

Applications of Quantitative Systems Pharmacology Modelling for Vaccine Development

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Background and Objective

- Vaccines play a crucial role in preventing diseases and thereby saving countless lives. To prevent the spread of diseases, it is important that vaccines are broadly available in all parts of the world. However, the development of vaccines is expensive and time consuming, limiting the availability of vaccines.
- We use our Vaccine Model to predict optimal dosing schemes for clinical trials in both adult and paediatric populations.
- We demonstrate how our Vaccine Model could have supported vaccine development for SARS-Cov-2 to reduce cost and time and could have been used to prevent costly trial extension.

Methods

- Our Vaccine Model integrates a QSP model of liquid nanoparticle (LNP) mRNA administration to an immune response model, model, simulating antigen, antibody, and immune biomarker concentration-time profiles (Figure 1).
- Our Vaccine Model is calibrated using literature data on B-cell biology and LNP mRNA distribution and translation.
- We then filter individuals (i.e. parameter sets) that obey early-phase clinical data bounds on IgG concentration and antigen concentration after vaccine administration (Figure 2), generating a virtual patient population that meet an a priori set of criteria.
- We simulate IgG concentration profiles for varying dosing schemes for adults and paediatric age groups.

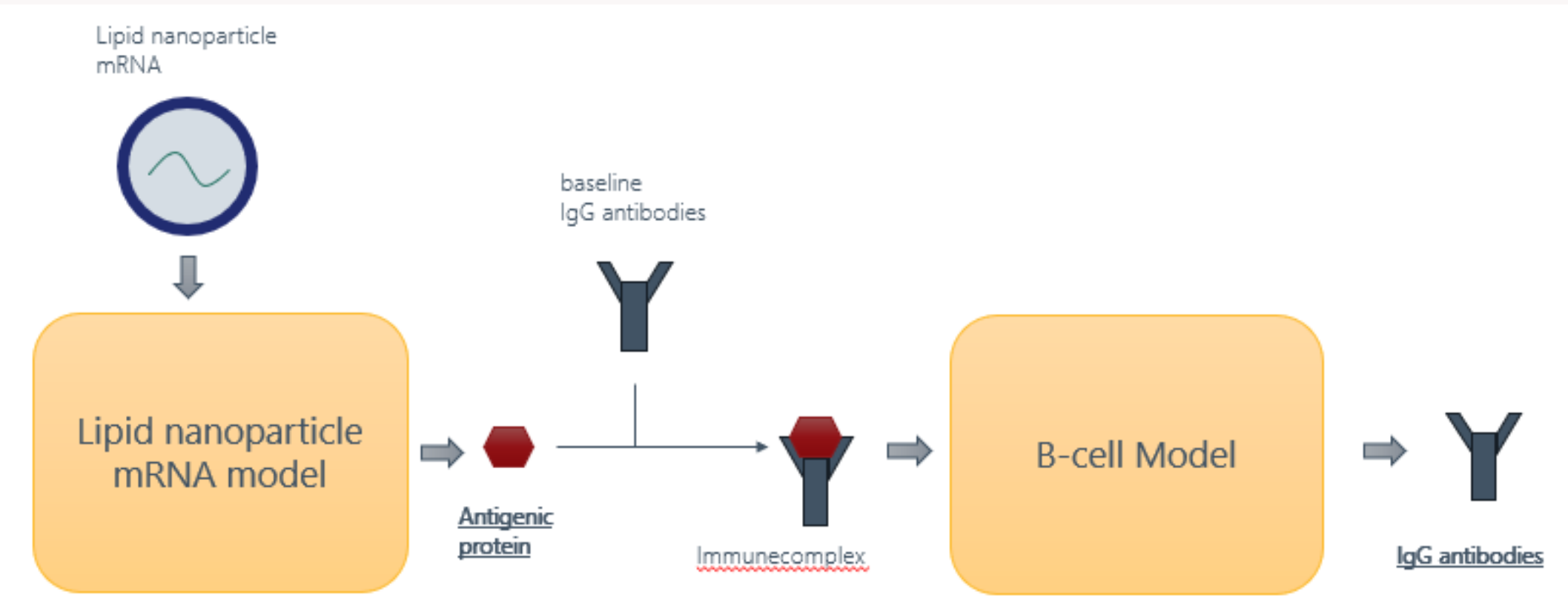


Figure 1: Schematic overview of the Vaccine Model

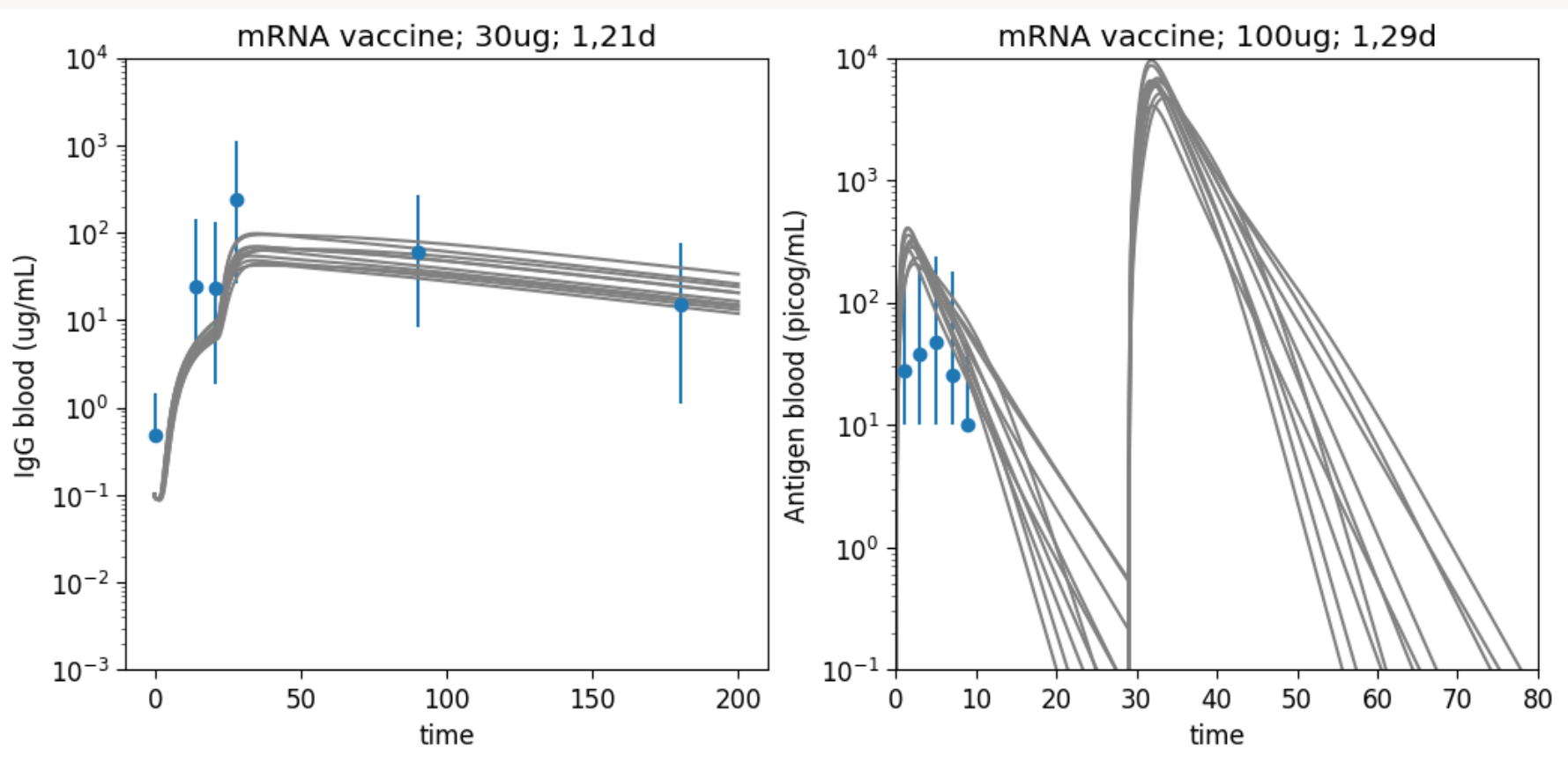


Figure 2: Early-phase IgG concentration profile¹ and antigen concentration profile² were used to generated a virtual patient population.

Optimal dosing interval for adults

- We use the generated virtual patient population to investigate the optimal interval between two doses of 100 µg LNP-mRNA.
- We find that, while the maximum IgG concentration varies between individuals, the maximum IgG concentration is achieved with a dose interval of 8 weeks across individuals, consistent with clinical results³.

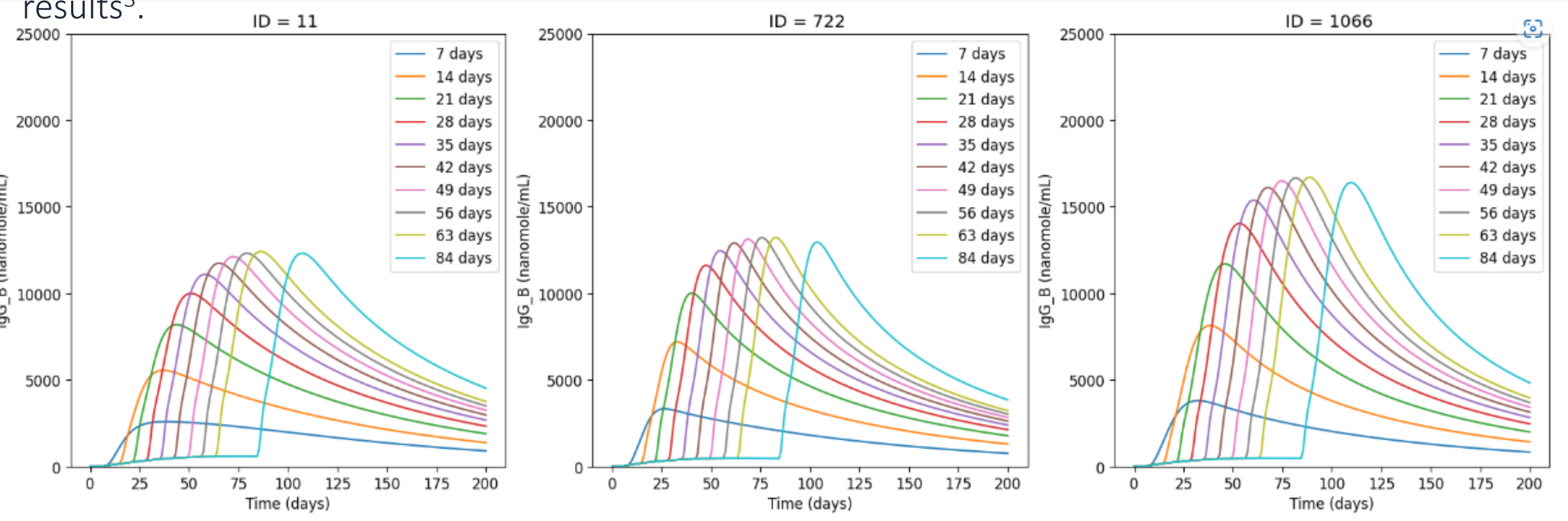


Figure 3: IgG concentration profiles for varying dose interval, shown for three different patients.

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Optimal dosing in paediatrics

- Virtual paediatric populations were created for the relevant age groups, scaling physiological parameters and initial B cell numbers relative to age and bodyweight⁴.
- SARS-CoV-2 neutralising titers were then simulated in both populations, used to calculate the GMR between the different age groups, and compared to ratios from the clinical trials (Table 1).
- We then simulate a dose selection trial, to find the optimal dose in 2-4 year old, reaching the immunobridging threshold after two doses (Figure 5).

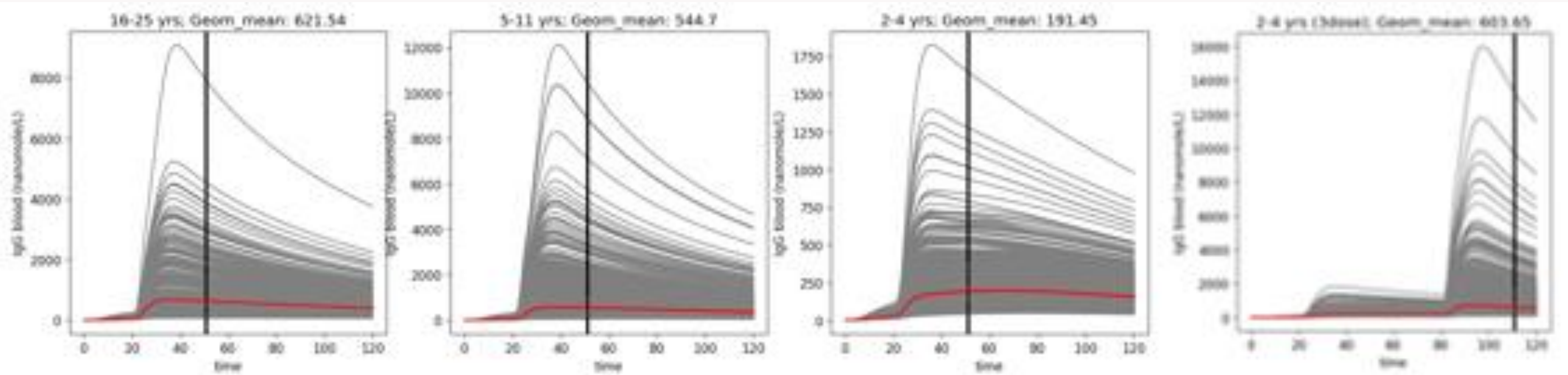


Figure 4: IgG concentration profile for a virtual patient population. Geometric mean (red line) is compared to different age groups at day 51 (black line)

Age group	Observed GMR for 2 doses	Predicted GMR for 2 doses	Observed GMR for 3 doses	Predicted GMR for 3 doses
5-11 years	1.04 (0.93 – 1.18)	0.90	-	-
2-4 years	0.61 (0.53 – 0.70)	0.37	1.30 (1.13 – 1.50)	0.99

Table 1: Overview of predicted and observed geometric mean ratios for Tozinameran Paedatric Immunobridging trials^{5,6}

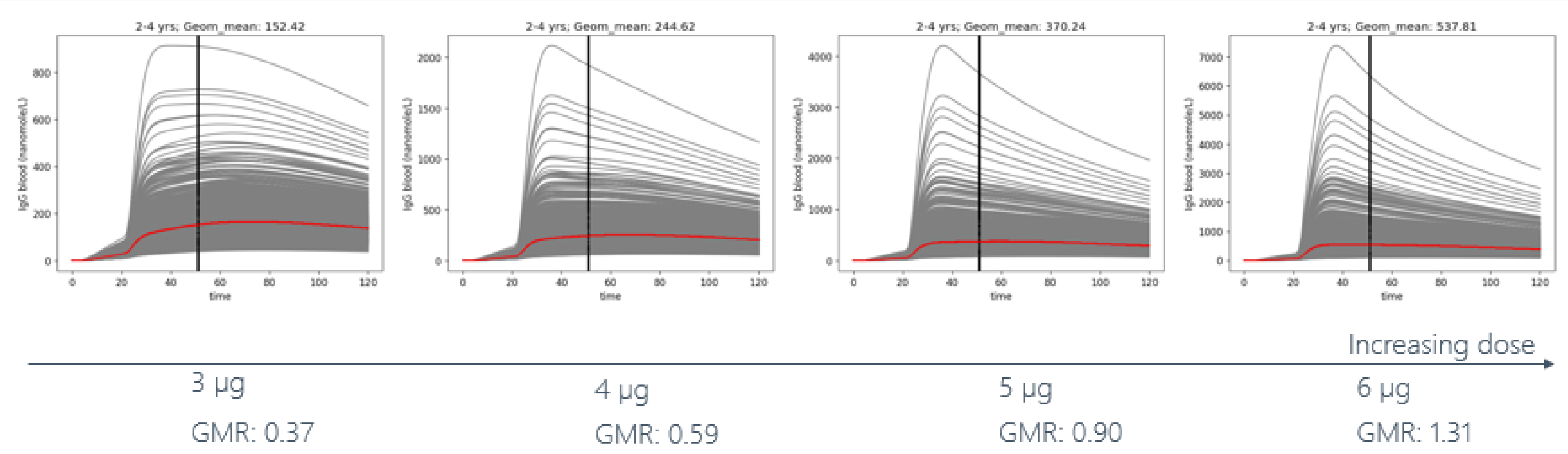


Figure 5: Predicted geometric mean ratio for increasing dose

Conclusions

- Using our virtual population-based approach our Vaccine Model predicts an optimal dosing interval for adults of 8 weeks, consistent with clinical results³ .
- We have extrapolated our model to paediatric age groups and have accurately predicted that two doses of 3 µg for the 2-4 year old would not have been sufficient to meet the immunobridging threshold and that a third dose was necessary, as was observed in the clinical study⁵.
- We predict that a dose of 5 µg, administered on days 0 and 21, would be sufficient to pass the immunobridging threshold in the 2-4 y.o. population without the need to administer an additional dose (Figure 5).
- In conclusion, prospective use of our QSP model in paediatric COVID-19 vaccine development could have prevented a failed trial and resulted in a more convenient dosing regimen.

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