Is a different methodology needed for RCT's and non RCT data sets?

Stephen Evans

Emeritus Professor of Pharmacoepidemiology

Department of Medical Statistics

London School of Hygiene & Tropical Medicine

Improving health worldwide

www.lshtm.ac.uk

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Outline

- Key features of randomised trials of vaccines in pregnancy
- Differences in non-randomised studies
- Designing non-randomised studies to be like an RCT
- Analysing non-randomised studies for validity

Features of randomised trials not replicated in non-randomised studies

- Gestational age at vaccination (GAV) is same in both groups
  - *NRS will have different GAV in general*
- risk factors, on average, same in both groups
  - *NRS have known and unknown differences*
- follow-up is the same in both groups
  - *NRS may have subtle differences*

Target trial emulation

- NRS cohort design like an RCT
  - selection of participants
  - definition of start of follow-up
  - completeness of ascertainment of outcome
- Choice of comparison (control) group
  - An alternative vaccinated group simplest
    - must take timing of vaccination into account
  - Unvaccinated group much more complex
    - Choice of start of follow-up (FU)

Hernán MA et al. Target Trial Emulation: A Framework for Causal Inference From Observational Data. *JAMA*. 2022;328(24):2446–2447.

“Immortal time” bias

- Those vaccinated cannot have an “event” before vaccination
- if start of FU for vaccinated begins before vaccination this is “immortal time”
- If start of FU in unvaccinated is potentially before vaccination, then events are counted which would not occur in the vaccinated
  - Xu, R et al. (2012) Pharmacoepidemiol Drug Saf, 21: 844-850
  - Matok, I et al (2014), Birth Defects Research A: 100: 658-662
  - Regan AK et al. Pediat Inf Dis J (2025) 44(2S):S108-S110

Analysis

- As with RCTs, methods should take time interval from vaccination to birth into account
- Time-updated Cox model
  - From start of follow-up all included in unvaccinated person-time
  - Vaccination is a variable that is updated when it occurs
- Other covariates may or may not adequately address other biases
- Confidence intervals do not account for all the uncertainty
- Only use information available at start of follow up as fixed covariates (don't use information from the future)

Target Trials: **Guideline**: Cashin AG et al. BMJ 2025;390:e087179.

Methods for case-control: Dickerman BA et al. Int J Epid; 49, 1637–46.

Confounding

- Are confounding variables known & can be included?
- Many, especially with vaccination, are unmeasured
- All results must be treated cautiously
- Self-controlled methods require major assumptions
  - "event" cannot occur before vaccination

Conclusions

- Non-randomised much more complex
  - and much more subject to bias
  - so uncertainty much greater
- Be very careful with definitions of start time
- Make comparisons with other vaccines when possible (as well as unvaccinated?)