Immunity to COVID after vaccination in First Nations peoples is affected by comorbidities

First Nations peoples of Australia have disproportionate rates of chronic comorbidities such as diabetes and renal disease. A study of COVID vaccination in First Nations peoples reveals that perturbed antibody responses can occur in individuals with comorbidities in a way strongly associated with altered IgG glycosylation patterns.

This is a summary of:
Zhang, W. et al. Robust and prototypical immune responses toward COVID-19 vaccine in First Nations peoples are impacted by comorbidities. *Nat. Immunol*. https://doi.org/10.1038/s41590-023-01508-y (2023).

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The question

Australian First Nations peoples are at increased risk of COVID-19-associated morbidity and mortality for many reasons, including higher rates of pre-existing chronic conditions, marginalization from health services and overcrowded housing conditions[1]. However, data that describe immunological responses to SARS-CoV-2 infection and COVID-19 vaccination are lacking in this population. In our study, we sought to define immune responses to COVID-19 vaccination in Australian First Nations peoples. Vaccine hesitancy, mistrust in health systems and English as a second or third language pose potential barriers to vaccine programs in First Nations peoples[2,3]. To enable sovereignty about decision making and informed consent[4], we co-designed 23 individually localized COVID-19 vaccine information videos in 9 First Nations languages and English. These were shared through social media as part of the broader vaccine rollout and played to individuals as part of the recruitment process for this study.

The discovery

We recruited First Nations and non-Indigenous Australian people vaccinated with the BNT162b2 COVID-19 vaccine and assessed their immunity before and after vaccination at six time points. To evaluate humoral immunity, we analyzed antibodies directed to the receptor binding domain (RBD) as well as neutralizing antibodies for both the ancestral SARS-CoV-2 strain and variants of concern. We further assessed antibody glycosylation patterns and inflammatory milieu as these immune parameters can affect immune responses. As B cells and T cells establish long-lived immunological memory pools to mediate rapid protection against subsequent infection, we assessed B cell and T cell activation and durability directly ex vivo using spike protein-specific probes, peptide–HLA class I and II tetramers, and activation and functional assays. We further analyzed immune responses to COVID-19 vaccination relative to comorbidities in First Nations and non-Indigenous participants.

We found that Australian First Nations peoples elicit effective immune responses to COVID-19 vaccination, including the production of neutralizing antibodies, antibodies to the RBD and spike-protein-specific B cells, $CD4^+$ and $CD8^+$ T cells. In First Nations participants, antibody levels correlated with body mass index and negatively correlated with age. However, vaccinated participants with chronic conditions such as diabetes or renal disease showed reduced antibodies (Fig. 1a), spike-specific B cells and follicular helper T cells compared with participants without these conditions. Diabetes and renal disease were also strongly associated with altered antibody IgG glycosylation patterns (Fig. 1b) and increased IL-18 levels before vaccination. These immune perturbations were also found in non-Indigenous people with comorbidities, which indicates that they were related to comorbidities rather than ethnicity.

The implications

Our study provides an immunological basis to support current vaccine recommendations in Australian First Nations populations and has important implications for vaccination regimens in individuals with chronic conditions, particularly diabetes and renal disease. The findings on comorbidity and immune response are particularly important for Australian First Nations peoples, who have disproportionate rates of these chronic conditions compared to the non-Indigenous population. Our study supports Australian recommendations for earlier and/or additional booster doses of COVID-19 vaccines for high-risk groups and indicates that the use of monoclonal antibodies and immunomodulatory therapies might also be important considerations.

Many Indigenous populations in countries other than Australia show disproportionately high rates of diabetes and renal disease compared to non-Indigenous populations, with death rates from these chronic conditions before COVID-19 being higher than non-Indigenous populations[5]. Future immunological studies in other Indigenous populations are crucial to understand the specific vaccination needs of these populations.

Our observations suggest that antibody glycosylation patterns, together with IL-18 levels, before vaccination might serve as a biomarker for humoral responses after vaccination, for COVID-19 or other infectious diseases. Further studies that unravel the link between antibody glycosylation patterns, high IL-18 levels and reduced humoral immunity might inform future vaccination and immunotherapy protocols.

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EXPERT OPINION

"This is an interesting report that assesses the immune response to vaccination in a cohort of First Nations peoples in Australia. This group has been at higher risk of COVID-19 over the past 2 years and the work seeks to uncover the determinants that might underlie this risk. The major finding is that First Nations peoples have higher levels of comorbidity that correlate with higher levels of non-glycosylated antibodies and impaired humoral immunity." **Paul Moss, University of Birmingham, Birmingham, UK.**

FIGURE

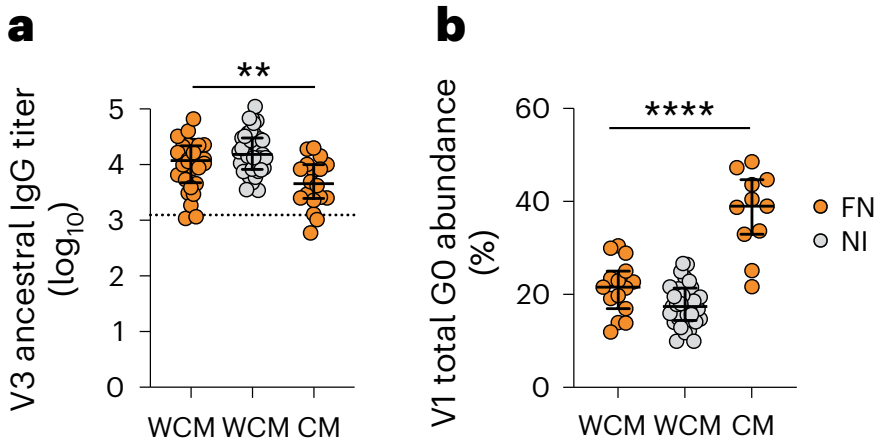

Fig. 1 | Lower anti-RBD IgG antibody levels and increased bulk IgG G0 glycosylation levels in First Nations people with comorbidities. a, ELISA showing ancestral RBD IgG in individuals with or without comorbidities (CM or WCM, respectively) at visit 3 (V3, 28 days after vaccination with BNT162b2). FN, First Nations peoples; NI, non-Indigenous cohort. **b**, Glycan profiling showing bulk IgG without galactose (G0) in individuals with or without comorbidities such as diabetes and renal diseases; data were collected at visit 1 (V1, before vaccination).

BEHIND THE PAPER

As an infectious diseases clinical researcher in the Northern Territory of Australia, the potentially devastating effect of COVID-19 for First Nations communities was front and center when planning this study. However, owing to strict public health measures, not one First Nations person in the Northern Territory of Australia had been infected with SARS-CoV-2 at the time of the vaccine roll out and commencement of our study. In this context, vaccine misinformation and mistrust of health systems meant trusted partnerships, information in participants' first language, and ensuring informed consent were more crucial than ever. Our team's previous collaborative work looking at influenza vaccine responses enabled us to use our established relationships to guide community consultation and feedback to participants before, during and after the study. In my opinion, trusted relationships and true respectful collaborations led to the success of this study. **J.D.**

REFERENCES

1. Yashadhana, A., Pollard-Wharton, N., Zwi, A. B. & Biles, B. Indigenous Australians at increased risk of COVID-19 due to existing health and socioeconomic inequities. *Lancet Reg. Health West. Pac.* **1**, 100007 (2020).
   This paper reviews socioeconomic, health and environmental factors that increase COVID-19 risk in Australian First Nations peoples.
2. Graham, S. et al. Aboriginal peoples' perspectives about COVID-19 vaccines and. Motivations to seek vaccination: a qualitative study. *BMJ Global Health* **7**, e008815 (2022).
   This paper describes mistrust in governments that contribute to vaccine hesitancy and preference for trusted health providers.
3. Cass, A. et al. Sharing the true stories: improving communication between patients and healthcare workers. *MJA* **176**, 466–470 (2002).
   This article highlights that to enable effective communication, interpreters plus resources to achieve shared understandings are needed.
4. Kerrigen, V., Park, D., Ross, C., Davies, J. & Ralph, A. P. Co-design effective health-literacy videos. *Lancet* **401**, 343 (2023).
   This paper highlights the need for vaccine information and health communication to be co-designed with communities.
5. Kochanek, K. D., Murphy, S. L., Xu, J. & Arias, E. Final data for 2017. *Natl Vital Stat. Rep.* **68**, 1–77 (2019).
   This report presents 2017 data on US death rates, life expectancy and infant mortality stratified by age, gender, ethnicity, state of residence and cause of death.

FROM THE EDITOR

"Indigenous populations globally have high rates of mortality from COVID-19. This is a rare study that comprehensively analyzed the antibody and cellular immune response to COVID-19 vaccination in a cohort of Australian First Nations peoples. Focusing on this group allowed the authors to uncover correlates between specific immune parameters and a high comorbidity burden that apply across both Indigenous and non-Indigenous groups, underscoring the value of studying underserved populations." **Ioana Visan, Senior Editor, *Nature Immunology***