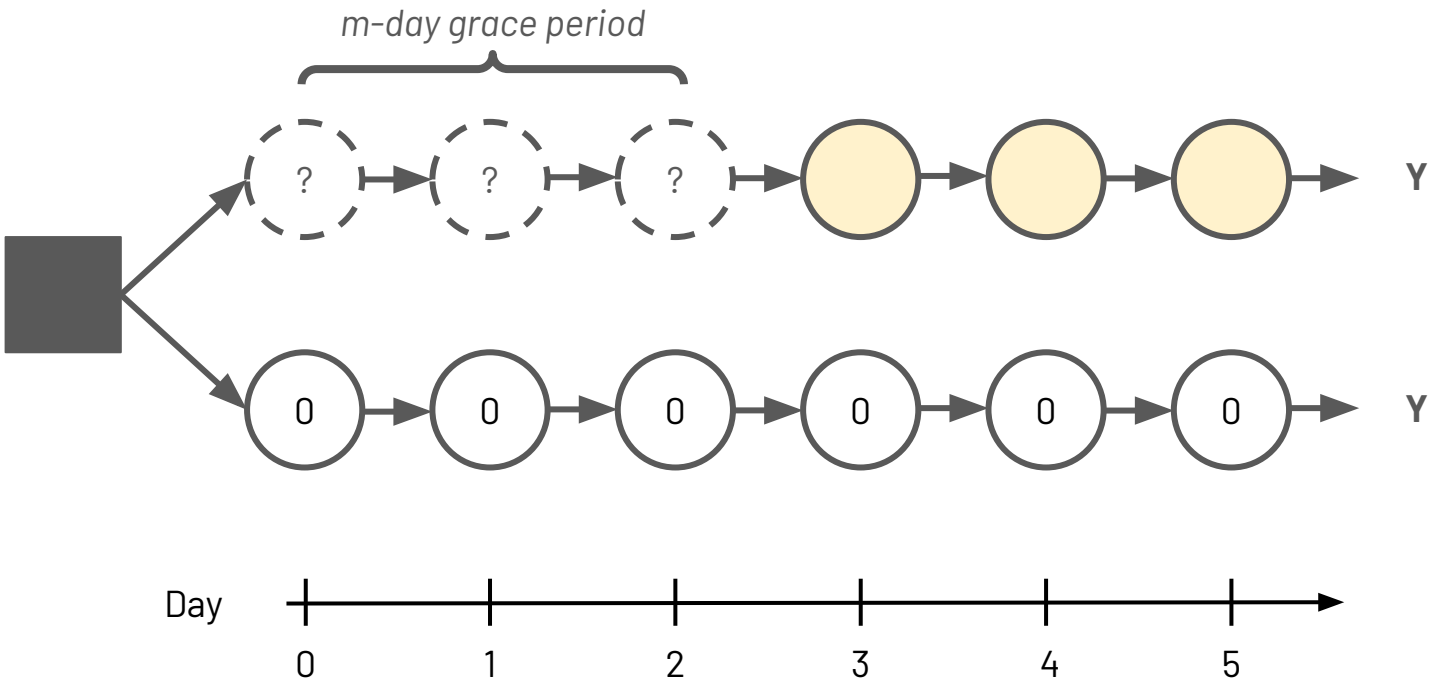
- Create a copy ("clone") of each individual and "assign" them to the strategy.
- Follow them forward until the deviate from the assigned strategy.
- Use inverse probability of censoring weights to adjust for informative censoring and bootstrapping to adjust for non-independence of "clones".
- For design 2: we can use marginal structural model to borrow information across strategies.

Data manipulation and analysis steps

For design 3, we use **daily nested sequential trials**

- Create a copy for a trial starting on day 0, 1, 2, 3, …, W postexposure
- Subset to those eligible (i.e. those who are symptom-free and haven't previously been infected).
- Assign those who are vaccinated on that day to vaccine group and those who aren't to control.
- Follow up and censor when they deviate.
- Use inverse probability of censoring weights to adjust for informative censoring and bootstrapping to adjust for non-independence of "clones"

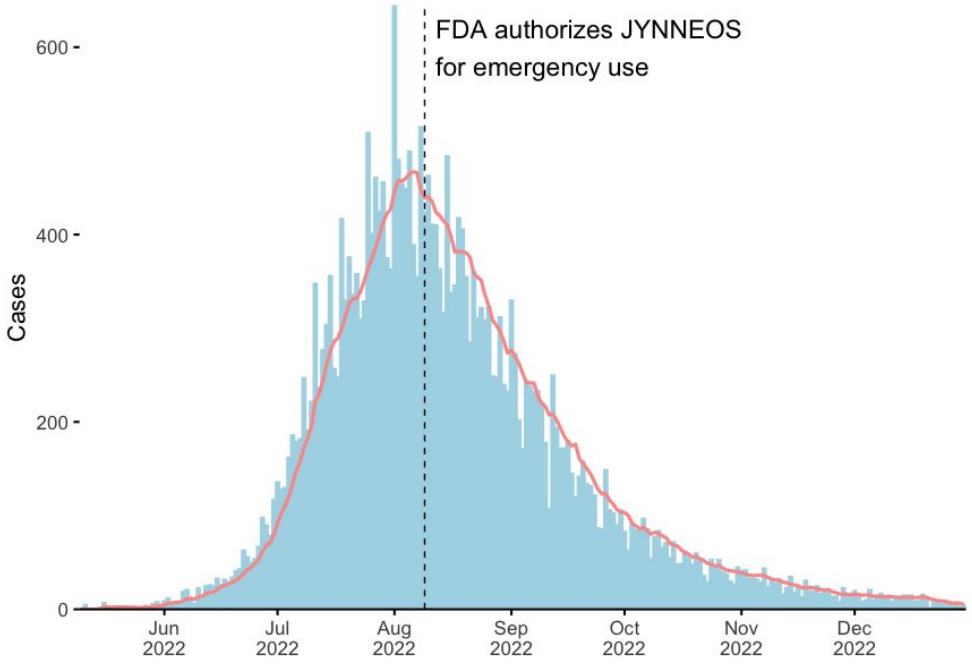
More complex strategies: adding a grace period



Application: JYNNEOS vaccine as post-exposure prophylaxis during Mpox outbreak

Mpox 2022 Outbreak

- An outbreak in several countries prompts WHO to declare public health emergency.
- FDA authorizes JYNNEOS for emergency use in August 2022.
- Initial guidance suggests vaccine be administered as postexposure prophylaxis.
- However, to date no trial exists.



New York City contact-tracing study

- During outbreak, NYC Department of Health interviewed individuals with laboratory confirmed mpox.
- Contacts named by cases who had **high or intermediate-risk exposures** were referred for JYNNEOS™ vaccine subcutaneously as PEP if 1st vaccine dose could be administered **≤ 14 days of last exposure.**
- **Mandatory vaccination reporting:** Executive Order suspended the requirement for obtaining consent from adults to report their JYNNEOS™ doses to the immunization registry and mandated reporting.
- DoH linked registry, contact-tracing, with centralized laboratory.

Previous analysis

- Retrospective cohort of eligible contacts of confirmed cases.
- Exposure definitions (**retrospective**):
    - **PEP** - Individuals who received at least one dose of JYNNEOS vaccine anytime within first 14 days from day of exposure and *prior to symptom onset*, if applicable
    - **No PEP** - Individuals who never received JYNNEOS, or who received JYNNEOS after 14 days from day of exposure *or after symptom onset*, if applicable.
- Multivariable logistic regression adjusting for exposure risk (High vs. Intermediate) and race/ethnicity
- VE calculated as (1 - OR) x 100%

PEP timing	N	Received PEP		Did Not Receive PEP		PEP effectiveness (95% CI)	
		Developed mpox	Did not develop mpox	Developed mpox	Did not develop mpox	Original	Target trial
0 to 14 days after last exposure	594	**10 (3%)**	323	**29 (11%)**	232		
0 to 14 days after first exposure	471	**6 (3%)**	177	**29 (10%)**	259		

PEP timing	N	Received PEP		Did Not Receive PEP		PEP effectiveness (95% CI)	
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0 to 14 days after last exposure	594	10 (3%)	323	29 (11%)	232	**78% (50%, 91%)**	
0 to 14 days after first exposure	471	6 (3%)	177	29 (10%)	259	**73% (31%, 91%)**	

Observations

- The median time to vaccinate was **7 to 9 days** (depending on definition)
    - This was the result of a number of factors: potential delays seeking care, laboratory confirmation of case-patients, identification and notifications of exposed individuals, and presentation of exposed individuals for vaccination.
- The median time to symptom onset was **shorter than expected (6 to 7 days).**
    - Could be that exposure through sexual contact may be more potent or that exposure window is hard to measure/ill-defined.

Trial protocol

Specified a protocol for the trial we would like to conduct but cannot:

- a 14 day fixed-enrollment period design
- pragmatic (unblinded)
- outcome is 21 day cumulative incidence of mpox

Table 1: Example protocol for the specification and emulation of a target trial of postexposure vaccination for prevention of mpox.

Protocol component	Target trial specification	Emulation
Eligibility	High[a] or intermediate[b] risk exposure to a PCR-confirmed mpox case within the first 14 days postexposure AND negative PCR for mpox or orthopox virus at enrollment AND no symptoms AND no prior history of JYNNEOS vaccination	same
Treatment strategies	(1) JYNNEOS vaccination immediately upon enrollment (2) no JYNNEOS vaccination during 21 days postexposure	same
Treatment assignment	non-blinded 1:1 random assignment to either (1) or (2) at enrollment	same but randomization is emulated by conditioning on covariates
Outcomes	21-day cumulative incidence of disease defined as symptom onset and PCR-confirmed mpox or orthopox	same
Follow up	Start at exposure date and follow until clinical disease onset, loss to follow up, or 21 days have elapsed, whichever is first	same
Causal contrast	Intention to treat (ITT) Per protocol	observational analog of per protocol effect
Statistical analysis	ITT: compare cumulative incidence of clinical disease under each strategy, adjusting for loss to follow up and prognostic factors to increase efficiency Per protocol: Use IPW/g-formula/ g-estimation to account for non-adherence.	same as per protocol

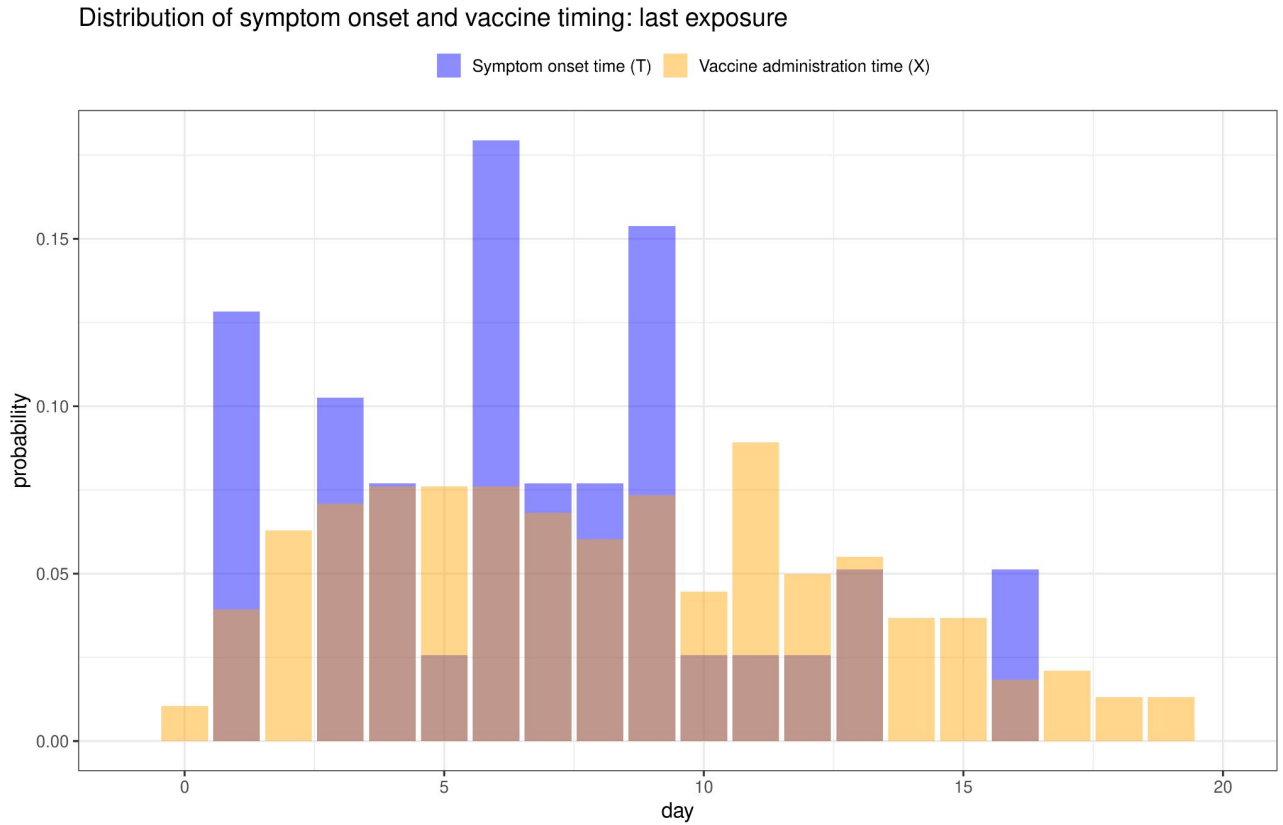
[a] *High risk:* direct mucosal or broken skin contact with lesions or bodily fluids OR any sexual or intimate mucosal contact OR indirect mucosal or broken skin contact with lesions or bodily fluids via linens, clothing, or other materials.

[b] *Intermediate risk:* unmasked exposure to respiratory droplets (within 6 ft for >3 hours) OR direct contact between intact skin and lesions or bodily fluids OR indirect contact between intact skin and lesions or bodily fluids via linens, clothing, or other materials OR indirect contact between exposed individual's clothing with linens or bodily fluids.

Emulation

- Emulated a **fixed-enrollment period trial** using a sequence of 15 nested daily trials starting each day after exposure from day 0 to day 14.
- "Assigned" eligible individuals to a treatment group (PEP vs. no PEP) based on their status on each day (e.g. if PEP on day 3, count as unvaccinated on trials beginning on days 0, 1, 2).
- Individuals assigned to no PEP group in a particular trial were **censored on the day of vaccination** if they were later vaccinated.
- Follow-up until either outcome (mpox) occurred or until the end of follow-up (21-day incubation period).
- Pooled nested trials and estimated VE as (1 - OR) x 100% from pooled logistic regression model.
- Adjustment for **non-adherence** using inverse probability of censoring weights.

PEP timing	N	Received PEP		Did Not Receive PEP		PEP effectiveness (95% CI)	
		Developed mpox	Did not develop mpox	Developed mpox	Did not develop mpox	Original	Target trial
0 to 14 days after last exposure	594	10 (3%)	323	29 (11%)	232	78% (50%, 91%)	**19% (-54%, 57%)**
0 to 14 days after first exposure	471	6 (3%)	177	29 (10%)	259	73% (31%, 91%)	**-7% (-144%, 53%)**


Distribution of symptom onset and vaccine timing: last exposure
Symptom onset time (T)
Vaccine administration time (X)
probability
0.15
0.10
0.05
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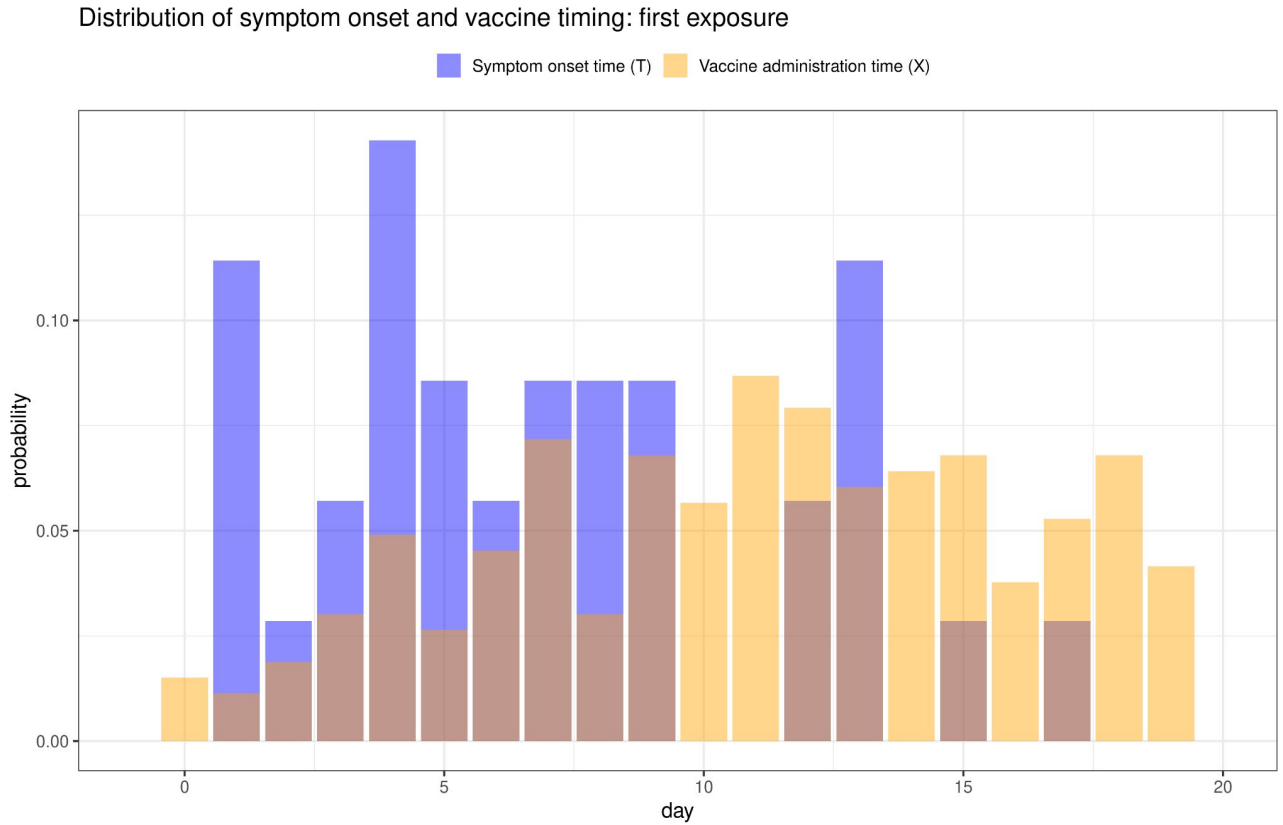
Distribution of symptom onset and vaccine timing: first exposure
Symptom onset time (T)
Vaccine administration time (X)
probability
0.10
0.05
0.00
0
5
10
15
20
day

Conclusions

- Previous analysis was biased by ***immortal time***, caused by short incubation periods and delays in vaccination.
- Target trial emulation resolves these issues, but results are **inconclusive** as estimates of PEP effectiveness were **imprecise** (i.e. wide confidence intervals).
- **Target trial emulation** should be used in future PEP effectiveness studies to address immortal time bias from conventional methods
- **Pooling of data across multiple jurisdictions** to have sufficient sample size might be helpful for overcoming the realities of delayed PEP which make effectiveness evaluations challenging.
- Alternatively, innovations in **how to get PEP to people faster** can also increase power and help reduce concerns about immortal time.

References

Boyer, C., & Lipsitch, M. (2024). "Defining and emulating target trials of the effects of postexposure vaccination using observational data." *American Journal of Epidemiology (in press).* https://doi.org/10.1101/2023.05.03.23289471

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Impact

- Presented at the Advisory Committee on Immunization Practices meeting in July.
- Currently working with trialists in DRC who are trying to run a randomized postexposure trial to inform design.