Investigation of the interplay between sex and age in antibody responses to SARS-CoV-2 infection and vaccination

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Introduction: Sex differences in the response to SARS-CoV-2 infection, vaccination and long-term recovery are increasingly recognized. While infection prevalence is largely sex independent, some evidence suggest higher infection rates in females. In contrast, males are more likely to experience severe disease, combined with hospitalization rates and higher mortality. Increased severity is observed in elderly males.

Objective: Antibody response profiles to SARS-CoV-2 proteins in the Stop the Spread Ottawa cohort were investigated with several novel analytical tools to determine the differences in response to infection and/or immunizations between sex and age cohorts.

Methods: Serial serum samples were collected from 970 individuals starting in Oct 2020 (total 3666 samples). Here samples are grouped by vaccination period, age, sex and COVID19 natural immunity status (i.e. no previous SARS-CoV-2 infection: "Negative" and history of SARS-CoV-2 infection, confirmed by anti–receptor-binding domain (RBD) status "Positive"). For each sample, data includes antibody titers (international units, BAU) specific to SARS-CoV-2 receptor binding domain (R), spike (S) and nucleocapsid (N) corresponding IgG, IgA and IgM isotypes and ACE2 neutralization (%). Analytical methods included machine learning cluster analysis such as Fuzzy C-means, statistical methods and distance correlation.

Overview of the dataset

	Pre-vaccination (male/female)	Vaccine Dose 1 (male/female)	Vaccine Dose 2 (male/female)
Unique subjects per group (total 970)	198 / 394	122 / 244	140 / 290
Samples	393 / 643	205/ 422	440 / 1012
COVID19 Positive	177 / 163	84 / 90	119 / 168
COVID19 Negative	216 / 480	121 / 332	321 / 844
Age < 40	98 / 246	58 / 163	124 / 398
Age 40-60	173 / 275	79 / 174	198 / 454
Age > 60	118 / 119	68 / 85	118 / 160

Results

Figure 1. Unsupervised analyses highlights the dominant effect of vaccination on the data. Shown is Principal Component Analysis of log transformed and scaled dataset. D1 etc. corresponds to Vaccine Dose 1.

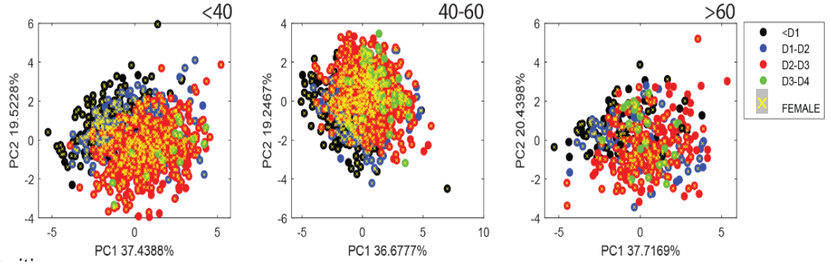


Figure 3. Fuzzy C-means Clustering of serology measures within cohorts showing differences in grouping with Neutralization males and females separately. Bar graphs correspond to weights for each features' association to the cluster with the strongest association of Neutralization.

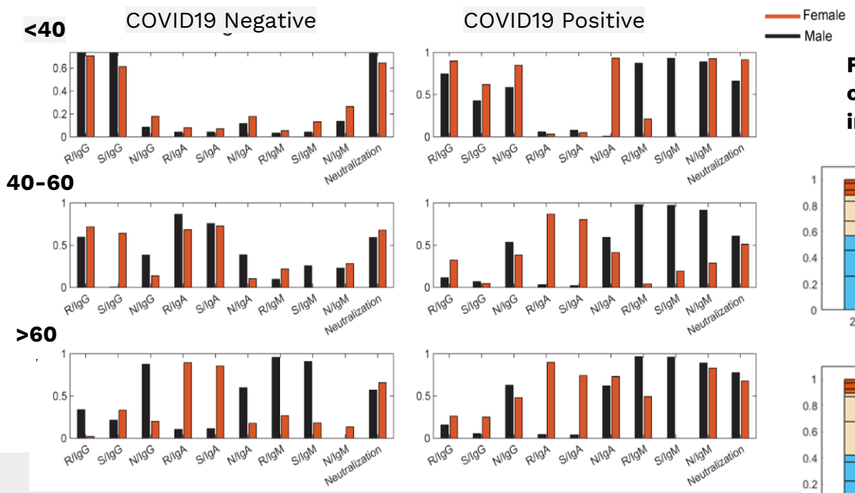


Figure 2. In each subgroup there are some statistically significant differences in feature concentrations between sexes. F-test selection of significantly different features between males and females in age and COVID19 status separated cohorts. Red line indicates statistical significance (p<0.05).

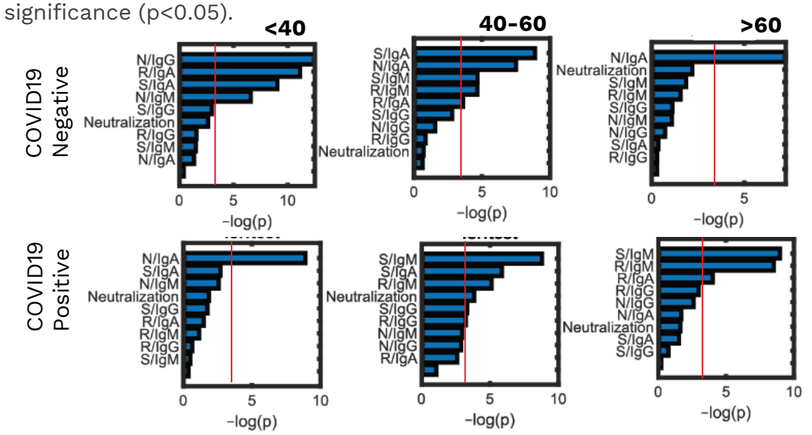
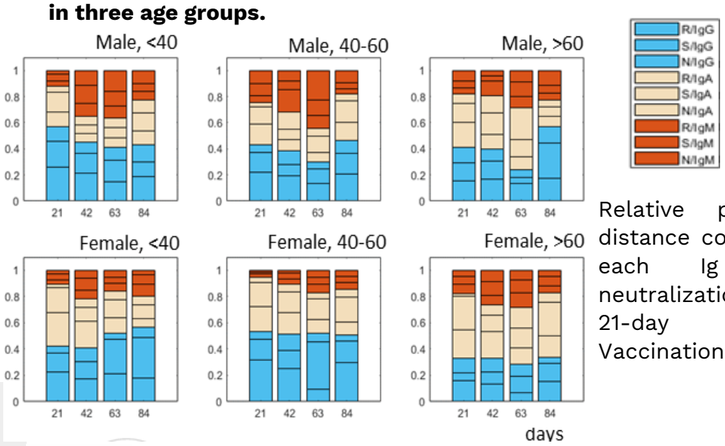


Figure 4. Relative contributions of measured antibodies to Neutralization changes over time with different behaviour observed in males and females in three age groups.



Relative pair-wise square distance correlation between each Ig factor and neutralization calculated for 21-day periods post Vaccination Dose 2.

Conclusions: Sex and age differences in the response to COVID19 infection and immunization lie in the level of relative contribution of the antibodies to neutralization. Immune response profiles described in this way offer an integrated view of correlates of protection that may best inform the design and efficacy of future vaccination.

The identification of population-level immune response profiles, rooted in antibody responses, will inform our subsequent evaluation of concurrent cell-mediated immune responses (i.e., T-cells) and other systemic biomarkers.

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