Antibody response may drive COVID-19 outcomes

February 18 2021, by Rachel Leeson

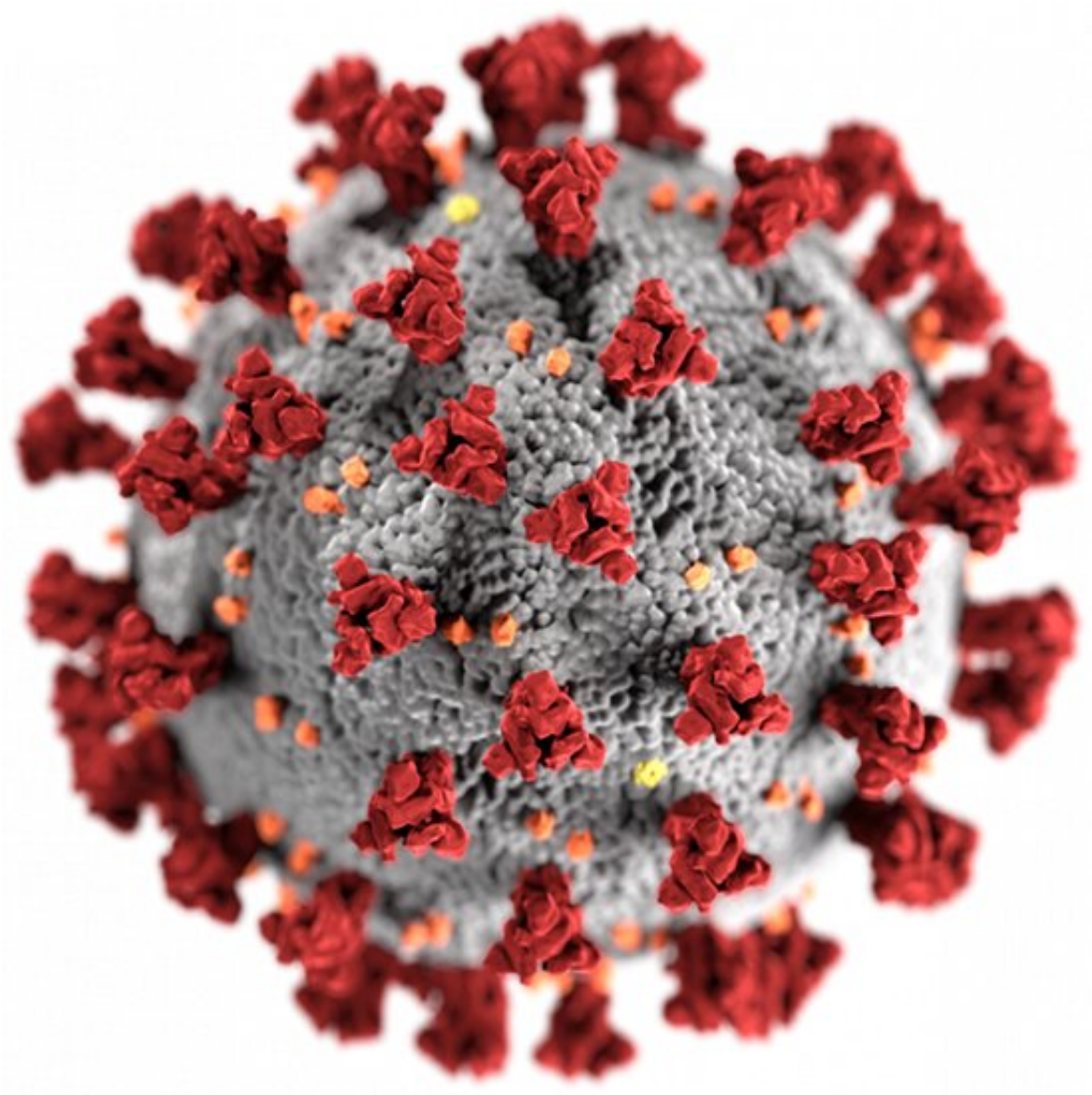

Image of the ultrastructural morphology exhibited by the 2019 Novel Coronavirus (2019-nCoV). Credit: CDC

COVID-19, the source of the current pandemic, may be caused by a single virus, but it has a variety of presentations that make treatment difficult. Children, for example, almost exclusively experience mild or asymptomatic COVID-19, while adults can develop severe or even fatal COVID-19. But children who contract COVID-19 are at risk for a rare but serious syndrome called multisystem inflammatory syndrome in children (MIS-C). Severe cases of MIS-C can lead to cardiac disease and ventricular failure, and require hospitalization and intense medical support.

Researchers Galit Alter, Ph.D., core member of the Ragon Institute of MGH, MIT and Harvard, and Lael Yonker, MD, director of the Massachusetts General Hospital Cystic Fibrosis Center, are working to understand why COVID-19 can lead to such distinctly different outcomes in different populations. In a study recently published in *Nature Medicine*, they and their team identified specific types of antibodies that may be driving these different responses, including one specific to severe disease in adults and another specific to MIS-C in children.

"We noticed children who developed MIS-C after COVID disease or exposure had high levels of a specific type of antibody called IgG," says Yonker. "Normally, IgG acts to control an infection, but with MIS-C, the IgG is triggering activation of immune cells, which may be driving the severe illness seen in MIS-C."

Specifically, explains Yonker, IgG antibodies interact with cells called macrophages, which live throughout the body's tissues. If there are too many IgG bodies activating these macrophages, this could cause inflammation in many different organs and systems, which is seen in MIS-C. These high levels of IgG antibodies were only found in children

who developed MIS-C after contracting or being exposed to COVID-19.

Yonker, a pediatric pulmonologist at MGH and assistant professor at Harvard Medical School (HMS), runs a biorepository that collects samples from pediatric cystic fibrosis patients. When the pandemic hit, she began to collect samples from children with mild cases of COVID-19. When Yonker and other pediatricians began seeing children hospitalized with what is now called MIS-C, which typically onsets three to six weeks after developing COVID-19, she quickly began collecting those samples too. She wanted to understand how a mild case of COVID-19 could lead to severe MIS-C weeks after recovery.

Seeking a detailed understanding of the immune response, Yonker teamed up with Alter, who is also a professor at HMS and an immunologist in the Department of Infectious Diseases at MGH. Alter's team used her unique "systems serology" technology to carefully perform a detailed comparison of the immune responses in children—17 with MIS-C and 25 with mild COVID-19—to the responses of 26 adults with severe disease and 34 adults with mild disease.

"We were expecting the children's immune responses to look drastically different from the adults', regardless of the severity of disease," says Alter. "But instead, we found that adults with mild COVID-19 and children with COVID-19 had remarkably similar immune responses. It was only the adults with severe COVID-19 whose immune responses looked different."

For adults with severe COVID-19, Alter explains, they saw increased levels of IgA antibodies, which interact with a type of immune cells called neutrophils and cause the neutrophils to release cytokines. If there are too many IgA antibodies, the neutrophils may be pushed to release too many cytokines, which could contribute to a cytokine storm, one of the symptoms of severe COVID-19.

In both cases, the study shows, it may be a high level of a specific type of antibody causing the disease severity. "In MIS-C, high levels of IgG antibodies may be activating macrophages, which can drive inflammation in organs throughout the body," says Yannic Bartsch, Ph.D., the study's first author and a research fellow at the Ragon Institute. "In adults with severe COVID-19, high levels of IgA antibodies could be driving neutrophils to release too many cytokines, with the potential of causing a cytokine storm."

Identifying the immune mechanisms of multiple, distinct responses to the same virus is the first step to understanding why it mounts different responses in divergent populations. Discovering how the immune system's response shapes the disease and its outcome in both children and adults can help researchers develop treatments that can prevent or modulate the immune response, keeping its protective functions but lessening the unintentional, yet harmful, ones.

More information: Yannic C. Bartsch et al, Humoral signatures of protective and pathological SARS-CoV-2 infection in children, *Nature Medicine* (2021). DOI: 10.1038/s41591-021-01263-3

Provided by Massachusetts General Hospital