



## Impact of covid-19 vaccination on long covid

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Cite this as: *BMJMED* 2023;2:e000470. doi:10.1136/bmjmed-2022-000470

Received: 11 January 2023  
Accepted: 18 January 2023



► <http://dx.doi.org/10.1136/bmjmed-2022-000229>

Some beneficial effects are likely but estimating the size of the effect currently remains a challenge

Vaccines have had an important role in reducing mortality and morbidity from the covid-19 pandemic, with an estimated 14.4 million lives saved globally over the first year of vaccination.<sup>1</sup> As the pandemic continues, attention has focused on whether vaccines have any additional role in preventing longer term symptoms in patients with covid-19 (long covid). This long term condition remains a major public health problem, with an estimated 2.1 million people (3.3% of the UK population) continuing to have self-reported symptoms lasting more than four weeks after infection with covid-19.<sup>2</sup>

Two public health questions are related to vaccines and long covid: whether vaccination before infection reduces the risk of long covid, and whether vaccination in patients with long covid alters symptomatology. In *BMJ Medicine*, two new papers shed some light on these questions.

Byambasuren and colleagues did a systematic review of 17 observational studies (doi:10.1136/bmjmed-2022-000385), 12 looking at the effect of vaccination before covid-19 infection and five looking at the effect after covid-19 infection.<sup>3</sup> The authors should be commended for their systematic approach, although the ability to interpret the results remains limited by the paucity of high quality studies. Many studies used symptoms coded by ICD-10 (international classification of diseases, 10th revision), rather than patient reported symptoms of long covid. While this approach allows large datasets to be analysed remotely, we cannot assume that an ICD-10 code reflects the lived experience of patients with long covid. Another limitation was inconsistency in the long covid definition between the studies, or whether a definition was provided at all. Differing duration of symptoms of long covid can represent a different disease syndrome to that captured in the World Health Organization's definition.<sup>4</sup> Additionally, as with many observational studies on vaccination, the study had clear potential confounders, with those patients who take up vaccination generally healthier than those who do not (the so-called healthy vaccine effect).<sup>5</sup>

Regardless of these challenges, it is reassuring that most included studies supported a reduction in long covid in patients who received vaccination before infection, in line with supporting observational data and consistent with the other beneficial effects of vaccination. By contrast, the data on whether vaccination after covid-19 infection alters symptomatology remains more difficult to interpret. In addition to the healthy vaccine effect, the authors had the

challenge of modelling multiple time varying covariates (ie, timing of infection, timing of symptoms), and the potential placebo effect of vaccination. Thus, it is unsurprising that all five studies looking at vaccination effects after covid-19 infection in Byambasuren et al's review were subject to some degree of potential bias. A recent paper also supported the results of this review, showing a reduction in longer term symptoms in those individuals vaccinated before infection in a large Israeli health cohort.<sup>6</sup>

In another paper, Tran and colleagues reported an emulated target trial of patients with long covid (the ComPaRe cohort<sup>5</sup>), some of whom who were subsequently vaccinated (doi:10.1136/bmjmed-2022-000229).<sup>7</sup> Emulated target trials provide a formal framework in which to place observational data and to emulate a randomised controlled trial as closely as possible.<sup>8</sup> In these studies, a protocol that matches as close as possible to a potential trials is written a priori. Tran et al made an excellent and detailed attempt to perform a target trial in a cohort of 455 matched pairs. The researchers attempted to account for time varying covariation by generating three separate emulated target trials over three time periods, with each one comparing those patients vaccinated in that period with those who remained unvaccinated. Combinations of estimates from each cohort showed a small reduction in mean number of symptoms of long covid (mean difference -1.8, 95% confidence interval -3.0 to -0.5) and a doubling of patients in remission (hazard ratio 1.93, 1.18 to 3.14) at 120 days after vaccination. By contrast to many studies, they also measured a patient symptom derived score<sup>5</sup> (although the cohort used to derive the score was the same used as that to assess vaccine effectiveness) as a secondary outcome and showed improvements in the lived experience of patients with covid-19.

Owing to its timing, the Tran study did not capture the delta or omicron variant waves, and no patients were vaccinated before infection.<sup>7</sup> The immunological landscape has progressed with high vaccination and seropositive rates, and different variants are now in circulation. Additionally, the cohort included self-referred patients with symptoms of long covid, with a disproportionate number of women (80.5%) and participants not in hospital (91.1%). These issues limit interpretability of the results within the covid-19 pandemic landscape and generalisability to a wider population.

Conversely, two of the papers included in the Byambasuren study suggested no benefit of vaccination in patients with long covid.<sup>3</sup> Wisnivesky and colleagues described 453 patients with at least one long covid symptom, 73% of whom subsequently

received a covid-19 vaccine.<sup>9</sup> No difference was seen in the change in long covid symptoms at six months between the groups. However, researchers saw baseline differences between the groups and a healthy vaccine effect is likely. Wynburg and colleagues reported on 36 pairs of individuals, again with at least one long covid symptom, matched by age, sex, and obesity.<sup>10</sup> The researchers saw no difference in mean number of symptoms or in recovery from long covid at three months, although the small numbers precluded detailed analysis.

Where do these data leave us with vaccines and long covid? Given new and existing evidence, covid-19 vaccination is likely to have some beneficial effect on long covid through reducing case severity as well as incidence. However, estimating the size of the effect (and the effect of further vaccine doses) remains a challenge in observational data. The evidence of benefit after infection is much more unclear and harder to interpret given the current rate of seropositivity and vaccine uptake in many countries. While these studies are encouraging, trials comparing vaccination with placebo in patients with long covid (as defined by WHO criteria) are required to definitively recommend for or against vaccination to improve symptoms of long covid. Until then, vaccination should continue to be based on the most up-to-date evidence available for the prevention of covid-19 related infection, hospital admission, and death.

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Contributors FE drafted the initial editorial, FWH reviewed it. Both authors agreed the final text.

Competing interests We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review Commissioned; not externally peer reviewed.

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