Designing clinical trials to enhance decision-making

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Background

- (Most) clinical trials are used to compare treatments/interventions
- Researchers **design** clinical trials to answer **specific** questions
  - E.g., what is the *average* effect of treatment X on outcome Y in population Z?
- Trial design determines the research question/s to be (potentially) answered

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A toy example

- Research Question: **Which vaccine (A or B) offers the greatest protection?**
- Measurement: **Immune response to vaccination**
- Outcome: **Log_{10} antibody concentration**
- Hypothesis: **Vaccine B produces a greater antibody concentration than Vaccine A**
- Statistical Model: **Bayesian linear regression with unequal variance**

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Some algebra

- Let y_{ij} be the $\log_{10}$ antibody concentration for participant i receiving vaccine $j \in \{A, B\}$
- Let μ_j be the **mean** antibody concentration for vaccine j
- Let σ_j be the **standard deviation** antibody concentration for vaccine j
- The statistical model is then: $y_{ij} \sim \text{Normal}(\mu_j, \sigma_j^2)$
- In other words:

  Responses from vaccine A: $y_{iA} \sim \text{Normal}(\mu_A, \sigma_A^2)$

  Responses from vaccine B: $y_{iB} \sim \text{Normal}(\mu_B, \sigma_B^2)$

- We are interested in $\theta = \mu_B - \mu_A$

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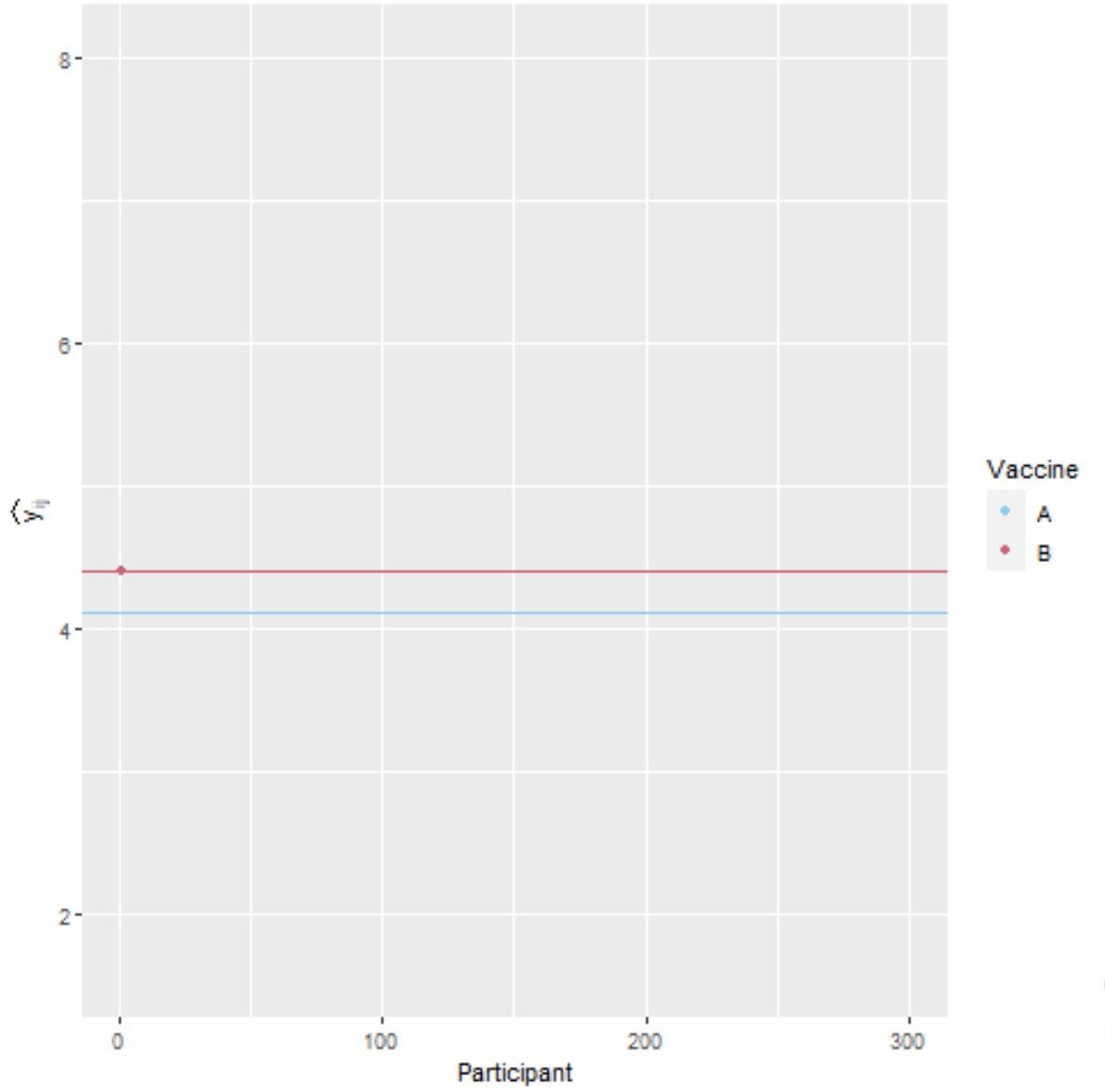
Let's simulate some data

- Simulated data for participants receiving Vaccine A or B
- Points are observations (y_{ij})
- Lines are sample means
- What do you notice?



Let's model the data

$\overline{y_{iA}} =$

$E[\widehat{\mu_A}]$

$\overline{y_{iB}} =$

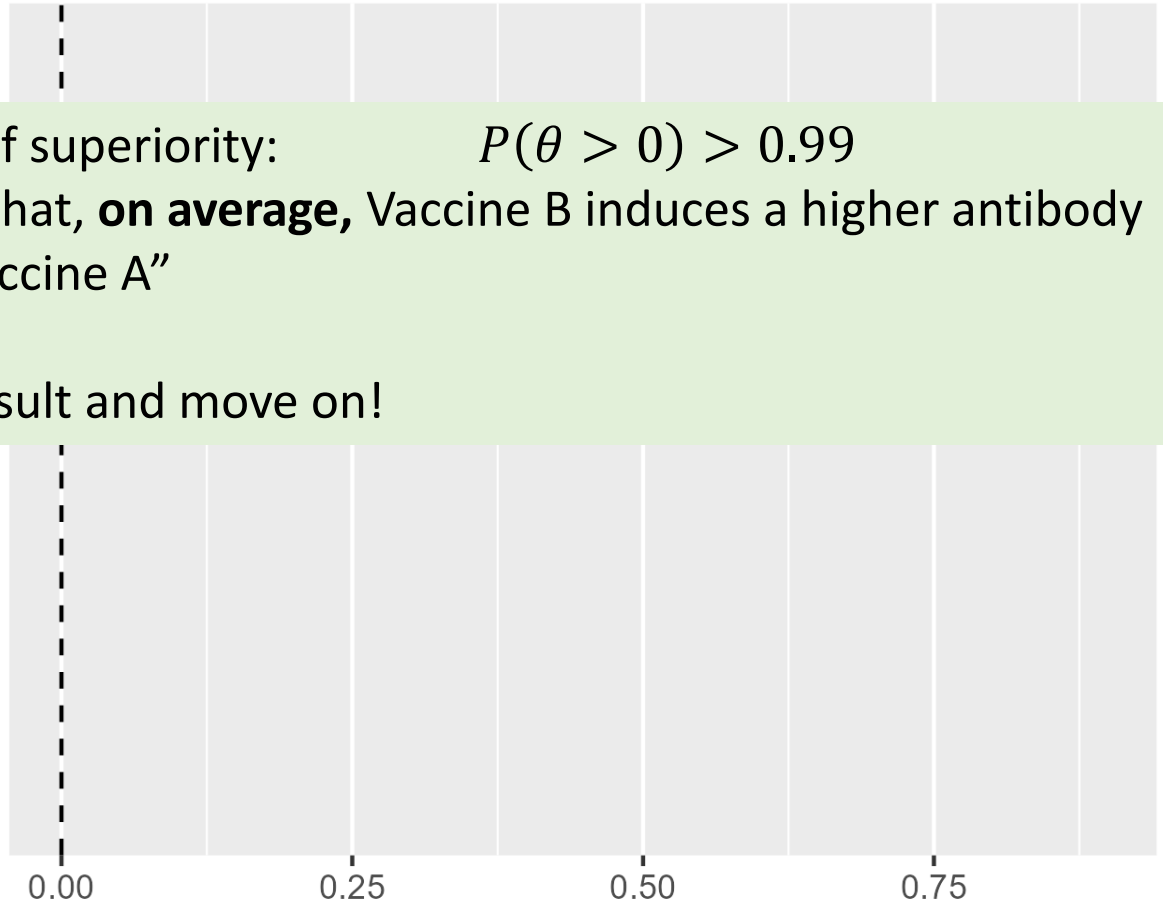
$E[\widehat{\mu_B}] = 4.63$

$E[\hat{\theta}] = 0.67$

Posterior probability of superiority: $P(\theta > 0) > 0.99$

"Significant evidence that, **on average,** Vaccine B induces a higher antibody concentration than Vaccine A"

Time to publish the result and move on!



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Are we missing anything?

$s_A = 0.$

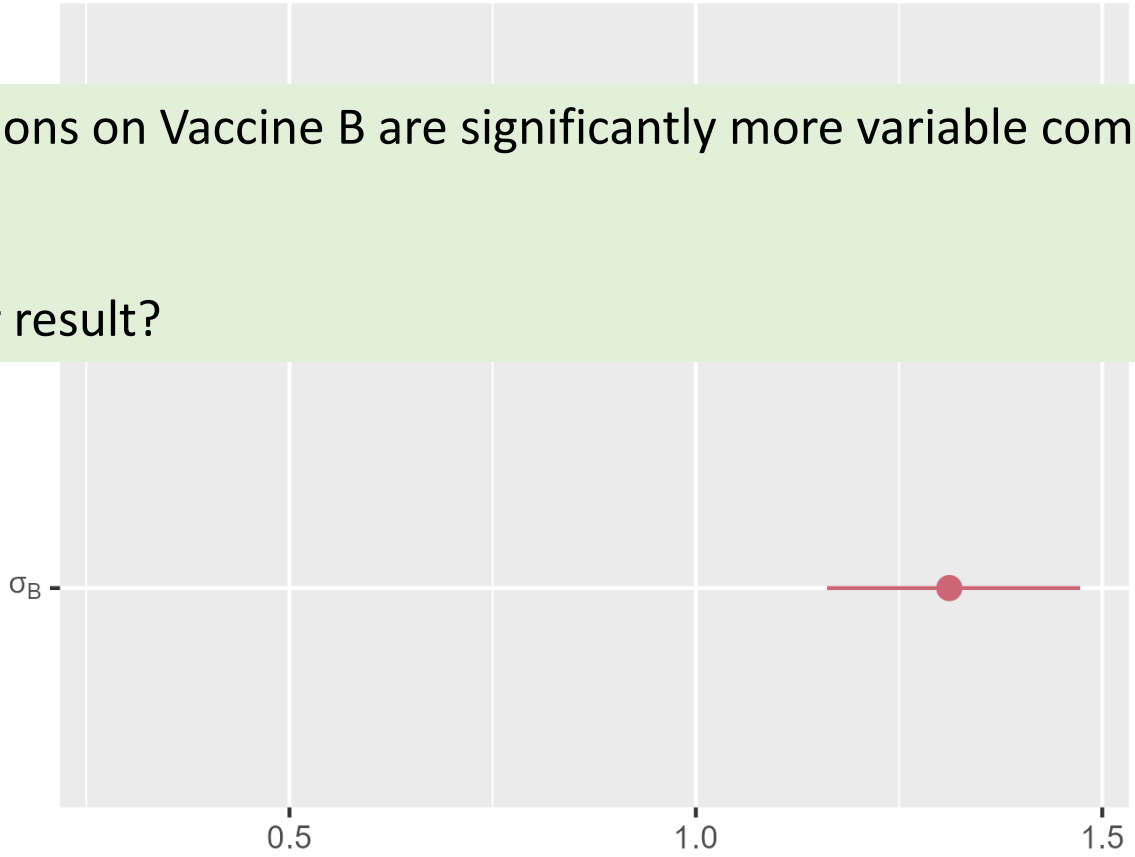
$E[\widehat{\sigma_A}]$

Antibody concentrations on Vaccine B are significantly more variable compared to Vaccine A

Does this change our result?

$s_B = 1.70$

$E[\widehat{\sigma_B}] = 1.31$



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It depends!

- Revisit the research question: **Which vaccine (A or B) offers the greatest protection?**
- Did we answer it sufficiently?
- No! We determined which vaccine induces a higher **average** antibody response
- Why did we do that?
- Because **means are nice** (convenient mathematical properties and easy to communicate)
- Are there other ways to compare the vaccines?

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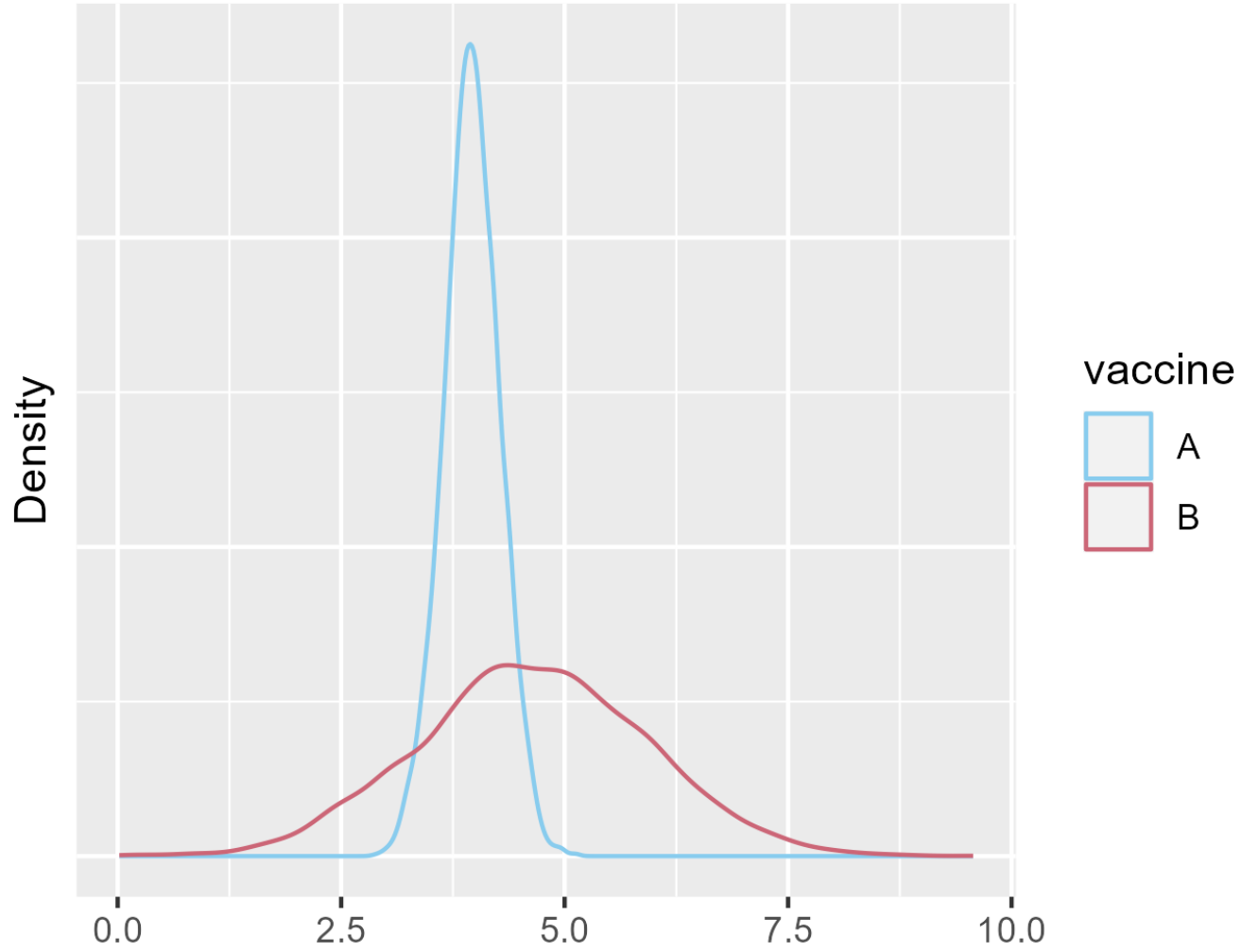
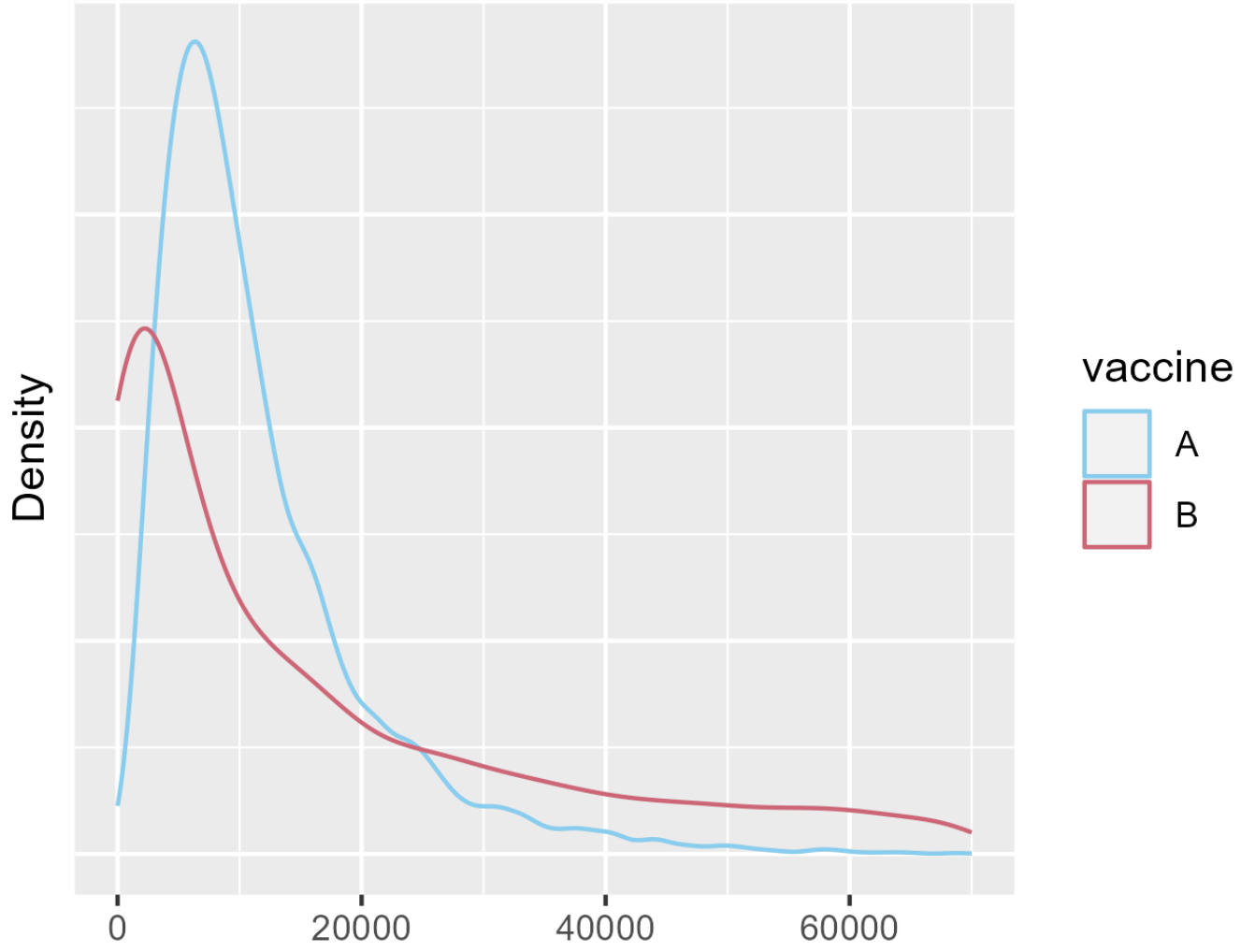
What happens if we account for the variability?

Posterior predicted distributions “predict” future participants’ individual level responses



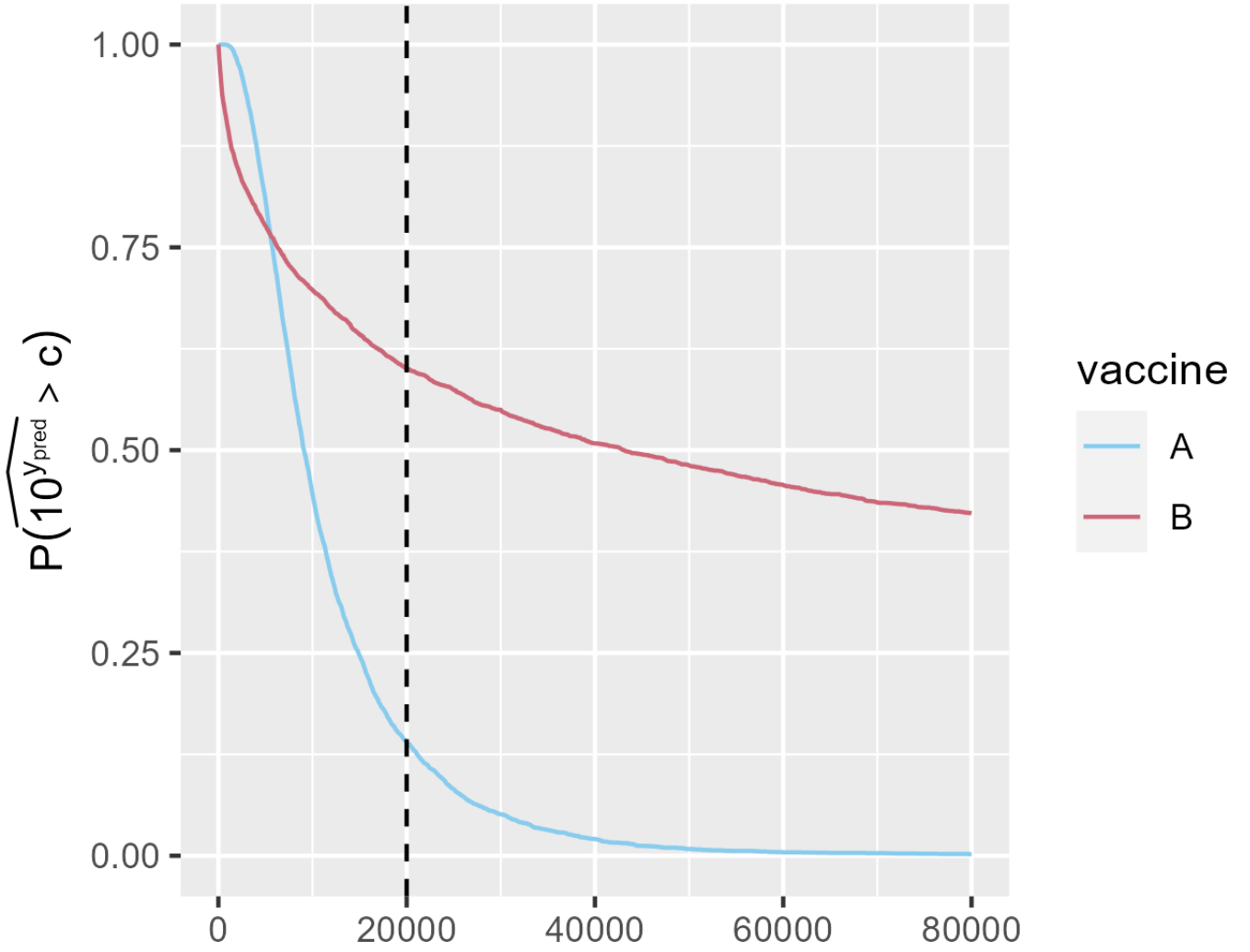
What if we look at the “antibody” scale?

Posterior predicted distributions “predict” future participants individual level responses



What if there is a threshold for protection?

Posterior predicted distributions “predict” future participants individual level responses



So which vaccine is better?

- It’s not obvious and cannot be summarised in one statistic (i.e., difference in means)
- Different stakeholders (decision makers) will interpret the results differently
  - How would a policy maker decide which vaccine to recommend?
  - How would a clinician decide which vaccine to prescribe?
  - How would a consumer decide which vaccine to take?
  - Is the answer the same for each stakeholder??

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What should we do?

- We should **gather evidence** that directly answers the research question
- We should model the **statistical quantities** that matter
- We should **present** the results that will influence decision-making
- We should design our clinical trials in **consultation** with the decision makers
- We should design our clinical trials with **informing decision-making** as the primary objective

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What's my plan?

- I plan on designing (and testing) statistical methods so that we can design decision-theoretic based clinical trials
- I plan on developing an expert elicitation process to efficiently elicit decision-making preferences from decision makers during trial design
- I plan on implementing this process for future clinical trials

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Some final (open) questions for future research

Publicly funded research is intended to improve the *health* of the (future) population.

- What (ethical) responsibility do we have as publicly funded researchers to design our studies with improving *health* as the objective?
- How can we design clinical studies to inform the decision-making of policy makers, clinicians and consumers?
- How can we report our results to best inform decision-making?
- How should we handle multiple (possibly competing) endpoints (e.g., efficacy vs safety)?
- How can we implement our research to drive policy? (Instead of back filling the evidence)

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