Understanding drivers of differential immune responses to mRNA and adenovirus vectored COVID-19 vaccines: A data-driven dynamic modelling analysis

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Immunity conference Hong Kong

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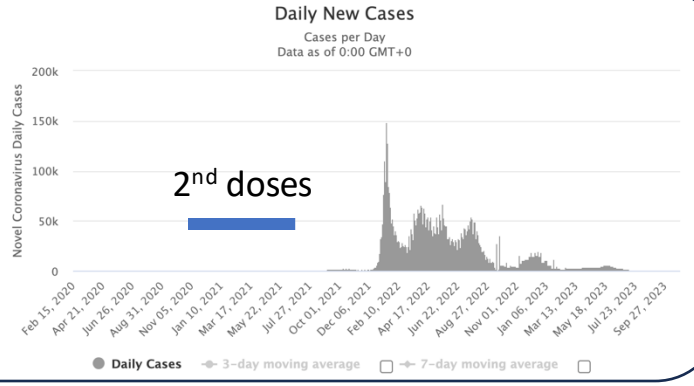
Motivation: Data

Does Repeat Influenza Vaccination Constrain Influenza Immune Responses and Protection?

Prospective cohort study (NCT05110911, 2020-Present)

Australia (various sites)

- In 2021: Pivot to consider the impact of SARS-CoV-2 vaccination



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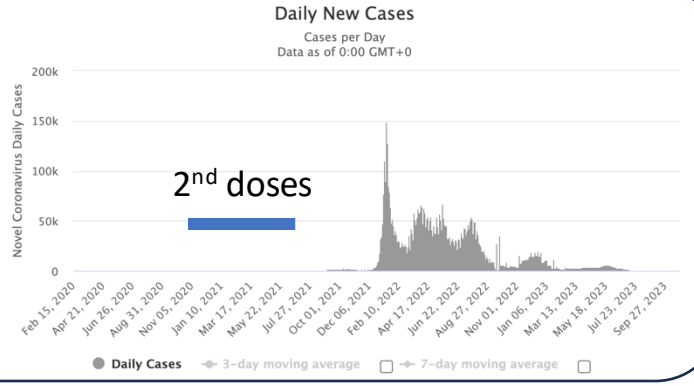
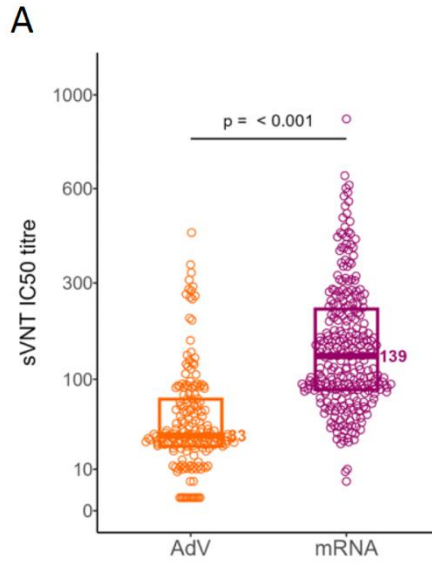
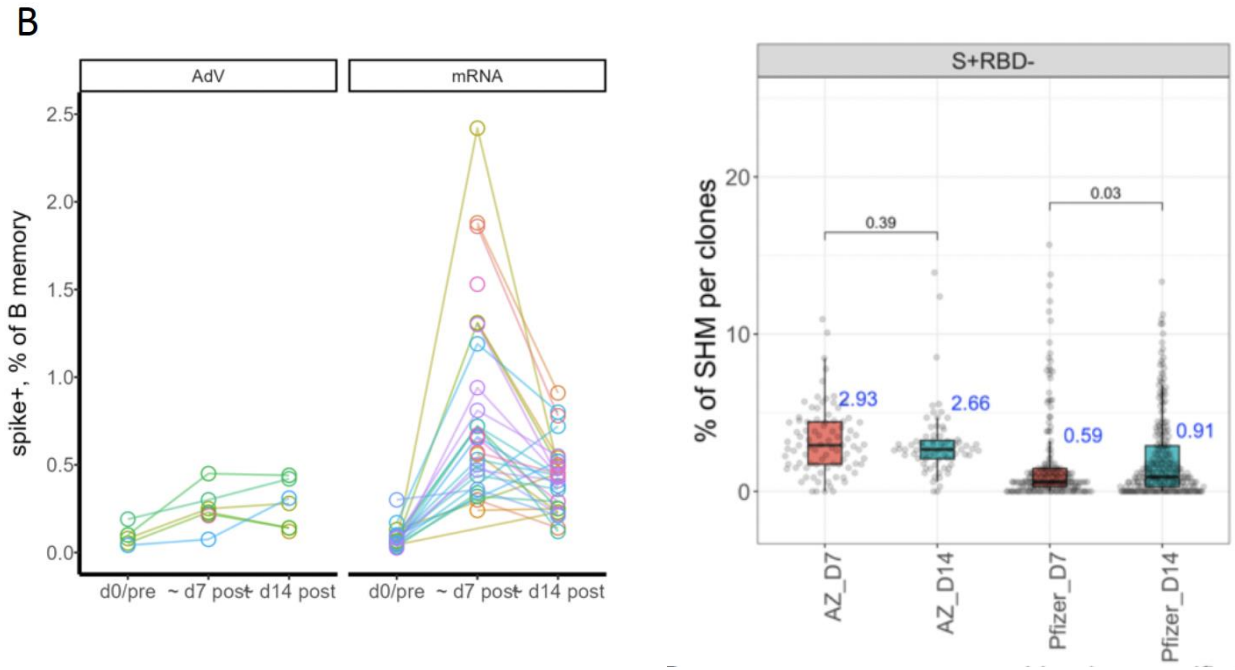


sVNT titres to Ancestral spike

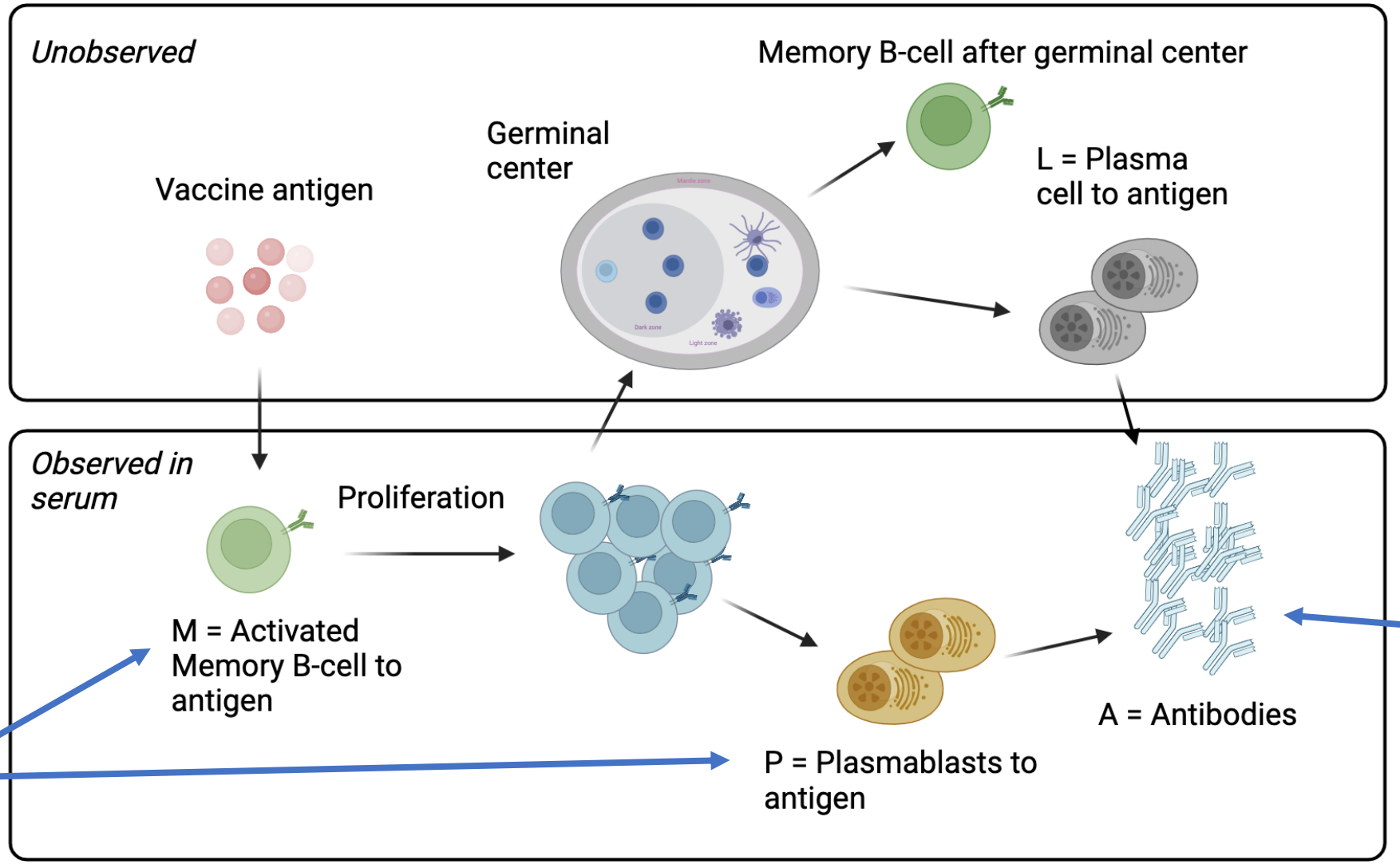


Activated memory B-cells to Ancestral spike

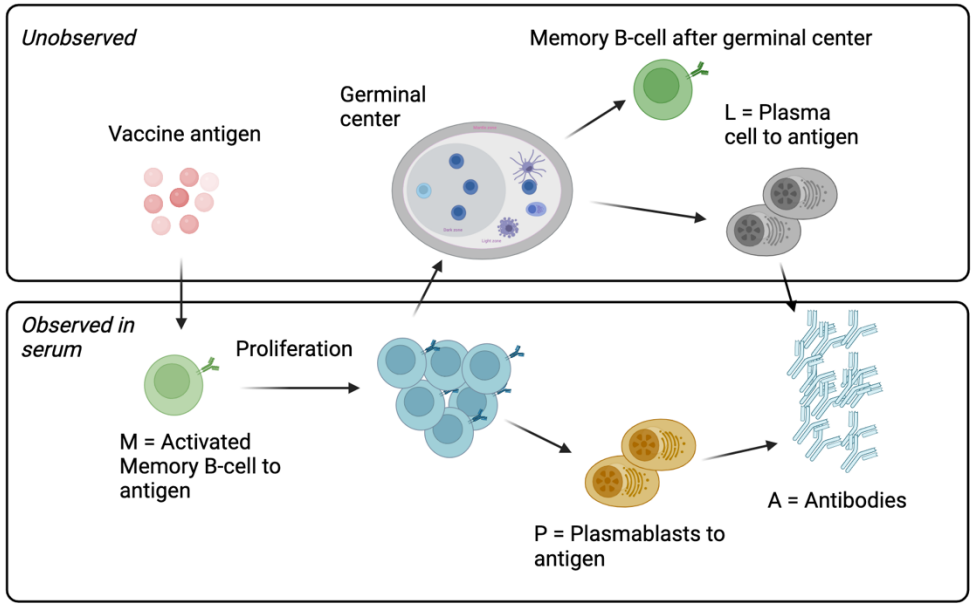
Liu et al. 2023 *Vaccine*

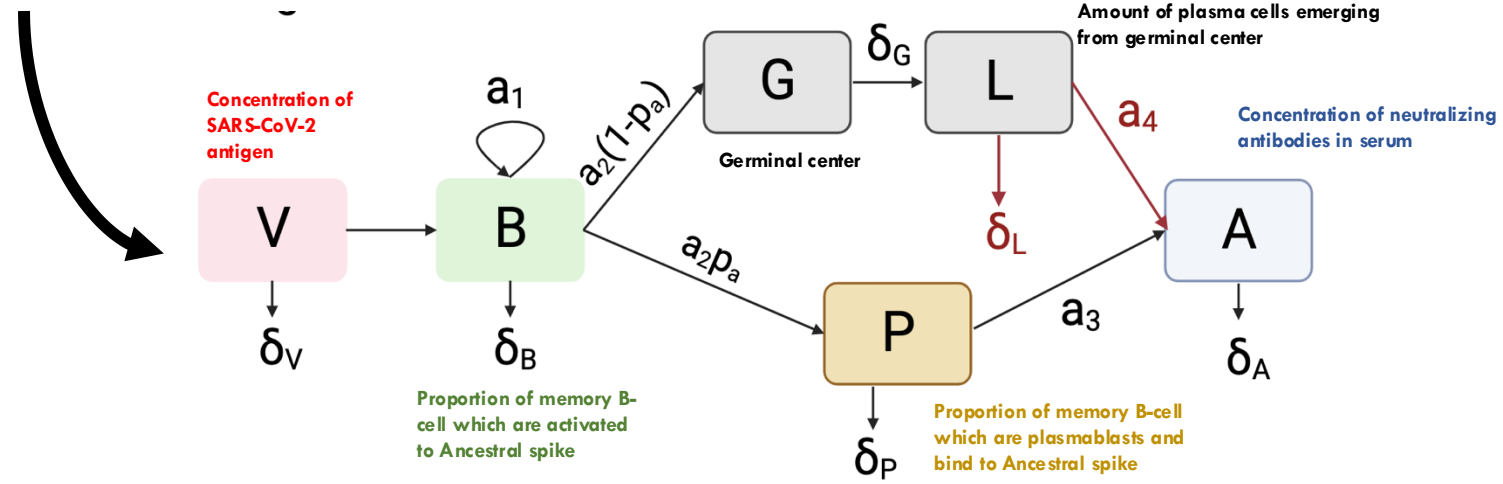


Motivation: Immunological assumptions



Methods: Model overview





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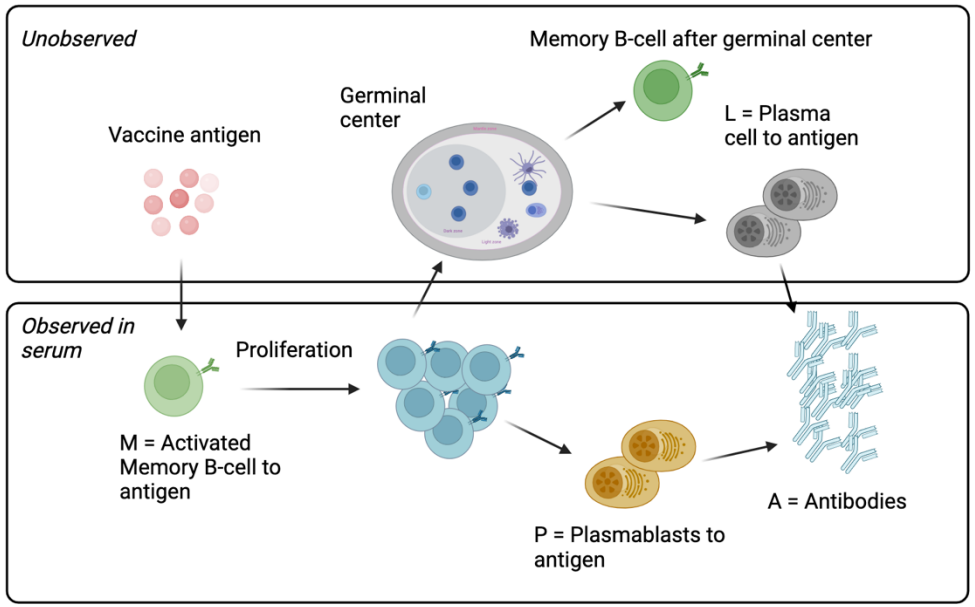
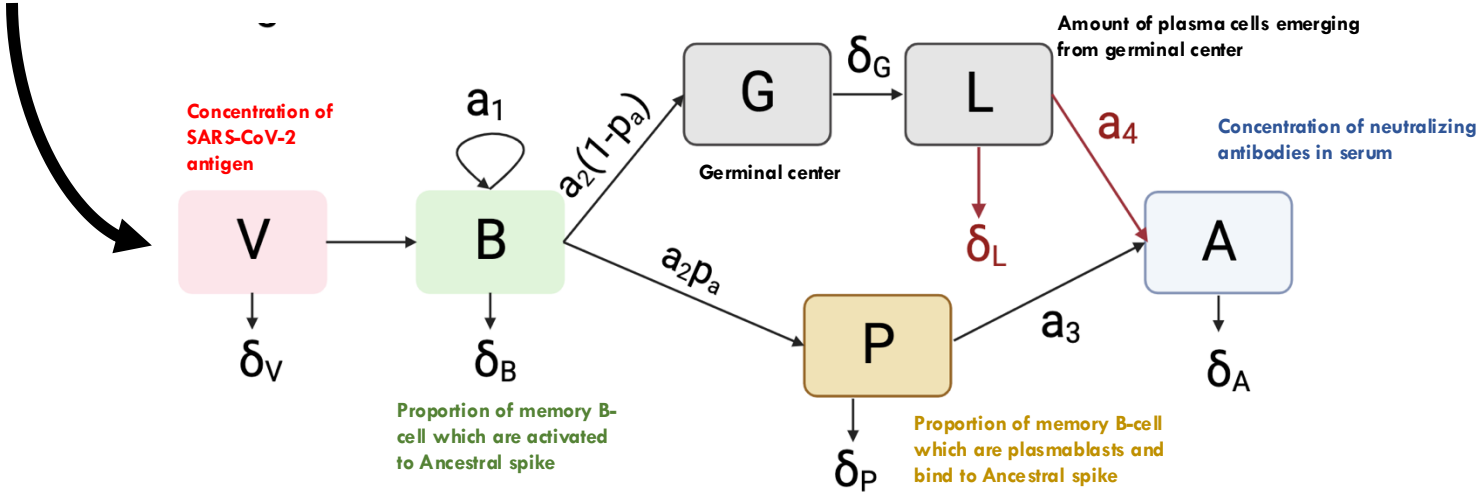
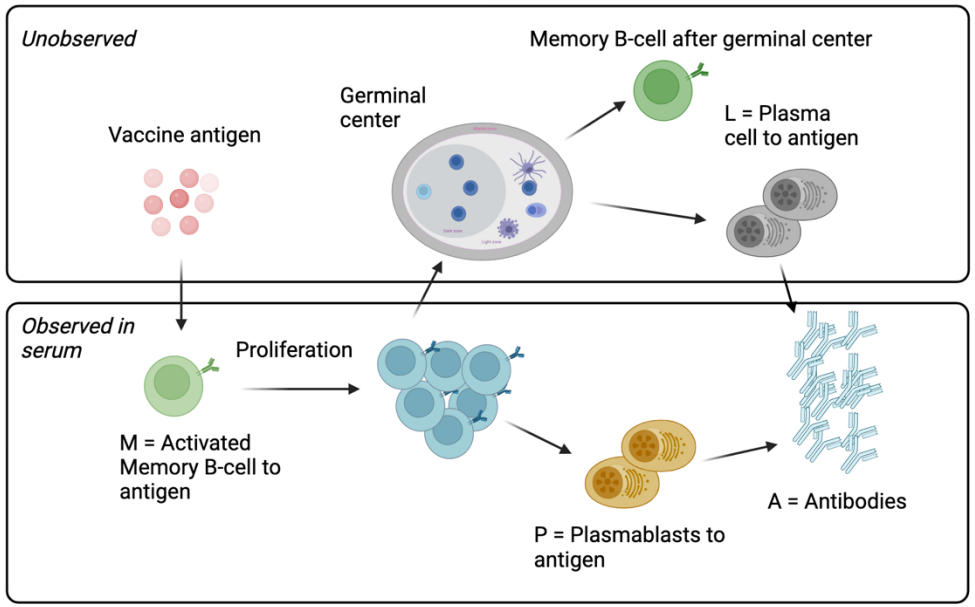




Decay rates

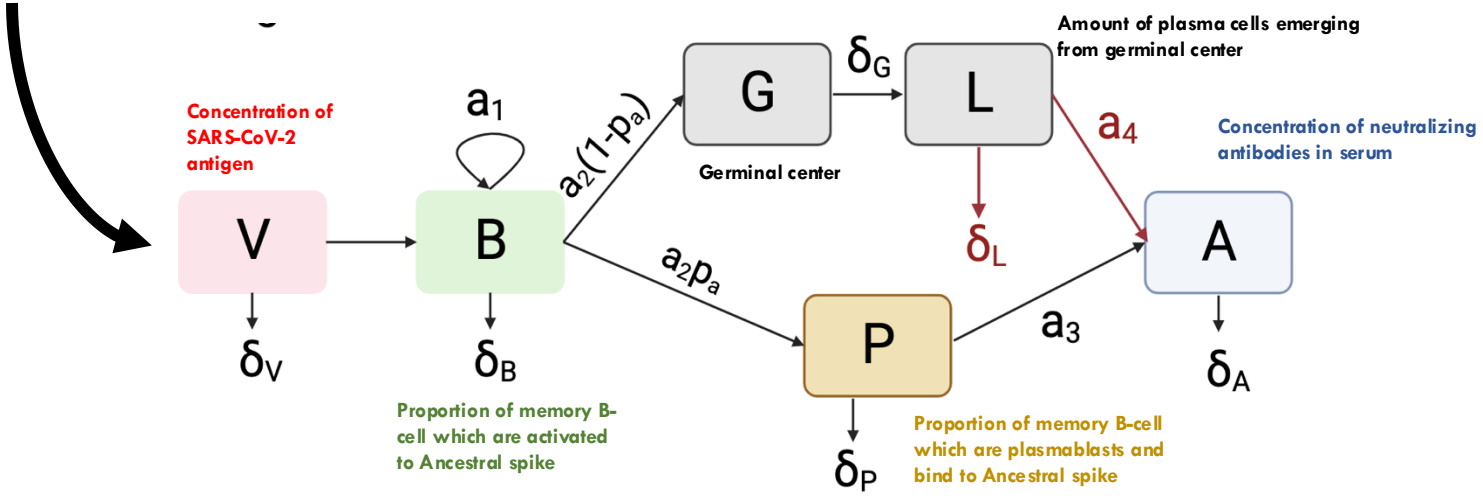
δ_V	Rate of decay of vaccine antigen	Uniform(1, 30) days
δ_B	Rate of decay of memory B-cells	~1000 days
δ_P	Rate of decay of plasmablasts	$N(4, 1)$ days
δ_G	Time for germinal centres to produce affinity maturated plasma cells	$N(14, 3)$ days
δ_L	Rate of decay of plasma cells	$N(730, 200)$ days
δ_A	Rate of decay of neutralizing antibodies	$N(30, 5)$ days

Methods: Model overview



Antibody production

Parameter	Description	Prior
a_1	**Immunogenicity of vaccine** Rate of proliferation of memory B-cells per vaccine dose per day	Uniform(0, 2)
a_2	Rate of differentiation of memory B-cells to plasmablasts/plasma cells per vaccine dose per day	Uniform(0, 1)
a_3	**Affinity of vaccine-induced antibodies from plasmablasts** Rate of production of neutralizing antibodies per conc. of plasmablasts per day	Uniform(0, 3)
a_4	**Affinity of vaccine-induced antibodies from plasma cells** Rate of production of neutralizing antibodies per conc. of plasma cells per day	Uniform(0, 1)
p_1	Proportion of differentiated memory B-cells which become plasmablasts	$N(0.6, 0.1)$



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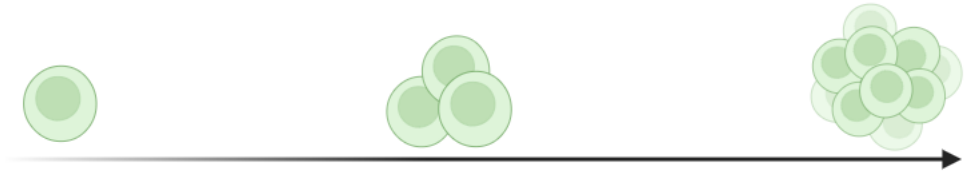
Methods: Interpretation of parameters

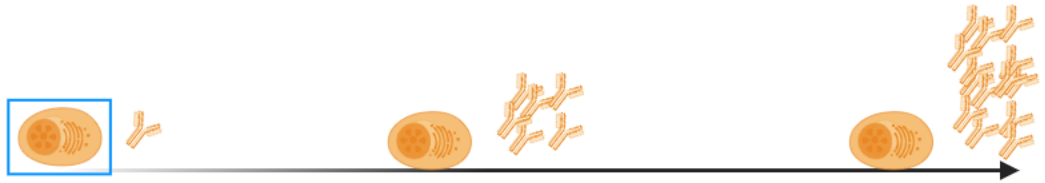
Immunogenicity of vaccine dose

a_1: Rate of proliferation of memory B-cells per vaccine dose per day



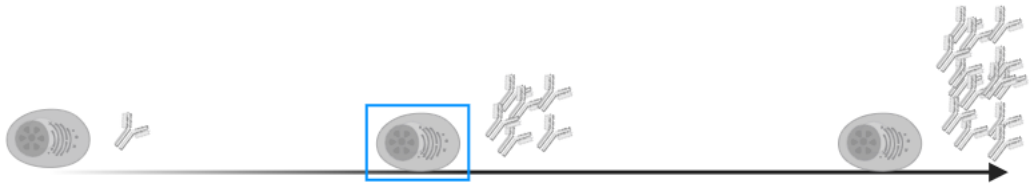
Affinity of antibodies from plasmablasts

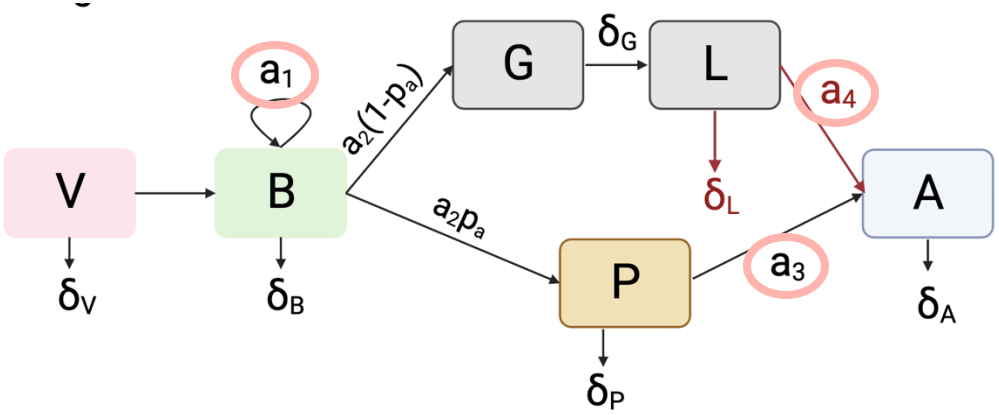
a_3: Rate of production of neutralizing antibodies per conc. of plasmablasts per day



Affinity of antibodies from plasma cells

a_4: Rate of production of neutralizing antibodies per conc. of plasma cell per day





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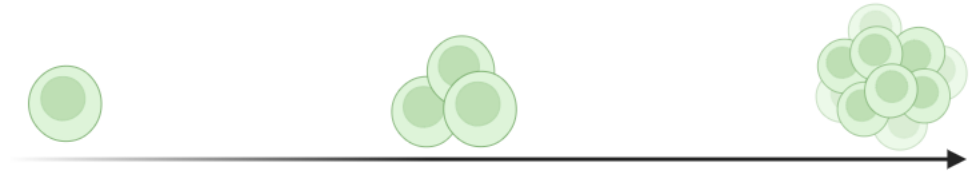

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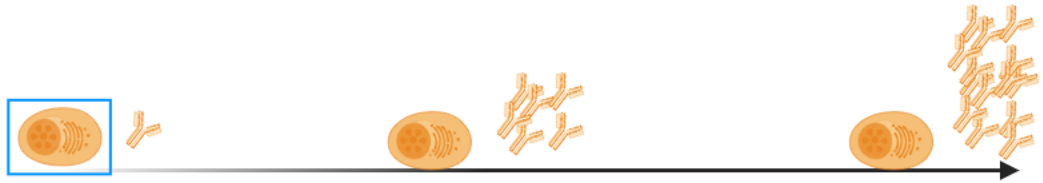

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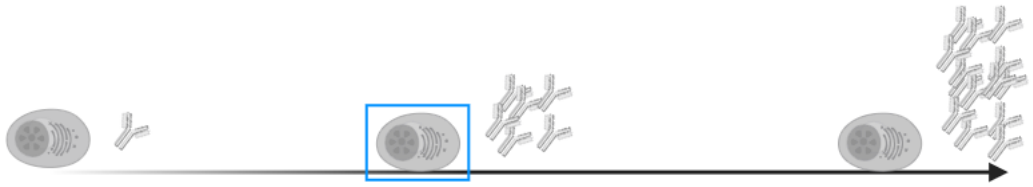

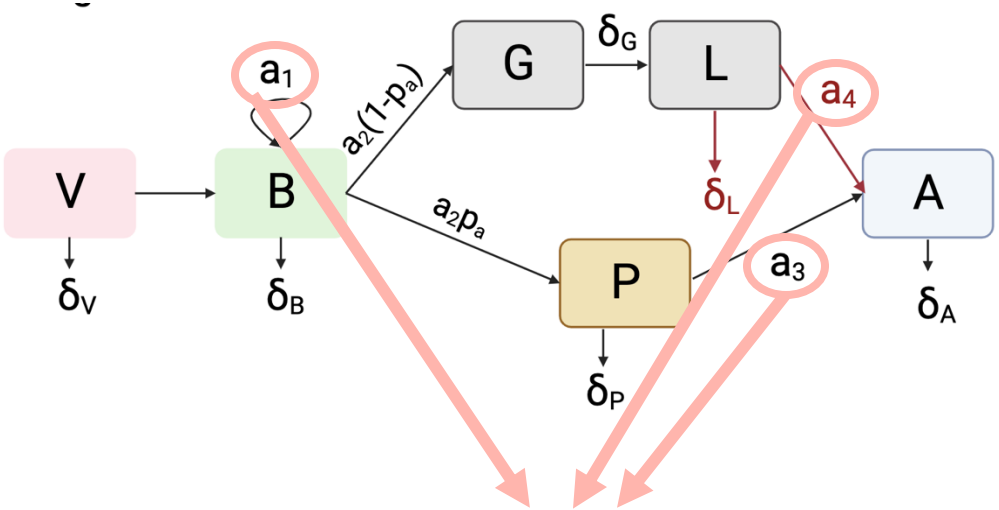

Hierarchical effects (mixed effects)

- Vaccine type, *v*, {AdV, mRNA}
- Time since last dose, *t*, {<28 days, ≥28 days}
- Age group, *a*, {<30, 30–39, 40–49, 50–59, 60+}
- Individual-level effects

See how immunogenicity + antibody affinity changes between individuals

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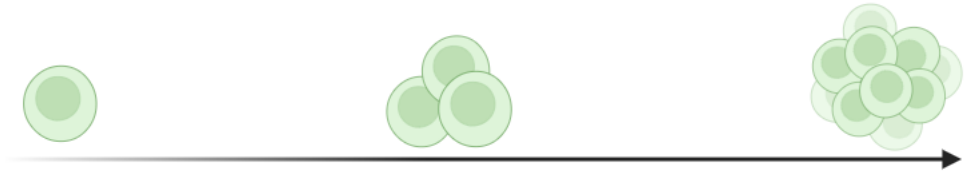

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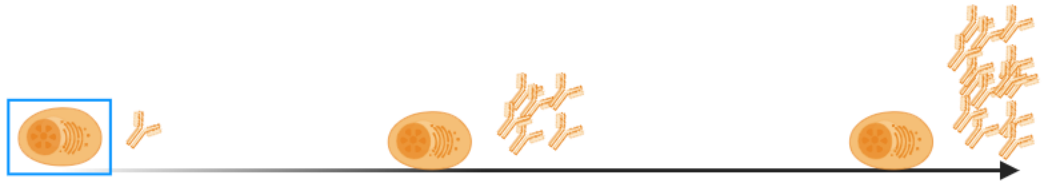

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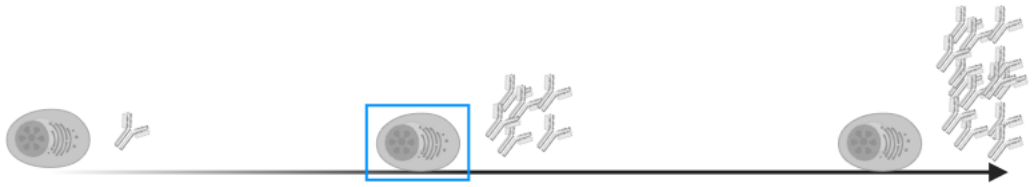

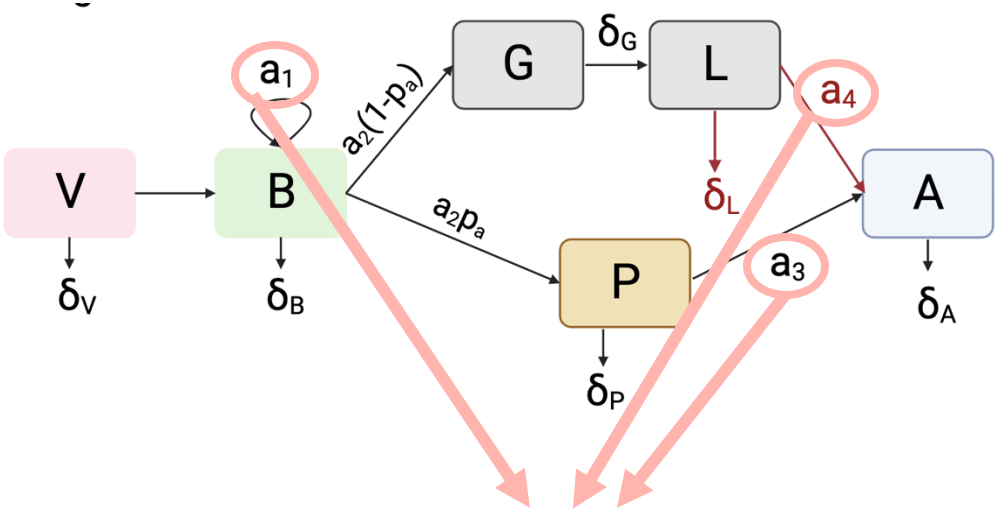

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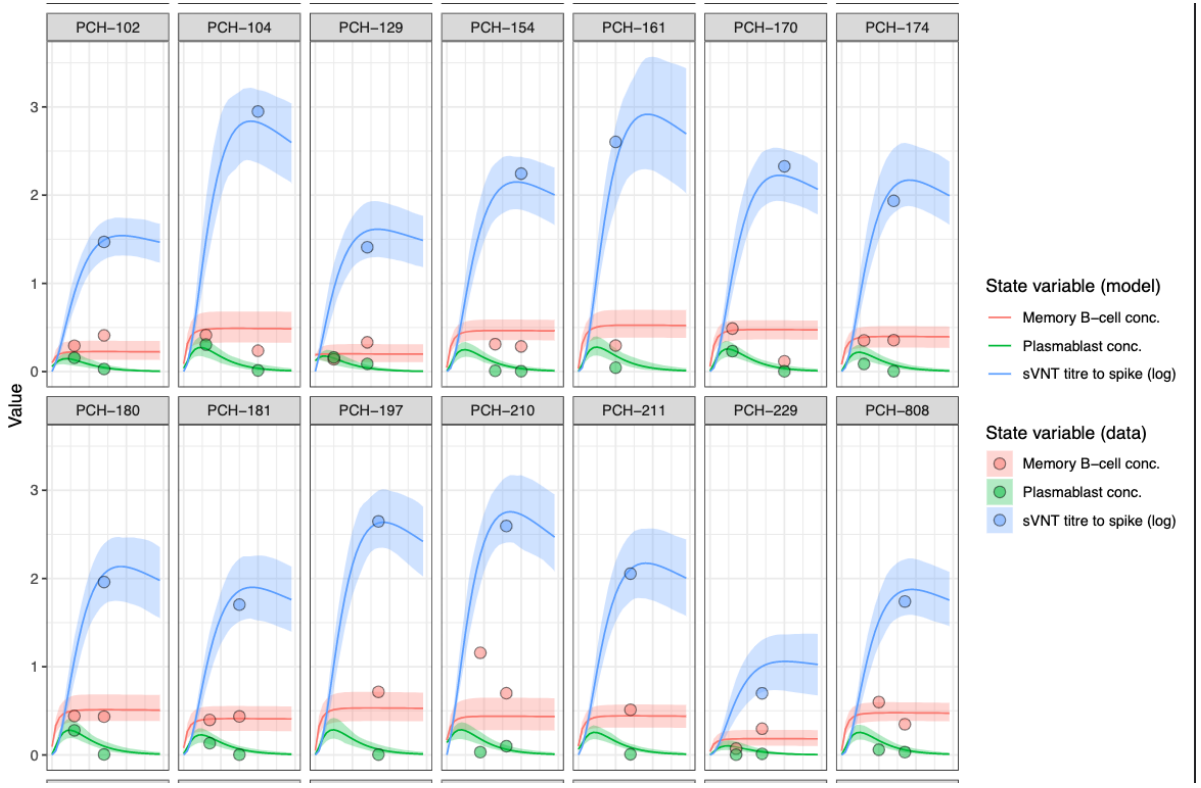
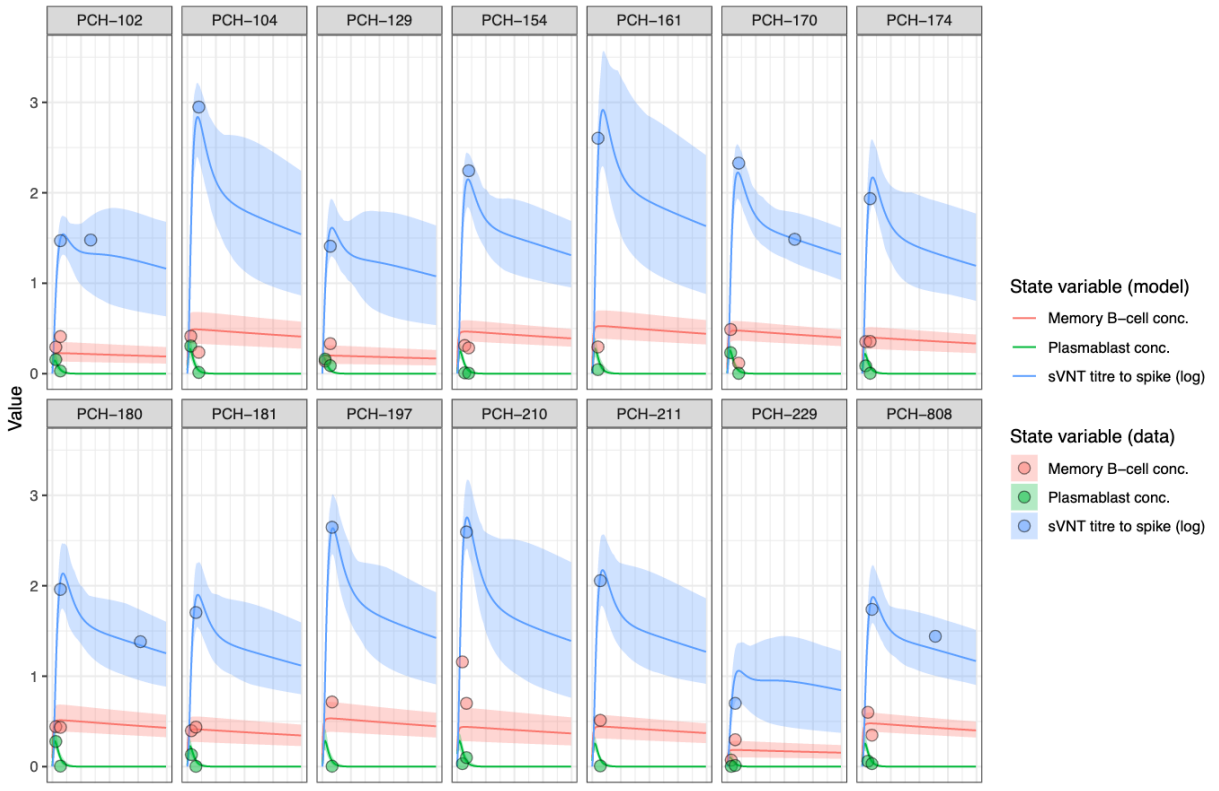
ODE with hierarchal effects fit to data using HMC in stan

Results: Individual-level fits

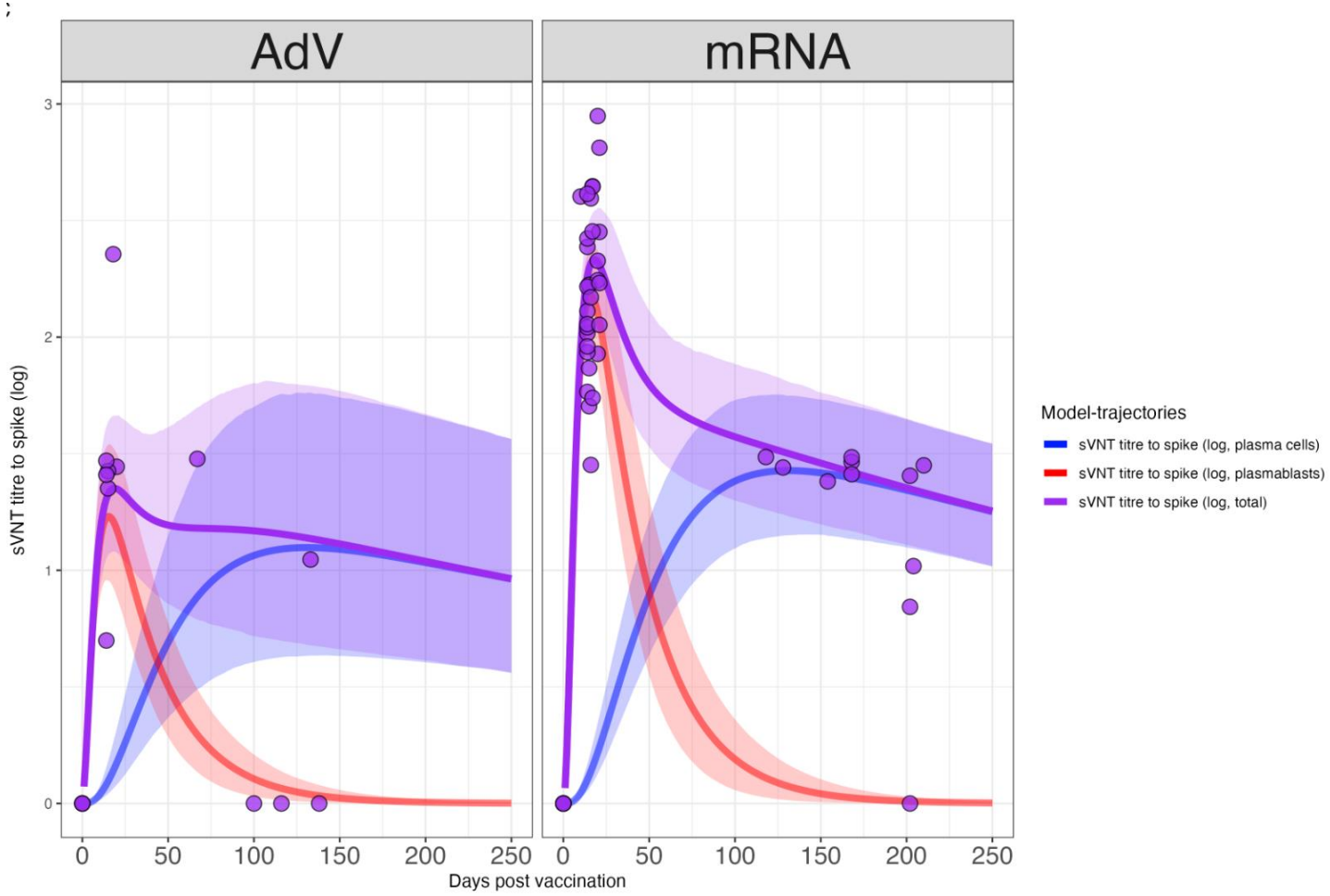
First 30 days

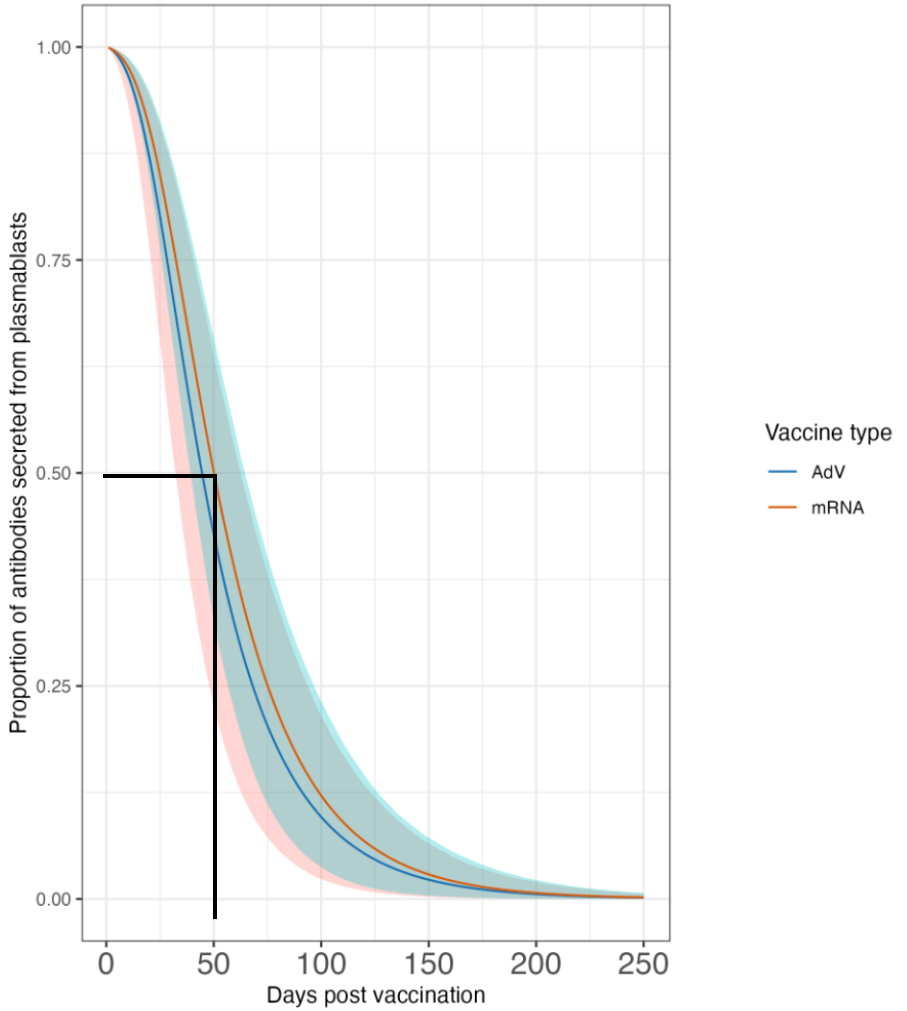


First 220 days



Results: Antibody kinetics inference

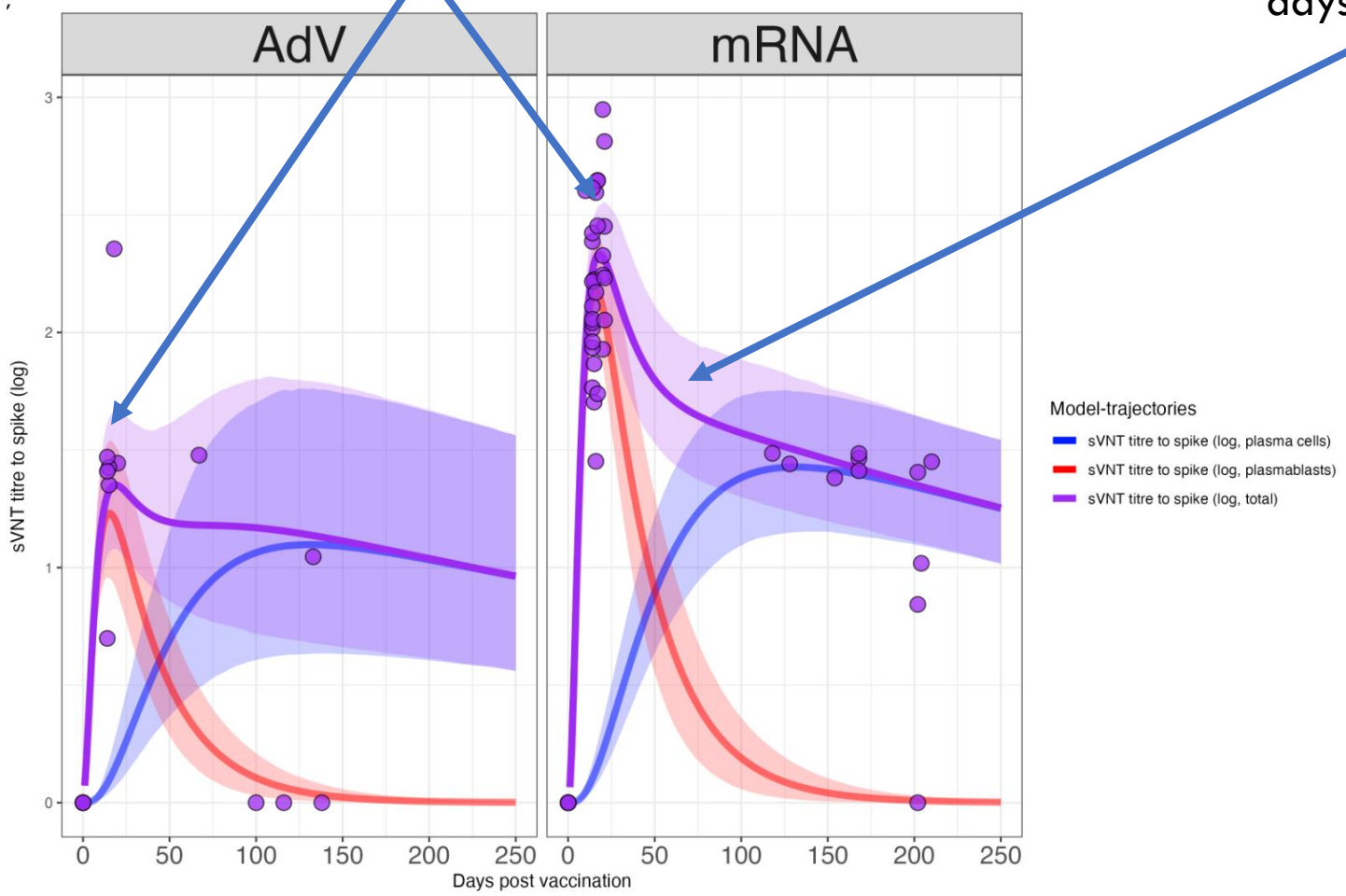


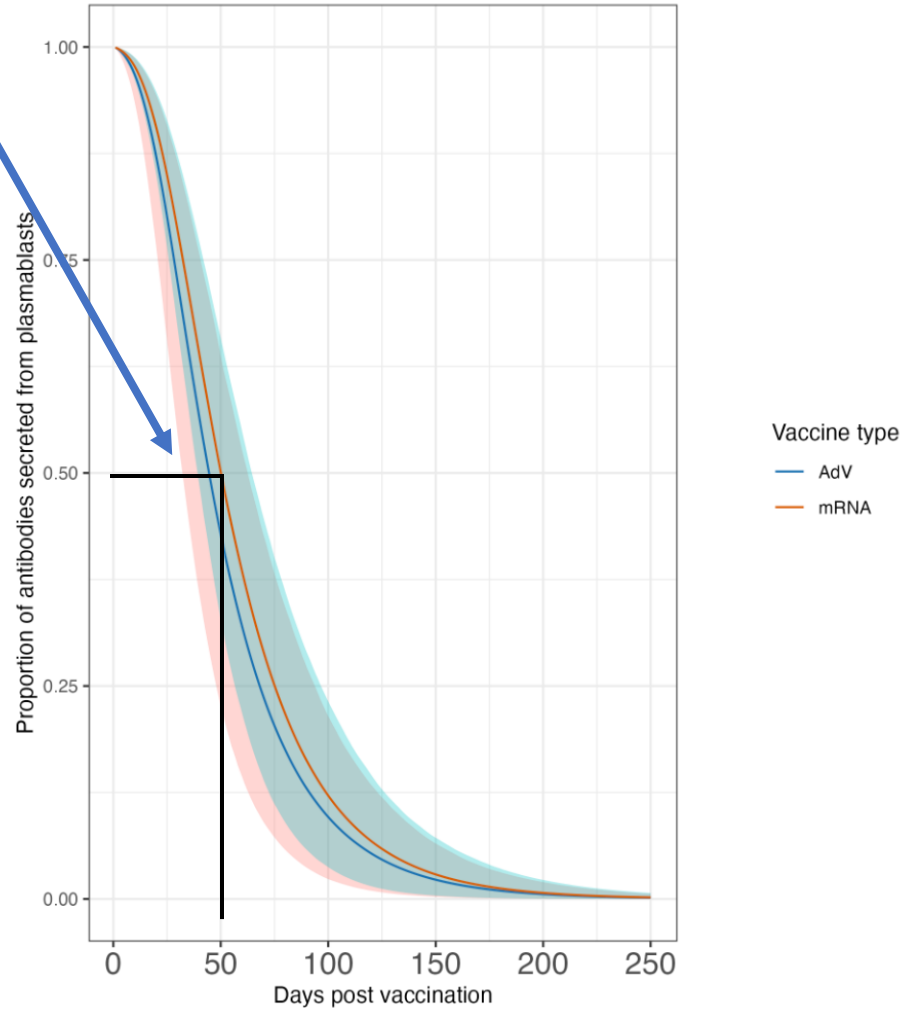


Results: Antibody kinetics inference

Antibody peak at ~14 post vaccination

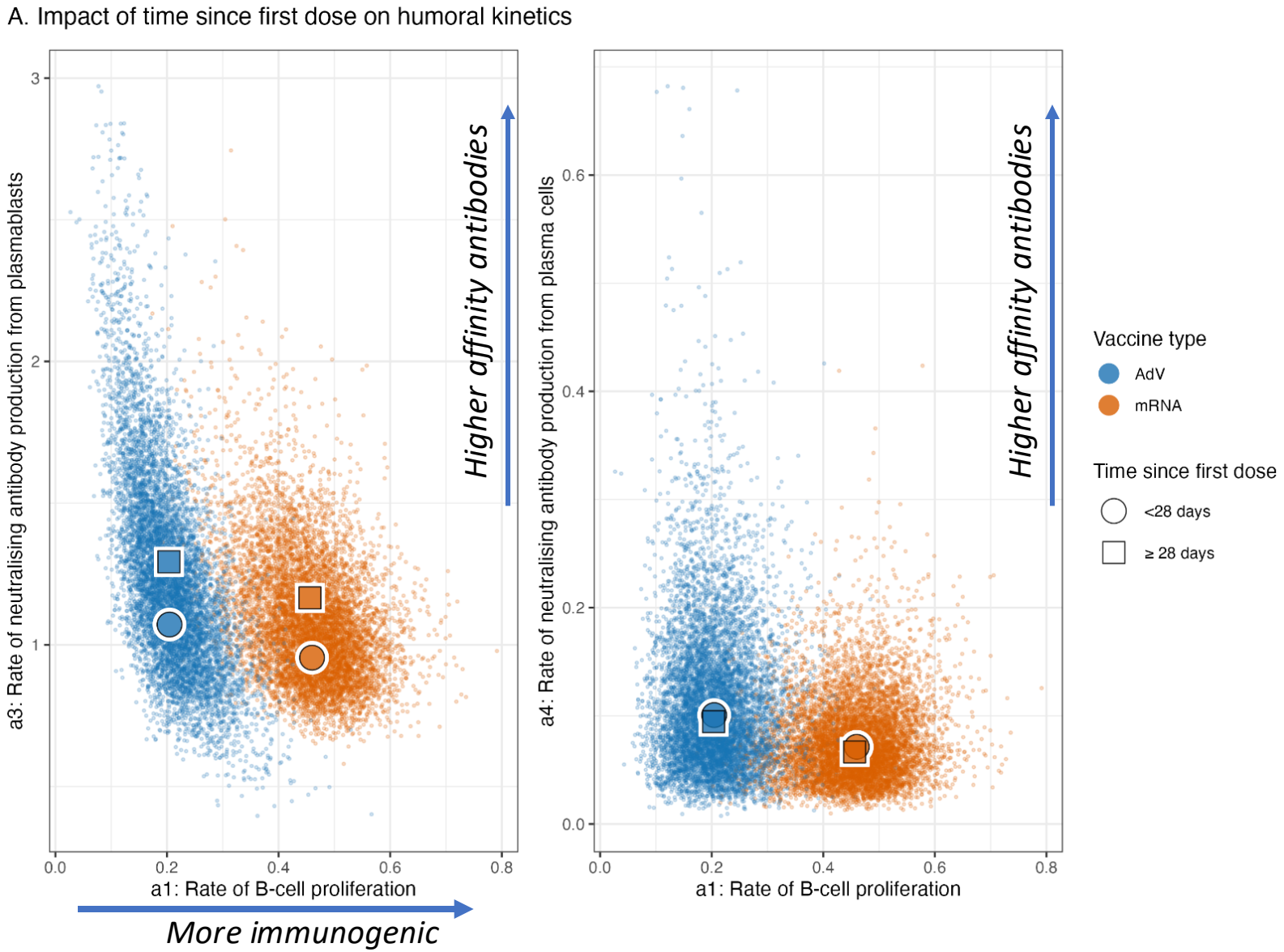
Plasma cell antibodies dominate response after 50 days





Results: Immunogenicity vs antibody affinity

- Marginal posteriors so adjusted for potential confounding



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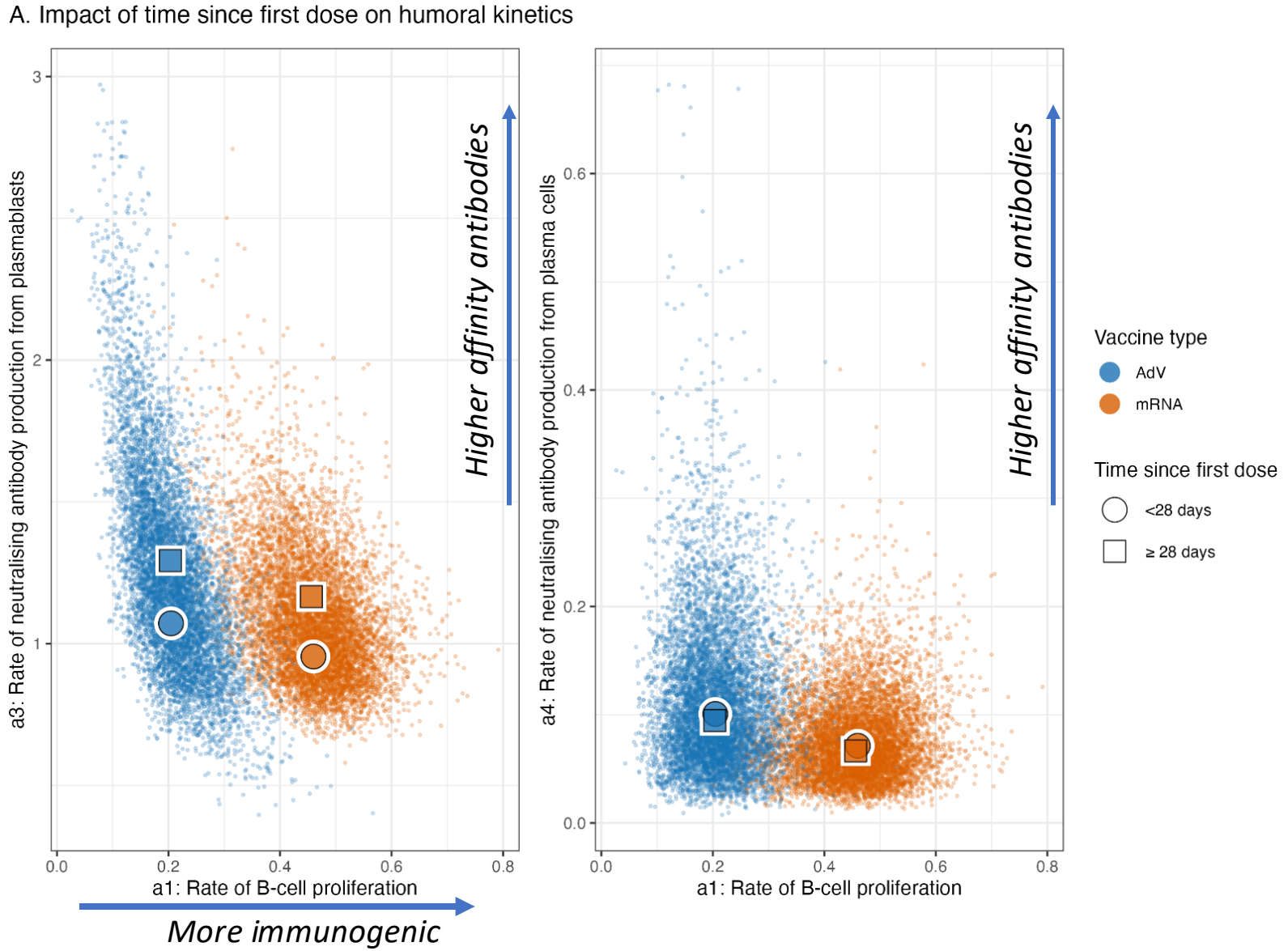
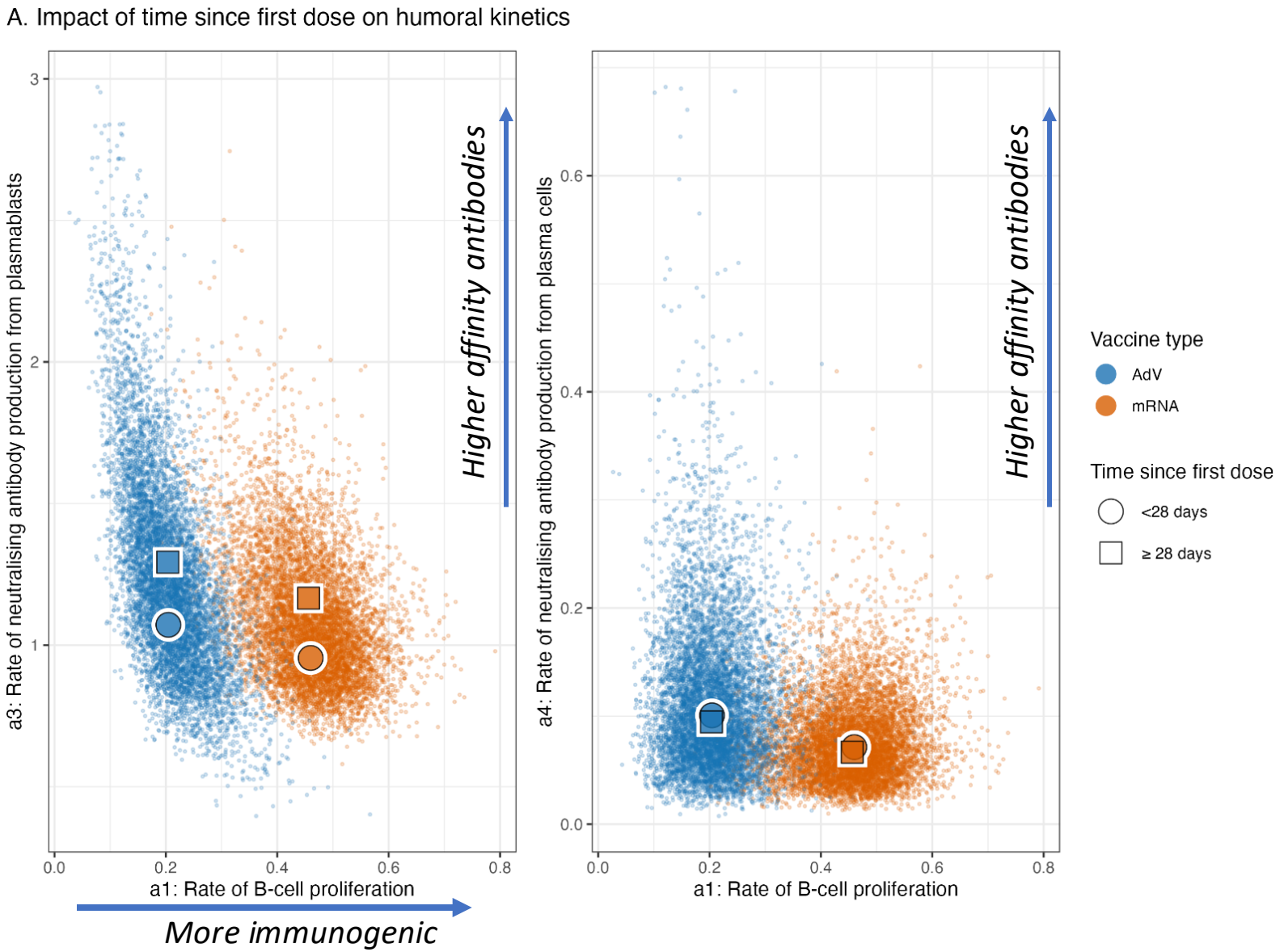


Results: Immunogenicity vs antibody affinity

- Marginal posteriors so adjusted for potential confounding
- mRNA 2.3 times immunogenic than AdV
- Longer between doses -> higher affinity antibodies from plasmablasts
- No strong effect of timing between doses and antibody affinity form plasma cells
- AdV has higher affinity antibodies than AdV?



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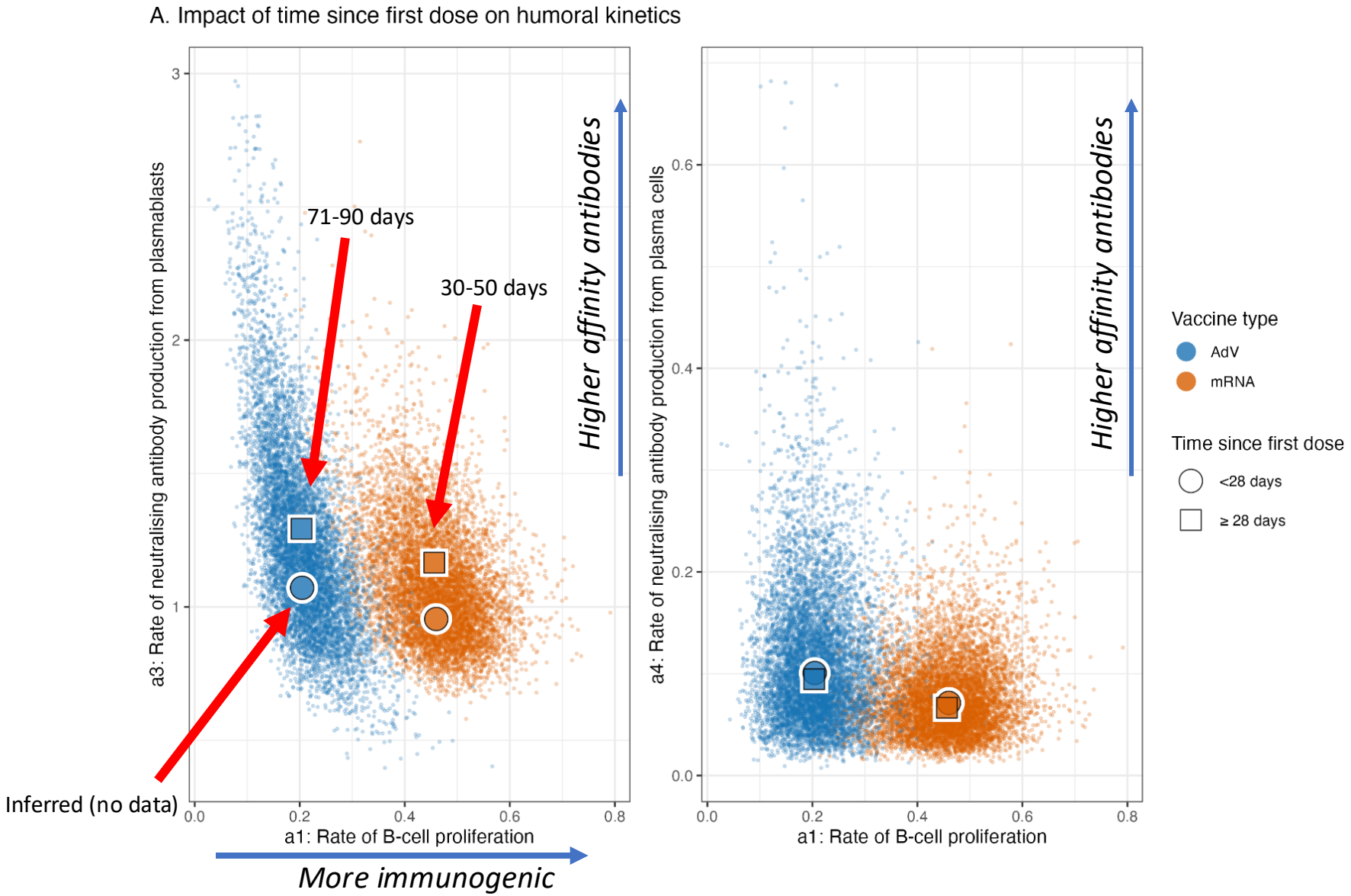
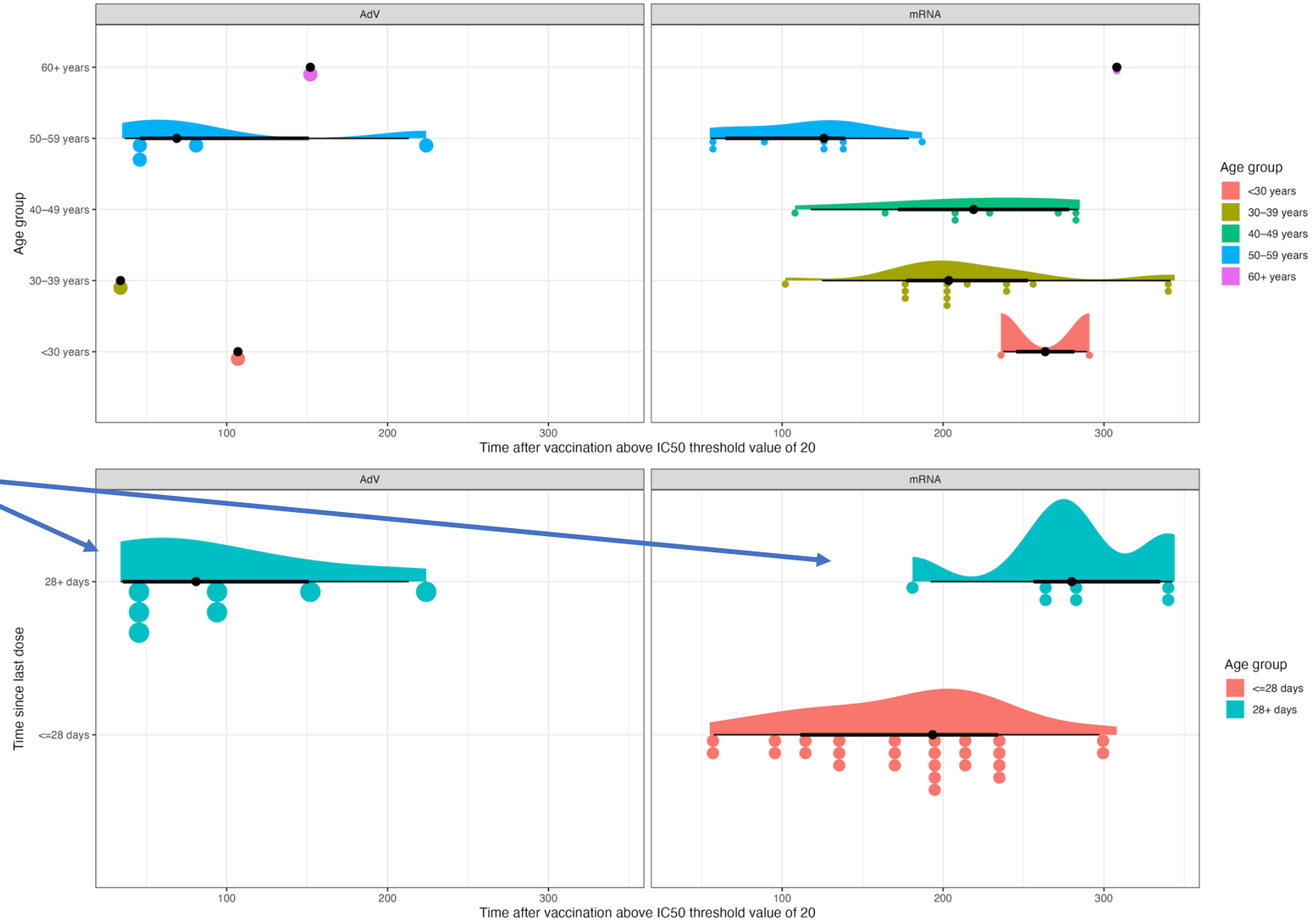


Results: Antibody persistence

mRNA with <28 days between doses provides longer protection than AdV with 3 months

Superior mRNA immunogenicity dominates responds, even if AdV has increased antibody affinity per plasmablasts



Take homes

ANTIBODY KINETICS

- Antibodies from plasma cells dominate the antibody response after ~50 days post-vaccination

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AdV vs mRNA

- mRNA stimulates B-cell proliferation 2-times higher rates than AdV
- Antibody affinity per plasmablasts is greater the longer between vaccine doses
  - It is difficult to determine which vaccine has superior antibody affinity due to confounding with duration between doses
- Despite higher levels of SHM and antibody affinity in AZ, the higher immunogenicity of mRNA vaccine provides more persistent antibody levels

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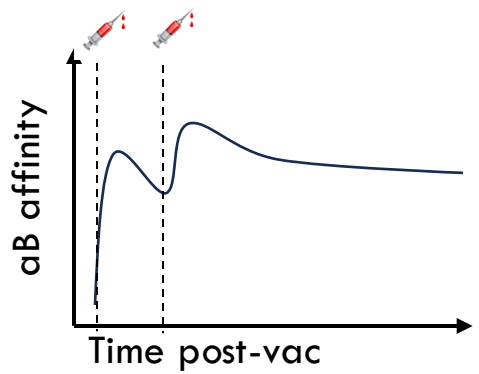
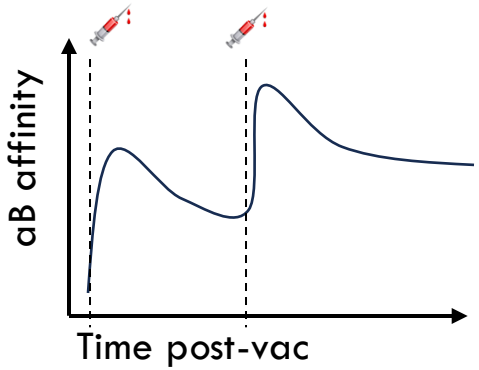
Mechanism behind high antibody affinity when longer between doses?





- Longer in germinal center means more somatic hyper mutation and affinity maturation
- Likely to produce high affinity antibodies when stimulated
- Better to be highly vaccinated with lower antibody affinity? Less vaccinated with better antibody affinity?

Looking forward

Similar data on infection with Omicron post third dose of vaccine

- Similar analysis on-going
- Understand the influence of vaccine type/timings, on immunogenicity and antibody affinity
- The added complexity of antigenic distance between B-cell populations and infecting antigen
- VERY HIGH immunogenicity compared to vaccination

Interested in applying data-driven ODEs to other immunological mechanisms as well.
Could have ODE data-drive approaches to:

- Cell-mediated immunity
- Antibody effector functions dynamics
- Innate immune dynamics

Let me know if you are interested!
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Acknowledgements

Data collection and serological analysis

WHO Collaborating Centre for Reference and Research on Influenza at the Victorian Infectious Diseases Reference Laboratory (VIDRL)

Prof. Sheena Sullivan
+ Team

Dr. Annette Fox Marsh
+ Team

Mathematical modelling

Prof. Adam Kucharski

david.hodgson@lshtm.ac.uk

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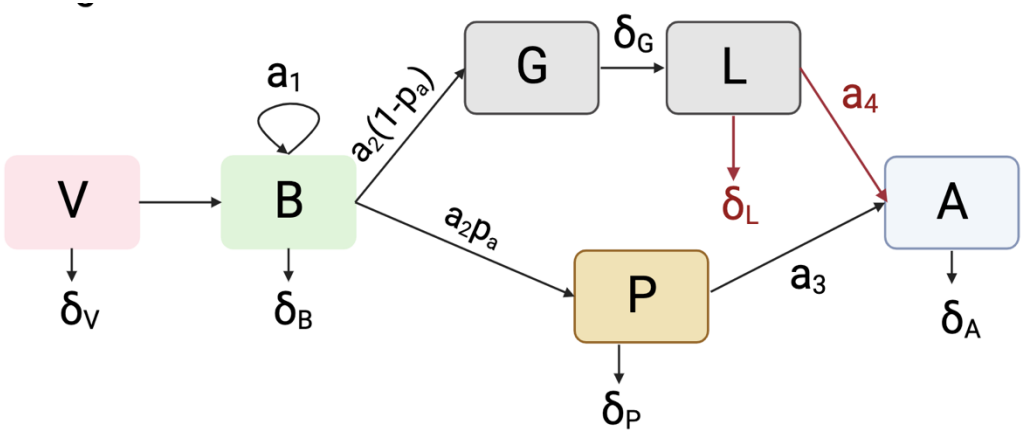


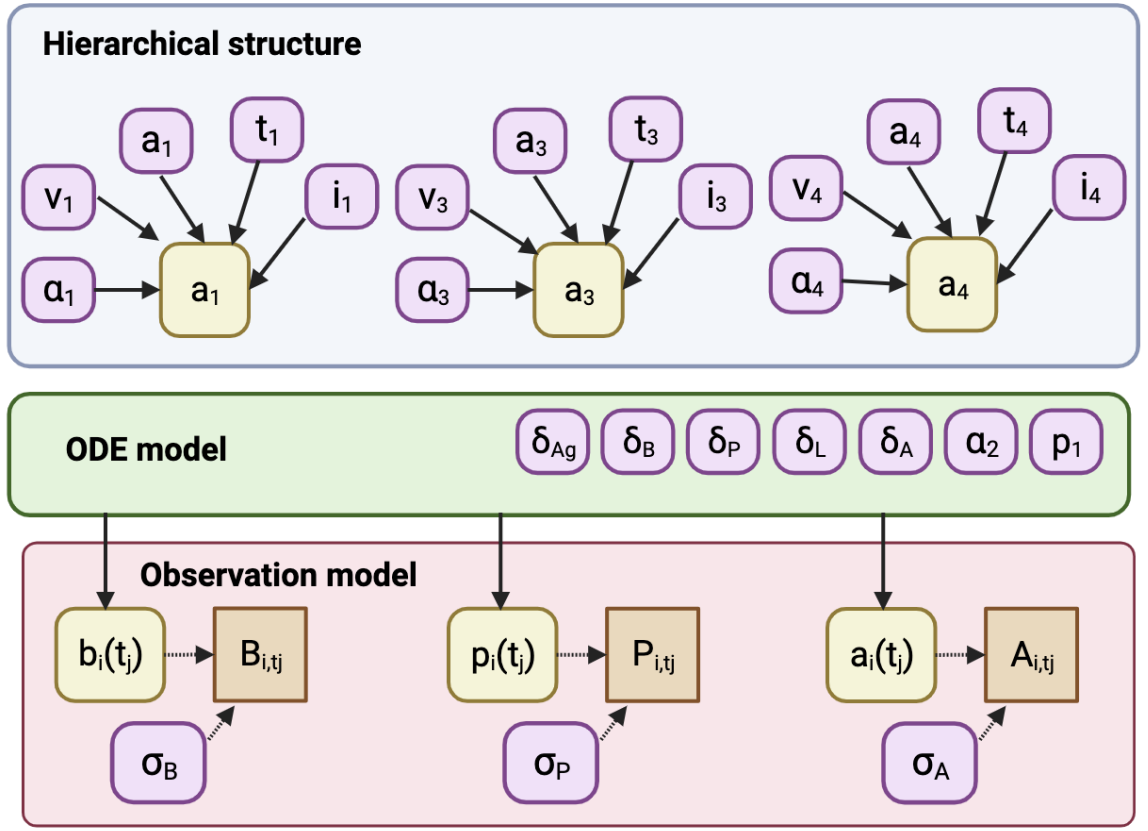
$$V = A_0 \exp(-t\delta_V),$$

$$\frac{dB_{mem}}{dt} = \exp(-t\delta_V)\tilde{a_1} - \exp(-t\delta_V)M\tilde{a_2} - M\delta_M,$$

$$\frac{dP}{dt} = \exp(-t\delta_V)M\tilde{a_2}p_a - \delta_P,$$

$$\frac{dL}{dt} = \exp(-t\delta_V)\tilde{a_2}(1-p_a),$$

$$\frac{dA}{dt} = a_3 P - A\delta_A,$$



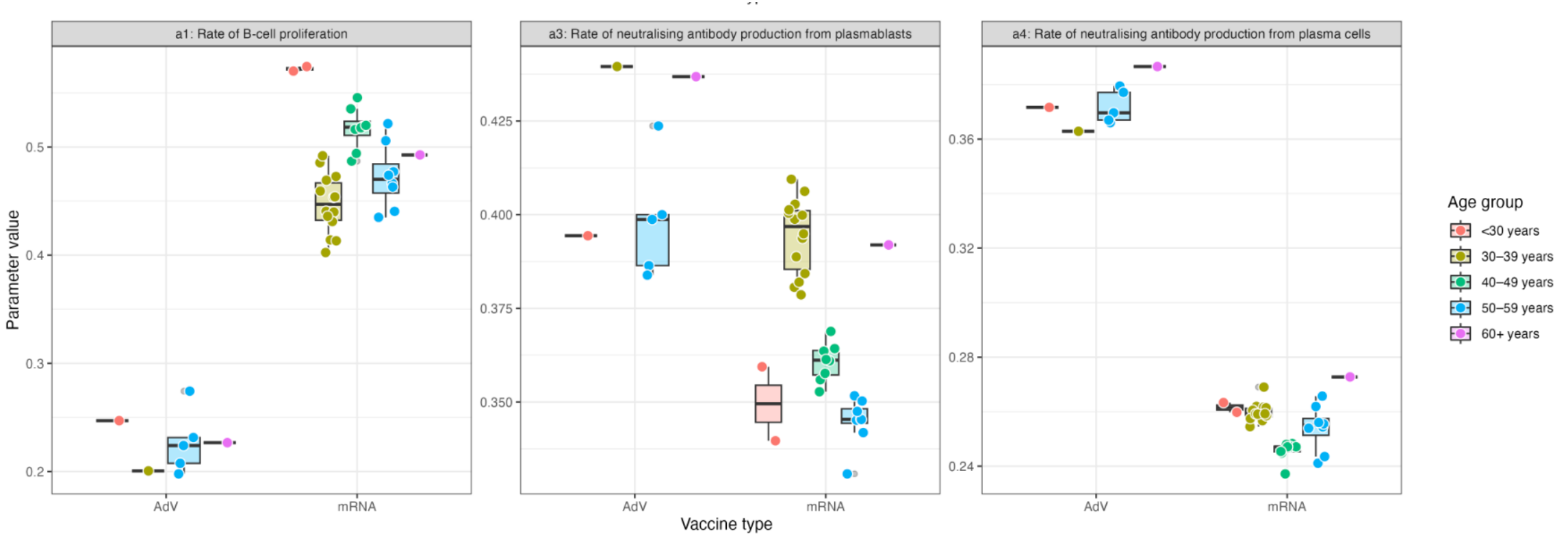
Deterministic relationships ⟶

$a_1 = \alpha_1 + v_1(v) + a_1(a) + t_1(t) + i_1(i)$

Stochastic relationships ⟶

$B_{i,tj} \sim Cauchy(b_j(t_j), \sigma_B)$ $P_{i,tj} \sim Cauchy(p_j(t_j), \sigma_P)$ $A_{i,tj} \sim Cauchy(a_j(t_j), \sigma_A)$

Results: Effect of age

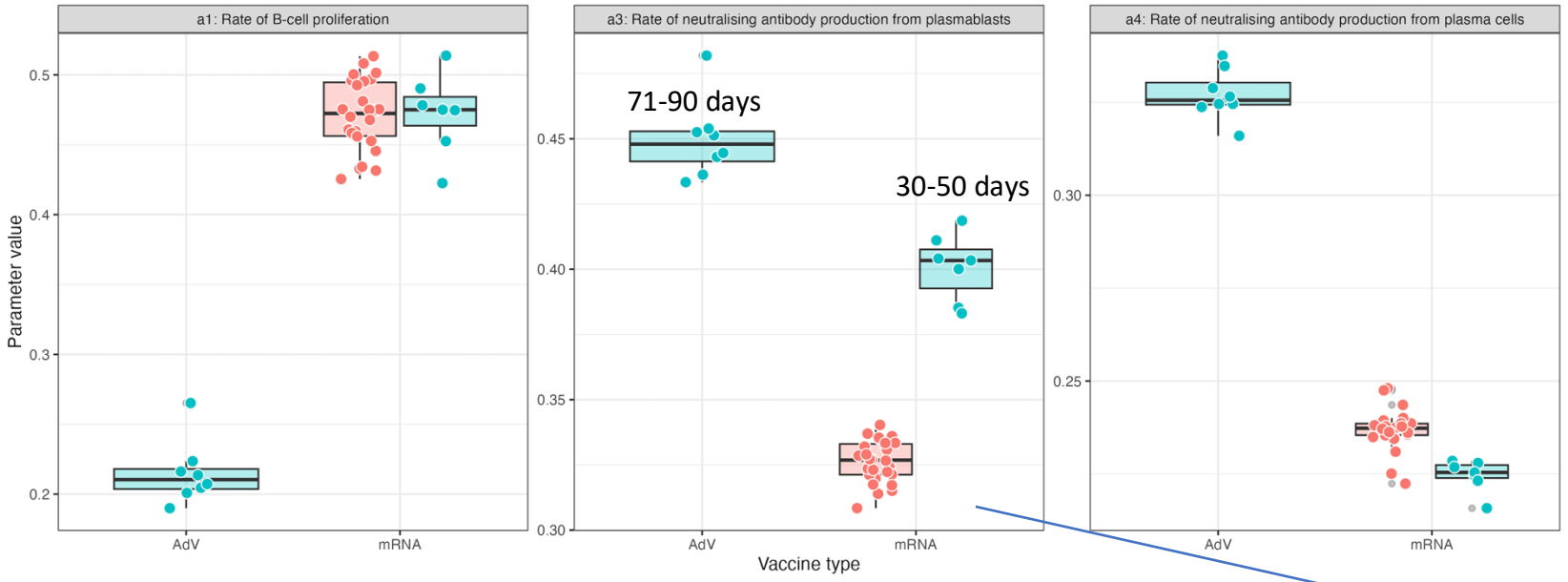


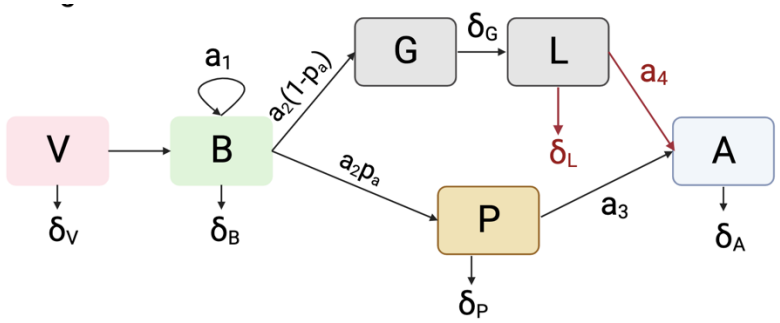
Immunogenicity and antibody affinity doesn't seem to have an age trend

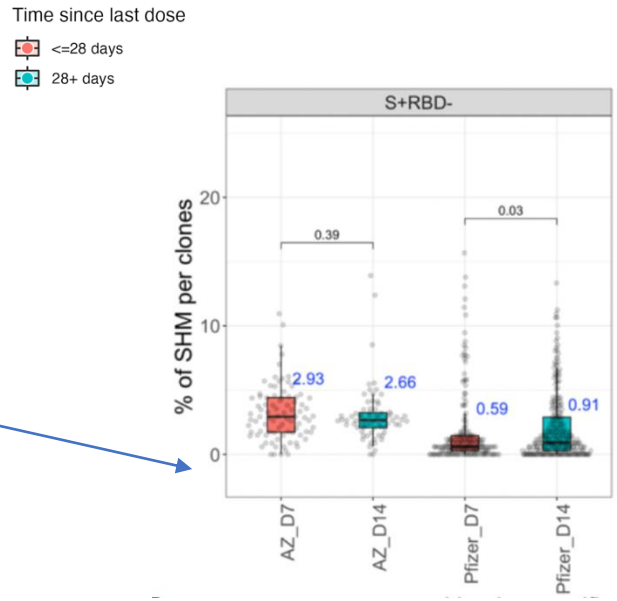
Most people 30–60 years old.

Results: Impact of time since last dose

- Individual-level effects (may be confounded)







High antibody affinity and somatic hypermutation for AdV compared to mRNA may be driven by longer time between vaccine doses

Methods: Impact of covariates

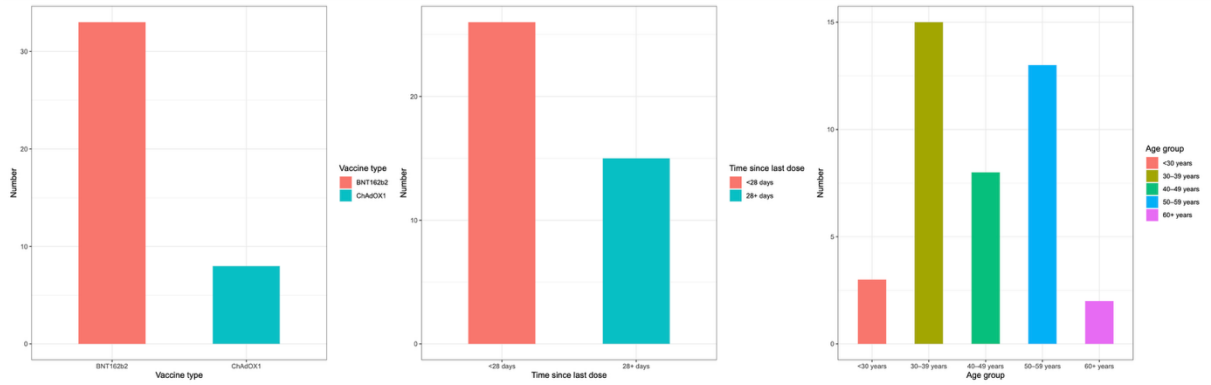
41 individuals with B-cell + sVNT titres

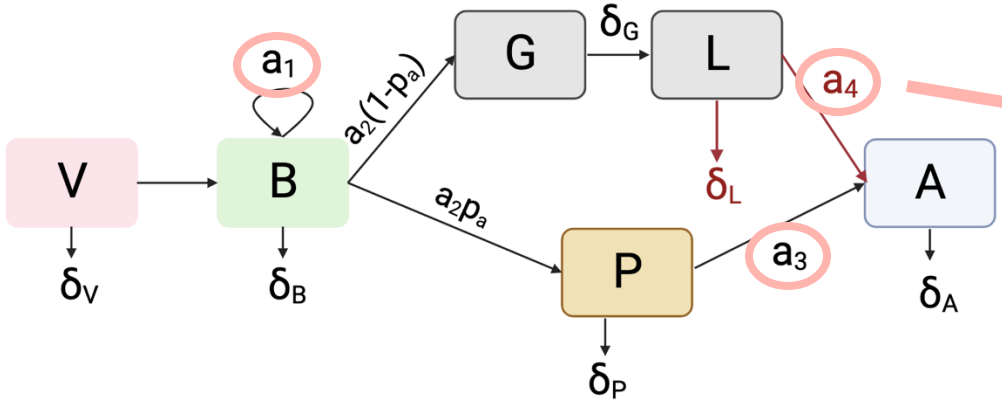
Covariates considered

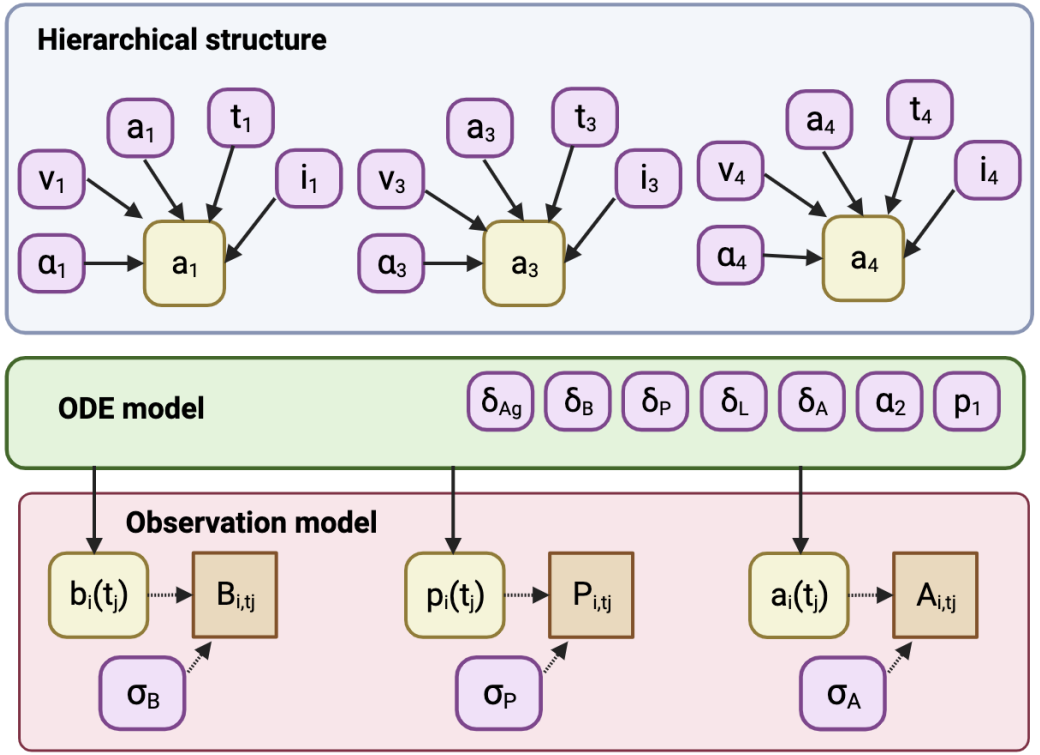
Vaccine type, v, {AdV, mRNA}

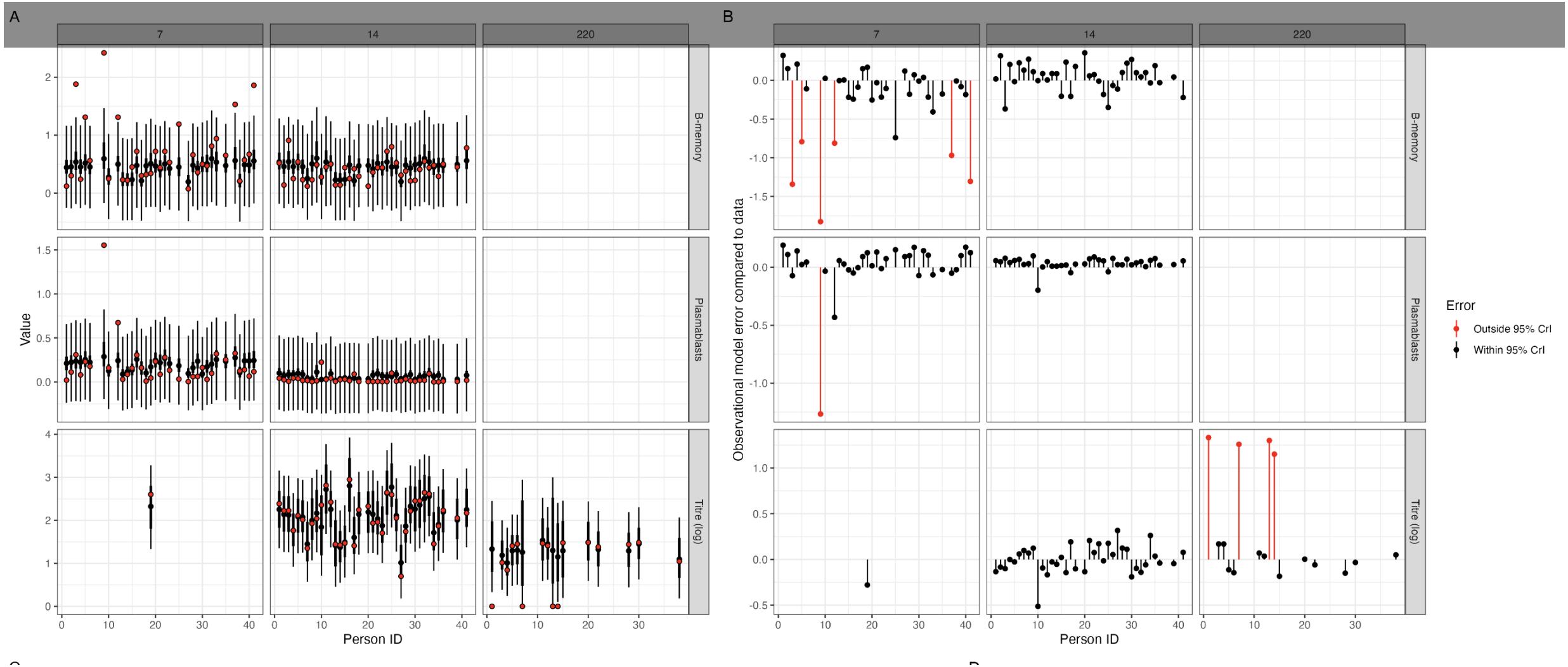
Time since last dose, t, {<28 days, ≥28 days}

Age group, a, {<30, 30–39, 40–49, 50–59, 60+}








A
B
7
14
220
B-memory
Plasmablasts
Titre (log)
Value
Person ID
Observational model error compared to data
Error
Outside 95% CrI
Within 95% CrI