Addressing confounding in studies of vaccine effectiveness

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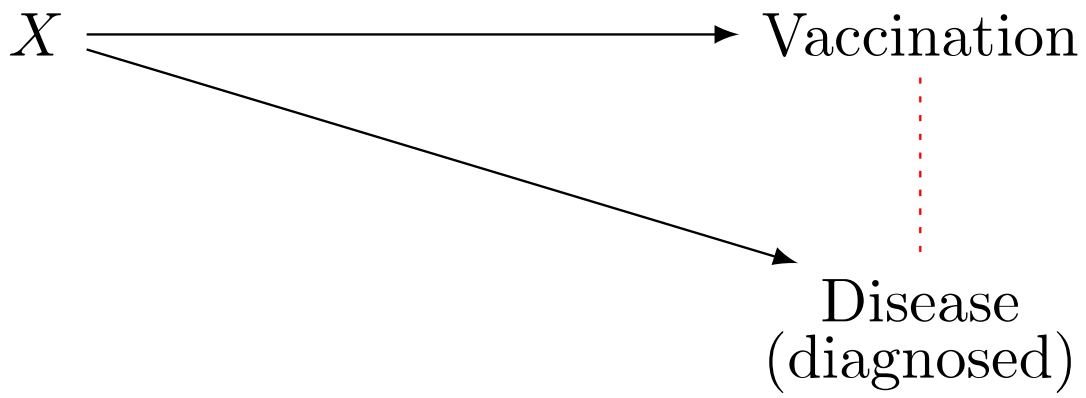
WHO Global Consultation for Vaccine Effectiveness Studies

14 September, 2023

Confounding

- Confounding in epidemiology refers to a situation in which the exposure and outcome share a common cause ("*X*" in the diagram below)
- This phenomenon can lead to the appearance of an association between the exposure and the outcome, even when the exposure has no causal effect on the outcome
- Our objective is to estimate the effect of the exposure on the outcome, ***controlling*** for any association driven by the confounding variable



What are some confounders we might want to consider?

Confounder	Possible effect on exposure	Effect on outcome
Older age	More likely to receive vaccine	Possibly higher risk of severe disease
Comorbid conditions	More likely to receive vaccine	Possibly risk of severe disease
High healthcare seeking behavior	More likely to receive vaccine	Possibly better health status (less likely to experience disease), or greater likelihood of diagnosis if infected
Living in a community with low healthcare access	Less likely to receive vaccine	Possibly higher risk of infection, but possibly lower likelihood of diagnosis if infected
Limited language proficiency	Less likely to receive vaccine	Possibly higher risk of infection, but possibly lower likelihood of diagnosis if infected

Example—higher PCV13 uptake among age groups at greater risk of pneumonia

Older individuals have higher likelihood of disease and higher likelihood of being vaccinated with PCV13

Age	PCV13 not received, *n* (%) *N*=73,377	PCV13 received, *n* (%) *N*=476,873	Any pneumonia *n* (%) *N*= 59,003	aHR (95% CI)[2]
65-69y	37,726 (51.4)	143,645 (30.1)	12,188 (3.9)	ref.
70-74y	17,879 (24.4)	139,161 (29.2)	13,071 (5.4)	1.15 (1.12, 1.18)
75-79y	9,030 (12.3)	89,731 (18.8)	11,990 (7.7)	1.44 (1.40, 1.48)
80-84y	4,913 (6.7)	57,454 (12.0)	10,837 (10.8)	1.84 (1.78, 1.89)
85-89y	2,456 (3.3)	31,202 (6.5)	7,872 (14.1)	2.32 (2.25, 2.40)
≥90y	1,373 (1.9)	15,680 (3.3)	5,475 (20.3)	3.30 (3.18, 3.42)

Failure to adjust for age would cause vaccination to appear to increase individuals' risk of pneumonia

Data from Lewnard et al., *Clin Infect Dis* 2022

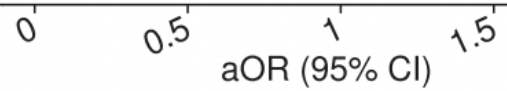
Counterexample: the “healthy vaccinnee” effect

	No Masks Worn	Mask Used by Participant or Contact
	n (%)	n (%)
	N = 816	N = 188
Unvaccinated	539 (69.5)	108 (62.8)
Partially vaccinated	64 (8.3)	19 (11.0)
Fully vaccinated	172 (22.2)	45 (26.2)

Vaccination may be associated with taking other precautions

Failure to adjust for this would make vaccination appear more protective than it truly is

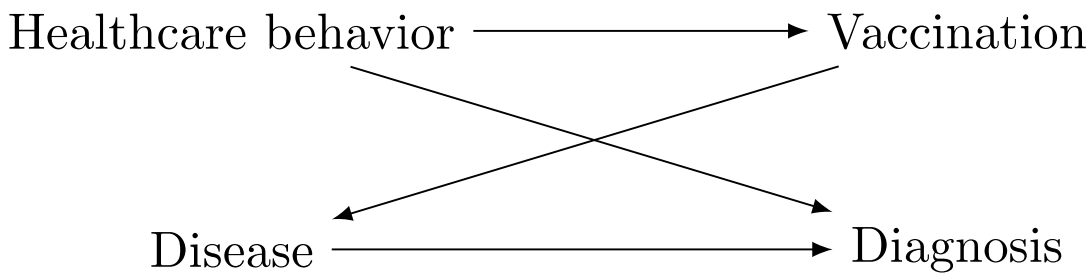
	Total n (%)	Cases n (%)	Controls n (%)	aOR (95% CI)
Mask usage at interaction				
No mask usage at interaction	816 (81.2)	648 (86.5)	168 (65.9)	ref.
Mask usage by either party	188 (18.7)	101 (13.5)	87 (34.1)	0.50 (0.29, 0.85)
Vaccination status of participant				
No vaccine doses	649 (68.4)	546 (75.3)	103 (46.0)	ref.
Incomplete vaccination series	83 (8.7)	56 (7.7)	27 (12.1)	0.30 (0.15, 0.60)
Full vaccination series	217 (22.9)	123 (17.0)	94 (42.0)	0.25 (0.15, 0.43)



Data from Andrejko et al., *Clin Infect Dis* 2021

Vaccination and healthcare-seeking behavior

- Receiving a diagnosis for the disease of interest may be dependent on individuals engaging with healthcare (seeking testing or care)
- The likelihood of seeking care, especially for nonsevere disease, may be associated with the likelihood of seeking vaccination
- Information on the reason individuals receive a diagnosis is rarely available **and should be collected** in observational studies



In many study designs, we want to infer the relationship between Vaccination and Disease, but instead observe the outcome of "Diagnosis". Factors influencing both vaccination and the likelihood of diagnosis need to be accounted for.

Example

Even after subsetting by cases/control status, vaccinated individuals were more likely to have sought (surveillance/screening) testing for SARS-CoV-2 than unvaccinated individuals, and were less likely to have sought testing due to symptoms

	Controls		Cases	
Reasons[a]	Unvaccinated (n = 313)	Vaccinated[b] (*n* = 185)	Unvaccinated (n = 454)	Vaccinated (n = 71)
Contact with positive case	28 (8.9)	8 (4.3)	143 (31.5)	30 (42.3)
Contact with symptomatic individual	12 (3.8)	4 (2.2)	18 (4.0)	2 (2.8)
Told by public health worker to get tested	1 (0.3)	1 (0.5)	3 (0.7)	0 (0.0)
Routine screening for my work or school	120 (38.3)	113 (61.1)	29 (6.4)	17 (23.9)
Test required for medical procedure or hospital admittance	43 (13.7)	25 (13.5)	16 (3.5)	5 (7.0)
Someone in household had contact with a positive case	4 (1.3)	0 (0.0)	11 (2.4)	0 (0.0)
Test required to attend public event/share public space	2 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)
I just wanted to see if I was infected	71 (22.7)	18 (9.7)	43 (9.5)	4 (5.6)
Concerned about symptoms	43 (13.7)	13 (7.0)	262 (57.7)	26 (36.6)
Pre- or post-travel screening	21 (6.7)	7 (3.8)	17 (3.7)	4 (5.6)

Data are presented as n (%).

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Since interviewers indicated all reasons listed by participants, reasons will not sum to the total sample size.

[b]An individual is considered vaccinated if they have had at least 1 dose of an SARS-CoV-2 mRNA vaccine.

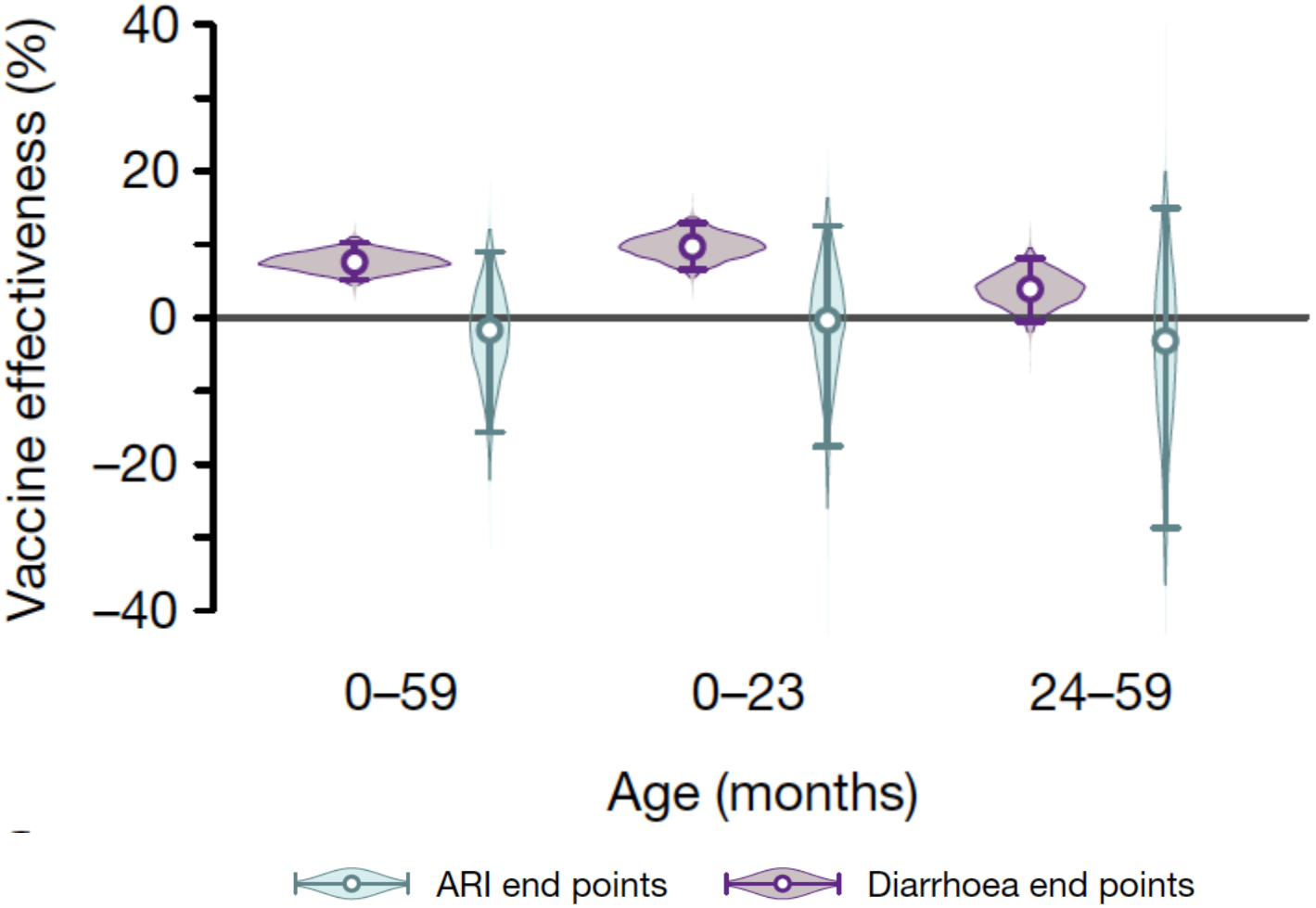
Data from Andrejko et al., *CID* 2021

Potential strategies for adjustment

- Are confounders observed?
  - (In a case-control study) match cases and controls on several factors
    - Challenges: efficiency
    - Compute stratified (matched) odds ratio to measure effect
  - Control for covariates via regression

- Are confounders unobserved?
  - Define negative control outcome (not affected by vaccination, but similar confounding pathways apply)
  - Define negative control exposure (will not affect the outcome, but possibly associated with vaccination through similar pathways to the source of confounding)

Successful example: negative control outcomes



Estimated effects of rotavirus vaccine against acute diarrhea (purple) and acute respiratory tract infection (blue)

Lack of effect on ARI despite similar confounding pathways suggests the relationship observed between vaccination and diarrhea outcomes may be causal

Data from Lewnard et al., *Nature* 2020

Concerning example

Adjusted Odds Ratios for Influenza Vaccination

		Among all participants aOR (95 % CI) *n* = 1261	Among participants with ≥ 1 COVID-19 vaccination aOR (95 % CI) *n* = 971	Among participants who have not received COVID-19 vaccination aOR (95 % CI) *n* = 290
COVID-19 Vaccination[1]	No doses	ref.	–	–
	≥ 1 dose (not boosted)	3.72 (2.15, 6.43)	–	–
	Boosted	16.50 (10.10, 26.97)	–	–
SARS-CoV-2 Infection Status	SARS-CoV-2 negative (control)	ref.	ref.	ref.
	SARS-CoV-2 positive (case)	0.64 (0.50, 0.82)	0.52 (0.40, 0.67)	0.70 (0.32, 1.51)
Use of face masks in indoor public settings[3]	No mask use in public settings	ref.	ref.	ref.
	Mask use in public settings	1.32 (0.90, 1.94)	1.09 (0.74, 1.62)	1.69 (0.44, 6.54)
Attended social gathering[4]	Did not attend social gathering	ref.	ref.	ref.
	Attended social gathering	1.08 (0.86, 1.36)	1.28 (0.98, 1.66)	1.44 (0.57, 3.65)

SARS-CoV-2 infection should not be associated with influenza vaccination status

Suggests that strategies used here to adjust for confounding between COVID-19 vaccination and SARS-CoV-2 infection are inadequate

Data from Andrejko et al., *Vaccine* 2022

Key points

- Many factors may be associated with both the likelihood of vaccination and the outcome of interest
- These concerns may be especially pronounced when observing the outcome is related to individuals' healthcare seeking behavior
- Relevant confounders may be observed or unobserved
- Negative control outcomes or exposures can provide a good basis to test for unobserved confounding and measures its extent

Thank you

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