Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Brief Commentary

Neuropsychiatric sequelae of COVID-19 after vaccination: A gathering storm?

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Before the widespread availability of SARS-CoV-2 vaccination, large-scale analyses of health records and of primary studies had identified a high frequency of neuropsychiatric symptoms during and after recovery from acute COVID-19 (Taquet et al., 2021; Taquet et al., 2021; Rogers et al., 2021; Badenoch et al., 2022). Vaccination created a new epoch in which deaths and acute critical illness are greatly reduced, but in which SARS-CoV-2 infection continues – in millions of people every week, multiple waves, and novel variants (WHO, 2022). It is therefore increasingly important to know whether vaccines also reduce the longer-term sequelae of COVID-19; discussed here through the lens of our interest in its neuropsychiatric consequences.

In their recent paper in *Brain, Behavior, and Immunity*, Taquet and colleagues (Taquet et al., 2022) found that vaccination protected against severe acute illness, stroke, seizures, and psychotic disorders after breakthrough COVID-19, but may not protect from fatigue and other post-covid behavioural and cognitive symptoms. To reach this conclusion they studied a large retrospective cohort of n = 9479 individuals who developed COVID-19 despite SARS-CoV-2 vaccination, well-matched to controls. Because vaccine hesitancy may influence health behaviours (Troiano and Nardi, 2021), Taquet et al. used a specific control group of individuals who had not been vaccinated against COVID-19 but who *had* been vaccinated against influenza. This decision helped to control for differences in health behaviour between people who accept vaccines and extreme anti-vaxxers. Confounding could not be excluded but it is difficult to think of a much better retrospective design.

Our interest was drawn particularly to the lack of an observed effect of vaccination on post-COVID fatigue, cognitive symptoms, or affective disorders, in contrast to a clear risk reduction for stroke, seizures and psychosis. What conclusions – even if tentative – could we draw from this result?

One broad conclusion is that if vaccination protects against some but not all persisting symptoms, then it is reasonable to speculate that mechanisms underlying persistence may vary between symptoms, and by extension that 'Long Covid' may in many cases be a multi-factorial disorder. Even if this is inaccurate, the many gaps in our knowledge suggest that entrenched views on causation are premature (Matta et al., 2022) and we join those encouraging researchers and activists to keep open minds about mechanisms underlying post-COVID neuropsychiatric symptoms. Plausible candidates span a bio-psycho-social gamut from acquired brain injury to chronic inflammation, exacerbation of pre-existing disorders, cognitive-behavioural feedback loops, the impact of healthcare disparities, and more besides (Frontera and Simon, 2022). In clinical settings, therefore, an individualised and holistic formulation of persisting symptoms may be useful.

More specifically it is possible that by lowering the severity of acute COVID-19, vaccination reduces the inflammatory burden to the central nervous system. Human single-cell RNA sequencing data suggest that severe COVID-19 triggers pro-inflammatory relay mechanisms between choroid plexus epithelium and CNS astrocytes, oligodendrocytes, microglia, and excitatory neurons (Yang et al., 2021). In light of this the data from Taquet et al. suggest a hypothesis that inflammatory mechanisms underlying objective outcomes like stroke, seizures, and psychosis differ mechanistically from those underlying more subjective symptoms like persisting fatigue, cognitive symptoms, and affective changes. The latter outcomes are unfortunately a lot more common than the former (Badenoch et al., 2022) and so far, there is little or no evidence that vaccines can be relied on to mitigate their potential impact on health-care services and economies.

Taquet et al. convey an important public health message

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nevertheless: vaccines don't just prevent death, they also disarm many disabling sequelae of COVID-19, especially its more objectively measurable consequences. This message is particularly important for the young, whose risk of mortality with COVID-19 is much lower yet in whom vaccination was *more* protective for many secondary outcomes than it was among older patients.

To date however, the effectiveness of vaccines in preventing more subjective – but no less disabling – post-COVID neuropsychiatric outcomes remains unclear. Prospective studies are needed of the long-term clinical and societal impact of breakthrough COVID-19 from dominant new variants; and of the range of potential mechanisms underlying common and complex symptoms like fatigue and cognitive impairment. It bears repeating that COVID-19 is a new disease that is being allowed to spread and mutate globally before its neuropsychiatric and multisystem consequences – and their cumulative impact over many years – are fully mapped. The best preventive strategy of all remains to try and avoid catching it, for until our knowledge matures it is impossible to dismiss the risk of a gathering storm.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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