Epib 605

A few random thoughts

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Week 3

Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly

> ** Abstract Conclusion**

"During 10 seasons, influenza vaccination was associated with significant reductions in the risk of hospitalization for pneumonia or influenza and in the risk of death among community-dwelling elderly persons."

Obvious red flag

> ** Abstract Result**

"…48% reduction in the risk of death (adjusted odds ratio, 0.52; 95% CI, 0.50 to 0.55)…"

Influenza deaths usually account for < 5% of all-cause mortality in elderly persons so seeing a 50% reduction in all-cause mortality is highly suspicious.

Strengths

- Important question
- Large sample covering multiple years
- Representative sample of community dwelling individuals
- Extensive control of confounding using PS
- Sensitivity analysis for unmeasured confounding
- No commercial sponsorhip - COI should be minimized

Some weaknesses

- Red flag of mortality benefit magnitude
- Possible yearly heterogeneity not considered
- Possible exposure misclassification (immortal time bias)

How to be a good critic of published article

- be a critical reader
- show your critique to be "tenable"
- remember ATOM ("Accept uncertainty. be Thoughtful, Open, and Modest.")

What to avoid

- Hit-and-run criticism: Pointing out flaws without providing alternative explanations.
- Dogmatic criticism: Relying on rigid principles (e.g., all unblinded RCTs are biased).
- Speculative criticism: Offering untested alternative explanations.
- Tubular criticism: Ignoring evidence that contradicts the critique.

Residual confounding

Authors examined confounder that was associated with 50% reduction in vaccination and 2-3 times more likley to die than those without confounder

Even with 60% prevalence of confounder, adjusted OR for death = 33% reduction

Conclude "indicate how our estimates of vaccine effectiveness would be lower, though still significant, after adjustment for the effect of a strong hypothetical unmeasured confounder".

How would you measure the strength of confounding needed to explain away the observed effect?

E values

E-values work in both directions - quantify the minimum strength of unmeasured confounding (on the risk-ratio scale) that would be needed to:

1. Explain away an observed association (move it to the null) or
2. Create an observed association from a truly null effect (move the true null to a non-null observed effect).

```r
library(EValue)
# Observed protective effect
rr_obs <- 0.52; ci_lo  <- 0.50; ci_hi  <- 0.55

evalues.RR(est = rr_obs, lo = ci_lo, hi = ci_hi, true = 1)
```

```
            point lower    upper
RR       0.520000   0.5 0.550000
E-values 3.255424    NA 3.037855
```

Therefore a unmeasured confounder that has a 3.26 RR for exposure and a 3.26 RR for the outcome is required to generate an apparent 48% reduction in the null was true.
This is a very strong confounder and unlikely to exist here.

Reference: VanderWeele, T. J., & Ding, P. (2017). Sensitivity Analysis in Observational Research: Introducing the E-Value. Annals of Internal Medicine, 167(4), 268–274.

So if not confounding then what bias could explain the results?

Clue: "All noninstitutionalized members of the plans were included in that season's cohort if they were 65 years of age or older as of October 1, had been continuously enrolled in the plan for the preceding 12 months, were alive on the first day of the influenza season, and were either continuously enrolled or died during the outcome period."

Since virtually impossible that the vaccinated individuals all received their vaccination on Oct 1 of each flu season, it appears that the researchers looked in the future to determine their vaccinated and unvaccinated groups. This leads to a misclassification of exposure time.

Look to the past - Lancet publication (Hill 1937)

Person-time matters

Consider scenario where the null effect is true

20% event rate in both groups

Misclassifying exposure time -> RR = 0.5 (fallacious comparison)

Proper classification of person time exposure -> RR = 1.0 (correct comparison)

TABLE XVII

Inoculated at each point of time.	Inoculated.		Uninoculated.	
	Exposed to risk in each quarter of the year.	Attacks at 5 per cent. per quarter.	Exposed to risk in each quarter of the year.	Attacks at 5 per cent. per quarter.
Jan. 1st, 0	0	0	5000	250
Apr. 1st, 300	300	15	4700	235
July 1st, 600	900	45	4100	205
Oct. 1st, 100	1000	50	4000	200
Total at end of the year ..	1000	110	4000	890

Fallacious comparison.—Ratio of attacks to final population of group. Inoculated 110/1000 = 11·0 per cent. Uninoculated 890/4000 = 22·3 per cent.

True comparison.—Ratio of attacks to person-years of exposure. Inoculated $110/(300\times\frac{1}{4}) + (900\times\frac{1}{4}) + (1000\times\frac{1}{4})$ = 20 per cent. Uninoculated $890/(5000\times\frac{1}{4}) + (4700\times\frac{1}{4}) + (4100\times\frac{1}{4}) + (4000\times\frac{1}{4})$ = 20 per cent.

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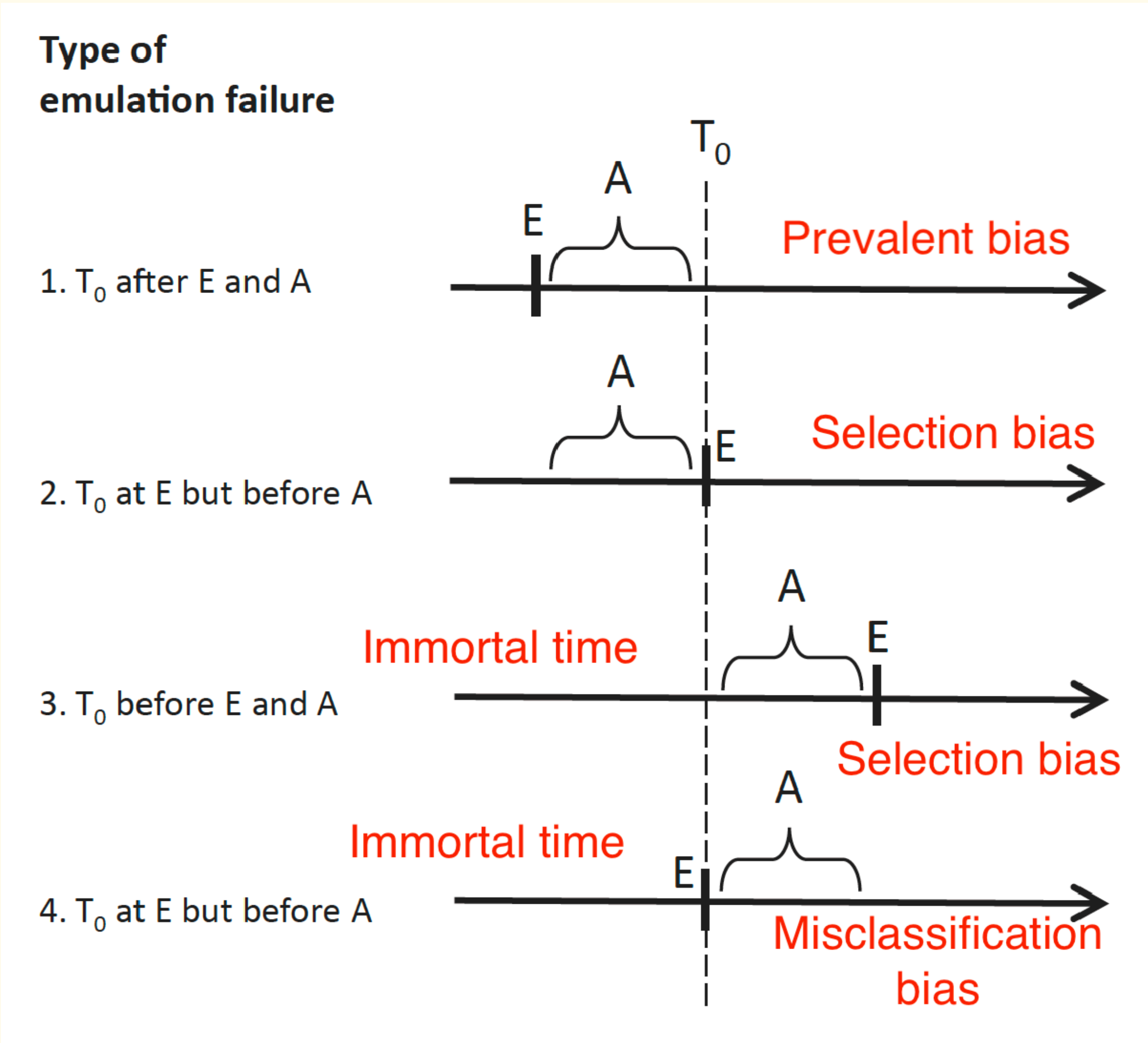
Avoiding bias in observational studies

Need to align T_0 (start of follow-up), treatment assignment (A), and eligibility criteria (E)



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Immortal time bias

Since person-time is important, its appropriate classification is essential
Misclassifying person-time can lead to immortal time bias - period of follow-up during which, by design, the outcome cannot occur.

Given:
Total vaccinated (415,249), unvaccinated (298,623) and deaths (8796)

Assume:
Not everyone vaccinated Oct 1
Nov 1, Dec 1 and Jan 1, 1/3 got vaccinated with 1% waiting until Feb 1
No Δ in death rates & monthly rate = 0.002058 (2/1000)

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Immortal time bias

Date	Vaccinated group				Unvaccinated group		
	% vaccinated	person/ seasons	deaths	person/ months	person/ seasons	deaths	person/ months
01-Oct	0.00	0	0		713872	1469	713872
01-Nov	0.33	137032	282	137032	575377	1184	573908
01-Dec	0.33	274064	563	273782	438342	902	437157
01-Jan	0.33	411097	845	410533	301310	620	300408
01-Feb	0.01	415249	853	414404	297158	612	296538
01-Mar		415249	853	414396	297159	612	296547
Totals		415249	3396	1650148	298623	5399	2618430
Table represents published data with the total number vaccinated (415,249), unvaccinated (298,623) and total number of deaths (8796)							
But we must assume the vaccination rates over time.							
Will also assume equal death rate per month in both groups = 0.002058							
Crude death rate vaccinated per 100 = 3396 / 415,249 = 0.82							
Crude death rate un vaccinated per 100 = 5399 / 298632 = 1.81							
Unadusted RR (vaccine risk / unvaccinated risk) = 0.82 /1.81 = 0.45							
Adjusted death rates / person month vaccinated							
Death rate / person month vaccinated = 3396 / 1650148 = 0.002058							
Death rate / person month unvaccinated = 5399 / 2618430 = 0.002061							
Adusted RR (vaccine risk / unvaccinated risk) = 0.002059 / 0.002061 = 1.00							

IOW, almost entire mortality effect explained by misclassification of exposure times.

A few slides

Is science self-correcting?

Original article has been cited 233 times,including 13 times in 2022 (last time I looked 1/2025)

Only 5 of these 233 citations was the term “bias” mentioned, still limited to confounding

These thoughts are in a paper “Something old and something older – Bias and the self-correcting nature of scientific publications”

Submitted as a teaching example to 5 major medical journals (refused - “does not meeting our priorities”)

MedRxiV preprint server also refused it “as not containing original research”

Bias avoidance, reproducibility, and science as a self correcting discipline don’t appear to always be priorities

Finally has a home @ OSF, where its impact is about nil (48 downloads since posted 1/2025)