PROPHECY

Newsletter

Issue 7 December 2024

As we approach the end of another remarkable year, the PROPHECY Executive wish to extend their gratitude to everyone for your contribution to the PROPHECY research project.

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PROPHECY Newsletter

what has changed in 2024

Since the peak of the COVID-19 pandemic, the nature of the SARS-COV-2 virus has evolved significantly with new variants complicating the landscape of infection control and the public health response.
The PROPHECY study is working to understand how best to protect our immunocompromised populations. from COVID-19.

The changing nature of the pandemic means the PROPHECY study will not pursue the detailed immunological analysis of the convalescence cohort. This is so the PROPHECY study can of focus on understanding protective immunity (cellular and serological) in a vaccinated population who have most likely been previously infected. Understanding responses from people who have only been infected without vaccination (as in the convalescence cohorts) was considered of little benefit to the main goals of the study. The required variation amendment to effect this change to the PROPHECY grant was submitted to the funding body, MRFF, and was subsequently approved in May 2024.

To date, five published research papers which reference PROPHECY study results and findings are contributing to the body of knowledge to inform vaccination guidelines and the updating of immunisation advice. Summaries of two of these papers can be found in this newsletter relating to healthy controls and kidney transplant recipients.
Recruitment is progressing steadily with 63.2% of target recruitment achieved at the half way point. Recruitment is always the biggest challenge for research and your continued effort and diligence in this area is appreciated by the whole PROPHECY team.

Remodelling and customisation of the REDCap database has been completed and the Executive extends their thanks for your patience during this extended process. Although continued refining of the database is expected, it is now more suited to the requirements of the study and the needs of the users. We welcome your continued input to correcting glitches or issues that you may discover.

We have navigated numerous challenges and achieved significant milestones, contributing valuable insights to the scientific community and advancing our understanding of vaccine efficacy. The PROPHECY Executive would like to thank all staff involved at clinical sites (Alfred and Monash Health, Royal Children's Hospital) and laboratories (Monash University, Burnet Institute and MCRI). Most importantly, we would like to acknowledge the contribution of the participants who have given up their time and valuable samples to increase our understanding of SARS-CoV-2 immunity.
We will continue to observe, assess the relevance, contexture and materiality of the evolving COVID-19 infection landscape to the PROPHECY study

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PROPHECY Publications

Humoral immunity and B-cell memory in response to SARS-CoV-2 infection and vaccination

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This study, published in the Journal of Infection, compares the immune response elicited by fourth-dose bivalent and monovalent COVID-19 boosters in healthcare workers who had prior vaccinations. The goal was to understand how these vaccines affect the development of memory B cells (Bmem), which are crucial for long-term immunity, particularly against evolving SARS-CoV-2 Omicron subvariants.

Key Findings:

1. **Enhanced Cross-Reactive Bmem after Bivalent Boosters:** The bivalent vaccines (targeting both the original WH1 strain and Omicron subvariants BA.1 or BA.5) produced stronger cross-reactive Bmem responses than the monovalent vaccine (targeting only WH1). Bivalent boosters increased Bmem that recognized not only the targeted Omicron subvariant but also more recent BQ.1.1 and XBB.1.5 subvariants highlighting their potential for broader variant recognition.

2. **Higher Neutralizing Antibody (NAb) Titers:** Both types of bivalent vaccines generated higher neutralizing antibodies against Omicron subvariants BA.1 and BA.5 than the monovalent booster. In particular, the BA.5 bivalent booster elicited the highest NAb titers and broader cross-variant recognition.

3. **Memory B Cell Activation and Subclass Specificity:** After vaccination, Bmem responses were dominated by IgG1+ cells, which play a significant role in long-term immunity. Notably, a higher frequency of IgG4+ Bmem cells was observed in participants whose primary vaccination series included mRNA vaccines, suggesting a sustained impact on B cell subclass specificity influenced by initial vaccine type.

4. **Reduced Omicron-Specific Bmem in Monovalent Boosters:** The monovalent booster did not increase Bmem specific to Omicron subvariants as effectively as the bivalent boosters. This finding indicates that variant-based boosters better stimulate the immune system to recognize and respond to new SARS-CoV-2 strains.

Clinical Implications:

The study suggests that using bivalent boosters could improve immune memory against emerging SARS-CoV-2 variants, potentially offering longer-lasting and more adaptive protection. This research supports recommendations for variant-based booster vaccinations to enhance the immune system's adaptability to future COVID-19 variants, aiming to reduce the risk of severe disease across diverse strains

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Serological responses and clinical outcomes following a three-dose primary COVID-19 vaccine schedule in kidney transplant recipients and people on dialysis

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This study, published in Clinical and Translational Immunology (July 2024) investigates the serological and clinical responses to a three-dose primary COVID-19 vaccination schedule in two high-risk groups: kidney transplant recipients (KTRs) and individuals on dialysis. Both groups are more vulnerable to severe COVID-19 due to immunosuppressive medications and renal dysfunction. The research evaluates antibody and neutralizing antibody (NAb) responses to the original SARS-CoV-2 strain and the Omicron BA.2 variant.

Key Findings:

Weaker Responses in KTRs: KTRs showed significantly lower anti-Spike receptor-binding domain (RBD) IgG and NAb levels compared to dialysis patients. After the third vaccine dose, 51.9% of KTRs had a positive ancestral NAb response, while only 40.7% neutralized Omicron BA.2. Dialysis patients had stronger responses, with 92.9% and 78.6% achieving positive NAb responses for ancestral and Omicron strains, respectively.

Impact of Immunosuppressive Therapy: High doses of mycophenolate (above 1 g/day) and low B-cell counts correlated with poor vaccine responses in KTRs, indicating a dose-dependent reduction in immunogenicity.

Vaccine Type and Schedule: mRNA vaccine schedules were more effective than those involving viral vector vaccines like ChAdOx1. Dialysis patients receiving three mRNA doses showed stronger antibody and NAb responses compared to mixed schedules.

Predictors of Vaccine Efficacy: High CD19+ B-cell counts and low monocyte counts were associated with better responses in dialysis patients, highlighting immune cell involvement. However, KTRs had overall poorer responses due to immunosuppression.

Breakthrough Infections: Over a 12-month period, 47% of KTRs experienced breakthrough infections, compared to 29% of dialysis patients. Severe cases and hospitalizations were more frequent in KTRs, with antibody level changes between doses potentially predicting infection risk. Clinical Implications: The study recommends tailored vaccination strategies for these populations. For KTRs, additional boosters, mRNA vaccines, and adjustments to immunosuppressive regimens could improve outcomes. Dialysis patients also benefit from mRNA vaccines but generally exhibit better immune responses.

Conclusion: KTRs face weaker vaccine responses, higher breakthrough infection risks, and more severe COVID-19 outcomes than dialysis patients. Customized vaccination protocols are essential to enhance protection for these vulnerable groups.

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REDCap
Research Electronic Data Capture

After a time of quiescence, PROPHECY REDCap is now renovated, refined and ready for data entry.

It has been a considerable undertaking to finesse the PROPHECY database to ensure your collected data can be captured and recorded with ease and in a timely manner. As the PROPHECY REDCap database ultimately performs as the collection tool for analysis in identifying the trends and patterns between the variables identified by the PROPHECY study it has been a comprehensive and time-consuming process.

The database will also serve as the validated source for PROPHECY recruitment statistics once it is up to date. However, as all data entry may not be up to date by the end of December, a final email request to confirm recruitment numbers from you for the December 2024 MRFF report will be needed.

Although we expect the data base will have some teething problems as users enter data, we have secured the services of an external consultant to assist in overseeing the rectification of any issues. This will speed up REDCap platform optimisation which has, unfortunately, been hampered in recent months by the lack of resources at Monash University Helix which administers the REDCap platform.

We encourage the coordinators to commence the entry of data. Please also review data previously entered (it has been transferred across to the new PROPHECY Study database) as additional data fields have been added which require completion.

Any queries or problems should be emailed to Prophecy.study@monash.edu

JN 1 Vaccine Update

The TGA has now provided full registration for two new COVID-19 vaccines to address the more recent circulating SARS-CoV-2 variants. The first of these vaccines (COMIRNATY JN.1) is expected to be available to the Australian public from 9 December 2024

Pfizer Australia Pty Ltd

COMIRNATY JN.1 (bretovameran)

COVID-19 vaccine
30 micrograms/0.3 suspension for injection multidose vial

ARTG Date: 11 October 2024

https://www.tga.gov.au/resources/artg/457677

Moderna Australia Pty Ltd

SPIKEVAX JN.1 (SARS-CoV-2 JN.1 mRNA)

COVID-19 vaccine
0.1 mg/ml suspension for injection pre-filled syringe

ARTG Date: 15 November 2024

https://www.tga.gov.au/resources/artg/458805

NEW COMMERCIAL-SCALE MRNA MANUFACTURING FACILITY IN VICTORIA

On 4th December 2024, Moderna, a global biotechnology company pioneering mRNA vaccines and therapeutics, officially opened the Moderna Technology Centre – Melbourne (MTC-M), Australia's first and only commercial-scale mRNA vaccine manufacturing facility. As the Southern Hemisphere's only mRNA manufacturing facility, MTC-M has opened in Clayton, Victoria ensuring world-class mRNA vaccines and medicines can be made in Australia.

The facility will have the capacity to produce up to 100 million vaccine doses each year for respiratory diseases including influenza, Respiratory Syncytial Virus (RSV), and COVID-19.

BioNTech commenced construction mid 2024 of their clinical manufacturing facility, at La Trobe University, Bundoora.

The new facility will produce next generation mRNA vaccines and treatments (including oncology treatments) for clinical trials for medical research institutes, biotech and life science companies, as well as BioNTech's own investigational drug and vaccine candidate products. It will also produce research grade RNA materials for Australian researchers to develop early stage and clinical vaccines and therapies in their laboratories.
The BioNTech Clinical Manufacturing Facility is an anchor tenant for the La Trobe University City of the Future, a $5 billion precinct transforming the Bundoora Campus

With Moderna and also BioNTech establishing major hubs in the state, Victoria is the only place in the world where both mRNA leaders host research and development (R&D) and manufacturing operations.

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PROPHECY Symposium 2024

11th October 2024