

Mucosal immune responses following a fourth SARS-CoV-2 vaccine dose

We previously highlighted the importance of mucosal IgA, but not IgG, in preventing SARS-CoV-2 infection.¹ Although intramuscular SARS-CoV-2 vaccines might strengthen mucosal IgA antibody responses in previously infected individuals,² the effect on mucosal immune responses upon repeated booster doses is largely unknown. Here we investigated SARS-CoV-2 spike-specific IgA and IgG responses in the mucosa (nasal samples) and serum following booster mRNA vaccination (fourth dose) in individuals with and without previous SARS-CoV-2 infection.

Participants were enrolled via an ongoing prospective cohort study of health-care workers,¹ with repeated serological measurements taken every four months since April, 2020. Serum and mucosal anti-spike antibodies were measured at 0, 3, 7, 14, and 30 days after booster mRNA vaccination (fourth dose) in 24 participants (appendix pp 6–7). Previous SARS-CoV-2 infection was confirmed with a positive qPCR test recorded in the national communicable diseases register or within the regular qPCR screening programs within the study protocol, a self-reported positive rapid diagnostic test, seroconversion at any follow-up visits before vaccination, or seroconversion to SARS-CoV-2 nucleocapsid antigen after vaccination.

Serum wild-type anti-spike IgG concentrations increased following the booster dose, as anticipated, both

in participants without (n=5) and with (n=19) previous infection (appendix pp 8–10). Notably, anti-spike serum-IgA and nasal-IgA antibody concentrations against wild-type or BA.5 did not increase regardless of previous infection (appendix pp 8–12, 15). Nasal wild-type anti-spike IgA concentrations correlated strongly with nasal wild-type anti-spike secretory IgA concentrations, (correlation coefficient [r]=0.91, $p<0.001$; appendix p 13), but there was no correlation between the fold changes of nasal anti-spike IgA and serum anti-spike IgG ($r=0.1$, $p=0.8$; appendix p 14). Conversely, nasal wild-type anti-spike IgG increased in both SARS-CoV-2 naive participants (n=5) and previously infected participants (n=19; appendix pp 8–9) and fold change in nasal wild-type anti-spike IgG correlated strongly to serum wild-type anti-spike IgG ($r=0.78$, $p<0.0001$; appendix p 14), suggesting a passive transudation of plasma IgG into the mucosa.

Although a fourth vaccine dose provides increased protection against severe disease and death in frail individuals,³ protection against infection is restricted⁴ and viral transmission is abundant also in populations with a high vaccine uptake. Our previous work shows a mucosal correlate of protection mediated by nasal IgA acquired from previous infection.^{1,5} Our current findings show that mucosal IgA responses are poorly boosted by systemic mRNA vaccines, also in immunocompetent individuals with previous infection, emphasising the need for alternative vaccine platforms enhancing mucosal immunity.

This study was supported by grants from the Jonas and Christina af Jochnick Foundation, Region

Stockholm, SciLifeLab, the Knut and Alice Wallenberg Foundation, the Leif Lundblad Family Foundation, the Swedish Research Council, the Swedish Heart and Lung Foundation, the Bill & Melinda Gates Foundation, and the Center for Innovative Medicine. We declare no competing interests.

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Published Online
April 19, 2023
[https://doi.org/10.1016/S2666-5247\(23\)00102-7](https://doi.org/10.1016/S2666-5247(23)00102-7)

See Online for appendix