COVID-19 and the Common Cold—Preexisting Coronavirus Antibodies May Hinder SARS-CoV-2 Immunity

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Our seasonal coronaviruses—2 of which are betacoronaviruses, like SARS-CoV-2—cause about 30% of common colds. Instead of helping to fight off COVID-19, antibodies to these pathogens may interfere with the SARS-CoV-2 immune response, a recent study of health care workers suggests. Although these preexisting antibodies are ubiquitous, individuals’ varying levels of them might factor into the broad spectrum of responses to the novel coronavirus, which range from immunity against infection all the way to severe respiratory distress and death.

The Backstory
Almost since the COVID-19 pandemic began, scientists have investigated how immunity to the seasonal coronaviruses might influence infections with SARS-CoV-2, a new but related virus. A number of reports now show that preexisting common cold coronavirus antibodies are active in SARS-CoV-2 infections, according to Patrick Wilson, PhD, a professor of pediatrics and a scientist in the Gale and Ira Drukier Institute for Children’s Health at Weill Cornell Medicine, who was not involved with the new study.

Last year, Wilson and colleagues at the University of Chicago, where he was based at the time, found that people with severe acute SARS-CoV-2 infections had substantial numbers of antibody-secreting B cells that reacted to common cold coronaviruses. The cells had highly mutated and variable genes, likely indicating that they predated the patients’ novel coronavirus infections. As for an influence on COVID-19, one early 2021 University of Pennsylvania study concluded that preexisting antibodies to common cold coronaviruses did not correlate with SARS-CoV-2 protection.

But the overall findings have been inconsistent. Taken together, it’s hard to say which way they lean because the studies’ scope, participants, and methods have varied, according to Maureen McGargill, PhD, the senior author of the recent health care workers study and an associate faculty member in immunology at St Jude Children’s Research Hospital, where the research took place.

“Keeping these caveats in mind, there were seven reports that concluded high levels of common coronavirus immunity was beneficial, while four reported that it was detrimental, and three reported that it did not have an impact,” McGargill wrote in an email to JAMA.

In her study, published in Cell Host & Microbe this January, she and St Jude colleagues investigated whether different levels of preexisting immunity to common cold coronaviruses influenced the likelihood of becoming infected with SARS-CoV-2 or accounted for diverse outcomes following infection.

“This is important to study as we still do not understand why some individuals are more susceptible than others to SARS-CoV-2 infection,” she explained.

The Design
The researchers analyzed data from more than 1200 hospital employees who volunteered for the St Jude Tracking of Viral and Host Factors Associated with COVID-19 (SJTRC) study. Basic and clinical researchers in infectious diseases and immunology developed the project to track multiple aspects of the SARS-CoV-2 immune response and factors that may affect COVID-19 susceptibility. In the study:

• Participants provided a baseline blood sample and underwent weekly nasal swab screening for SARS-CoV-2 infection.
• Those who tested positive also provided blood samples at 2 subsequent time points.
• Those who did not become infected provided blood samples after they were vaccinated against COVID-19.

During the H1N1 influenza pandemic in 2009, SJTRC investigators learned the importance of collecting baseline samples from individuals before they became infected. With that insight, they designed the COVID-19 study to collect blood samples prior to infection or vaccination. The researchers therefore were able to measure antibody levels from the same individual before and after SARS-CoV-2 infection, the biggest methodological difference from most of the prior studies, according to McGargill.

They also measured 3 different types of antibodies—IgM, IgG, and IgA, which arise in response to infection all the way to severe respiratory distress and death.

What the Analysis Found
• Nearly every participant had IgG antibodies against the seasonal betacoronavirus antibodies which are betacoronaviruses, like SARS-CoV-2 infections, accounted for diverse outcomes following infection. The researchers therefore were able to measure antibody levels from the same individual before and after SARS-CoV-2 infection.

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They also measured 3 different types of antibodies—IgM, IgG, and IgA, which arise in that order during an infection with a novel virus—to get a more comprehensive analysis and studied how preexisting common cold coronavirus immunity affected mice challenged with SARS-CoV-2.

What the Analysis Found
• Almost all participants had prior immunity to all 4 common cold coronaviruses but the antibody levels varied dramatically among them.
• Nearly every participant had IgG antibodies to all 4 seasonal viruses. IgM antibodies were the least prevalent.
• Preexisting seasonal betacoronavirus antibodies increased after SARS-CoV-2 infection, an immunological phenomenon known as “back-boosting.” In several participants, IgG antibodies against 1 of the seasonal betacoronaviruses increased within 5 days of infection. For more than 50% of the patients, IgA antibodies against both seasonal betacoronaviruses increased within 10 days.
However, high levels of preexisting common cold antibodies were not associated with protection from SARS-CoV-2 infection.

In contrast, high levels of preexisting common cold antibodies were associated with higher antibody levels against SARS-CoV-2 after infection, which in turn were an indicator of greater disease severity. But few participants became severely ill, which limited the ability to examine whether the common cold antibody levels factored into severe COVID-19.

Neither baseline seasonal antibody levels nor increased levels after vaccination correlated with postvaccination SARS-CoV-2 antibody levels.

In the animal model, prior immunization with common cold coronavirus proteins profoundly inhibited the mice from generating SARS-CoV-2 neutralizing antibodies. “Together, these data indicate that preexisting betacoronavirus IgA and IgG correlate with a higher antibody response to SARS-CoV-2 following infection, but not vaccination,” the researchers wrote. “As increased SARS-CoV-2 antibodies after infection correlated with greater disease, these findings raise the possibility that preexisting betacoronavirus IgG and IgA negatively impact the immune response to SARS-CoV-2, which results in greater duration of antigen and therefore more SARS-CoV-2 antibodies.”

The Scientists’ Takeaway
According to McGargill, the finding that immunity to common cold coronaviruses is boosted early after SARS-CoV-2 infection indicates that memory B cells contribute to the initial immune response. What’s more, the researchers did not observe many IgM antibodies before IgG or IgA antibodies, which also suggests that the initial antibody response is derived from memory B cells rather than more adaptable naive B cells. All this indicates that part of the SARS-CoV-2 immune response is imprint by past bouts of the common cold.

To McGargill and her team, the data collectively suggest that variations in levels of preexisting immunity to common cold coronaviruses are 1 factor that may affect outcomes following SARS-CoV-2 infection. Prior immunity to a related, yet distinct, coronavirus could hinder immunity to a new coronavirus.

A Note on Age
The researchers theorized in their article that older adults’ preexisting coronavirus antibody repertoire may be less adaptable than that of younger individuals, which might help to explain less COVID-19 disease severity in the latter group.

The concept comes from prior studies investigating immunity to different influenza virus subtypes. In one 2019 study, Wilson found that as individuals age and encounter different pathogens, their proportion of B cells that can mutate and adapt decreases, while their more specified memory B cells increase. Accordingly, older individuals may be well protected against previously circulating viruses but may not be able to mount strong immunity to new viruses, McGargill explained.

A Methodological Lesson
Because some of the common cold antibodies increased early in SARS-CoV-2 infection, and because their levels varied dramatically among participants, McGargill said the study shows it’s not possible to accurately determine an individual’s level of preexisting immunity unless a sample is collected from that person prior to infection.

This could affect how related research is interpreted. For example, a different study published around the same time came to a similar overall conclusion as the St Jude study but used different methodologies. That analysis did not have samples from the same individuals before and after SARS-CoV-2 infection. “Thus,” McGargill wrote, “while they identified differences in [common cold coronavirus] antibodies between noncritical and critically ill SARS-CoV-2 patients, it is not possible to know if these were preexisting differences.”

More to Come
In McGargill’s study, researchers primed mice with common cold coronavirus spike proteins and then boosted them with SARS-CoV-2 spike protein. Wilson explained that the rodents’ immune responses were driven to shared portions of these spikes, which do not tend to provide direct protection.

“This implies that high levels of preexisting antibodies to common-cold coronaviruses, or B cells that can make such antibodies, will drive a less protective immune response to SARS-CoV-2,” Wilson wrote.

He emphasized, however, that the idea that preexisting antibodies to common cold coronaviruses lead to increased SARS-CoV-2 susceptibility or COVID-19 severity still needs to be proven: “That is only conjecture at this point.”

If the idea bears out, it could have implications for vaccine effectiveness. McGargill said it will be important to test whether immunity to the vaccine strain negatively influences protection from variants like Omicron that are substantially different. If so, there could be an additional argument for updating COVID-19 vaccines.

Conflict of Interest Disclosures: None reported.

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