Could prior exposure to common cold viruses affect the severity of SARS-CoV-2 symptoms?

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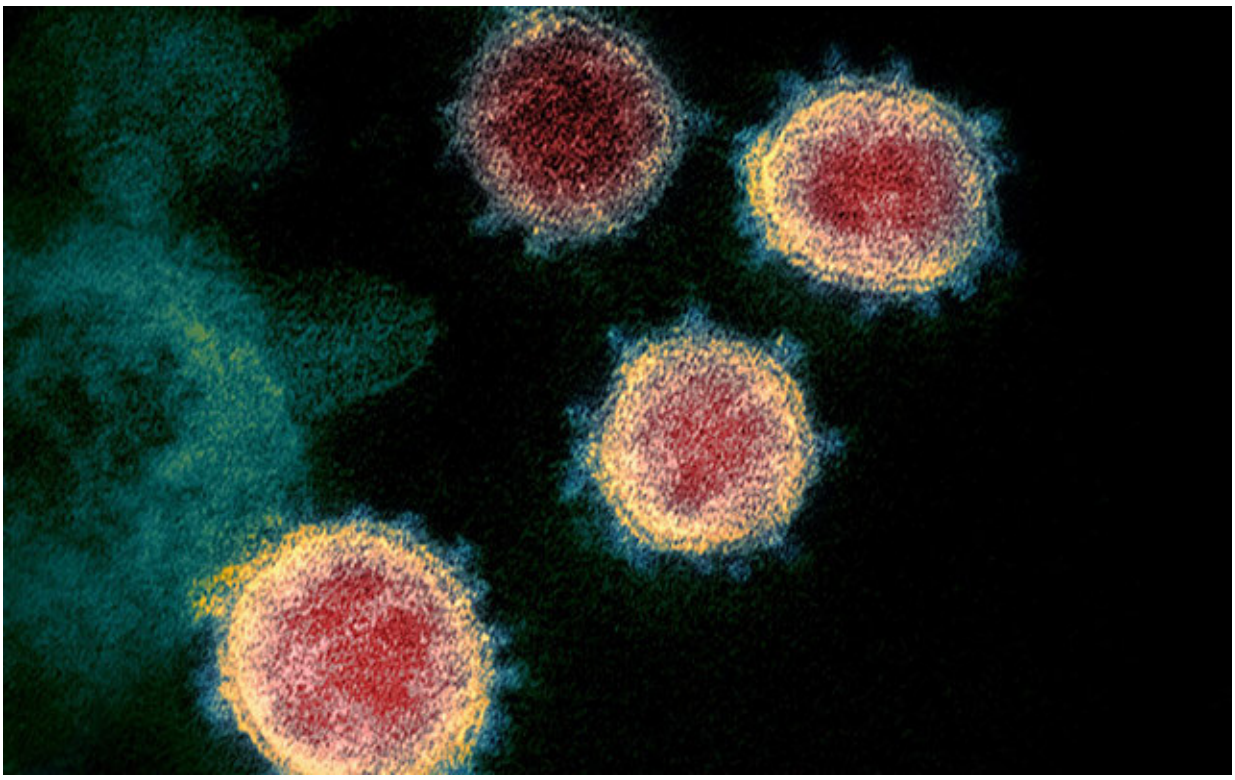

A colorized scanning electron micrograph of the SARS-CoV-2 virus. Credit: NIAID

Universitätsmedizin Berlin and the Max Planck Institute for Molecular Genetics (MPIMG) show that some healthy individuals possess immune

cells capable of recognizing the novel coronavirus, SARS-CoV-2. The reason for this might be found in prior infections with 'common cold' coronaviruses. Whether or not this cross-reactivity has a protective effect on the clinical course in individuals infected with SARS-CoV-2 will now be addressed by the 'Charité Corona Cross' study.

Why is it that some people develop severe symptoms following infection with the novel coronavirus, while others hardly notice the infection? The answer to this question is multilayered and is the subject of intensive research. One potentially crucial factor has now been identified by a team of researchers from Charité and the MPIMG: prior exposure to harmless 'common cold' coronaviruses. This insight is based on research involving T-helper cells, a type of specialized white blood cell which is essential to the regulation of our immune response. The researchers found that one in three people with no prior exposure to SARS-CoV-2 nonetheless have T-helper cells capable of recognizing the virus. The likely reason for this is that SARS-CoV-2 shares certain structural similarities with coronaviruses which are responsible for the common cold.

For their study, the researchers isolated immune cells from the blood of 18 COVID-19 patients receiving treatment at Charité and confirmed PCR positive for SARS-CoV-2. They also isolated immune cells from the blood of 68 healthy individuals who had never been exposed to the novel coronavirus. The researchers then stimulated these immune cells using small, synthetic fragments of SARS-CoV-2 'spike proteins', the characteristic, crown-like protrusions on the outer surface of coronaviruses which enable the virus to enter human cells. The researchers subsequently tested whether the T-helper cells would be activated by contact with these protein fragments. They found that this was the case in 15 out of 18 patients with COVID-19 (85%). "This was exactly what we had expected. The immune system in these patients was in the process of fighting this novel virus, and therefore showed the

same reaction in vitro," explains one of the study's three lead authors, Dr. Claudia Giesecke-Thiel, head of the Flow Cytometry Facility at the MPIMG. She adds: "The fact that not all patients with COVID-19 showed this T-helper cell response to viral fragments is probably due to fact that T cells cannot be activated outside the human body during an acute or particularly severe phase of an illness."

The team were, however, surprised to find memory T-helper cells capable of recognizing fragments of SARS-CoV-2 in the blood of healthy individuals. They were found in a total of 24 out of 68 healthy individuals tested (35%). In fact, the researchers noticed that the immune cells of COVID-19 patients reacted to different fragments of the viral envelope than the immune cells of healthy individuals. While the T-helper cells of patients recognized the spike protein in its full length, the T-helper cells isolated from healthy individuals were primarily activated by sections of the spike protein which showed similarity to corresponding sections found in the spike proteins of harmless 'common cold' coronaviruses. "This suggests that the T-helper cells of healthy individuals react to SARS-CoV-2 because of previous exposure to the endemic 'common cold' coronaviruses," says Dr. Giesecke-Thiel. She goes on to explain: "One of the characteristics of T-helper cells is that they are not only activated by a pathogen with an 'exact fit', but also by pathogens with 'sufficient similarity'." Notably, the researchers were able to show that the T-helper cells isolated from healthy participants who reacted to SARS-CoV-2 were also activated by various 'common cold' coronaviruses—displaying what is known as 'cross-reactivity'.

What effects this cross-reactivity might have on a previously healthy person infected with SARS-CoV-2 was not addressed in the current study. "Generally speaking, it is possible that cross-reactive T-helper cells have a protective effect, for instance by helping the immune system speed up its production of antibodies against the novel virus," explains

co-lead author Prof. Dr. Leif Erik Sander of Charité's Medical Department, Division of Infectious Diseases and Respiratory Medicine. He adds: "In this case, a recent bout of the common cold would probably result in less severe COVID-19 symptoms. However, it is also possible that cross-reactive immunity could lead to a misdirected immune response and potentially negative effects on the clinical course of COVID-19. We know this can occur with dengue fever, for instance."

Prospective studies will be needed in order to conclusively determine whether previous 'common cold' coronavirus infections confer protection against subsequent infection with SARS-CoV-2—and whether this might explain the high variability in clinical manifestations. One such study, which will be led by Charité and conducted in collaboration with Technische Universität Berlin and the MPIMG, has just been launched. Funded by the Federal Ministry of Health (BMG) and the Federal Institute for Drugs and Medical Devices (BfArM), the 'Charité Corona Cross Study' will investigate the impact of cross-reactive T-helper cells on the course of COVID-19.

In Germany, coronaviruses are responsible for up to 30 percent of all seasonal colds, says Prof. Dr. Andreas Thiel, a Charité researcher based at both the Si-M ('Der Simulierte Mensch—literally 'The Simulated Human', a joint research space of Charité and Technische Universität Berlin) and the BIH Center for Regenerative Therapies (BCRT). "Current estimates suggest that the average adult will contract an infection caused by one of the four endemic coronaviruses approximately every two to three years," explains Prof. Thiel, who is the article's third co-lead author and responsible for coordinating the Charité Corona Cross Study. He adds: "If we assume that these cold viruses are capable of conferring a certain level of immunity against SARS-CoV-2, this would mean that people who have had frequent exposure to such infections in the past, and who test positive for cross-reactive T-helper cells, should have better protection. This group of people will therefore

be a particular focus of the 'Charité Corona Cross Study'." The researchers will simultaneously follow COVID-19 risk populations over several months. Ultimately, the study aims to help predict the clinical course of COVID-19, both in people with and without previous SARS-CoV-2 infections. "This is of paramount importance, both in terms of people's day-to-day lives and the treatment of patients," explains Prof. Thiel.

The study includes a comprehensive immunological investigation of child daycare staff, pediatric practice staff and care home residents, which will last well into next year. Swabs collected from participants will be tested for SARS-CoV-2 using PCR-based testing. Additional tests will include tests for antibodies against the virus and for T cell reactivity. Should study participants subsequently contract SARS-CoV-2, the researchers will be able to establish links between the course of the disease and individual patients' immunological parameters.

The researchers also plan to collect blood samples from a minimum of 1,000 recovered COVID-19 patients. These will then be tested for a range of immunological factors in order to study how they correlate with symptoms. The team hope to be able to identify other potential parameters which influence COVID-19 severity and clinical course. The researchers are currently looking for individuals who were confirmed cases of COVID-19 and subsequently recovered from the illness. They would also like to hear from individuals who, at some point over the past few years, developed infections subsequently confirmed as caused by 'common cold' coronaviruses like 229E, C43, NL63 or HKU1.

More information: Julian Braun et al, SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19, *Nature* (2020). DOI: 10.1038/s41586-020-2598-9