Evidence Brief on the associations and safety of COVID-19 vaccination and post COVID-19 condition: update 2

July 2022

Public Health Agency of Canada
Agence de la santé publique du Canada

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Également disponible en français sous le titre :
Synthèse portant sur les données probantes au sujet des associations et de l'innocuité de la vaccination contre la COVID-19 et le syndrome post-COVID-19 : mise à jour 2

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Publication date: July 2022

Cat.: HP5-183/2024E-PDF
ISBN: 978-0-660-69547-1
Pub.: 230685

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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 who 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 by 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 five vaccines have been authorized: Comirnaty (Pfizer-BioNTech, BNT162b2), Spikevax (Moderna, mRNA-1273), Vaxzevria (AstraZeneca, ChAdOx1-S, AZD1222), Janssen (Johnson & Johnson, Ad26.COV2.S), and Nuvaxovid (Novavax, COVID-19 Vaccine (recombinant, adjuvanted)) (Table 4). 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 of COVID-19 vaccination and PAS or PCC by addressing three sub-topics: the association between vaccination and risk of developing PAS or PCC, the association between vaccination and changes in PAS or PCC symptoms, and whether the adverse event following immunization profile is different in individuals with PAS or PCC vs. those who did not have these post-infection sequelae. This evidence brief updates previous January 13 and April 14, 2022 versions with seven new studies published up to July 7, 2022. Previous versions can be requested from ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca.

Key points

There were 30 studies identified, including seven that were added in this update, that evaluated the associations and/or safety of COVID-19 vaccination and PAS or PCC,

including 13 prospective cohort studies from the UK [6, 7, 8, 9, 10] (n=5), USA [11, 12, 13] (n=3), Italy [14], France [15], Hungary [16], Scotland [17], and Turkey [18]; six retrospective cohort studies from the USA [19, 20] (n=2), Germany [21], Indonesia [22], UK [23], and multiple countries [24]; nine cross-sectional studies from India [25, 26] (n=2), Israel [27, 28] (n=2), UK [29], France [30], Indonesia [31], Switzerland [32], and the US [33]; and two case-control studies from the UK [34] and Morocco [35]. Of the 30 studies, 15 were peer-reviewed, 13 were preprints, and two were a letter to the editor.

Twenty-three studies provided PCC outcomes where symptoms were assessed at 12 or more weeks after acute infection [8, 9, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 27, 28, 29, 31, 32, 33, 35] (aligned with the WHO definition [1]), and seven studies provided PAS outcomes where symptoms were assessed between 4-12 weeks after acute infection [6, 10, 11, 22, 26, 30, 34].

Does COVID-19 vaccination before or after COVID-19 infection decrease the risk of developing PAS or PCC?

COVID-19 vaccination before COVID-19 infection was associated with a reduced risk of developing PAS/PCC in twelve studies for those with 3 doses (n=1), 2 doses (n=9), 1 dose (n=2), or an unspecified number of doses (n=1) [6, 8, 11, 17, 18, 19, 20, 22, 25, 28, 33, 34] and no change in risk of PCC for either one or two doses in one study [24]. No studies indicated an increased risk of PCC or PAS with COVID-19 vaccination before infection. Four studies were prospective cohorts, one was case-control and the remaining seven studies were retrospective or cross-sectional. Thus there is some evidence of a protective association against PAS/PCC from vaccination. Two vaccine doses prior to COVID-19 infection was consistently associated with a reduced risk of PCC (HR 0.85 [19], aOR 0.55 [25], aOR 0.59 [8], aOR 0.53 [18], no estimate [28]) and a reduced risk of PAS (aOR 0.25 [6], aOR 0.31 [22], aOR 0.51 [34], aRR 0.70 [11]) in nine studies. One study reported a further reduced risk of PAS with 3 vaccine doses (aOR 0.16 vs. aOR 0.25 with 2 doses [6]). Receipt of a single vaccine dose prior to COVID-19 was protective in two studies [17, 20] and there was no association with PAS/PCC in three other studies, two of which reported a protective association with two doses [24, 25, 34]. One cross-sectional study found that those who were unvaccinated were ~2.5 times more likely to suffer from PCC compared to those who were vaccinated (dose number unspecified) 33. For both one and two vaccine doses prior to COVID-19 infection, there was a lower risk of reporting certain PCC symptoms including reductions in fatigue (14-18%), myalgia (15-30%), dyspnea (11-20%) [24, 28] and cognitive symptoms (13-25%) [17, 24].

COVID-19 vaccination after COVID-19 infection was reported in four studies. One prospective cohort study did not find an association with vaccination (one or two doses) and the risk of developing PCC among convalescent individuals (OR 1.36, 95%CI 0.62-3.00, p=0.441) [14], which is in agreement with a case-control that found no difference

(54% vs. 45%) between the same groups [35]. Another prospective cohort study with monthly follow-up assessments 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 type received (Comirnaty, Spikevax or Vaxzevria) [7]. The time between infection and vaccination was not a significant moderator of the vaccination – PCC relationship in the prospective cohort [7]. However, a retrospective cohort found at least one vaccine dose 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) [20].

Among those who already have PAS or PCC, does COVID-19 vaccination after COVID-19 change their symptoms?

There were eleven studies examining associations between COVID-19 vaccination among individuals with PAS or PCC and changes in PAS or PCC symptoms. Results across studies were highly variable. Five prospective cohort studies conducted in France [15], the UK [9], [10], Italy [14], and Hungary [16], and two cross-sectional studies from Switzerland [32] and Indonesia [31] found beneficial associations, measured as improvement, resolution, or a decreased proportion of symptoms in those who received one or two doses of a vaccine post COVID-19 infection compared to those post-infection who were not vaccinated. Improvement or resolution of PCC symptoms were reported in 10%-28% more participants who were vaccinated compared to those unvaccinated in four studies [9, 14, 15, 32] and, in another study, fully vaccinated individuals reported higher health-related quality of life than those who were partially vaccinated or unvaccinated [31]. One study on PAS suggested there were fewer general practitioner visits for PAS symptoms (adjusted incidence rate ratio (aIRR) 0.5) among those that were vaccinated post COVID-19 compared to unvaccinated [10]. Specific symptoms, such as loss of taste and/or smell, muscle pain, chest tightness, tinnitus, and cough, were lower among PAS cases who received vaccination post COVID-19 (aIRR range 0.15-0.71) compared to those who remained unvaccinated [10]. Four additional studies, two US prospective cohorts on PCC [12, 13], a Germany retrospective cohort on PCC 21 and a French cross-sectional study on PAS [30], did not find an association with one or two vaccine doses post COVID-19 and change in PCC or PAS symptoms. Vaccine type (Comirnaty, Spikevax, Vaxzevria, Janssen, or Nuvaxovid) was not associated with PCC or PAS outcomes [12, 14, 30.]

Is it safe to get a COVID-19 vaccine for individuals who have PAS or PCC?

Two studies examined the safety of single dose vaccination in individuals with PCC. A small cross-sectional study from the UK of vaccinated healthcare workers (1 dose Comirnaty) reported no significant difference in the number of vaccine side effects and

their duration after receiving the first dose of Comirnaty between those with and without PCC [29]. A large prospective cohort study in France found that 5.7% of PCC cases self-reported an adverse event after their first vaccine dose (Vaxzevria, Comirnaty, Spikevax, or Janssen) [15]. Four serious adverse events (0.88%) were reported. 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) [15]. There were no statistics to show that the rate of adverse events in this PCC cohort were similar to what would be expected in people without PCC, however the authors concluded these results showed COVID-19 vaccination was safe for people with PCC.

Overview of the evidence

Overall, there were 30 studies that reported on the associations and safety of COVID-19 vaccination and PAS or PCC, including prospective cohort studies (n=13) [6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18], retrospective cohort studies (n=6) [19, 20, 21, 22, 23, 24], cross-sectional studies (n=9) [25, 26, 27, 28, 29, 30, 31, 32, 33], and two case-control studies [34, 35]. Fifteen studies were peer-reviewed, 13 studies were preprints that have not completed the peer-review process, and two were letters to the editor. Compared to the previous April 2022 report that included studies until April 4, 2022, there are four new peer-reviewed studies, two new preprints, one letter to the editor, and three previously reported preprints are now published. Excluded studies were case reports; case series; studies only assessing antibody 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 changes in symptoms among 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 in all observational studies. Some studies adjusted for potential confounders [6, 7, 8, 10, 11, 19, 20, 23, 25, 26, 32, 34], while other studies did not try to control for possible confounding factors that could affect observed associations with

PAS or PCC (e.g., age, pre-existing conditions) [9, 21, 28, 30, 35]. In this review, no formal risk of bias assessment of included studies was conducted.

With the exception of the results from studies with two doses of vaccine prior to getting COVID-19, the evidence was limited or inconsistent across studies within other sub-topics. Potential explanations for conflicting evidence include recall and reporting bias in studies assessing self-reported changes in PAS or PCC symptoms using questionnaires [9, 13]. 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 [24], while prospective cohort studies relied on self-report questionnaires or presentation at a post COVID-19 clinic [7].

Three studies did not report whether vaccination was received before or after COVID-19 infection [23, 26, 27] and seven studies did not report the brand of vaccine received [16, 17, 22, 23, 25, 31, 33], which could potentially impact PAS or PCC outcomes. When this information was available, it was included in this section and in the evidence tables (Table 1, Table 2, Table 3). Throughout this review, fully vaccinated refers to individuals who received the two-dose series of Comirnaty, Spikevax, Vaxzevria, or Nuvaxovid, or one dose of Janssen.

There were seven additional studies added since April 2022 and those studies did not change any previous conclusions, but have added to the evidence on the association questions. For most sub-topics in this review there are a limited number of studies; nineteen studies on the association of COVID-19 vaccination and risk of developing PAS or PCC, eleven 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 to moderate 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 variants of concern (VOC), 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 become available for children aged 5 to 11 , and recently become available for children aged 6 months and up in Canada. As booster vaccinations are available 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 in affected individuals who are subsequently vaccinated 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.

Does COVID-19 vaccination before or after COVID-19 infection decrease the risk of developing PAS or PCC?

There is consistent evidence that two or three COVID-19 vaccine doses prior to COVID-19 is associated with a lower risk of developing PAS or PCC, however the evidence for one dose or post infection vaccination is inconsistent across nineteen studies. These studies include prospective cohort studies (n=7), retrospective cohort studies (n=5), cross-sectional studies (n=5), and case-control studies (n=2). 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.

COVID-19 vaccination before COVID-19 infection and its association with the risk of developing PAS or PCC was examined in thirteen studies. Studies show that COVID-19 vaccination is associated with a reduced risk (n=12) or no change (n=1) in risk of PAS or PCC, while no studies showed an increased risk.

- Nine studies found that receiving **two vaccine doses** was associated with a reduced risk of PAS (4 studies) or PCC (5 studies), One study showed a further reduced risk of PAS with three vaccine doses and one study found no overall association, but found associations with reduced risk of some symptoms.
    - In a large UK prospective cohort study, individuals who were fully vaccinated (2 doses: Comirnaty, Spikevax, or Vaxzevria) before infection had lower odds of PCC of any severity, compared to unvaccinated individuals (aOR 0.59, 95%CI 0.50-0.69). Fully vaccinated individuals also had lower odds of self-reported PCC symptoms that limited their ability to undertake daily activities (aOR 0.59, 95%CI 0.48-0.73). There was no significant difference between participants who received Vaxzevria vs. Comirnaty or Spikevax for PCC symptoms of any severity (p=0.25) and activity-limiting PCC symptoms (p=0.35) [8].
    - In a large USA prospective cohort study, individuals who were fully vaccinated (2 doses: Comirnaty or Spikevax) before infection had a lower risk of PAS symptoms at six weeks following COVID-19 infection, compared to unvaccinated controls (aRR 0.70, 95%CI 0.58-0.84). Those

who were vaccinated also had a lower risk of neurologic symptoms (aRR 0.71, 95% CI: 0.55-0.93), and any six-week symptom (aRR=0.76, 95% CI: 0.65-0.90). Vaccinated individuals had an earlier return to work than those who were unvaccinated (median=2 days earlier; 95% CI: 1-3 days; aHR 1.37; 95% CI: 1.04-1.79) [11].

- In a large prospective cohort study from Turkey, fully vaccinated individuals were less likely to report PCC symptoms compared to unvaccinated individuals (aOR 0.53, 95% CI 0.40–0.72) [18].
- A prospective cohort of health care workers (HCWs) who were not hospitalized for COVID-19 (n=739) in Italy showed having two or three doses of Comirnaty was associated with a reduced risk of PAS (OR 0.25, 95%CI 0.07-0.87 and OR 0.16, 95%CI 0.03-0.84, respectively) [6].
- In a large UK case-control study, individuals who were fully vaccinated (2 doses: Comirnaty, Vaxzevria, or Spikevax) before infection had a significantly lower odds of symptoms lasting ≥28 days (aOR 0.51, 95%CI 0.32-0.82, p=0.005), compared to unvaccinated controls [34].
- A large USA retrospective cohort study reported individuals who were fully vaccinated (2 doses: 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 0.85, 95%CI 0.82-0.89) [19]. Vaccinated individuals had a lower risk of PCC symptoms involving the following organ systems: metabolism (HR 0.61, 95%CI 0.44-0.85), pulmonary (HR 0.58, 95%CI 0.47-0.72), cardiovascular (HR 0.78, 95%CI 0.63-0.97), coagulation and hematologic (HR 0.57, 95%CI 0.38-0.85), gastrointestinal (HR 0.66, 95%CI: 0.51-0.85), kidney (HR 0.61, 95%CI: 0.41-0.89), and fatigue (HR 0.59, 95%CI 0.46-0.76) [19].
- In a large retrospective cohort study in Indonesia, individuals who were fully vaccinated (2 doses: inactivated or viral vector vaccine) at least 14 days before infection had lower odds of developing olfactory dysfunction at two or four weeks after COVID-19 recovery (aOR 0.31, 95%CI 0.10-0.94, p=0.039), compared to controls who were either unvaccinated, only received one dose, or became infected less than 14 days after the second dose [22].
- 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) [25].
- 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 [24]. 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), while there was no difference for a number of other symptoms [24].

- 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 [28].
    - 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 [28].
- Two studies found that a **single vaccine dose** before COVID-19 infection reduced the risk of PCC and three studies reported no association between PAS (1 study) or PCC (2 studies) and one vaccine dose, but one of these three studies found a lower risk of some PCC symptoms.
    - 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 [20].
    - A large prospective cohort study from Scotland reported those vaccinated prior to symptomatic infection were less likely to report persistent change in smell (HR 0.58, 95%CI: 0.44-0.75), change in taste (HR 0.60, 95%CI: 0.46-0.78), hearing problems (HR 0.62, 95%CI: 0.45-0.85), poor appetite (HR 0.73, 95%CI: 0.53-0.99), balance problems (HR 0.75, 95%CI: 0.56-0.99), confusion/difficulty concentrating (HR 0.76, 95%CI: 0.61-0.94), and anxiety/depression (HR 0.78, 95% CI: 0.65-0.94) at their latest follow-up compared to those who were not vaccinated [17].
    - In a large UK community nested case-control study, there was no significant difference in the odds of symptoms lasting ≥28 days for those who received one dose (Comirnaty, Vaxzevria, or Spikevax) before infection vs. unvaccinated controls (OR 1.04, 95%CI: 0.86-1.25, p=0.691) [34].

    - 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) [25].
    - 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 [24]. 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) [24].
- One cross-sectional study from the US found that those who were unvaccinated were ~2.5 times more likely to suffer from PCC compared to those who were **vaccinated (dose number unspecified)** [33].

COVID-19 vaccination after COVID-19 infection and its association with the risk of developing PCC was examined in four studies, three of which found that one or two doses received post-infection was associated with a reduced risk of developing PCC. Two studies found no change in risk of PCC among individuals who were vaccinated post-infection vs. unvaccinated.

- 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 [7]. The study 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 of PCC by 0.8% (95%CI: 1.2% to 0.4%) per week, up to a median 67 days after the second dose [7].
- In a retrospective cohort study from the USA, results of a linear regression model showed that, 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) [20]. The earlier the first dose was given after infection, the stronger the protective association of vaccination against PCC [20].
- In a prospective cohort study in Italy, there was no significant difference in the odds of developing PCC between those with post-infection vaccination with one or two doses (Comirnaty, Spikevax, Vaxzevria or Janssen) vs. unvaccinated post infection (OR 1.36, 95%CI 0.62-3.00, p=0.441) [14].

- A case-control study from Morocco found there was no significant difference in self-reported PCC symptoms between those who were vaccinated after COVID-19 (31/56; 55.4%) and those who were not vaccinated after COVID-19 (25/56; 44.6%) [35].

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 [26, 27], but one study found a reduced risk after two or three vaccine doses [27] and the other found increased risk after two doses with a vaccine not authorized in Canada [26].

- 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 [27]. 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, 95%CI 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 [27]. There was no significant difference in other PCC symptoms such as loss of concentration, sleeping problems, and persistent cough [27].
- 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 [26]. For one dose (Covaxin), there was no association (aOR1.88, 95%CI 0.84-4.22) and for two doses, there was a greater odds of PAS (aOR 2.32, 95%CI 1.17-4.58) [26]. The authors caution that this finding may be due to increased survival among fully vaccinated individuals [26], and Covaxin is not an approved vaccine in Canada.

Among those who already have PAS or PCC, does COVID-19 vaccination after COVID-19 change their symptoms?

Eleven studies assessed changes in PAS or PCC symptoms after COVID-19 vaccination and measured symptom resolution before vs. after vaccination or between vaccinated vs. unvaccinated individuals with PAS or PCC. These studies include prospective cohort studies (n=7), a retrospective cohort study (n=1), and cross-sectional studies (n=3). Studies reported on the improvement or no change in PAS or PCC symptoms, however 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 seven studies examining the association between receiving at least one dose of a COVID-19 vaccine in those with PAS or PCC symptoms.

- Four prospective cohort studies and two cross-sectional studies reported on the proportion of people vaccinated (at least one dose) vs. unvaccinated individuals experiencing an improvement in their 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) [15]. 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) [15].
    - 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 [9]. 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) measured 8 months post infection [9]. 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) [9].
    - A prospective cohort study from Italy reported a lower rate of PCC symptoms among those vaccinated with at least one dose of Comirnaty, Spikevax, Vaxzevria, and Janssen compared to unvaccinated individuals (33.3% vs. 45.2%, p=0.018), at six months post COVID-19 infection [14]. There was no significant difference at 12 months or between the median number of PCC symptoms [14]. Between 6 to 12 months post-infection two rare outcomes were associated with vaccination status: a lower proportion of those vaccinated (2.3%) experienced worsened ocular symptoms, compared to those unvaccinated (5.8%; p=0.021), and a higher proportion of unvaccinated individuals (3.7%) reported an improvement in hair loss, compared to those vaccinated (0%; p=0.033) [14]. There was no significant

difference in all other PCC symptom changes (improvement, worsening, or unchanged/unaffected symptoms) among vaccinated vs. unvaccinated individuals (p-value range: 0.104-0.965) [14].

- A small prospective cohort study from Hungary reported there were higher anti-SARS-CoV-2 antibody levels among vaccinated individuals (two doses of Comirnaty, Spikevax, viral vector-based vaccines, or inactivated vaccines; brand names unspecified) with complete PCC symptom remission, compared to those with incomplete symptom remission [16]. However, there was no significant difference in antibody levels among unvaccinated individuals with complete vs. incomplete PCC symptom remission [16].
- A large cross-sectional study from Indonesia reported on the impact of PCC at 6 months among participants who received 2 doses of CoronaVac post-COVID-19 infection compared to those unvaccinated [31]. Vaccinated participants had a better Health Related Quality of Life (HRQOL) score (Total score: 4.5), measured using the St. George Respiratory Questionnaire (Score Range: 0 to 100; higher score indicating worse HRQOL), compared to partially vaccinated (Total score: 5.5) and unvaccinated individuals (Total score: 9.6) [31].
- A large cross-sectional study from Switzerland found a 28% lower proportion of PCC symptoms including cognitive issues, loss of or altered smell or taste, fatigue, headache, and shortness of breath, among those with PCC symptoms who were subsequently vaccinated (one or two doses of Comirnaty or Spikevax) vs. unvaccinated individuals, adjusted for time since COVID-19 infection, comorbidities, sex, age, and smoking status (adjusted prevalence OR (aPOR) 0.72, 95%CI 0.56-0.92) [32]. Among individuals who received two doses of Comirnaty or Spikevax vs. those unvaccinated, there was a 40%, 62%, and 66% lower proportion of any one PCC symptom (aPOR 0.60, 95%CI 0.43-0.83), altered taste (aPOR 0.38, 95%CI 0.18-0.83), and shortness of breath (aPOR 0.34, 95%CI 0.14-0.82), respectively [32].

- PAS symptom resolution and decreased use of healthcare resources was reported after vaccination with at least one dose in one study.
  - 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 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 (aIRR 0.29-0.59) compared to before vaccination [10]. This suggests that there was an association with the

resolution of PAS post vaccination [10]. 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 [10]. A complete list of symptoms is provided in Table 2.

No change in PAS (1 study) or PCC (3 studies) symptoms was found in four studies assessing the association between those who were vaccinated with at least one dose of a COVID-19 vaccine after they had developed PAS or PCC symptoms compared to those unvaccinated.

- A large prospective cohort study from the USA reported no significant difference in PCC symptom changes over a six month period among PCC symptomatic individuals who were subsequently vaccinated (at least one dose of Comirnaty, Spikevax, or Janssen) vs. unvaccinated individuals, including respiratory symptoms, shortness of breath, loss of smell, quality of life and mental health conditions, [12]. The number of doses (one or two) of Comirnaty, Spikevax, or Janssen was not associated with change in PCC symptoms from baseline to 6 month follow-up [12].
- A large retrospective cohort study from Germany reported similar proportions of PCC symptomatic individuals who were subsequently vaccinated (one or two doses of Comirnaty, Spikevax, Vaxzevria, or Janssen) vs. unvaccinated individuals experiencing PCC symptoms [21].
- A large cross-sectional study from France reported a similar number of symptoms among those with PAS who were subsequently vaccinated and unvaccinated individuals [30]. There was no difference in the type of vaccine received (Comirnaty, Spikevax, Vaxzevria, or Janssen) and the change (improvement or worsening) in PAS symptoms [30].
- A small prospective cohort study from the US demonstrated that overall there was no significant improvement in symptoms in vaccinated individuals compared to those unvaccinated at follow-up [13].

Is it safe to get a COVID-19 vaccine for individuals who have PAS or PCC?

Two studies reported on vaccine adverse events after one dose of a 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 were no statistics to show that the rate of adverse events in the PCC cohort was similar to what would be expected in other populations [15]. 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 [15]. Other vaccine adverse events included relapse of PCC symptoms (2.8%, n=13), as well as local and systemic reactions to vaccination (1%, n=5) [15].
- 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 [29]. Five systemic vaccine adverse events were associated with previous COVID-19 status, while no vaccine adverse event was associated with PCC status [29].

Methods

A daily scan of the COVID-19 literature (published and pre-published) has been conducted by the Emerging Science Group, PHAC since the beginning of the outbreak. 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 258 citations (73 from the initial search up to December 3, 2021 with new references identified at updated searches: 11 on December 16, 2021, 13 on January 13, 2022, 40 on April 4, 2022, and 121 on July 7, 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 July 7, 2022.

Acknowledgements

Prepared by Tricia Corrin and Lisa Waddell, National Microbiology Laboratory, Emerging Science Group, Public Health Agency of Canada.

Editorial review, science to policy review, peer-review by a subject matter expert and knowledge mobilization of this document was coordinated by the Office of the Chief Science Officer: ocsoevidence-bcscdonneesprobantes@phac-aspc.gc.ca.

Evidence tables

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

Study	Method	Key outcomes
Cohort studies (n=12)		
Azzolini (2022) [6] LTE new Prospective cohort study Italy Mar 2020 – Mar 2022	This prospective cohort includes data on regular testing of HCWs (n=2560) at 9 Italian institutions. Vaccination (Comirnaty) doses 1 and 2 were received in Jan/Feb 2021 and dose 3 in Nov/Dec 2021. A survey on long COVID was conducted February – April 2022. Thus PAS symptoms were self-reported. A multivariate logistic regression model explored relationships between comorbidities, demographics and vaccination status by risk of developing PAS (symptoms lasting >28 days).	739/2560 (29%) HCWs had COVID-19. Of whom 31.0% (95%CI 27.7-34.5) (229/739) developed PAS. By wave the prevalence of PAS decreased 48% in wave 1 (Mar-Sep 2020) to 16.5% in wave 3 (Oct 2021-Mar 2022). The number of vaccine doses was associated with lower PAS prevalence: ● Unvaccinated: 41.8% (95%CI 37.0-46.7) ● 1 dose: 30.0% (95%CI 6.7-65.2) ● 2 doses: 17.4% (95%CI 7.8-31.4) ● 3 doses: 16.0% (95%CI 11.8-21.0) ● Multivariate analysis, with a reference group of unvaccinated females in wave 1 with no allergies or comorbidities, 2 vaccine doses (OR 0.25, 95%CI 0.07-0.87, P = 0.03), 3 vaccine doses (OR 0.16, 95%CI 0.03-0.84, P = 0.03) and male sex (OR 0.65, 95%CI 0.44-0.98, P = 0.04) were associated with a lower probability of long COVID. Older age (OR 1.23, 95%CI 1.01-1.49, P = .04), allergies (OR 1.50, 95%CI 1.06-2.11, P = 0.02), and an increasing number of comorbidities (OR 1.32, 95%CI 1.04-1.68, P = 0.03) were associated with a higher probability. Among vaccinated individuals (n = 265), time between the second vaccination dose and infection was not associated with long COVID (OR 0.66, 95%CI 0.34-1.29).

Ayoubkhani (2022)[8] Preprint Prospective cohort study Apr 2020-Nov 2021 UK	This study examined whether pre-infection vaccination with 2 doses (Vaxzevria, Comirnaty, Spikevax) was associated with the likelihood of developing PCC symptoms ≥12 weeks after COVID-19 infection. Researchers analyzed data from COVID-19 Infection Survey participants (aged 18-69) who were recruited from randomly selected households and tested SARS-CoV-2 positive (self-reported results from national testing program). Those who were double-vaccinated ≥14 days before infection (n=3090, median follow-up from infection 96 days) were 1:1 matched to those unvaccinated at the time of infection (median follow-up from infection 98 days). Matching was based on socio-demographic characteristics (age, sex, ethnicity, country/region of residence, area deprivation quintile group, self-reported pre-existing health/disability status) and time from infection to follow-up for PCC. Activity-limiting symptoms refers to participants who self-reported their symptoms limited their ability to undertake daily activities. Single vaccinated, suspected COVID-19 or post infection serology positive participants were excluded. Note, most (99%) double vaccinated were infected after May 17, 2021 (Delta dominant timeframe), while unvaccinated controls (99.7%) were infected prior to this date.	Logistic regression analysis adjusted for socio-demographic characteristics and time from infection to follow-up, comparing vaccinated (2 doses) vs. unvaccinated: ● PCC was reported by 294/3090 (9.5%, 95%CI 8.5-10.6%) double vaccinated participants and 452/3095 (14.6%, 95%CI 13.4-15.9%) unvaccinated participants. ● Vaccinated individuals had lower adjusted odds of PCC of any severity (aOR 0.59, 95%CI 0.50-0.69), including those who received Vaxzevria only (aOR 0.62, 95%CI 0.51-0.75) and Comirnaty or Spikevax only (aOR 0.50, 95%CI 0.37-0.69) and vaccine type was not significant (p=0.25). ● Activity limiting symptoms were reported by 170 (5.5%, 95%CI 4.8-6.4%) double vaccinated and 268 (8.7%, 95%CI 7.7-9.7%) unvaccinated controls. ● Vaccinated individuals had lower adjusted odds of activity-limiting PCC (aOR 0.59, 95%CI 0.48-0.73), including those who received Vaxzevria only (aOR 0.63, 95%CI 0.49-0.80) and Comirnaty or Spikevax only (aOR 0.50, 95%CI 0.34-0.75) and vaccine type was not significant (p=0.35). ● There was no significant difference by time from infection to follow-up for PCC, for symptoms of any severity (p=0.65) and for activity-limiting symptoms (p=0.68). ● Sensitivity analysis was conducted, but did not result in a large change in magnitude for the primary outcomes.

	Logistic regression of data at ≥12 weeks from infection was used to estimate odd ratios, adjusted for all covariates included in matching.	
Emecen (2022) [18] **new** Prospective cohort study Turkey Nov 2020 – Nov 2021	This study aimed to evaluate associated factors contributing to PCC. Researchers invited adult patients with confirmed RT-PCR COVID-19 infection to participate in the study. Self-reported symptoms were collected at 1, 3, and 6 months post-COVID-19 diagnosis using a telephone questionnaire. Overall, 5610 respondents were followed for a mean of 168.3±46.8 days after infection. Of these 3727, 3200, and 2927 individuals completed the questionnaire at 1, 3, and 6 months, respectively. Participants were considered fully vaccinated 2 weeks after 2-doses of the CoronaVac or Comirnaty.	Vaccinated vs unvaccinated: ● Those who were fully vaccinated prior to COVID-19 infection were less likely to report PCC symptoms within 6 months of infection compared to unvaccinated individuals (aOR 0.53, 95% CI 0.40–0.72).
Mohr (2022) [11] Preprint Prospective cohort study USA Dec 2020-Oct 2021	Researchers conducted surveys or interviews with 419 healthcare personnel (HCP) with a symptomatic COVID-19 infection at baseline at six weeks (42 days) following acute COVID-19 infection. This was to determine the relative risk, risk difference, and prevalence of PAS symptoms six weeks following infection among those unvaccinated vs. vaccinated (two doses). HCP were either unvaccinated or vaccinated with two doses before infection (positive test ≥ 14 days after second dose). Of the vaccinated participants, 87.8% (n=158)	Multivariable Poisson regression comparing vaccinated (two doses) vs. unvaccinated: ● There was a decreased prevalence of PAS symptoms at six weeks following COVID-19 infection among those vaccinated (60.6%) vs. unvaccinated (79.1%). ● Vaccinated individuals had a lower risk of PAS symptoms at six weeks following COVID-19 infection (aRR=0.70, 95%CI 0.58-0.84), consistent with a 24.1% RD (95%CI 11.6%-36.6%). Those who were vaccinated also had a lower risk of neurologic symptoms (aRR=0.71, 95%CI 0.55-0.93;

	received Comirnaty and 12.2% (n=22) received Spikevax. A secondary analysis was performed to determine the length of time to return to work following infection, among those unvaccinated vs. vaccinated (two doses). PAS symptoms assessed included fever, shortness of breath, loss of taste/smell, cough, fatigue, headache, diarrhea, nausea/vomiting, sore throat, cognitive problems related to memory, concentration, and confusion, dizziness, exercise/sleeping/movement problems, joint/chest/abdominal pain, congestion, and muscle weakness. The multivariable model adjusted for race, ethnicity, age, and comorbidities.	RD= 17.9% decrease, 95%CI 5.1%-30.7%), and any six week symptom (aRR=0.76, 95%CI 0.65-0.90; RD=20.1% decrease, 95%CI 8.0%-32.1%). ● Vaccinated individuals had an earlier return to work than those who were unvaccinated (median=2 days earlier; 95%CI 1-3 days; aHR=1.37; 95%CI 1.04-1.79). ● Vaccinated individuals (78.9%) had a lower likelihood of returning to work greater than 10 days following acute infection, compared to unvaccinated individuals (87.5%) (RR=0.90; 95% CI: 0.82-0.99). ● Vaccinated individuals (49.4%) had a lower likelihood of experiencing PAS symptoms when returning to work, compared to unvaccinated individuals (66.2%) (RR=0.83, 95% CI: 0.67-1.03).
Ayoubkhani (2022)[7] Prospective cohort study UK 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, and had been vaccinated post-infection (1 or 2 doses, with Vaxzevria, Comirnaty, or Spikevax). Logistic regression analysis estimates and odds ratios are adjusted for age, sex, white or	● Before vaccination, the odds of experiencing PCC decreased by 0.3% (95%CI: −0.9% to +0.2%) per week after infection. Before vs. after vaccination (1 dose): ● 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 risk of 0.3% per week (95%CI: -0.6 to 1.2%) until receiving the second dose. ● Receiving the first vaccine dose post-infection reduced the odds of experiencing activity-limiting PCC to aOR 0.877 (0.805 to 0.955)/

	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.	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. ● The odds of PCC 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-PCC relationship. Before vs. after vaccination (2 doses): ● 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. ● 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. ● There was no significant difference in the odds of PCC between receiving Vaxzevria vs. Comirnaty or Spikevax. ● Symptoms: After first vaccination, the largest numerical decreases

		were observed for loss of smell (-12.5%, 95%CI:- 21.5% to -2.5%), loss of taste (-9.2%, 95%CI: -19.8% to +2.7%), and trouble sleeping (-8.8%, 95%CI: - 19.4% to +3.3%). After second vaccination, the largest numerical decreases were observed for fatigue (-9.7%, 95%CI: -16.5% to -2.4%), headache (-9.0%, 95%CI: -18.1% to +1.0%), and trouble sleeping (-9.0%, 95%CI: -18.2% to +1.2%). 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.
Pell (2022) [17] Preprint **new** Prospective cohort study Scotland Apr 2020 – May 2021	This study evaluated factors associated with the risk of developing PCC. Every adult over the age of 16 in Scotland with a positive PCR test for SARS-CoV-2 was invited to participate. These individuals were matched 3:1 with individuals who had a negative test by age, sex, and area-based socioeconomic deprivation quintile. The cohort consisted of 31,486 symptomatic and 1,795 asymptomatic COVID-19 infected individuals, and 62,957 individuals who had never been infected. Of those who had received a vaccine pre-infection, most had only received one does (2361/2727 in uninfected and 1074/1154 infected). Self-reported recovery status, symptoms, quality of life, impaired daily activities, hospitalization and death were ascertained through online questionnaires answered at 6, 12,	Vaccinated vs unvaccinated: ● After adjusting for potential confounders, those vaccinated prior to symptomatic infection were less likely to report persistent change in smell (HR 0.58, 95%CI: 0.44-0.75), change in taste (HR 0.60, 95%CI: 0.46-0.78), problems hearing (HR 0.62, 95%CI: 0.45-0.85), poor appetite (HR 0.73, 95%CI: 0.53-0.99), balance problems (HR 0.75, 95%CI: 0.56-0.99), confusion/difficulty concentrating (HR 0.76, 95%CI: 0.61-0.94), and anxiety/depression (HR 0.78, 95% CI: 0.65-0.94) at their latest follow-up compared to those who were not vaccinated. ● Since the majority of those who were vaccinated had only received 1-dose, these results suggest possible protection against persistent symptoms from partial vaccination.

	and 18-months follow-up, and linkage to hospitalization and death records. Logistic regression models were adjusted incrementally for: socioeconomic factors (age, sex, ethnic group, deprivation); pre-existing health conditions (count, respiratory and coronary heart disease, depression, diabetes); vaccination status; and dominant SARS-CoV-2 variant.	
Peghin (2022)[14] Prospective cohort study Italy Mar 2020 – May 2021	This study aimed to assess the impact of post-infection COVID-19 vaccination and immune responses on the development of and changes in PCC symptoms. Researchers conducted interviews with individuals (≥18 years) who had a previous COVID-19 infection at 6 months (n=599) and 12 months (n=479 of the 599) following infection. At 12 months (median 13.5 months from diagnosis) 27.6% (n=132/479) of the participants received at lease one dose of a COVID-19 vaccine [Comirnaty=90.5% (n=114/126); Spikevax=3.2% (n=4/126); Vaxzevria=5.6% (n=7/126); Janssen=0.8% (n=1/126); timing of vaccination post infection=12.4 months, SD=1.9 months], 23.2% (n=111) received the second dose of Comirnaty/Spikevax (timing of vaccination post infection=13.5 months, SD=2.3 months), and 72.4% (n=347) were unvaccinated. Interviews were conducted between 15 to 140 days following first or second dose vaccination.	● No significant difference in the odds of developing PCC between those who received post infection vaccination and those that were unvaccinated post infection (OR=1.36, 95%CI: 0.62-3.00, p=0.441).

	The impact of vaccine-induced and infection immune responses on PCC among those vaccinated vs. unvaccinated was examined using a subgroup of 546 participants in a parallel study. Odds ratios to examine associations between vaccination status, immune responses, and PCC were estimated using univariable and multivariable logistic regression. Changes in PCC symptoms reported in Table 2.	
Herman (2022)[22] Preprint Retrospective cohort study Jul-Dec 2021 Indonesia	This study examined the association between pre-infection vaccination and the occurrence of olfactory dysfunction (anosmia and hyposmia) after COVID-19 recovery. Researchers retrospectively analyzed data from participants (n=442) who had completed an online questionnaire at 2 and 4 weeks after COVID-19 recovery (defined as negative PCR results and clinical recovery). Olfactory dysfunction was assessed using the Self-Mini Olfactory Questionnaire. Vaccinated participants (n=221) had received two doses and were infected more than 14 days after the second dose. The average duration between vaccine receipt and infection was 88.36 ± 42.88 days. Participants received two doses of an inactivated viral vaccine (n=220) or a viral-vector vaccine (n=1); brand names were not specified. Control participants (n=221) were either unvaccinated, only received one dose, or became	At 2-4 weeks after recovery from acute COVID-19 (PAS): ● Vaccinated individuals (infected more than 14 days after the second dose) had lower odds of developing olfactory dysfunction at two or four weeks after COVID-19 recovery, compared to controls (aOR 0.31, 95%CI 0.102-0.941, p=0.039). ● A longer duration between receiving the second vaccine dose and infection was associated with an increased risk of developing olfactory dysfunction at two or four weeks after COVID-19 recovery (aOR 1.01, 95%CI 1.00-1.02, p=0.015). ● No significant difference in the odds of developing olfactory dysfunction at 4 weeks after COVID-19 recovery between those infected more than 88 days after the second dose vs. those infected less than 88 days after.

	infected less than 14 days after the second dose. Vaccinated participants were matched 1:1 to control participants, based on occupation, education, island, type of living area (rural, urban, or capital), living companion (alone vs. living with others prior to infection), age, and hypertension status. Vaccine type not specified. A generalized estimating equation was used to examine the association between vaccination and developing olfactory dysfunction. A Cochran Mantel-Haenszel test was used to compare the odds of developing olfactory dysfunction between those who were infected more than 88 days after the second dose vs. those infected less than 88 days after.	
Al-Aly (2022) [19] Retrospective cohort study USA Feb–Dec 2021	Breakthrough COVID-19 infections in 33,940 individuals who were fully vaccinated with the Comirnaty, Spikevax, or Janssen vaccine were compared to 4,983,491 control participants without COVID-19, and 113,474 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. Covariates including smoking status, age, race, sex, pre-existing conditions, and BMI were considered in the analysis.	Fully vaccinated vs. unvaccinated COVID-19 cases: ● There was a lower risk (HR 0.85, 95%CI 0.82-0.89) of at least one PCC symptom among individuals with a breakthrough COVID-19 infection. ● The risk of PCC involving metabolism (HR 0.61, 95%CI 0.44-0.85), the pulmonary system (HR 0.58, 95%CI 0.47-0.72), cardiovascular system (HR 0.78, 95%CI 0.63-0.97), coagulation and hematologic (HR 0.57, 95%CI 0.38-0.85), gastrointestinal system (HR 0.66, 95%CI 0.51-0.85), kidney (HR 0.61, 95%CI 0.41-0.89), and fatigue (HR 0.59, 95%CI 0.46-0.76) was lower in people with a breakthrough COVID-19 infection.

		● There was no significant difference in the risk of PCC symptoms related to the neurologic system (HR 0.80, 95%CI 0.61-1.06), musculoskeletal system (HR 0.88, 95%CI 0.72-1.07), and mental health (HR 0.87, 95%CI 0.75-1.02). Vaccinated vs. controls without COVID-19: ● There was an increased risk (HR 1.50, 95%CI 1.46-1.54) of experiencing PCC among individuals with a breakthrough COVID-19 infection and the risk was evident in non-hospitalized (HR 1.25, 95%CI 1.20-1.30), and increased in hospitalized (HR 2.95, 95%CI 2.80-3.10) and those admitted to ICU (HR 3.75, 95%CI 3.38-4.16). ● There was an increased risk of PCC among individuals who survived a breakthrough infection up to 30 days, involving disorders of the pulmonary system (HR 2.48, 95%CI: 2.33-2.64), cardiovascular system (HR 1.74, 95%CI: 1.66-1.83), metabolic system (HR 1.46, 95%CI: 1.37-1.56), musculoskeletal system (HR 1.53, 95%CI: 1.42-1.64), gastrointestinal system (HR 1.63, 95%CI 1.54-1.72), neurological system (HR 1.69, 95%CI 1.52-1.88), as well as fatigue (HR 2.00, 95%CI 1.82-2.21) and conditions affecting the kidneys (HR 1.62, 95%CI 1.47-1.77), coagulation and hematologic disorders (HR 2.43, 95%CI 2.18-2.71), and mental health (HR 1.46, 95%CI 1.39-1.53). ● There was a higher risk of at least one PCC symptom and organ involvement in those who were

		immunocompromised before breakthrough COVID-19 infection. ● There was no significant difference in the odds of PCC between receiving Comirnaty or Spikevax.
Meza-Torres (2022)[23] **new** Retrospective cohort study UK Mar 2020 – Sep 2021	In this analysis, pre-specified PCC identified by the Office of National Statistics comparing symptoms presented between 1-6 months after their index infection were matched with the same months one year previously. Using data from the nationally representative Primary Care Sentinel Cohort of the Oxford-Royal College of General Practitioners Research and Surveillance Centre, 428,588 COVID-19 cases were identified of which 7,628 had a diagnosis or referral for PCC. In individuals with PCC, 96.4% were unvaccinated prior to their PCC diagnosis, 3.5% had received 1-dose, and 0.1% had received 2-doses. Vaccine type was not specified.	COVID-19 without PCC vs those with PCC: ● There was no association (unadjusted) with risk of PCC post COVID-19 among those with 1 dose (OR 0.90, 95%CI 0.79-1.01) or 2 doses (OR 0.74, 95%CI 0.39-1.37) of vaccine prior to COVID-19. However, there were very few people with 1 or 2 doses of vaccine prior to COVID-19 in this cohort. Hospitalized PCC vs non-hospitalized PCC: ● There was a higher odds of PCC among those hospitalized compared to the community cases among those with one dose of vaccine OR 1.66 (95%CI 1.25-2.20) and good few people with two doses to determine an association OR 0.55 (95%CI 0.07-4.33). In this study few people had vaccines prior to COVID-19, thus the vaccinated groups were likely HCWs or elderly. The latter would be at higher risk for hospitalization due to COVID-19 which may explain any associations identified.

Taquet (2022)[24] Retrospective cohort study USA, India, Australia, Malaysia, Taiwan, Spain, UK, Bulgaria 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. PCC or "Long covid features" included: abdominal symptoms, abnormal breathing, anxiety/depression, chest/throat pain, cognitive symptoms, fatigue, headache, myalgia, other pain.	Vaccinated (1 or 2 doses) vs. unvaccinated: ● 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). ● 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. ● 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). Vaccinated (1 dose) vs. unvaccinated: ● 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). ● 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. ● 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. Vaccinated (2 doses) vs. unvaccinated: ● There was no significant difference in the risk of any PCC 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). ● 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. ● 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), 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)[20] Preprint Retrospective cohort study USA 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. 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: ● 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. ● Individuals who received a single dose of any of the three COVID-19 vaccine after a COVID-19 diagnosis, had lower odds of experiencing any PCC symptom: ○ 0 to 4 weeks post COVID-19 diagnosis (OR = 0.382, 95%CI: 0.353-0.413, p<0.005). ○ 4 to 8 weeks post COVID-19 diagnosis (OR = 0.535, 95%CI: 0.506-0.567, p<0.005). ○ 8 to 12 weeks post COVID-19 diagnosis (OR = 0.747, 95%CI: 0.713-0.784, p<0.005). ○ 12 weeks post COVID-19 diagnosis (OR<1.0, p<0.005). ● Individuals who received a single dose of any of the three COVID-19 vaccine after a COVID-19 diagnosis, had lower odds of experiencing more than one PCC symptom: ○ 0 to 4 weeks post COVID-19 diagnosis (OR = 0.189, 95%CI: 0.163-0.220, P<0.005). ○ 4 to 8 weeks post COVID-19 diagnosis (OR = 0.317,

		95%CI: 0.289-0.348, P<0.005). ○ 8 to 12 weeks post COVID-19 diagnosis (OR = 0.458, 95%CI: 0.426-0.493, P<0.005). ● 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).
Case-control studies (n=2)		
Antonelli (2022)[34] Case-control study Dec 2020-Jul 2021 UK	In a community-based nested case control study, the association between pre-infection vaccination (Comirnaty, Vaxzevria, or Spikevax) and SARS-CoV-2 symptom duration of ≥28 days was examined. Self-reported data was collected from adult participants (18+) through the COVID Symptom Study mobile phone application. All participants had used the app for at least 14 consecutive days after SARS-CoV-2 testing. Cases were those who tested SARS-CoV-2 positive at least 14 days after one dose (n=3825) or at least 7 days after the second dose (n=906). The two case groups were matched 1:1 with unvaccinated controls who had tested COVID-19 positive. Cases and controls were matched by sex, age, BMI, date of positive test, and healthcare worker status. Univariate logistic regression models (adjusted for age, BMI,	In univariate analysis adjusted for age, BMI, sex, frailty, and presence of at least one comorbidity: ● For all participants, those who received two doses had a significantly lower odds of PAS symptoms lasting ≥28 days (aOR 0.51, 95%CI 0.32-0.82, p=0.005), compared to unvaccinated controls, while there was no association with one dose of vaccine (aOR 1.04, 95%CI 0.86-1.25, p=0.691). ● Among adults aged 18-59 years old, two doses was associated with significantly lower odds of PAS symptoms lasting ≥28 days (aOR 0.21, 95%CI 0.08-0.59, p=0.003), while there was no significant association with one dose (aOR 1.2, 95%CI 0.92-1.57, p= 0.18). ● Among older adults (60+ years), there was no significant difference in the odds of PAS symptoms lasting ≥28 days between unvaccinated controls and those with one dose (aOR 0.88, 95%CI 0.68-1.15, p=0.353) or two doses

	and sex) were used to analyse the associations between risk factors and post-vaccination infection, and the associations of individual symptoms, overall disease duration, and disease severity with vaccination status.	(aOR 0.58, 95%CI 0.33-1.04, p=0.067). Sensitivity analyses are presented in the paper, however results remained consistent in direction and magnitude. Note: A significantly higher proportion of those vaccinated with one dose had at least one comorbidity (23.3%) compared to matched controls (21.2%, p=0.026), while there was no significant difference between those with two doses and matched controls.
El Otmani (2022) [35] **new** Case-control study Morocco Feb – Apr 2021	This case-control study aimed to estimate the prevalence, symptoms, and signs extending beyond the acute phase of COVD-19 compared to the general population and to assess the factors influencing the occurrence of these symptoms. Cases included healthcare workers infected with PCR confirmed COVID-19 infection (n=118). These cases were matched with controls that have never been infected with COVID-19 (n=118). Of those with COVID-19 infection, 53.4% had received the vaccine after contracting the virus and 49.2% of those without COVID-19 infection were vaccinated (CoronaVac or Vaxzevria). PCC was defined as symptoms continuing for more than 12 weeks. Self-reported data was collected through an email survey.	Vaccinated vs unvaccinated: ● There was no significant difference in self-reported PCC symptoms between those who were vaccinated after developing COVID-19 (31/56; 55.4%) and those who were not vaccinated but had COVID-19 (25/56; 44.6%).
Cross-sectional studies (n=5)		
Clark (2022) [33] Preprint **new**	An online survey of 695 Oregon residents was conducted to evaluate insights on perceptions of the pandemic, vaccinations, PCC, and testing. Type of vaccine not reported.	● 6% of vaccinated and 14% of unvaccinated individuals reported suffering from PCC for a mean of 8.4 months/median 6 months. Vaccinated vs unvaccinated:

Cross-sectional study US May 2022	The survey and this report defined PCC as "a set of symptoms that may affect different body systems (lungs, heart, muscles, cognitive, etc). These symptoms often start 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis."	● Those who were unvaccinated were ~ 2.5 times more likely to suffer from PCC compared to those who were vaccinated. This difference is statistically significant.
Blumberg (2022) [28] Preprint Cross-sectional study Israel 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. 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. 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: ● 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%). ● 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). ● 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). ● On average, vaccinated individuals reached 95% of their predicted peak $V'O_2$ compared to 83% for unvaccinated individuals (p=0.044). Note: 14% of the unvaccinated group had comorbidities (diabetes mellitus and hypertension) vs. 0% of the vaccinated group.
Kuodi (2022) [27]	An online survey (cross-sectional nested within an on-going cohort	Vaccinated (at least 2 doses) vs. unvaccinated:

Preprint Cross-sectional study Israel Mar 2020-Nov 2021	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. 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. Binomial regression analysis risk ratios are adjusted for duration of follow-up and presence of symptoms at baseline. Risk ratios 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.	● 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). ● 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). Vaccinated (1 dose) vs. unvaccinated: ● 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 analysis was not provided for single vaccination vs. unvaccinated. 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. 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.
Arjun (2022) [26] Preprint Cross-sectional study India 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. 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. 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: ● Receiving one dose was not significantly associated with experiencing PAS (aOR=1.88, 95%CI: 0.84-4.22, p=0.13). ● 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). 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.
Senjam (2021) [25] Preprint Cross-sectional study India Jan-Jul 2021	A semi-structured questionnaire was conducted among 773 adults (≥18 years of age) who tested positive for SARS-CoV-2, of which 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	Vaccinated (1 or 2 doses) vs unvaccinated: ● Among individuals (22.6%, 175/773) who received one dose of a COVID-19 vaccine before COVID-19 infection, 37.1% (65/175) developed PCC, while 62.9% (110/175) did not develop PCC (p = 0.05). ● 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).

	unvaccinated individuals. Outcomes were not differentiated by PAS vs. PCC, therefore outcomes were interpreted as PCC. A multivariable logistic regression model was used to determine the odds of developing PCC among those vaccinated vs. unvaccinated.	● 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.

Abbreviations: aOR, adjusted odds ratio; aRR, adjusted risk ratio; HCW, healthcare worker; HR, hazard ratio; PAS, post-acute sequelae; PCC, post COVID-19 condition; RD, risk difference

Table 2: Observational studies on the associations between COVID-19 vaccination and changes in PAS or PCC symptoms (n=11)

Study	Method	Key outcomes
Cohort studies (n=8)		
Tran (2021) [15] Preprint Prospective cohort study France 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. 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. PCC outcomes included disease severity (measured using the 53-point Mean Long COVID Symptom Tool Score), rate of remission, disease	At 120 days post baseline: ● 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). ● 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). ● 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). ● 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).

	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). Vaccine safety outcomes are in Table 3.	
Wisnivesky (2021) [12] Prospective cohort study USA Jul 2020 – Aug 2021	This study aimed to determine changes in PCC (n=453) following post-infection COVID-19 vaccination, among the vaccinated cohort (n=324) with at least one dose of the Comirnaty, Spikevax, or Janssen vaccine, compared to the unvaccinated cohort (n=129), over a period of six months. PCC symptoms including loss of smell (measured on a 5-point scale based on the PhenX toolkit); shortness of breath (4 point mMRC scale); cough, mucus and wheezing (4-point St. George questionnaire); depression (PHQ-8 tool), anxiety (GAD-7 instrument); post-traumatic stress disorder (PTSD) (PCL-5 checklist), and changes in quality of life (PROMIS-29 v2.0 scale) were the measured outcomes. Other health measures including body mass index (BMI) (kg/m^2), and blood pressure (mmHg) were also assessed.	No significant difference in the mean change from baseline to 6 month follow-up for any PCC symptoms in those vaccinated (at least 1 dose) vs. unvaccinated: ● Respiratory symptoms: mucus (mean difference (MD) -0.47, 95%CI -0.87-0.10), wheezing (MD -0.16, 95%CI -0.83-0.50), cough (MD -0.17, 95%CI -0.55-0.22), shortness of breath (MD 0.05, 95%CI -0.15-0.25) ● Anosmia (MD -0.02, 95%CI -0.35-0.31) ● Mental health conditions such as PTSD due to COVID-19 (MD 2.53, 95%CI -3.06-8.12), depression (MD 0.02, 95%CI -1.18-1.22), and anxiety (MD 0.51, 95%CI -0.93-0.04). ● Quality of life, in terms of pain (MD -0.02, 95%CI -2.74-2.70), physical ability (MD -1.16, 95%CI -3.35-1.02), anxiety (MD -0.29, 95%CI -2.84-2.27) and depression (MD -1.12, 95%CI -3.80-1.56), fatigue (MD -1.42, 95%CI -4.15-1.32) and sleep (MD 1.51, 95%CI -0.86-3.87). No significant difference regarding changes in PCC symptoms was shown with one versus two doses of a COVID-19 vaccine.

Ali (2022) [13] **new** Prospective cohort study US May 2020 – Aug 2021	This study assessed the evolution of neurologic symptoms and self-perceived recovery of non-hospitalized individuals with COVID-19 (n=27) and without COVID-19 (n=25) at 6-9 months after their initial COVID-19 clinic evaluation. Of these, 22 (81%) and 18 (72%) of individuals with and without COVID-19 were vaccinated between the first clinic visit and follow-up (2 doses of Spikevax or 1 or 2 doses of Comirnaty), respectively. Those with COVID-19 reported receiving their most recent vaccine at a longer period prior to follow-up than COVID-19 negative patients (median 110 days before follow-up vs. 57 days). The Neuro-COVID-19 questionnaire was completed by all individuals either by telephone or email. The questionnaire assessed patients' self-perceived recovery, current neurologic, and extraneurologic symptoms associated with COVID-19, quality of life in cognition and fatigue domains, anxiety, depression, sleep disturbances, medications tried for COVID-19, and details about COVID-19 vaccination status.	Vaccinated vs unvaccinated: ● The subjective recovery in vaccinated patients improved between the two time points (median 67.5% vs. 75%, p = 0.1) and improved significantly in the unvaccinated patients (median 45% vs. 62.5%, p = 0.03). ● A retrospective analysis demonstrated that patients who would go on to become vaccinated reported significantly higher impression of recovery at the initial clinic visit (median 67.5% vs. 45%, p = 0.03) and endorsed higher impression of recovery at follow-up compared to the unvaccinated group (median 75% vs. 62.5%, p = 0.53). ● Quality of life scores for cognition increased significantly in vaccinated individuals only (median 34 vs. 40.8, p < 0.01).
Varnai (2022) [16]	This study examined the effect of post-infection vaccination on the associations between SARS-	At follow-up (median 143 days post-baseline): ● Among vaccinated individuals (2 doses), those with complete

Prospective cohort study Hungary Oct 2020-May 2021	CoV-2 antibody levels and symptom outcomes in those with PCC. 139 unvaccinated individuals (18+) infected with COVID-19 were recruited more than 30 days after symptom onset. 107 completed follow-up 17-24 weeks after enrollment. Individuals were excluded if they were already vaccinated, were immunocompromised or had acute coronary syndrome. Date of symptom onset and vaccination status was determined based on electronic health records. At baseline and follow-up vaccination status, symptoms and SARS-CoV-2 antibodies of participants (n=107) were assessed (median 143 days later, IQR 119-170). Baseline was a median 65 days (IQR 46-99) after symptom onset, and follow-up was a median 207 days (IQR 179-241) after symptom onset. At baseline and follow-up, symptoms were assessed by a visual analog scale (VAS) and the Chalder Fatigue Scale (CFQ-11). Severe fatigue was defined as a bimodal score of 4 or more, while non-severe fatigue was 0-3. At follow-up, complete disease remission was defined as fatigue bimodal score=0 (less than usual or no more than usual level of fatigue) and VAS scale=0. At baseline and follow-up, blood samples were collected	remission had a significantly higher median serum anti-SARS-CoV-2 nucleocapsid Ig level compared to those with incomplete remission or progression (median: 100 U/mL, IQR 50-158 vs. 32, IQR 16-94; p = 0.024). However, among unvaccinated individuals, there was no significant difference between those with complete remission vs. incomplete remission. ● Among vaccinated individuals (2 doses), those with severe fatigue had a significantly lower median serum NC-Ig level compared to those with non-severe fatigue (median: 28 U/mL, IQR 16-94 vs. 97, IQR 38-155; p = 0.022). However, among unvaccinated individuals, there was no significant difference between those with severe vs. non-severe fatigue. ● In both the vaccinated and unvaccinated groups, there was no significant difference in median serum anti-SARS-CoV-2 Spike Ig level between those with severe vs. non-severe fatigue and those with complete vs. incomplete remission. There was no difference at follow-up in fatigue status (severe vs. non-severe) by vaccination status p=0.4.

	and an immunoassay was used to detect antibodies against the SARS-CoV-2 nucleocapsid protein and Spike protein. At follow-up, 84 participants were vaccinated (2 doses) and 23 unvaccinated. Vaccinated participants received homologous doses of Comirnaty or Spikevax (n=63); vector-based vaccines (n=14); or inactivated (n=7) vaccines. Vector-based and inactivated vaccine brand names were not specified.	
Whittaker (2021)[10] Prospective cohort study UK 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. 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,	Pre vs. post vaccination (at least 1 dose) controlling for time since COVID-19 diagnosis: ● 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,

	09, 2021 or death). Rates were adjusted based on sex, age, comorbidities, smoking status, time period from COVID-19 diagnosis, and BMI.	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). ● After vaccination, there were reduced GP consultation rates for diseases including 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). ● 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). 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).
Peghin (2022)[14] Prospective cohort study Italy Mar 2020 – May 2021	This study aimed to assess the impact of post-infection COVID-19 vaccination and immune responses on the development of and changes in PCC symptoms. Researchers conducted interviews with individuals (≥18 years) who had a previous COVID-19 infection at 6 months (n=599) and 12 months (n=479/ 599) following infection. At 12 months (median 13.5 months from diagnosis)	At 6 months 40.2% (95%CI 36.4-44.3) had PCC which increased to 47.2% (95%CI 42.6-51.8) at 12 month follow-up: ● Vaccinated (one or two doses) vs. unvaccinated results show no association with PCC, but also support vaccination regardless of infection history as there was no detrimental impacts: At 6 months post-infection there was less PCC among vaccinated individuals(33.3%) vs.

	27.6% (n=132/479) participants received at lease one dose of a COVID-19 vaccine [Comirnaty=90.5% (n=114/126); Spikevax=3.2% (n=4/126); Vaxzevria=5.6% (n=7/126); Janssen=0.8% (n=1/126); timing of vaccination post infection=12.4 months, SD 1.9 months], 23.2% (n=111) received the second dose of Comirnaty/Spikevax (timing of vaccination post infection=13.5 months, SD 2.3 months), and 72.4% (n=347) were unvaccinated. Interviews were conducted between 15 to 140 days following first or second dose vaccination. The impact of vaccine-induced and infection immune responses on PCC among those vaccinated vs. unvaccinated was examined using a subgroup of 546 participants in a parallel study. Odds ratios to examine associations between vaccination status, immune responses, and PCC were estimated using univariable and multivariable logistic regression. PCC development outcomes reported in Table 1. PCC symptoms were self-reported, therefore, this may have biased the results.	unvaccinated individuals (45.2%, p=0.018). ● Between 6 to 12 months post-infection, a lower proportion of vaccinated individuals experienced unchanged/unaffected PCC symptoms (65.9% vs. 71.2%) and improved PCC symptoms (11.4% vs. 13.0%), while a higher proportion of vaccinated individuals experienced symptom worsening (22.7% vs. 15.8%, p=0.21) compared to those unvaccinated. Differences were not significant. ● Between 6 to 12 months post-infection, a lower proportion of vaccinated individuals experienced worsened ocular symptoms (2.3% vaccinated vs. 5.8% unvaccinated; p=0.021), while a higher proportion of unvaccinated individuals experienced improvement in hair loss (0% vaccinated vs. 3.7% unvaccinated; p=0.033). Both these outcomes are based on a small number of people. ● Between 6 to 12 months post-infection, no significant difference in the improvement, worsening, or unchanged/unaffected PCC symptoms was found for fatigue (p=0.616), loss of smell (p=0.947), shortness of breath (p=0.965), cough (p=0.507), chest pain (p=0.544), headache (p=0.175), rheumatic (p=0.104) / gastrointestinal (p=0.340) /

		neurologic (p=0.707) / psychiatric (p=0.505) disorders, skin lesions (p=0.627), and upper respiratory tract infection symptoms (p=0.614) between vaccinated vs. unvaccinated individuals. ● At 12 months post-infection, there was no significant difference in changes in PCC symptoms among those who received Comirnaty/Spikevax (45.8%) vs. Vaxzevria/Janssen (12.5%; p=0.137), and those who received one vaccine dose (38.1%) vs. two vaccine doses (45.9%; p=0.507). ● At 12 months post-infection, there was no significant difference in the number of PCC symptoms between those vaccinated (median=2, IQR=1-2) vs. unvaccinated (median=1, IQR=1-2) (p=0.084).
Arnold (2021) [9] Preprint Prospective cohort study UK 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	1 month after vaccination: ● 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. ● There was no significant difference in quality of life between vaccinated vs. unvaccinated individuals

	assessment at a matched time point. 82% of participants in both groups had at least 1 PCC persistent symptom at 8 months.	(mental composite score: p=0.5, physical composite score: p=0.6) after controlling for age, sex and 8-month quality of life. ● There was no significant difference in quality of life (based on mental and physical composite scores) between those who received Comirnaty vs. Vaxzevria. ● There was no significant difference in mental well-being compared to before vaccination. 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.
Schultheiss (2021)[21] Preprint Retrospective cohort study Germany 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	Vaccinated (1 or 2 doses) vs. unvaccinated: ● 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. ● 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. Note: Estimates of proportions were determined from pie charts (no numerical estimates were provided).

	unvaccinated. Individuals participated in the questionnaire a median of 8 months after a COVID-19 diagnosis. 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=3)		
Scherlinger (2021)[30] Cross-sectional study France 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: ● 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. Among vaccinated individuals: ● 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). ● 52.8% (201/380) of patients reported that PAS symptoms changed after COVID-19 vaccination. ● 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%). ● 21.8% (83/380) of patients reported the improvement of PAS symptoms, mainly the improvement of loss of smell (62%), and brain fog (51%). ● 47.4% (179/380) of patients reported no change in PAS symptoms.
Suyanto (2022)[31] Cross-sectional study Indonesia Aug 2021	The St. George Respiratory Questionnaire (SGRQ) was administered to 853 individuals (>18 years) living in two urban (45%) and four rural (55%) areas of Riau Province, Sumatera Island, Indonesia who had confirmed COVID-19 Dec 2020-Feb 2021. This was to assess whether individual characteristics such as post-infection COVID-19 vaccination (vaccine type information not collected; however it was assumed to be CoronaVac based on the study period) affected the Health Related Quality of Life (HRQOL) among those who had a previous COVID-19 infection (time since hospital discharge to questionnaire=6 months). The questionnaire evaluated scores among four domains: symptoms (perceptions of symptoms including breathing issues, cough, and chest pain), activity (problems with	At 6 months post hospitalization with COVID-19 infection (PCC): ● For the SGRQ symptom score, those who were fully vaccinated had a lower score (9.7, range=2.4-17.7) indicating higher HRQOL, compared to partially vaccinated (10.5, range=0-19.6) and unvaccinated (10.5, range=2.6-21.3) individuals. Differences were not statistically significant. ● For the SGRQ activity score, those who were fully vaccinated had a significantly lower score (0, range=0-24.6) indicating higher HRQOL vs. unvaccinated (11.2, range=0-41.6) and partially vaccinated scores (0, range=0-18.5), were also lower, but not significant compared to unvaccinated individuals. ● For the SGRQ impact score, those who were fully vaccinated had a significantly lower score (4.0, range=0-15.2) indicating higher HRQOL, compared to

	physical activity), impact (problems with psychosocial functioning), and total score, measured from 0 to 100 with higher scores indicating worse HRQOL. Of the individuals from rural areas (n=468), 62.6% (n=293) were fully vaccinated, 9.8% (n=46) were partially vaccinated, and 27.6% (n=129) were unvaccinated. Of the individuals from urban areas (n=385), 48.3% (n=186) were fully vaccinated, 12.5% (n=48) were partially vaccinated, and 39.2% (n=151) were unvaccinated.	unvaccinated (8.0, range=0-27.5) individuals and partially vaccinated (4.0, range=0-11.7) were not significantly different than unvaccinated. ● For the SGRQ total score, those who were fully vaccinated had a significantly decreased score (4.5, range=0.8-17.7) indicating higher HRQOL, compared to unvaccinated (9.6, range=2.4-27.8) individuals and partially vaccinated (5.5, range=2.1-13.7) were not significantly different than unvaccinated. ● The activity, impact, and total scores of the SGRQ were significantly associated with full vaccination (activity coefficient= -2.98, 95%CI -8.68-1.61; impact coefficient= -3.99, 95%CI -5.90-3.15; total score coefficient= -3.96, 95%CI -5.87-2.88) and partial vaccination (activity coefficient= -2.98, 95%CI -7.86-2.83; impact coefficient= -3.84, 95%CI -4.32-0.25; total score coefficient= -3.00, 95%CI -5.15-0.61) vs. no vaccination (activity coefficient=0; impact coefficient=0; total score coefficient=0).
Nehme (2022) [32] Cross-sectional study	An online survey was conducted among 1,596 individuals that developed symptoms after a COVID-19 infection were included in the analysis (average time since infection=250.3 ± 72.1 days, range 3 to >12 months), to determine their COVID-19	Vaccinated (one or two doses) vs. unvaccinated >3 months after COVID-19 infection: ● Following vaccination 30.8% indicated PCC symptoms disappeared and 4.7% indicated they improved, while 3.3% indicated symptoms worsened. Respondents that

Switzerland Apr-July 2021	vaccination status (average time since vaccination= 40.3 ± 29.2 days) and the presence of PCC symptoms. This was to assess whether post-infection COVID-19 vaccination was associated with changes in PCC symptoms, compared to being unvaccinated. The PCC symptoms assessed were cognitive issues related to concentration and memory, loss of or altered smell and/or taste, fatigue, headache, and shortness of breath. Of symptomatic participants with PCC (n=1,596), 424 received one dose, 347 received two doses, and 825 were unvaccinated. Of the vaccinated PCC cases, 60.7% received Spikevax, and 38.5% received Comirnaty. Odds ratios were adjusted for time since COVID-19 infection, comorbidities, sex, age, and smoking status.	reported changes in symptoms indicated this occurred within 5 days of vaccination for >70%. ● There was an overall lower prevalence of six PCC symptoms including cognitive issues (related to concentration and memory), loss of or altered smell or taste, fatigue, headache, and shortness of breath, among individuals who received one or two doses of Comirnaty or Spikevax post-infection (aOR=0.72, 95%CI 0.56-0.92). ● Two doses of Comirnaty or Spikevax post-infection was associated with a lower prevalence of any one PCC symptom (aOR=0.60, 95%CI 0.43-0.83), shortness of breath (aOR=0.34, 95%CI 0.14-0.82), and altered taste (aOR=0.38, 95%CI 0.18-0.83).

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) [15] Preprint	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	At 120 days post baseline: ● Among vaccinated individuals with PCC, self-reported adverse events post vaccination occurred in 5.7% (26/455). Of these, by

Prospective cohort study France Nov 2020-Sept 2021	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. 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. 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.	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). • 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)[29] LTE Cross-sectional study UK Study period not specified (published May 2021)	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 PCR and/or antibody result, and adverse effects after vaccination. Those with PCC were previously infected and had persistent symptoms for a median duration of 9.3 months (range 2.8-10.4).	● 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. ● Five systemic vaccine side effects were significantly associated with previous COVID-19 status, while no vaccine side effect was associated with PCC status.

Abbreviations: PCC, post COVID-19 condition.

Appendix

Table 4: 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
Nuvaxovid	COVID-19 Vaccine (recombinant, adjuvanted)	Novavax Inc.
(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)

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