

How does exposure history shape SARS-CoV2 viral and immune dynamics?



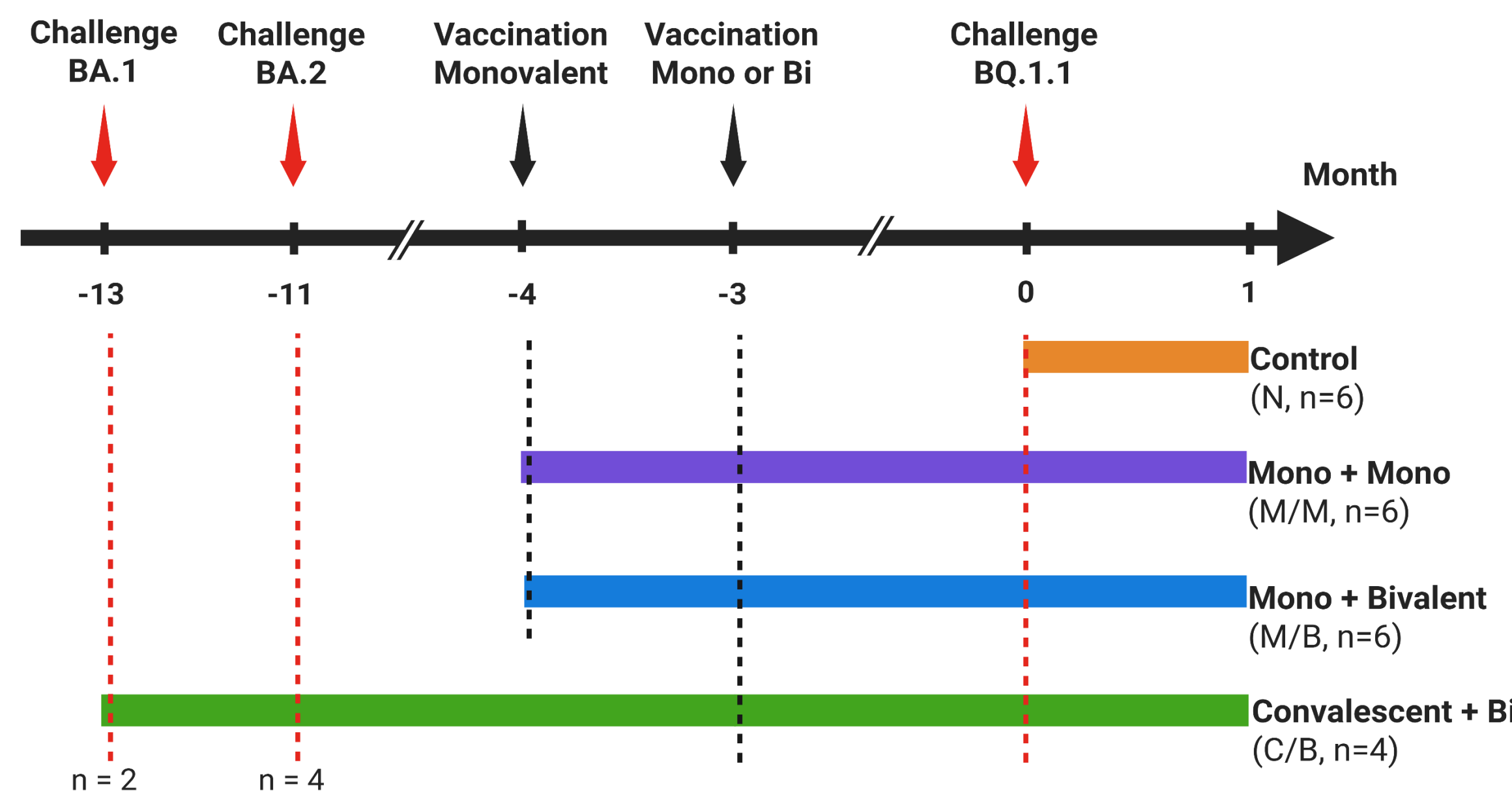
Adrien Mitard^{1,2}, Cécile Hératé³, Romain Marlin³, Flora Donati⁴, Yannis Rahou⁴, Sylvie van der Werf⁴, Etienne Simon-Loriere⁵, Roger Le Grand³, Mélanie Prague^{2,6}, Jérémie Guedj¹



¹Université Paris Cité and Sorbonne Université, IAME, INSERM F-75018 Paris, France, ²Inria Bordeaux Sud-Ouest, Inserm, Bordeaux Population Health Research Center, SISTM Team, UMR 1219, University of Bordeaux, France, ³Université Paris-Saclay, Inserm, CEA, Center for Immunology of Viral, Auto-immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT)UMRS1184, Fontenay-aux-Roses & Le Kremlin-Bicêtre, France, ⁴National Reference Center for Respiratory Viruses, Institut Pasteur, Paris, France, ⁵Evolutionary Genomics of RNA Viruses, Institut Pasteur, Université Paris Cité, Paris, France, ⁶Vaccine Research Institute, France,

Context

- SARS-CoV-2 still circulating at a high rate as vaccines fail to contain viral spread despite adaptations to the emergence of Omicron strains
 - Part of the population, mainly immunocompromised, remains at risk
 - Low viral load associated with drops in mortality [1] and transmission [2,3]
 - Efficient viral load models (mostly among naïves) have been developed both in humans and Non Human Primates (NHP) [4,5,6]
 - But **individual history** with the virus has become **diverse and complex**:
 - Number of exposures, time since last exposure
 - Vaccination (mono or bivalent) vs infection ? Hybrid immunity ? mABs ?
- Study the viral replication under different immune backgrounds (EMERGEN project)
- Vaccination with BNT162b2, mono and bivalent (Wuhan/BA.4-BA.5)
 - Longitudinal follow-up of viral and immune biomarkers

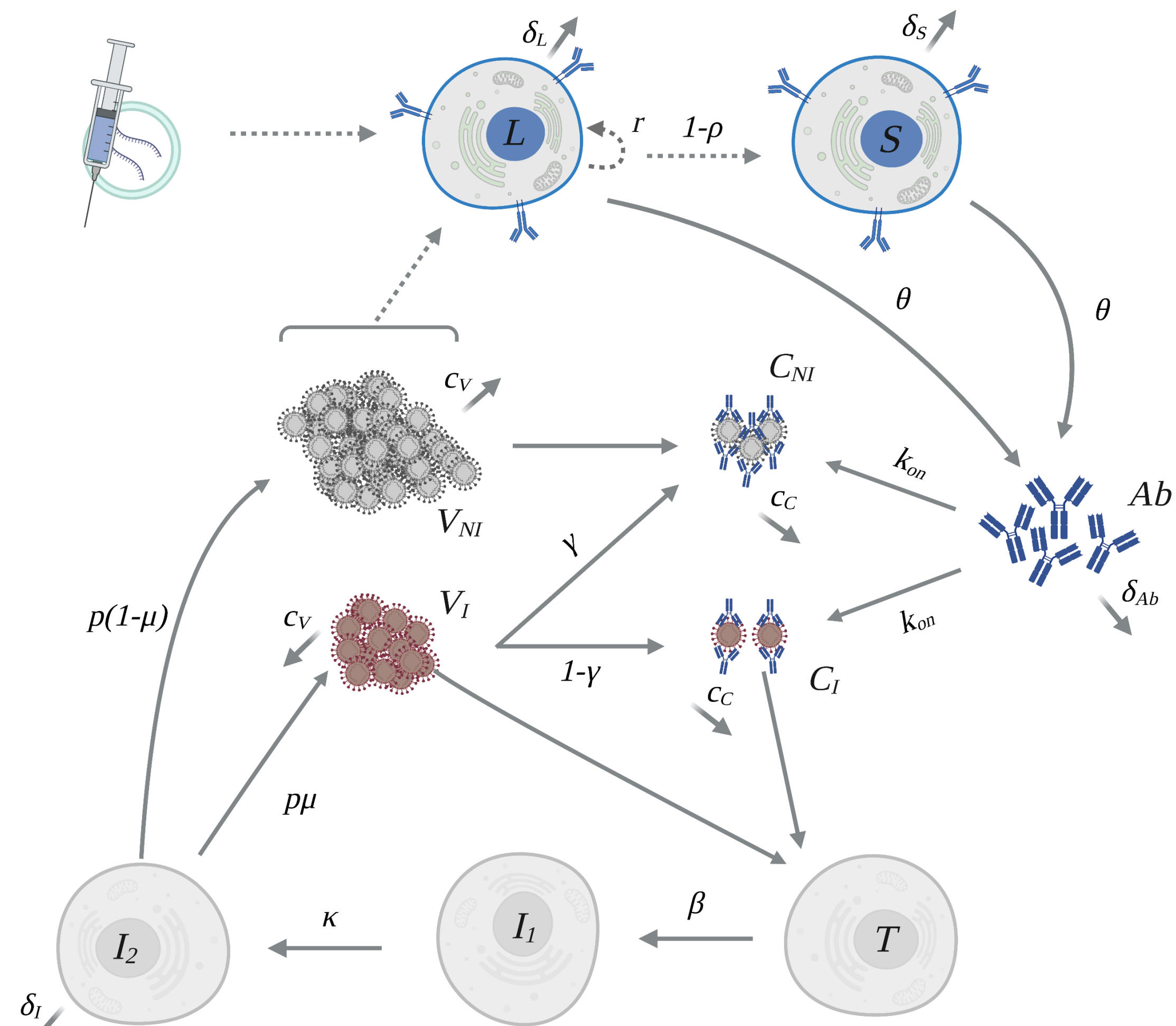


Objectives:

- Model the mechanisms linking antibodies and viral replication
- Explain different infection trajectories through immune levels and exposure history
- Discuss Correlates of Protection (CoP) against infection and transmission

Mathematical model

- Based on Target Cell Limited models [4,6]
- Dashed arrows: only happens if the immune response is triggered ($t < \tau_{vac}$ or $VL > \phi$)
- L is a proxy of the memory compartment
- Immune complex C : faster clearance, $c_V = 3 c_C$ [7]

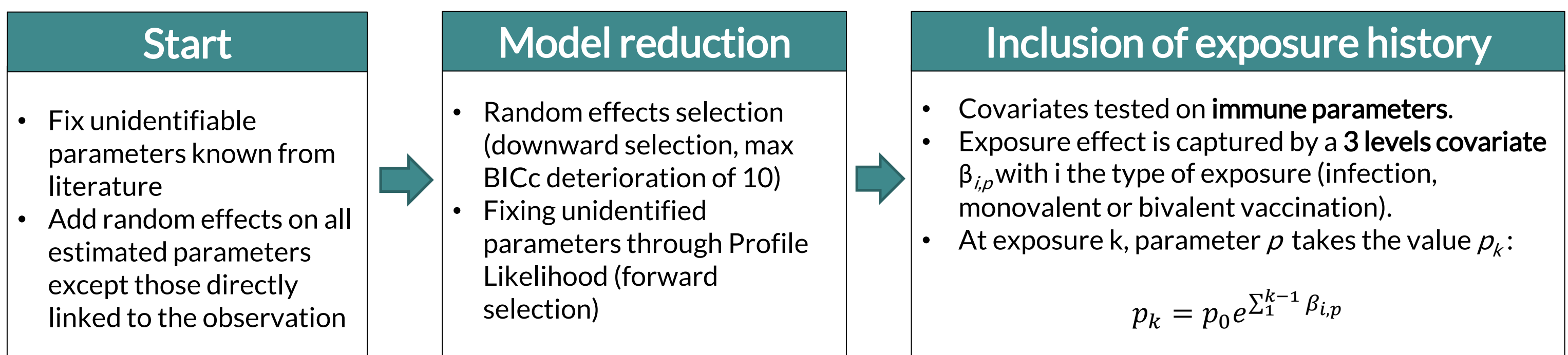


Infected Cells	$I_1' = \beta T(V_I + C_I) - \kappa I_1$	Short-lived Secreting Cells	$S' = (1 - \rho)rL(A_{vac} + A_{VL}) - \delta_S S$
Producing Infected Cells	$I_2' = \kappa I_1 - \delta_I I_2$	Long-lived Secreting Cells	$L' = \rho rL(A_{vac} + A_{VL}) - \delta_S L$
Infectious Virus	$V_I' = \mu p I_2 - (c_V + k_{on} Ab)V_I - \beta T V_I$	Antibodies	$Ab' = \theta(S + L) - \delta_{Ab} Ab$
Infectious Immune Complex	$C_I' = k_{on} Ab(1 - \gamma)V_I - \beta T C_I - c_C C_I$	Neutralisation	$ID50 = ID50_{max} \frac{k_{on} \gamma Ab}{k_{on} \gamma Ab + K_N}$

	Monovalent + Monovalent	Monovalent + Bivalent	Convalescent + Bivalent
Efficacy of neutralisation, γ	0.15 [0.05 - 0.31]	0.41 [0.24 - 0.64]	0.75 [0.54 - 0.90]
Half-life of infected cells (hours)	13 [11 - 15]	7.3 [6.1 - 8.7]	0.5 [0.2 - 1.5]

Methods

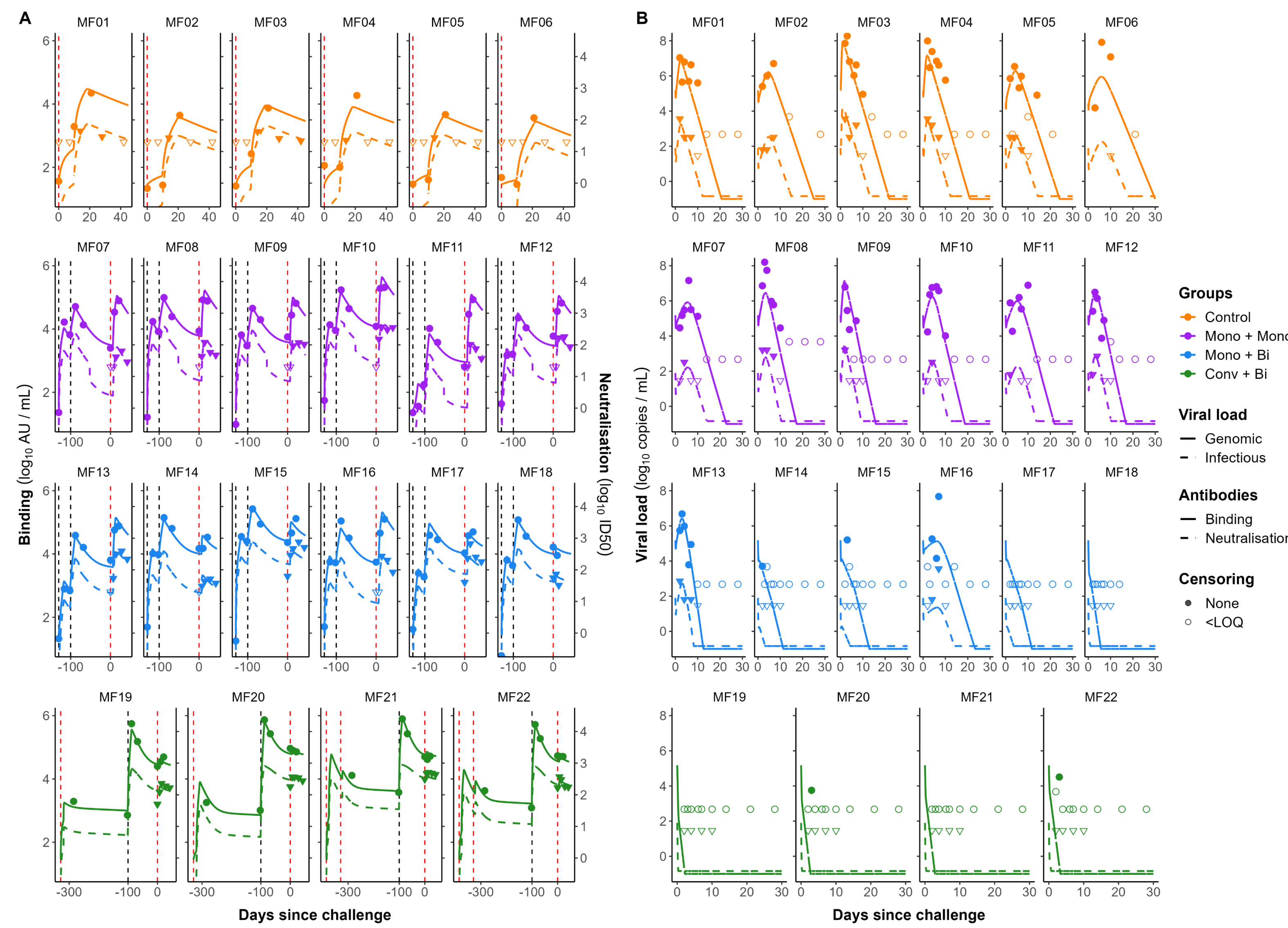
We used a non linear mixed effects framework. Parameter estimations are conducted using maximum likelihood estimation via the stochastic approximation expectation-maximization (SAEM) algorithm [8], implemented in Monolix 2023R1. We compare models using the BICc [9].



References

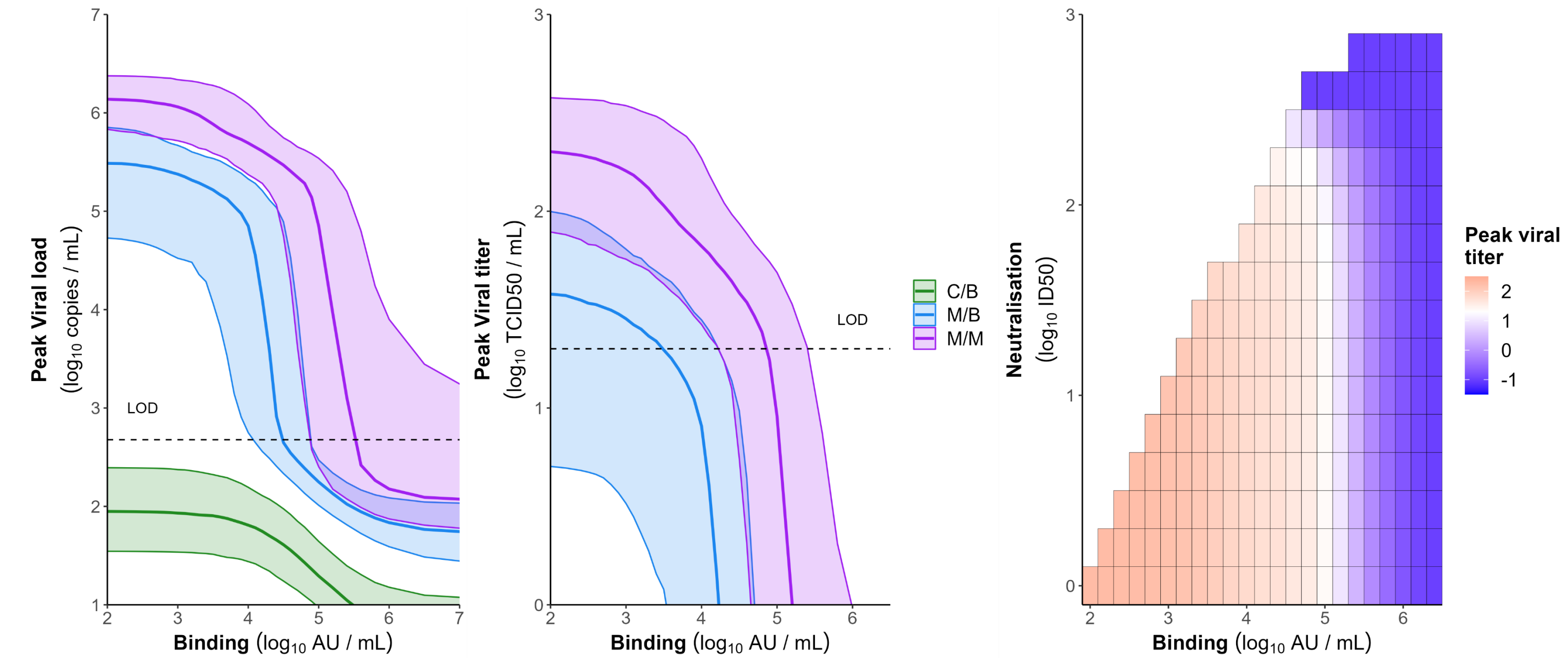
- 1: Néant et al, *PNAS*, 2021. 2: Goyal et al, *eLife*, 2021. 3: Marc et al, *eLife*, 2021. 4: Gonçalves et al, *PLOS Comp Biology*, 2021. 5: Alexandre et al, *eLife*, 2022. 6: Marc et al, *PLOS Comp Biology*, 2023. 7: Igarashi et al, *Nature Medicine*, 1999. 8: Kuhn et Lavielle, *CSDA*, 2005. 9: Delattre et al, *EJS*, 2014. 10: Killingley et al, *Nature Medicine*, 2022. 11: Kadowaki et al, *Journal of Infectious Diseases*, 2024.

Results



Correlates of Protection

Simulations of human-like infections (inoculum of 10 infectious particles [10]) using the NHP model with different protection levels (binding, neutralization and infected cells' loss rate)



Antibody levels at time of infection is associated with viral replication and transmission risks

Conclusion

- Bivalent vaccination reduces Omicron viral replication. The effect was more dramatic with hybrid immunity as the C/B group is fully protected.
- The protection against infection and transmission can be quantified using a model integrating binding and neutralisation.
- Infection is averted for binding levels of 3×10^4 and 4×10^5 AU/mL for M/B and M/M groups.
- Those model-based CoP, high compared to the population protection at the time, are coherent with the fast spread of the Omicron wave [11].
- Hybrid immunity could be further investigated as highlighted by the need for covariates that suggest a strong role of the T response