



# Are vaccines a potential treatment for long covid?

Benefits are possible, but we need more evidence and a mechanism of action

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Cite this as: *BMJ* 2022;377:o988  
<http://dx.doi.org/10.1136/bmj.o988>

Published: 18 May 2022

Vaccines in the covid-19 pandemic have been a game changer in reducing rates of SARS-CoV-2 infection and hospital admission for, and death with, covid-19. They also reduce the chance of developing long covid by about half among people who are vaccinated before they develop covid-19.<sup>1</sup> However, the effect of vaccines for people who already have long covid is a contentious area for both patients and healthcare professionals. In a linked paper, Ayoubkhani and colleagues (doi:10.1136/bmj-2021-069676) report findings from the largest published study on this topic to date.<sup>2</sup> From a random sample of the UK population, they identified 28 356 adults (18-69 years) who were vaccinated after a positive SARS-CoV-2 test result, of whom 6729 (23.7%) reported long covid symptoms (>12 weeks) of any severity at least once during follow-up. Participants were followed for seven months to determine the relationship between vaccination, long covid, and symptom profiles after the first and second dose of either an adenovirus vector or mRNA vaccine.<sup>2</sup>

In an interrupted time series model adjusting for prespecified covariates, the authors found a 12.8% reduction in the odds of reporting long covid immediately after the first vaccine dose, but this reduction was not sustained over the following 12 weeks. However, an 8.8% reduction in the odds of long covid after a second dose was sustained over the next nine weeks. The authors suggested inadequate immune response as a reason for lack of sustained effect after the first dose.

Although Ayoubkhani and colleagues' study was large, lack of a contemporaneous control arm without vaccination was a limitation. Natural recovery from long covid was accounted for by comparing symptom trajectories before and after vaccination. Determining the clinical course of long covid is complicated by differences in the cohorts studied, differences in definitions used, and in the actual symptoms tracked over time. Evidence so far suggests that 20-50% of patients with covid-19 report persistent symptoms at four weeks. Half of this group recover by 12 weeks.<sup>3,4</sup> The latest survey by the UK's Office for National Statistics shows that 44% of people with self-reported long covid have had symptoms for at least one year. Furthermore, two thirds of all respondents with long covid report symptoms severe enough to limit their day-to-day activities such as work.<sup>5</sup> For many people, long covid is a chronic condition with a fluctuating course and relapses linked to physical, cognitive, and emotional exertion.<sup>6</sup>

Several smaller studies have looked at the effect of vaccination on long covid,<sup>1</sup> including one from France, not yet peer reviewed, exploring the resolution of symptoms post-vaccination in a cohort

of 910 adults with long covid.<sup>7</sup> Four hundred and fifty five adults vaccinated in a particular 60 day period were propensity score matched to an equal number of adults who remained unvaccinated during the same period. At 120 days, 16.6% of those vaccinated reported complete resolution of symptoms, compared with 7.5% of those who were unvaccinated. The difference was significant (hazard ratio for resolution of symptoms was 1.97, 95% confidence interval 1.23 to 3.15). Persistent symptoms were reported by people in both study arms at final follow-up, with only a marginal difference in symptom severity score between the groups.

Another small study by Tsuchida et al measured antibody titres and symptoms post-vaccination in 42 adults with long covid: 61% reported no change in symptoms, 21% reported worse symptoms, and 16% reported an improvement during the two weeks after vaccination.<sup>8</sup> Unlike Ayoubkhani and colleagues, these authors measured post-vaccination antibody titre ratios, and they found significantly higher titres in the group reporting worse symptoms after vaccination compared to those with no change or improvement in symptoms. They hypothesised that an excessive immune response induced by the vaccine may be responsible.<sup>8</sup>

The mechanisms underpinning changes in long covid symptoms after vaccination are not fully understood. However, as Ayoubkhani and colleagues suggest, vaccination can increase antibody titres and potentially eliminate viral reservoirs.<sup>2</sup> Given the small numbers of patients reported to benefit (an 8.8% reduction in odds of long covid after two vaccine doses) and the uncertainty around the true effect of vaccines relative to natural recovery, a clear explanation for how vaccines might reduce the multisystem manifestations of long covid is still lacking. Particularly for people already well past the stage of systemic inflammatory responses, and those with end organ damage from covid-19, such as lung fibrosis.

Several plausible mechanisms underlying long covid are currently being investigated, including the persistence of viral antigens and abnormalities in T cells, platelets, vascular endothelium, and clotting factors.<sup>9,10</sup> People with long covid need timely investigation, management, and rehabilitation in specialist clinics, including identification of thrombotic phenomena, cardiac dysrhythmias, and dysautonomia.<sup>11</sup>

Vaccination to reduce risk of reinfection remains important for people with long covid, and evidence so far suggests that benefits are likely to outweigh any harms. Three outcomes are possible after vaccination: no change in symptoms (most likely),

improvement (best case), or deterioration (worst case).<sup>1</sup>

Unfortunately, many unknowns remain about the long term prognosis of long covid, including the effect of booster vaccines or recurrent covid-19. More research is needed on the link between antibody titres and symptoms over time before we can hope to predict the effects of vaccination on individuals.

The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: None.

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Provenance and peer review: Commissioned; not externally peer reviewed.

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