Differential depletion of susceptibles

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Differential depletion of susceptibles

• Estimates of vaccine effectiveness (VE) over time are subject to bias from differential depletion of susceptibles between vaccinated and unvaccinated.

• Bias occurs when individuals who are no longer at risk of infection due to protection from past infection are included in the analysis.

• Assuming VE >0, these individuals are more likely to be unvaccinated than vaccinated (differential depletion by vaccine status).

• Over time, more previously-infected and unvaccinated individuals who are at low/no risk of infection are included in the analysis, biasing VE estimates downward (spurious waning).

• Can also occur due to heterogeneous risk in the population.
Example: true VE = 60%
Biased VE

Vaccinated

- Infected: 2
- Enrolled: 10

Unvaccinated

- Infected: 2
- Enrolled: 10
Biased VE

\[ Estimated \, VE = 1 - \frac{2/10}{3/10} = 33\% \quad \text{True VE} = 60\% \]
Unbiased VE

Vaccinated

Infected

Enrolled

Unvaccinated

Not at risk
Unbiased VE

\[ \text{Estimated VE} = 1 - \frac{2/10}{3/6} = 60\% \]

True VE = 60\%

Vaccinated

Unvaccinated

Infected

Enrolled

Not at risk
Challenges with examples

• True waning and spurious waning due to differential depletion of susceptibles can occur at the same time
  • Disentangling these different effects can be hard

• Defining susceptibles
  • Reinfection – people with prior infection become susceptible again
Example: SARS-CoV-2

- Waning began to be observed a few months after vaccine introduction
  - Question: could this be driven by bias?

- Simulations
  - Larger bias when initial VE is lower
  - Larger bias in test-negative design than cohort studies

- Given the high initial VE, these findings suggested the waning was not all due to bias
Example: Influenza

• When differential depletion of susceptibles is a concern:
  • 1) after periods of high incidence during which some were already vaccinated and others weren't AND
  • 2a) when immunizing events are often not observable (i.e. very mild infections that are not identified) OR
  • 2b) there is high heterogeneity in exposure or susceptibility to infection that is not adjusted for in the analysis
Thank you!