Correlates of Protection through multidimensional immune modelling across respiratory viruses

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TALK AIM

"To systematically identify and compare correlates of protection across multiple biomarkers for respiratory viruses using rigorous statistical methods"

Specific objectives

1. Develop a framework for determining CoP in natural history cohort studies
   - Estimate CoR and CoP using serological and infection history data
   - Address key challenge: cannot directly measure exposure in real-world setting

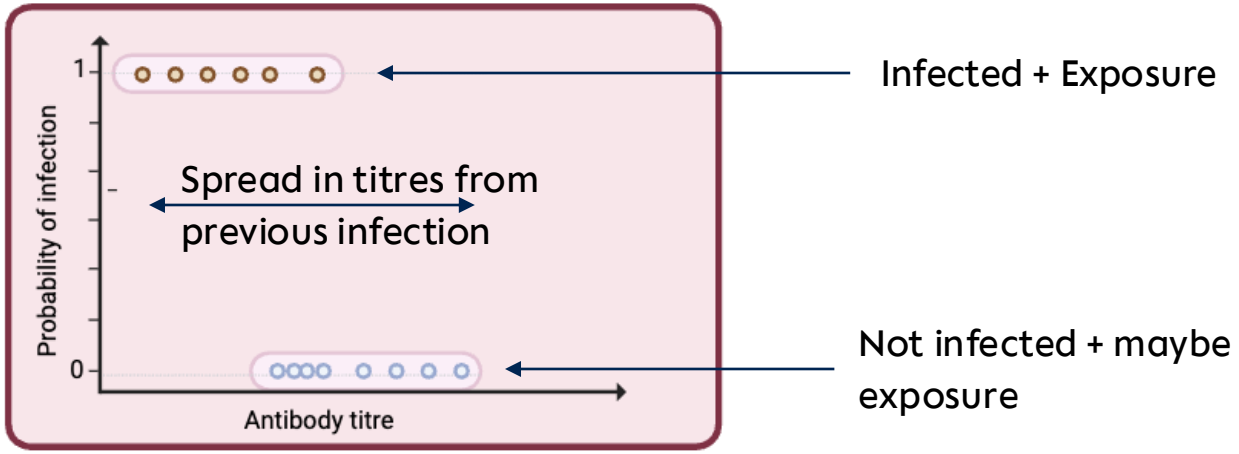
2. Identify the "best" single biomarker CoP of biomarkers
   - Compare predictive capacity across multiple serum and mucosal biomarkers
   - Apply rigorous statistical criteria (AUC, out of sample prediction)

3. Assess value of combined biomarker CoP models
   - Test whether combining serum and mucosal markers improves predictive capacity
   - Quantify added benefit beyond single biomarkers

NATURAL HISTORY STUDIES (NOT RCT)

Use of cohort studies

- In cohort studies, we can identify correlates by studying people who've been naturally infected previously



Limitation

- Don't know who's exposed
- No randomisation, hard to say anything truly causal as about these correlates of protection
- Thus, a correlate of risk and correlate of protection in this context has literal interpretation

STATISTICAL METHODS

Assume a continuous relationship between titre and infection

We fit a (bayesian) generalised logistic curve to the CoR/infection risk with:

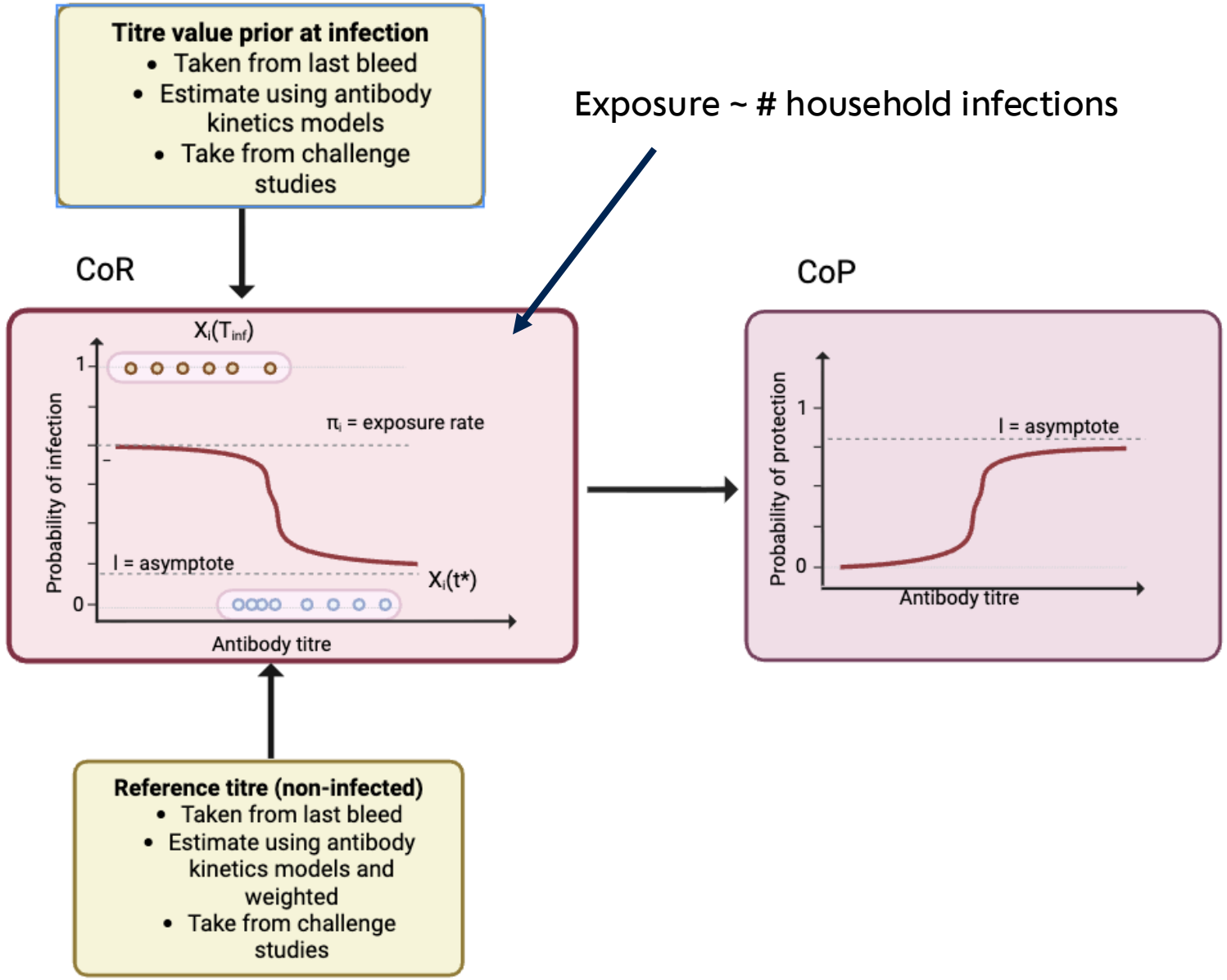
- Upper asymptope = exposure rate
- Lower asymptope = antibody doesn't provide full protection

To get CoP, marginalise out the exposure and find the inverse.

In maths:

COR := $\pi[1 - f(\mathbf{x}, \boldsymbol{\beta})]$ <- we fit this

COP := $f(\mathbf{x}, \boldsymbol{\beta})$



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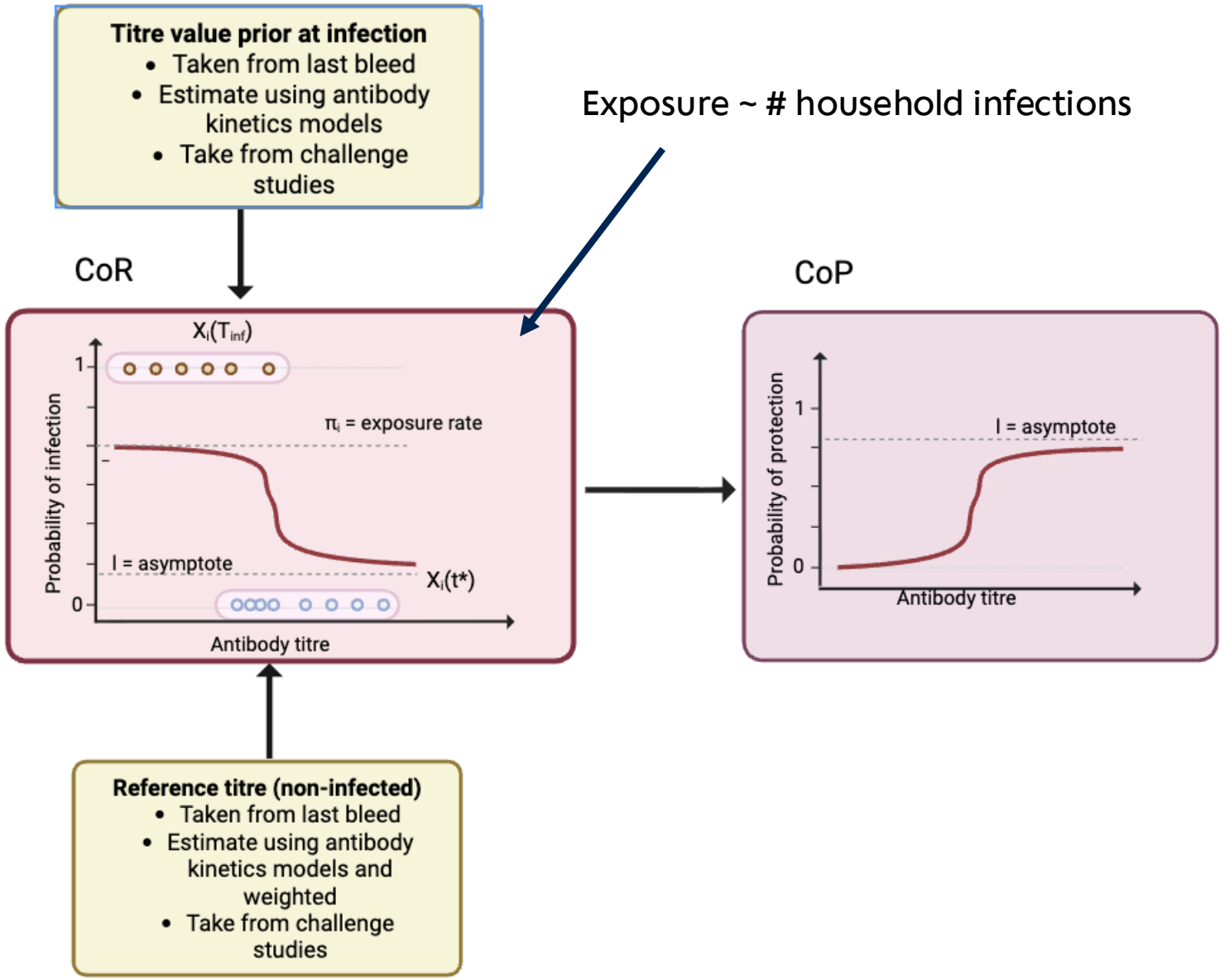
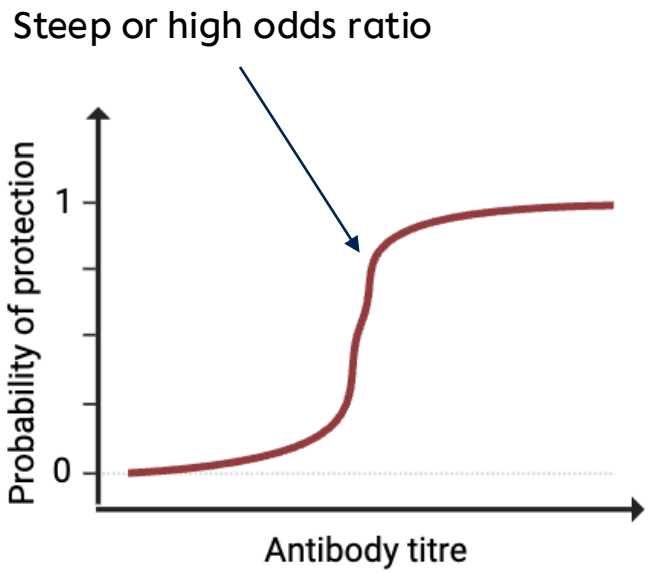
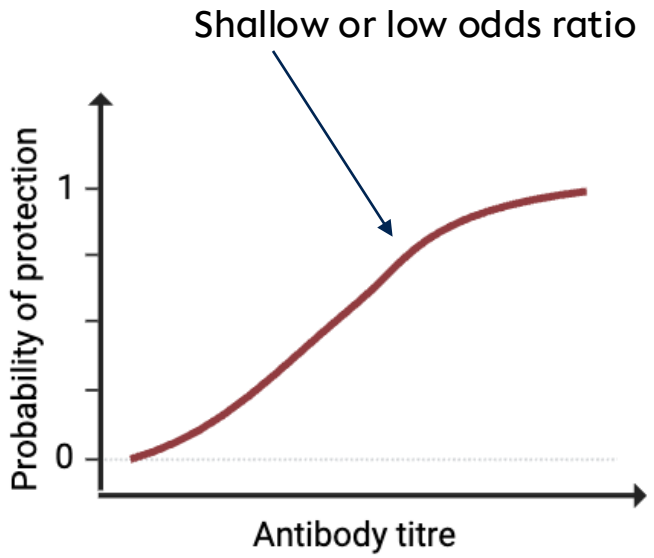
-> 2 biomarkers, multidimensional logistical regression



ASSESSMENT OF "GOODNESS" OF COP





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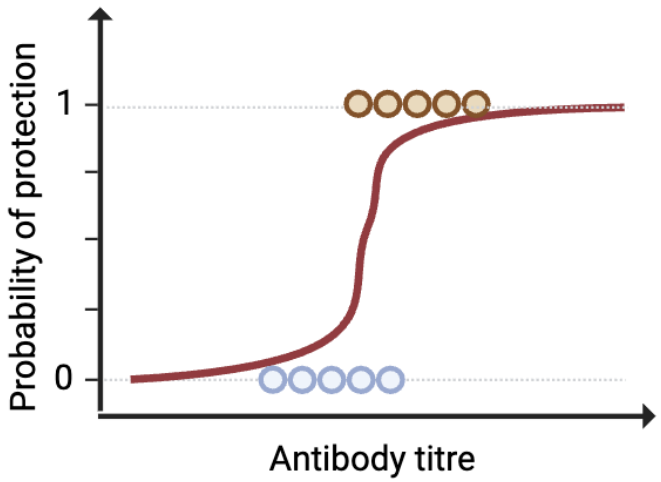

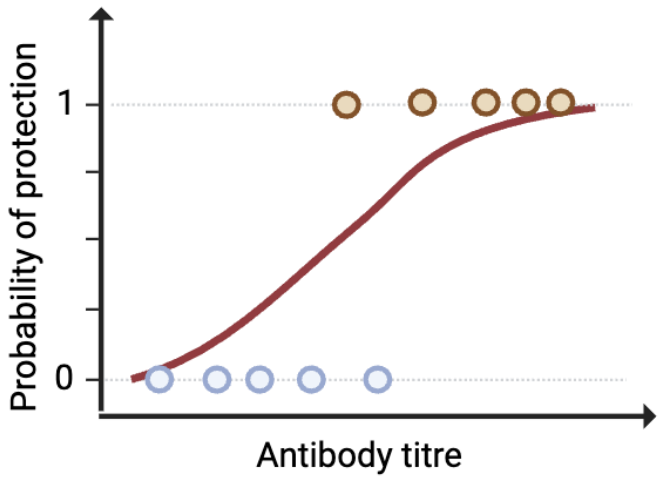

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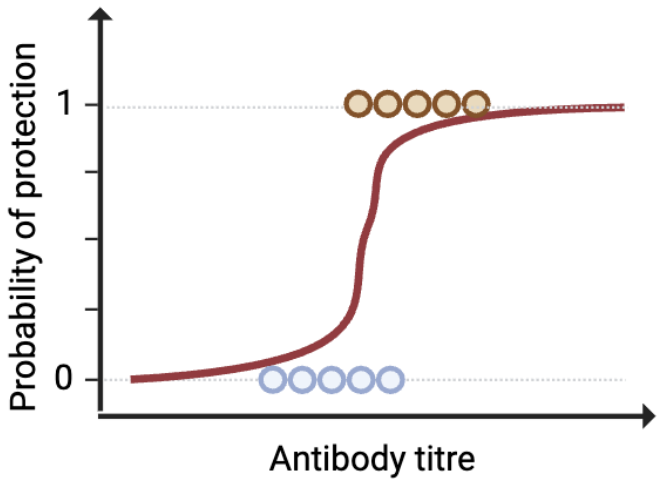
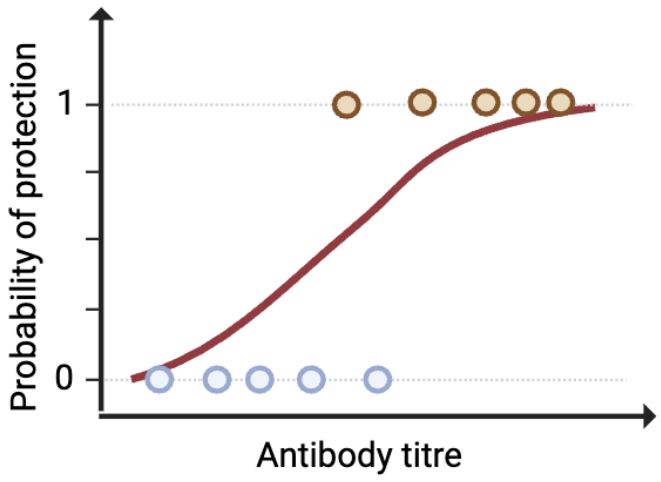
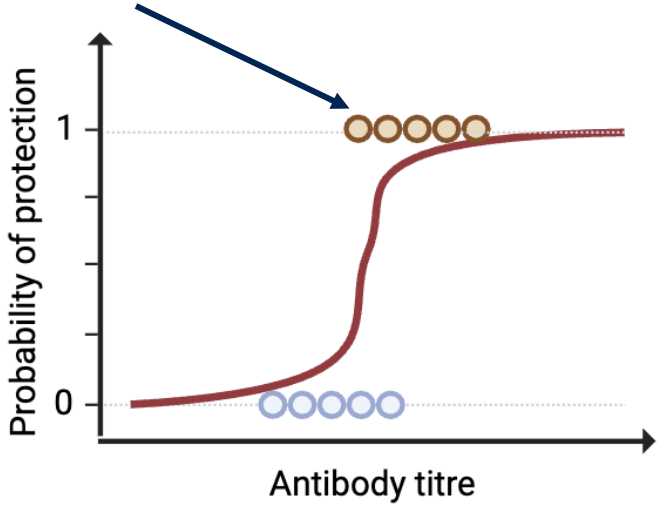




If you are making inferences using fitted model which isn't able to discrimate between those who are infection and those who are not, then it has limited practical use as a CoP => more of an association of protection

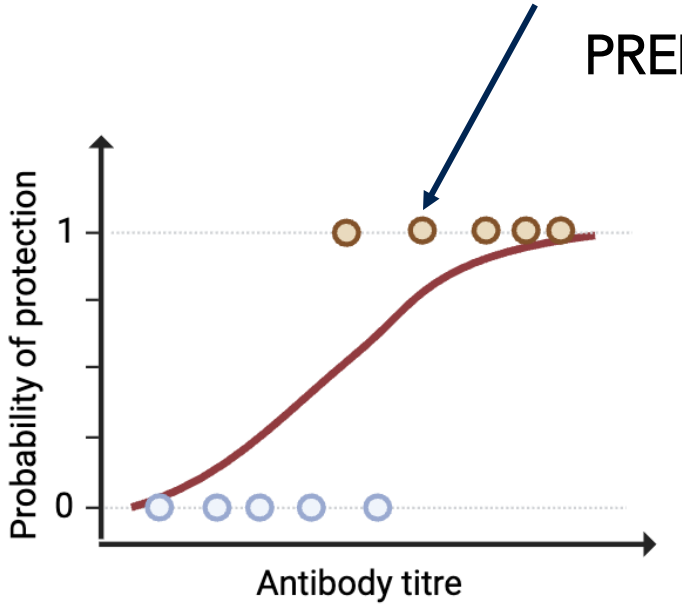
ASSESSMENT OF "GOODNESS" OF COP

Could have poor predictive performance



Could have better predictive performance

PREFERRED!!



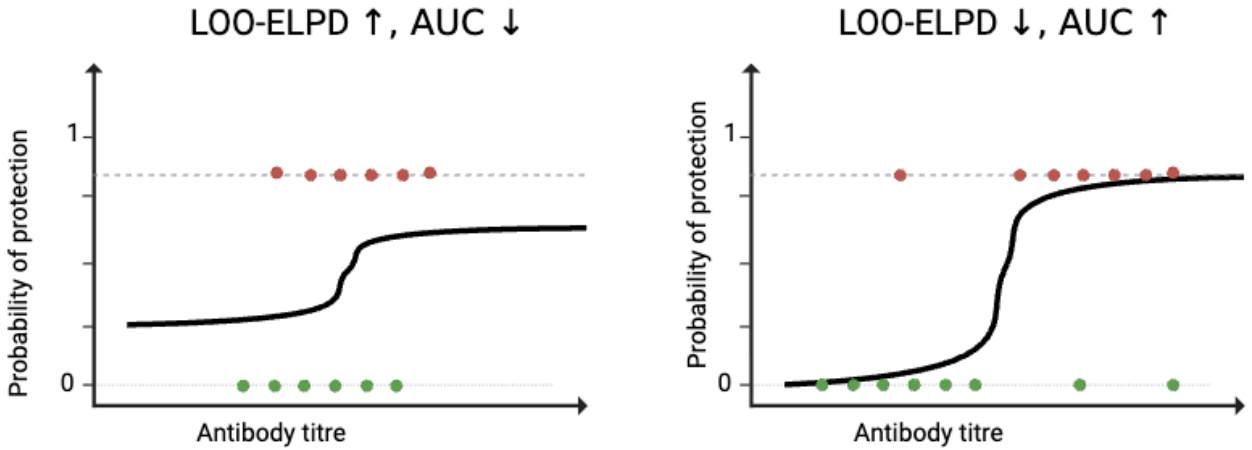
PLAN:

- Compare predictive performance of the fitted curve for each correlate
- Choose the biomarker with the best predictive performance -> better support for causality
- SIDE NOTE: generally in 1D [odds ratio + p-value] ≈ performance, but not true in higher dimensions

METRICS USED

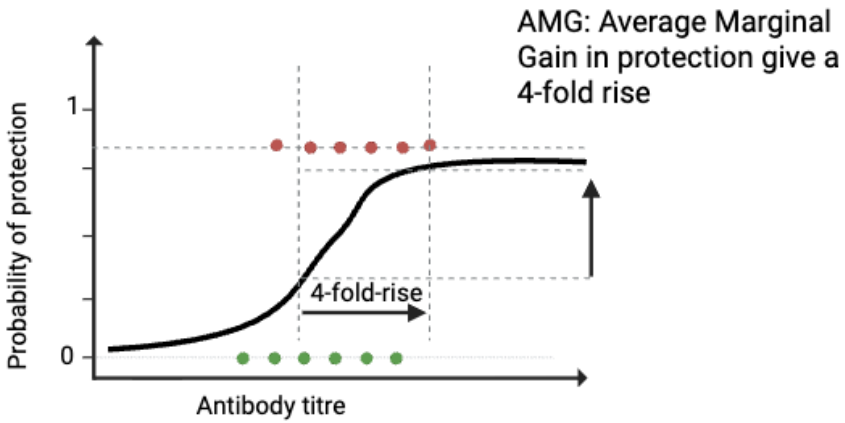
Predictive performance

- Discrimination: AUC
- Out-of-sample predictive fit: LOO-ELPD



Protection impact and applicability

- Impact: AMG, β
- Applicability: Coverage



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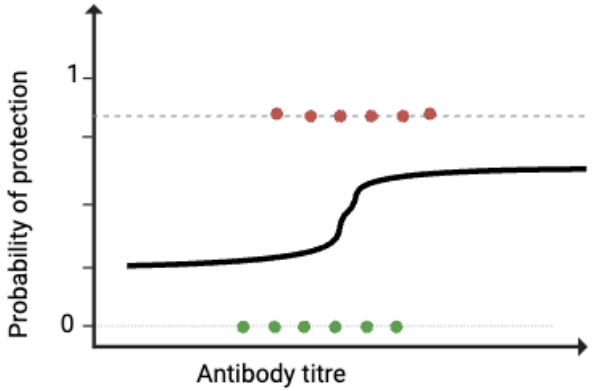
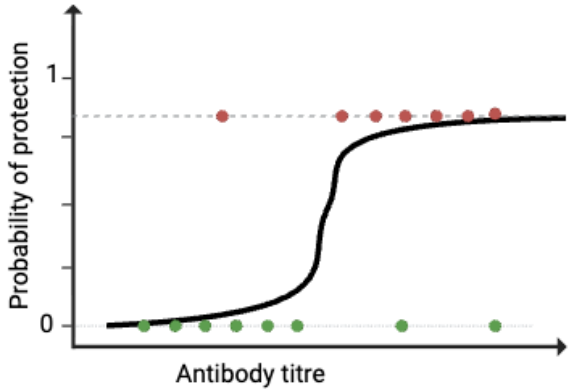
Trans-dimensionally comparable

LOO-ELPD ↑, AUC ↓



LOO-ELPD ↓, AUC ↑



Protection impact and applicability

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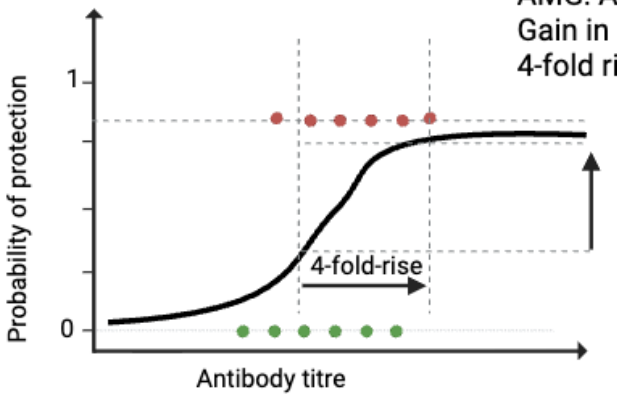
AMG: Average Marginal Gain in protection give a 4-fold rise



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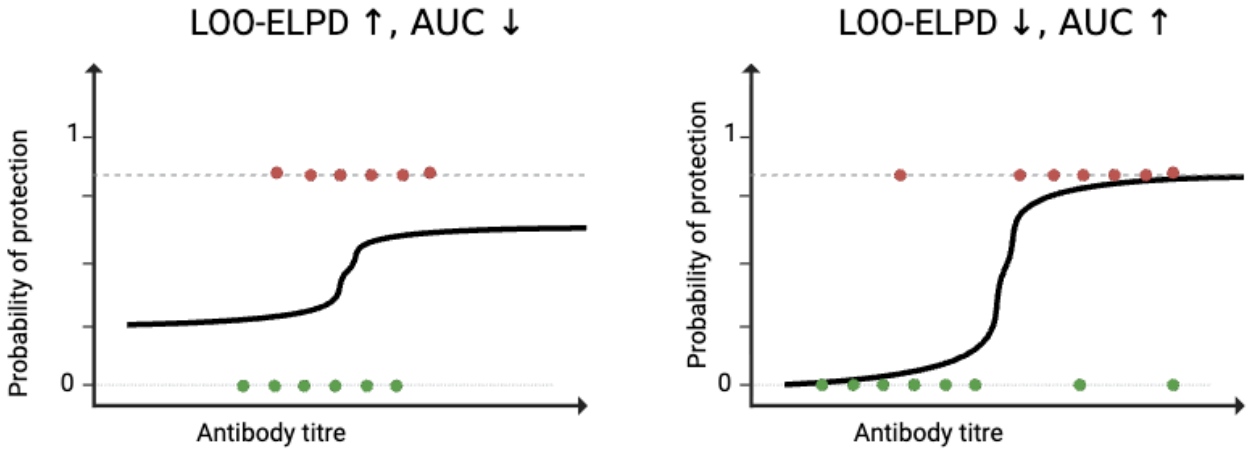

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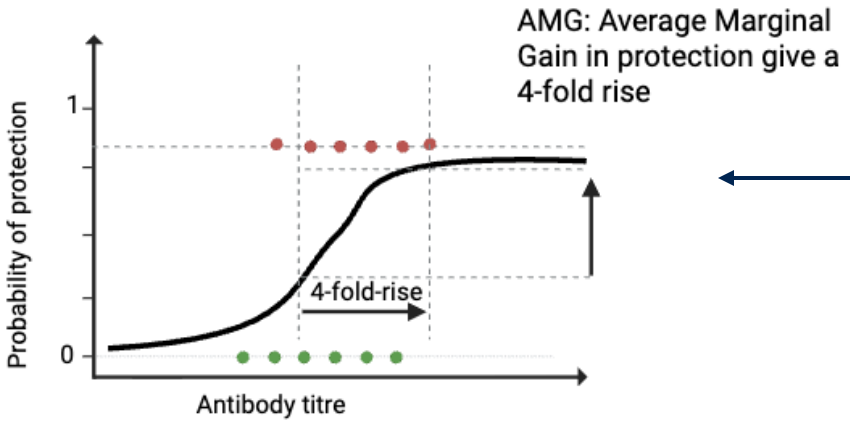


If we boosted everyone's pre-exposure titre by 4-fold, how much more protected would the population be?

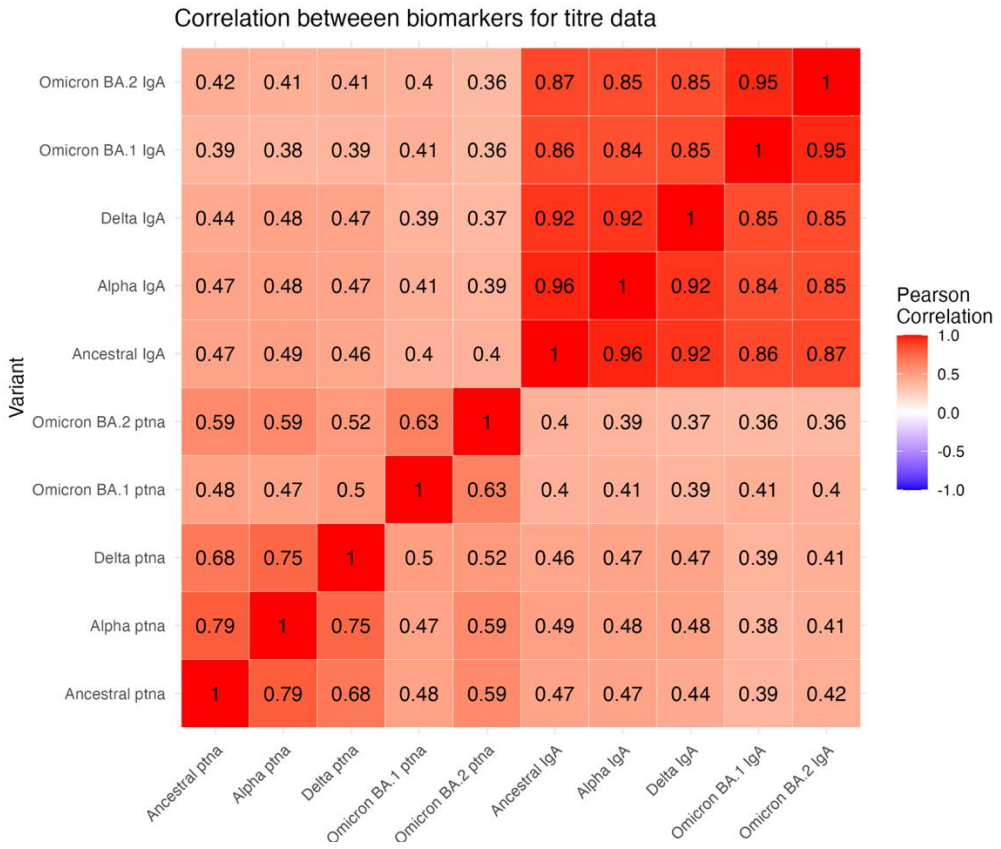
CASE 1: SARS-CoV-2 in The Gambia

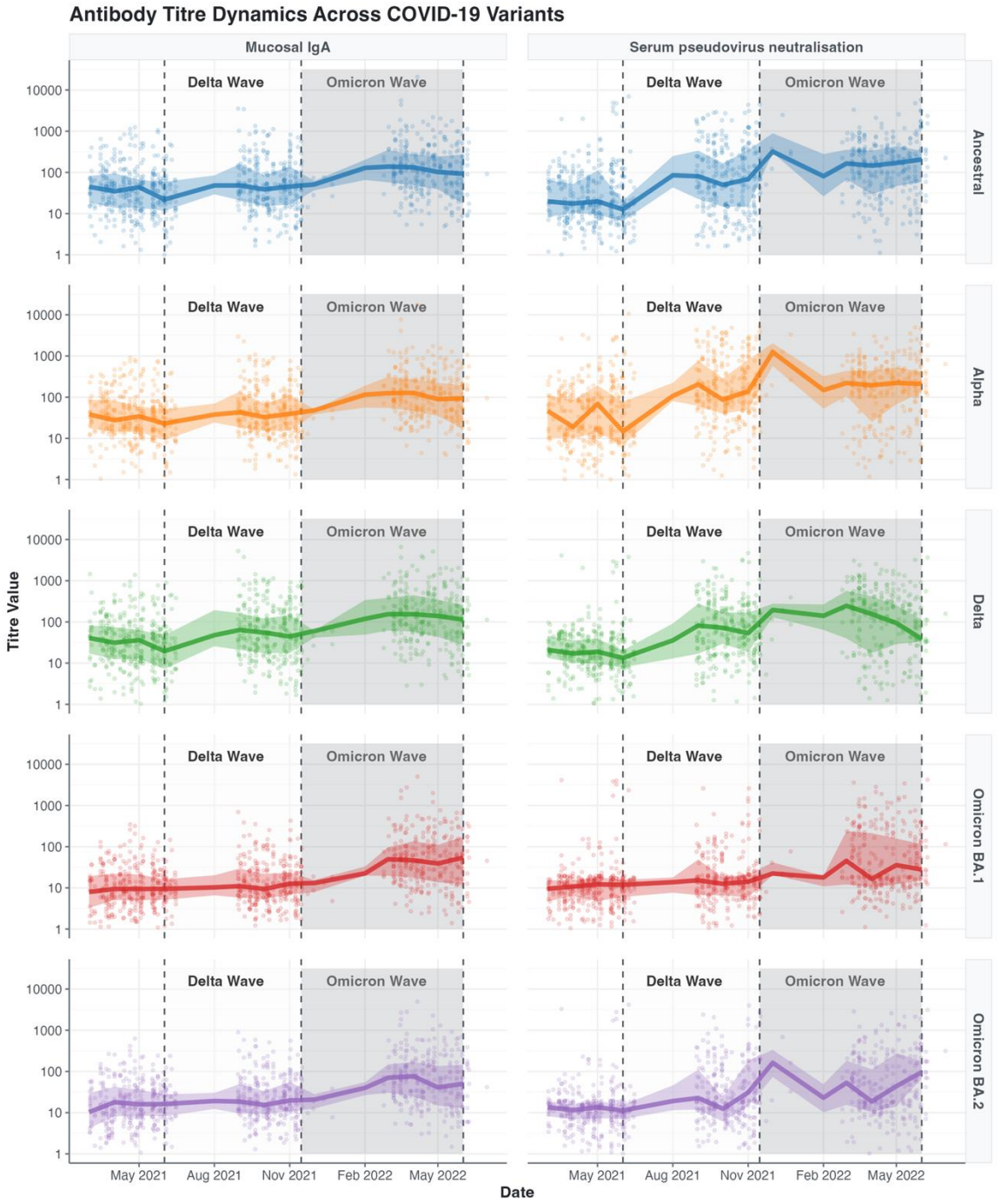
TRANSVIR Study (vaccine naïve)

N = 256 people, 308 days, 2 bleeds person,

Two wave; Delta wave and Omicron BA.1 wave

PCR swabbing weekly, CoP against infection (~70% asymptomatic)





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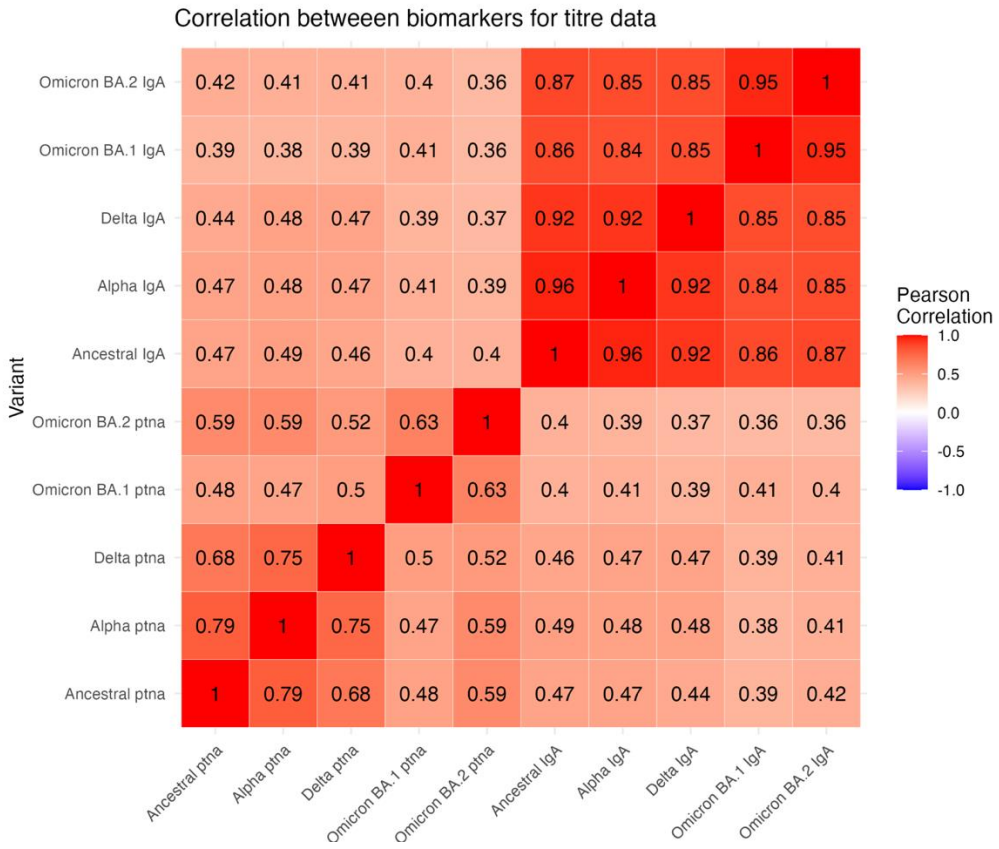
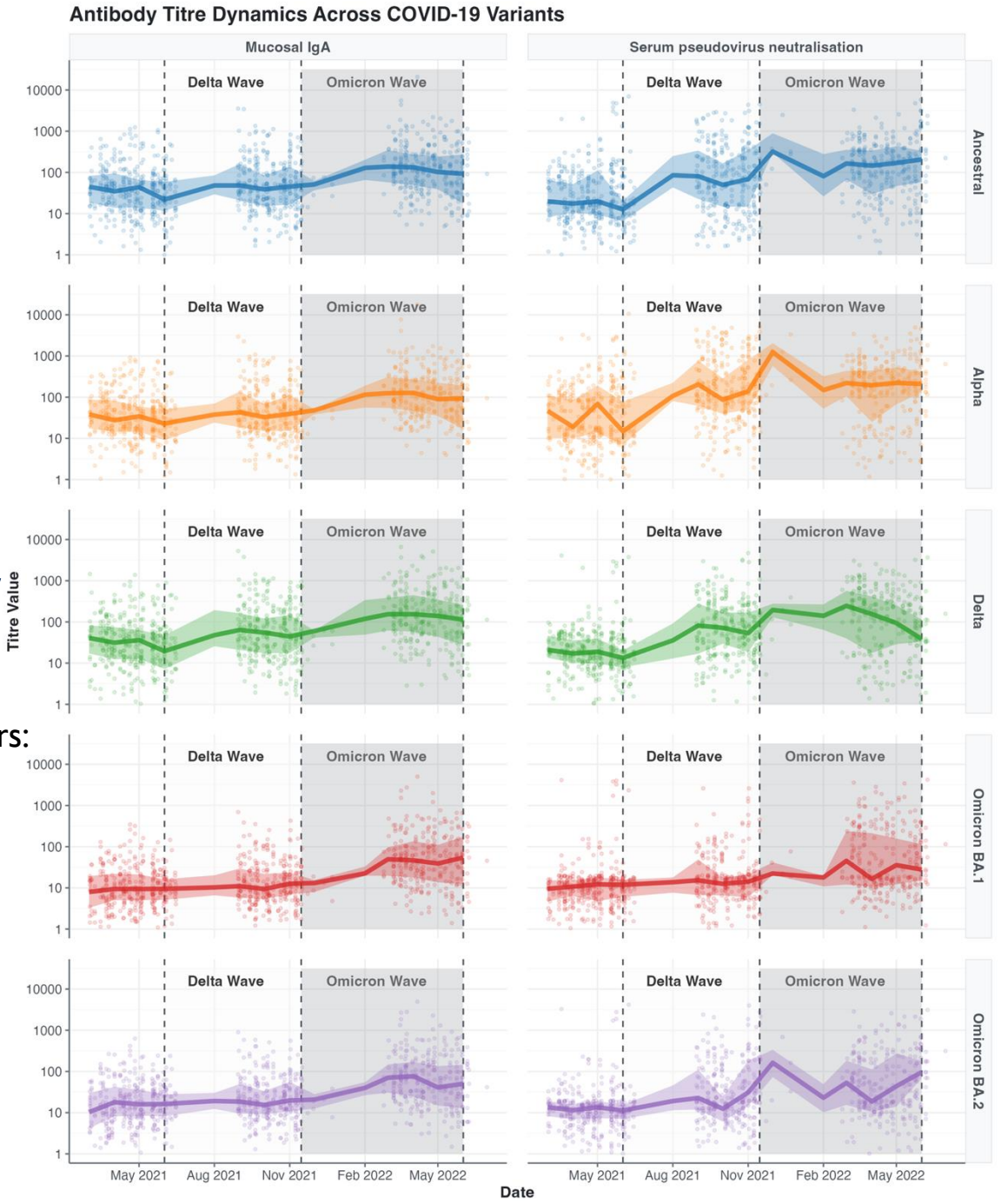


10 biomarkers:



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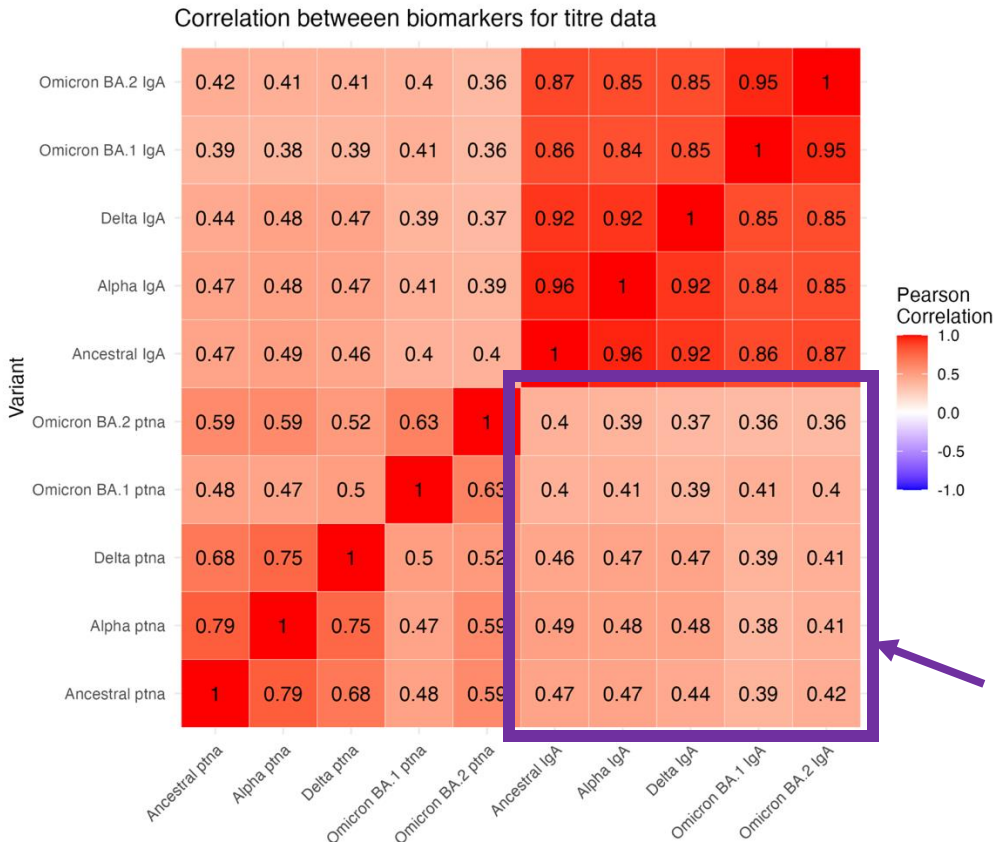
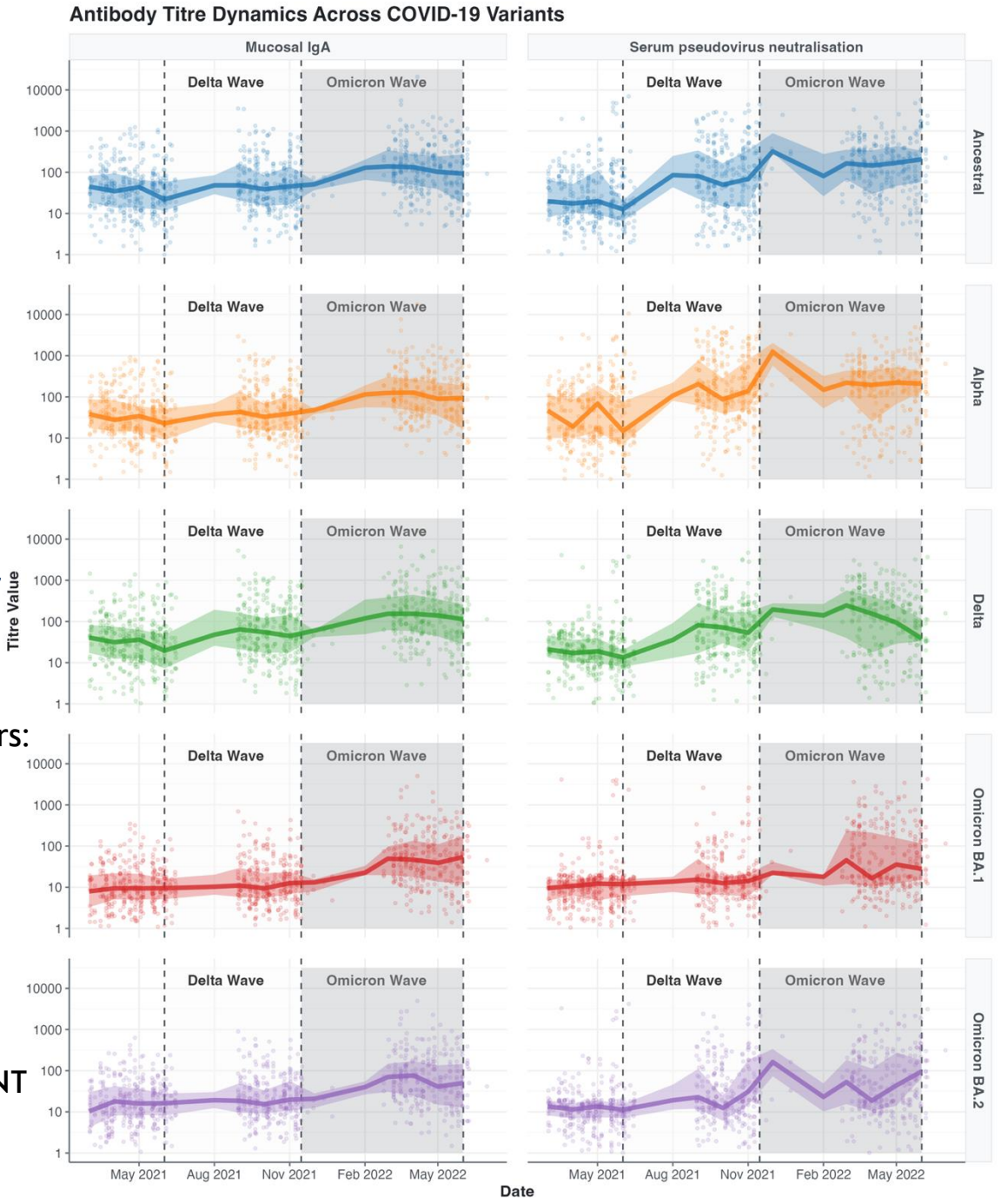
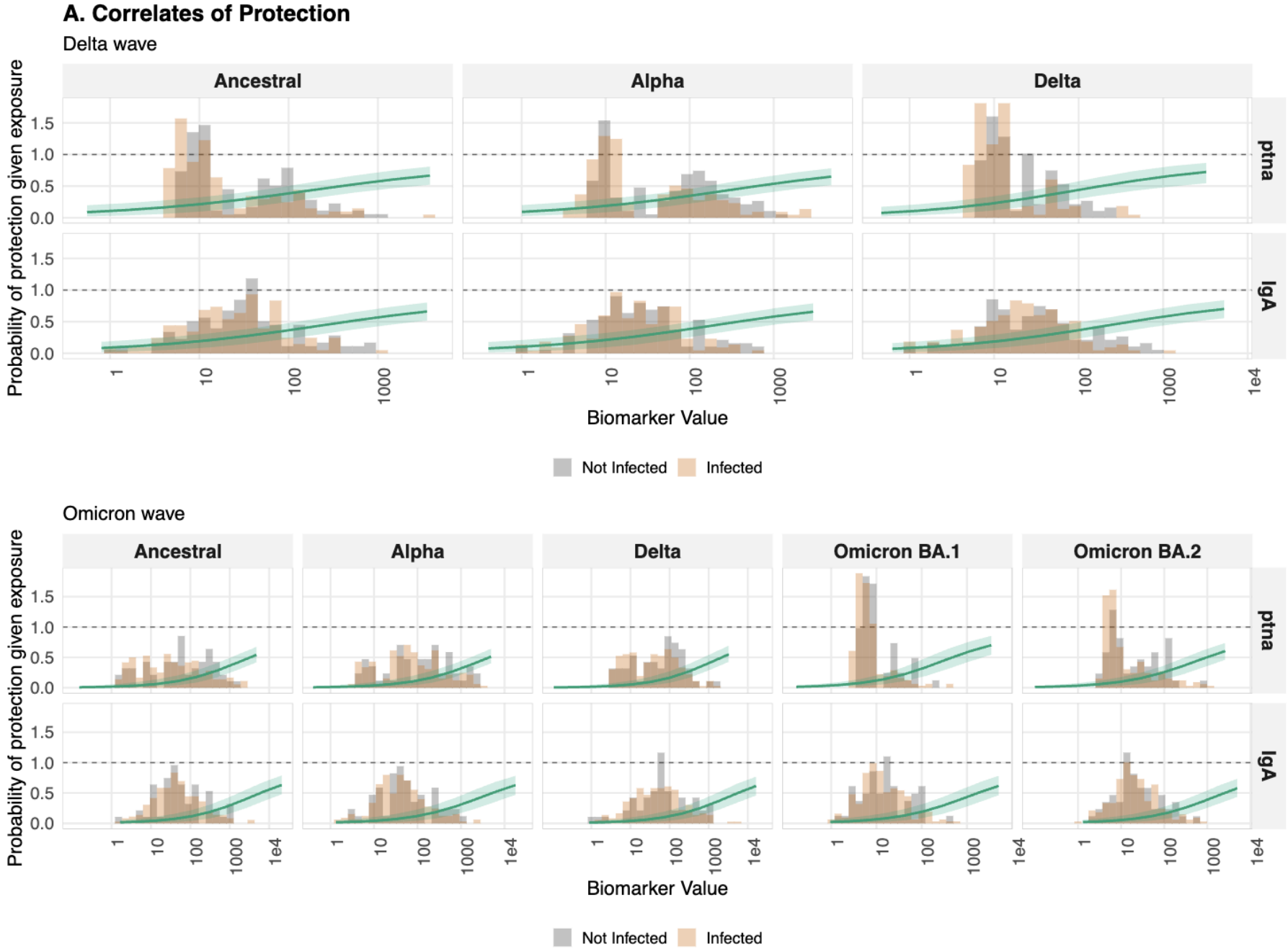


10 biomarkers:

Medium correlation between pVNT and mIgA



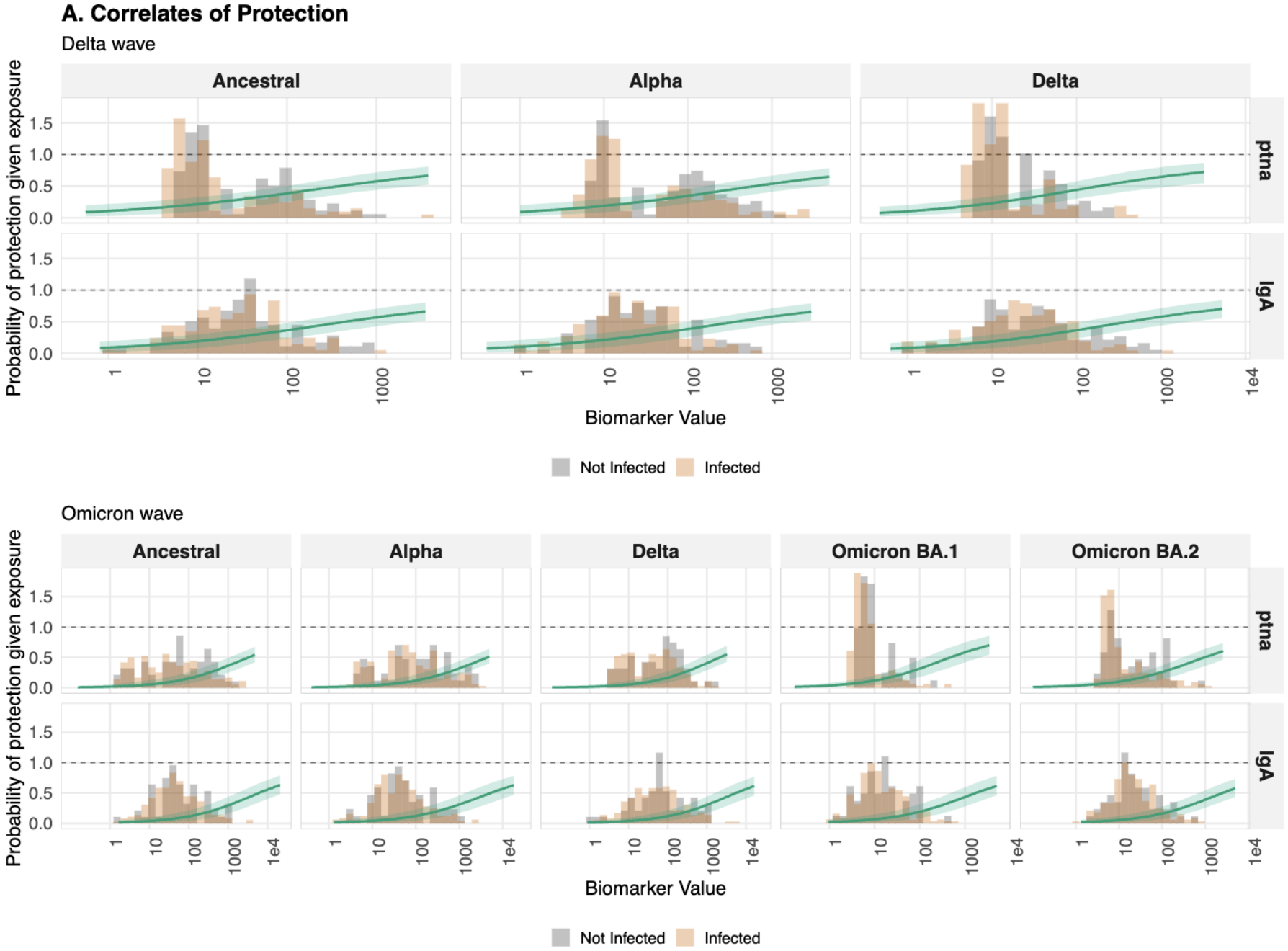
RESULTS FOR SARS-CoV-2



RESULTS FOR SARS-CoV-2

Which of these biomarkers is the best COP?

Determine predictive capacity!!



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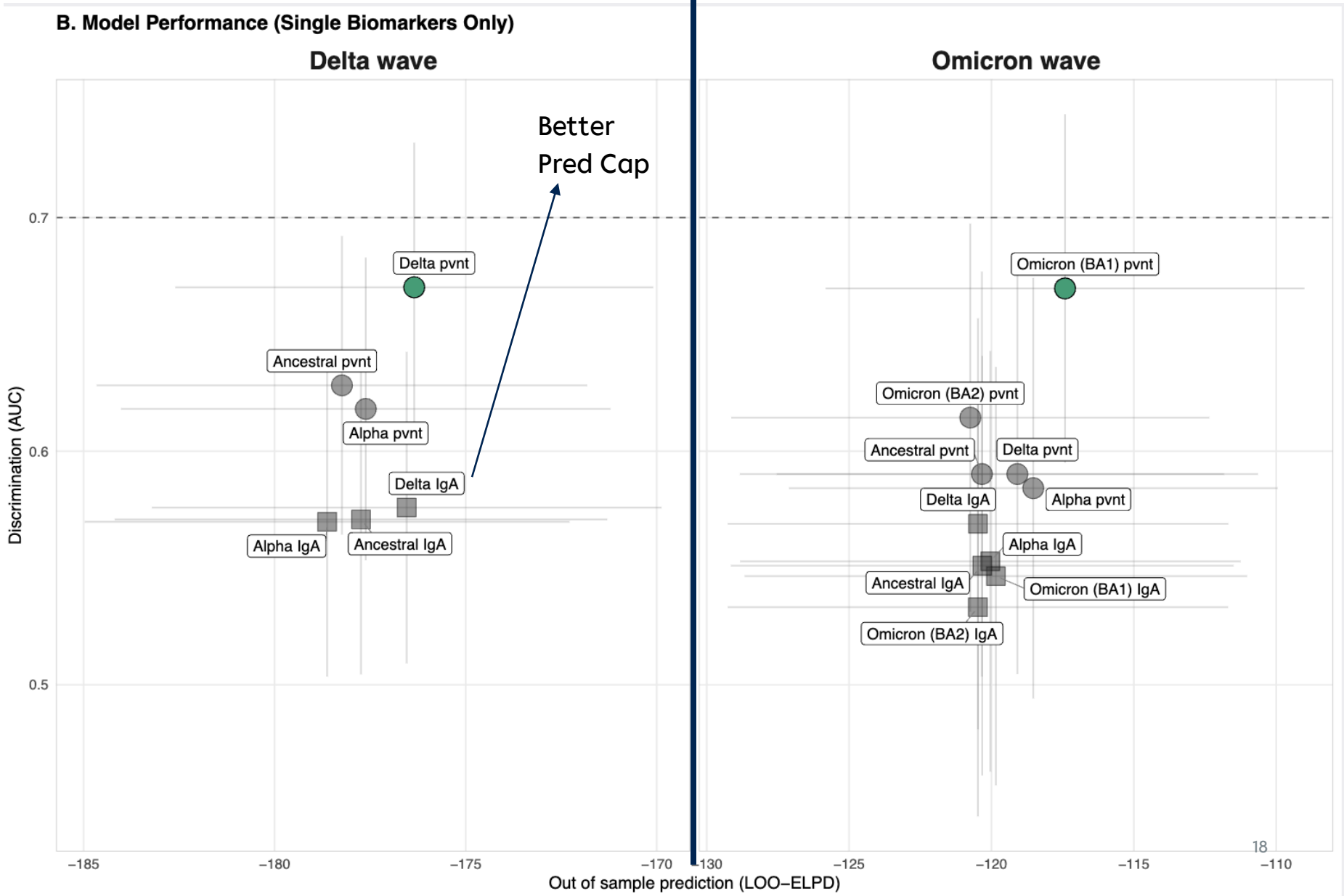

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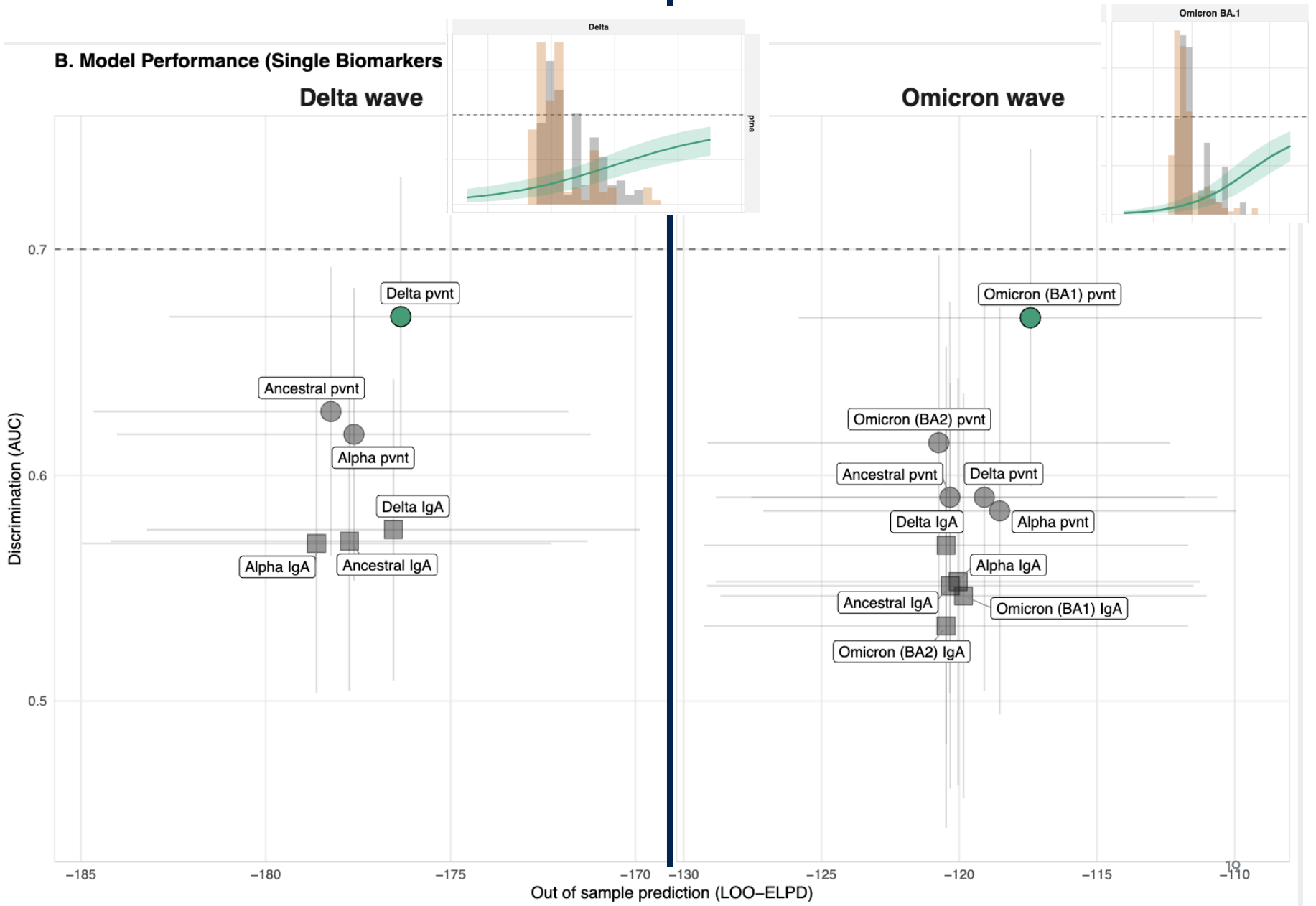
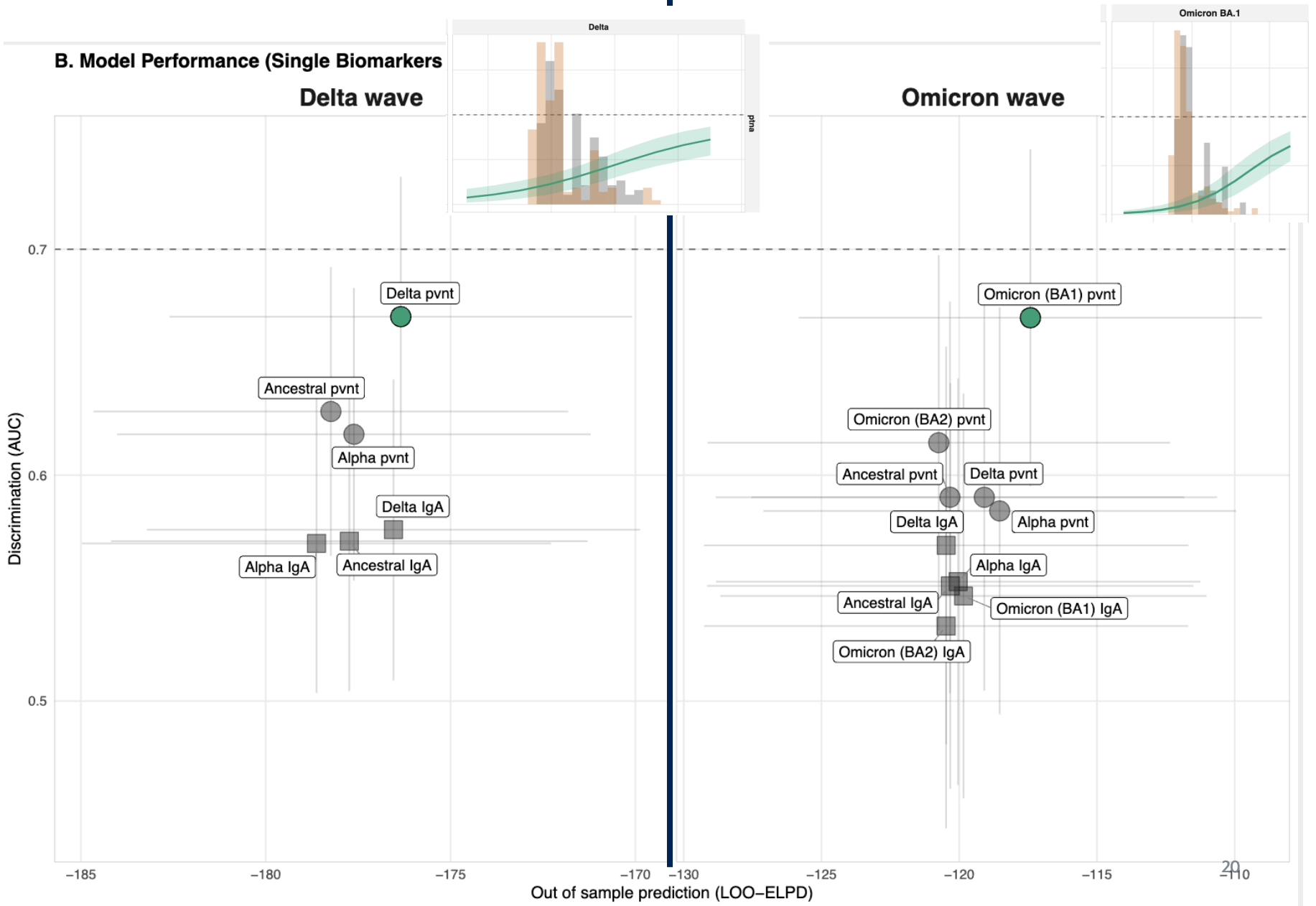


RESULTS FOR SARS-CoV-2

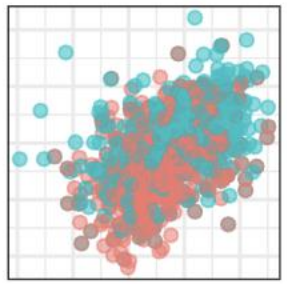
What happens if we look at combining Delta pNTA and Delta mIgA?



RESULTS FOR SARS-CoV-2

Adding mIgA to pTNA decreases predictive capacity!

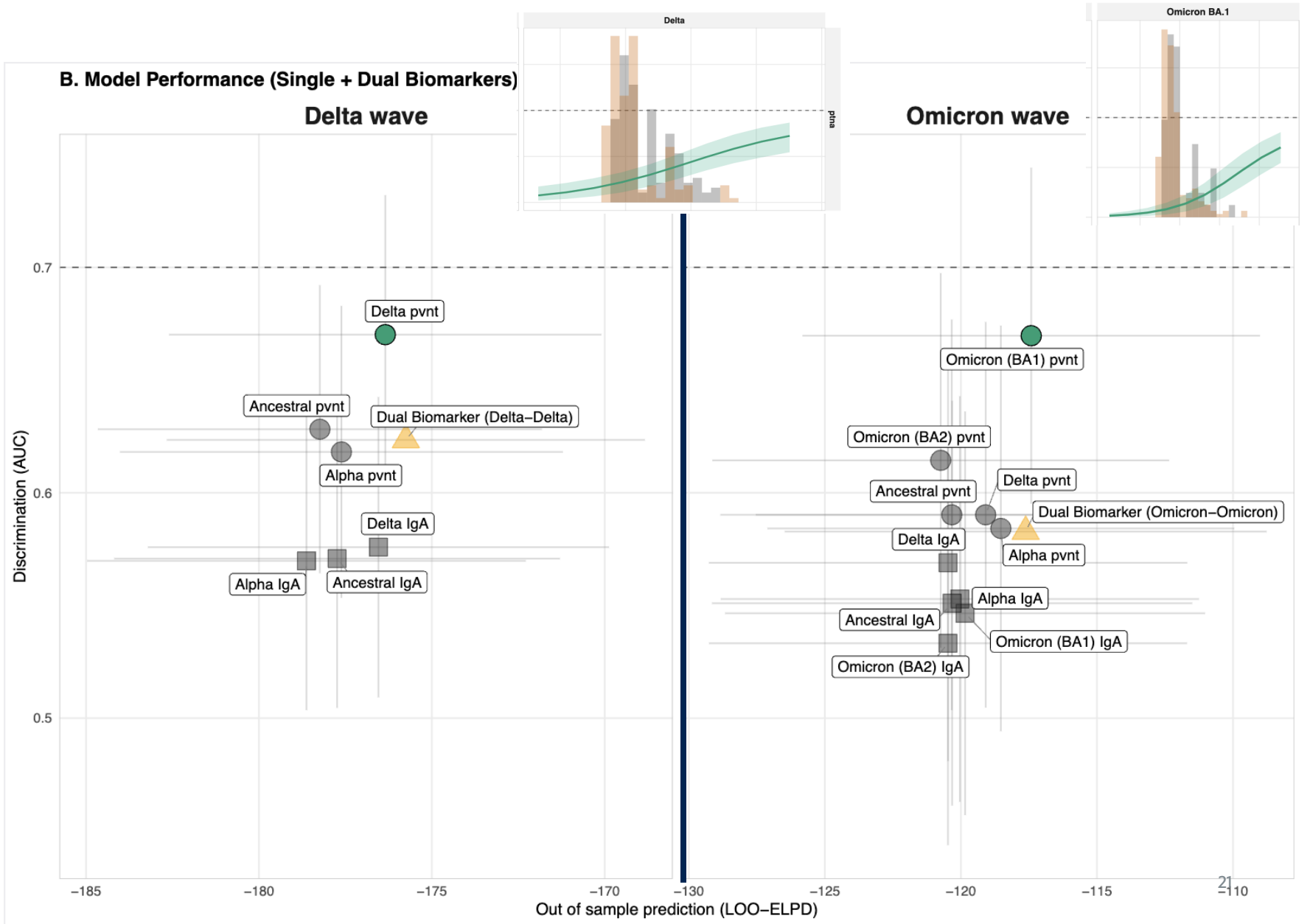
Why?



* Correlation between pTNA and mIgA
* mIgA very noisey

2 dimensional model overfits—pTNA only better

Best to stick to pTNA only
Make sense, pTNA is a functional measure, dominated binding assay



CASE 2: RSV in The Gambia

TRANSVIR Study (vaccine naïve)

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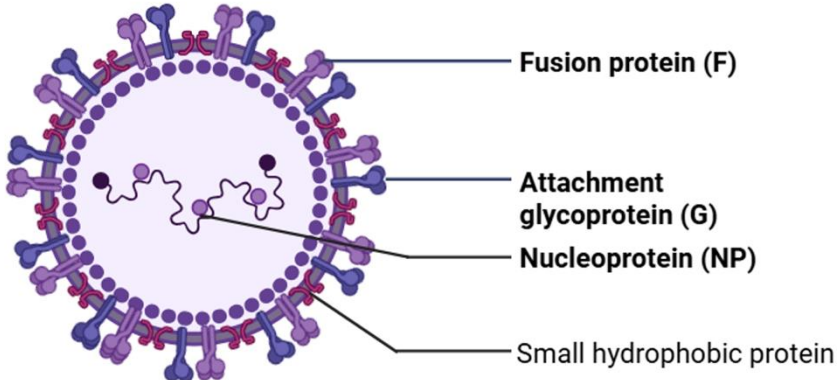
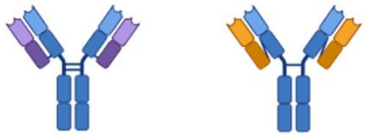




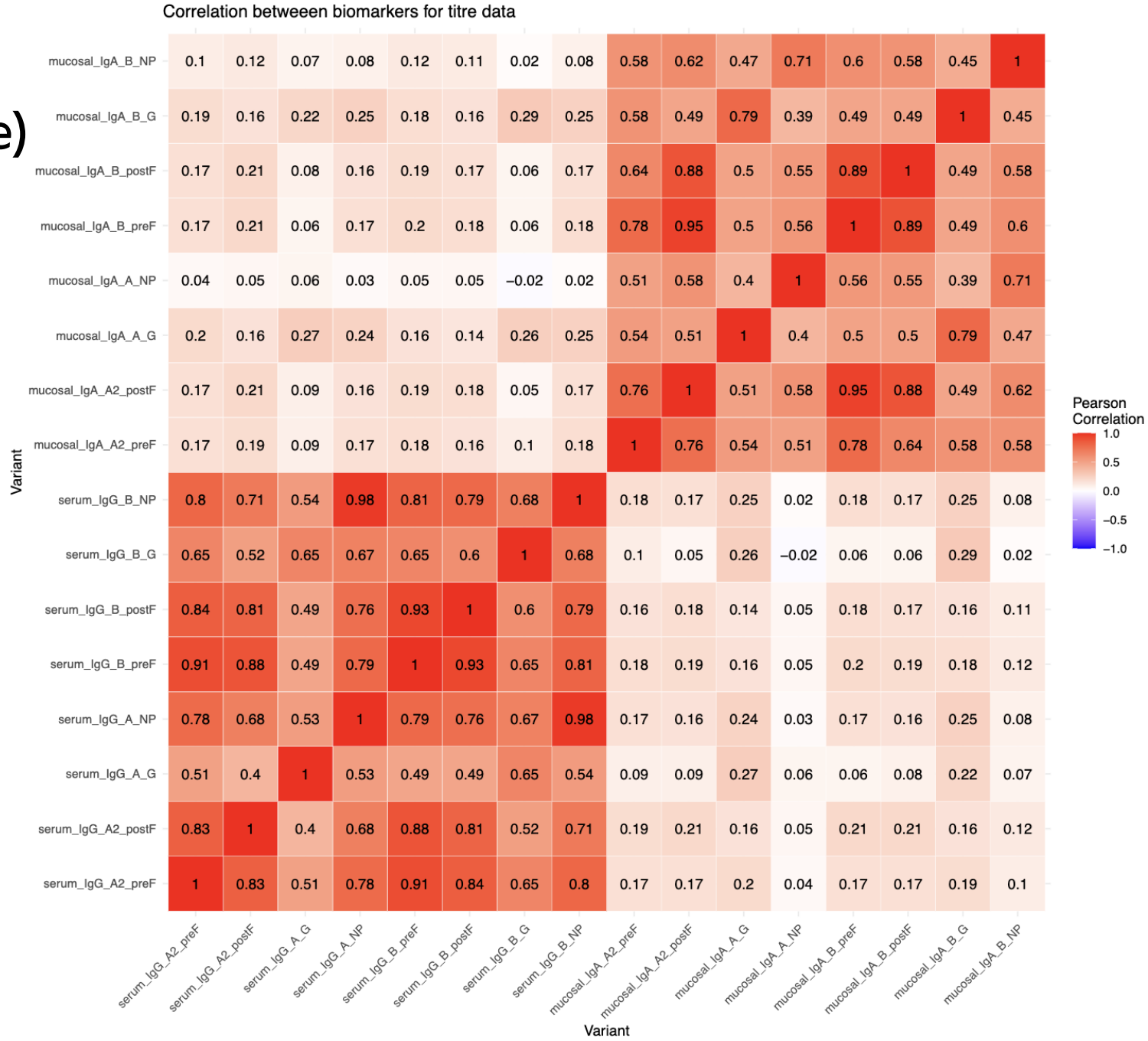
IgG levels in serum/ plasma

IgA levels in mucosal lining fluid

PreF, PostF, G, NP

- A and B serotype
- mIgA and **sIgG**

SH)



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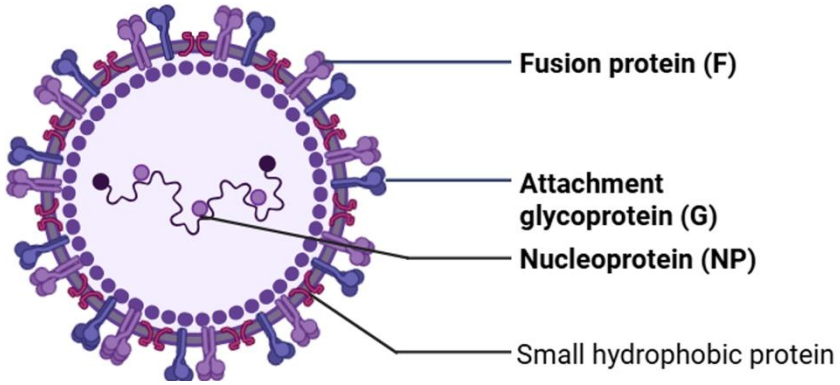

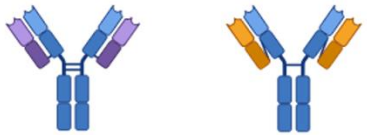

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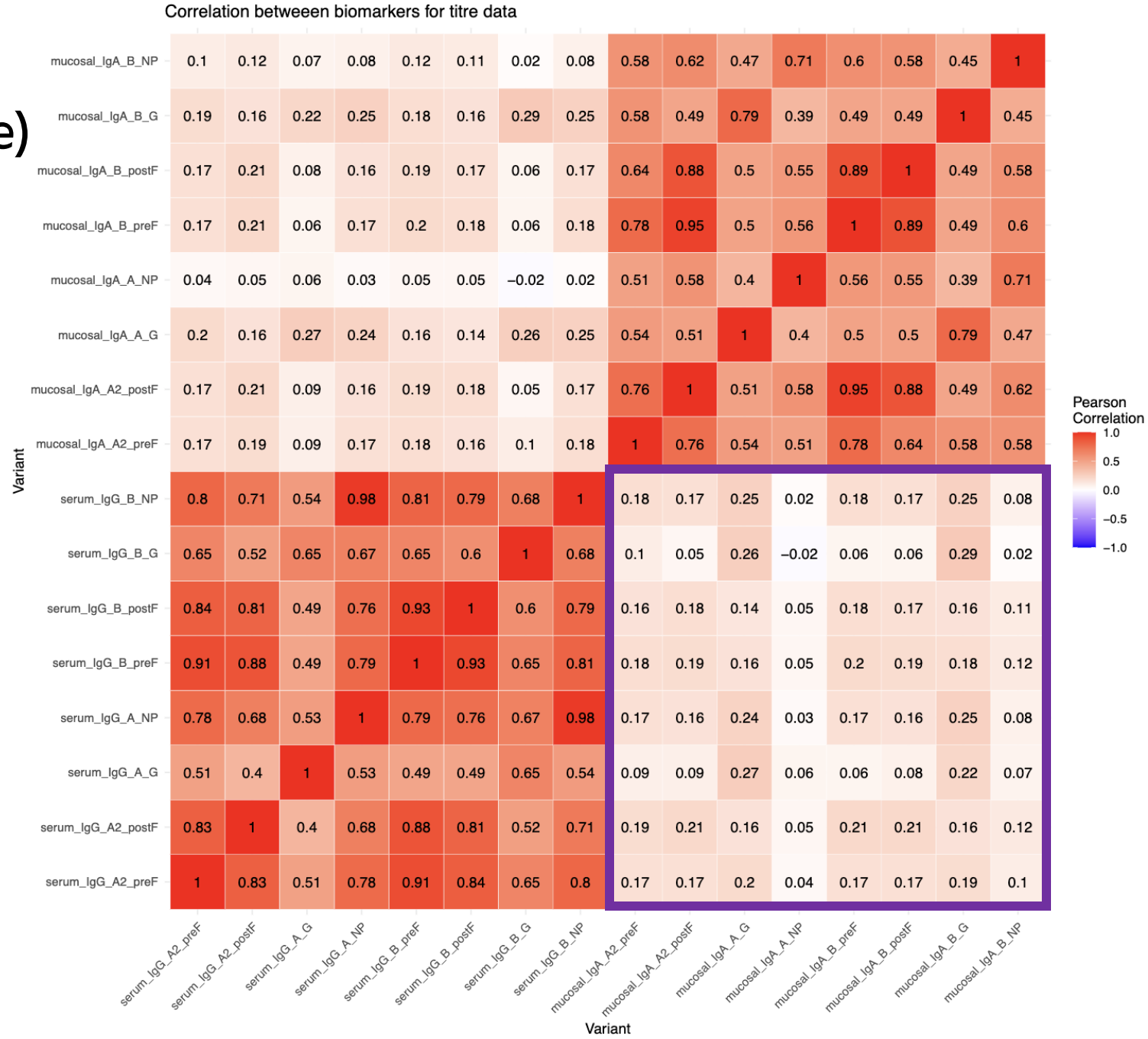
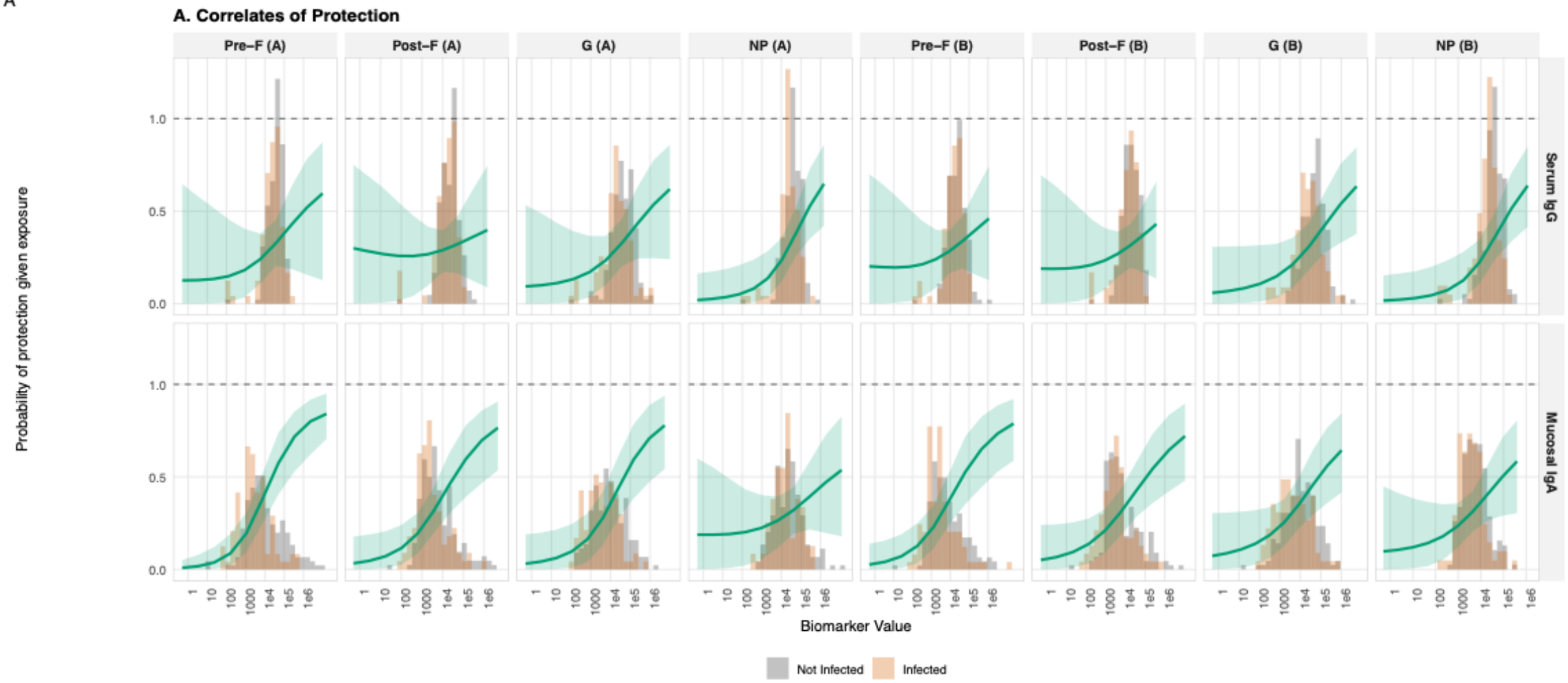


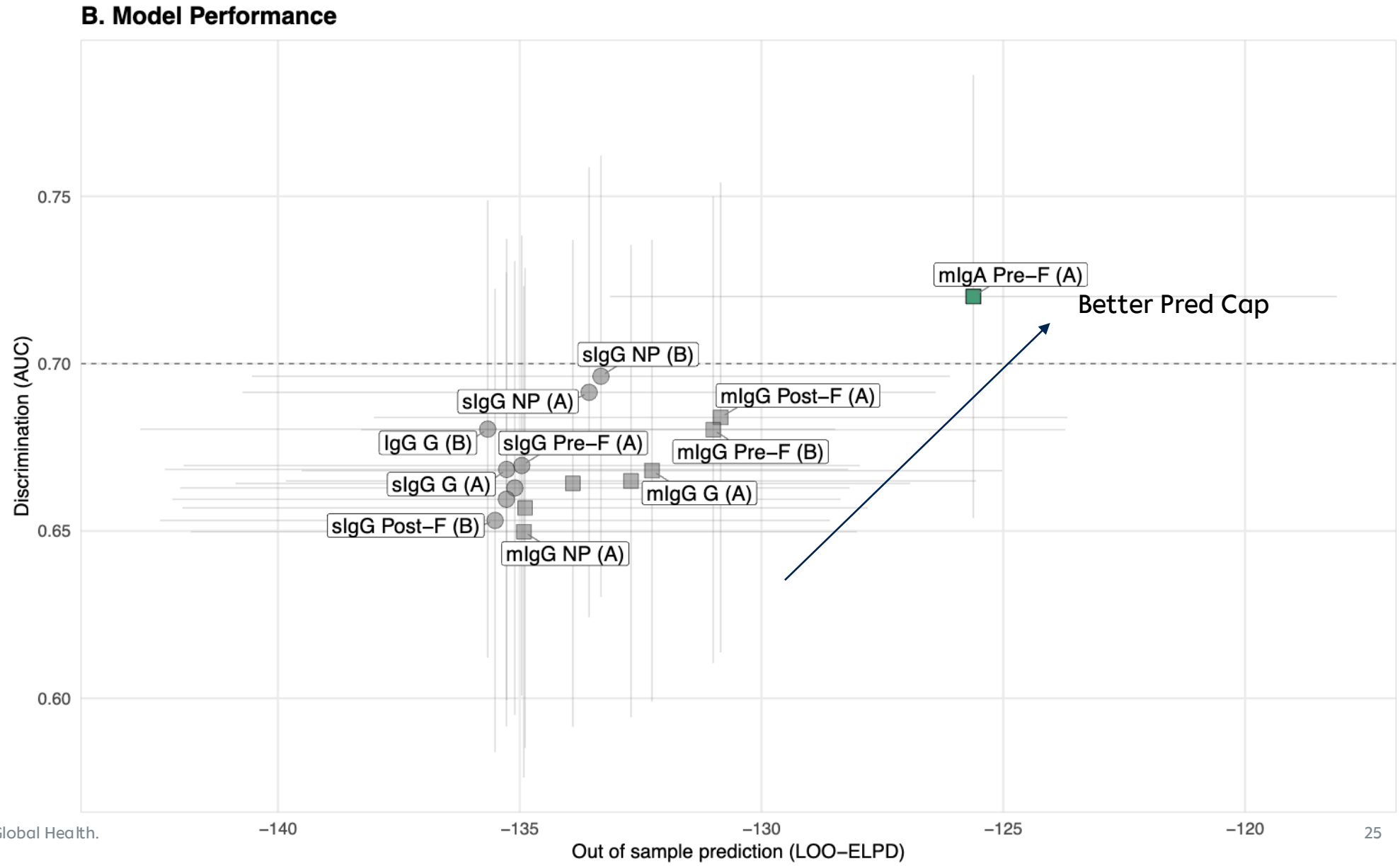
FITTED COP FOR RSV

A



B

BEST PREDICTIVE MODEL FOR COP



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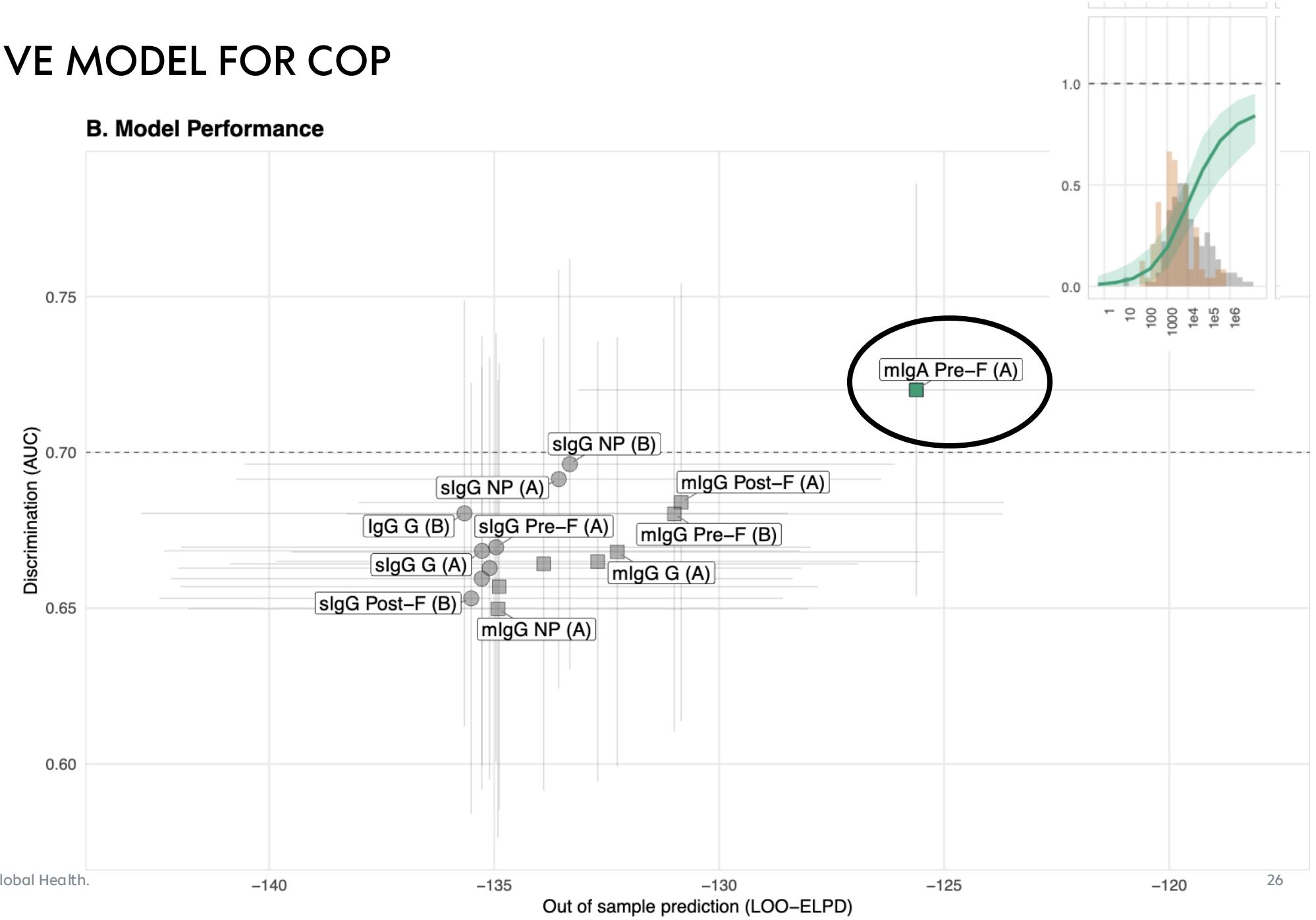

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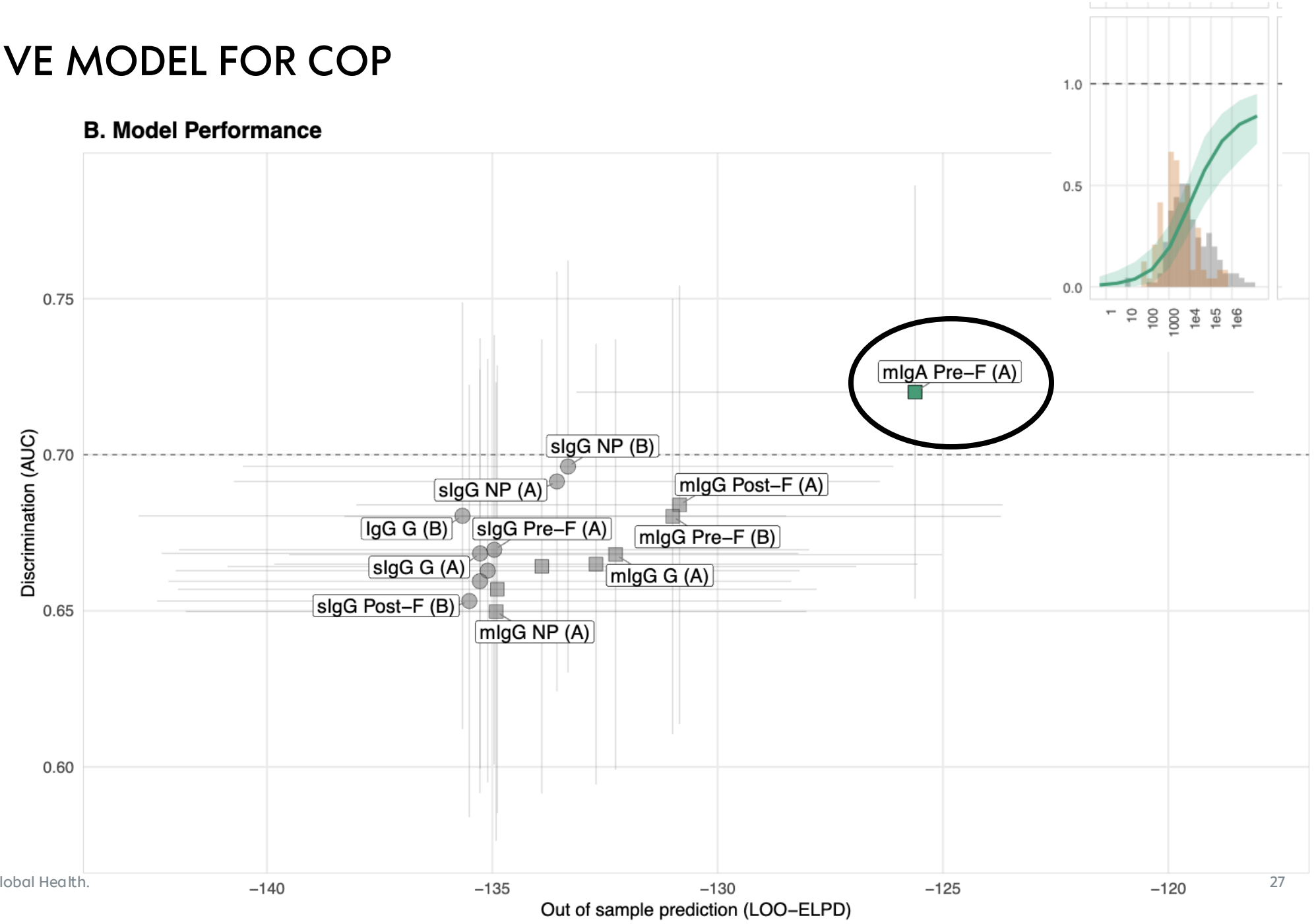
What happens when we add sIgG to mIgA?



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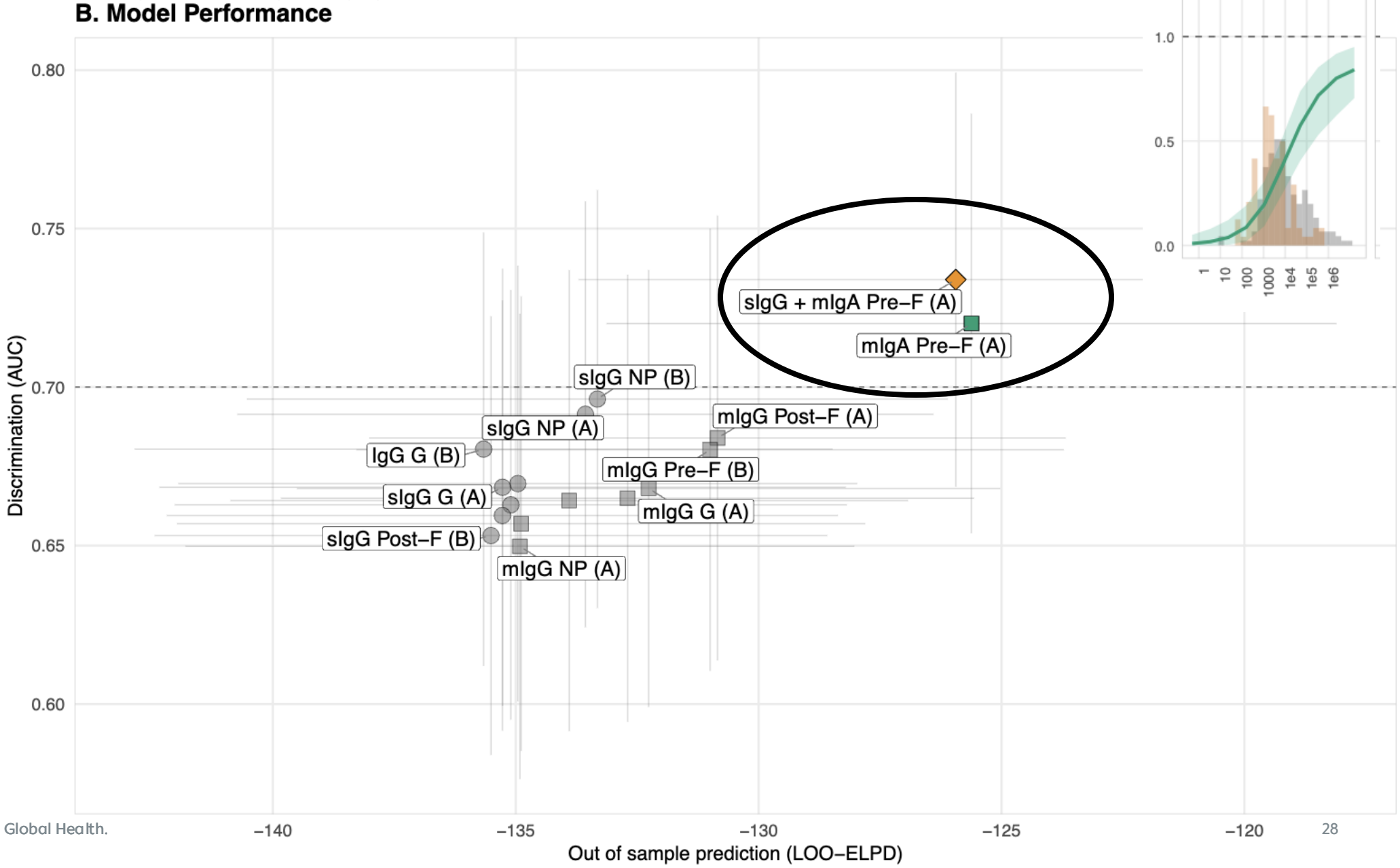
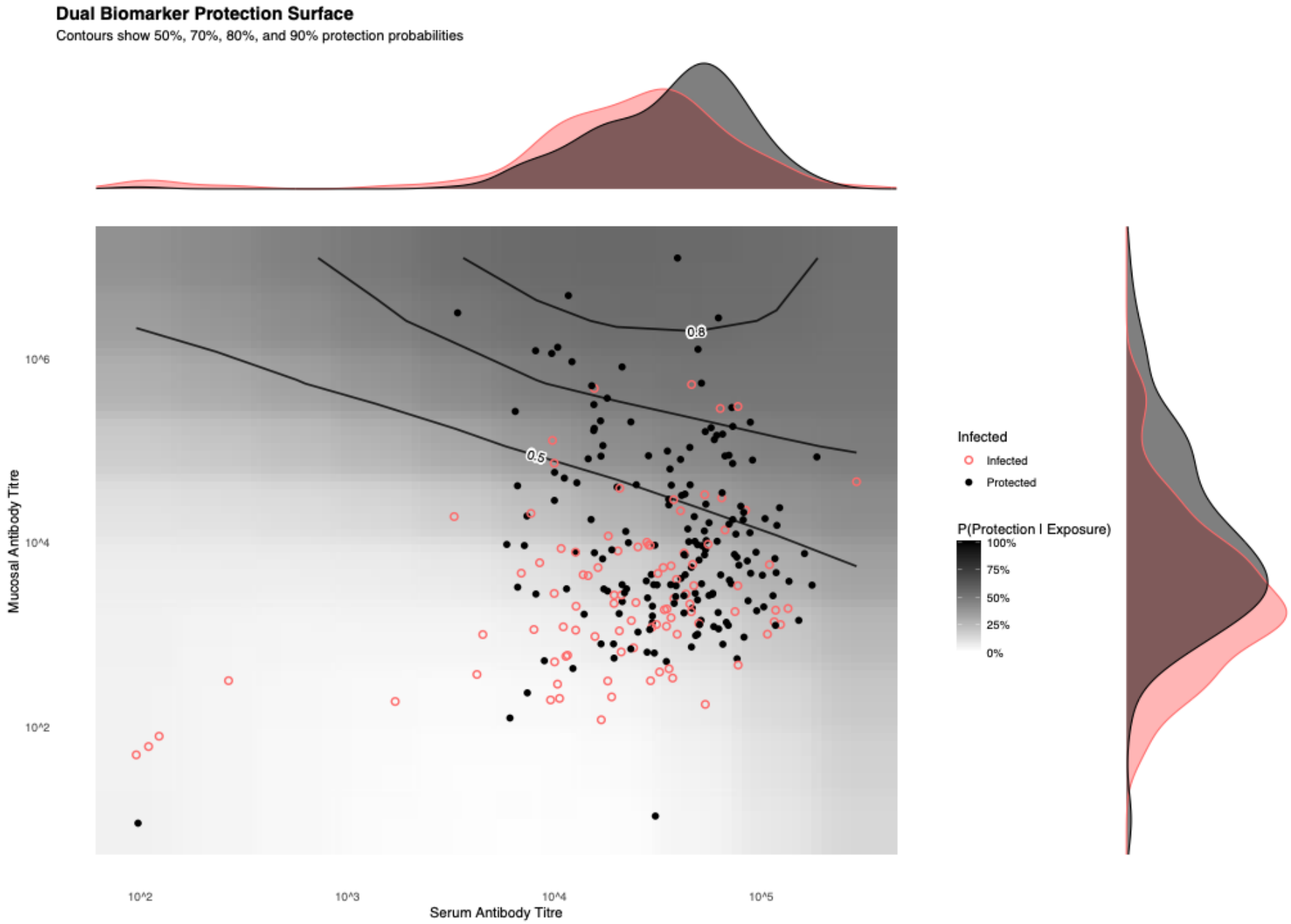
What does surface look like?



Cowling(?) CoP surface for RSV Pre-F

2D correlate of Protrection surface:

Questionable practical use?



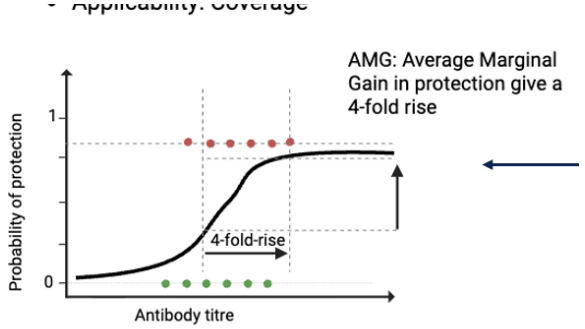
Counterfactual analysis

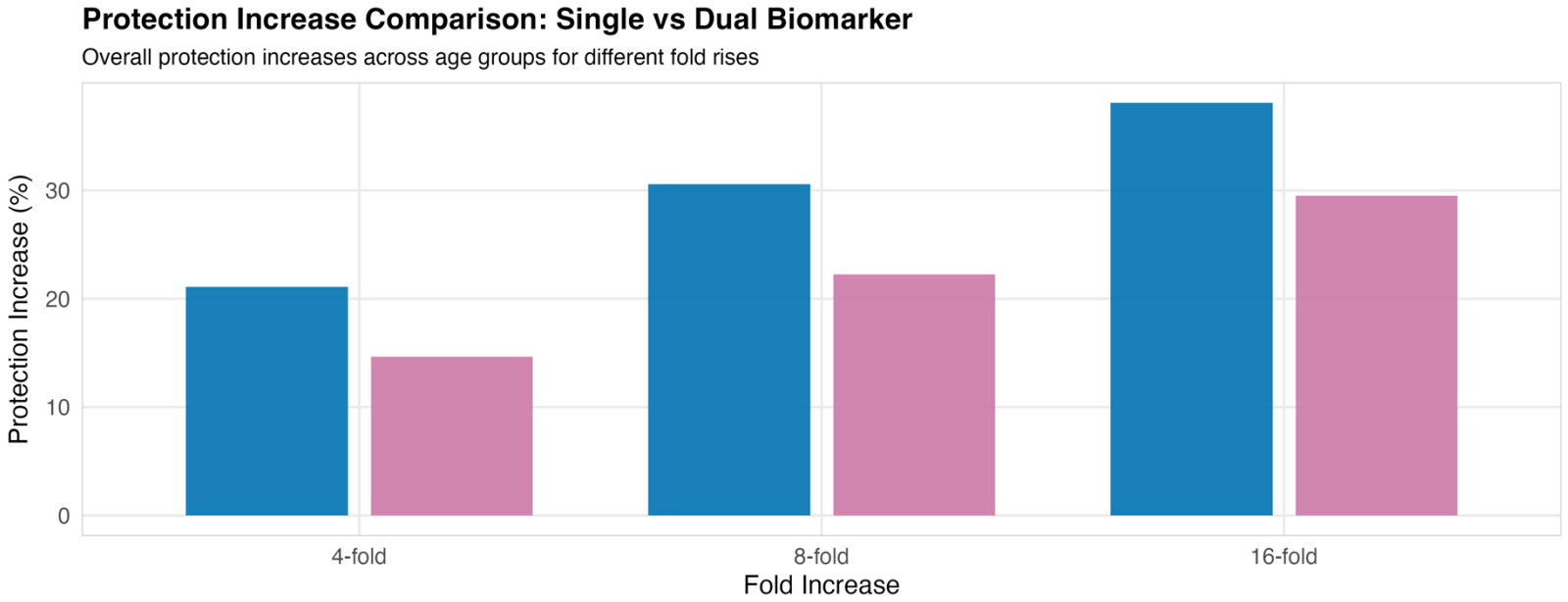
In a counterfactual anaysis: X-fold rise in mIgA and sIgG for PreF faciltates better protection than just X-fold rise in mIgA

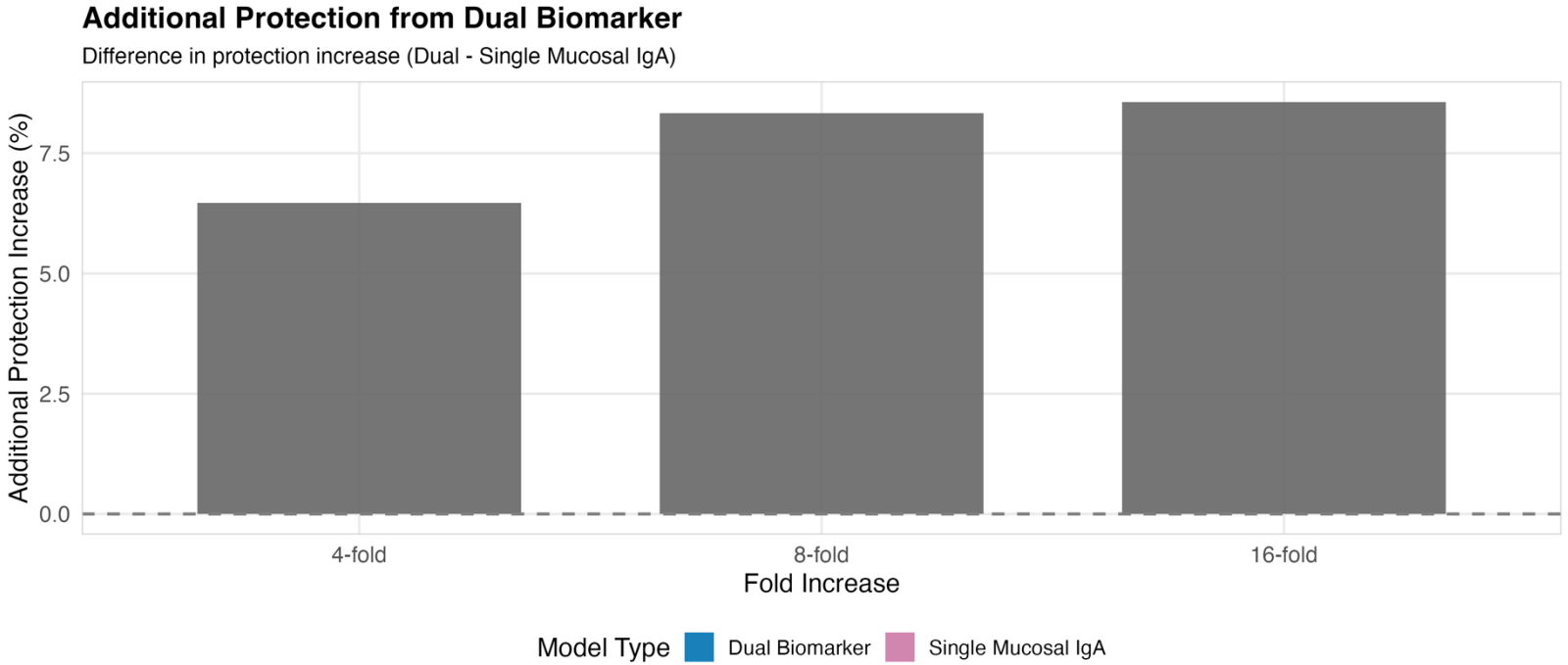
AND

The model has better discrimination !

Remember:







DISCUSSION

IMPACT

- Developing robust statistical methods for establishing CoP from natural history studies important;
  - Not enough time/money to run a clinical trial in humans to determine a CoP causally (MoP)
  - A lot of pathogens have no vaccine -> can used as preliminary work to determine candidate CoP in clinical trials in humans/animals
  - Potential for better CoP using multiple biomarkers
    - Better discrimination + better counterfactual impact

EXTENSIONS

- Add hierarchical effects to logistic function to see how CoP varying across covariates (infection history and/or age)
- Similar stuff using ML; good at discovering unexpected patterns in complex data; blackbox-y so not good for regulatory-acceptable evidence

LIMITATIONS

- Setting and seasonal specific, unsure how well this generalises

CONCLUSIONS

1. We have developed a framework for for CoP; broad application
- Will be implemented as an *R package* and an online widget

Coming soon!

2. We identify the "best" single biomarker form lots of biomarkers
- ***SARS-CoV-2*:** Best single biomarker is serum pTNA to Delta for Delta wave, and Omicron BA.1 pTNA to Omicron wave
- ***RSV*:** Best single biomarker is mIgA PreF to infection

3. Assessed value of combined biomarker models
- ***SARS-CoV-2*:** Adding mIgA binding assay information has worse predictive power
- ***RSV:*** *Combing with sIgG to PreF has similar predictive capacity, but better AMG (ensuring both biomarker have a four-fold rise)*

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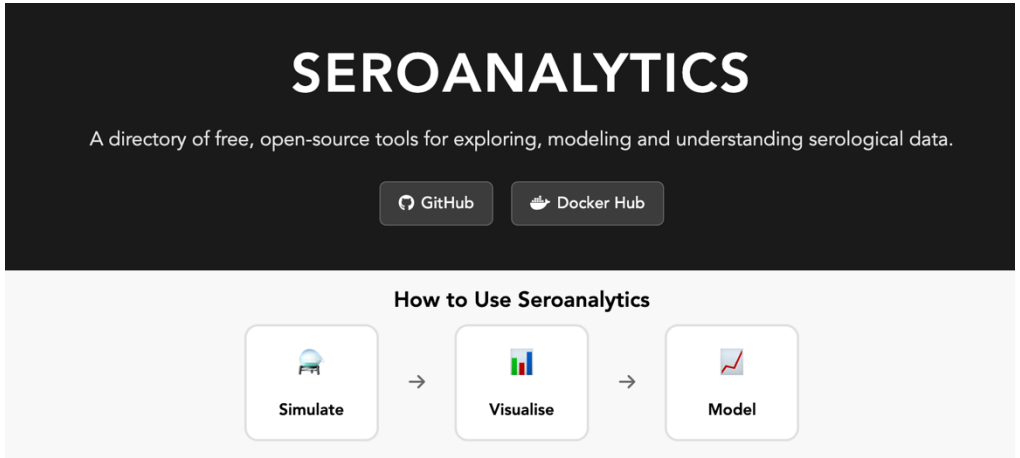

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EXTRA SLIDES

MOTIVATION

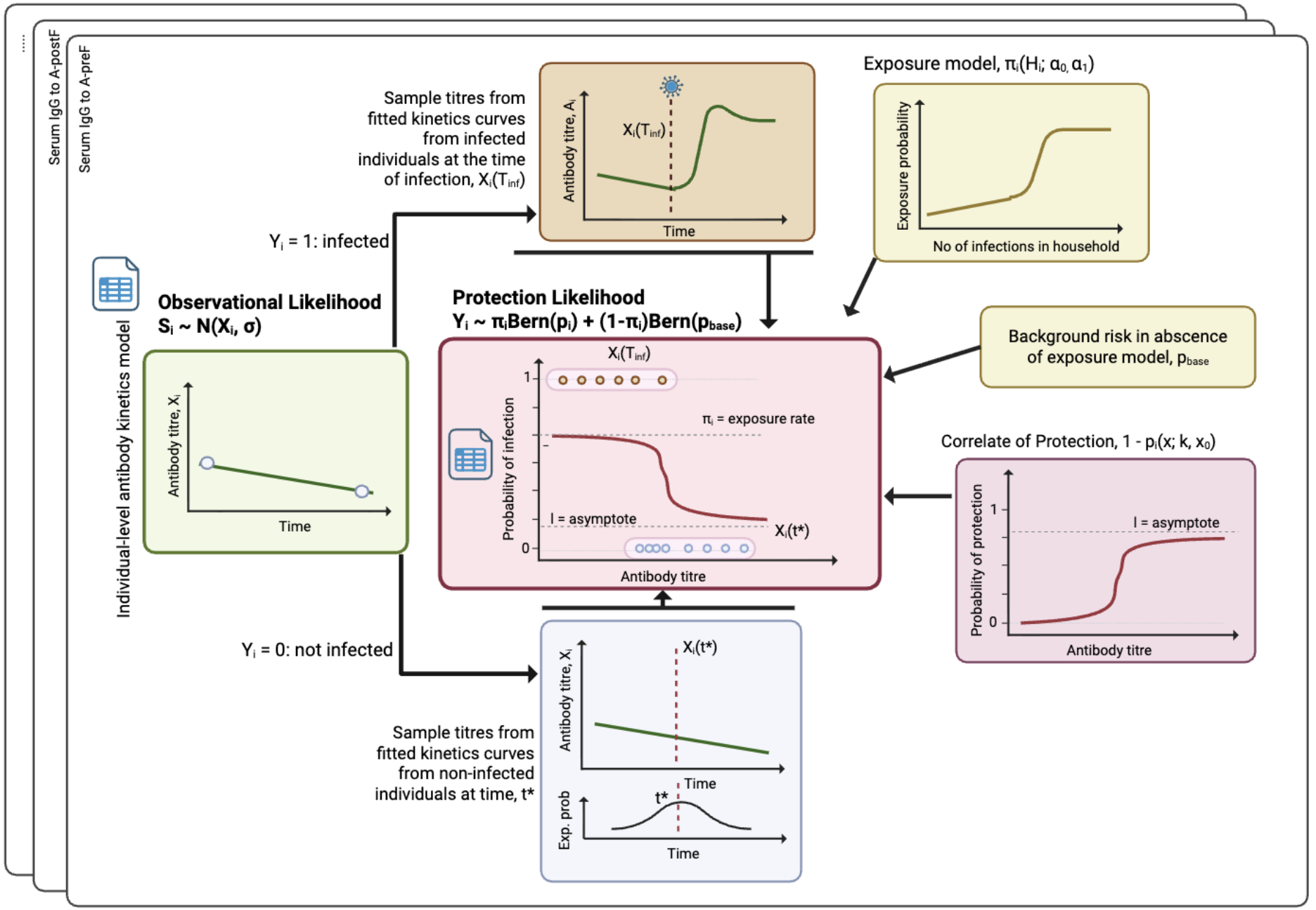
The Problem:

- Without CoPs => vaccine trials require large sample sizes, long follow-up periods, and are resource-intensive
- Current CoPs (assessed in vaccine trials) rely on single biomarkers (typically serum antibodies), which may miss important aspects of protective immunity.

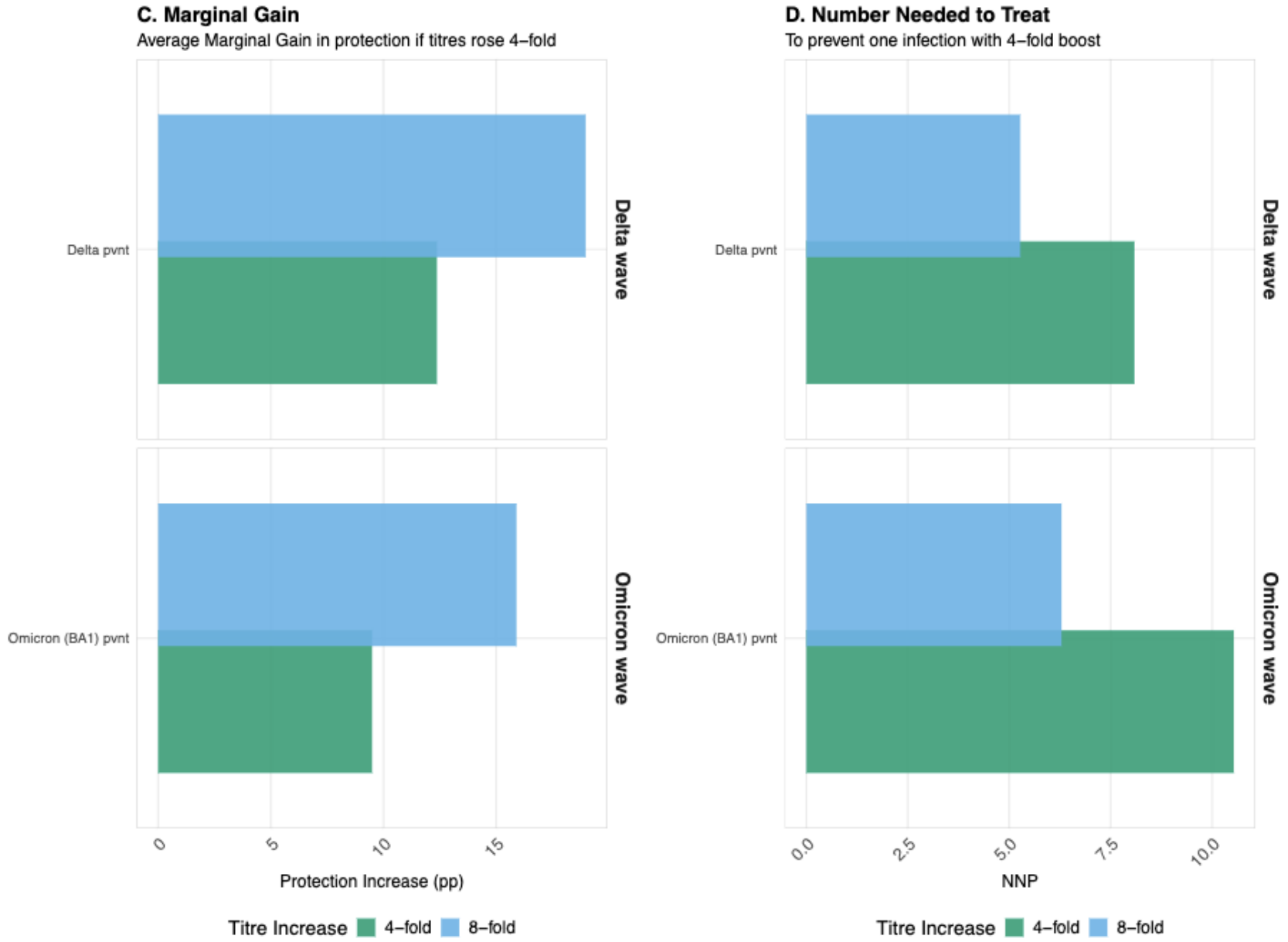
The Gap:

- Mucosal immunity is the frontline defence for respiratory pathogens, yet (historically) rarely measured in CoP studies
- Rigorous statistical framework needed to compare multiple biomarkers and identify the "best" CoP in a natural history setting
- Limited data on whether combining biomarkers improves prediction of protection

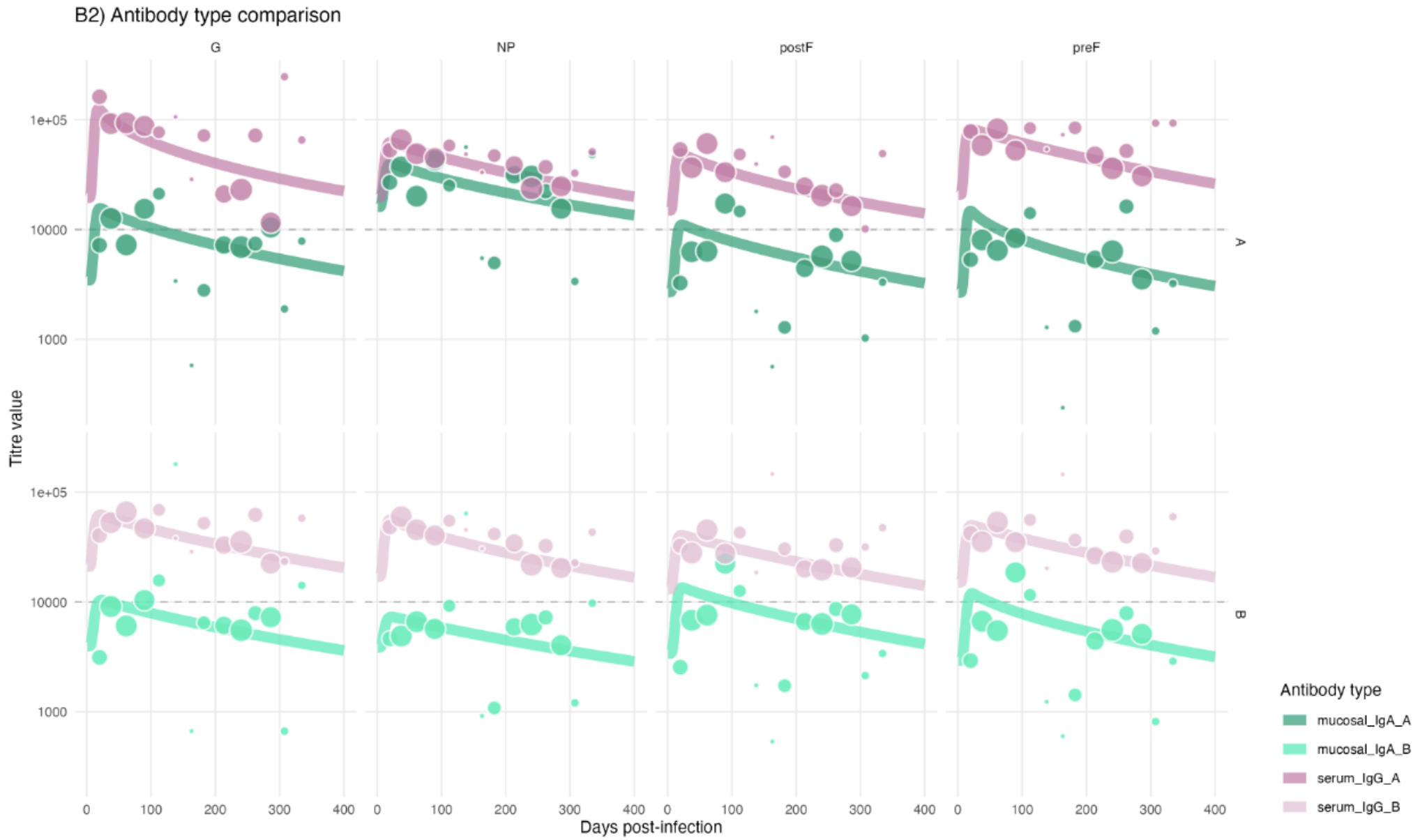
For each of G suptype, A and B, we have serum IgG and muscoal IgA to Pre-F, post-F, G, and NP BA2



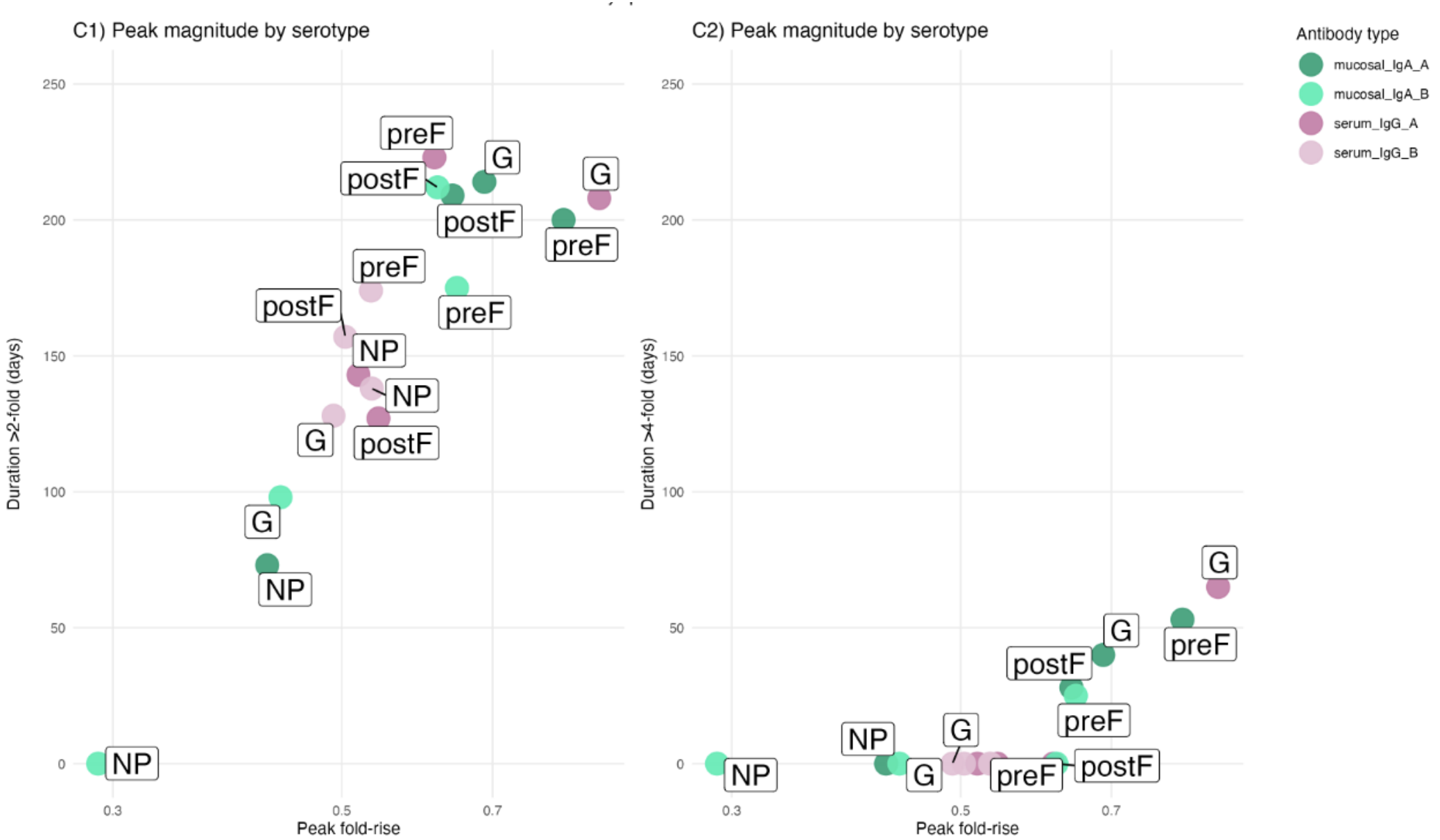
RESULTS FOR SARS-CoV-2



RSV kinetics

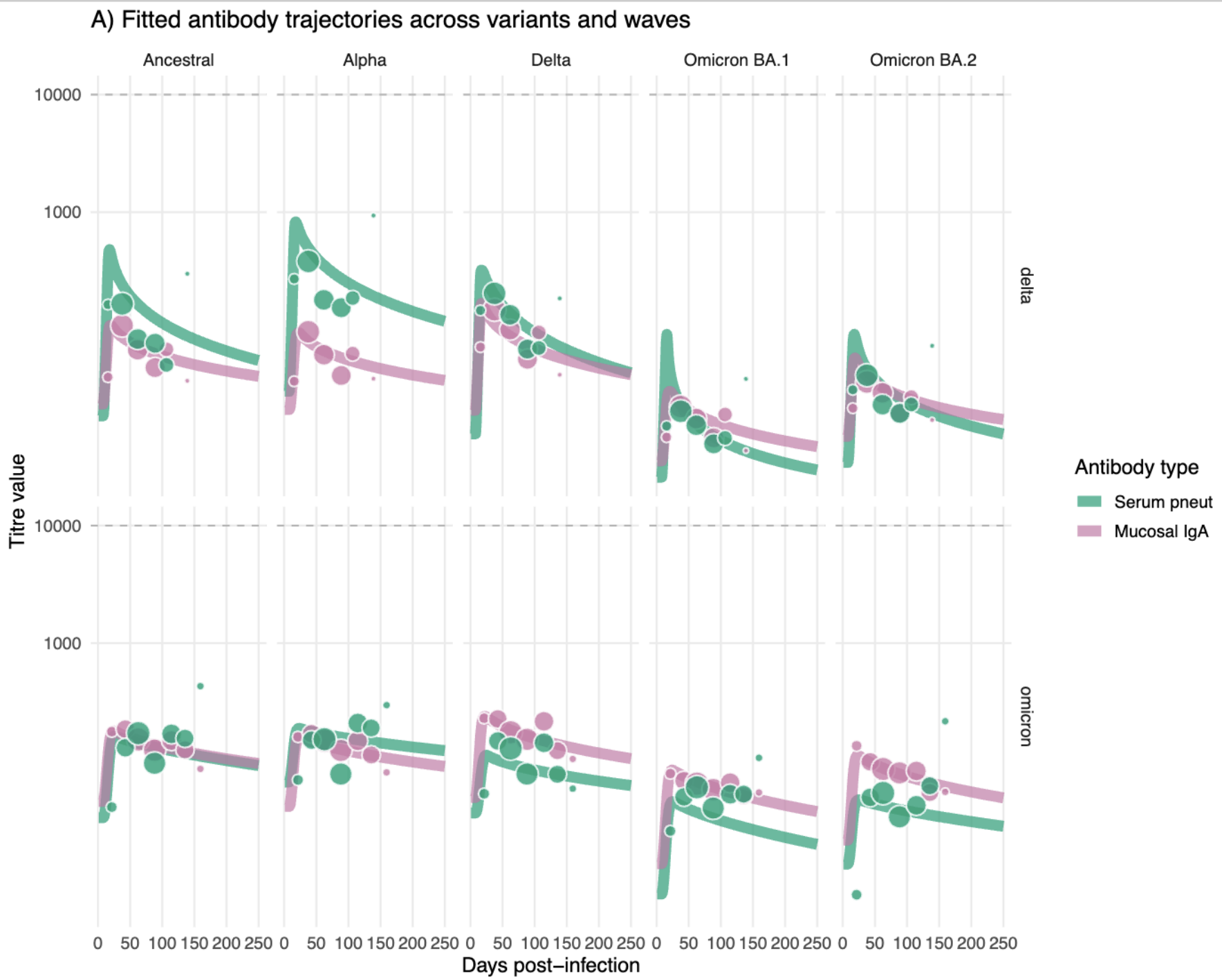


RSV kinetics



CHARITÉ

SARS-CoV-2 Kinetics



SARS-CoV-2 Kinetics