Ultrasensitive blood test detects viral protein, confirms vaccine activates robust immune response

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The carefully orchestrated dance between the immune system and the viral proteins that induce immunity against COVID-19 may be more complex than previously thought. A new study by investigators at Brigham and Women's Hospital used an ultrasensitive, single-molecule array (Simoa) assay to detect extremely low levels of molecules in the blood and measured how these levels change over the days and weeks following vaccination. The team found evidence of circulating protein subunits of SARS-CoV-2, followed by evidence of the body mounting its immune response and then clearing the viral protein to below the level of single-molecule detection. Results are published in *Clinical Infectious Diseases*.

"Because of our ultra-sensitive method, we're able to corroborate that the mRNA vaccine is operating as intended, stoking the body's immune response," said co-corresponding author David Walt, Ph.D., a member of the faculty in the Department of Pathology at the Brigham. Walt is also a member of the Wyss Institute and is a Howard Hughes Medical Institute Professor. "We were able to detect extremely low levels of viral protein and see that as soon as the body begins generating antibodies, those levels declined to undetectable." Walt has a financial interest in Quanterix Corporation, the company that developed the ultra-sensitive digital immunoassay platform used in this work.

To conduct their study, Walt and colleagues measured levels of SARS-CoV-2 protein subunits in plasma samples collected from 13 participants who received two doses of the Moderna (mRNA-1273) vaccine. Specifically, the team measured levels of SARS-CoV-2 antigens Spike, S1, and Nucleocapsid. The team examined plasma collected at 10-13 timepoints between 1 and 29 days after the first injection and 1-28 days after the second injection. The average age of participants was 24 and the percentage of female participants was 46.

The team found that 11 of 13 participants had low levels of SARS-CoV-2 protein (S1 subunit) as early as one day post-vaccination. S1 subunit protein level peaked on average five days after the first injection. In all participants, the level of S1 protein declined and became undetectable by day 14. Spike protein was detected in 3 of 13 participants an average of 15 days after the first injection. After the second vaccine dose, no S1 or Spike was detectable.

The team collected corresponding antibody data and showed that the immune response began to mount after the viral proteins were produced. Increased antibody levels correlated with viral protein clearance from plasma.

The researchers note that the level of translated

protein detected was extremely low and disappeared once antibodies were detected. All participants in the study were healthy volunteers who were vaccinated but not infected with SARS-CoV-2.

"The vaccine is designed to introduce mRNA into the body, which is then translated into the Spike protein. It is the Spike protein that can activate the immune system, which in turn creates antibodies to prevent future infections," said co-first author Alana Ogata, Ph.D., a postdoctoral fellow in the Walt lab. "We observed that antibodies that target Spike and S1 proteins are generated as early as 1-2 days after circulating S1 is detected, followed by the clearance of proteins. Additionally, we see that the second dose does not result in circulating protein but does provide an additional boost in antibody levels, as expected."

Researchers note that limitations of the current study include the small sample size and potential biases that result from enrolling healthy, young adults, which may not be representative of the general population. The research team plans to continue their plasma studies in other populations, including pregnant people and children, to further understand the dynamics between viral proteins and the immune response.

More information: Alana F Ogata et al, Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients, *Clinical Infectious Diseases* (2021). DOI: 10.1093/cid/ciab465

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