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A systematic review of the evidence on the associations and safety of COVID-19 vaccination and post COVID-19 condition

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Review

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Abstract

Post COVID-19 condition (PCC) refers to persistent or recurring symptoms (>8 weeks) occurring ≤12 weeks following acute COVID-19. The objective of this systematic review was to assess the evidence on the risk of PCC with vaccination before or after COVID-19 or after developing PCC, and the safety of vaccination among those already experiencing PCC. A search was conducted up to 13 December 2022 and standard systematic review methodology was followed. Thirty-one observational studies were included. There is moderate confidence that two doses of vaccine given pre-infection reduced the odds of PCC (pooled OR (pOR) 0.67, 95% CI 0.60–0.74, I2 = 59.9%), but low confidence that one dose may not reduce the odds (pOR 0.64, 95% CI 0.31#x2013;1.31, I2 = 99.2%), and the evidence is very uncertain about the effect of three doses (pOR 0.45, 95% CI 0.10#x2013;1.99, I2 = 30.9%). One of three studies suggested vaccination shortly after COVID-19 may offer additional protection from developing PCC compared to unvaccinated individuals, but this evidence was very uncertain. For those with PCC, vaccination was not associated with worsening PCC symptoms (10 studies) and appears safe (3 studies), but it is unclear if vaccination may change established PCC symptoms.

Introduction

Individuals who have been infected with SARS-CoV-2 may continue to experience persistent symptoms beyond the acute phase of COVID-19 disease. The World Health Organization (WHO) defines post COVID-19 condition as persistent symptoms occurring 12 or more weeks after an acute COVID-19, which have persisted or re-occurred for a minimum of eight weeks and cannot be explained by alternative diagnoses [1]. Many studies also report on post-acute sequelae (PAS) during the period immediately following acute infection from 4 to 12 weeks post-diagnosis [2]. The predominant symptoms experienced with PCC include fatigue, dyspnea (shortness of breath), other respiratory issues, cardiovascular issues, pain, sleep disturbances, decrease in quality of life, cognitive impairment, and anxiety or depression [1, 3, 4].

The variability in what defines sequelae following COVID-19, including the range of reported symptoms and durations, has made true case counts difficult to ascertain; however, the burden of PCC has been estimated to affect approximately 10-20% of individuals following COVID-19 [5, 6]. Higher proportions (more than 50%) have been reported for those with at least one symptom related to PCC beyond 12 weeks after infection in studies of hospitalised cases that had severe COVID-19 [4]. Following the COVID-19 vaccine rollout in 2021, more than 13.3 billion vaccine doses have been administered globally as of 24 February 2022 [7]. Given the high estimated burden of PCC, it is important to assess the global evidence of the impact of COVID-19 vaccination on PCC, including potential benefits and/or safety concerns.

A few systematic reviews investigating the impact of COVID-19 vaccination on PCC have been completed to date and have all included outcomes on PAS [8–11]. This review addresses the impact of vaccination on only PCC and extends included outcomes to all options for the timing of vaccination relative to infection and/or PCC (pre-infection, post-infection, and post PCC) and provides an updated synthesis of the rapidly evolving literature. Assessing the evidence related to only PCC may reduce the heterogeneity in results. Therefore, the objective of this systematic review (SR) and meta-analysis was to assess the global evidence on the associations and safety of COVID-19 vaccination and PCC (symptoms >12 weeks from infection) through the following questions: Does COVID-19 vaccination 1) before or 2) after COVID-19 decrease the risk of developing PCC?; 3) Among those who already have PCC, does subsequent COVID-19 vaccination change their symptoms?; and 4) Is it safe to get a COVID-19 vaccine for individuals who have PCC?

Methods

This SR adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was conducted following standard SR methods outlined by the Cochrane Collaboration [12, 13]. A protocol outlining the SR question and methodology was determined *a priori* and registered in PROSPERO (CRD42022365386). All deviations from the original protocol, mainly additional information extracted, have been noted in the updated protocol document in PROSPERO.

Research question and eligibility criteria

The research questions of this SR were as follows: 1) Does COVID-19 vaccination before COVID-19 decrease the risk of developing PCC or the risk of developing specific PCC symptoms?; 2) Does COVID-19 vaccination after COVID-19 decrease the risk of developing PCC or the risk of developing specific PCC symptoms?; 3) Among those that already have PCC, does COVID-19 vaccination lead to symptom changes?; and 4) Is it safe to get a COVID-19 vaccine for individuals who have PCC?

We followed a universal case definition of PCC, in accordance with the World Health Organization (WHO), defined as persistent symptoms occurring 12 or more weeks after acute COVID-19, which persist or reoccur for a minimum of eight weeks [1]. The population of interest was anyone who had COVID-19. All age groups were considered for inclusion, and children and elderly were summarised separately, where possible. The intervention was vaccination (analysis to be sub-grouped by number of doses) with any type of authorised COVID-19 vaccine, and vaccination could occur before or after COVID-19 or after developing PCC. The comparison group was unvaccinated individuals who had COVID-19 or comparison between doses of COVID-19 vaccination among those who had COVID-19. The primary outcomes of interest were the risk of developing PCC or resolution of PCC, and secondary outcomes were measurements of development of individual symptoms associated with PCC, changes to PCC symptoms among those with PCC, and adverse events following COVID-19 vaccination among those with PCC depending on the research question being assessed. Both published and preprint primary research studies with an observational or experimental study design were considered for inclusion, and preprint studies were continuously monitored for the availability of a published version.

Studies were excluded from the systematic review if they were not primary research, that is, did not present data collected by the author. Descriptive studies (i.e., case reports or case series), studies only assessing antibody responses to vaccination among individuals with PCC, predictive modelling studies, and studies only assessing changes in symptoms among vaccinated individuals with PCC with no comparator group were excluded. Studies were also excluded if they only examined people with PAS or if the sample included those with PAS and PCC where the results specific to PCC could not be extracted; a list of excluded studies is in Supplementary Table S1.

Search strategy

A database of COVID-19 literature has been continuously curated since February 2020 within the agency [14]. Updates were conducted daily until May 2022 and twice per week up to the search date. A COVID-19 search algorithm was adapted to and implemented in the following databases: PubMed, Scopus, and preprint servers BioRxiv, MedRxiv, ArXiv, SSRN, and Research Square, which were searched via EuropePMC since June 2022. Full scan results are maintained in a bibliographic management software Endnote and searchable Excel line lists. The search algorithm for this SR was run within the Endnote database with no restrictions on language and included a combination of PCC OR non-specific symptom terms AND vaccination terms (see protocol for details). The search was conducted on 21 September 2022 and updated on 13 December 2022.

Search verification

The reference lists of five relevant review articles were searched as part of search verification [8–10, 15, 16]. This process yielded two studies that were subsequently included within the screening process [17, 18].

Study selection and data extraction

The search results were imported into EndNote20 (Clarivate, Philadelphia, PA) and de-duplicated. Unique references were imported into DistillerSR software (DistillerSR. Version 2.35. DistillerSR Inc.; 2022) for systematic review management. Title/abstract and full-text relevance screening forms and a data extraction form were developed *a priori* and piloted by all three reviewers to determine functionality. Title/abstract and full-text screening were performed in duplicate by two independent reviewers. Study characterisation and data extraction of relevant articles were also performed in duplicate by two independent reviewers and included publication details (e.g., language, year), funding and conflict of interest, study design, sample location and sampling frame, study period, population characteristics (e.g., demographics, COVID-19 severity), vaccination information (e.g. number of doses, vaccine product/brand received, additionally relevant details such as sample size per treatment group), time to outcome assessment, outcome measurement/ diagnostic tools used, and outcome data. Conflicts at each stage of screening and data extraction were resolved by consensus or by a third reviewer, where necessary. Upon publication of a previously captured preprint, the publication was updated and re-evaluated to make sure all extracted data and risk of bias assessment reflected the most up-to-date version of the article.

Risk of bias assessment

The articles included in this SR were evaluated for their risk of bias (ROB) using the Newcastle–Ottawa Scale (NOS) [19], which was selected over the Risk Of Bias In Non-randomised Studies of Interventions because, while both are commonly used, NOS is more efficient and easier to implement, and the relationship between COVID-19 vaccination and development or remissison of PCC may not be a direct relationship [20]. Two pre-existing NOS forms for case–control and cohort studies were used as well as a modified tool for cross-sectional studies to perform the ROB assessment [21]. The ROB was assessed in duplicate by two independent reviewers. Across tools some of the specific questions differed by study design, but generally assessed possible selection bias (e.g., inappropriate or non-representative sampling frame), information bias (e.g., misclassification or inadequate measurement of variables), confounding bias (e.g., inadequate consideration or control of possible confounding variables), and/or reporting bias (e.g., insufficient reporting of key details to allow possible replication

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and informed inferences). Each tool was pretested on one article by all reviewers prior to proceeding with independent assessment of the remaining articles by two reviewers. Conflicts were resolved through discussion and consensus.

Data synthesis

The complete dataset was exported into Microsoft Excel (2016), where results were grouped according to the review question addressed, and tabulated to summarise the primary and secondary outcomes, and any moderating variables identified that may change the association between vaccination and PCC outcomes. Narrative synthesis of the data for each review question was performed. We expected *a priori* that there would be high heterogeneity between studies due to variability in study design, sample, timing of the study, vaccination, time since last vaccine, and measurement of the outcome, despite restricting the review to PCC outcomes at 12 or more weeks and sub-grouping by number of vaccine doses. When there were two or more studies measuring the same association for a main outcome, random-effects meta-analyses using the restricted maximum likelihood estimator for between-study variance were developed using STATA17 (StataCorp 2021) sub-grouped by number of COVID-19 vaccination doses received and the reported outcome measures. The sub-group meta-analyses allow the reader to visualise the precision of individual studies measuring the same association and agreement across studies coupled with a GRADE assessment of the certainty of the evidence. For meta-analysis, risk ratios (RR) and prevalence ratios (PR) were converted to odds ratios (OR) to calculate a pooled effect (pOR) [22, 23]. Hazard ratios (HR) and incidence rate ratios (IRR) were pooled together but kept separate from ORs because HRs and IRRs measure rate of change over a defined period, whereas OR and RR report the associations across the entire study period, and thus their meaning and value are different [24]. The impact of risk of bias (low, moderate, high) was examined for outcomes considered for meta-analysis. Testing for small study effects was only considered where meta-analyses included more than ten observations/lines of data; none of the analyses met this criterion. As part of the sensitivity analysis for meta-analysis sub-groups with more than three studies, the Hartung-Knapp-Sidik-Jonkman method for estimating more conservative confidence intervals was examined and reported in Supplementary Table S2 [25], and the prediction intervals were calculated to provide a plausible range of effect size in a future, new study and reported in Table 2 and Supplementary Table S2 [26].

Certainty of evidence

Grading the quality of evidence and the strength of recommendations (GRADE) criteria are summarised across groups of similar studies and the GRADE framework was applied to indicate the level of confidence in the current evidence for the main outcomes of development or resolution of PCC [27]. The GRADE domain's risk of bias, inconsistency, imprecision, indirectness, and dose response were evaluated to determine a one- to four-star grade. Given the expected observational study designs, higher risk of bias, and heterogeneity, GRADE ratings were expected to be very low to low for most outcomes unless there were consistent results across several large studies for an outcome; details of the evaluation scheme are available in the GRADE guide (Supplementary Table S2). The grading system indicates the following: ****high confidence that the effect estimate is close to the true effect; ***moderate confidence in the effect estimate, but future studies may be substantially different; **limited confidence in the estimate of effect, the true effect may be substantially different; and *very little confidence in the estimate of effect, the true effect is likely to be substantially different. The outcomes with one study resulted in a very little confidence rating. A summary of findings table including the GRADE for the main outcomes is available in Table 2.

Results

Study selection

There were 1,367 citations screened for relevance, 101 potentially relevant citations underwent full-text screening, and 31 have been included in this SR: 24 peer-reviewed research articles, 5 preprints, one letter to the editor, and one short communication (Figure 1 and Supplementary Tables S3–S6). Articles that only assessed PAS (n = 22), or that did not differentiate between study participants with PAS and PCC (n = 12), as well as studies that did not report the timing of vaccination (n = 8) were excluded (Supplementary Table S1).

Characteristics of the included studies

The included studies addressed the association and/or safety of COVID-19 vaccination and PCC according to the following subtopics: the effect of vaccination administered 1) before (n = 18) or 2) after (n = 3) COVID-19; 3) among previously unvaccinated individuals already experiencing PCC (n = 10); and 4) adverse events post-vaccination among those with PCC (n = 3). All studies had an observational study design (prospective cohort, n = 16; retrospective cohort, n = 5; cross-sectional, n = 9; case–control, n = 1) and had high (n = 17), moderate (n = 13), and low (n = 1) risk of bias (Table 1). None of the studies were funded by the pharmaceutical industry, and none of the authors declared conflicts of interest (Supplementary Tables S3–S6). Most studies were conducted in Europe (n = 18) or North America (n = 7), and two had a multinational sampling frame. More than half (n = 22) assessed individuals with mixed severities of COVID-19. Two studies reported on elderly populations, and no studies reported on children. Vaccine products received were mostly BNT162b2 (Pfizer-BioNTech, Comirnaty, n = 21) and mRNA-1273 (Moderna, Spikevax, n = 14). More than half of the studies (n = 23) included individuals who had received two doses of a COVID-19 vaccine, and six studies included individuals vaccinated with three doses.

(Q1) Risk of developing PCC in those vaccinated before COVID-19

The association between PCC and COVID-19 vaccination before COVID-19 was assessed in 18 studies, including 9 prospective cohorts, 5 retrospective cohorts, 1 case-control study, and 3 cross-sectional studies (Table 1). Fifteen studies stratified their analyses by dose-specific vaccination status (one dose, n = 4; two doses, n = 11; three doses, n = 3) (Supplementary Table S3) and 12 contributed to the meta-analyses (Figures 2 and 3) [23, 28–38].

Twelve studies reported the main outcome of developing PCC, as shown in Table 2. These results were pooled by number of doses; each sub-group was assessed for the certainty of evidence, and an illustrative example of the reduction in cases with vaccination was calculated using a baseline of 25% of unvaccinated Canadians report suffering from PCC after COVID-19 [39]. There is moderate to high heterogeneity across studies in each meta-analysis sub-group, which suggests that the pooled associations should be used with caution; however, there are few studies for most outcomes so

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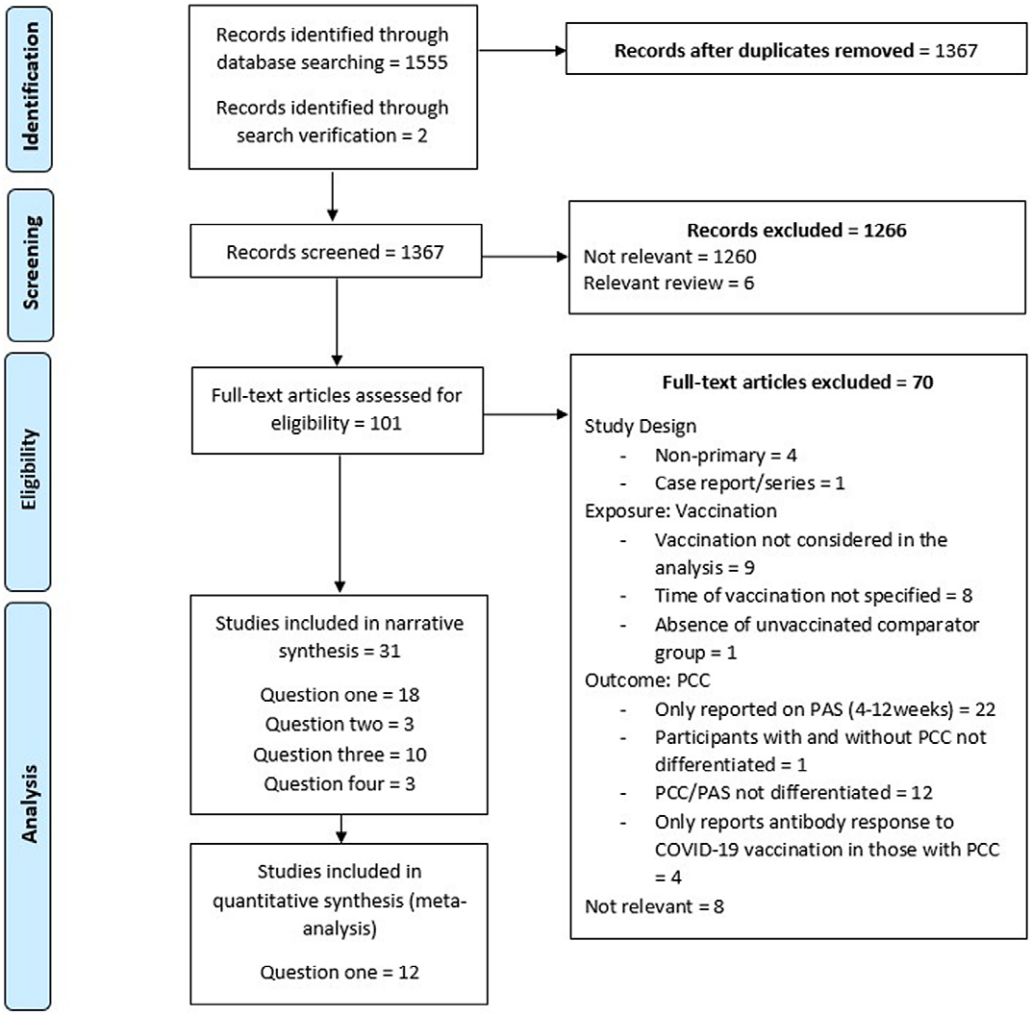

Figure 1. PRISMA flow diagram of articles through the systematic review process.

there is limited exploration of heterogeneity. One dose of vaccine prior to COVID-19 may not reduce the odds of developing PCC compared to unvaccinated individuals across four studies (pOR 0.64, 95% CI 0.31 – 1.31, four studies) with high heterogeneity (I^2 = 99.2%) (Figure 2).

Two doses of vaccine prior to COVID-19 likely reduced the odds of developing PCC compared to unvaccinated individuals (pOR 0.67, 95% CI 0.60–0.74, I^2 = 59.9%, five studies) with a 95% prediction interval of 0.49–0.90 indicating a protective association would likely be present in a future study (Figure 2). A sixth study that combined those with one and two doses aligned with the two-dose analysis (pOR 0.49, 95% CI 0.31–0.79). Across four studies reporting hazard ratios, one or two doses of vaccine prior to COVID-19 may have little to no effect on the average hazard of developing PCC up to a six-month follow-up, but the evidence was very uncertain (HR one dose 0.96, 95% CI 0.89–1.03; pHR two doses 0.81, 95% CI 0.67–0.98, I^2=96.6%, four studies) (Figure 3). In the two-dose hazard ratio analysis, the two studies reporting a reduction in the hazard of PCC were at moderate risk of bias and the others were at high risk of bias; however, this did not explain a lot of the between-study heterogeneity (Table 2). Further sensitivity analysis indicated that the removal of Brannock et al. resulted in an estimate of no association, and the 95% prediction interval was wide (0.39–1.69) suggesting the results were imprecise [31]. Sensitivity analyses of the other outcomes indicated no individual study had a large impact on the meta-analysis as the removal of each study did not alter the significance or direction of the meta-analysis. The evidence is very uncertain for the effect of three doses of vaccine prior to COVID-19 on the odds (pOR 0.45, 95% CI 0.10–1.99, I^2= 30.9%) of developing PCC in one small underpowered study that reported observations separately for Delta and Omicron infections (Figure 2) [30]. In this study, a reduced odds of PCC was reported for people with three doses when Omicron was circulating, but there were too few observations when Delta was circulating to detect an association.

The nine studies that reported data on the impact of vaccination prior to COVID-19 on individual PCC symptoms were heterogeneous across the studies. In some studies vaccination was associated with a lower odds of common PCC symptoms including anxiety/depression in 3/5 studies, fatigue in 2/4 studies, dyspnea in 2/4 studies, and change/loss of smell in 1/3 studies (Supplementary Table S3). No association was found with headache in 2/2 studies and no studies reported associations with worse symptoms among those vaccinated compared to the unvaccinated. There was a reduced incidence rate of several PCC symptoms among those with three versus two doses up to four months post Omicron infection (physical symptoms: IRR 0.91, 95% CI 0.88–0.94, depression: 0.82, 0.77 – 0.88, anxiety; 0.84, 0.80–0.89, fatigue: 0.95, 0.93–0.97, and

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Table 1. General characteristics of the 31 included primary research publications on post COVID-19 condition and vaccination, grouped by research question[a]

Category	Risk of developing PCC or PCC symptoms in individuals vaccinated before COVID-19 (*n* = 18)	Risk of developing PCC or PCC symptoms in individuals vaccinated after COVID-19 (*n* = 3)	Changes to PCC symptoms following vaccination in individuals who already have PCC (*n* = 10)	Safety and/or adverse events of vaccination in individuals who already have PCC (*n* = 3)
Type of document				
Preprint	3	1	2	0
Primary peer-reviewed research	13	2	8	2
Letter to the editor/short communication	1			1
Risk of bias				
High	7	2	7	3
Moderate	10	1	3	
Low	1			
Continent (countries)[a]				
Europe (United Kingdom, Spain, France, Hungary, Denmark, Italy, Netherlands, Scotland, Switzerland, Norway, Serbia)	9	1	7	3
Americas (USA, Canada, Brazil)	7	1	1	
Asia (Indonesia, Türkiye)	1		1	
Africa (South Africa)	1	1		
Multi-national	1		1	
Observational study design[a]				
Prospective cohort	9	1	7	1
Retrospective cohort	5	1		
Case–control	1			
Cross-sectional	3	1	3	2
Number of vaccine doses[a]				
1 dose	7	2	10	3
2 doses	15	2	5	
3 doses	6			
Population[a]				
General public	10	2	5	1
Patients of a single or specified group of hospitals/clinics	6	2	5	
Healthcare workers	2			2
Veterans	2			
Specific evidence topics addressed[a]				
Compared vaccinated (stratified by number of doses) vs. unvaccinated	15	1	7	
Compared number of doses among vaccinated	1		2	
Compared vaccine brands	2		4	
Timing of vaccination	3	1	1	
Assessed effect of SARS-CoV-2 variant	2			
Sex- and gender-based analysis			1	

[a]Each group may sum to >31 because studies can be included in more than one category and more than one question.

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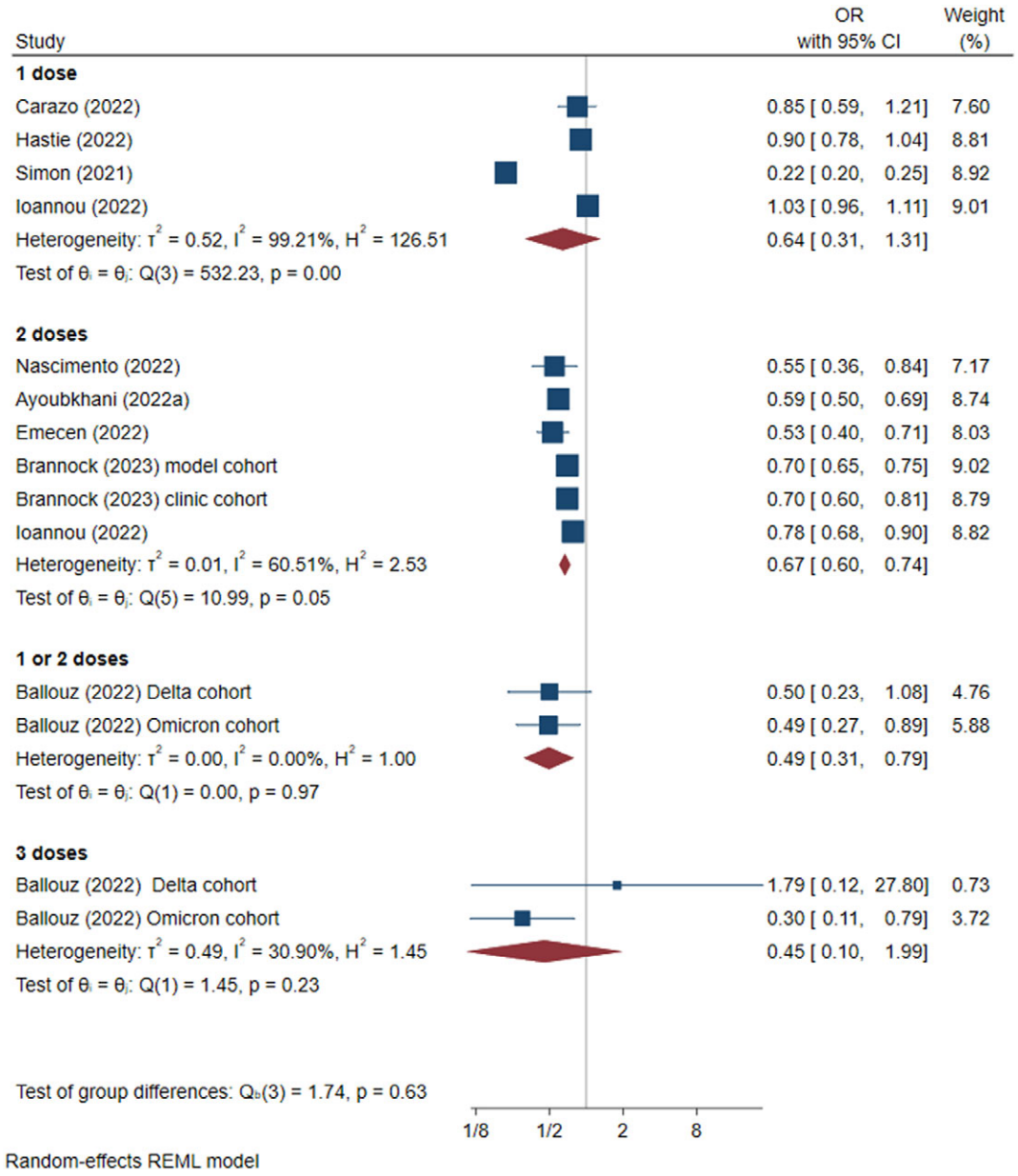

Figure 2. Meta-analysis of the effect of vaccination prior to COVID-19 compared to unvaccinated on the odds of developing PCC, stratified by number of doses.

cognitive complaints: 0.91, 0.88–0.94) [40]. There was no association between one to three vaccine doses before infection and the number of PCC symptoms reported (aRR 1.27, 95% CI 0.82–1.94) compared to the unvaccinated [41].

Two studies addressed differences between vaccine products, and both showed that all vaccine products reduced the risk of developing PCC. One showed that mRNA vaccines resulted in a decreased risk of PCC compared to Ad26.COV2.S (Johnson & Johnson) (aHR 0.89, 95% CI 0.81–0.97) [28], while the other found no significant difference between mRNA (BNT162b2 and mRNA-1273) and ChAdOx1 (AstraZeneca) vaccines [42]. The timing of vaccination before infection was assessed in three studies. One small study found that vaccination (one to three doses) within six months of Omicron infection was associated with a lower odds of PCC compared to those vaccinated more than six months before Omicron infection, but time of last vaccine before Delta infection was not associated with the odds of developing PCC [30].

One study stratified their analysis by age groups (<60 and >60 years old); however, no significant difference in the hazard of developing PCC was found between the age groups compared and the unvaccinated groups [38]. None of the studies reported a different association or interaction between males and females and vaccination prior to COVID-19 and the risk of developing PCC.

(Q2) Risk of developing PCC in those vaccinated after acute COVID-19

Three studies assessed the association between PCC and vaccination post-infection (up to 12 weeks post COVID-19), including one prospective cohort, one retrospective cohort, and one cross-sectional study (Supplementary Table S4). These studies included participants vaccinated with one dose (n = 1), two doses (n = 1), or one or two doses (n = 1) of COVID-19 vaccines.

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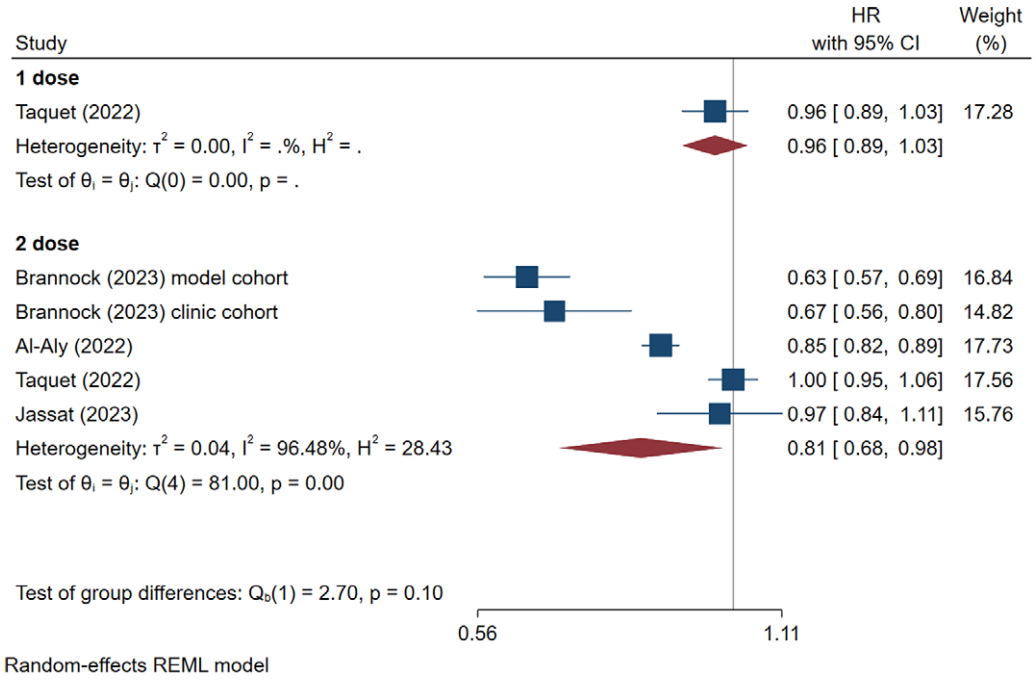

Figure 3. Meta-analysis of the hazard ratios for developing PCC in those vaccinated prior to COVID-19 compared to unvaccinated, stratified by number of doses.

Only one study established vaccination post-infection was administered prior to PCC development. The protective effect was stronger when one dose of vaccine was given earlier post-infection (aOR 0–4 weeks post-infection 0.38, 95% CI 0.35–0.41; aOR 4–8 weeks post-infection 0.54, 95% CI 0.51–0.57; aOR 8–12 weeks post-infection 0.75, 95% CI 0.71–0.78) compared to the unvaccinated (Table 2) [37].

Vaccination prior to PCC development was not clearly established in the other two studies. One study found no difference in cognition, grey matter volume, white matter hyperintensities, or functional connectivity between those with one or two doses of vaccine versus the unvaccinated, but vaccinated individuals performed better on visual, object, and space perception battery discrimination [43]. The third study found no difference in the rate of PCC at the six-month follow-up in those vaccinated with two doses post- versus pre-infection (aIRR 0.91, 95% CI 0.75–1.10) (Table 2) [35].

(Q3) Changes in PCC following vaccination among individuals with established PCC

Ten studies looked at the effect of COVID-19 vaccination on individuals with PCC (prospective cohort, n = 7; cross-sectional, n = 3). Follow-up times were between 3 and 14 months post-infection and 0.5–6 months post-vaccination with one (n = 10) or two doses (n = 5). Except for two studies, most were completed in early 2021 at the beginning of the vaccine rollout (Supplementary Table S5).

Among seven studies that compared vaccinated and unvaccinated individuals with established PCC [44–50], three studies addressed the main outcome of PCC resolution following one dose, two of which did not demonstrate an association [46, 49] and the third reported double the remission rate among vaccinated individuals [45] (Table 2). Three studies compared self-reported outcome data pre- and post-vaccination, all of which found beneficial outcomes after the first dose [42, 51, 52]. Individuals were more likely to experience symptom improvement after vaccination in two studies [51, 52], and the third study found the odds of PCC were slightly reduced following both the first (OR 0.87, 95% CI 0.81–0.93) and second doses (OR 0.91, 95% CI 0.86–0.97) [42]. Despite an apparent improvement, one study reported that 50% of the respondents who had reduced or worsened symptoms following vaccination returned to pre-vaccination levels within three weeks [51]. Other studies reported on mean difference in symptoms or composite symptom score [44, 47, 52] – proportions of those reporting improved, worsened, or no symptom changes [48, 51] – or various quality of life scores [44, 50] and were inconsistent in finding an association with one dose of vaccine.

Five studies reported on two doses of vaccine post-infection, of which two studies found no significant differences in any PCC symptoms after one or two doses [47, 48]. One showed an incremental benefit to the second dose after the first dose [42], and two studies found that two doses was a significant predictor for a better quality of life score [50] and was significantly protective against persistent PCC symptoms compared to no vaccination (Table 2) [49]. The latter study also stratified by age and sex finding that only elders (≥60 years) who received two doses post-infection had significantly lower odds of persistent PCC (but not younger individuals) and males and females had an equally lower odds of persistent PCC after two doses post-infection.

Seven studies reported changes to individual symptoms following vaccination [42, 44, 47-49, 51, 52], two of which did not report extractable quantitative data [44, 52]. Few studies reported that vaccinated individuals had significant improvements in specific symptoms including fatigue in 2/5 studies, loss of smell in 1/4 studies, dyspnea in 1/5 studies, and other symptoms not associated with vaccination (Supplementary Table S5).

Four studies compared mRNA and adenoviral vector vaccines, three of which found no significant differences between participants who received mRNA vaccines (BNT162b2 or mRNA-1273) and adeno-viral vector vaccines (ChAdOx1 or Ad26.COV2.S) [42, 44, 48]. However, one study suggested mRNA-1273 reduced

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Table 2. Summary of findings table for the main outcomes of PCC development or remission. Separated by odds ratios/hazard ratios, number of vaccine doses, and type of vaccine

Population: general population who had COVID-19 Setting: any Exposure: COVID-19 vaccination by dose 1, 2, 3, or more, specified in the question. Comparison: no COVID-19 vaccination or vaccinated with different dose/timing specified in the question						
	Illustrative comparative in cases of PCC per 100 COVID-19 cases					
Exposure	Baseline without vaccine	Corresponding risk with vaccine	Relative effect (95%CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Question 1: the risk of developing PCC or PCC symptoms in those vaccinated before (*n*=12) COVID-19						
PCC – 1 dose	25	16 (7.8–32.8)	pOR 0.64 (0.31–1.31)	340,315 [4]	* Very low	One dose of COVID-19 vaccine prior to COVID-19 may have little to no effect on the risk of developing PCC, but the evidence is very uncertain. High heterogeneity (I^2 99.2) across studies and 95% prediction interval (0.02–20.9). Studies were from early 2021 at the beginning of COVID-19 vaccine rollout [23, 33, 34, 37]
	25	24.0 (22.3–25.8)	HR 0.96 (0.89–1.03)	18,958 [1]	* Very low	One dose of COVID-19 vaccine may have little to no effect on the risk of developing PCC within six months of having COVID-19, but the evidence is very uncertain [38]
PCC – 2 doses	25	16.8 (15.0–18.5)	pOR 0.67 (0.60–0.74)	324,055 [5]	*** Moderate	Two doses of COVID-19 vaccine prior to COVID-19 likely reduces the risk of developing PCC. Moderate heterogeneity (I^2 59.9%) across studies and 95% prediction interval (0.49–0.91) suggests the results are precise [29, 31, 32, 34, 36]
	25	20.3 (16.8–24.5)	pHR 0.81 (0.67–0.98)	417,322 [4]	* Very low	Two doses of COVID-19 vaccine prior to COVID-19 may have little to no effect on the average hazard of developing PCC, but the evidence is uncertain. High heterogeneity (I^2 = 96.6%) and the 95% prediction interval (0.40–1.66) suggest the results are imprecise [28, 31, 35, 38]
PCC – 1 or 2 doses	25	12.3 (7.8–19.8)	OR 0.49 (0.31–0.79)	1350 [1]	* Very low	The association of one or two doses of COVID-19 vaccine prior to COVID-19 on the odds of developing PCC in one study was consistent with the two-dose meta-analysis; however, a single study is considered uncertain evidence [30]
PCC – 3 doses	25	11.3 (2.5–49.8)	OR 0.45 (0.10–1.99)	1350 [1]	* Very low	The evidence is very uncertain about the effect of three doses of COVID-19 vaccine prior to COVID-19 on the odds of developing PCC in one study [30]. The study was under powered and reported results for the Delta wave and Omicron wave (I^2 = 30.9%), the latter showed an association
PCC – mRNA vs adenovirus vaccines	25	15.5 (12.8–18.8) vs. 12.5 (9.3–17.3)	adenovirus OR 0.62 (0.51–0.75) vs. mRNA OR 0.50 (0.37–0.69)	6180 [1]	* Very low	Receiving either an mRNA vaccine (BNT162b2/mRNA-1273) or an adenovirus vaccine (ChAdOx1-S) prior to COVID-19 showed an equivalent reduction in the odds of developing PCC, but the evidence is uncertain [29]
	25	22.3 (20.3–24.3)	HR 0.89 (0.81–0.97)	147,414 [1]	* Very low	Receiving an mRNA vaccine (BNT162b2/mRNA-1273) compared to adenovirus vaccine (Ad26.COV2.S) prior to COVID-19 may further reduce the hazard of developing PCC. Overall vaccination was associated with an aHR 0.85 (0.82–0.89) in vaccinated compared to unvaccinated individuals [28], but the evidence is uncertain
Question 2: the risk of developing PCC or PCC symptoms in those vaccinated with one dose after COVID-19 based on time from infection to vaccination (1 study)						

(*Continued*)

Table 2. (*Continued*)

Population: general population who had COVID-19 Setting: any Exposure: COVID-19 vaccination by dose 1, 2, 3, or more, specified in the question. Comparison: no COVID-19 vaccination or vaccinated with different dose/timing specified in the question						
	Illustrative comparative in cases of PCC per 100 COVID-19 cases					
Exposure	Baseline without vaccine	Corresponding risk with vaccine	Relative effect (95%CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
PCC- 1 dose	25	vaccinated post COVID-19 0–4 wks: 9.5 (8.8–10.3) 4–8 wks: 13.5 (12.8–14.3) 8-12 wks: 18.8 (17.8–19.5)	aOR for those vaccinated post COVID-19 0-4 wks: 0.38 (0.35–0.41) 4-8 wks: 0.54 (0.51–0.57) 8-12 wks: 0.75 (0.71–0.78)	240,648 [1]	* Very low	One dose of COVID-19 vaccination after COVID-19 may result in a reduction in the odds of developing PCC and the effect may be stronger if the vaccine is received within 4 weeks of COVID-19 compared to later time points up to 12 weeks; however, the evidence is very uncertain [37]
Question 2: the risk of developing PCC or PCC symptoms in those vaccinated before COVID-19 vs. after COVID-19 (1 study)						
PCC- 2 doses	25	22.8 (18.8–27.5)	aIRR 0.91 (0.75–1.10)	2535 [1]	* Very low	There was no association with the timing of vaccination, two doses before or after COVID-19; however, the evidence is very uncertain [35]
Question 3: the resolution of PCC after COVID-19 vaccination among those with PCC (4 studies, cannot be combined)						
PCC – 1 and 2 doses	25	Change in level After 1 dose 21.8 (20.3–23.3) After two doses 19.8 (18.7–21.1)	aOR Change in level 1 dose: 0.87 (0.81–0.93) 2 doses: 0.91 (0.86–0.97) Change in trajectory per week after 1 dose: 1.01 (1.00–1.02) 2 doses: 0.99 (0.98–1.00)	13,356 [1]	* Very low	The odds of PCC persisting after vaccination may decrease after each dose of vaccine; however, between the first and second doses the trajectory may increase slightly but was shown to be flat and decreasing slightly after the second dose; the evidence is very uncertain [42]
PCC- 1 and 2 doses	25	1 dose 20.5 (15.3–27) 2 doses 15 (10.8–20.8)	aOR 1 dose 0.82 (0.61–1.08) 2 doses 0.60 (0.43–0.83)	1596 [1]	* Very low	Vaccination may be associated with a reduced odds of persistent PCC symptoms after two doses of COVID-19 vaccine; however, the evidence is very uncertain [49]
PCC- 1 dose	25	15.9 (4.3–54.3)	aOR 1.57 (0.46–5.84)	72 [1]	* Very low	The odds of recovery from PCC after the first COVID-19 vaccination was the same as the unvaccinated; however, the evidence is very uncertain [46]
PCC- 1 dose	25	12.7	Remission in vaccinated 16.6% and in unvaccinated 7.5%. aHR remission 1.93 (1.18–3.14)	910 [1]	* Very low	The rate of remission of PCC 3 months after baseline in the vaccinated group (1 dose) may be almost double that of the unvaccinated group; however, the evidence is very uncertain [45]

Note: The illustrative example is based on a PCC prevalence of 25% in the unvaccinated population. For explanations see the GRADE data in Supplementary Table S2.
Abbreviations: aHR, adjusted HR; aIRR, adjusted incidence rate ratio; aOR, adjusted OR; CI, confidence interval; GRADE, grade of evidence; HR, hazard ratio; OR: odds ratio; pHR: pooled HR; pOR: pooled odds ratio.
*The basis for the *assumed risk* was a base rate of 25.0% (95%CI 21.5–28.8) reported by unvaccinated Canadians and 13.2% (11.3–15.3%) for those with two doses of COVID-19 vaccine up to 31 August 2022 in the Canadian COVID-19 Antibody and Health Survey [39]. The *corresponding risk* (and its 95% confidence interval) is based on the assumed risk in the intervention group and the *relative effect* of the intervention (and its 95% CI). GRADE, grade of evidence based on a four-star scale of **** high confidence to * very low confidence in the evidence.

some PCC symptoms significantly better than ChAdOx1 including fatigue, brain fog, myalgia, gastro-intestinal symptoms, and autonomic dysfunction [51].

(Q4) Safety and risk of adverse events following COVID-19 vaccination among individuals with PCC

Three studies reported on the safety or adverse events among those with PCC following COVID-19 vaccination, all of which included participants following one dose of a COVID-19 vaccine (Supplementary Table S6). Only one study included a comparator group of individuals vaccinated with no history of COVID-19 and found no significant difference in the number or type of side effects following one dose of a vaccine (BNT162b2) among those with PCC compared to controls [53]. The study concluded that having a history of COVID-19, but not PCC, was associated with an increased risk of adverse events following vaccination. However, only a small subset of the study participants (n = 30/944) had reported experiencing PCC. A large prospective cohort study also found that COVID-19 vaccination was safe in individuals with PCC, finding that only 5.7% (n = 26/455) of participants self-reported adverse events post-vaccination (ChAdOx1, BNT162b2, mRNA-1273, or Ad26.COV2.S) [45]. However, the control group was those with PCC that were unvaccinated, so no statistical analysis was performed to support the finding that the effects of vaccination were like those without PCC. Lastly, in a small survey of 67 healthcare workers experiencing PCC, 72% (n = 48) reported immediate, but self-limiting side effects at two weeks post-vaccination (BNT162b2) [54].

Discussion

The results of this SR are aligned with other evidence syntheses completed on this topic to date, which have agreed that vaccination administered before COVID-19 confers some protection against the risk of developing PCC [8–11]. The evidence for a protective association with vaccination was most consistent, moderate certainty, when two doses of vaccine were received prior to COVID-19, suggesting a decreased odds of PCC by 33% compared to the unvaccinated. Vaccination shortly following COVID-19 may offer additional protection against developing PCC compared to no vaccination, but the evidence was very uncertain from only one study. Vaccination was not associated with a higher risk of developing PCC or worsening PCC symptoms in any study.

This SR restricted inclusion to only studies addressing PCC (symptoms still present >12 weeks from infection), but also included a wider range of results according to the timing of vaccination (i.e., pre-infection, post-infection, and post development of PCC) compared to other syntheses. Most of the reviews conducted to date have included PAS outcomes measured in the post-acute phase of COVID-19 at 4-12 weeks after infection, which may provide different associations with vaccination compared to studies of PCC [8–11].

As part of the updated evidence included in this SR, preliminary evidence on the effect of three or more doses and SARS-CoV-2 variants were identified [30, 35, 40, 41]. A third dose of a COVID-19 vaccine may offer additional protection against PCC, however in the two versus three dose analyses, it is unclear whether the additional protection is due to the shorter time between the last vaccine dose received and COVID-19 [30]. Vaccination also appeared to be more protective against PCC in individuals post Omicron infection compared to Delta in some studies [30, 41]. However, the lack of significant findings within Delta-infected groups may also be due to sample size limitations as the vaccine rollout of dose 1 and 2 was underway and booster doses were not widely available prior to the surge in Delta cases.

Vaccination prior to COVID-19 that does not prevent infection has been shown to be associated with reduced severity of infection due to established immune response, which may also be the basis for a reduced risk of developing PCC, but vaccination post-infection may not have this benefit. Only one study directly addressed vaccination 0–12 weeks post COVID-19 diagnosis and reported a more protective association against PCC when the first dose was given closer to infection [37]. This paucity of evidence about post-infection vaccination was not surprising given that vaccination closely following COVID-19 was not consistent with public health guidance.

Vaccination following diagnosis with PCC was safe in a few studies from early in vaccine rollout. However, the evidence was uncertain on whether vaccination may reduce PCC symptoms or result in faster resolution of symptoms. Most studies only assessed symptom changes following the first dose, and follow-up time may not have been sufficient to establish temporary versus permanent relief of symptoms post-vaccination. Some of the variability may be the result of self-reported outcome assessments that may be at high risk of recall bias.

Few studies examined interaction of sociodemographic variables on the association of PCC and vaccination. Factors such as sex, age, and severity of initial COVID-19 have been reported as risk factors for PCC [32, 33, 36] and were controlled for in many of the included studies. Any differences would be important to consider when developing treatment recommendations and equitable resource allocation. Finally, no study looked at the effect of vaccination on PCC given multiple COVID-19s. As the pandemic continues, re-infection is increasingly common and may compound the risk of PCC [55]. Understanding the role of vaccination against PCC given multiple infections is therefore extremely important.

Many of the limitations in synthesising the included studies relate to methodological differences for how PCC was defined and classified. For example, prospective studies often relied on self-reported data while retrospective studies looked at electronic health records and ICD-10 codes, both of which could have resulted in the misclassification of PCC due to sequelae that are actually related to other conditions. In addition, variable reporting of PCC symptoms made it difficult to compare across studies. Research and development of validated tools and diagnostics for PCC will be critical to improving our understanding and management of this condition.

Some limitations regarding our SR process include the fact that this SR explores a rapidly evolving topic and while an updated search was conducted on 13 December 2022, it is likely that the evidence has continued to evolve, and the findings of this SR may change with emerging evidence. The risk of bias assessment of the included observational studies used the NOS tool, for which a publication describing its validation is still forthcoming and an adaptation of the tool for cross-sectional study designs was used [21].

Conclusion

From the evidence included in this SR, there is moderate confidence that having two or more doses of COVID-19 vaccines prior to COVID-19 reduces the odds of developing PCC. For those with PCC, getting a COVID-19 vaccine appears to be safe, but it is

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unclear if vaccination improves PCC symptoms that have already developed. Given the high case counts of COVID-19 and the high estimated burden of PCC, it is expected that the COVID-19 pandemic will have substantial health impacts beyond acute infection. Understanding the impact of vaccination on PCC therefore has important implications for practice and policy.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268823001279.

Data availability statement. The data that support the findings of this study are openly available in Supplementary Tables S1–S6.

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Competing interest. The authors declare none.

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