Estimating the risk of influenza under differing distributions of vaccination among university students

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Disclaimer: views (and errors) are mine and not those of NIH or colleagues

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[1] Footnotes are for asides or references, but are fair game for questions

Influenza

Influenza causes substantial morbidity, mortality, economic costs

Influenza prevention among university students

- Elevated risk of infection, low vaccination rates, importance for further transmission[2]
- A key prevention strategy is vaccination

Prior research on university students has focused on

- Direct, or unit-treatment, effect of vaccination
- Focused on vaccination uptake as outcome

Not influenza incidence under large scale changes in vaccination

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[2] Layde et al. *JID* 1980;142(3):347-352, Bednarczyk et al. *Vaccine* 2015;33(14):1659-1663

Motivation

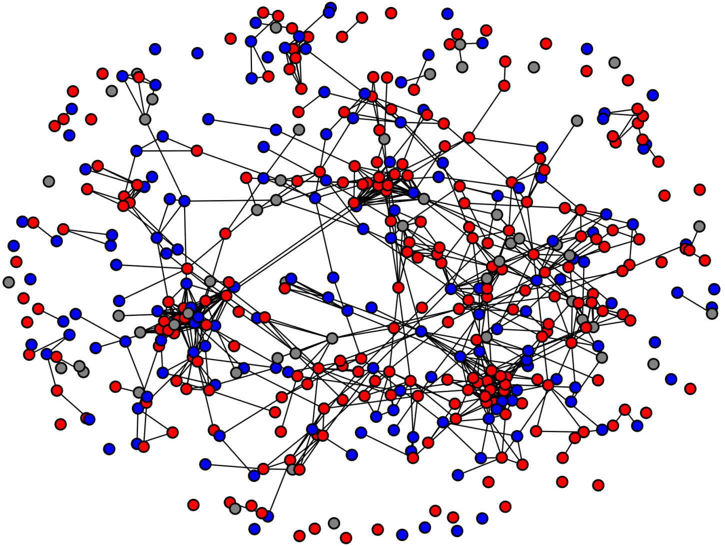
Question: What would the risk of influenza infection be under plans that increase the probability of influenza vaccination uptake among university students at a midwest university from January to April 2013?

Data: eX-FLU cluster randomized trial ($n = 454$)[3]

- Randomized 3-day self-isolation
- 10-weeks of follow-up
- Collected information on vaccination, risk factors for respiratory infections, respiratory infections

[3] Aiello AE et al. 2016 *Epidemics*; 15:38-55

In-Person Contacts Between Students



Challenges

1. Interference & spillover effects
   - Vaccination of one affects another
2. Missing vaccination data
3. Measurement error of contacts

Parameter

Notation

Y_i: observed outcome (i.e., influenza infection) for unit i

A_i: observed action (i.e., vaccination) for unit i

- $\mathcal{A} = \{0, 1\}$ is the support of A
- $\mathbf{A} = (A_1, ..., A_n)$

$Y_i(\mathbf{a}) = Y_i(a_1, ..., a_n) = Y_i(a_i, a_{-i})$: potential outcomes

W_i: vector of covariates for unit i

- $\mathcal{W}$ is the support of W
- $\mathbf{W} = (W_1, ..., W_n)$

$\mathfrak{G}$: $n \times n$ adjacency matrix

- $\mathfrak{G}_{ij} = 1$ if edge between i, j, and 0 otherwise

Parameter of Interest

Given n units in a network $\mathfrak{G}$, parameter is

$$\psi = \frac{1}{n} \sum_{i=1}^{n} E\left[\sum_{\mathbf{a} \in \mathcal{A}} Y_i(\mathbf{a}) \Pr^*(\mathbf{A} = \mathbf{a} \mid \mathbf{W}) \mid \mathbf{W} \right]$$

Mean of Y if $\mathbf{A}$ had been set according to the plan $\Pr^*$, holding the network structure, $\mathfrak{G}$, and $\mathbf{W}$ fixed

Interpretation: Under vaccination plan $\Pr^*$, the incident proportion of influenza would have been ψ for given network

Stochastic Plans

Vaccination Plans

Consider hypothetical interventions that address common reasons for not receiving the influenza vaccine

- **Educational**: correct misconceptions about influenza
- **Non-financial**: ease, availability
- **Financial**: remove monetary costs

Plans

- Based on self-reported reasons
- Shift probability of being vaccinated
- Not vaccinate those with contraindications

Shifts Under Vaccination Plans

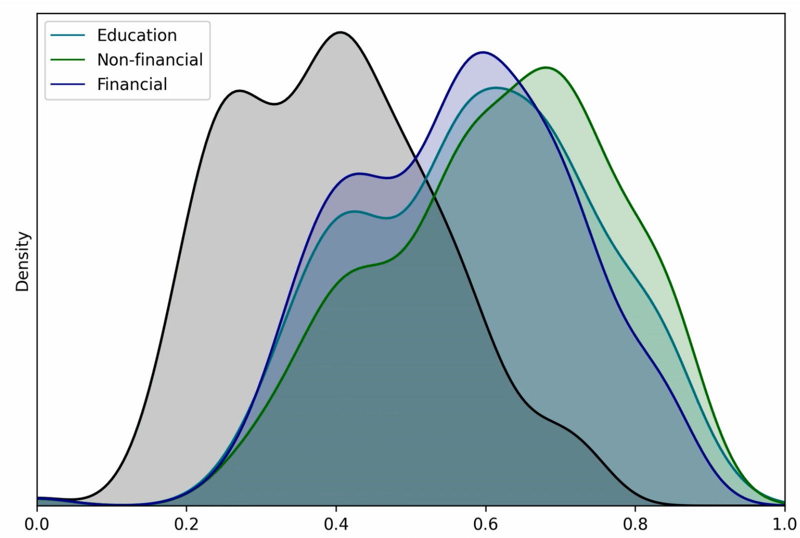
Plan specified in terms of $\Pr^*(A_i = a \mid \mathbf{W}_i)$

Estimate $\rho = \Pr(A_i = 1 \mid \mathbf{W}_i)$ then shift by

$$\rho^* = \begin{cases} \text{expit}\left[\text{logit}(\rho) + \omega\right] & \text{if targeted} \\ \text{expit}\left[\text{logit}(\rho) + \omega/3\right] & \text{otherwise} \end{cases}$$

for $\omega \in [0, 3]$

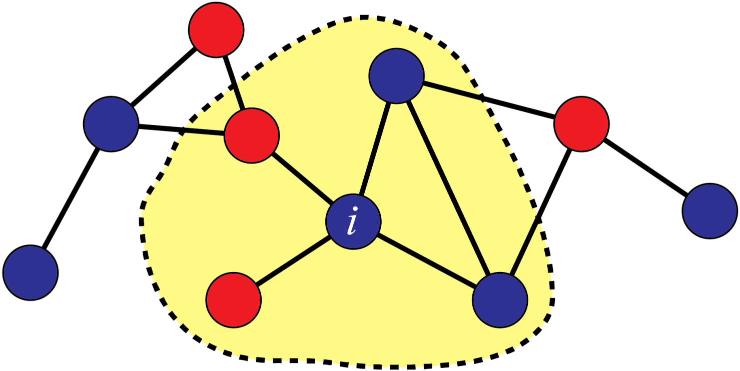
Probability Shifts Under Plans



Identification

Simplifying Interference – Weak Dependence

Learning $Y_i(\mathbf{a})$ is difficult



Covariate Mappings

Rely on a *parametric mapping*

$$Y_i(a_i, a_{-i}) = Y_i(a_i, a_i^s) \neq Y_i(a_i)$$

where a_i^s is a parametric map of i's direct contacts

Here a^s denotes a general covariate mapping of direct contacts

- But need to choose something specific[4]
- Assume parametric mapping is correct

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[4] These definitions treat all contacts as equivalent but relax via edge weights or multiple edge types

Covariate Mapping Examples

Count

$$X_i^s := \sum_{j \in n} X_j \mathfrak{G}_{ij}$$

Proportion

$$X_i^s := \frac{\sum_{j \in n} X_j \mathfrak{G}_{ij}}{\sum_{j \in n} \mathfrak{G}_{ij}}$$

Threshold

$$X_i^s := I \left\{ \left(\sum_{j \in n} X_j \mathfrak{G}_{ij} \right) >= t \right\}$$

Identification Assumptions

Causal consistency

$$\text{if } a = A_i, a^s = A_i^s \text{ then } Y_i = Y_i(a_i, a_i^s)$$

Exchangeability

$$Y_i(a, a_s) \amalg A_i, A_i^s \mid W_i, W_i^s$$

Positivity

$$\text{if } \Pr^*(A = a, A^s = a^s \mid W, W^s) > 0 \text{ then}$$
$$\Pr(A = a, A^s = a^s \mid W, W^s) > 0$$

Other Systematic Errors

Missing Data

Missing data on vaccination and covariates

Multivariate Imputation with Chained Equations (MICE)

- Modified MICE to include A^s, W^s in models

100 imputed data sets

Measurement Error of Contacts

Self-reported contacts are known to be misreported[5]

Multiple Imputation for Measurement Error (MIME)

- Bayesian procedure with stochastic block model[6]
- Sensitivity and specificity informed by Bluetooth data collected on subset of students

100 networks for each imputed data set

- Summarized 10,000 imputations using nested Rubin's Rule

[5]Mastrandrea et al. *PloS ONE* 2015;10(9):e0136497
[6]Young et al. *Journal of Complex Networks* 2021;8(6)

Estimation

Targeted Maximum Likelihood Estimation (TMLE)

TMLE for network dependent data[7]

1. Fit nuisance model for $Y \mid A, A^s, W, W^s$
2. Fit nuisance model for $A, A^s \mid W, W^s$
3. Fit targeting model
4. Targeted prediction(s)
5. Inference via influence function

[7] van der Laan *Journal of Causal Inference* 2014;2(1):13-74, Sofrygin & van der Laan *Journal of Causal Inference* 2017;5(1):20160003, Zivich et al. *Stats in Med* 2022;41(23):4554-4577

Step 1: Outcome Nuisance Model

Treat observations as if they are independent and fit a model for[8]

$$E[Y \mid A, A^s, W, W^s]$$

Then generate predicted values from this model, $\hat{Y}$, with A, A^s

Here, logistic regression with L_2 penalty

[8] This is the g-computation analog for network-dependent data

Step 2: Action Nuisance Model

For the targeting step, need[9]

$$\frac{\pi_i^*}{\pi_i} = \frac{\Pr^*(A_i = a, A_i^s = a_i^s \mid W_i, W_i^s)}{\Pr(A_i = a, A_i^s = a_i^s \mid W_i, W_i^s)}$$

Factor A, A^s and model as if independent

Use a Monte Carlo procedure to go from

$$\Pr^*(A_i = a \mid W_i, W_i^s) \rightarrow \Pr^*(A_i = a, A_i^s = a^s \mid W_i, W_i^s)$$

Here, logistic regression and Poisson[10]

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[9]This is the weight for the IPW analog with network-dependent data

[10]A^s was chosen to be count mapping

Step 3: Targeting Step

Fit the following weighted model

$$\text{logit}\left\{\Pr(Y_i = 1)\right\} = \eta + \text{logit}(\hat{Y}_i)$$

where weights are $\frac{\pi_i^*}{\pi_i}$ from the previous step

Step 4: Interest Parameter

Monte Carlo procedure

a. Set actions according to $\Pr^*(A_i = a \mid W_i, W_i^s)$.[11]
b. Compute $\hat{Y}^*$ under A^*, A^{s*}.
c. Update $\hat{Y}^*$ using $\hat{\eta}$, then take mean.
d. Repeat (a.) through (c.) k times.
e. Take average of the k different means as $\hat{\psi}$.

[11] Can simplify by reusing copies from Step 2

Step 5: Inference

Influence function variance estimator with latent dependence[12]

$$\frac{1}{n}\sum_{i=1}^{n}\sum_{j=1}^{n}\left[\frac{\pi_i^*(\hat{\alpha},\hat{\gamma})}{\pi_i(\hat{\alpha},\hat{\gamma})}\left(Y_i - \hat{Y}_i\right)\right] \times \left[\frac{\pi_j^*(\hat{\alpha},\hat{\gamma})}{\pi_j(\hat{\alpha},\hat{\gamma})}\left(Y_j - \hat{Y}_j\right)\right] \times \mathbb{G}_{ij}$$

- where $\mathbb{G}_{ij} = \mathfrak{G}_{ij}$ for $i \neq j$ and $\mathbb{G}_{ij} = 1$ otherwise

[12] Dependence up to second-order contacts. Ogburn EL et al. *JASA* 2024;119(545):597-611

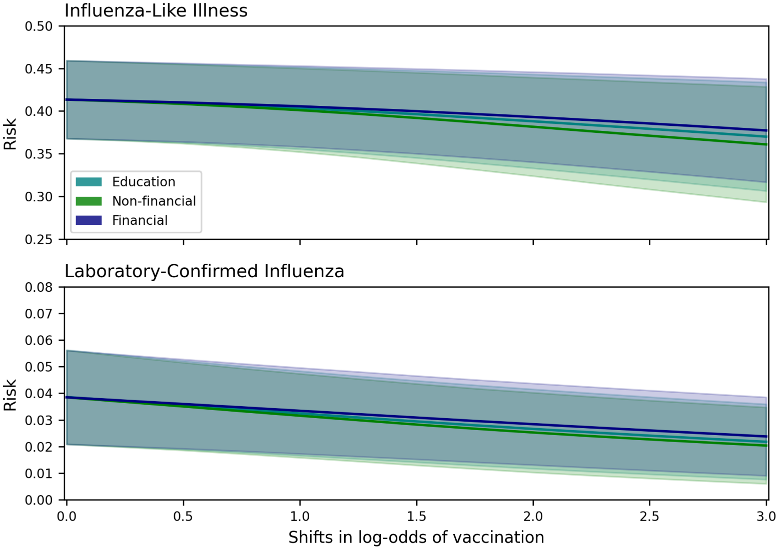
Results

Descriptive Summary

	Overall ($n = 454$)
Influenza-Like Illness	190 (42%)
Laboratory-confirmed	17 (4%)
Vaccination	161 (40%)
Missing	52 (11%)

	Unvaccinated ($n = 241$)
Educational	50 (11%)
Non-financial	93 (20%)
Financial	18 (4%)
Contraindication(s)	2 ($<$1%)

Results


Influenza-Like Illness
Risk
0.50
0.45
0.40
0.35
0.30
0.25
Education
Non-financial
Financial
Laboratory-Confirmed Influenza
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Shifts in log-odds of vaccination

Conclusions

Conclusion

Interference is common in epidemiology

- Modifies how we should view parameters
- Consider what is meaningful for public health
- Need methods (and data) that can accommodate

But there are still many challenges

Practical Challenges

Collection of network data

- Measure large networks
- Reduce measurement error

Modeling

- Weak dependence
- Covariate mappings

Missing data

- Dependence between observations

Partially observing network

Inference doesn't incorporate that $\Pr^*$ is based on estimated probabilities

Future Directions

Longitudinal Network TMLE

- Weak dependence only in interval

Covariate mappings

- Explore flexible specification approaches

Compare against alternative approaches[13]

[13] Tchetgen Tchetgen et al. *JASA*, 2021;116(534):833-844.

Thank You!

Questions?

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Appendix

Identification in Example

Covariates included in W

- gender, race, stress (Perceived Stress Scale-10), optimal hand hygiene, high-risk conditions, sleep quality, alcohol use, trial arm, number of unique contacts

Covariate mappings

- Vaccination: count
- Gender, race, hand hygiene, high-risk, alcohol use, trial arm: count
- stress: variance

Plans

Educational

- Target those: influenza vaccine causes influenza, don't get influenza, didn't know they could get the influenza vaccine

Non-financial

- Target those: never got around to it, did not have transportation, hours available were inconvenient

Financial

- Target those: health plan did not cover, no health insurance

Probability Weights Monte Carlo

Monte Carlo procedure to get π_i^*

a. Create copy of data
b. Set A according to $\Pr^*(A_i = a \mid W_i, W_i^s)$ to get A^*, A^{s*}
c. Repeat (a.) and (b.) for k copies of data
d. Fit models for $\Pr(A_i^* = a, A_i^{s*} = a_i^s \mid W_i, W_i^s)$ using all k copies
e. Predict probability using models from (d.) and *observed* W, W^s, A