Waning Immunity

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Introduction

• Unlike the other topics discussed in the current session, waning immunity is not a bias.

• Rather, it is simply the biological course of the immune reaction to certain vaccines (and specifically, to the Covid-19 mRNA vaccines).

• The challenge and possible bias is in how we model and estimate this waning.
Serological Trajectories

![Graph showing serological trajectories over weeks for different doses.](image-url)
Estimated Vaccine Effectiveness
Sidestepping the Problem

• We always have the option of choosing not to address waning

• A single estimate encompassing the entire period from treatment to end-of-follow-up is statistically and epidemiologically valid

• Just, arguably,
  • Not very scientifically interesting
  • Less informative for forming public health policy
Tackling the Problem

• Waning is usually modeled by dividing the follow-up into discrete periods (e.g., 7-30 days, 31-60 days, etc.) and estimating the effectiveness in each period

• These are discrete-time hazards: Given that a person has survived until the start of the period, what then is the effect of the vaccine over the period?

• Technically, this is usually done with either Poisson or Cox proportional hazards regression

• However, this approach has a substantial flaw
The Problem

• (This being the last talk of the session, these issues have probably already been discussed, so I’ll be brief)

• The problem is easy to understand if we think in terms of a “target trial”

• When estimating effectiveness for, e.g., 30-60 days after vaccination, the target trial would be:
  • Randomize and vaccinate at time 0
  • **Seclude study participants until day 30**
  • Have both groups remain exposed until day 60 and estimate
The Problem (2)

• The issue is of course that individuals do not remain unexposed until day 30
• And individuals who become infected between the beginning of the study and the start of the period are excluded
• This is the “classic” issue with hazards suffering from selection bias due to conditioning on survival until the start of the period
• The effect estimated is then a mixture of the real effect (encompassing the waning) and this selection bias, and does not have a clear causal interpretation
The Problem (3)

- For the sake of intuition, imagine that there is no waning, but that everyone that was going to be infected, became infected in the first week
- It would incorrectly seem as though the vaccine has lost all effectiveness
In Practice

• I do not know of a “gold standard” solution to this issue

• In practice, estimating waning immunity is a scientific and policy necessity, so researchers (myself included) acknowledge the difficulty, but nonetheless perform the analysis and interpret the findings in the context of waning immunity