# Emerging Evidence on COVID-19

# Evidence Brief on the associations and safety of COVID-19 vaccination and post COVID-19 condition

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## Table of Contents



## Introduction

**This review summarizes the global evidence on three questions: Does COVID-19 vaccination before or after COVID-19 infection decrease the risk of developing post-acute sequelae (PAS) or post COVID-19 condition (PCC)? Among those that already have PAS or PCC, does COVID-19 vaccination after COVID-19 change their symptoms? Is it safe to get a COVID-19 vaccine for individuals who have PAS or PCC?**

According to a recent definition developed with the World Health Organization (WHO), post COVID-19 condition (PCC) refers to persistent symptoms occurring 12 weeks or more after an acute COVID-19 infection, which persist or reoccur for a minimum of 8 weeks [1]. The most common symptoms include fatigue, cognitive problems (e.g., memory, concentration), respiratory issues, and mental health issues (e.g., anxiety, depression)

[1, 2]. PCC is also referred to as long COVID, post-acute sequelae, post COVID-19 symptoms, and post-acute COVID-19 syndrome. Prior to the WHO definition, a number of studies reported on post-acute sequelae (PAS) from 4 to 12 weeks post diagnosis [1, 3]. Due to the small number of studies available PAS and PCC studies are included in this review[1, 3].

COVID-19 vaccination has become widely available in Canada and currently four vaccines have been approved: Comirnaty (Pfizer-BioNTech, BNT162b2), SpikeVax (Moderna, mRNA-1273), Vaxzevria (AstraZeneca, ChAdOx1-S, AZD1222), and Janssen (Johnson & Johnson, Ad26.COV2.S). The impacts of vaccination on PCC or PAS, either positive or negative, are important, since early estimates of the burden of PCC suggest >50% of individuals with confirmed COVID-19 infection have reported at least one PCC symptom more than 12 weeks after diagnosis [4, 5]. This evidence brief summarizes the literature regarding the associations and safety ofCOVID-19 vaccination and PAS or PCC by addressing three sub-topics: the association of vaccination and risk of developing PAS or PCC, the association of vaccination and changes in PAS or PCC symptoms, and whether the adverse event profile is different in individuals with PAS or PCC vs. those who did not have these post-infection sequelae. This evidence brief contains literature up to January 13, 2022.

# Key points

There were 14 studies identified that evaluated the associations and safety of COVID-19 vaccination and PAS or PCC, including four prospective cohort studies from the UK (n=3) and France [6, 7, 8, 9]; four retrospective cohort studies from the USA (n=2), Germany, and multiple countries [10, 11, 12, 13]; and six cross-sectional studies from India (n=2), the UK, France, and Israel (n=2) [14, 15, 16, 17, 18, 19]. Of the 14 studies, one was peer-reviewed, twelve were preprints, and one was a letter to the editor.

Ten studies provided PCC outcomes since they assessed symptoms at 12 or more weeks after acute infection [6, 8, 9, 10, 11, 13, 14, 16, 18, 19] (aligned with the WHO definition [1]), and four studies provided PAS outcomes since they assessed symptoms lasting four or more weeks after acute infection [7, 12, 15, 17].

### Is there an association between COVID-19 vaccination and development of PAS or PCC?

**COVID-19 vaccination prior to COVID-19 infection** was associated with a reduced risk of developing PCC in four studies[10, 11, 14, 19] and no change in one study [13]. No studies indicated an increased risk of PCC. All studies were retrospective or cross-sectional studies, thus the evidence of a protective association from vaccination is not strong. Two doses of vaccine prior to COVID-19 was associated with a reduced risk of PCC Hazard Ratio (HR) 0.87 [10] and an Adjusted Odds Ratio (aOR) 0.55[14] in two studies and no association in one study [13]. Receipt of a single dose of vaccine prior to COVID-19 was protective (OR 0.22 [11]) in one study and there was no association in two other studies [13, 14]. For both one and two doses of vaccine prior to COVID-19, there was a lower risk of reporting certain symptoms including reductions in fatigue 14-18%, myalgia 15-30%, dyspnea 11-20% [13, 19] and cognitive symptoms 13-19% [13].

**Post COVID-19 vaccination** was reported in two studies, one was a prospective cohort with monthly follow-up assessments that 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 (Comirnaty, Spikevax or Vaxzevria) [8]. A retrospective cohort also suggested a reduced risk of PCC with at least one dose of vaccine 0-20 weeks post COVID-19 diagnosis reduced the risk of PCC and suggested this was most protective when received closer to diagnosis (OR 0.38 at 0-4 weeks vs. OR 0.75 at 8-12 weeks) [11]. The change based on time between infection and vaccination was not a significant moderator of the vaccination – PCC relationship in the prospective cohort [8].

**Is post COVID-19 infection vaccination associated with changes in PAS or PCC symptoms?**

There were five studies examining associations between COVID-19 vaccination among individuals with PAS or PCC and changes in PAS or PCC symptoms. Three prospective cohort studies conducted in France [9] and the UK [6, 7] found protective associations, measured as improvement or resolution of symptoms, between post COVID-19 infection vaccination (one or two doses) and those not vaccinated. Improvement in PCC symptoms was reported in ~10% more people who were vaccinated compared unvaccinated [9, 6] and there were fewer general practitioner visits for PAS (adjusted incidence rate ratio (aIRR) 0.5) in another study [7], In the latter study, certain symptoms such as loss of taste and/or smell, muscle pain, chest tightness, tinnitus, and cough were lower among PAS cases that received vaccination post COVID-19 (aIRR range 0.15-0.71) compared to unvaccinated, controlling for time since diagnosis in the analysis [7]. Vaccine type (Comirnaty, Spikevax, Vaxzevria or Janssen) was not associated with PCC or PAS outcomes. Two additional studies, a retrospective cohort on PCC [12] and a cross-sectional study on PAS [17], did not find an association with one or two doses of COVID-19 vaccination post COVID-19 and change in PCC or PAS symptoms.

**Is there an increased risk of adverse events from COVID-19 vaccination in individuals with PCC?**

Two studies examined the safety of single dose vaccination in individuals with PCC. A small cross-sectional study from the UK of healthcare workers with PCC did not reported a significant difference in the number of vaccine side effects and their duration after receiving the first dose of Comirnaty [16]. A large PCC prospective cohort study reported 5.7% of PCC cases self reported an adverse event after their first vaccine dose (Vaxzevria, Comirnaty, SpikeVax, or Janssen) [9]. Four were serious adverse events (0.88%). Events that were not considered serious included relapse of PCC symptoms (2.8%, n=13) and local and systemic reactions (e.g., arm pain, fever) (1%, n=5) [9]. There are no statistics to show the rate of adverse events in this PCC cohort were similar to what would be expected in people without PCC, however the authors indicated these results showed COVID-19 vaccination was safe for people with PCC.

## Overview of the evidence

Overall, there were 14 studies that reported on the associations and safety of COVID-19 vaccination and PAS or PCC, including prospective cohort studies (n=4), retrospective cohort studies (n=4), and cross-sectional studies (n=6). One study was peer-reviewed, twelve studies were preprints that have not completed the peer-review process, and one study was a letter to the editor. Excluded studies were case reports; cases series; studies on vaccine effectiveness and immune responses to vaccination among individuals with PAS or PCC; predictive modelling studies estimating the number of PAS or PCC cases prevented due to vaccination; studies only assessing vaccinated individuals with PAS or PCC with no comparator group of unvaccinated individuals with PAS or PCC; and studies comparing the changes in PAS or PCC symptoms among vaccinated COVID-19 positive vs. negative individuals.

Cross-sectional studies have a moderate to high risk of bias and they cannot establish that the exposure preceded the outcome, therefore causal inferences cannot be made. Retrospective cohort studies have a moderate to high risk of bias because researchers do not have the ability to control for missing information, outcome measurement and recall errors, when retrospectively analyzing data. Among all the study designs included in this review, prospective cohort studies have the lowest risk of bias, because participants are selected based on exposure status and followed up prospectively for a period of time and outcome measurement can be standardized and uniformly applied. Therefore, a temporal relationship can be established between the exposure and outcome. Confounding bias is a risk of bias in all observational studies.

Some studies adjust for potential confounders, while some studies did not try to control for possible confounding factors that could affect PAS or PCC outcomes (e.g., age, pre-existing conditions) [6, 12, 17, 19]. In this review, no formal risk of bias was conducted.

There was conflicting evidence across studies within different sub-topics, and potential explanations for conflicting evidence include recall and reporting bias in studies assessing self-reported changes in PAS or PCC symptoms using questionnaires [6]. In addition, perceptions of the presence and severity of symptoms are highly variable across individuals. Since no validated diagnostic test for PCC is currently available, some symptoms reported as "PCC" may be caused by other conditions. Another explanation for heterogeneous evidence is variation in how individuals with PAS or PCC were identified: retrospective cohort studies identified these individuals from health records using a pre-defined PAS or PCC symptom list [13], while prospective cohort studies relied on self-report questionnaires [8].

Two studies did not report whether vaccination was received before or after COVID-19 infection [15, 18] and one study did not report the type of vaccine received [14], which could potentially impact PAS or PCC outcomes. When this information was available, it was included in this section and in the evidence tables (Appendix Table A1). Throughout this review, fully vaccinated refers to individuals who received the two-dose series of Comirnaty, SpikeVax or Vaxzevria, or one dose of Janssen.

There were few studies on each of the sub-topics addressed in this review; eight studies on the association of COVID-19 vaccination and risk of developing PAS or PCC, five studies on the association of COVID-19 vaccination and changes in PAS or PCC symptoms,, and two studies on the safety of COVID-19 vaccination in individuals with PAS or PCC. As such there is low confidence that the outcomes of this review will not change with future research. Future investigations could assess whether there is variation in results depending on the SARS-CoV-2 variant. Studies included in this review were conducted mainly in 2021 during the emergence of Alpha through Delta VOCs, but none of the studies analysed the VOC as a potential risk factor. In this review, no studies examined the impact of vaccination on PAS or PCC in children, therefore future investigations should study this age group, especially as vaccination has recently become available for children aged 5 to 11 in Canada. As booster vaccination has become available for adults in Canada, it is important for future studies to examine how booster doses impact the development and symptoms of PAS or PCC. Long-term prospective cohort studies assessing PAS or PCC symptoms after vaccination are also needed to determine if any changes in symptoms are sustained over time. Future studies could adopt the WHO definition of PCC to improve consistency and comparability across studies.

### Association between COVID-19 vaccination and development of post-acute sequelae or post COVID-19 condition

There is conflicting evidence across eight studies as to whether single or two dose COVID-19 vaccination is associated with a lower risk of developing PAS or PCC. These studies include a prospective cohort study (n=1), retrospective cohort studies (n=3), and cross-sectional studies (n=4). High-level summaries of the studies are listed below by whether vaccination was received before or after COVID-19 infection and details on individual studies can be found in Table 1.

**Pre-infection vaccination** and its association with the risk of developing PCC was examined in five studies. Studies show that COVID-19 vaccination is associated with a reduced risk (n=4) or no change (n=1) in risk of PCC, while no studies showed an increased risk.

- Two studies found that receiving two doses of vaccine was associated with a reduced risk of PCC and one study found no overall association, but found associations with some symptoms.

- A large USA retrospective cohort study reported individuals who were fully vaccinated (Comirnaty, SpikeVax, or Janssen) before infection had a lower risk of experiencing at least one PCC symptom over six months, compared to unvaccinated individuals (HR = 0.87, 95%CI: 0.83-0.92) [10]. Vaccinated individuals had a lower risk of PCC involving metabolism (HR 0.81, 95%CI 0.69-0.96), the pulmonary system (HR 0.75, 95%CI 0.68-0.83), cardiovascular system (HR 0.80, 95%CI 0.71-0.91), coagulation (HR 0.54, 95%CI 0.44-0.66), and fatigue (HR 0.83, 95%CI 0.70-0.98) [10].
- In a large cross-sectional study from India, multivariable analysis showed that individuals who received two doses of a vaccine (type unspecified) before infection had lower odds of developing PCC symptoms, compared to unvaccinated individuals (aOR = 0.55, 95%CI: 0.37-0.85) [14].
- In a large global retrospective cohort study, there was no significant difference in the risk of PCC within six months of infection between those who were vaccinated with two doses (Comirnaty or SpikeVax) before infection vs. those who were unvaccinated [13]. However, vaccinated individuals had a significantly lower risk of abnormal breathing (HR 0.89, 95% CI 0.81-0.98, p=0.01), cognitive symptoms (HR 0.87, 95% CI 0.76-0.99, p=0.04), fatigue (HR 0.86, 95% CI 0.77-0.96, p=0.005), myalgia (HR 0.70, 95% CI 0.59-0.84, p<0.0001), or other pain (HR 0.85, 95% CI 0.76-0.96, p=0.007) [13].

- A small cross-sectional study from Israel reported a lower proportion of PCC symptoms among those who received one or two doses prior to COVID-19 infection compared to unvaccinated individuals [19].
  - A lower proportion of individuals vaccinated with one or two doses (Comirnaty) before infection reported PCC symptoms including fatigue (33% vs. 50%), muscle or body aches (13% vs. 28%), effort dyspnea (33% vs. 53%), and loss of taste or smell (13% vs. 17%), compared to unvaccinated individuals [19].

- One study found that a single vaccine dose before COVID-19 infection reduced the risk of PCC.
  - A large retrospective cohort study from the USA reported individuals who received a single dose (Comirnaty, SpikeVax, or Janssen) before COVID-19 diagnosis had significantly lower odds (OR = 0.22, 95%CI: 0.12-0.26, p<0.005) of experiencing any PCC symptom and significantly lower odds (OR = 0.11, 95%CI: 0.09-0.14, p<0.005) of experiencing more than one PCC symptom [11].

- Two studies found no overall association between receiving one dose prior to COVID-19 infection and development of PCC [13, 14], but one of these studies found a lower risk of some PCC symptoms [13].
  - In a large cross-sectional study from India, multivariable analysis showed that there is no association between receiving one dose of a vaccine (type unspecified) before infection and developing PCC symptoms (aOR = 1.00, 95%CI: 0.66-1.49) [14].
  - In a large global retrospective cohort study, there was no significant difference in the risk of any PCC symptom within six months of infection, between those who were vaccinated with one dose (Comirnaty or SpikeVax) before infection vs. those who were unvaccinated [13]. However, vaccinated individuals had a significantly lower risk of cognitive symptoms (HR 0.81, 95%CI: 0.68-0.97, p=0.02) and myalgia (HR 0.75, 95%CI: 0.59-0.97, p=0.03) [13].

**Post-infection vaccination** and its association with the risk of developing PCC was examined in two studies, which found that one or two doses received post-infection was associated with a reduced risk of developing PCC.

- In a large UK prospective cohort study, receiving the first vaccine dose (Comirnaty, SpikeVax, or Vaxzevria) up to 6 months after COVID-19 reduced the odds of experiencing PCC by 12.8% (95%CI -18.6 to -6.6%) immediately after vaccination, compared to before vaccination [8]. In a retrospective cohort from the USA

results of a linear regression model showed, receiving one dose 0 to 20 weeks after a COVID-19 diagnosis reduced the likelihood and number of PCC symptoms (parameter = -0.85, 95%CI -0.88 to -0.82, p<0.0005) [11]. The earlier the first dose was given after infection, the stronger the protective association of vaccination against PCC [11].

- The UK prospective cohort also reported two vaccine doses (Comirnaty, SpikeVax, or Vaxzevria) post-infection reduced the odds of experiencing PCC by 8.8% (95%CI -14.1% to -3.1%) immediately after vaccination, followed by a continued decrease in the odds by 0.8% (95%CI: -1.2% to -0.4%) per week, up to a median 67 days after the second dose [8].

**Vaccination before and after COVID-19 were combined** in two cross-sectional studies that examined the association between vaccination and risk of developing PAS or PCC. Both studies reported no association with one dose of vaccine[15, 18], but one study found a reduced risk after two or three vaccine doses [18] and the other found increased risk after two doses[15].

- In a large cross-sectional study from Israel, when comparing those vaccinated with one dose (Comirnaty) before or after infection vs. unvaccinated, there was no significant difference in PCC symptoms [18]. However, two or three doses before or after infection was significantly associated with a lower risk of fatigue (aRR 0.36, 95%CI 0.19-0.71), headache (aRR 0.46, 95%CI 0.26-0.83), weakness in arms and legs (aRR 0.43, 0.20-0.94), persistent muscle pain (aRR 0.32, 95%CI 0.11-0.88), hair loss (aRR 0.17, 95%CI 0.06-0.60), dizziness (aRR 0.26, 95%CI 0.09-0.79), and shortness of breath (aRR 0.23, 95%CI 0.07-0.84), compared to unvaccinated individuals [18]. There was no significant difference in other PCC symptoms such as loss of concentration, sleeping problems, and persistent cough [18].
- A large cross-sectional study from India included people that were vaccinated before and after COVID-19 infection and only reported overall associations with PAS for one dose (Covaxin) there was no association (aOR1.88 95%CI 0.84-4.22) [15] and for two doses there was aa greater odds of PAS (aOR2.32 95%CI 1.17-4.58) [15]. The authors caution that this finding may be due to increased survival among fully vaccinated individuals, and Covaxin is not an approved vaccine in Canada [15].

### Association of post COVID-19 infection vaccination with changes in post-acute sequelae or post COVID-19 condition symptoms

Five studies assessed changes in PAS or PCC symptoms after post-infection COVID-19 vaccination and measured symptom resolution before vs. after vaccination or between vaccinated vs. unvaccinated individuals with PAS or PCC. The prospective cohort studies (n=3) identified some associations between COVID-19 vaccination and an improvement in PAS or PCC symptoms, whereas a retrospective cohort study and a cross-sectional study did not report any associations and no studies reported worsening of PAS or PCC. High level points are listed below, and details on individual studies can be found in Table 2.

**Improvement** of PAS or PCC symptoms was determined in three studies examining the association between receiving at least one dose of a COVID-19 vaccine post-infection and changes in symptoms.

- Two prospective cohort studies reported on the proportion of post-infection vaccinated (at least one dose) vs. unvaccinated individuals experiencing an improvement in PCC symptoms.
    - A large prospective cohort study from France reported that a greater proportion of vaccinated individuals (16.6%) with one dose of Comirnaty, SpikeVax, Vaxzevria, or Janssen experienced the remission of PCC symptoms, compared to unvaccinated individuals (7.5%, HR 1.97, 95%CI 1.23-3.15) [9]. Vaccinated individuals also experienced significantly less severe PCC symptoms (Score: 13.0), measured using the 53-point Mean Long COVID Symptom Tool Score, compared to unvaccinated individuals (Score: 14.8; Mean Difference= -1.8, 95%CI: -2.5 to -1.0) [9].

  - A small prospective cohort study from the UK reported an overall improvement in PCC symptoms one month post vaccination with at least one dose of Comirnaty or Vaxzevria [6]. A greater proportion of vaccinated individuals (23.2%) experienced an improvement, a lower proportion experienced worsening (5.6%), and most (71.1%) experienced unchanged PCC symptoms, compared to unvaccinated individuals (15.4% for improvement, 14.3% for worsening, and 70.3% for unchanged; p=0.035) [6]. However, this study found no significant difference in mental and physical quality of life between those vaccinated vs. unvaccinated (mental and physical composite scores: 0.5 and 0.6, respectively, measured using the Short Form-36 point questionnaire) or between vaccine type received (Comirnaty vs. Vaxzevria) [6].

- A large prospective cohort study from the UK reported a lower rate of general practitioner (GP) consultation and healthcare resource use among individuals with PAS before vs. after COVID-19 vaccination with at least one dose of Comirnaty, SpikeVax, or Vaxzevria, while controlling for time since COVID-19 diagnosis in the analysis[7]. This suggests that there was an association with the resolution of PAS post vaccination [7].
  - Reduced healthcare resource use post vaccination (aIRR 0.50, 95%CI: 0.48-0.51, p<0.001), including primary care visits (aIRR 0.50, 95%CI: 0.48-0.51, p<0.001), hospital admissions (aIRR 0.29, 95%CI: 0.21-0.38, p<0.001), and emergency department visits (aIRR 0.59, 95%CI: 0.50-0.70, p<0.001), was reported compared to before vaccination [7].
  - GP consultation incidence rates were reduced among individuals with PAS after vaccination, for several PAS symptoms including chest tightness, pain, fatigue, fever, breathlessness, cough, palpitations, diarrhea, nausea, delirium, insomnia, dizziness, paresthesia, earache, sore throat, skin rash, tinnitus, anorexia, headache, and loss of taste and/or smell (aIRR range 0.15-0.71), compared to before vaccination [7]. A complete list of symptoms is provided in Table 2.

**No change** in PAS or PCC symptoms was found in two studies assessing the association between those who were vaccinated with at least one dose of a COVID-19 vaccine post COVID-19 compared to unvaccinated.

- A large retrospective cohort from Germany reported similar proportions of post-infection vaccinated (one or two doses of Comirnaty, SpikeVax, Vaxzevria, or Janssen) vs. unvaccinated individuals experiencing PCC symptoms [12].
- A large cross-sectional study from France reported a similar number of symptoms among those with PAS between post-infection vaccinated and unvaccinated individuals[17]. There was no difference in the type of vaccine received (Comirnaty, SpikeVax, Vaxzevria, or Janssen) and a change (improvement or worsening) of PAS symptoms[17].

### Risk of adverse events following COVID-19 vaccination for individuals with post COVID-19 condition

Two studies reported on vaccine adverse events after one dose of COVID-19 vaccine in individuals with PCC. High-level points are listed below and details on individual studies can be found in Table 3.

- A large prospective cohort study from France reported vaccination was safe for individuals with PCC although there are no statistics to show the rate of adverse evens in the PCC cohort were similar to what would be expected in other populations. In the cohort 0.88% of respondents self-reported a serious adverse event after their first vaccine dose (Vaxzevria, Comirnaty, Janssen, or SpikeVax), two (0.44%) of which led to hospitalization and two (0.44%) of which led to emergency room visits [9]. Other vaccination adverse events included relapse of PCC symptoms (2.8%, n=13), as well as local and systemic reactions to vaccination (1%, n=5) [9].

- In a UK cross-sectional study involving a small sample (n=30) of healthcare workers with PCC vs. those without PCC (n=944), there was no significant difference in the number of vaccine adverse events and their duration after receiving the first dose of Comirnaty [16]. Five systemic vaccine adverse events were associated with previous COVID-19 status, while no vaccine adverse event was associated with PCC status [16].

# Methods

A daily scan of the literature (published and pre-published) is conducted by the Emerging Science Group, PHAC. The scan has compiled COVID-19 literature since the beginning of the outbreak and is updated daily. Searches to retrieve relevant COVID-19 literature are conducted in Pubmed, Scopus, BioRxiv, MedRxiv, ArXiv, SSRN, Research Square and cross-referenced with the COVID-19 information centers run by Lancet, BMJ, Elsevier, Nature and Wiley. The daily summary and full scan results are maintained in a Refworks database and an Excel list that can be searched. Targeted keyword searching was conducted within these databases to identify relevant citations on COVID-19 and SARS-CoV-2. Search terms included: 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 (73 from the initial search up to December 3, 2021, 11 from the second search conducted on December 16, 2021, and 13 from the third search conducted on January 13, 2022), which were screened for relevance to the review. Each potentially relevant reference was examined to confirm it had relevant data, which was then extracted into the review. This review contains research published up to January 13, 2022.

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# Evidence tables

### Table 1: Observational studies on the associations between COVID-19 vaccination and development of PAS or PCC (n=8)

| STUDY | METHOD | KEY OUTCOMES |
|---|---|---|
| **Cohort studies (n=4)** | | |
| Ayoubkhani (2021) [8]<br>Preprint<br><br>Prospective cohort study<br><br>UK<br><br>Feb-Sep 2021 | Researchers used data from the COVID-19 Infection Survey, a longitudinal survey of randomly sampled households in the UK. The interrupted-time-series analysis included 28,356 participants aged 18-69 from the survey who responded to the PCC question at least once in the study period, had confirmed SARS-CoV-2 at least 12 weeks before their final assessment, | Before vaccination:<br>• The odds of experiencing PCC decreased by 0.3% (95%CI: −0.9% to +0.2%) per week after infection.<br>Before vs. after vaccination (1 dose):<br>• Receiving the first vaccine dose post-infection reduced the odds of experiencing PCC to aOR= 0.872 (0.814 to 0.934)/ 12.8% (95%CI: -18.6 to -6.6%) change in odds immediately after vaccination, followed by an increase in |

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| | and had been vaccinated post-infection (1 or 2 doses, with Vaxzevria, Comirnaty, or SpikeVax).<br><br>Logistic regression analysis estimates and odds ratios are adjusted for age, sex, white or non-white ethnicity, region/country, area deprivation quintile group, health status, whether a patient-facing health or social care worker, whether hospitalised with acute COVID-19, and calendar time of infection. | risk of 0.3% per week (95%CI: -0.6 to 1.2%) until receiving the second dose.<br>• Receiving the first vaccine dose post-infection reduced the odds of experiencing activity-limiting PCC to aOR 0.877 (0.805 to 0.955)/ 12.3% (95%CI: -19.5% to -4.5%) change in odds immediately after vaccination, followed by an increase of 0.9% (95%CI: -0.2% to +1.9%) per week until receiving the second dose.<br>• The odds of Long Covid after first vaccination numerically decreased with duration from infection, with estimated decreases of 24.8%, 16.5%, and 4.8% for participants first vaccinated 9, 12, and 15 months after infection. However, duration from infection to first vaccination was not a statistically significant moderator of the vaccination-Long Covid relationship.<br><br>Before vs. after vaccination (2 doses):<br>• Receiving the second vaccine dose post-infection reduced the odds of experiencing PCC by aOR 0.912 (0.859 to 0.969)/ 8.8% (95%CI: -14.1% to -3.1%) change in odds immediately after vaccination, followed by a continued decrease of 0.8% (95%CI: -1.2% to -0.4%) per week, up to a median 67 days following second vaccination.<br>• Receiving the second vaccine dose post-infection reduced the odds of experiencing activity-limiting PCC by aOR 0.909 (0.844 to 0.979)/ 9.1% (95%CI: -15.6% to -2.1%) change in odds immediately after vaccination, followed by a continued decrease of 0.5% (95%CI: -1.0% to +0.05%) per week.<br>• There was no significant difference in the odds of PCC between receiving Vaxzevria vs. Comirnaty or SpikeVax.<br>• Symptoms: After first vaccination, the largest numerical decreases were observed for loss of smell (-12.5%, - 21.5% to -2.5%), loss of taste (-9.2%, -19.8% to +2.7%), and trouble sleeping (-8.8%, - 19.4% to +3.3%). After second vaccination, the largest numerical decreases were observed for fatigue (-9.7%, -16.5% to - |

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| | | 2.4%), headache (-9.0%, -18.1% to +1.0%), and trouble sleeping (-9.0%, -18.2% to +1.2%).<br><br>Note: The authors described the change in likelihood of experiencing PCC symptoms as occurring immediately after vaccination, however, this could occur over a period of days or weeks after vaccination. |
| Al-Aly (2021) [10]<br>Preprint<br><br>Retrospective cohort study<br><br>USA<br><br>Feb–Oct 2021 | Breakthrough COVID-19 infections in 16,035 individuals who were fully vaccinated with the Comirnaty, SpikeVax, or Janssen vaccine were compared to 3,569,525 control participants without COVID-19, and 48,536 unvaccinated COVID-19 cases. This was to determine if breakthrough infections can lead to the development of PCC outcomes, six months following a COVID-19 diagnosis.<br><br>Covariates including smoking status, age, race, sex, pre-existing conditions, and BMI were considered in the analysis. | Fully vaccinated vs. unvaccinated COVID-19 cases:<br>• There was a lower risk (HR 0.87, 95%CI 0.83-0.92) of at least one PCC symptom among individuals with a breakthrough COVID-19 infection.<br>• The risk of PCC involving metabolism (HR 0.81, 95%CI 0.69-0.96), the pulmonary system (HR 0.75, 95%CI 0.68-0.83), cardiovascular system (HR 0.80, 95%CI 0.71-0.91), coagulation (HR 0.54, 95%CI 0.44-0.66), and fatigue (HR 0.83, 95%CI 0.70-0.98) was lower in people with a breakthrough COVID-19 infection.<br>• There was no significant difference in the risk of PCC symptoms related to the gastrointestinal system (HR 0.96, 95%CI 0.82-1.12), kidney (HR 0.90, 95%CI 0.77-1.05), neurologic system (HR 0.92, 95%CI 0.76-1.13), and mental health (HR 0.96, 95%CI 0.87-1.06).<br>Vaccinated vs. controls without COVID-19:<br>• There was an increased risk (HR = 1.59, 95%CI: 1.53-1.65) of experiencing PCC among individuals with a breakthrough COVID-19 infection and the risk was higher in non-hospitalized (HR 1.30, 95%CI 1.24-1.36) vs. hospitalized (HR 2.91, 95%CI 2.72-3.13).<br>• There was an increased risk of PCC among individuals who survived a breakthrough infection up to 30 days, involving disorders of the cardiovascular system (HR = 2.01, 95%CI: 1.85-2.20), nervous system (HR = 1.79, 95%CI: 1.55-2.06), digestive system (HR = 1.48, 95%CI: 1.34-1.64), metabolic system (HR = 1.46, 95%CI: 1.29-1.66), and musculoskeletal system (HR = 1.75, 95%CI: 1.57-1.95), as well as fatigue (HR = 2.16, 95%CI: 1.92-2.43) and conditions affecting the kidneys (HR = 1.92, 95%CI: 1.69-2.18), coagulation (HR = 2.93, |

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| | | 95%CI: 2.52-3.42), and mental health (HR = 1.42, 95%CI: 1.32-1.53). |
| Taquet (2021) [13]<br>Preprint<br><br>Retrospective cohort study<br><br>USA, India, Australia, Malaysia, Taiwan, Spain, UK, Bulgaria<br><br>Jan-Aug 2021 | This study examined the 6-month incidence of health outcomes in patients who had confirmed SARS-CoV-2 infection, by retrospectively analyzing electronic health records. The vaccinated cohort (n=9.479) consisted of patients who became infected at least 14 days after receiving a vaccine (Comirnaty, SpikeVax, or Janssen). The matched unvaccinated cohort (n=9,479) consisted of patients who had not received any COVID-19 vaccine before their infection.<br><br>PCC or "Long covid features" included:<br>abdominal symptoms, abnormal breathing, anxiety/depression, chest/throat pain, cognitive symptoms, fatigue, headache, myalgia, other pain. | Vaccinated (1 or 2 doses) vs. unvaccinated:<br>• There was no significant difference in the risk of any PCC symptom within 6 months of infection (HR 1.01, 95%CI 0.96-1.05, p=0.83).<br>• Vaccinated individuals (1 or 2 doses) had a significantly lower risk of fatigue (HR 0.89, 95%CI 0.81-0.97, p=0.01), myalgia (HR 0.78, 95%CI 0.67-0.91, p-0.001), and other pain (HR 0.90, 95%CI 0.81-0.99, p=0.03) within 6 months of infection.<br>• No significant difference in the risk of abdominal symptoms (p=0.62), abnormal breathing (p=0.36), anxiety/depression (p=0.06), chest/throat pain (p=0.66), cognitive symptoms (p=0.18), or headache (p=0.23).<br>Vaccinated (1 dose) vs. unvaccinated:<br>• There was no significant difference in the risk of any PCC symptom within 6 months of infection (HR 0.96, 95%CI 0.89-1.03, p=0.24).<br>• No significant difference in the risk of abdominal symptoms (p=0.65), abnormal breathing (p=0.95), anxiety/depression (p=0.43), chest/throat pain (p=0.75), fatigue (p=0.07), headache (p=0.16), other pain (p=0.07) within 6 months of infection.<br>• Vaccinated individuals (1 dose) had a significantly lower risk of cognitive symptoms (HR 0.81, 95%CI 0.68-0.97, p=0.02) or myalgia (HR 0.75, 95%CI 0.59-0.97, p=0.03) within 6 months of infection.<br>Vaccinated (2 doses) vs. unvaccinated:<br>• There was no significant difference in the risk of any long covid feature within 6 months of infection between those who were vaccinated (2 doses) vs. unvaccinated (HR 1.00, 95%CI 0.95-1.06, p=0.98).<br>• No significant difference in the risk of abdominal symptoms (p=0.99), anxiety/depression (p=0.55), chest/throat pain (p=0.2), or headache (p=0.95) within 6 months of infection.<br>• Vaccinated individuals (2 doses) had a significantly lower risk of abnormal breathing (HR 0.89, 95%CI 0.81-0.98, p=0.01), cognitive symptoms (HR 0.87, 95%CI 0.76-0.99, p=0.04), |

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| | | fatigue (HR 0.86, 95%CI 0.77-0.96, p=0.005), myalgia (HR 0.70, 95%CI 0.59-0.84, p<0.0001), other pain (HR 0.85, 95%CI 0.76-0.96, p=0.007) within 6 months of infection. |
| Simon (2021) [11]<br>Preprint<br><br>Retrospective cohort study<br><br>USA<br><br>Feb 2020–May 2021 | A retrospective analysis of the medical records of 240,648 COVID-19 patients examined the effect of pre- and post-COVID-19 infection vaccination with one dose of the Comirnaty, SpikeVax, or Janssen vaccine. This aimed to assess the impact of vaccination on the development of PCC symptoms (lasting 3 to 5 months after COVID-19 diagnosis), compared to remaining unvaccinated.<br><br>Linear and logistic regression models were used, and considered factors such as age, sex, ethnicity, race, pre-existing conditions, and COVID-19-related hospitalization. | Vaccinated (1 dose) vs. unvaccinated:<br>• Individuals who received a single dose of any of the three COVID-19 vaccines, prior to receiving a COVID-19 diagnosis, had lower odds (OR = 0.220, 95%CI: 0.196-0.245, p<0.005) of experiencing any PCC symptom and lower odds (OR = 0.113, 95%CI: 0.090-0.143, P<0.005) of experiencing more than one PCC symptom.<br>• Individuals who received a single dose of any three COVID-19 vaccine after a COVID-19 diagnosis, had lower odds of experiencing any PCC symptom:<br>  ○ 0 to 4 weeks post COVID-19 diagnosis (OR = 0.382, 95%CI: 0.353-0.413, p<0.005).<br>  ○ 4 to 8 weeks post COVID-19 diagnosis (OR = 0.535, 95%CI: 0.506-0.567, p<0.005).<br>  ○ 8 to 12 weeks post COVID-19 diagnosis (OR = 0.747, 95%CI: 0.713-0.784, p<0.005).<br>  ○ 12 weeks post COVID-19 diagnosis (OR<1.0, p<0.005).<br>• Individuals who received a single dose of any three COVID-19 vaccine after a COVID-19 diagnosis, had lower odds of experiencing more than one PCC symptom:<br>  ○ 0 to 4 weeks post COVID-19 diagnosis (OR = 0.189, 95%CI: 0.163-0.220, P<0.005).<br>  ○ 4 to 8 weeks post COVID-19 diagnosis (OR = 0.317, 95%CI: 0.289-0.348, P<0.005).<br>  ○ 8 to 12 weeks post COVID-19 diagnosis (OR = 0.458, 95%CI: 0.426-0.493, P<0.005).<br>• In a linear regression model, receiving one dose of a COVID-19 vaccine, 0 to 20 weeks after a COVID-19 diagnosis, and the likelihood and number of PCC symptoms were negatively associated (parameter = -0.85, 95%CI: (-0.88) – (-0.82), p<0.0005). |
| **Cross-sectional studies (n=4)** | | |
| Senjam (2021) [14]<br>Preprint | A semi-structured questionnaire was conducted among 773 adults (≥18 years of age) who tested positive for SARS-CoV-2, of which | Vaccinated (1 or 2 doses) vs unvaccinated:<br>• Among individuals (22.6%, 175/773) who received one dose of a COVID-19 vaccine before COVID-19 infection, 37.1% (65/175) |

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| Cross-sectional study<br><br>India<br><br>Jan-Jul 2021 | 52.7% (n=407) were unvaccinated, 22.6% (n=175) received one dose, and 24.7% (n=191) received two doses of a COVID-19 vaccine (type unspecified) prior to diagnosis. This study aimed to assess the impact of pre-infection, one or two dose COVID-19 vaccination on PAS (lasting between 4 to 12 weeks after diagnosis) and PCC (lasting ≥ 12 weeks after diagnosis), compared to unvaccinated individuals. Outcomes were not differentiated by PAS vs. PCC, therefore outcomes were interpreted as PCC.<br><br>A multivariable logistic regression model was used to determine the odds of developing PCC among those vaccinated vs. unvaccinated. | developed PCC, while 62.9% (110/175) did not develop PCC (p = 0.05).<br>• Among individuals (24.7%, 191/773) who received two doses of a COVID-19 vaccine before COVID-19 infection, 26.5% (50/191) developed PCC, while 73.5% (141/191) did not develop PCC (p = 0.05).<br>• While there is no association between receiving one dose of a COVID-19 vaccine before infection and developing PCC (aOR = 1.00, 95%CI: 0.66-1.49), individuals who received two doses of a COVID-19 vaccine before infection had a lower odds of developing PCC, compared to unvaccinated individuals (aOR = 0.55, 95%CI: 0.37-0.85). Therefore, being unvaccinated is an independent risk factor for developing PCC. |
| Kuodi (2022) [18]<br>Preprint<br><br>Cross-sectional study<br><br>Israel<br><br>Mar 2020-Nov 2021 | An online survey (cross-sectional nested within an on-going cohort study) was conducted with 951 individuals (over 18 years old) who had reported testing positive for SARS-CoV-2 by RT-PCR. 340 had received one Comirnaty vaccine dose and 294 had received at least two doses, while 317 were unvaccinated (the study started 9 months before vaccines were available in Israel). Individuals were vaccinated before or after COVID-19 infection.<br><br>The median time between COVID-19 symptom onset and the survey response date was 302 days for all participants, 114.5 days for fully vaccinated (2+ doses), 348 days for partially vaccinated (1 dose), and 246.5 days for unvaccinated.<br><br>Binomial regression analysis risk ratios are adjusted for duration of follow-up and presence of symptoms at baseline. Risk ratios | Vaccinated (at least 2 doses) vs. unvaccinated:<br>• Individuals vaccinated with two or three doses had significantly lower risk of fatigue (aRR 0.361, 95%CI 0.185-0.706, p=0.003), headache (aRR 0.461, 95%CI 0.255-0.834, p=0.010), weakness in arms and legs (aRR 0.428, 0.196-0.936, p=0.033), persistent muscle pain (aRR 0.317, 95%CI 0.114-0.881, p=0.028), hair loss (aRR 0.174, 95%CI 0.056-0.598, p=0.005), dizziness (aRR 0.263, 95%CI 0.087-1.794, p=0.018), and shortness of breath (aRR 0.233, 95%CI 0.065-0.839, p=0.026).<br>• No significant difference in loss of concentration (p=0.408), sleeping problems (p=0.264), persistent cough (p=0.483), or recovery from COVID-19 (p=0.856).<br>Vaccinated (1 dose) vs. unvaccinated:<br>• In unadjusted binomial regression, no significant difference in fatigue (p=0.667), headache (p=0.590), weakness in arms and legs (p=0.815), persistent muscle pain (p=0.465), loss of concentration (p=0.315), hair loss (p=0.612), sleeping problems (p=0.189), dizziness (p=0.578), persistent cough (p=0.971), shortness of breath (p=0.764), or recovery from COVID-19 (p=0.778). Adjusted |

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| | were provided for the ten most commonly reported PCC symptoms among all participants. The "recovery from COVID-19" outcome was based on participants' self-reported feelings of recovery. | analysis was not provided for single vaccination vs. unvaccinated.<br><br>Note: In the vaccinated group, participants were older ($p<0.001$) and pre-existing chronic conditions were more frequently reported ($p<0.05$), compared to unvaccinated controls.<br><br>Note: The authors suggest that those with one dose were most likely vaccinated after infection and those with two doses were vaccinated before infection, based on Israel's vaccination policy (recommending one dose for previously infected individuals). However, vaccination status at the time of infection was not assessed by the survey in this study. |
| Blumberg (2022) [19]<br>Preprint<br><br>Cross-sectional study<br><br>Israel<br><br>Mar-Dec 2021 | 43 participants (aged 18-65) with previous COVID-19 infection performed a symptom-limited cardio-pulmonary exercise test (CPET) on a bicycle ergometer. 28 were unvaccinated and 15 were vaccinated with Comirnaty before infection (2 received one dose and 13 received at least two doses). The CPET test was conducted a mean 119±24 days (appx. 4 months) after acute infection.<br><br>During the test, cardiac electrical activity was measured continuously (using electrocardiography), while blood pressure and perceived exertion were measured every two minutes. The CPET results were compared to predicted values within each group.<br><br>The CPET provided cardiopulmonary metrics for participants including oxygen consumption ($V'O_2$), heart rate (HR), minute ventilation (VE), workload (WR), minute ventilation/carbon dioxide production ($V'E/VCO_2$) and rate of perceived exertion (RPE). | Vaccinated (1 or 2 doses) vs. unvaccinated:<br>• A lower proportion of vaccinated individuals reported PCC symptoms including fatigue (33% vs. 50%), muscle or body aches (13% vs. 28%), effort dyspnea (33% vs. 53%), and loss of taste or smell (13% vs. 17%).<br>• Regarding cardiopulmonary metrics, vaccinated individuals had significantly higher mean $V'O_2$/kg ($p=0.026$), mean HR ($p=0.0004$), and mean VE ($p=0.004$).<br>• No significant difference in mean $V'O_2$ ($p=0.129$), mean $V'O_2$/HR ($p=0.71$), mean WR ($p=0.2$), mean $V'E/VCO_2$ ($p=0.152$), and mean RPE ($p=0.166$).<br>• On average, vaccinated individuals reached 95% of their predicted peak $V'O_2$ compared to 83% for unvaccinated individuals ($p=0.044$).<br><br>Note: 14% of the unvaccinated group had comorbidities (diabetes mellitus and hypertension) vs. 0% of the vaccinated group. |

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| Arjun (2022) [15]<br>Preprint<br><br>Cross-sectional study<br><br>India<br><br>Apr–Oct 2021 | This study aimed to determine the prevalence, characteristics, and predictive factors of PAS (assessed ~4 weeks after COVID-19 infection) among individuals (aged ≥ 18 years; n= 487), whose data was collected a median of 44 days after COVID-19 diagnosis.<br><br>Of the participants, the majority were vaccinated with Covaxin, of which 16.6% (n=81) were vaccinated with one dose, 58.9% (n=287) were vaccinated with two doses, and 24.5% (n=119) were unvaccinated. The timing of vaccination (pre vs. post-infection) was not specified.<br><br>The assessed outcomes were body mass index (BMI), vaccination status, and self-reported PAS symptoms. | Multivariable logistic regression comparing vaccinated (1 or 2 doses) vs. unvaccinated:<br>• Receiving one dose was not significantly associated with experiencing PAS (aOR=1.88, 95%CI: 0.84-4.22, p=0.13).<br>• Individuals who received two doses of a COVID-19 vaccine had greater odds of experiencing PAS (aOR=2.32, 95%CI: 1.17-4.58, p=0.01).<br><br>Note: Increased odds of developing PAS among those who received two doses may be due to increased survival among those with PAS. The cause of death was not investigated among participants who died, therefore, it is unknown if some deaths may have been due to PAS. |

Abbreviations: aRR, adjusted risk ratio; aOR, adjusted odds ratio; HR, hazard ratio; PAS, post-acute sequelae; PCC, post COVID-19 condition.

**Table 2: Observational studies on the associations between COVID-19 vaccination and changes in PAS or PCC symptoms (n=6)**

| STUDY | METHOD | KEY OUTCOMES |
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| **Cohort studies (n=5)** | | |
| Arnold (2021) [6]<br>Preprint<br><br>Prospective cohort study<br><br>UK<br><br>Apr 2020-Jan 2021 | Patients admitted to a hospital with COVID-19 were followed up to discharge and at 3 months and 8 months post-admission. Participants (n=44) who received at least one dose of the Comirnaty or Vaxzevria vaccine (after 8 months post-admission) were telephoned a median 32 days after vaccination to assess quality of life (measured using the Short Form-36 questionnaire) and changes in symptoms. Unvaccinated matched controls (n=22) were telephoned with the same assessment at a matched time point. | 1 month after vaccination:<br>• 71.1% of vaccinated individuals reported unchanged PCC symptoms, 23.2% improved, and 5.6% worsened vs. 70.3% of unvaccinated individuals reported unchanged, 15.4% improved, and 14.3% worsened (p=0.035), thus vaccinated individuals had an overall improvement in PCC symptoms compared to unvaccinated controls.<br>• There was no significant difference in quality of life between vaccinated vs. unvaccinated individuals (mental composite score: p=0.5, physical composite score: p=0.6) after controlling for age, sex and 8-month quality of life. |

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| | 82% of participants in both groups had at least 1 PCC persistent symptom at 8 months. | • There was no significant difference in quality of life (based on mental and physical composite scores) between those who received Comirnaty vs. Vaxzevria.<br>• There was no significant difference in mental well-being compared to before vaccination.<br><br>Note: The vaccinated group was older (median age 64 vs. 55) and more comorbid (heart disease: 25% vs. 9.1%, chronic lung disease: 32% vs. 9.1%) compared to the unvaccinated controls, which may confound results. |
| Tran (2021) [9]<br>Preprint<br><br>Prospective cohort study<br><br>France<br><br>Nov 2020-Sept 2021 | The study population consisted of adult patients (18+) enrolled in the ComPaRe long COVID cohort, who had confirmed or suspected COVID-19 infection, symptoms lasting more than 3 weeks past initial infection, and reported at least one symptom attributable to prior infection at baseline. Participants were followed-up every 60 days to complete an online questionnaire. PCC outcomes were assessed at 120 days (4 months) post baseline. Vaccination status was assessed through a different online questionnaire every 45 days.<br><br>A target trial emulation was conducted to construct the vaccinated cohort (n=455), which included those who received their first vaccine dose (Vaxzevria, Comirnaty, Janssen, or SpikeVax) between baseline and 60 days, and the matched unvaccinated cohort (n=455), which included those who did not receive a vaccine in the same time period.<br><br>PCC outcomes included disease severity (measured using the 53-point Mean Long COVID Symptom Tool Score), rate of remission, disease impact on patients' lives (measured using the 60-point Long | At 120 days post baseline:<br>• Severity of PCC was significantly lower in vaccinated individuals vs. unvaccinated (mean Long Covid Symptom Tool score 13.0 vs. 14.8, respectively; mean difference=-1.8, 95%CI -2.5 to -1.0).<br>• 16.6% of vaccinated individuals reported a remission of all PCC symptoms vs. 7.5% of unvaccinated individuals (HR 1.97, 95%CI 1.23-3.15).<br>• The impact of PCC on patients' lives was significantly lower in vaccinated individuals vs. unvaccinated (mean long covid Impact Tool score 24.3 vs. 27.6, respectively; mean difference=-3.3, 95% CI -6.2 to -0.5).<br>• An unacceptable symptom state was reported in 38.9% of vaccinated vs. 46.4% of unvaccinated individuals (risk difference: -7.5%, 95% CI -14.4 to -0.5). |

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| | COVID Impact Tool Score), and the proportion of patients reporting unacceptable symptom state (using the Patient Acceptable Symptom State threshold).<br><br>Vaccine safety outcomes are in Table 3. | |
| Whittaker (2021) [7]<br><br>Prospective cohort study<br><br>UK<br><br>Aug 2020–May 2021 | This study investigated GP consultation rates for PAS symptoms, diseases, prescription drugs, as well as healthcare resource use among post COVID-19 infection vaccinated individuals (aged ≥ 18 years) with PAS (outcomes occurring ≥ 4 weeks after COVID-19 diagnosis) who received at least one dose of Comirnaty, SpikeVax, or Vaxzevria. Participants (n=437,943) were non-hospitalized individuals who managed their COVID-19 infection in the community.<br><br>Negative binomial regression was used to compare the incidence rate ratios of outcomes occurring one month pre-vaccination (from date of COVID-19 diagnosis to date of receiving the first vaccine dose) vs. post-vaccination (date of receiving the first vaccine dose to May, 09, 2021 or death). Rates were adjusted based on sex, age, comorbidities, smoking status, time period from COVID-19 diagnosis, and BMI. | Pre vs. post vaccination (at least 1 dose) controlling for time since COVID-19 diagnosis:<br>• There were reduced GP consultation rates for PAS symptoms including chest tightness (aIRR 0.15, 95%CI: 0.07-0.36, p<0.0001), chest pain (aIRR 0.40, 95%CI: 0.33-0.48, p<0.0001), abdominal pain (aIRR 0.44, 95%CI: 0.38-0.52, p<0.0001), joint pain (aIRR 0.55, 95%CI: 0.51-0.60, p<0.0001), muscle pain (aIRR 0.71, 95%CI: 0.53-0.95, p=0.0198), general pain (aIRR 0.64, 95%CI: 0.46-0.89, p=0.0079), all pain (aIRR 0.54, 95%CI: 0.52-0.58, p<0.0001), fatigue (aIRR 0.42, 95%CI: 0.35-0.50, p<0.0001), fever (aIRR 0.47, 95%CI: 0.27-0.82, p=0.0071), breathlessness (aIRR 0.48, 95%CI: 0.42-0.56, p<0.0001), cough (aIRR 0.40, 95%CI: 0.34-0.47, p<0.0001), palpitations (aIRR 0.63, 95%CI: 0.48-0.83, p=0.0009), diarrhea (aIRR 0.45, 95%CI: 0.31-0.66, p<0.0001), nausea (aIRR 0.43, 95%CI: 0.29-0.66, p<0.0001), delirium (aIRR 0.44, 95%CI: 0.24-0.83, p=0.0116), insomnia (aIRR 0.44, 95%CI: 0.30-0.63, p<0.0001), dizziness (aIRR 0.49, 95%CI: 0.39-0.62, p<0.0001), paresthesia (aIRR 0.48, 95%CI: 0.34-0.66, p<0.0001), earache (aIRR 0.52, 95%CI: 0.37-0.71, p=0.0001), sore throat (aIRR 0.55, 95%CI: 0.42-0.73, p<0.0001), skin rash (aIRR 0.40, 95%CI: 0.32-0.50, p<0.0001), loss of smell / taste / or both (aIRR 0.32, 95%CI: 0.17-0.58, p=0.002), tinnitus (aIRR 0.39, 95%CI: 0.25-0.59, p<0.001), anorexia (aIRR 0.32, 95%CI: 0.16-0.64, p=0.0013), and headache (aIRR 0.64, 95%CI: 0.54-0.77, p<0.0001), post-vaccination, except for neuropathic pain (aIRR 0.71, 95%CI: 0.36-1.40, p=0.3231) and cognitive impairment (aIRR 0.81, 95%CI: 0.47-1.39, p=0.4463).<br>• After vaccination, there were reduced GP consultation rates for diseases including |

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| | | ischaemic heart disease (aIRR 0.41, 95%CI: 0.27-0.63, p<0.001), gastroesophageal reflux disease (aIRR 0.68, 95%CI: 0.51-0.89, p=0.006), and asthma (aIRR 0.63, 95%CI: 0.49-0.82, p<0.001).<br>• There were significantly lower prescription rates for drugs including diuretics (aIRR 0.72, 95%CI: 0.66-0.78, p<0.0001), bronchodilators (aIRR 0.80, 95%CI: 0.74-0.86, p<0.0001), inhaled corticosteroids (ICS) (aIRR 0.89, 95%CI: 0.81-0.99, p=0.0246), non-steroidal anti-inflammatory drugs (NSAIDS) (aIRR 0.82, 95%CI: 0.75-0.88, p<0.0001), weak opiates (aIRR 0.71, 95%CI: 0.65-0.78, p<0.0001), and neuropathic pain medication (aIRR 0.89, 95%CI: 0.81-0.99, p=0.0246) post-vaccination, except for strong opiates (aIRR 0.89, 95%CI: 0.77-1.03, p=0.1292) and paracetamol (aIRR 0.85, 95%CI: 0.73-1.00, p=0.0454).<br>• After vaccination, there were lower rates of all healthcare resource use (aIRR 0.50, 95%CI: 0.48-0.51, p<0.001), including primary care visits (aIRR 0.50, 95%CI: 0.48-0.51, p<0.001), hospital admissions (aIRR 0.29, 95%CI: 0.21-0.38, p<0.001), and emergency department visits (aIRR 0.59, 95%CI: 0.50-0.70, p<0.001). |
| Schultheiss (2021)[12]<br>Preprint<br><br>Retrospective cohort study<br><br>Germany<br><br>Oct 2021 | A questionnaire was administered to the study population (aged > 14 years) consisting of 258 individuals with previous COVID-19 infection who have persisting symptoms, and 36 individuals without COVID-19 in the same household as those with previous infection. This was to determine the impact of post-infection COVID-19 vaccination with one or two doses of Comirnaty, SpikeVax, Vaxzevria, or Janssen, on resolving PCC symptoms. Among participants with previous COVID-19 infection, 53.1% (n=137) were vaccinated with one dose, 22.9% (n=59) were vaccinated with two doses, and 24% (n=62) were unvaccinated. Individuals participated in the questionnaire a | Vaccinated (1 or 2 doses) vs. unvaccinated:<br>• The proportion (between 25%-50%) of individuals with ongoing PCC was similar among those who received vs. those who did not receive post-infection COVID-19 vaccination.<br>• Among individuals with PCC who received post-infection COVID-19 vaccination, the proportion of individuals with resolved vs. ongoing PCC was the same (~75%), indicating that post-infection COVID-19 vaccination was not associated with the resolution of PCC.<br><br>Note: Estimates of proportions were determined from pie charts (no numerical estimates were provided). |

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| | median of 8 months after a COVID-19 diagnosis.<br><br>Of the participants with previous COVID-19 infection, 27.5% (n=71) had symptoms 0 to 4 weeks post-infection, 11.6% (n=30) had symptoms 4 to 12 weeks post-infection, and 56.2% (n=145) had symptoms > 12 weeks post-infection. Since over half of the participants had symptoms aligned with the WHO definition of PCC, the study results were reported as PCC (rather than PAS). | |
| **Cross-sectional studies (n=1)** | | |
| Scherlinger (2021) [17]<br>Preprint<br><br>Cross-sectional study<br><br>France<br><br>Aug 2021 | An anonymous nationwide online survey was conducted among 567 adults with PAS (symptoms lasting > 4 weeks after a COVID-19 diagnosis), of which 70% (n=397; 380 were included in the analysis) were vaccinated with at least one dose of a COVID-19 vaccine (Comirnaty, SpikeVax, Vaxzevria, or Janssen) post-infection, and 30% (n=170) were unvaccinated. This was to determine the impact of COVID-19 vaccination on PAS symptoms. | Vaccinated (at least 1 dose) vs. unvaccinated:<br>• There was no significant difference in the number of persisting PAS symptoms between vaccinated (median = 12, IQR: 9-15) vs. unvaccinated (median = 13, IQR: 10-15) individuals.<br>Among vaccinated individuals:<br>• There was no difference in the type of COVID-19 vaccine received, and the impact on PAS symptoms (i.e., no change, improvement, or worsening) (p = 0.60).<br>• 52.8% (201/380) of patients reported that PAS symptoms changed after COVID-19 vaccination.<br>• 31% (117/380) reported the worsening of PAS symptoms, of which fever/chills (74%) was the most commonly reported worsened symptom, followed by gastrointestinal symptoms (70%), paresthesia (64%), and joint stiffness (63%).<br>• 21.8% (83/380) of patients reported the improvement of PAS symptoms, mainly loss of smell (62%), and brain fog (51%).<br>• 47% (179/380) of patients reported no change in PAS symptoms. |

Abbreviations: aIRR, adjusted incidence rate ratio; GP, general practitioner; HR, hazard ratio; IQR, interquartile, range; PAS, post-acute sequelae; PCC, post COVID-19 condition.

### Table 3: Observational studies on the safety of COVID-19 vaccination among individuals with PCC (n=2)

| STUDY | METHOD | KEY OUTCOMES |
|---|---|---|

| | | |
|---|---|---|
| **Cohort studies (n=1)** | | |
| Tran (2021)[9]<br>Preprint<br><br>Prospective cohort study<br><br>France<br><br>Nov 2020-Sept 2021 | The study population consisted of adult patients (18+) enrolled in the ComPaRe long COVID cohort, who had confirmed or suspected COVID-19 infection, symptoms lasting more than 3 weeks past initial infection, and reported at least one symptom attributable to prior infection at baseline. Participants were followed-up every 60 days to complete an online questionnaire. PCC outcomes were assessed at 120 days (4 months) post baseline. Vaccination status was assessed through a different online questionnaire every 45 days.<br><br>A target trial emulation was conducted to construct the vaccinated cohort (n=455), which included those who received their first vaccine dose (Vaxzevria, Comirnaty, Janssen, or SpikeVax) between baseline and 60 days, and the matched unvaccinated cohort (n=455), which included those who did not receive a vaccine in the same time period.<br><br>PCC outcomes included disease severity (measured using the 53-point Mean Long COVID Symptom Tool Score), rate of remission, disease impact on patients' lives (measured using the 60-point Long COVID Impact Tool Score), and the proportion of patients reporting unacceptable symptom state (using the Patient Acceptable Symptom State threshold). PCC outcomes reported in Table 2. | At 120 days post baseline:<br>• Among vaccinated individuals with PCC, self-reported adverse events post vaccination occurred in 5.7% (26/455). Of these, by PHAC's definition, 4/455 (0.88%) were serious adverse events: 2 (0.44%) were hospitalized for deep vein thrombosis and meningitis, 2 (0.44%) had emergency room visits. Other events included relapse of PCC symptoms (2.8%, n=13), as well as local (e.g., shoulder pain) and systemic (e.g., fever) reactions to vaccination (1%, n=5).<br>• The authors suggest that only 2 hospitalizations due to adverse vaccine events suggests that it is safe for people with PCC to get the COVID-19 vaccine. However, there is no comparator or statistics presented to support this conclusion. |
| **Cross-sectional studies (n=1)** | | |
| Raw (2021)[16]<br>LTE<br><br>Cross-sectional study | An online questionnaire was conducted in 974 healthcare workers (30 of which had PCC) who received the first dose of the Comirnaty vaccine. The questionnaire evaluated self-reported COVID-19 symptoms, a prior positive | • After controlling for age and gender, there was no significant difference in the number of vaccine side effects and their duration for those with PCC vs. without.<br>• Five systemic vaccine side effects were significantly associated with previous COVID- |

| | | |
|---|---|---|
| UK<br><br>Study period not specified (published May 2021) | PCR and/or antibody result, and adverse effects after vaccination.<br><br>Those with PCC were previously infected and had persistent symptoms for a median duration of 9.3 months (range 2.8-10.4). | 19 status, while no vaccine side effect was associated with PCC status. |

Abbreviations: PCC, post COVID-19 condition.

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# Appendix

### Table A1: COVID-19 vaccine brand names, generic names and manufacturers

| Brand Name | Generic Name | Manufacturer |
|---|---|---|
| Vaxzevria | ChAdOx1-S (AZD1222) | AstraZeneca/ Covishield |
| Comirnaty | BNT162b2 | Pfizer-BioNTech |
| (N/A) | Ad26.COV2.S | Janssen (Johnson & Johnson) |
| SpikeVax | mRNA-1273 | Moderna |
| (N/A) | NVX-CoV2373 | Novavax |
| (N/A) | CoronaVac | Sinopharm |
| (N/A) | BBIBP-CorV | Sinopharm |
| Covaxin | BBV152 | Bharat Biotech |
| Sputnik V | Gam-COVID-Vac | Russian vaccine- produced by 14 companies via partnership (Aug-21) |