

Clinical Reading Questions #7

HST 190: Introduction to Biostatistics

These discussion questions are based on Xu et al. (2026).

1. What is the main research question of this study? How does examining the association of interest across vaccine types and force of infection (FoI) levels relate to effect modification? What practical implications can a finding of a difference in the association within some stratum of the population have?
2. Who was included in this study? Did the process used for the selection of participants raise concerns about potential bias or limitations in generalizability? Table 1 reports the number of accrued COVID-19 endpoints in each trial; why is it the number of endpoints, not the number of participants enrolled, that informs the power of this analysis?
3. How are vaccine efficacy (VE) and FoI defined in this study? How do these definitions differ from the variables measured? Note that the reported VE is not measured directly but recovered from an estimated hazard ratio—what is the relationship between the two?
4. Rather than comparing the proportion of participants infected in each arm, the authors chose to model the *hazard* of COVID-19; what is a hazard, and why did the authors apply techniques from survival analysis? The Cox model used assumes *proportional hazards*: what does this assumption assert? Why does vaccine *waning* motivate including an interaction between treatment group and time since most recent vaccination?
5. The main analysis used several Cox regression models, adjusting for age, sex, and race as potential confounders. Compare the distributions of these variables within studies, as shown in Table 3. Do the distributions differ within studies? What rationale might have supported the decision to adjust for these variables?
6. Discuss the findings in Figure 1. Do they support the authors' conclusion that the association between FoI and VE follows an inverted U-shaped relationship? To explain, contrast panel (c) with panel (d), note that efficacy is read off at a fixed 45 days since vaccination, and consider the authors' own observation that FoI_G varied only about six-fold across the data available to them.
7. Examine the interaction coefficients reported in Table 2. What sign convention do the authors use—that is, which sign indicates that vaccine efficacy *falls* as force of infection rises? Note that only one of the five analyses recovers a statistically significant association (AZD1222 US: $HR = 0.62$, 95% CI: $[0.42, 0.91]$, $p = 0.01$). Interpret that result, and explain why the four null results cannot be interpreted as evidence of no association.

8. In Table 2, note ^a, the calculations of AstraZeneca VE for two values of FoI_S are shown. The regression formula includes coefficients for treatment (vaccine versus placebo) and for interaction terms with FoI_S and time since vaccination. However, no information on age, sex, or race is used. Why? Consider the Cox model the authors fitted, with specification given below, and identify which estimated coefficients were used in the calculations of VE. What would it mean, scientifically, if the coefficient β_5 on the interaction term between treatment and FoI_S were exactly zero?

$$\lambda(t) = \lambda_0(t) \exp\{\beta_0 \text{AgeGroup} + \beta_1 \text{Sex} + \beta_2 \text{Race} + \beta_3 \text{Treatment} + \beta_4 \text{FoI}_S(t) + \beta_5 (\text{Treatment} \times \text{FoI}_S(t)) + \beta_6 (\text{Treatment} \times \text{TimeSinceVaccination})\}$$

References

- Xu, Jing, M Elizabeth Halloran, Mia Moore, et al. 2026. “Association Between COVID-19 Vaccine Efficacy and Epidemic Force of Infection.” *Npj Vaccines* 11 (1): 54. <https://doi.org/10.1038/s41541-026-01374-3>.