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

Alexa Keeshan[1,2], Aliisa Heiskanen[1,2], Erin Collins[1,2], Corey Arnold[3], Yannick Galipeau[3], Raphael Saginur[4,5,6], Ronald Booth[7,8], Julian Little[1,2,9,10], Michaeline Mcguinty[4,5], Angela Crawley[3,9,11,12], Marc-André Langlois[3,9,12], Curtis L. Cooper[1,2,4,5,9,12]

[1]School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Canada. [2]Clinical Epidemiology, Ottawa Hospital Research Institute, Canada. [3]Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Canada. [4]Division of Infectious Diseases, Department of Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Canada. [5]Faculty of Medicine, University of Ottawa, Canada. [6]Ottawa Health Science Network Research Ethics Board (OHSN-REB), Ottawa Hospital Research Institute, Canada. [7]Department of Pathology and Laboratory Medicine, University of Ottawa, Canada. [8]Immunology Section, Eastern Ontario Regional Laboratory Association (EORLA), Canada. [9]Coronavirus Variants Rapid Response Network (CoVaRR-Net), Faculty of Medicine, University of Ottawa, Canada. [10]The Knowledge Synthesis and Application Unit (KSAU), University of Ottawa, Canada. [11]Chronic Disease Program, Ottawa Hospital Research Institute, Canada. [12]Centre for Infection, Immunity and Inflammation (CI3), University of Ottawa, Canada.

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) Range	45.0 (13.9) 18-79	44.4 (13.7) 18-79	46.8 (14.6) 22-76	0.02*
Male, n (%) Female, n (%)	340 (32.9) 694 (67.1)	254 (31.6) 549 (68.4)	86 (37.2) 145 (62.8)	0.11
IC, n (%) NIC	316 (30.6) 718 (69.4)	247 (30.8) 556 (69.2)	69 (29.9) 162 (70.1)	0.80
Vaccines, n (%) mRNA-mRNA AZ-AZ mRNA & AZ	811 (87.5) 10 (1.1) 106 (11.4)	626 (87.1) 7 (1.0) 86 (12.0)	185 (88.9) 3 (1.4) 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.

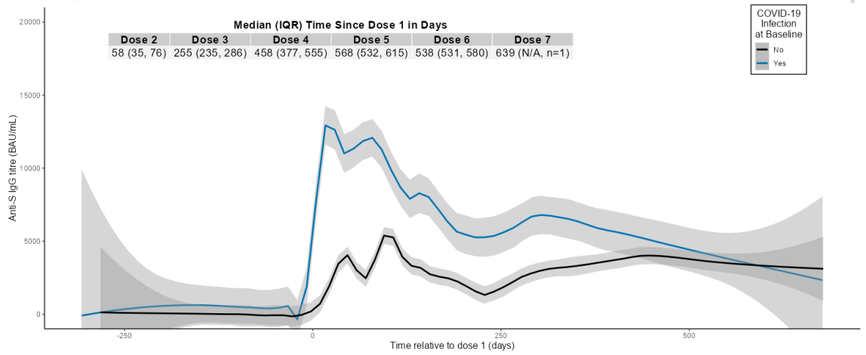
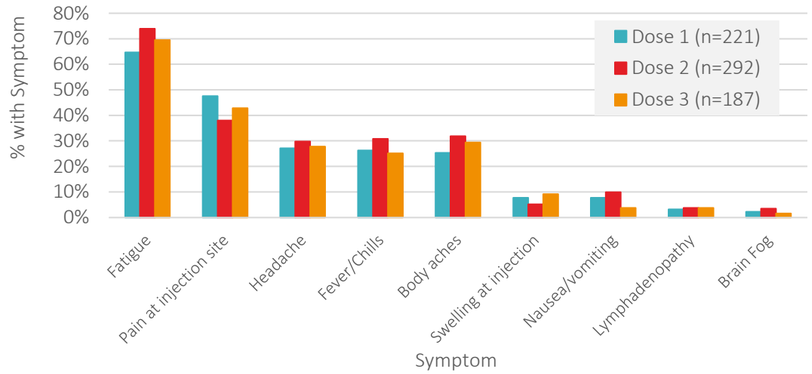


Table 2. Difference in median anti-S IgG titres (log10 BAU/mL) among those with no prior infection 2-4 months post dose 2 by MV quantile regression analysis. *A two-sided alpha-level of 0.05 was used.

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) -0.1353 (-0.2313, -0.0392)	0.95 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).

STOP THE SPREAD OTTAWA