Transporting the effect of an infectious disease intervention to a target population

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Motivation

There is a desire to transport effects of infectious disease interventions from a source to a target population.

Examples:

- Changes in contact behavior.
- Changes in population immunity.
- Changes to the pathogen (antigenic shift/drift).

Existing methods that standardize effects to the covariate distribution in the target population **are insufficient**.

Setup

Define:

- X is vector of baseline covariates,
- S is an indicator of the source (1: index trial, 0: target population sample),
- A is an indicator of treatment (1: treated, 0: untreated),
- E is exposure to the infectious agent (assume for now 1: exposed, 0: unexposed),
- Y is incident infection by the end of follow up (1: infected, 0: not infected).

Data Structure

We have access to:

- Data from the index trial or observational study, assumed to be realizations of

$$(X_i, S_i = 1, A_i, Y_i)$$

for $i = 1, \ldots, n_1$.

- Data from a random sample of the target population, assumed to be realizations of

$$(X_i, S_i = 0)$$

for $i = 1, \ldots, n_0$.

Standard Transportability Analysis

- Target: $\mathrm{E}[Y^a|S=0]$
- Assumptions:
  - (A1) Consistency
  - (A2) Exchangeability in trial
  - (A3) Positivity in trial
  - (A4) Exchangeability over S given X
  - (A5) Positivity in target
- Result: $\mathrm{E}[Y^a|S=0] = \mathrm{E}[\mathrm{E}[Y|X,S=1,A=a]|S=0]$

The Problem of Interference

- Standard assumption: No interference (SUTVA).[1]

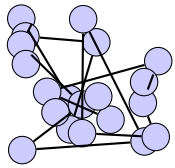
$$Y_i^{\mathbf{a}} = Y_i^{\mathbf{a}'} = Y_i \text{ when } A_i = A_i' \text{ for all individuals } i.$$

- In infectious diseases: One person's treatment can affect others' outcomes.

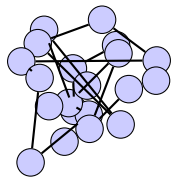
$$Y_i^{\mathbf{a}} \neq Y_i^{\mathbf{a}'} \text{ when } A_i = A_i' \text{ for all individuals } i.$$

[1] Here, we consider a population of n units with vector of treatment allocations $\mathbf{A} \equiv (A_1, \ldots, A_n)$ and possible realizations $\mathbf{a}$ and $\mathbf{a}'$.

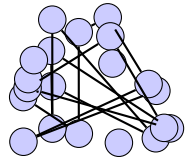
Cluster-Based Transport Under Partial Interference



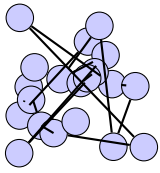
cluster 1



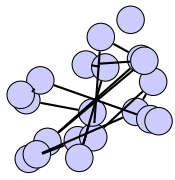
cluster 2



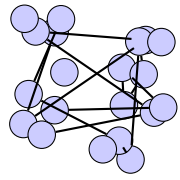
cluster 3



cluster 4



cluster 5



cluster 6

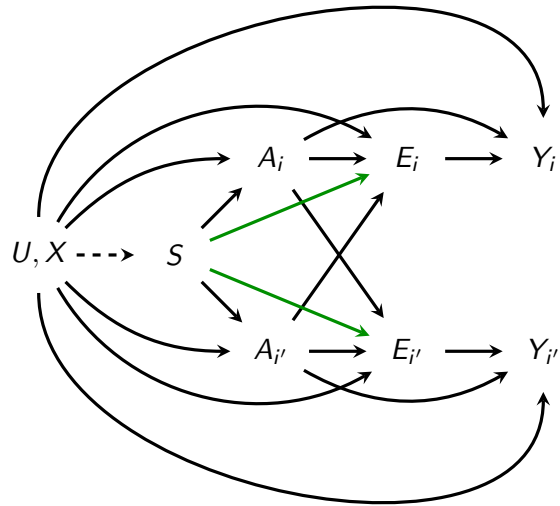
Robertson, Steingrimsson, and Dahabreh (2022)

- Partition population into clusters: assume *partial interference* within but not between clusters.
- $S = 1$: cluster randomized trial; $S = 0$: target population of clusters
- Target: $\mathrm{E}[\bar{Y}^a | S = 0]$ where $\overline{Y}_j^a = \frac{1}{N_j} \sum_{i=1}^{N_j} Y_{j,i}^a$ are cluster-level averages
- Assumptions:
  - (B1) Consistency of cluster-level outcomes
  - (B2) Exchangeability in cluster-randomized trial
  - (B3) Positivity in trial
  - (B4) Exchangeability over S given $\mathbf{X}$
  - (B5) Positivity in target
- Result: $\mathrm{E}[\bar{Y}^a | S = 0] = \mathrm{E}[\mathrm{E}[\bar{Y} | \mathbf{X}, A = a, S = 1] \mid S = 0]$

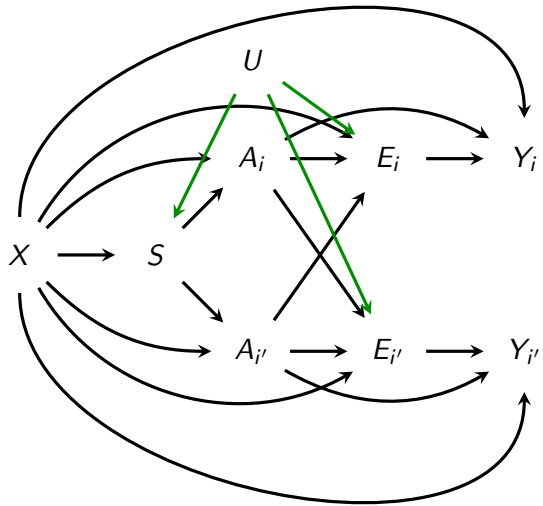
Post-Baseline Exposure Threatens Assumptions

- Participation may alter contact behavior.
- Target and trial may differ in contact patterns.

Effects of participation on exposure



Different contact patterns in source and target

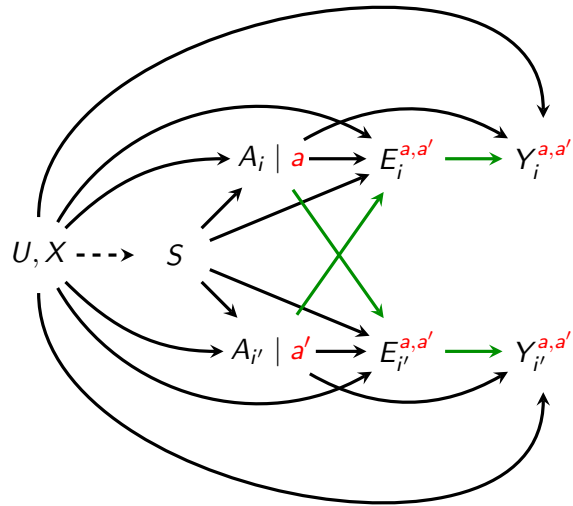


An Alternative: Per-Exposure Effects[2]

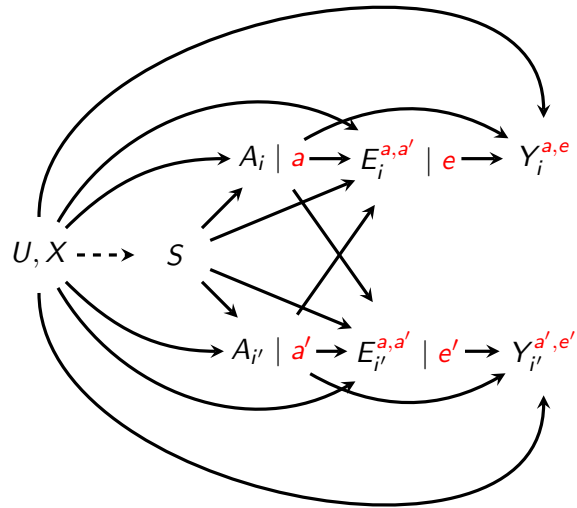
- Jointly intervene on A and E.
- Assumes $Y^{a,e} = Y$ if assigned $(A_i, E_i) = (a, e)$.
- Not subject to interference due to infection/contagion

[2] O'Hagan, Lipsitch, and Hernán 2014

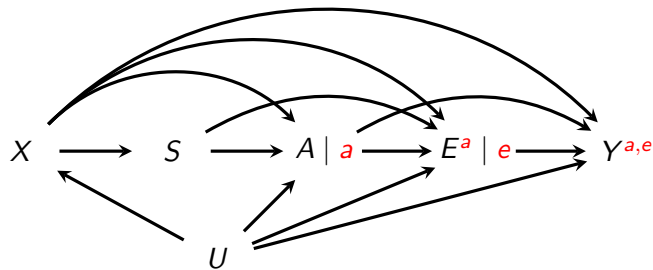
Intervening on exposure removes interference



Intervening on exposure removes interference



A simplified causal model under joint intervention



Example: Human Challenge Trials

Efficacy of FLU-v, a broad-spectrum influenza vaccine, in a randomized phase IIb human influenza challenge study

Olga Pleguezuelos, Emma James, Ana Fernandez, Victor Lopes, Luz Angela Rosas, Adriana Cervantes-Medina, Jason Cleath, Kristina Edwards, Dana Neitzey, Wenjuan Gu, Sally Hunsberger, Jeffery K. Taubenberger, Gregory Stoloff & Matthew J. Memoli

npj Vaccines **5**, Article number: 22 (2020) | Cite this article

Abstract

FLU-v, developed by PepTcell (SEEK), is a peptide vaccine aiming to provide a broadly protective cellular immune response against influenza A and B. A randomized, double-blind, placebo-controlled, single-center, phase IIb efficacy and safety trial was conducted. One hundred and fifty-three healthy individuals 18–55 years of age were randomized to receive one or two doses of adjuvanted FLU-v or adjuvanted placebo subcutaneously on days −43 and −22, prior to intranasal challenge on day 0 with the A/California/04/2009/H1N1 human influenza A challenge virus. The primary objective of the study was to identify a reduction in mild to moderate influenza disease (MMID) defined as the presence of viral shedding and clinical influenza symptoms. Single-dose adjuvanted FLU-v recipients ($n = 40$) were significantly less likely to develop MMID after challenge vs placebo ($n = 42$) (32.5% vs 54.8% $p = 0.035$). FLU-v should continue to be evaluated and cellular immunity explored further as a possible important correlate of protection against influenza.

Transporting Effects from Human Challenge Trials

- $S = 1$: human challenge trial[3]; $S = 0$: target population
- Target: $\mathrm{E}[Y^{a,e=1}|S = 0]$.
- Assumptions:
  - (C1) Consistency under $E_i = 1$ and $A_i = a$
  - (C2) Exchangeability of A and E in challenge trial
  - (C3) Positivity in challenge trial
  - (C4) Exchangeability over S
  - (C5) Positivity in target
- Result: $\mathrm{E}[Y^{a,e=1}|S = 0] = \mathrm{E}[\mathrm{E}[Y|X, S = 1, A = a, E = 1]|S = 0]$

[3]Now data structure for human challenge trial is $(X_i, S_i = 1, A_i, E_i = 1, Y_i)$ for $i = 1, \ldots, n_1$

Link to Infectious Disease Modeling

- Define stochastic allocation $g(\mathbf{a}) = \Pr^{\dagger}[\mathbf{A} = \mathbf{a}|X]$ and post-treatment exposure sequence $g(\mathbf{e}) = \Pr^{\dagger}[\mathbf{E} = \mathbf{e}|X, \mathbf{A} = \mathbf{a}]$.
- For a population of N units, an Individual-Based Model simulates:

$$\mathrm{E}[Y^{g(\mathbf{a}),g(\mathbf{e})}|S = 0] = \sum_{\mathbf{a}\in\mathcal{A}(n)} \sum_{\mathbf{e}\in\mathcal{E}(n)} \sum_{i=1}^{N} \mathrm{E}[Y^{a_i,e_i}|X, S = 0] \Pr^{\dagger}[\mathbf{E} = \mathbf{e}|X, \mathbf{A} = \mathbf{a}] \Pr^{\dagger}[\mathbf{A} = \mathbf{a}|X]$$

- In theory, equals $E[Y^{g(\mathbf{a})}|S = 0]$ when

$$\Pr^{\dagger}[\mathbf{E} = \mathbf{e}|X, \mathbf{A} = \mathbf{a}] = \Pr[\mathbf{E}^{\mathbf{a}} = \mathbf{e}|X, \mathbf{A} = \mathbf{a}]$$

Alternative: Stensrud and Smith (2023)

- Trial: A randomized and placebo-controlled, E natural (unmeasured).
- Target: $ECE = \dfrac{\mathrm{E}[Y^{a=1,e=1}|E=1]}{\mathrm{E}[Y^{a=0,e=1}|E=1]}$.
- Assumptions:

  (D1) Consistency under $E_i = 1$ and $A_i = a$

  (D2) Exchangeability of A in placebo-controlled trial

  (D3) Positivity in placebo-controlled trial

  (D4) Exposure necessity for infection. I.e., $E_i = 0 \implies Y_i = 0$.

  (D5) No effect of assignment on exposure. I.e., $E_i^{a=1} = E_i^{a=0}$

- Result: $\dfrac{\mathrm{E}[Y^{a=1,e=1}|E=1]}{\mathrm{E}[Y^{a=0,e=1}|E=1]} = \dfrac{\mathrm{E}[Y|A=1]}{\mathrm{E}[Y|A=0]}$

Transportability of conditional ECE

- $S = 1$: placebo controlled trial; $S = 0$: target population sample
- Target: $\mathrm{E}[Y^{a,e=1}|S = 0]$.
- Assumptions:

  (D6) Exchangeability of **relative effects** over S

  (D7) Positivity in target

  (D8) Unavailability of treatment in target population

- Result:

$$\mathrm{E}[Y^{a=1,e=1}|S = 0] = \mathrm{E}\left[\frac{\mathrm{E}[Y|X, S = 1, A = 1]}{\mathrm{E}[Y|X, S = 1, A = 0]}\mathrm{E}[Y|X, S = 0]\right]$$

Summary

- Standard transportability fails under interference.
- Cluster-level estimands possible under partial interference.
- Per-exposure effects may be more transportable.
- Requires different assumptions, data (e.g., challenge or contact studies).

Collaborators

Juan Gago, Issa Dahabreh, Matts Stensrud, and Marc Lipsitch

Slide deck

`https://christopherbboyer.com/talks`

Funding

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Questions?

Thank you!

References

- O'Hagan, Justin J., Marc Lipsitch, and Miguel A. Hernán (2014). "Estimating the Per-Exposure Effect of Infectious Disease Interventions". In: *Epidemiology* 25.1, p. 134.
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