Long-term infectious sequelae after SARS-CoV-2 infection should be considered in mild cases too

From the pandemic's onset through to the end of 2024, WHO recorded over 777 million confirmed cases of COVID-19 and more than 7 million confirmed deaths across 234 countries.[1] As longitudinal data accumulate, our understanding of COVID-19's long-term sequelae continues to expand. In *The Lancet Infectious Diseases*, Miao Cai and colleagues[2] contribute important insights into a previously underexplored consequence: the elevated rates of subsequent infections following SARS-CoV-2 infection, including in people who had not been admitted to hospital for COVID-19 or developed post-COVID-19-condition (also known as long COVID).

Using a data-driven approach, Cai and colleagues first compared results of a battery of 65 different laboratory tests for infectious illnesses between a cohort of 231 899 individuals who accessed the US Department of Veterans Affairs (VA) health-care system who tested positive for COVID-19 and 605 014 matched individuals who tested negative. During 12 months of follow-up, people who were admitted to hospital for COVID-19 had higher rates of positive results in more than 70% of the examined laboratory tests, after accounting for multiple comparisons. Similarly, patients who tested positive for COVID-19 who were not admitted to hospital had higher rates in 32% of the laboratory-based outcomes compared to those who tested negative for SARS-CoV-2. Particularly high rates were observed for respiratory viral infections, including PCR-confirmed rhinovirus, respiratory syncytial virus (RSV), and influenza A virus.

These findings align both with and extend the scope of other large-scale epidemiological studies. An analysis of 1·7 million infants admitted to hospital in the USA during the 2021 RSV seasonal peak showed that children with previous confirmed COVID-19 had significantly increased rates of RSV infection (hazard ratio [HR] 1·32 [95% CI 1·12–1·56]) compared to those without documented COVID-19.[3] This rate increased to 1·62 (1·27–2·07) when the analysis was restricted to patients with laboratory-confirmed RSV. Similarly, a nationwide analysis of adults aged 50 years and older in Denmark identified an association between a history of COVID-19 and subsequent influenza infection, with an HR of 1·24 (95% CI 0·97–1·58) for influenza occurring 180 days or more after SARS-CoV-2 infection.[4] Interpretation of these findings requires careful consideration of temporal confounders. Influenza and RSV activity patterns were greatly disrupted in 2020, with initial declines following the implementation of physical distancing and other non-pharmaceutical interventions.[5] The subsequent rapid return of RSV and influenza outbreaks in 2021–22 might partly explain the observed associations, occurring through population-level effects rather than due to individual immunological changes.

To establish whether these increased infection rates were unique to SARS-CoV-2, Cai and colleagues conducted comparative analyses with patients who were admitted to hospital for influenza. Patients admitted to hospital for COVID-19 showed higher rates of all-cause admissions to hospital and infectious illness-related hospitalisations, including sepsis and positive urine and blood cultures, compared with patients admitted to hospital for influenza. These findings complement a previous VA cohort study from the same group, which showed 51% greater all-cause mortality hazard in the COVID-19 group versus the influenza group.[6]

A key advancement of Cai and colleagues' study[2] is the identification of increased infection rates among patients who were not admitted to hospital. While previous research has primarily shown elevated rates of infection in patients with long-COVID, or in those requiring admission to hospital, this analysis demonstrates substantial increases in infection rates even in those with mild initial disease. These associations remained robust in models adjusting for baseline characteristics and time-varying diagnostic testing and health care-seeking behaviour during follow-up. This builds upon another analysis of VA health-care data, which showed increased rates of various non-communicable conditions in patients with COVID-19 who were not admitted to hospital, including pulmonary diseases, hyperglycemia, diabetes, kidney disease, and gastrointestinal complications.[7]

These findings have important implications for understanding the potential impact of COVID-19 on long-term immune function and susceptibility to pathogens. The evidence suggests effects extending

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beyond the acute phase of infection, affecting even mild cases. This growing body of research on post-acute COVID-19 sequelae supports a bidirectional relationship between non-communicable diseases and infectious diseases, resulting in persistently increased risk of adverse outcomes in the months and years after initial SARS-CoV-2 infection.

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I declare no competing interests.

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