THE BEST OF THE WEEK (23 mag – 29 mag 2022)

G. Arbor et al.

SARS-CoV-2 vaccination diversifies the CD4+ spike-reactive T cell repertoire in patients with prior SARS-CoV-2 infection

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Abstract

Background COVID-19 mRNA vaccines elicit strong T and B cell responses to the SARS-CoV-2 spike glycoprotein in both SARS-CoV-2 nay¨ve and experienced patients. However, it is unknown whether the post-vaccine CD4+ T cell responses seen in patients with a history of COVID-19 are due to restimulation of T cell clonotypes that were first activated during natural infection or if they are the result of new clones activated by the vaccine.

Methods To address this question, we analyzed the SARS-CoV-2 spike glycoprotein-specific CD4+ T cell receptor repertoire before and after vaccination in 10 COVID-19 convalescent patients and 4 SARS-CoV-2 nayive healthy donor vaccine recipients. We used the viral Functional Expansion of Specific T cells (ViraFEST) assay to quantitatively identify specific SARS-CoV-2 and common cold coronavirus CD4+ T cell clonotypes post COVID-19 disease resolution and post mRNA SARS-CoV-2 vaccination.

Findings We found that while some preexisting T cell receptor clonotypes persisted, the post-vaccine repertoire consisted mainly of vaccine-induced clones and was largely distinct from the repertoire induced by natural infection. Vaccination-induced clones led to an overall maintenance of the total number of SARS-CoV-2 reactive clonotypes over time through expansion of novel clonotypes only stimulated through vaccination. Additionally, we demonstrated that the vaccine preferentially induces T cells that are only specific for SARS-CoV-2 antigens, rather than T cells that cross-recognize SARS-CoV-2/common cold coronaviruses.

Interpretation These data demonstrate that SARS-CoV-2 vaccination in patients with prior SARS-CoV-2 infection induces a new antigen-specific repertoire and sheds light on the differential immune responses induced by vaccination versus natural infection.

M.R. Chang et al.

Analysis of a SARS-CoV-2 convalescent cohort identified a common strategy for escape of vaccineinduced anti-RBD antibodies by Beta and Omicron variants

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Abstract

Background Evolutionary pressure has led to the emergence of SARS-CoV-2 variants, with the most recent Omicron variant containing an unparalleled 30 mutations in the spike protein. Many of these mutations are expected to increase immune evasion, thus making breakthrough cases and re-infection more common.

Methods From June 2020 to December 2021 serial blood samples (initial post recovery, 6 months, 12 months) were collected from a COVID-19 convalescent cohort in Boston, MA. Plasma was isolated for use in Mesoscale Discovery based antibody binding assays. Unvaccinated donors or those vaccinated prior to the primary blood draw were excluded from this analysis, as were those who did not have at least two blood draws. Wilcoxon signed rank tests were used to compare pre- and post-vaccination titers and antibody response against different variants, while McNemar tests were used to compare the proportions of achieving 4 fold increases against different variants.

Findings Forty-eight COVID convalescent donors with post-infection vaccination (hybrid immunity) were studied to evaluate the levels of cross-reactive antibodies pre- and post- vaccination against various SARS-CoV-2 Spike and receptor binding domain (RBD) proteins. Vaccination with BNT162b2, mRNA-1273 or Ad26.COV2.S led to a 6¢3 to 7¢8 fold increase in anti-Spike antibody titers and a 7¢0 to 7¢4 fold increase in anti-WT, Alpha and Delta RBD antbody. However, a lower response was observed for Beta and Omicron RBDs with only 7/48 (15%) and 15/48 (31%) donors having a 4 fold increase in post-vaccination titers against Beta and Omicron RBDs. Structural analysis of the Beta and Omicron RBDs reveal a shared immune escape strategy involving residues K417-E484-N501 that is exploited by these variants of concern.

Interpretation Through mutations of the K417-E484-N501 triad, SARS-CoV-2 has evolved to evade neutralization by the class I/II anti-RBD antibody fraction of hybrid immunity plasma as the polyclonal antibody response post-vaccination shows limitations in the ability to solve the structural requirements to bind the mutant RBDs.

G. Nattino et al.

Association Between SARS-CoV-2 Viral Load inWastewater and Reported Cases, Hospitalizations, and Vaccinations in Milan, March 2020 to November 2021

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Abstract

Several studies have demonstrated that wastewater surveillance can be used to monitor SARS-CoV-2 incidence. This surveillance intends to overcome the limitations of traditional surveillance indicators, such as the number of positive tests, which depends on test availability and indications, or COVID-19–related hospitalizations, which occur weeks after the spread of SARS-CoV-2 and do not include mild or asymptomatic cases. This study evaluated the association between SARS-CoV-2 load in urban wastewater and surveillance indicators of infection prevalence and severity in Milan, Italy.

Methods

Sewage samples were collected approximately once a week from March 2020 to November 2021 in the Nosedo wastewater treatment plant, serving about 50% of the Milan population. SARS-CoV-2 RNA was measured in wastewater by amplifying the nucleocapsid gene, and viral load was calculated correcting for daily wastewater flow and population (eMethods in the Supplement). Aggregate epidemiological data about Milan were supplied by the Lombardy Region and included daily numbers of SARS-CoV-2–positive cases, COVID-19 hospitalizations, and individuals

completing the vaccination cycle (2 doses for 2-dose vaccines or 1 for Ad26.COV2.S [Janssen/Johnson & Johnson]) by age group and sex. According to Italian legislation, informed consent and ethics committee approval were not required because the analyzed data were anonymous.

The SARS-CoV-2 load in wastewater was graphically compared with surveillance indicators of infection prevalence. Local polynomial regression was conducted and 95% confidence intervals calculated to assess trends in SARS-CoV-2 loads. Positive cases and COVID-19 hospitalizations in Milan were used to estimate the prevalence of infection and severe infection, assuming a 15-day viral excretion for each positive or hospitalized individual (eMethods in the Supplement). The daily proportion of vaccinated individuals was computed and standardized by age and sex to the population of patients with COVID-19 hospitalized before the vaccination campaign started. Such standardization was performed to measure the coverage of individuals at higher risk of hospitalization after SARS-CoV-2 infection. Analyses were performed with R version 4.0.2.

Results

Figure 1 presents positive cases and hospitalizations over the study period. Figure 2 presents wastewater SARS-CoV-2 loads. The vaccination campaign began in January 2021 and coverage progressively increased, reaching 75% (>85% for individuals at increased risk of hospitalization) in November 2021. The curves for wastewater load and hospitalized patients are similar until the increase in vaccination coverage. The curves for wastewater load and positive cases also are similar except during the first wave, which was characterized by a shortage of tests. Curves for positive cases and hospitalizations diverge from the curve for wastewater load as vaccination coverage increased, with decreases in cases and hospitalizations and increases in wastewater viral load. On November 30, 2021, despite the limited number of positive cases (n = 4672) and hospitalizations (n = 252), the wastewater load was 7.25×10^9copies/d/1000 people (95% CI, 2.43-24.80 $\times 10^9$), comparable with values observed during the second wave (November 10, 2020; 12.30×10^9copies/d/1000 people, 95% CI, 4.71-22.31 $\times 10^9$), before the vaccination campaign started.

Discussion

In Milan, high wastewater SARS-CoV-2 loads were found when vaccination coverage was high and traditional surveillance indicators suggested limited SARS-CoV-2 prevalence. This result suggests that there was significant circulating virus in the population during this period, including among vaccinated individuals. The SARS-CoV-2 circulation among vaccinated individuals may create modest evolutionary pressure toward resistance to the host's immune response, making variants with significant transmission advantages more competitive. The current spread of the Omicron variant supports this theory.

This study is limited by the difficulty in translating SARS-CoV-2 wastewater loads into infection prevalence because the variability of loads is affected by factors that can be controlled only partially.Nonetheless, the magnitude of the observed trends supports the value of wastewater surveillance to monitor the spread of SARS-CoV-2. In addition, the study was limited to a single city.

The results suggest that vaccines are effective in protecting against symptomatic and severe disease, but that, with high vaccination rates, standard surveillance metrics may not accurately estimate the spread of SARS-CoV-2. Thus, wastewater surveillance may be important as an early warning of virus circulation. These results strengthen the scientific basis of the recommendations from the Centers for Disease Control and Prevention National Wastewater Surveillance System and European Commission to establish systematic SARS-CoV-2 wastewater surveillance networks.