# Humoral Immune Responses to Hybrid Immunity and Heterologous COVID 19 Vaccination: A Stop the Spread Ottawa (SSO) Analysis

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## Introduction

Many questions remain regarding the immunogenicity of novel SARS-CoV-2 vaccines. The generalizability of phase I-III randomized clinical trials for COVID-19 vaccines were limited due to eligibility criteria that excluded older, younger, and pregnant individuals.[1,2] Observational research in diverse populations is needed to determine the effect of dose type, number, timing, & natural infection. SSO is a 34-month prospective longitudinal cohort formed to address these gaps.

## Objectives

1) Determine the impact of demographics & comorbidities, vaccine type, number & timing, & COVID-19 infection history on vaccine immunogenicity and identify key predictors. 2) Report vaccine safety and reactogenicity.

## Methods

1,034 adults in the Ottawa region at risk for or who have been infected with SARS-CoV-2 were recruited starting in September of 2020 and followed for 10 months, with an optional 24-month extension phase. Participants with a history of COVID-19 infection or vaccination were allocated to the **convalescent cohort** and provided monthly blood draws for serum analysis. Those in the **surveillance cohort** with no history of infection provided baseline blood draws. Participant characteristics and vaccination details and positive COVID-19 PCR/rapid antigen test results were collected in questionnaires. Participants were classified as immune compromised (IC) if they had a primary/secondary immunodeficiency, were receiving immunosuppressants, or consumed excessive alcohol.

IgG titres against SARS-CoV2 Spike (S), receptor binding domain (RBD), and nucleocapsid (N) proteins (BAU/mL) were quantified through a high-throughput assay. IgG titres were log-adjusted and predictors of vaccine immunogenicity were identified through multivariable quantile regression.

## Results

**Table 1.** Characteristics according to baseline cohort. *A two-sided alpha-level of 0.05 was used. NIC=Non-immune compromised, AZ=AstraZeneca.

| Variable | All participants (n=1,034) | Surveillance Cohort (n=803) | Convalescent Cohort (n=231) | P value |
|---|---|---|---|---|
| Age (mean, SD)<br>Range | 45.0 (13.9)<br>18-79 | 44.4 (13.7)<br>18-79 | 46.8 (14.6)<br>22-76 | 0.02* |
| Male, n (%)<br>Female, n (%) | 340 (32.9)<br>694 (67.1) | 254 (31.6)<br>549 (68.4) | 86 (37.2)<br>145 (62.8) | 0.11 |
| IC, n (%)<br>NIC | 316 (30.6)<br>718 (69.4) | 247 (30.8)<br>556 (69.2) | 69 (29.9)<br>162 (70.1) | 0.80 |
| Vaccines, n (%)<br>mRNA-mRNA<br>AZ-AZ<br>mRNA & AZ | 811 (87.5)<br>10 (1.1)<br>106 (11.4) | 626 (87.1)<br>7 (1.0)<br>86 (12.0) | 185 (88.9)<br>3 (1.4)<br>20 (9.6) | 0.56 |
| COVID Infection Ever, n (%) | 435 (42.1) | 204 (20.9) | 231 (100.0) | <0.01* |

**Figure 1.** Loess curve of anti-S IgG titres (BAU/mL) over time. Data following reinfections (convalescent) or first infections (surveillance) were excluded.

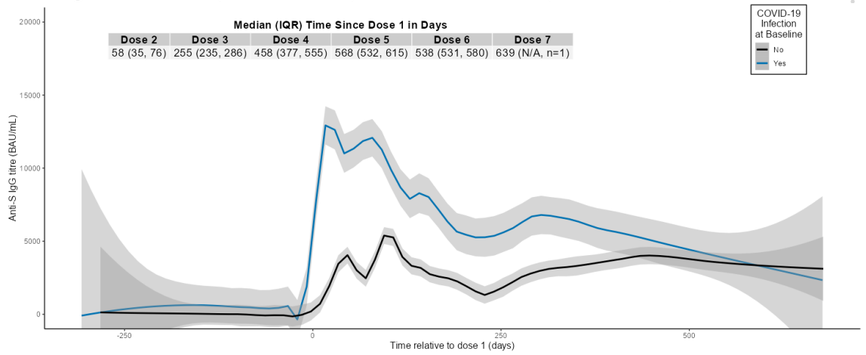
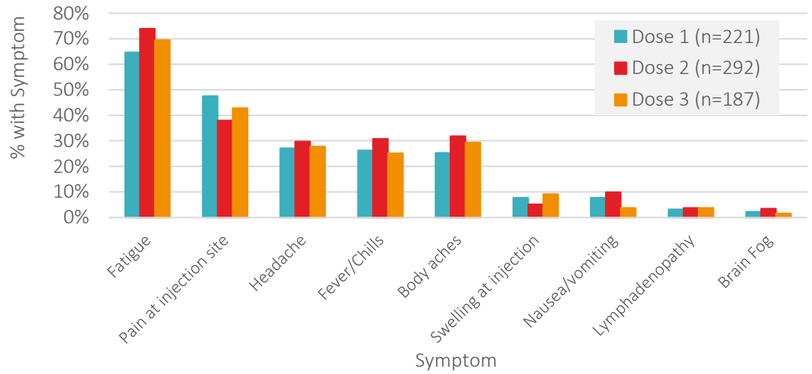



**Table 2.** Difference in median anti-S IgG titres (log10 BAU/mL) among those with no prior infection 2-4 months post dose 2 by MV quantile regression analysis. *A two-sided alpha-level of 0.05 was used.

| Variable (referent listed last) | Difference in median anti-S titre (log10 BAU/mL) (95% CI) | P value |
|---|---|---|
| Older age | -0.0041 (-0.0082, -0.0001) | 0.04* |
| Male vs Female | 0.0935 (-0.0045, 0.1915) | 0.06 |
| Non-white vs White Ethnicity | -0.0082 (-0.2440, 0.2276) | 0.95 |
| Higher Body Mass Index | -0.0044 (-0.0121, 0.0034) | 0.27 |
| IC vs NIC | -0.0959 (-0.1871, -0.0048) | 0.04* |
| Current vs Former vs Never Smoker | -0.0087 (-0.2871, 0.2696)<br>-0.1353 (-0.2313, -0.0392) | 0.95<br>0.006* |
| Allergies vs No Allergies | 0.0994 (0.0228, 0.1760) | 0.01* |
| AZ-mRNA vs mRNA-mRNA | 0.0790 (-0.0480, 0.2060) | 0.22 |
| Increasing Days between Dose 1 & 2 | 0.0004 (-0.0012, 0.0019) | 0.66 |

**Figure 2.** Symptoms following vaccination by dose number.




## Conclusions

- COVID-19 vaccination is safe, well-tolerated and highly immunogenic across a broad spectrum of vaccine recipients.

## References

1. Li, Z. et al. Efficacy, immunogenicity and safety of COVID-19 vaccines in older adults: a systematic review and meta-analysis. Frontiers in immunology vol. 13 965971 (2022).

2. Badell, M. L., Dude, C. M., Rasmussen, S. A. & Jamieson, D. J. Covid-19 vaccination in pregnancy. BMJ 378, e069741 (2022).

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