Post-vaccine HAI antibody kinetics are driven by pre-existing immune status

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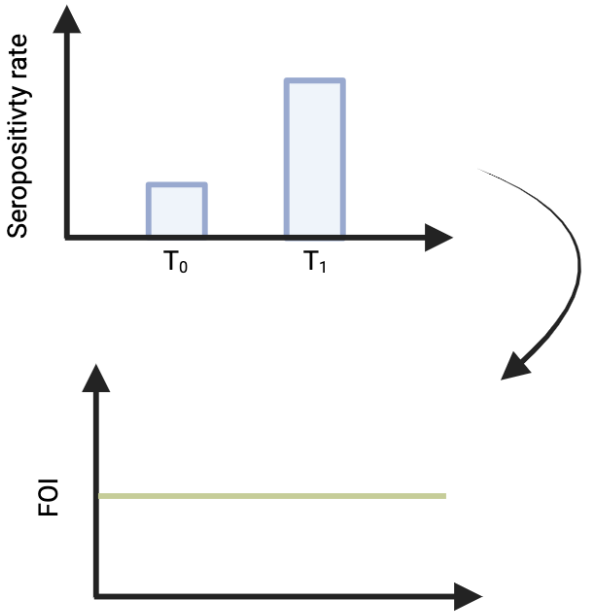
ESWI 2023
19/09/23

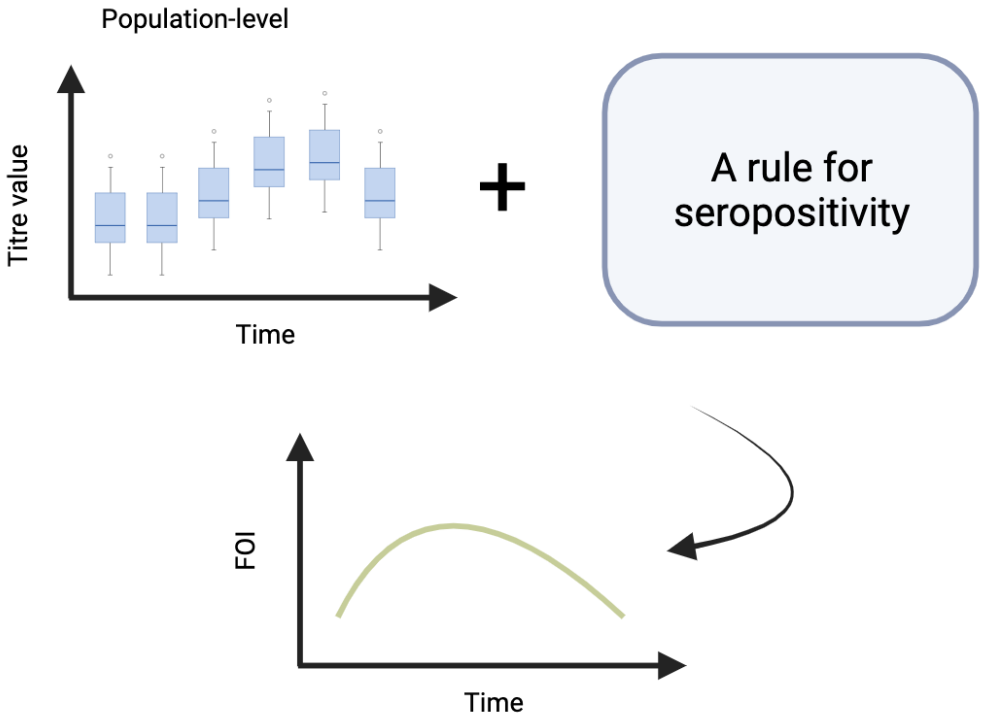
Motivation

Longitudinal serological studies useful in epidemiology

Sterilising immunity
(e.g. measles)



Temporary immunity (e.g. flu)

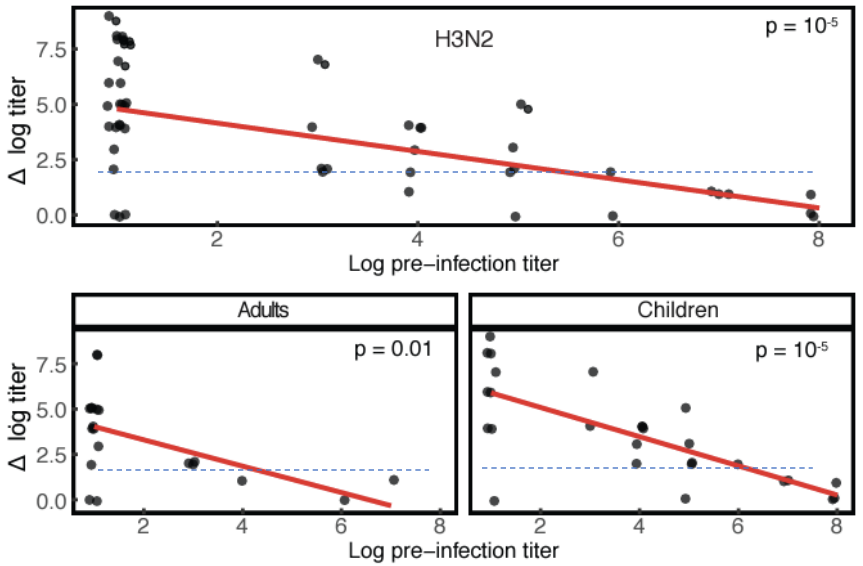


Motivation

Serological heuristics for Influenza

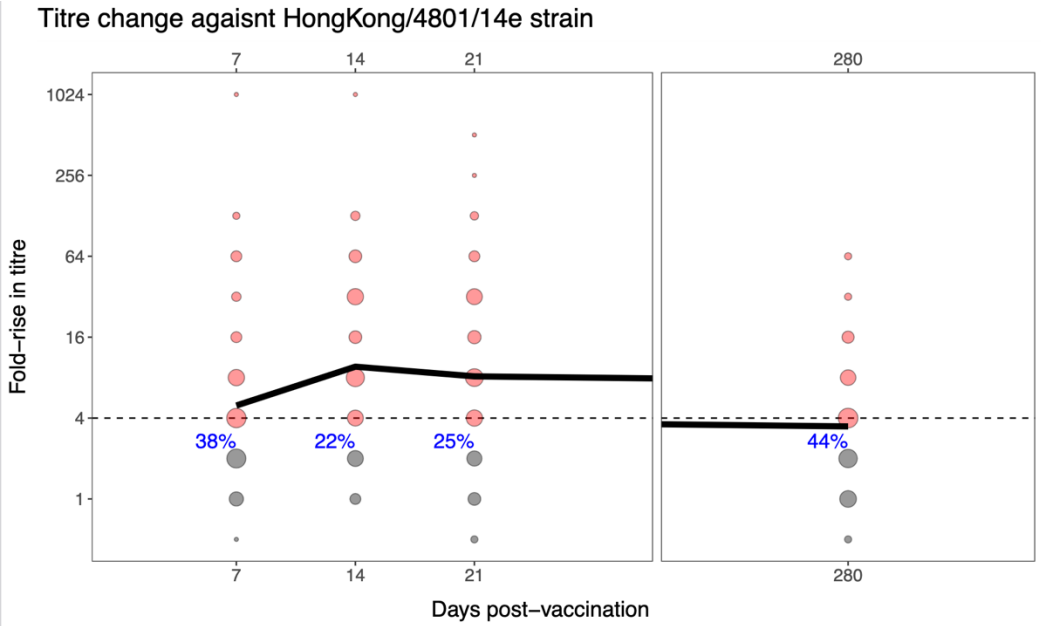
- **Seroconversion:** ≥ 4-fold rise in HAI titre
- **Protection:** HAI titre ≥ 1:40

Response to infection



Ranjeva et al. 2019 *Nat Comms*

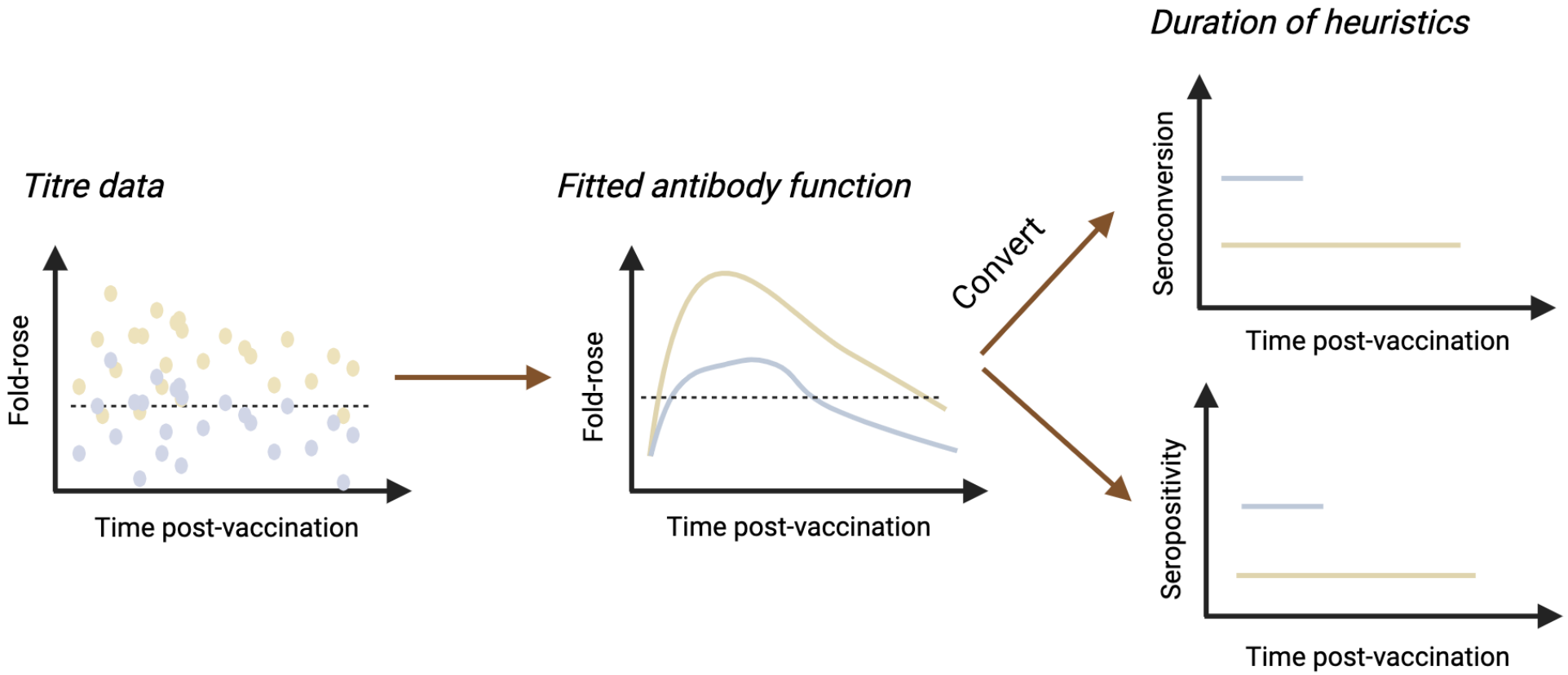
Response to vaccination



Auladell et al. 2022 *Nat Med*

Motivation

Taking longitudinal serological data:



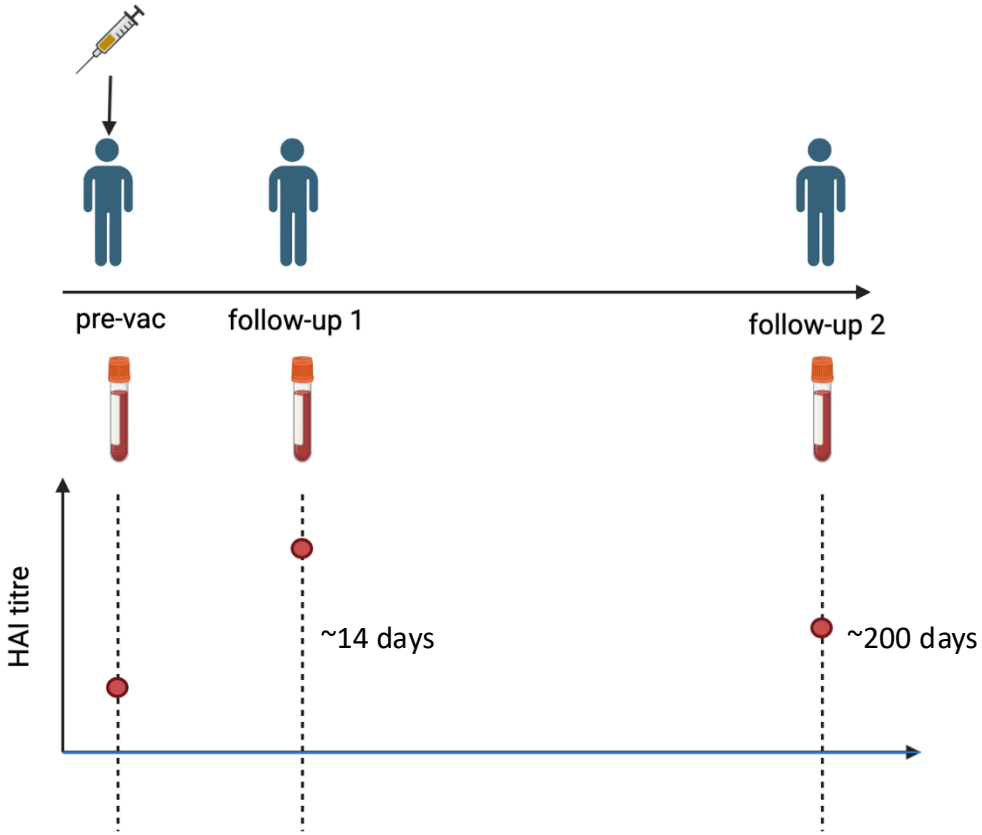
Methods: Data

Data from on-going NIH study in Australia [1]

- Healthcare workers, aged 20–65 years
- Vaccinated with quadrivalent Influenza vaccine
- Three seasons; 2020–2022
- 4,958 samples from 1,646 individuals
- Three strain types were tested for HAI titre:

	2020	2021	2022
A(H1N1) vaccinating	A/Brisbane/02/2018e	A/Victoria/2570/2019e	A/Victoria/2570/2019e
A(H3N2) vaccinating	A/South Australia/34/2019e	A/Hong Kong/2671/2019e	A/Darwin/09/2021e
A(H3N2) circulating	A/South Australia/34/2019	A/Darwin/726/2019	A/Darwin/09/2021

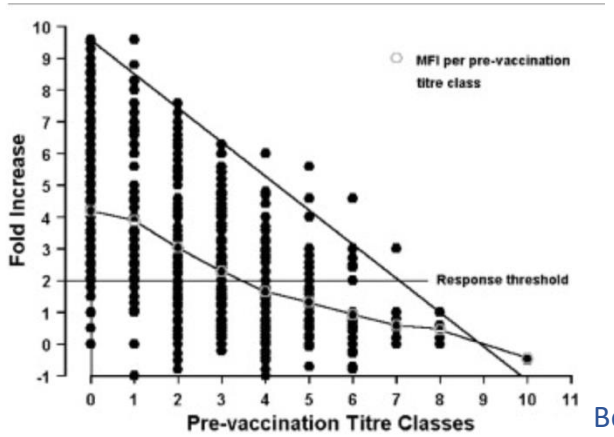
Schematic showing serological testing protocol



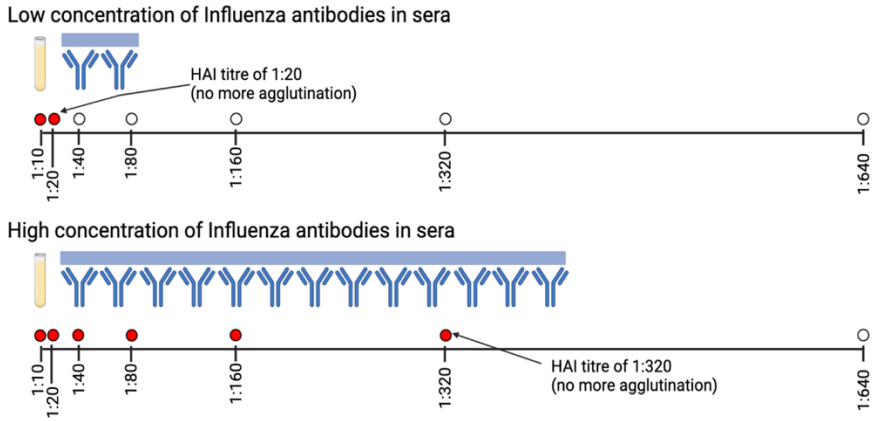
Clinical Trial: NCT05110911

Methods: Covariates considered

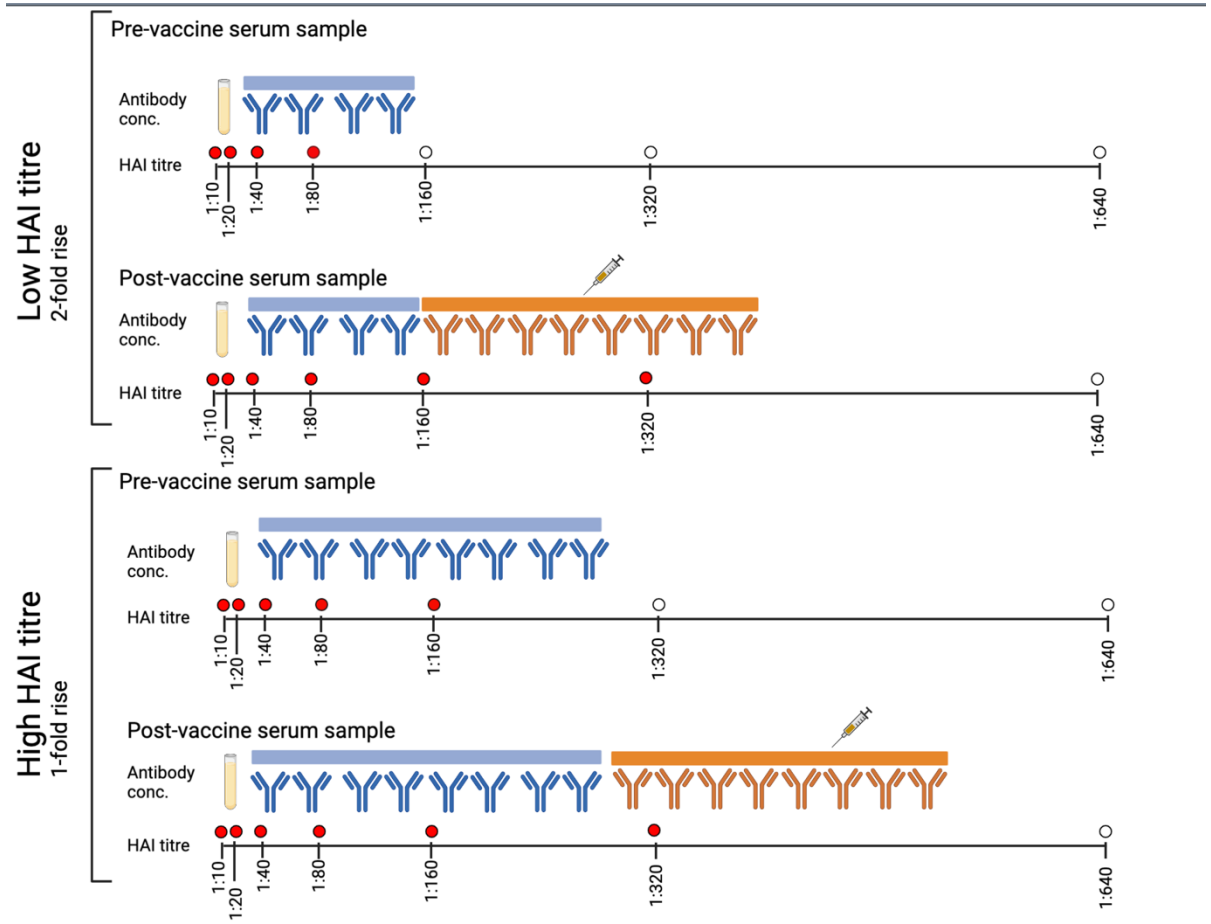
- **Pre-existing immune status** e.g. Current HAI titre to Influenza strain:



Beyer et al. 2004 *Virus Res*

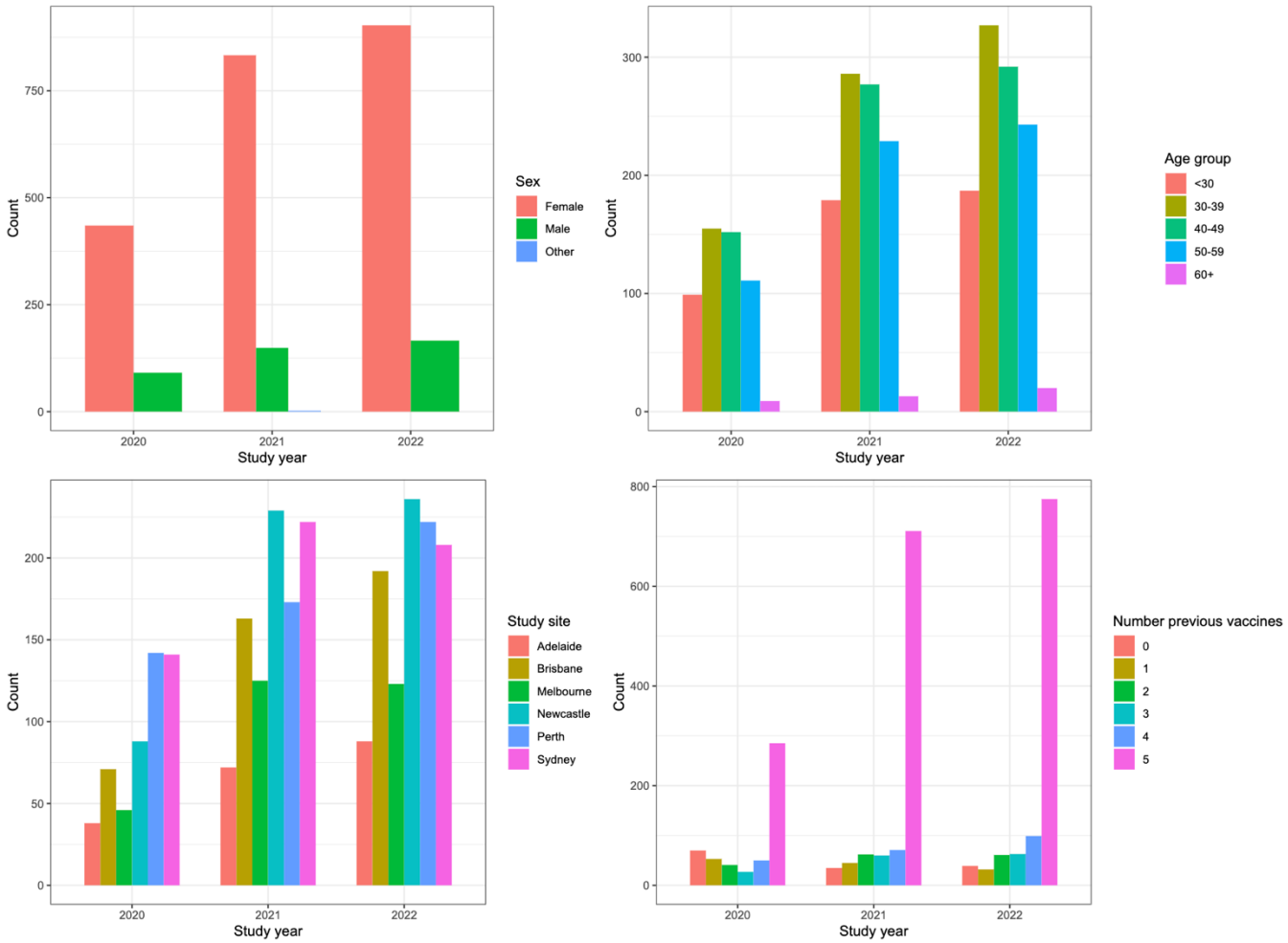


Post-exposure



Methods: Covariates considered

- **Pre-vaccination titre**
  - <1:10, 1:10, … 1:2560
- **Age group**
  - <30, 30–39, 40–49, 50–59, 60+
- **Sex**
  - Male, Female, Other
- **Study site**
  - Adelaide, Brisbane, …
- **Vaccination history**
  - 0, 1, 2, 3, 4, 5



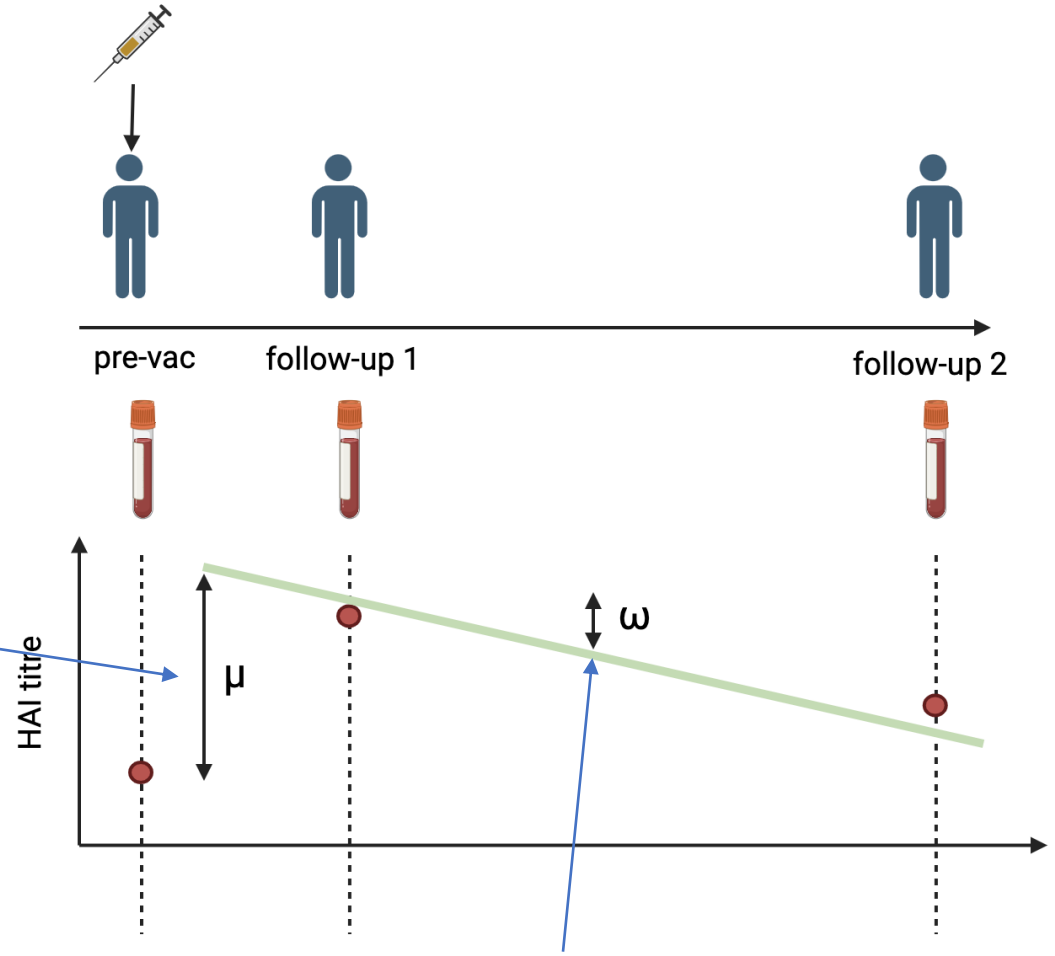
- **Season**—don't stratify by this as interested in mean effects

Methods: Inference rules

- Use a Bayesian hierarchical model which quantifies the individual-level kinetics of antibody boosting
- Boosting depends on;
  - Pre-vaccination HAI titre
  - Age
  - Study site
  - Sex
  - Vaccination history

- A covariate is significant if the marginal posterior distributions of the levels are significantly different (CrI don't overlap)

- Seroconversion: 4-fold rise
- Seropositivity: ≥ 1:40

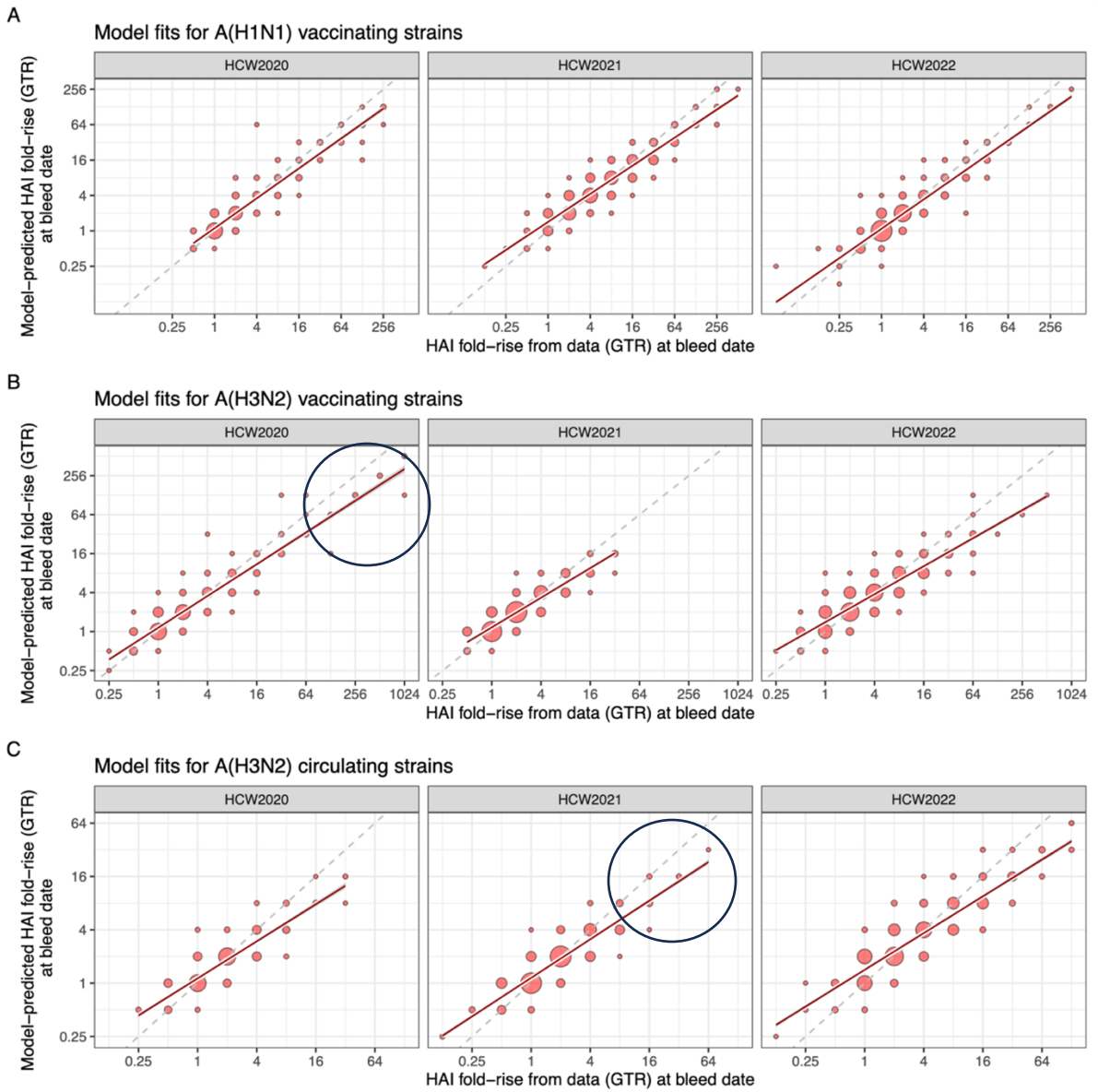


- Waning depends on Pre-vaccination HAI titre

Results: Model Fits

- Approx 96% of samples are within 1-fold error

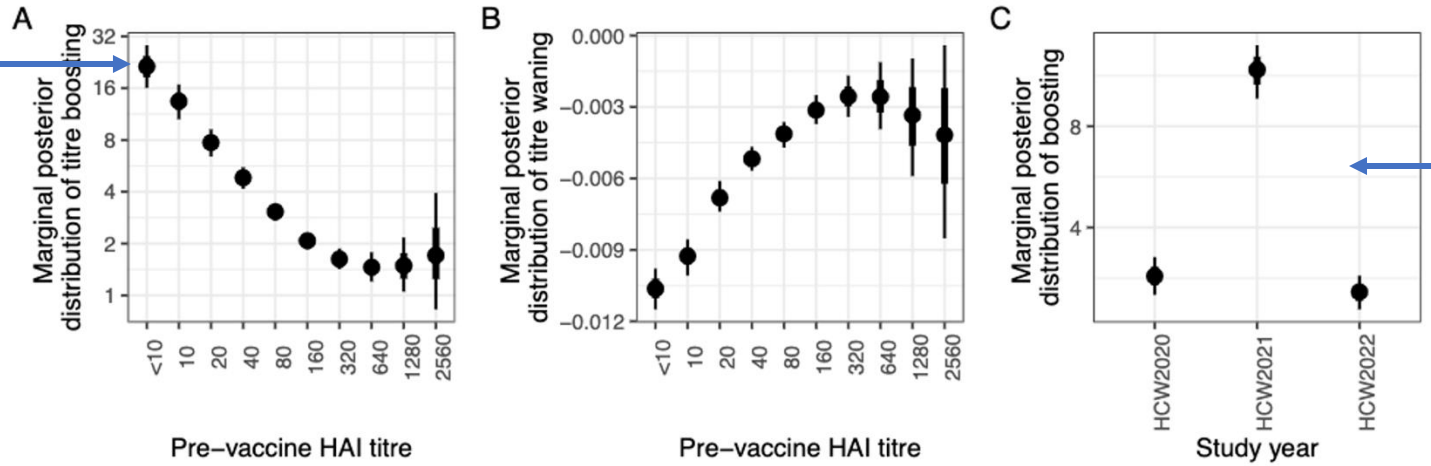
- Struggles most to capture very high titres boost



Results: Significance

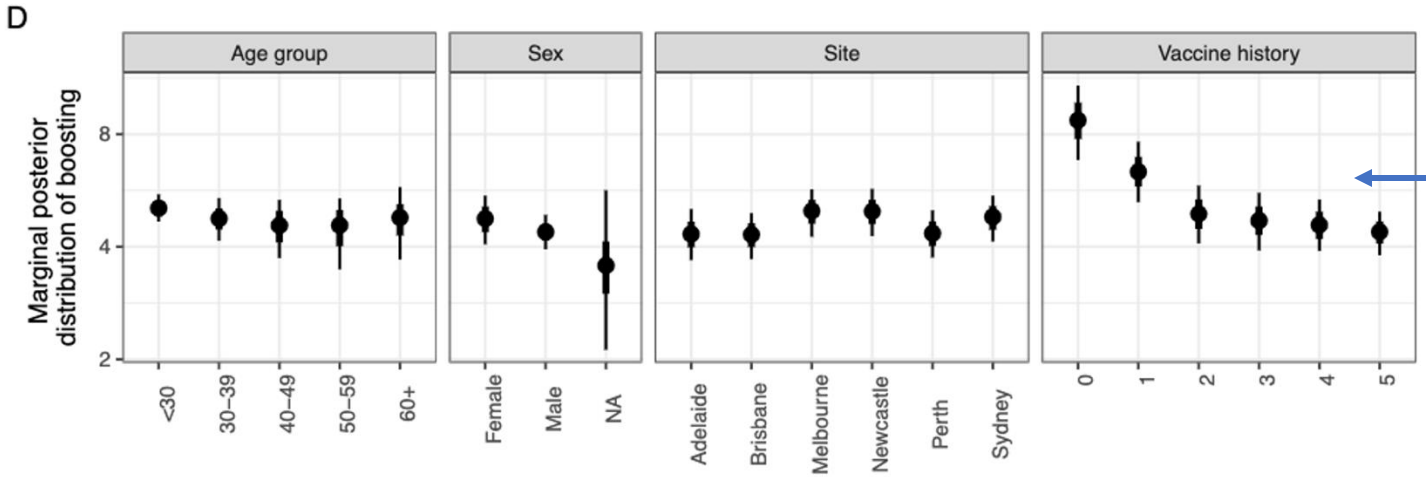
Marginal posterior distributions for A(H1N1) vaccinating:

Pre-vaccination titre significant effect on boosting



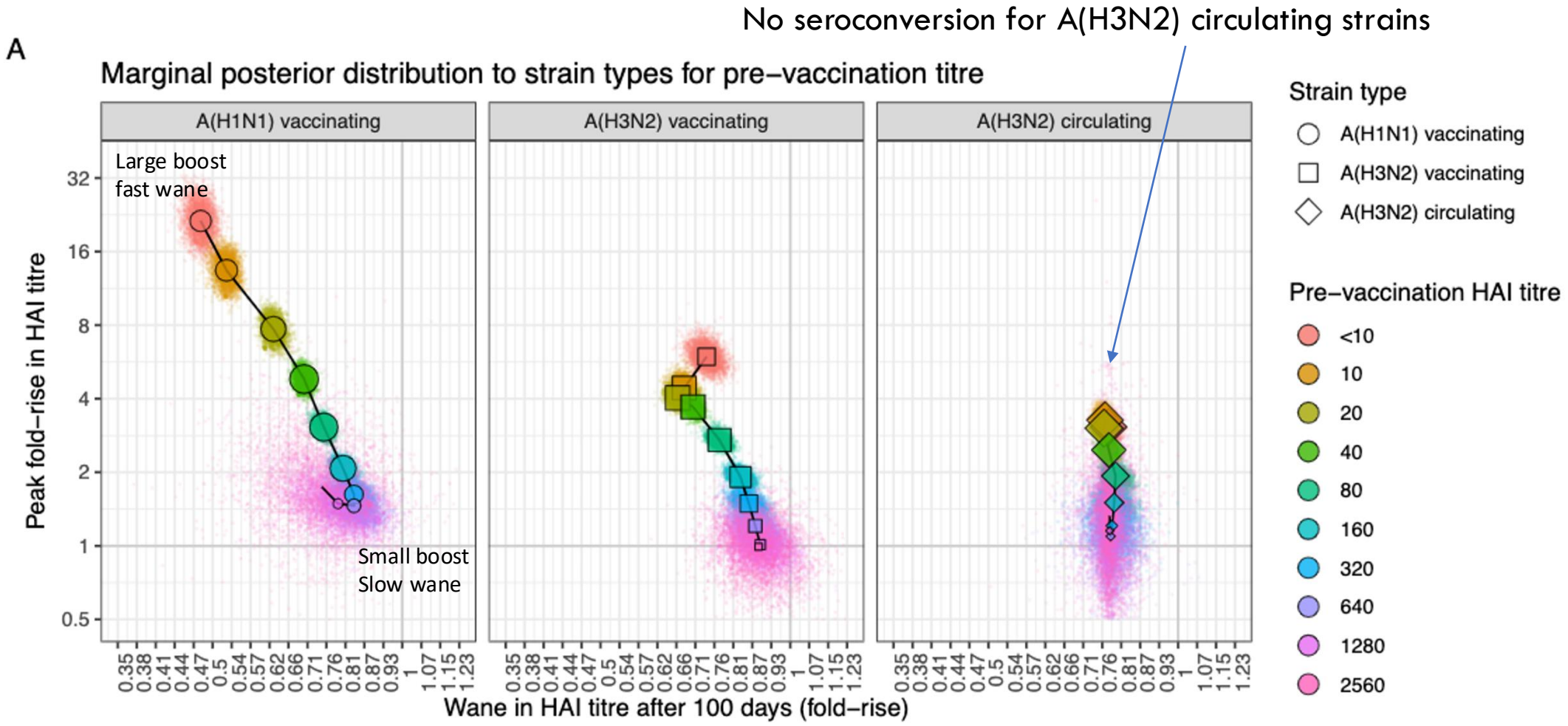
Study year significant also (but don't stratify by this)

Also found only pre-vaccination titre and vaccine history significant for A(H3N2) vaccinating and circulating



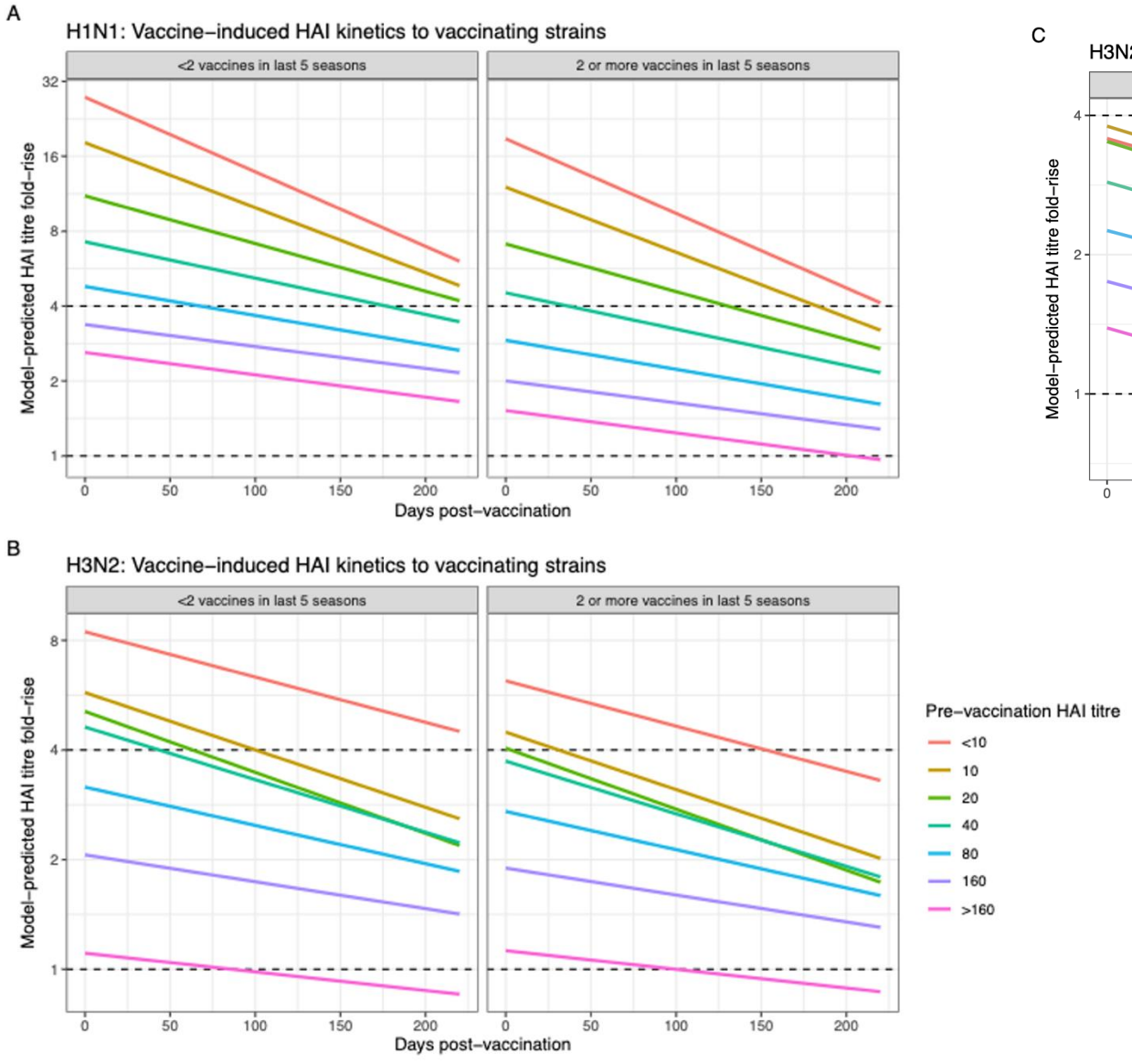
Vaccine history significant effect on boosting

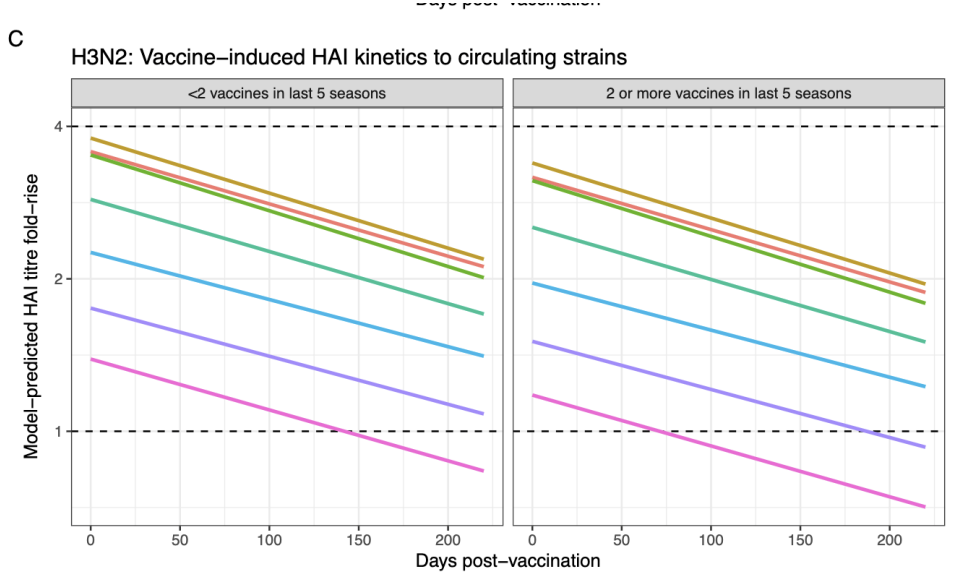
Results Marginal posteriors



HAI titre >1:40, little seroconversion across all strain types

Results: Latent antibody kinetics

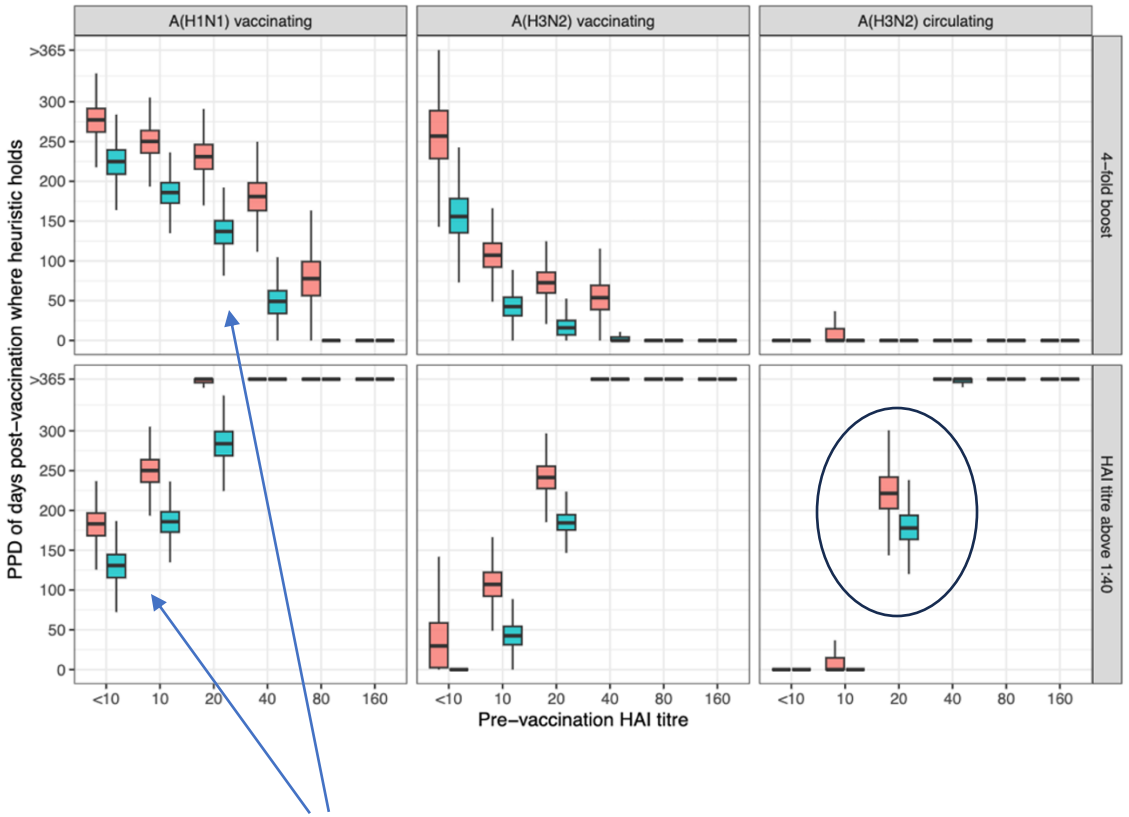




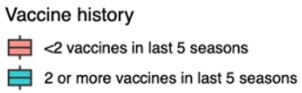
Fitted latent antibody trajectory

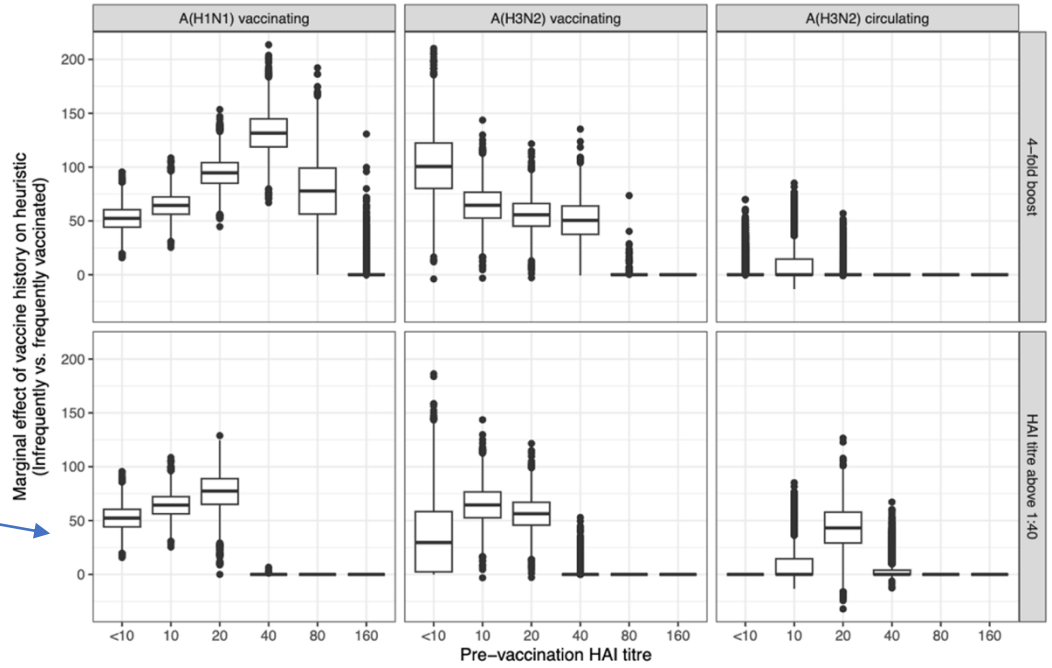
How does this influence duration of seropositivity and seroconversion?

Results: Inferred seroconversion + protection



HAI titre >1:40, little seroconversion for both vaccinated cohorts





Infrequently vaccinated have longer duration of seroconversion and protection compared to frequently vaccination

Limitations

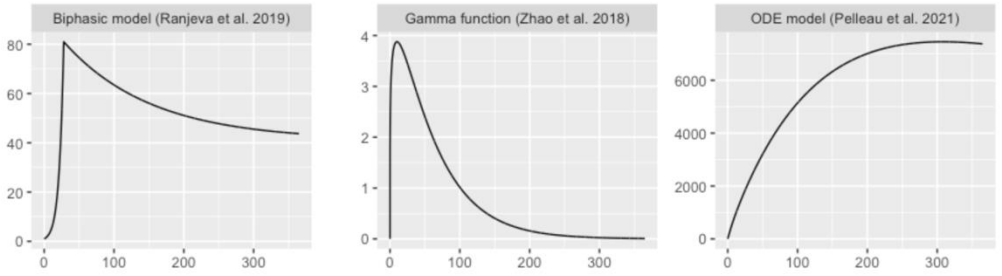
Infection history not included: not available before 2020

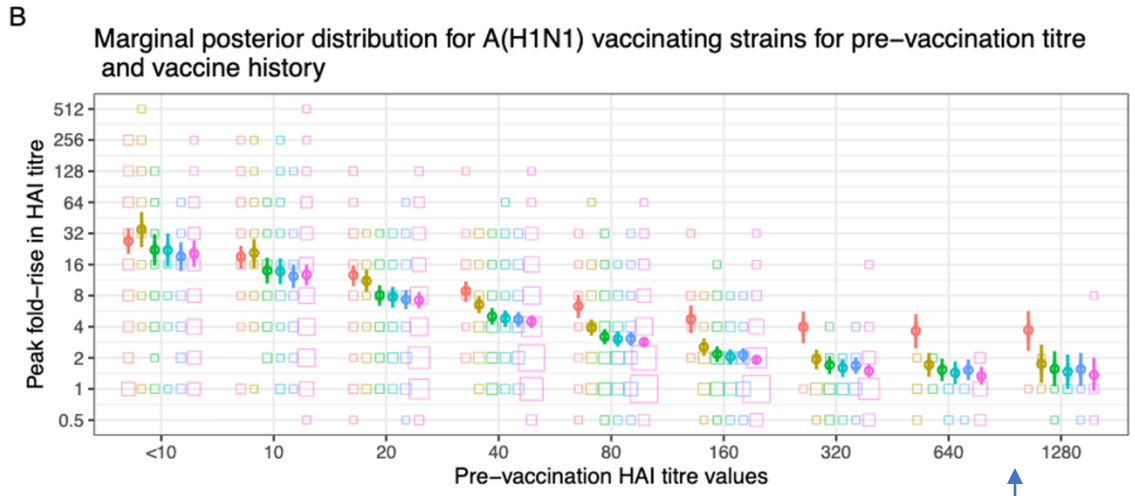
- Though no flu circulation in 2020–2021 in Australia
- Future model iterations should try and include infection history as well as vaccine history

Simple linear representation of antibody kinetics

- Hierarchal Bayesian structures get complicated quickly; simple enough given two time-points
- It is easier to interpret, representative provided we don't extrapolate too far
- Kinetics more complicated

Hay et al. 2023



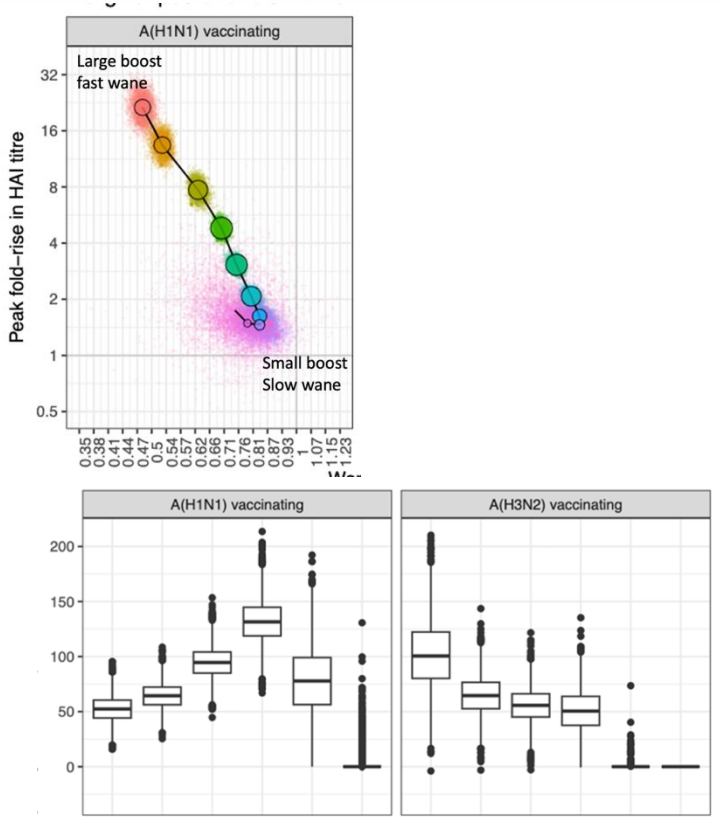


Large amounts of individual-level variability

- Due to innate immunity, cellular immunity, genetic polymorphism and epigenetic factors etc.
- Make prediction challenging

Take homes

- Established a quantifiable non-parametric relationship between pre-vaccination HAI titre and fold rise for the vaccinating strain
    - Four-fold rare given a pre-vaccination HAI titre of 1:40 across vaccination strains
    - Infrequently vaccinated experience longer durations of seroconversion and protection compared to frequently vaccinated (around 50-100 days), but magnitude depends on pre-vaccination titre
    - For strains antigenically distinct from vaccine strains (like circulating strains), boosting attenuated so seroconversion and protection are uncommon -> pre-vaccination titre and vaccine history no longer has an effect
    - Could explain observed heterogeneity in the influence of vaccination history on efficacy?



Jones-Gray 2022 Lancet RM

Aligns with antigenic distance hypothesis, says "antigenic distance is small between *v1* and *v2* ($v1 \approx v2$) but large between *v1* and the current epidemic (e) strain ($v1 \neq e$) then VE reduced" .
Future models could quantify this effect by tracking antigenic distance between vaccines and strains

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

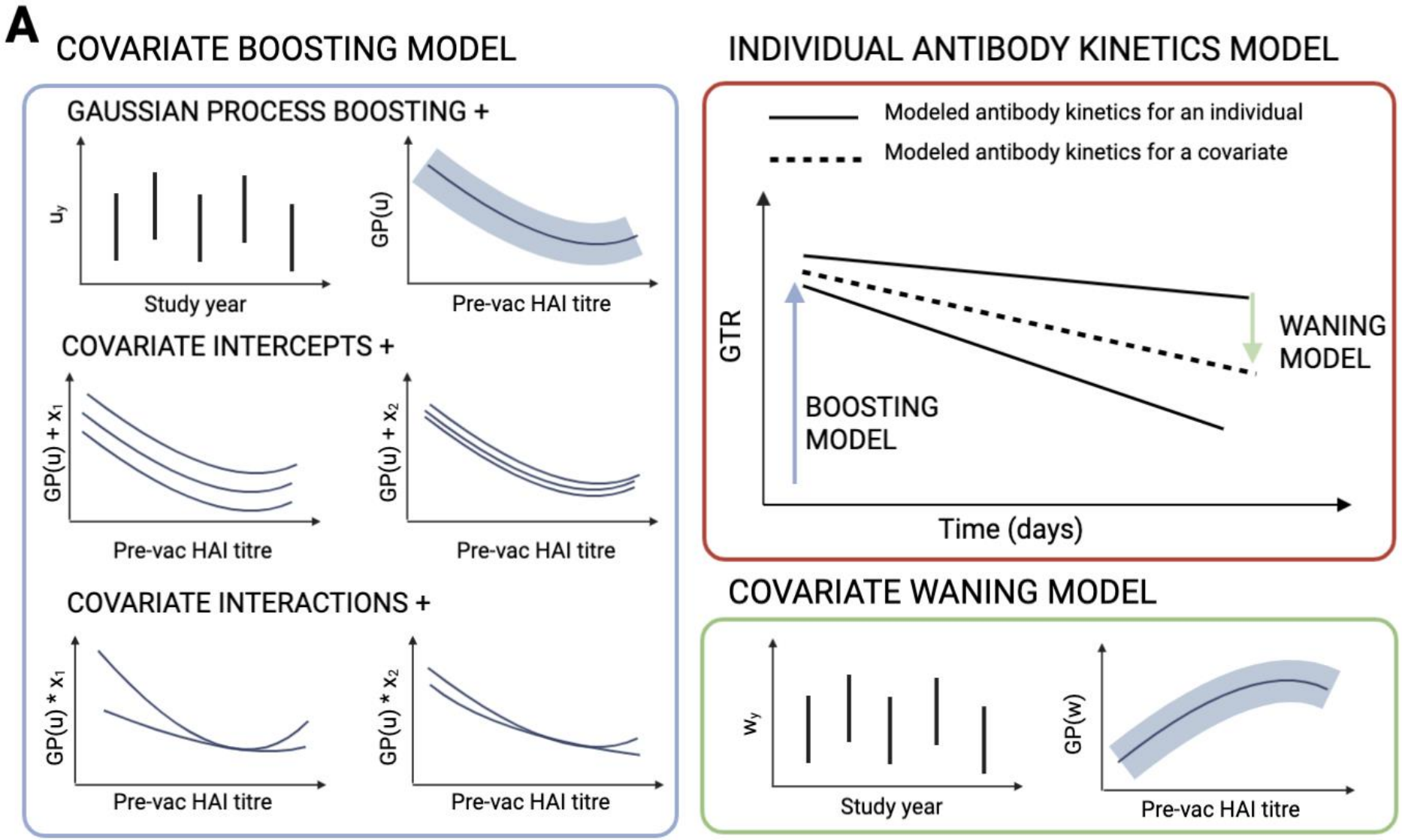
Dr. Annette Fox Marsh
+ Team

Mathematical modelling

Prof. Adam Kucharski

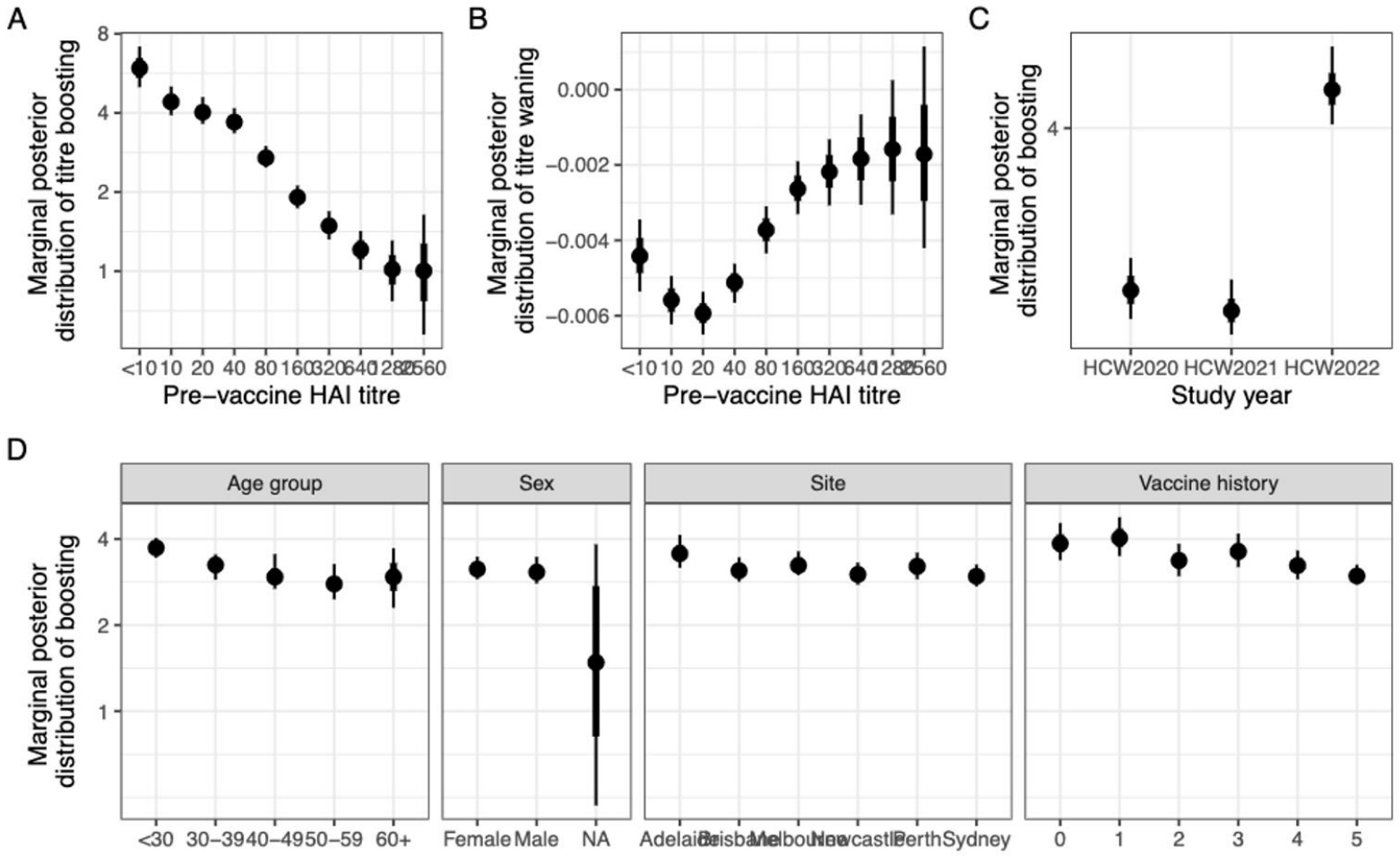
EXTRA SLIDES

Antibody kinetics model



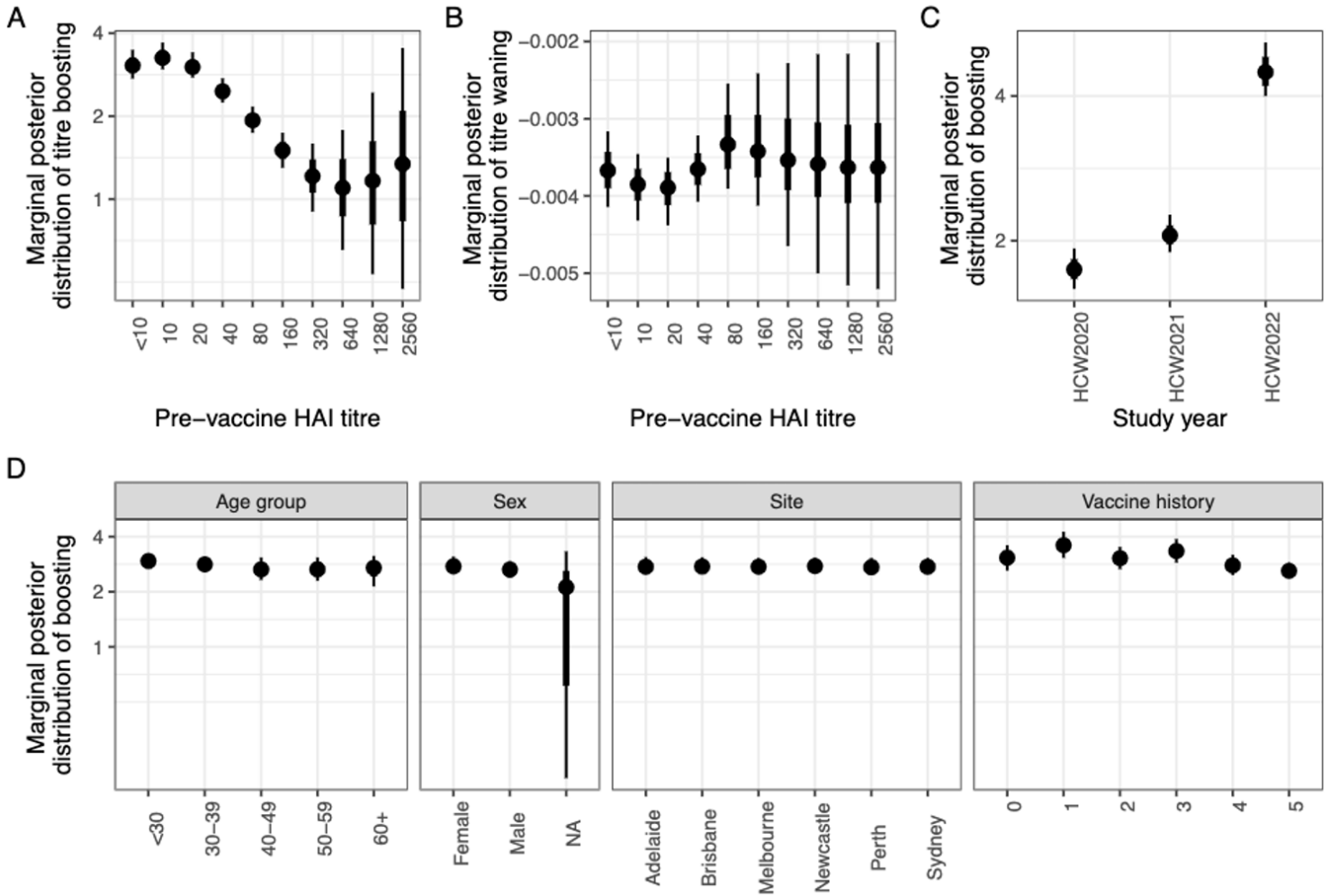
Antibody kinetics model

Marginal posterior distributions for A(H3N2) vaccinating:



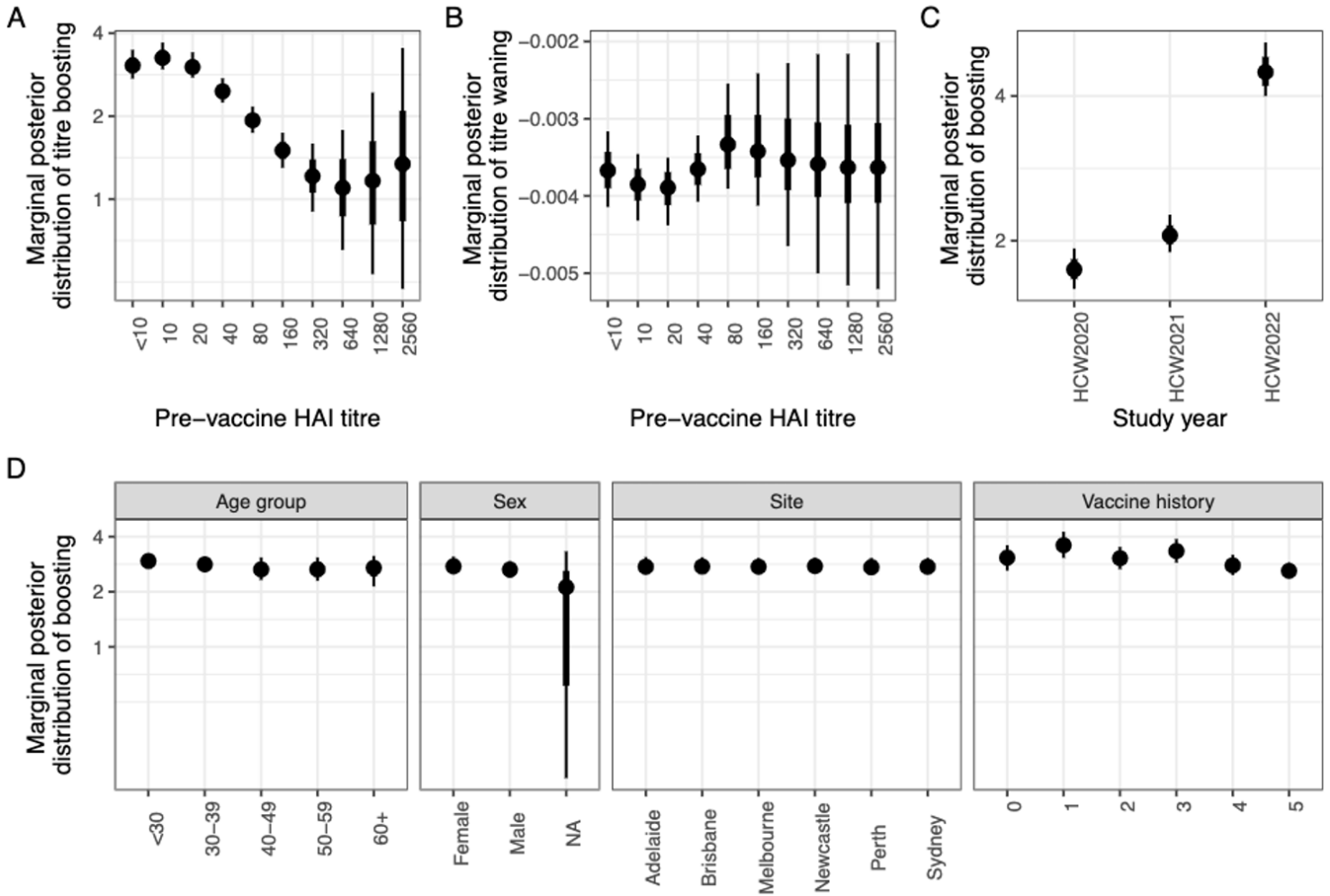
Antibody kinetics model

Marginal posterior distributions for A(H3N2) circulating:



Antibody kinetics model

Marginal posterior distributions for A(H3N2) circulating:



Antibody kinetics model