Evaluation of Health Policy Interventions for Contagious Outcomes

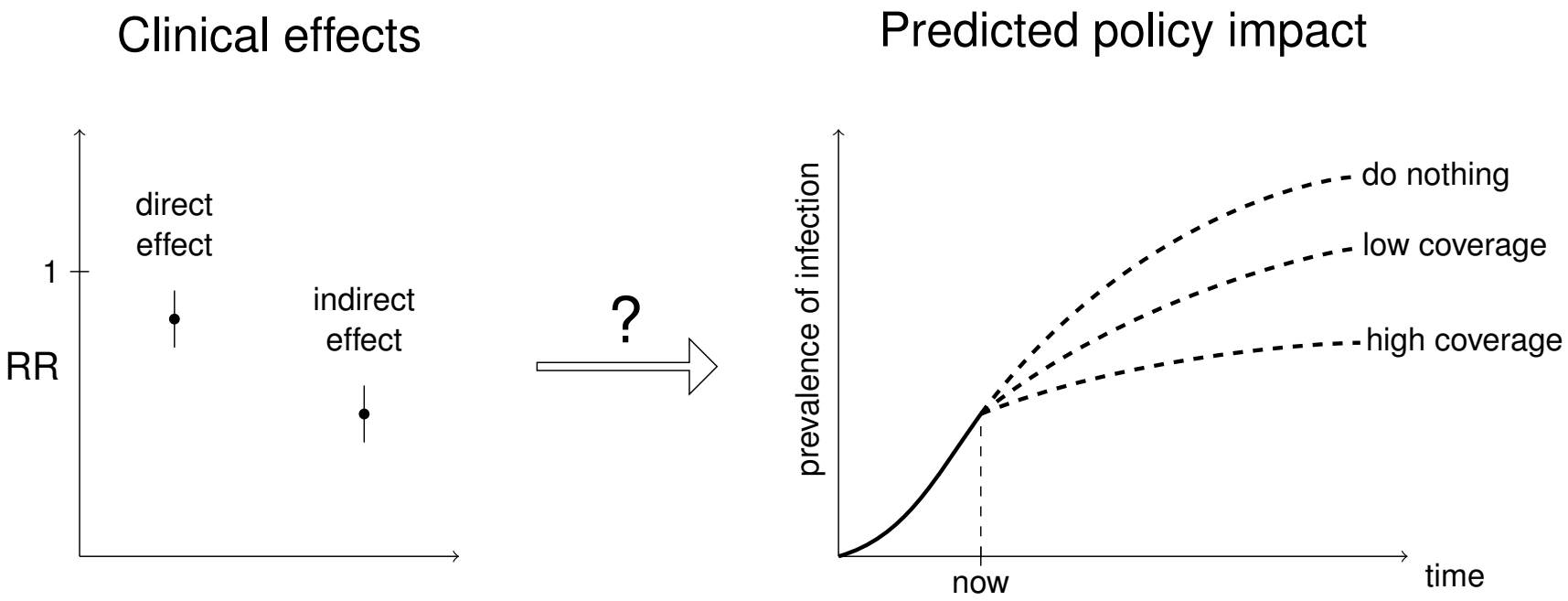
Olga Morozova

with Daniel J. Eck and Forrest W. Crawford

Yale Biostatistics,
Operations, Statistics and Data Science, Ecology & Evolutionary Biology

International Conference on Health Policy Statistics - 2020

Population-level effects of individual-level interventions

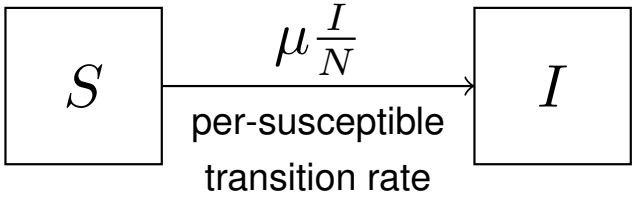


- Under no interference, population-level effect is the individualistic effect times the number of people receiving the intervention
- For interventions, like vaccines, the population-level effect is a complex function of individualistic effects

Overview

- Basic structure and assumptions of **transmission models** to evaluate population-level effects of vaccines and similar interventions
- Meaning of traditional **estimands of individualistic causal effects** under interference
- Parameters in transmission models and clinical effects of interventions: **do they mean the same thing, and what happens if they do not?**

Compartmental dynamic transmission models



$$S'(t) = -\mu \frac{I}{N} S$$

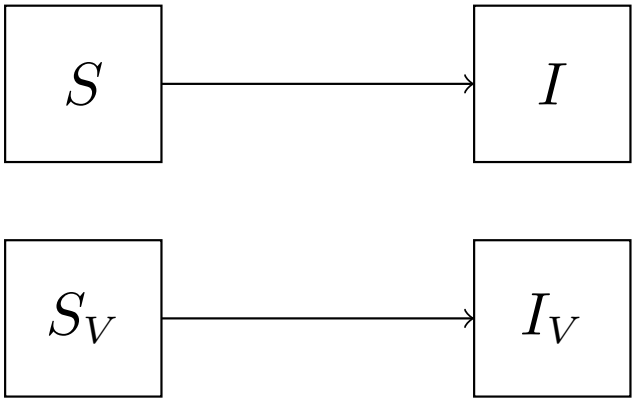
Transmission parameter $\mu =$

contact rate $\times \Pr($transmission per contact$)$

$\Pr($transmission per contact$) =$

(susceptibility of uninfected) $\times$ (infectiousness of infected)

Population-level effects of a hypothetical vaccine



$$S'(t) = -(\mu_{00}\frac{I}{N} + \mu_{01}\frac{I_V}{N})S$$

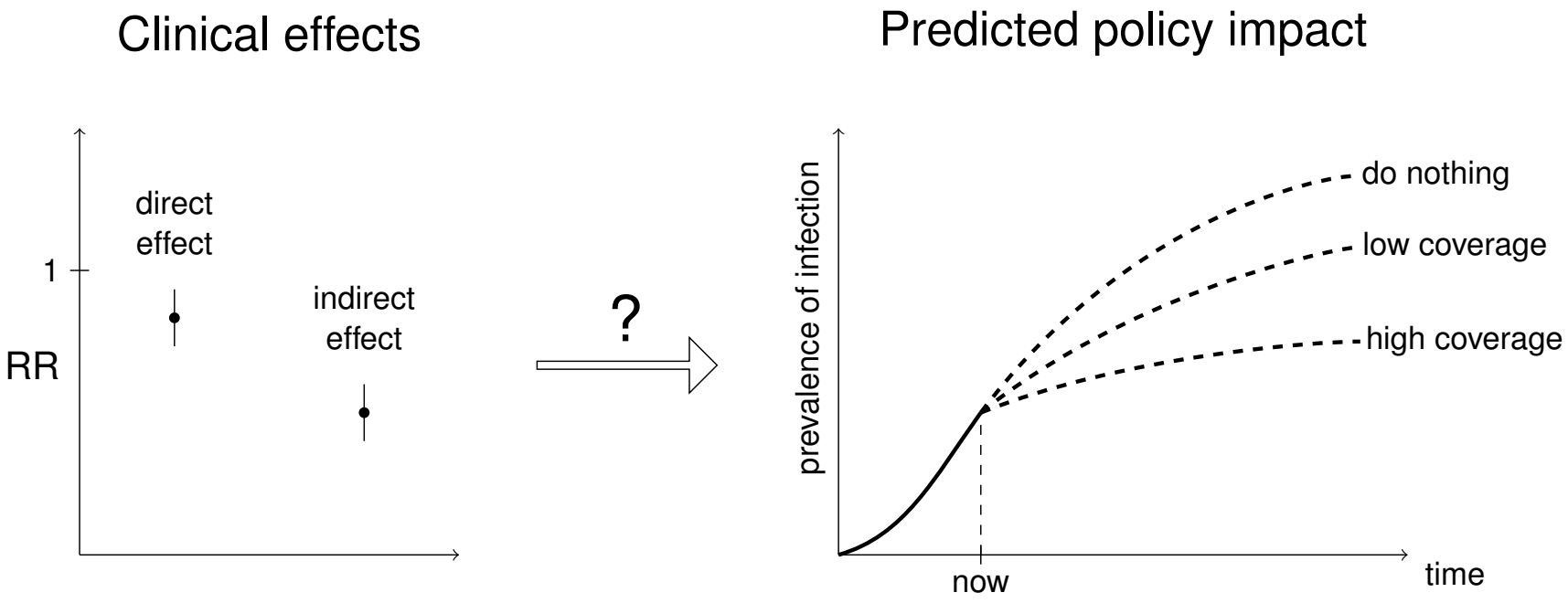
$$S'_V(t) = -(\mu_{10}\frac{I}{N} + \mu_{11}\frac{I_V}{N})S_V$$

$$\mu_{01} = \mu_{00}e^{\gamma}, \quad \mu_{10} = \mu_{00}e^{\beta},$$

$$\mu_{11} = \mu_{00}e^{\beta}e^{\gamma},$$

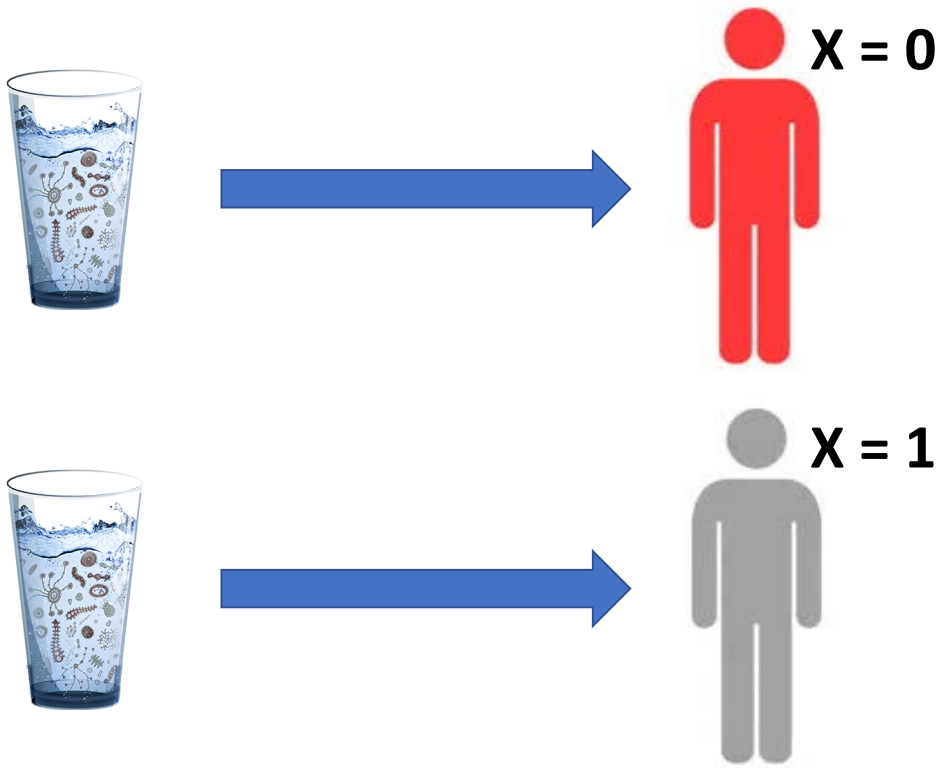
assuming constant contact rate.

μ_{00} : transmission parameter in the absence of vaccination
β : change in susceptibility due to vaccination
γ : change in infectiousness among vaccinated individuals, who became infected



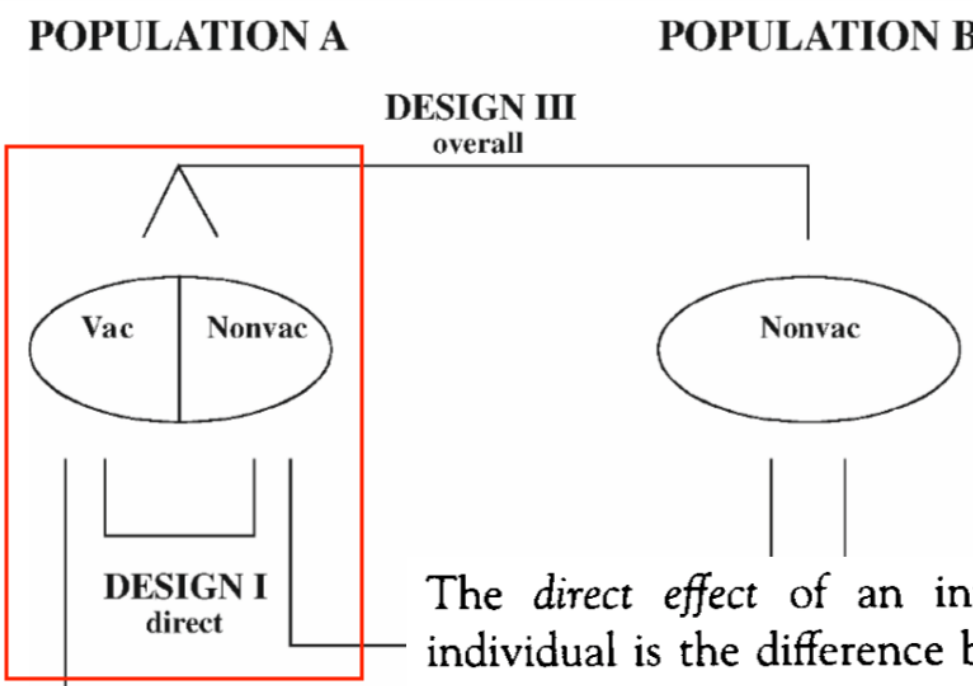
How do we translate estimates of vaccine efficacy from clinical trials to parameters in transmission models?

Ideal experiment: Randomized challenge study



The contrast between the infection risk among treated and untreated would be a measure of the **Susceptibility Effect**

Framework for the empirical evaluation of vaccine efficacy



The *direct effect* of an intervention received by an individual is the difference between the outcome in the individual with the intervention and what the outcome would have been without the intervention, all other things being equal.

After intervention, design I is the only design with comparable exposure to infection in the comparison groups.

Halloran and Struchiner. Study Designs for Dependent Happenings. *Epidemiology*, 1991.

Formal definition of the Direct Effect

Define the **individual average potential outcome** of j under treatment $X = x$ measured at time t as:

$$\overline{Y}_j(t, x) = \sum_{\mathbf{x}_{-j} \in \mathcal{X}^{n-1}} Y_j(t, x, \mathbf{x}_{-j}) \Pr(\mathbf{X}_{-j} = \mathbf{x}_{-j} | X_j = x),$$

where $\mathbf{x}_{-j}$ is a vector of treatment assignments to all cluster members except j, n is a cluster size, and $\mathcal{X}^n = \{0, 1\}^n$ is the set of all binary vectors of n elements.

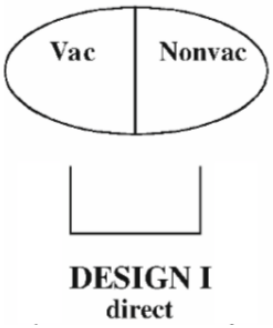
The **individual average direct effect**

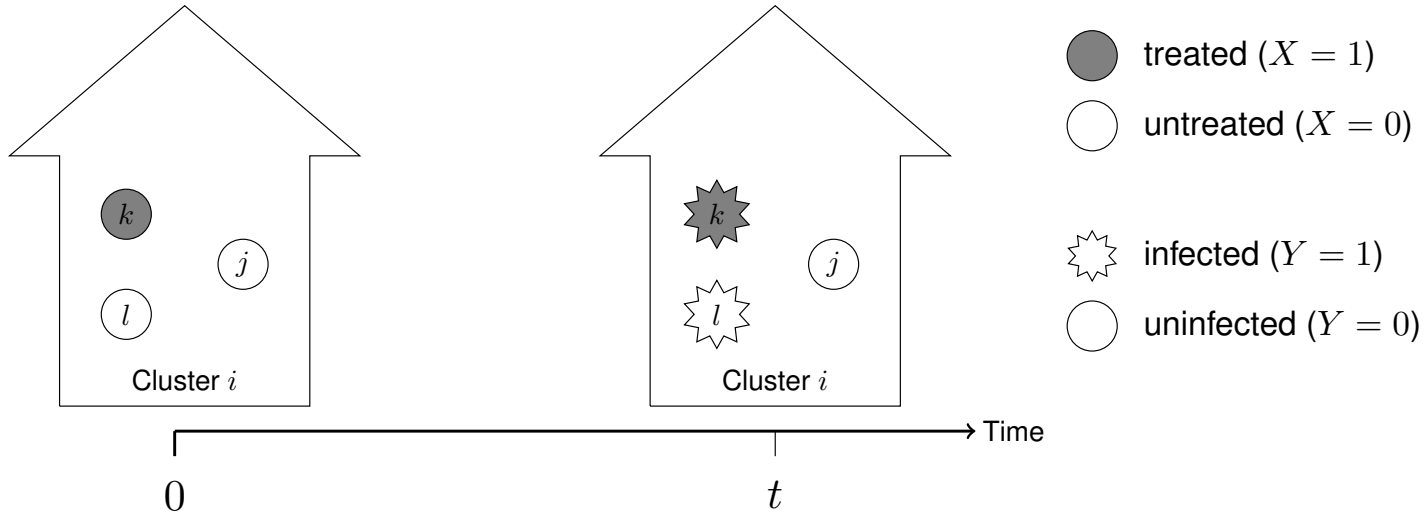
$$DE_j(t) = \overline{Y}_j(t, 1) - \overline{Y}_j(t, 0)$$

is the difference in individual average potential outcomes when $x_j = 1$ and when $x_j = 0$.

Hudgens & Halloran. Toward Causal Inference With Interference. *JASA*, 2008.

The Direct Effect in practice





Subjects may be infected outside of the cluster or by their cluster members

Y indicates occurrence of infection before time t

$$\text{DE} = \text{RD} = \mathbb{E}[Y(t) \mid x = 1] - \mathbb{E}[Y(t) \mid x = 0]$$

or

$$\text{DE} = \text{RR} = \frac{\mathbb{E}[Y(t) \mid x = 1]}{\mathbb{E}[Y(t) \mid x = 0]}$$

The model of hazard under contagion

The hazard of infection to individual j at time t is:

$$\lambda_j(t, x_j, \mathbf{x}_{-j}) = \underbrace{\exp(x_j\boldsymbol{\beta} + \eta_j)}_{\text{susceptibility}} \underbrace{\left(\overbrace{\alpha(t)}^{\substack{\text{exogenous} \\ \text{force of infection}}} + \overbrace{\sum_{k=1}^{n} y_k(t) \exp(x_k\boldsymbol{\gamma} + \xi_k)}^{\text{within-cluster force of infection}} \right)}_{\text{exposure to infection}}$$

η_j: untreated susceptibility of j

$\boldsymbol{\beta}$: susceptibility effect of x

ξ_k: untreated infectiousness of k

$\boldsymbol{\gamma}$: infectiousness effect of x

$\alpha(t)$: exogenous force of infection

$y_k(t)$: outcome of k at time t

n: cluster size

The Susceptibility Effect and the Direct Effect

The **Susceptibility Effect (SE)** is:

$$HR = \frac{\lambda_j(t \mid x_j = 1, e_{infect})}{\lambda_j(t \mid x_j = 0, e_{infect})} = \exp(\beta),$$

at any time t under the constant force of infection $e_{infect} > 0$.

The **Direct Effect (DE)** is:

$$RR = \frac{\Pr[Y_j(T) = 1 \mid x_j = 1]}{\Pr[Y_j(T) = 1 \mid x_j = 0]},$$

where T is an observation time.

What happens if we use the DE (RR) as an approximation to the SE (HR)?

Common randomized study designs in clustered population

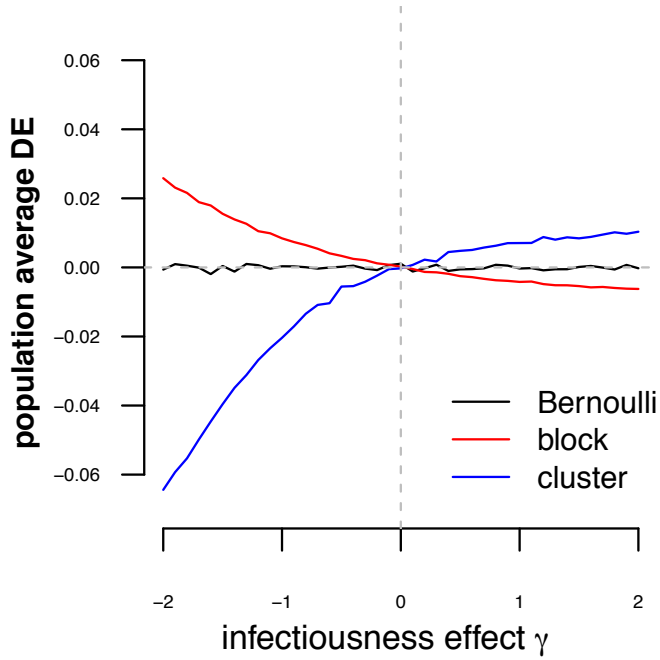
- *Simple Bernoulli randomization*: every subject is assigned to treatment independently with a given probability
- *Block randomization (completely randomized experiment)*: exactly m out of n subjects are selected randomly and assigned to treatment
- *Cluster randomization*: the entire clusters are randomized to receive treatment with some probability (everyone in a given cluster receives the same treatment)

All three randomization schemes guarantee **balance in personal baseline characteristics** of study participants - covariates that may influence susceptibility

Analytic results under the null of no susceptibility effect

Under the null of no susceptibility effect ($\beta = 0$):

- DE $= 0$ under **Bernoulli** randomization (———)
- Under **block** randomization (———), the direction of DE is opposite that of infectiousness effect γ
- Under **cluster** randomization (———), the direction of DE is the same as that of infectiousness effect γ



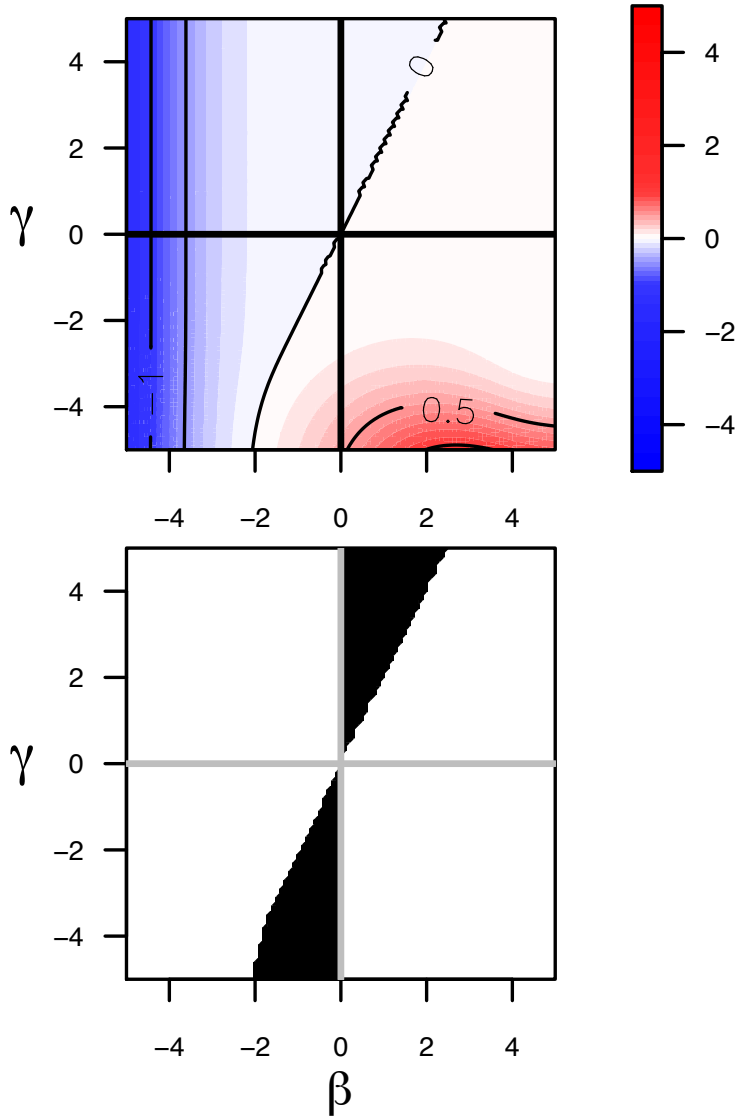
Eck DJ, Morozova O, Crawford FW. Randomization for the susceptibility effect of an infectious disease intervention. *arXiv*:1808.05593. 2018.

Analytic results under block randomization in clusters of size two

In clusters of size two, when exactly one subject is treated:

- When the infectiousness effect γ is in the same direction, but stronger than the susceptibility effect β, the DE **is guaranteed to point in the direction opposite that of** SE for long enough observation time

- Under this study design, the DE **is always a biased approximation** to the SE, even when they both point in the same direction



Morozova O, Cohen T, Crawford FW. Risk ratios for contagious outcomes. *JRSI*. 2018.

Hypothetical example: vaccination

Assume a hypothetical closed population of 100,000 individuals with one infected person at time zero and no recovery (SI-type process).

Assume that a protective vaccine is given to 20% of individuals: the true effect on susceptibility $e^{\beta} = 0.74$, and the true effect on infectiousness $e^{\gamma} = 0.37$.

Assume that the DE was used as a measure of the SE, and that it was evaluated in a block randomized experiment ($DE = 1.05$). Assume that the value of the infectiousness effect was estimated correctly.

Projected intervention effectiveness at the population level:

	# of infections	averted infections	cost	ICER
do nothing	35,596	-	-	-
true effect	11,098	24,498	USD 3M	USD 122
estimated effect	14,225	21,371	USD 3M	USD 140

Final thoughts

The **direct effect is a valid statistical estimand**, which may provide useful information about the mechanism of treatment spillover under some designs.

However, this quantity **does not always have an individualistic causal interpretation**, and may be misleading if incorrectly interpreted as an analogue of the susceptibility effect and used to **parameterize a transmission model** for the evaluation of population-level effects.

Thanks to Peter M. Aronow, Ashley L. Buchanan, Xiaoxuan Cai, Ted Cohen, Forrest W. Crawford, Daniel J. Eck, Edward H. Kaplan, Eben Kenah, Joseph Lewnard, Marc Lipsitch, Wen Wei Loh, A. David Paltiel, Donna Spiegelman, Jon Zelner, and friends from the Crawford Lab.

Funding: R36 DA042643, DP2 OD022614, R01 AI112438, R01 DA015612, R01 MH105203.

olga.morozova@yale.edu
http://campuspress.yale.edu/omorozova/

References:

Eck DJ, Morozova O, Crawford FW. Randomization for the susceptibility effect of an infectious disease intervention. *arXiv preprint* 1808.05593.

Morozova O, Cohen T, Crawford FW. Risk ratios for contagious outcomes. *JRSI.* 2018; 15(138):20170696.

Crawford FW, Morozova O, Buchanan AL, Spiegelman D. Interpretation of the individual effect under treatment spillover. *AJE.* 2019; 188(8): 1407-1409.

Hudgens MG, Halloran ME. Toward Causal Inference with Interference. *JASA.* 2008; 103(482):832-841.

Sävje F, Aronow PM, Hudgens MG. Average treatment effects in the presence of unknown interference. *arXiv preprint* 1711.06399.

O'Hagan JJ, Lipsitch M, Hernán MA. Estimating the Per-Exposure Effect of Infectious Disease Interventions. *Epidemiology.* 2014; 25(1): 134-138.

Halloran ME, Struchiner CJ. Study designs for dependent happenings. *Epidemiology.* 1991; 2(5): 331-338.