Estimating Vaccine Effects from Large, Routinely Collected Data

M. Elizabeth Halloran

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Dependent versus independent happenings

- Sir Ronald Ross (1916): the number of individuals becoming affected depends on how many are already affected
- Contrast to independent happenings
- Interference: the potential outcomes in individuals are affected by the treatment status of other individuals (Cox 1958).
- In the presence of interference, treatment may have several kinds of effects, such as indirect/ spillover effects on others.
- Demonstrating indirect effects of vaccination can have important consequences for global policies.

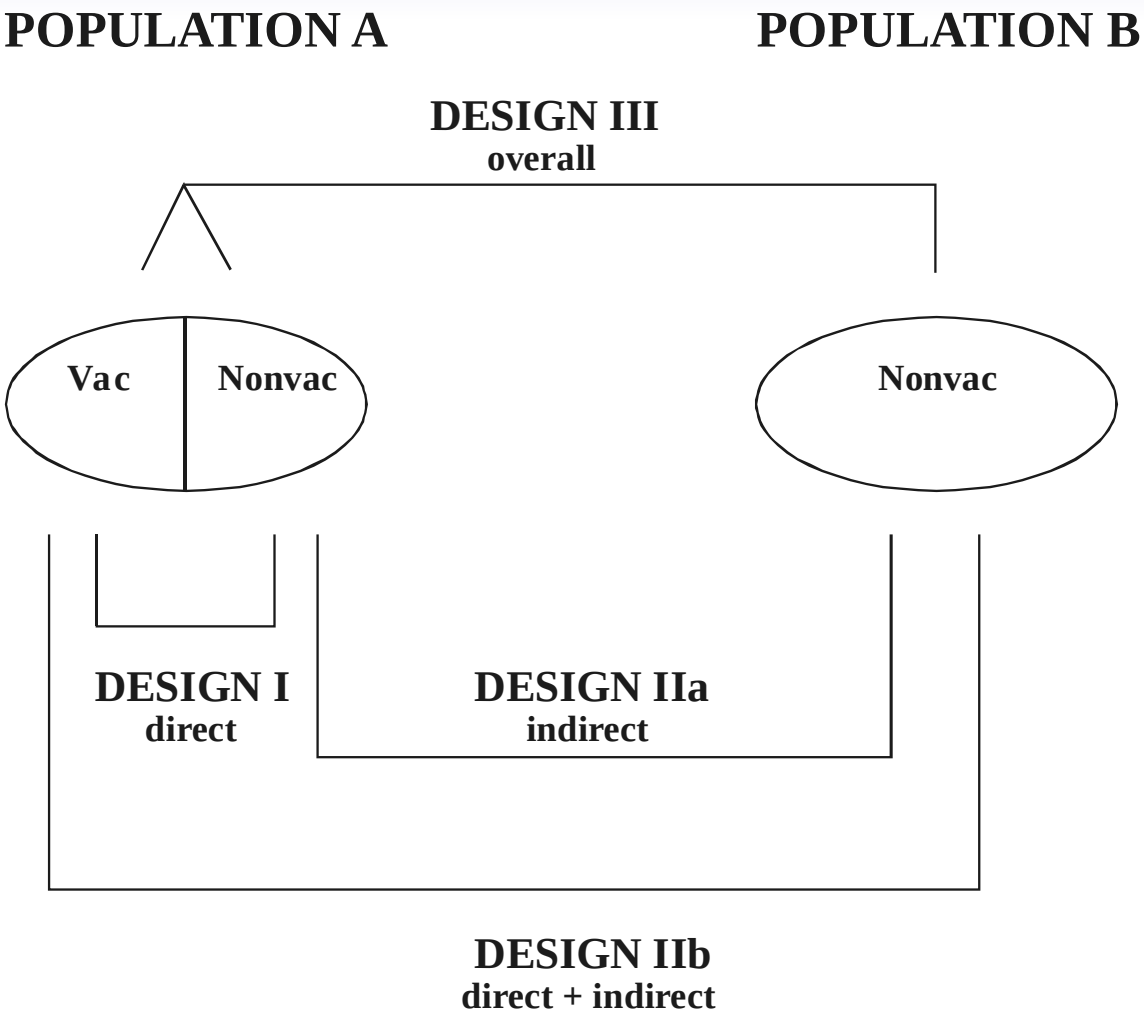

Figure : Study designs for dependent happenings; vaccination and vaccination programs (Halloran and Struchiner 1991, 1995).

Vaccine efficacy and effectiveness

- Generally estimated as one minus some measure of relative risk, RR, in the vaccinated group compared to the unvaccinated group:

$$VE = 1 - RR \ .$$

- The groups being compared could be composed of individuals or of populations or communities.
- Contrasts can be on other scales: risk ratio, risk difference, odds ratio

Causal Estimands

- Assuming partial interference (Sobel 2006), Hudgens and Halloran (2008) defined causal estimands:
- Population average **direct** effect when vaccine coverage is α:
  - $\overline{DE}(\alpha) = \overline{y}(0;\alpha) - \overline{y}(1;\alpha)$.
- Population average **indirect** effect coverages α and α':
  - $\overline{IE}(\alpha,\alpha') = \overline{y}(0;\alpha) - \overline{y}(0;\alpha')$.
- Population average **total** effect:
  - $\overline{TE}(\alpha,\alpha') = \overline{y}(0;\alpha) - \overline{y}(1;\alpha')$.
- **Overall** effect of vaccination:
  - $\overline{OE}(\alpha,\alpha') = \overline{y}(\alpha) - \overline{y}(\alpha')$.

Two-Stage Randomization

- Drawing inference about treatment effects generally requires knowledge or modeling of the mechanism by which individuals select or are assigned treatment.
- Assuming a sequential two-stage randomization procedure:
  1. Stage one: randomize groups to different strategies
  2. Stage two: randomize individuals within groups conditional on the group assigned strategy.
- Hudgens and Halloran (2008) obtained unbiased estimators of the causal estimands from the observed data. under a permutation randomization scheme.
- VanderWeele and Tchetgen Tchetgen (2012) derived under simple randomization.

Not Usually Two Stage Randomization

- Most studies are not randomized at two stages, at least not in the vaccine world.
- Usually randomized at the individual level, the cluster level, or neither.

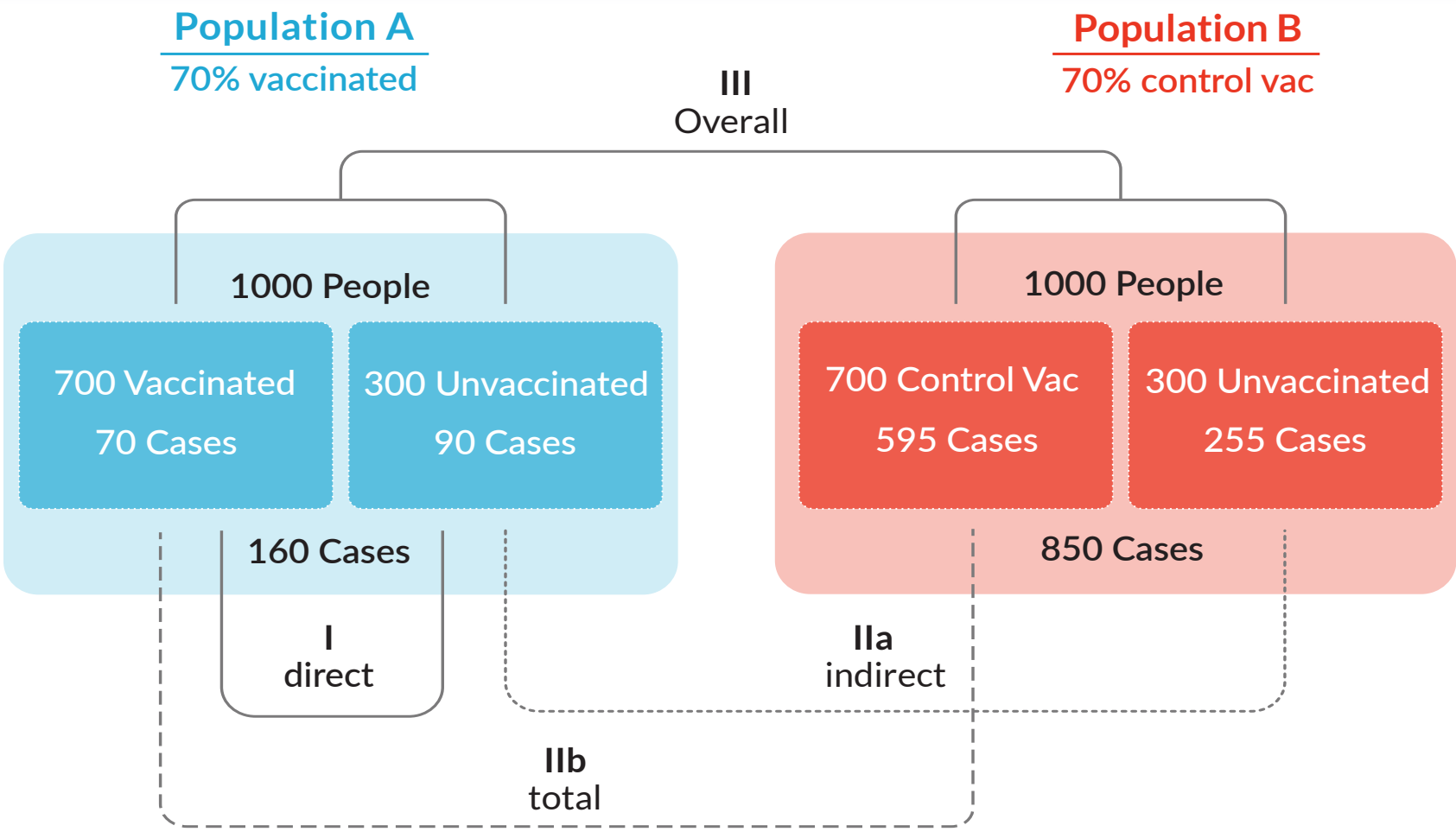

Figure : An example of estimating direct, indirect, total, and overall effects of vaccination with a control vaccine in a cluster-randomized study.

Use of Routinely Collected Data

- Formal methods have been developed for study designs and analysis that can estimate the different effects of vaccination.
- However, implementing field studies to evaluate the different effects of vaccination can be expensive, of limited generalizability, or unethical.
- It would be advantageous to use routinely collected data to estimate the different effects of vaccination.
- We show how different types of data are needed to estimate different effects of vaccination.

Estimating different effects of rotavirus vaccination

- Panozzo *et al.* 2014 estimated direct, indirect, total, and overall effectiveness of rotavirus vaccines in preventing gastroenteritis hospitalization in privately insured children in the US.
- The data were from the MarketScan Research Databases (Truven Health Analytics, Inc., Ann Arbor Michigan).
- The database contains information on over 110 million individuals throughout the United States with commercial health insurance.
- Interesting because the database has information on the outcomes linked to the individual vaccination status and covariates and on a baseline pre-vaccination period, allowing estimation of direct, indirect, total and overall effects.

Rotavirus Vaccination in the US, cont'd

- Two rotavirus vaccines for infants are licensed in the United States, one since February 2006, and one since April 2008.
- Infants between the ages of 8 and 20 months in the database were followed for rotavirus gastroenteritis.
- Infants vaccinated after 8 months of age were excluded from the analysis.
- Outcomes for rotavirus gastroenteritis and acute gastroenteritis were identified using the appropriate ICD-9-CM codes.
- Vaccination status was determined using appropriate Current Procedural Terminology codes.

Rotavirus Vaccination in the US, cont'd

- To increase the sensitivity of the vaccination status, they excluded infants living in any of the 13 states with state-funded rotavirus immunization programs.
- Infants funded by such a program would not have vaccination recorded in the private insurance database.
- They included only infants who had also received at least one dose of diphtheria, tetanus, and acellular pertussis vaccine, because children who failed to receive vaccines that are usually administered may differ from those who had received them.

Rotavirus Vaccination in the US, cont'd

- The analysis accounted for household-level variation in rotavirus vaccine coverage, disease, and mixing behaviors by examining the number of other dependent children less than 10 years of age covered by the same insurance holder as the infant.
- Geographical variation was accounted for by including the region and rurality of the child's residence as defined by the US Department of Agriculture, Economic Research Service, available on the web.

Estimating Rotavirus Vaccination Effectivenss

- Estimates of VE were based on Cox proportional hazards models to estimate hazard ratios of rotavirus gastroenteritis or acute gastroenteritis hospitalizations.
- Panozzo *et al.* (2014) estimated the hazard ratios in infants entering the cohort in 2007, 2008, 2009, and 2010, to get VE estimates by calendar year.
- The direct effects for each calendar year were estimated by comparing outcomes in the vaccinated and unvaccinated infants in each year from 2007 to 2010.

Estimating Rotavirus Vaccination Effectiveness

- To estimate indirect, total, and overall effectiveness during each calendar year, the comparison was made to the unvaccinated infants followed in the pre-vaccine baseline period 2001-2005.
- For example, indirect VE in 2007 was estimated by comparing unvaccinated infants followed in 2007 with the unvaccinated infants in the baseline period 2001-2005.
- Coverage with 1 or more dose grew from 51% in 2007 to 86% in 2010.

Estimating Rotavirus Vaccination Effectiveness

- After exclusions, in the final analytical cohort, 277,900 children were born during the pre-vaccine period,
- 627,818 were born during the rotavirus vaccine period, 476,576 of whom received rotavirus vaccine and 151,242 did not.
- Vaccination coverage ranged from 51% in 2007 to 86% in 2010.
- Despite over 900,000 children in the analytical cohort, the number of events of rotavirus gastroenteritis hospitalizations per group during the vaccine era was relatively small, ranging from 3 to 114 per year, with 722 events in the 277,900 children unvaccinated pre-vaccine era 2001-2005.

Rotavirus Vaccine Effectiveness Agains Rotavirus Gastroenteritis Hospitalizations

	Direct	Indirect	Total	Overall
2007	87 (58, 96)	14 (−14, 36)	91 (73, 97)	40 (20, 54)
2008	87 (80, 92)	44 (30, 55)	92 (88, 95)	75 (69, 79)
2009	92 (87, 95)	40 (24, 53)	95 (92, 97)	83 (79, 86)
2010	90 (75, 96)	82 (70, 90)	98 (96, 99)	96 (93, 97)

(95% CI)

Summary of this rotavirus vaccination analysis

- Key to estimating all four effects was having individual level data on outcomes and vaccination status, and a baseline pre-vaccine comparison group.
- A drawback of the inference is that each estimate of indirect, total, and overall effects was based on comparing just one intervention group (a calendar year) with one baseline group (the pre-vaccine years 2001-2005).
- Usual caveats to observational studies

Estimating overall and direct effects of rotavirus vaccine in Ghana

- Armah et al (2016) Clin Inf Dis. 62:Suppl 2, S200-S207
- Goal: estimate overall effect and direct effect of rotavirus vaccine against severe rotavirus diarrhea in Ghana
- Vaccine introduced into schedule in April 2012.
- Impressive high coverage of 97% for one dose and 90% for two doses achieved almost immediately, later even higher.

Estimating overall effects of rotavirus vaccine in Ghana

- Surveillance data on rotavirus disease was not linked to vaccine status in the analysis.
- Only overall effect estimated from the surveillance data from 7 sentinel sites.
- Data 40 months before and 31 months after rotavirus vaccine introduction was analyzed using the interrupted time series analysis.
- In three years post-introduction, overall rotavirus rate reduction in $<$5 year olds was 49% (32, 63).

Test-negative design to estimate direct effectiveness in Ghana

- Test-negative design in children presenting with diarrhea to estimate the direct effectiveness was embedded in the surveillance.
- Those who test positive for rotavirus are cases
- Those who test negative for rotavirus are non-cases
- Vaccination status confirmed by vaccination record.
- However, high vaccine coverage and across site heterogeneity precluded a robust VE estimate.

Results: VE-TND and VE-RCT estimates (95% CI)

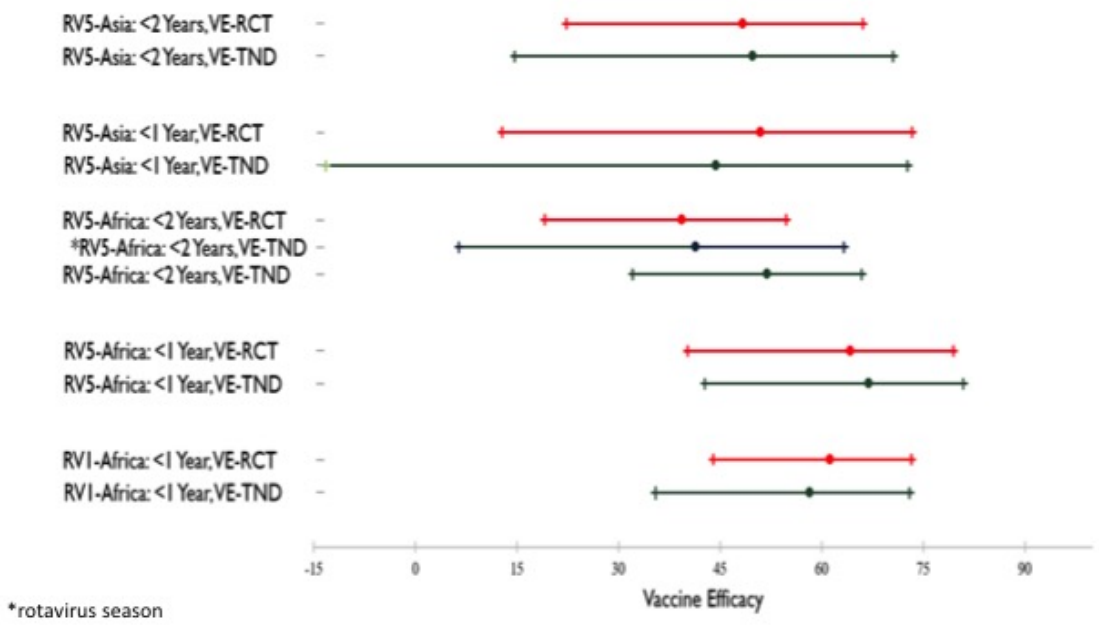

Figure : Schwartz, LM, Halloran, ME, Rowhani-Rahbar, A, Neuzil, KM, Victor, JC, *Vaccine* (2017) 35:184-190

Future Challenges

- Considerably more research left to be done to estimate direct, indirect, total, and overall effectiveness from routinely collected data.
- How can routinely collected data be enhanced so that all four effects can be estimated?
- Need to link vaccine status with outcome and covariate data.

Thank You!

- 9th Summer Institute in Statistics and Modeling in Infectious Diseases (NIGMS-supported)
- July 10-26, 2017, University of Washington, Seattle