Although COVID-19 vaccines and previous infection provide protection against SARS-CoV-2, some people still develop "breakthrough" infections. Understanding why this happens is important for designing next-generation vaccines to provide stronger protection against different variants that could ultimately block the spread of outbreaks.

In this study, we used a controlled human infection model, in which healthy vaccinated adults aged 18 to 30 years voluntarily received the Delta variant of SARS-CoV-2 through the nose under carefully monitored conditions. Participants were quarantined for up to two weeks after exposure and then followed for one year. The goal was to safely produce breakthrough infections and identify the immune responses associated with protection against infection.

A total of 46 volunteers took part. Twenty-two received lower doses of the virus, but none became infected. Twenty-four participants received the highest dose, and 18 of these were selected for relatively low levels of virus-neutralising antibodies before exposure. Among these 18 participants, six (33%) developed a sustained infection with mild to moderate symptoms. A further six participants showed only short-lived, transient infections. The amount of virus detected and the severity of symptoms varied considerably between individuals.

Participants with greater pre-existing immune measures were less likely to develop infection. The most important protective factors were higher levels of neutralising antibodies, antibodies against the virus's nucleocapsid (N) protein, and virus-specific T cells. These immune factors were also associated with lower levels of virus in those who did become infected. In addition, participants with higher levels of antibodies in the nose tended to experience milder symptoms. Those who developed only transient infections had stronger T cell responses before exposure than those who developed sustained infections.

Overall, this study suggests that breakthrough infection is more likely in people with lower levels of pre-existing antibodies, but more complete protection appears to depend on several parts of the immune system working together. These findings support the development of future vaccines that stimulate a broader range of immune responses, rather than focusing on antibodies alone.