Medical Xpress

The hunt is on for the telltale biomarker revealing precise degree of protection conferred by Moderna's mRNA vaccine

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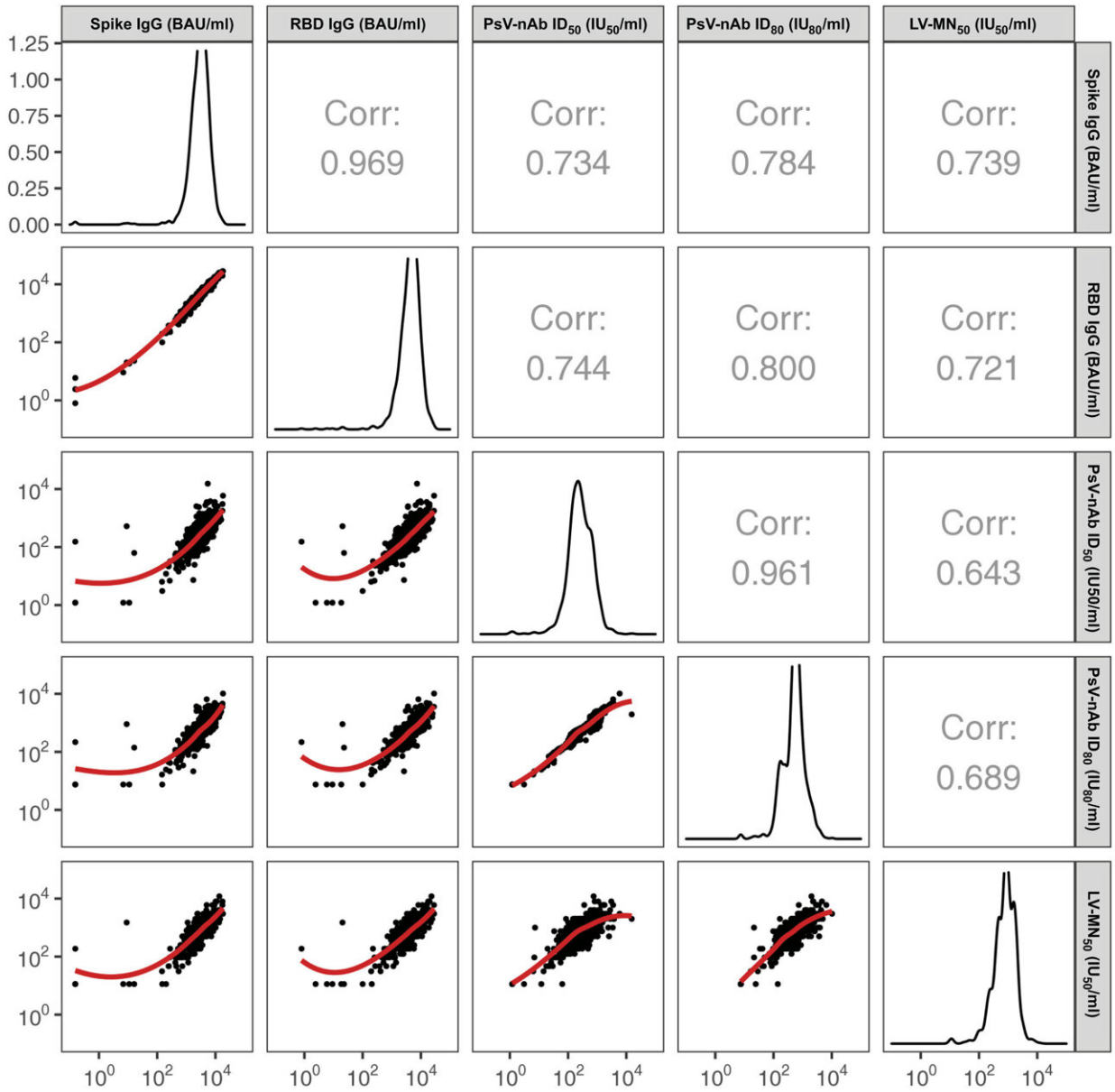

D57 LV-MN_{50} titers are more highly correlated with D57 spike IgG concentrations and with D57 RBD IgG concentrations than with D57 PsV-nAb ID_{50} titers or with D57 PsV-nAb ID_{80} titers.Analyses were conducted in baseline SARS-CoV-2–negative per-protocol vaccine recipients in the immunogenicity subcohort. Corr indicates the baseline variable-adjusted Spearman rank correlation. ID_{50}, 50% inhibitory dilution; ID_{80}, 80% inhibitory dilution; LV, live virus; MN_{50}, 50% microneutralization dilution; nAb, neutralizing antibody; PsV, pseudovirus. Correlations among spike IgG, RBD IgG, PsV-nAb, ID_{50}, and PsV-nAb ID_{80} were reported previously [figure S6 of (*10*)]. Serological assay readouts are expressed in values relative to the World Health Organization (WHO) International Standard for anti–SARS-CoV-2 immunoglobulin (*27*). bAb readouts were converted to bAb units per milliliter (BAU/ml), and PsV-nAb titers and microneutralization assay readouts were calibrated to international units per milliliter (IU_{50}/ml or IU_{80}/ml). Credit: *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.ade9078

A new analysis is shedding light on antibody measurements that can help predict the protective capabilities of the Moderna mRNA vaccine for COVID-19.

Investigators examined data from a phase 3 clinical trial as well as laboratory data, searching for potential correlates of protection—CoPs—a measurement of immunological markers, such as quantity of antibodies, associated with the level of vaccine protection. A CoP is a critical measure that provides data on how well any given vaccine will help shield people from infection. Looked at another way, a CoP is a telltale signature in the immune system that, once it's found, can reliably predict how well a vaccine will protect against infection or severe disease.

Potent predictors currently exist, but what scientists want is even greater precision. Hence, the search for more definitive CoPs.

Identifying such correlates is important because they measure the performance of a vaccine. So far, the new study shows that the titer of antibodies potentially shines as a strong predictor of Moderna's mRNA vaccine protection. A titer is the presence and amount antibodies that can neutralize a virus; in this case, SARS-CoV-2.

Writing in *Science Translational Medicine*, investigators analyzed immunological data from the COVE clinical trial as well as data from research in which a SARS-CoV-2-like pseudovirus was studied. The COVE study, which stands for The Coronavirus Efficacy (COVE) phase 3 trial, was launched in July 2020 to assess the safety and efficacy of the Moderna vaccine, dubbed mRNA-1273.

While an independent data and safety monitoring board determined that the vaccine met the pre-specified efficacy criteria at the first interim analysis, the new research drilled deeper into the immunological data to search for correlates of protection, the telltale signature in the immune system.

"The identification and validation of a correlate of protection, an immune biomarker that can be used to reliably predict the degree of vaccine efficacy against a clinically relevant outcome is a priority in COVID-19 vaccine research," writes Dr. David Benkeser of Emory University's Rollins School of Public Health, and lead author of the multi-center study.

"CoPs are valuable for expediting vaccine development and use. For example, for a vaccine with established efficacy, a CoP could serve as a primary endpoint for immunobridging of vaccine efficacy to a target population that was not included in the randomized trial," Benkeser

added.

Immunobridging is a clinical trial approach in which effectiveness is inferred for a vaccine candidate (or drug) through an accepted surrogate measure of efficacy. Immunobridging can fast-track treatments to patients. So it's important to find the biomarker or biomarkers that can help usher a vaccine to populations to fight a circulating virus.

"Common CoPs for licensed vaccines are measurements of binding antibodies—bAbs—or neutralizing antibodies—nAbs—and multiple lines of investigation have supported these immune markers as CoPs for COVID-19 vaccines."

In the research, the large multi-center team found at least one potent biomarker: "Across all analyses, evidence for correlates was stronger for nAbs measured by the pseudovirus-based versus live virus–based neutralization assay, consistent with the findings of a nonhuman primate challenge study," Benkeser wrote.

In addition to Benkeser and several team members from Emory University in Atlanta, collaborators hailed from multiple leading research institutions in the United States, including Duke University's Human Vaccine Institute in Durham, North Carolina; the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland; the Vaccine and Infectious Disease division of the Fred Hutchinson Cancer Center in Seattle, Washington, and Moderna, Inc. in Cambridge, Massachusetts.

Benkeser and colleagues say phase 3 trials, such as the COVE study, provide "particularly valuable evidence to support an immune biomarker as a CoP." The COVE trial was conducted at 99 clinical sites in the United States and involved 30,420 participants, who were randomized at a 1:1 ratio to receive either mRNA-1273 or a placebo. In the blinded

trial, vaccine efficacy was 93.2%, Benkeser and team members say.

Using a multivariate model, the researchers compared how various antibody markers, including a new one based on live virus neutralization, correlated with vaccine protection. They found that higher titers of antibodies against SARS-CoV-2's spike protein and titers of neutralizing antibodies against SARS-CoV-2 pseudovirus were strong correlates of risk. Additionally, titers of pseudovirus neutralizing antibodies were the strongest independent predictors of vaccine protection in modeling experiments.

"Given that the correlate analyses of COVE to date have been restricted to SARS-CoV-2 naïve individuals, COVID-19 endpoints by ancestral strain-like viruses, and antibodies measured to the ancestral strain…future analyses should provide multiple insights relevant for guiding vaccine development and use in the contemporary context of the COVID-19 pandemic," Benkeser and colleagues concluded.

More information: David Benkeser et al, Comparing antibody assays as correlates of protection against COVID-19 in the COVE mRNA-1273 vaccine efficacy trial, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.ade9078