

Waning Immunity

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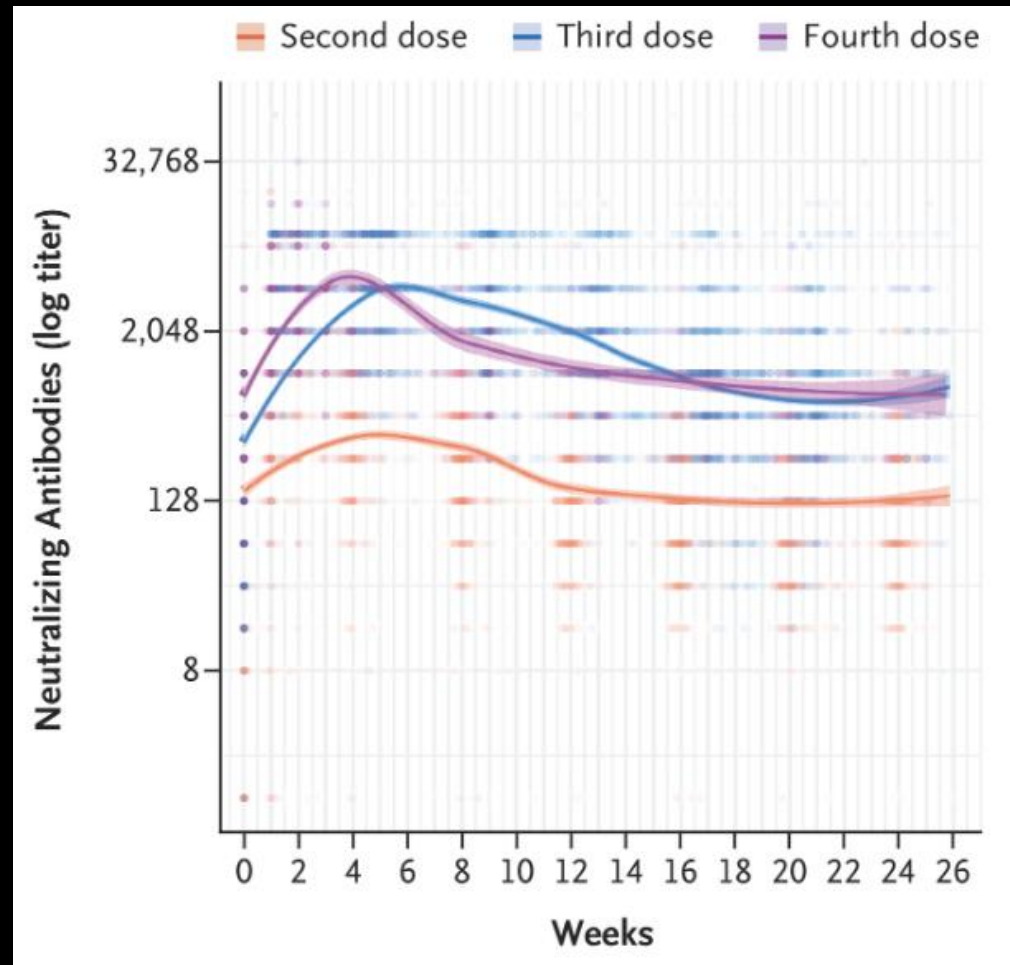
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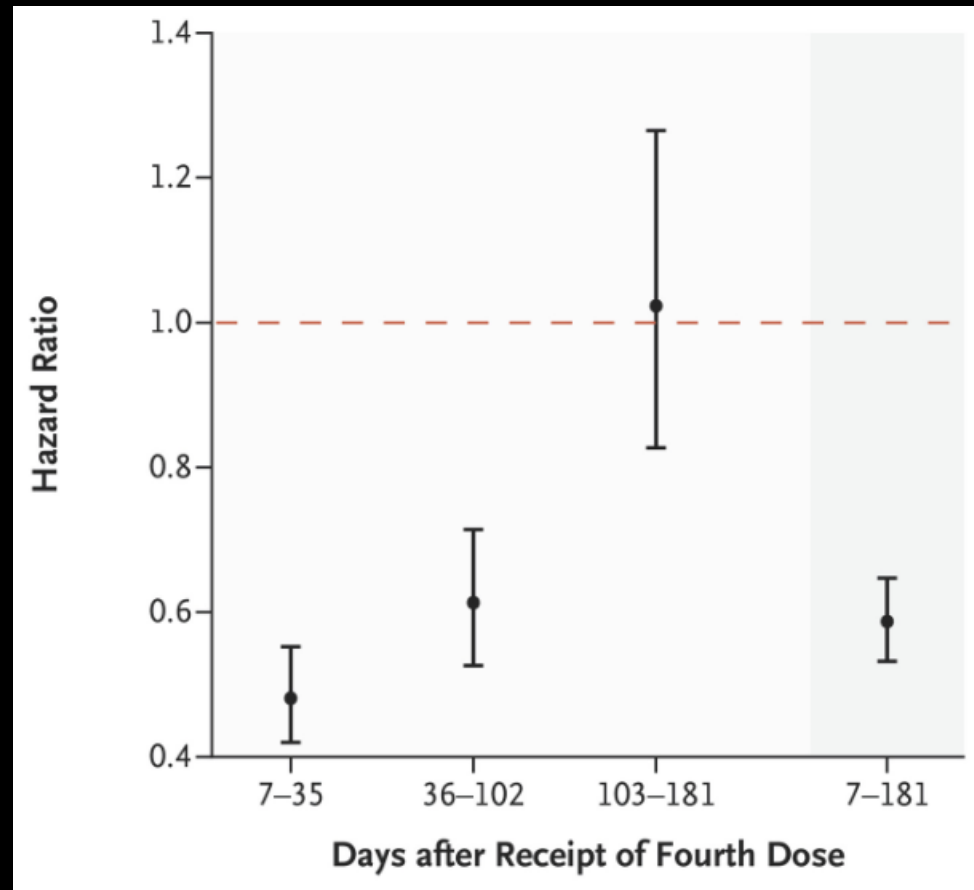
Introduction

- 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

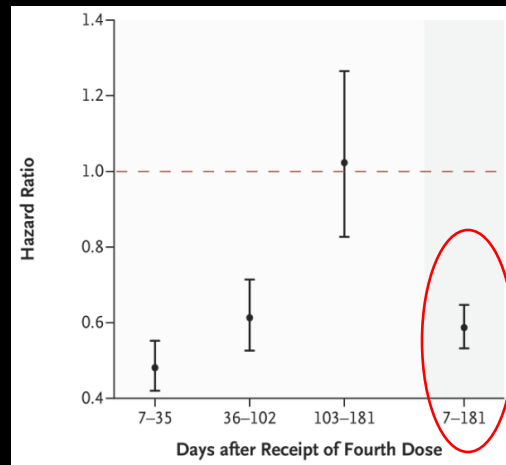


Estimated Vaccine Effectiveness



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