Are there clinically significant interactions between COVID-19 vaccination and post-COVID-19 condition (long COVID)?

Source: Emerging Science Group of the Public Health Agency of Canada. Evidence Brief on the associations and safety of COVID-19 vaccination and post-COVID-19 condition: January 13, 2022. Full report available from: ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca

Background: "Long COVID" has been studied both as post-acute sequelae (PAS), defined as symptoms 4 to 12 weeks post diagnosis, and as post-COVID-19 condition (PCC), defined by the World Health Organization as persistent or recurring symptoms lasting for at least 8 weeks and occurring 12 or more weeks after an acute COVID-19 infection (1). It is important to know if there are any beneficial or harmful effects of COVID-19 vaccination on PAS or PCC, or if PAS or PCC increases the risk of adverse events following vaccination. This report addresses three questions: Does COVID-19 vaccination before or after COVID-19 infection decrease the risk of developing PAS or PCC? Among those who already have PAS or PCC, does COVID-19 vaccination affect their symptoms? Is it safe to receive a COVID-19 vaccine after PAS or PCC?

Methods: Twenty databases and key websites were searched for relevant reviews, peer-reviewed publications and preprints up to January 13, 2022. Search terms included the following: immuniz*, immunis*, vaccin*, long covid, long-covid, post covid, post-covid, chronic covid, chronic-covid, long-term sequelae, long hauler and long-hauler. The search netted 97 citations, which were screened for relevance. Data were extracted from relevant studies into three evidence tables to address each of the questions.

Results: Fourteen relevant studies were identified: four prospective cohort studies; four retrospective cohort studies; and six cross-sectional studies. One was peer-reviewed, twelve were preprints and one was a letter to the editor. Twelve studies reported on vaccines authorized for use in Canada and are reported on here; the two others were on a vaccine authorized for use in India (2,3).

COVID-19 vaccination prior to developing PAS or PCC

All studies in this area were on PCC. Four situations were assessed: four studies assessed one or two doses of COVID-19 vaccine before COVID-19 infection and the risk of developing PCC; and two studies assessed having one or two doses of a COVID-19 vaccine after COVID-19 infection, but before developing PCC.

COVID-19 vaccination before COVID-19 infection

No studies found an increased risk of developing PCC subsequent to infection. All studies were retrospective or cross-sectional studies; thus, the evidence of a protective effect from vaccination was not strong.

- Two studies assessed one dose of a vaccine prior to COVID-19 infection. One study identified a decreased risk of PCC (odds ratio [OR] 0.22) (4) and one study found no difference (5).
- Two studies assessed two doses of a vaccine prior to COVID-19 infection. One study identified a decreased risk of PCC (hazard ratio [HR] 0.87) (6), two studies reported a lower proportion of some PCC symptoms among vaccinated people (5,7) and one study found no difference (5).

COVID-19 vaccination after infection and before post-COVID-19 condition

This was reported in two studies; both found a decreased risk of developing PCC.

- A prospective cohort described a temporary reduction in the risk of PCC (13%) post first dose and a 9% reduction post second dose followed by further decreases of 0.8% per week regardless of the vaccine received (8). Timing of the vaccine post-infection did not appear to affect results.
- A retrospective cohort that assessed at least one dose of a vaccine received 0–20 weeks post-COVID-19 diagnosis found a reduced risk of PCC, and this was most protective when received closer to diagnosis (OR 0.38 at 0–4 weeks *vs* OR 0.75 at 8–12 weeks) (4).

One study did not differentiate between vaccination before or after COVID-19 and reported no association with vaccination and development of PCC overall, however those vaccinated had a lower risk of certain symptoms (9).

COVID-19 vaccination after developing PAS or PCC

Five studies examined the effect of COVID-19 vaccination after developing PAS or PCC. Three studies showed a small beneficial effect and two studies showed no difference.

- A large prospective cohort study found that the PCC remission rate in vaccinated individuals was 16.6% *vs* 7.5% in unvaccinated individuals (10).

- A smaller prospective cohort study found that the PCC remission rate in vaccinated individuals was higher than the unvaccinated (23.2% *vs* 15.4%), the proportion with worsening symptoms was lower (5.6% *vs* 14.3%) and in the majority of vaccinated and unvaccinated people PCC symptoms were the same (71.1% *vs* 70.3%) (11).
- A third prospective cohort study found that there were fewer general practitioner consultations among individuals with PAS after vaccination compared with before vaccination (12).
- A retrospective cohort on PCC (13) and a cross-sectional study on PAS (14) found that there was no change in symptoms with vaccination status.

Safety of COVID-19 vaccination in those with PAS or PCC

Two studies reported on vaccine adverse events after one dose of a COVID-19 vaccine in individuals with PCC.

- A cross-sectional study of one dose of an mRNA vaccine found that there was no significant difference in the number or duration of vaccine adverse events in those with PCC (n=30) *vs* those without (n=944) (15).
- A large prospective cohort study of individuals with PCC concluded vaccination was safe with fewer than 1% reporting a serious adverse event (0.88%) (10).

Conclusion: Preliminary research findings suggest COVID-19 vaccination may decrease the risk of developing PCC and, in those who already have PCC or PAS, receiving a COVID-19 vaccination was not associated with an increase in adverse events and was associated with remission of PAS or PCC symptoms in some people. There is low confidence in these findings as the evidence was limited by the number of studies, lack of peer review and risk of bias in the retrospective studies. Peer-reviewed longer-term prospective studies are needed.

References

1. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Geneva (CH): WHO; 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1
2. Arjun M. C, Singh AK, Pal D, Das K, Gajjala A, Venkateshan M, Mishra B, Patro BK, Mohapatra PR, Subba SH. Prevalence, characteristics, and predictors of Long COVID among diagnosed cases of COVID-19. medRxiv 2022; 2022.01.04.21268536. DOI
3. Senjam SS, Balhara YPS, Kumar P, Nichal N, Manna S, Madan K, Ahmed NH, Gupta N, Sharma R, Gupta Y, Ray A, Gupta V, Vashist P, Kumar A, Dar L, Titiyal JS, Tandon R, Gulleira R. Assessment of Post COVID-19 Health Problems and its Determinants in North India: A descriptive cross section study. medRxiv 2021; 2021.10.03.21264490. DOI
4. Simon MA, Luginbuhl RD, Parker R. Reduced Incidence of Long-COVID Symptoms Related to Administration of COVID-19 Vaccines Both Before COVID-19 Diagnosis and Up to 12 Weeks After. medRxiv 2021; 2021.11.17.21263608. DOI
5. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. medRxiv 2021; 2021.10.26.21265508. DOI
6. Al-Aly Z, Bowe B, Xie Y. Long Covid after Breakthrough COVID-19: the post-acute sequelae of breakthrough COVID-19. Research Square. 2021. DOI
7. Blumberg Y, Edelstein M, Jabal KA, Golan R, Perets Y, Saad M, Levinas T, Dabbah S, Israeli Z, Yacoubi S, Raya AA, Amital A, Halabi M. Protective effect of BNT162b2 vaccination on aerobic capacity following mild to moderate SARS-CoV-2 infection: a cross sectional study, Israel, March-December 2021. medRxiv 2021; 2021.12.30.21268538. DOI
8. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, Khunti K, Alwan NA, Walker AS. Changes in the trajectory of Long Covid symptoms following COVID-19 vaccination: community-based cohort study. medRxiv 2021; 2021.12.09.21267516. DOI
9. Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Wiegler KB, Abu Jabal K, Dror AA, Nazzal S, Glikman D, Edelstein M. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021. medRxiv 2022; 2022.01.05.22268800. DOI
10. Tran V, Perrodeau E, Saldanha J, Pane I, Favaud P. Efficacy of COVID-19 vaccination on the symptoms of patients with long COVID: a target trial emulation using data from the ComPaRe e-cohort in France. SSRN. 2021. DOI
11. Arnold DT, Milne A, Samms E, Stadon L, Maskell NA, Hamilton W. Are vaccines safe in patients with Long COVID? A prospective observational study. medRxiv 2021; 2021.03.11.21253225. DOI
12. Whittaker HR, Gulea C, Koteci A, Kallis C, Morgan AD, Iwundu C, Weeks M, Gupta R, Quint JK. GP consultation rates for sequelae after acute covid-19 in patients managed in the community or hospital in the UK: population based study. BMJ 2021;375:e065834. DOI PubMed
13. Schultheiss C, Willscher E, Paschold L, Gottschick C, Klee B, Henkes S-S, Bosurgi L, Citzmann J, Sedding D, Freses T, Girndt M, Holl JI, Gekle M, Miolajczyk R, Binder M. From online data collection to identification of disease mechanisms: The IL-Iβ, IL-6 and TNF-a cytokine triad is associated with post-acute sequelae of COVID-19 in a digital research cohort. medRxiv 2021; 2021.11.16.21266391. DOI
14. Scherlinger M, Pijnenburg L, Chatelus E, Arnaud L, Gottenberg J-E, Sibilia J, Felten R. Effect of SARS-CoV-2 vaccination on symptoms from post-acute COVID syndrome: results from the national VAXILONG survey. medRxiv 2021; 2021.10.11.21264849. DOI
15. Raw RK, Kelly CA, Rees J, Wroe C, Chadwick DR. Previous COVID-19 infection, but not Long-COVID, is associated with increased adverse events following BNT162b2/Pfizer vaccination. J Infect 2021;83(3):381–412. DOI PubMed