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Evidence on the associations and safety of COVID-19 vaccination and post COVID-19 condition: an updated living systematic review

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Review

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Abstract

Post COVID-19 condition (PCC) refers to persistent symptoms occurring ≥12 weeks after COVID-19. This living systematic review (SR) assessed the impact of vaccination on PCC and vaccine safety among those with PCC, and was previously published with data up to December 2022. Searches were updated to 31 January 2024 and standard SR methodology was followed. Seventy-eight observational studies were included (47 new). There is moderate confidence that two doses pre-infection reduces the odds of PCC (pooled OR (pOR) 0.69, 95% CI 0.64–0.74, I^2 = 35.16%). There is low confidence for remaining outcomes of one dose and three or more doses. A booster dose may further reduce the odds of PCC compared to only a primary series (pOR 0.85, 95% CI 0.74–0.98, I^2 = 16.85%). Among children ≤18 years old, vaccination may not reduce the odds (pOR 0.79, 95% CI 0.56–1.11, I^2 = 37.2%) of PCC. One study suggests that vaccination within 12 weeks post-infection may reduce the odds of PCC. For those with PCC, vaccination appears safe (four studies) and may reduce the odds of PCC persistence (pOR 0.73, 95% CI 0.57–0.92, I^2 = 15.5%).

Introduction

After a COVID-19 infection, individuals may continue to have long-term symptoms for weeks or months. The World Health Organization (WHO) defines post COVID-19 condition (PCC) as persistent symptoms occurring 12 or more weeks after acute COVID-19, which have persisted or re-occurred for a minimum of 8 weeks and cannot be explained by alternative diagnoses [1]. Other institutions have adopted similar definitions, including the United States Centers for Disease Control and Prevention [2, 3]. The most common PCC symptoms include fatigue, insomnia, general pain and discomfort, shortness of breath, cognitive issues, and anxiety or depression [1, 4, 5].

The estimated prevalence of PCC after COVID-19 infection has varied widely from <10% to >50% of people affected by PCC depending on the sample population, definition of PCC used to define the outcome, how the outcome was collected, and time from infection to follow-up [6–9]. The most recent self-report survey data estimated that among adults who had COVID-19, 19% had experienced PCC in Canada (6.8% point prevalence in June 2023) [10] and 29.8% (95% CI 28.7–30.8) in the United States (8.7% point prevalence in September 2024) [11]. By the end of 2023, 56% of the world population had received a complete primary series, and 28% had received at least one booster dose of COVID-19 vaccines [12]. Given that COVID-19 and the burden of PCC continue to persist, it is important to evaluate the impact of COVID-19 vaccination on PCC, including potential benefits and/or safety concerns.

The systematic reviews (SRs) that have previously been completed on the impact of COVID-19 vaccination on PCC have all included post-acute sequalae (PAS) occurring 4 to 12 weeks post-infection [13–19], except for one SR that reported on the association between two doses and PCC development [20]. This living SR addresses the impact of vaccination on only PCC, which may reduce heterogeneity in the results, and includes all options for timing of vaccination relative to infection and/or PCC (pre-infection, post-infection, and post-PCC). The first version of this SR was published with data up to 13 December 2022 [21]. Therefore, the objective of this updated living 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), with data up to 31 January 2024.

Methods

This living SR was conducted using standard SR methodology outlined by the Cochrane Collaboration and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22, 23]. A protocol was determined *a priori* and registered

in PROSPERO (CRD42022365386); all deviations have been noted in the updated protocol document on PROSPERO.

Research question and eligibility criteria

The research questions of this SR were: (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? (4) Is it safe to get a COVID-19 vaccine for individuals who have PCC?

PCC was defined as persistent symptoms occurring 12 or more weeks after acute COVID-19, in accordance with WHO [1]. The population of interest was anyone who had COVID-19, and the intervention was vaccination with any authorized COVID-19 vaccine. The comparison group was individuals who had COVID-19 and were unvaccinated or received a different number of doses. The primary outcomes of interest were the risk of developing PCC or resolution of PCC. Published and preprint studies with an observational or experimental study design were considered for inclusion. The inclusion and exclusion criteria are detailed in the previously published review [21] and protocol. A list of excluded studies is provided in Supplementary Table S1.

Search strategy

The Public Health Agency of Canada curated a database of COVID-19 literature from February 2020 to August 2024 [24], with results maintained in the bibliographic management software EndNote20 (Clarivate, Philadelphia, PA). The search algorithm for this SR was run within the EndNote20 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 has been updated four times, most recently on 31 January 2024.

Search verification

In this update, the reference lists of six relevant review articles were searched as part of search verification [17–20, 25, 26], which yielded four studies that were added to the screening process [27–30].

Study selection and data extraction

Search results were imported into EndNote20 (Clarivate, Philadelphia, PA) and de-duplicated. Unique references were imported into DistillerSR software (DistillerSR, Inc.) for SR management. Title/abstract and full-text relevance screening forms and a data extraction form were developed *a priori* and piloted by all reviewers to determine functionality. Title/abstract screening, full-text screening, study characterization, and data extraction were performed in duplicate by two independent reviewers. Study characterization included publication details (e.g. language, year), funding, conflict of interest, and study design. Data extraction included country and sampling frame, study period, population characteristics (e.g. demographics, COVID-19 severity), vaccination information (e.g. number of doses, vaccine product), and outcome-related 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 reference was updated and re-evaluated to ensure all extracted data and risk of bias assessment reflected the published version of the article.

Risk of bias assessment

Included articles were evaluated for their risk of bias (ROB) using the Newcastle-Ottawa Scale (NOS) [31]. The NOS was selected over the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) because the NOS is more efficient and easier to implement on a range of observational studies, and the relationship between COVID-19 vaccination and development or remission of PCC may not be a direct relationship [32]. ROB assessments were performed in duplicate by two independent reviewers using two pre-existing NOS forms for case-control and cohort studies, as well as a modified tool for cross-sectional studies [33]. The forms used are available in the protocol; the questions assessed selection, information, confounding, and/or reporting biases. Each tool was pretested on one article by all reviewers, and then articles were independently assessed by two reviewers. Conflicts were resolved by 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 summarize the primary and secondary outcomes. Narrative synthesis of results was performed for each review question. When there were two or more studies measuring the same association for a primary outcome, random-effects meta-analyses using the restricted maximum likelihood estimator for between-study variance were performed on STATA18 (StataCorp). Meta-analyses were sub-grouped by number of doses received, the reported outcome measures, and population sub-groups including children. Those who received one dose of Janssen were considered to have a complete primary vaccine series and were placed into the two doses subgroup. For meta-analysis, risk ratios (RR) and prevalence ratios (PR) were converted to odds ratios (OR) to calculate a pooled effect (pOR) [34, 35]. 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, thus their meaning and value are different [36].

The impact of ROB (low, moderate, and high) was examined for outcomes considered in meta-analysis and reported in Supplementary Table S2a–b. Testing for small study effects was only considered where meta-analyses included more than ten observations/lines of data; only the meta-analysis on two doses before infection (OR) met this criterion. In the sensitivity analysis for meta-analysis subgroups with more than three studies, the Hartung-Knapp-Sidik-Jonkman method for estimating more conservative confidence intervals was examined and reported in Supplementary Table S2a–e [37]. For meta-analysis subgroups with at least three observations, prediction intervals were calculated to provide a plausible range of effect size in a future new study and reported in Supplementary Table S2a–e [38].

Certainty of evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria were used to indicate the level of confidence in the body of evidence for the primary outcomes of PCC development or resolution [39]. The GRADE domains risk of

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bias, inconsistency, imprecision, indirectness, and dose response were evaluated independently by two reviewers to determine a one-to-four-star grade. The evaluation scheme is provided in Supplementary Table S2f. Conflicts were resolved by consensus.

Results

Study selection

In this update, 971 new citations underwent title/abstract screening, of which 210 potentially relevant citations underwent full-text screening, and 47 new studies were included. This SR summarizes 78 studies: 74 peer-reviewed research articles, two preprints, one letter to the editor, and one short communication (Figure 1 and Supplementary Table S3–6). Articles that only assessed PAS (n = 29), did not differentiate between study participants with PAS and PCC (n = 73), or did not report the timing of vaccination (n = 41) were excluded (Supplementary Table S1).

Characteristics of the included studies

The included studies addressed the following subtopics: the effect of vaccination administered (1) before (n = 50) or (2) after (n = 2) COVID-19; (3) among previously unvaccinated individuals already

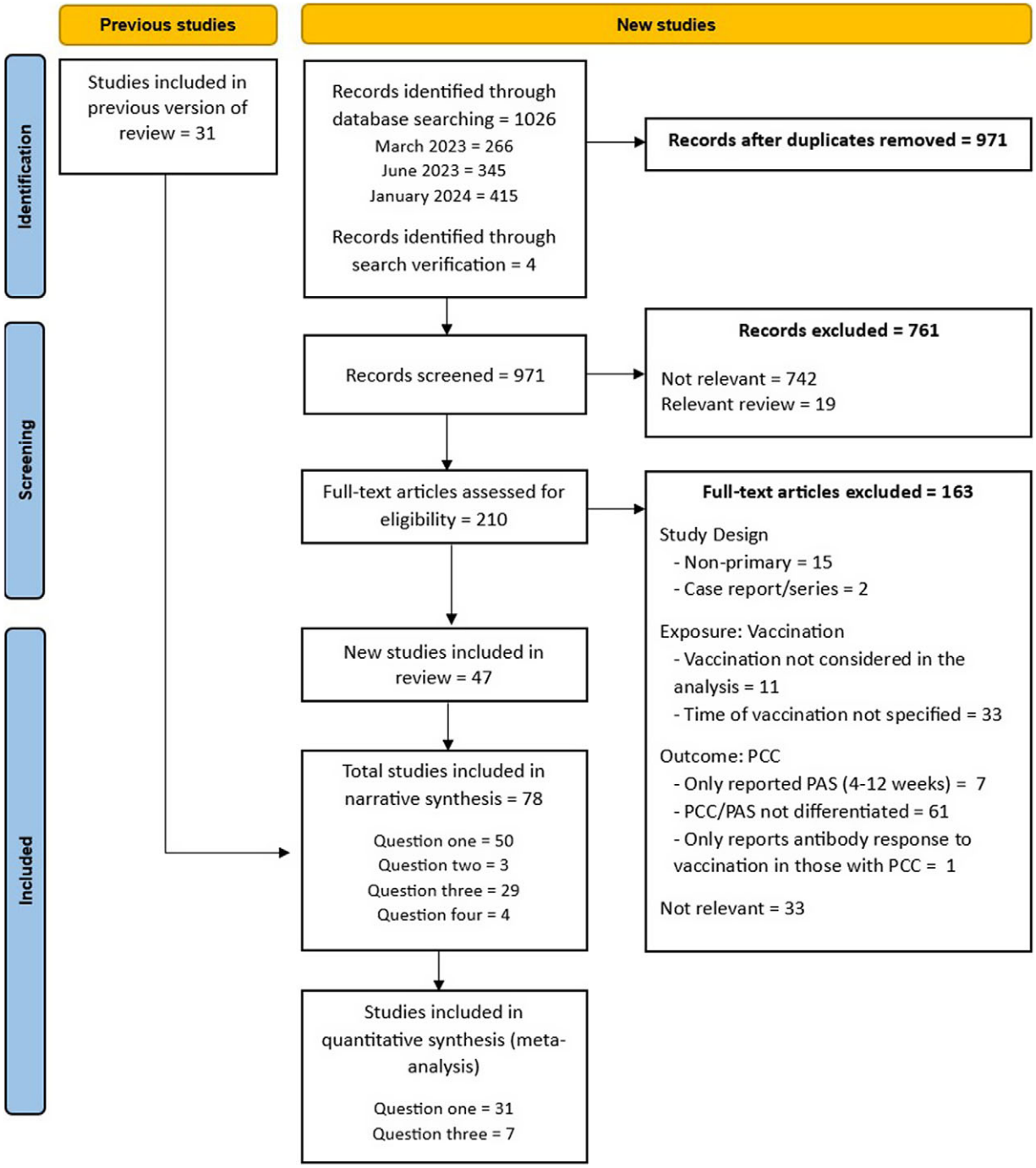

Figure 1. PRISMA flow diagram of articles through the systematic review process, including studies from the previous version and new studies in this update.

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experiencing PCC (n = 29); and (4) adverse events post-vaccination among those with PCC (n = 4). All studies were observational (prospective cohort, n = 39; retrospective cohort, n = 14; cross-sectional, n = 20; case-control, n = 5), and had high (n = 55), moderate (n = 21), or low (n = 2) risk of bias (Table 1). Three studies were funded by the pharmaceutical industry [40–42]; all were funded by Pfizer Inc. and examined the impact of the Pfizer-BioNTech COVID-19 vaccine or mRNA vaccines on PCC. For one of these studies, six authors were Pfizer employees [40], and in another study, an author had multiple conflicts related to PCC work [42] (Supplementary Table S3). Most studies were conducted in Europe (n = 40), Asia (n = 15), or North America (n = 14), with a few in South America (n = 4; all Brazil) and Africa (n = 2), and three had a multi-national sampling frame. More than half (n = 55)

Table 1. General characteristics of the 78 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 = 50)	Risk of developing PCC or PCC symptoms in individuals vaccinated after COVID-19 (n = 2)	Changes to PCC symptoms following vaccination in individuals who already have PCC (n = 29)	Safety and/or adverse events of vaccination in individuals who already have PCC (n = 4)
Type of document				
Preprint	1	1	1	0
Primary peer-reviewed research	48	1	28	3
Letter to the editor/short communication	1	0	0	1
Risk of bias				
High	30	1	26	4
Moderate	18	1	3	0
Low	2	0	0	0
Continent (countries)[a]				
Europe (United Kingdom, Spain, France, Germany, Denmark, Italy, Netherlands, Scotland, Switzerland, Norway, Serbia, Poland)	22	1	16	4
Americas (USA, Canada, Brazil)	14	1	4	0
Asia (Indonesia, Türkiye, India, China, Cyprus, Singapore, Pakistan, Saudi Arabia, Thailand, South Korea, Japan, Palestine, Israel)	9	0	8	0
Africa (South Africa, Egypt)	2	0	1	0
Multi-national	3	0	0	0
Observational study design[a]				
Prospective cohort	23	0	18	1
Retrospective cohort	14	1	2	0
Case–control	4	0	1	0
Cross-sectional	9	1	8	3
Number of vaccine doses[a]				
1 dose	33	1	23	4
2 doses	43	1	23	1
3 doses	20	0	9	1
4 doses	2	0	2	0
Population[a]				
General public	29	2	18	2
Patients of a single or specified group of hospitals/clinics	17	1	12	0
Healthcare workers	3	0	1	2

(*Continued*)

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Table 1. (*Continued*)

Category	Risk of developing PCC or PCC symptoms in individuals vaccinated before COVID-19 (n = 50)	Risk of developing PCC or PCC symptoms in individuals vaccinated after COVID-19 (n = 2)	Changes to PCC symptoms following vaccination in individuals who already have PCC (n = 29)	Safety and/or adverse events of vaccination in individuals who already have PCC (n = 4)
Veterans or military health system beneficiaries (active duty, dependents, and retirees)	4	0	1	0
Specific evidence topics addressed[a]				
Compared vaccinated (stratified by number of doses) vs. unvaccinated	45	1	16	0
Compared number of doses among vaccinated	5	0	4	0
Compared vaccine brands	3	0	4	0
Timing of vaccination	6	1	1	0
Assessed effect of SARS-CoV–2 variant	6	0	0	0
Sex- and gender-based analysis	0	0	2	1

[a]Each group may sum to >78 because studies can be included in more than one category and more than one question.

assessed individuals with mixed severities of COVID-19. Two studies reported on elderly populations, and five studies reported on children. Vaccine products received were mostly BNT162b2 (Pfizer-BioNTech, Comirnaty; n = 50) and mRNA-1273 (Moderna, Spikevax; n = 37). Most studies (n = 63) included individuals with a completed primary series (two vaccine doses for most individuals), while booster doses were examined in 28 studies that included individuals with three doses and four studies that included individuals with four doses.

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

The association between PCC and vaccination before COVID-19 was assessed in 50 studies, including 23 prospective cohorts, 14 retrospective cohorts, four case-control studies, and nine cross-sectional studies (Supplementary Table S3). Studies examined individuals with two doses (n = 43), three doses (n = 21), and four doses (n = 2). The following studies contributed to respective meta-analyses: 24 studies on vaccinated versus unvaccinated general population [35, 43–65]; three studies on a booster dose versus primary series [64, 66, 67]; and four studies on children [42, 68–70] (Figures 2–5). The certainty of evidence was evaluated for each subgroup in the meta-analyses and the GRADE Summary of Findings tables are provided in Tables 2–6. In many studies, individuals classified as unvaccinated before infection may have become vaccinated during the follow-up period and are therefore referred to as those 'unvaccinated before infection'.

One dose prior to COVID-19 may reduce the odds of developing PCC compared to those unvaccinated before infection, across eight studies (pOR 0.62, 95% CI 0.41–0.92) with high heterogeneity (I^2 = 96.9%) (Figure 2). When stratified by ROB, moderate ROB studies (n = 5) showed a pooled protective effect, while low (n = 1) and high ROB studies (n = 2) showed no association.

Two doses prior to COVID-19 likely reduced the odds of developing PCC compared to those unvaccinated before infection (pOR 0.69, 95% CI 0.64–0.74, I^2 = 35.16%, 13 studies) with a 95% prediction interval of 0.57–0.83 (Figure 2). There was no indication of small study effects in the two-dose subgroup (Egger test p = 0.36, Begg test p = 0.39; funnel plot was symmetrical). When studies were stratified by low ROB (n = 1), moderate (n = 7), or high (n = 5), protective associations were still found and there was no difference across subgroups. Two studies that examined those with one or two doses aligned with the two-dose analysis (pOR 0.32, 95% CI 0.14–0.73, I^2 = 81.87%). One study provided effect estimates of two or more doses separated by vaccine product (CoronaVac and Pfizer-BioNTech), and when these estimates were pooled together in meta-analysis, there was a protective association (pOR 0.28, 95% CI 0.14–0.57) [57].

Across two studies reporting hazard ratios, one dose prior to COVID-19 may have little to no effect on the average hazard of developing PCC from 6 months to 1 year post-infection (pHR 0.72, 95% CI 0.41–1.28) with high heterogeneity (I^2 = 96.8%) (Figure 3). This heterogeneity may be explained by Taquet et al. having high ROB [45] and only including those infected during Alpha or Delta waves, in contrast to Catala et al., which had low ROB and included those infected during Alpha, Delta, and Omicron [60].

Across four studies reporting hazard ratios, two doses prior to COVID-19 may have little to no effect on the average hazard of developing PCC from 6 months to 300 days post-infection (pHR 0.82, 95% CI 0.67–1.00) with high heterogeneity (I^2 = 96.7%) and a wide 95% prediction interval (0.39–1.73), suggesting the results are imprecise (Figure 3). The two studies reporting a reduction in the hazard of PCC were at moderate ROB and the two reporting no association were at high ROB.

Three or more doses prior to COVID-19 may have little to no effect on the odds of developing PCC compared to those unvaccinated before infection (pOR 0.82, 95% CI 0.62–1.08, I^2 = 60.5%, five studies) (Figure 2). The two moderate ROB studies (pOR 0.77, 95% CI 0.59–1.00) and three high ROB studies (pOR 0.80, 95% CI 0.44–1.44) showed no association. The finding of no association may be explained by individuals becoming vaccinated post-infection, re-infections, and different variants, which is detailed in the discussion. The multivariate analysis in Marra et al. demonstrated a strong protective effect with four doses before COVID-19

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Table 2. Summary of findings table for the main outcome of PCC development in individuals vaccinated before COVID-19, compared to unvaccinated. Separated by odds ratios/hazard ratios, number of vaccine doses, and type of vaccine. The illustrative example is based on a PCC prevalence of 25% in the unvaccinated population

Patient or population: general population who had COVID-19
Setting: any
Intervention: COVID-19 vaccination before infection, stratified by number of doses
Comparison: unvaccinated before infection or vaccinated with different vaccine brand specified in the question

	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)						
Exposure	Baseline without vaccine	Corresponding risk with vaccine	Risk difference	Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Q1: the risk of developing PCC in those vaccinated before COVID-19 compared to unvaccinated							
PCC – 1 dose, OR	25	15.5 (10.3 to 23)	9.5 fewer PCC cases (2 to 14.7 fewer)	pOR 0.62 (0.41 to 0.92)	333,033 (8 non-randomized studies)	⨁⨁◯◯ Low	One vaccine dose prior to COVID-19 may reduce the odds of developing PCC. High heterogeneity (I^2 = 96.9%) and 95% prediction interval (0.15–2.48) suggests the results are imprecise [35, 43, 44, 53, 54, 57, 59, 65].
PCC – 1 dose, HR	25	18 (10.3 to 32)	7 fewer PCC cases (14.7 fewer to 7 more)	pHR 0.72 (0.41 to 1.28)	888,111 (2 non-randomized studies)	⨁◯◯◯ Very low	One vaccine dose prior to COVID-19 may have little to no effect on the risk of developing PCC within 1 year of having COVID-19, but the evidence is very uncertain [45, 60].
PCC – 2 doses, OR	25	17.3 (16 to 18.5)	7.7 fewer PCC cases (6.5 to 9 fewer)	pOR 0.69 (0.64 to 0.74)	336,982 (13 non-randomized studies)	⨁⨁⨁◯ Moderate	Two vaccine doses prior to COVID-19 likely reduces the risk of developing PCC. Low heterogeneity (I^2 = 35.2%) across studies and 95% prediction interval (0.57–0.83) suggests the results are precise [46-49, 53-56, 59, 61-63, 65].
PCC – 2 doses, HR	25	20.5 (16.8 to 25)	4.5 fewer PCC cases (0 to 8.2 fewer)	pHR 0.82 (0.67 to 1.00)	409,123 (4 non-randomized studies)	⨁◯◯◯ Very low	Two vaccine doses 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 = 96.7%) and the 95% prediction interval (0.39–1.73) suggest the results are imprecise [45, 49-51].
PCC – 1 or 2 doses, OR	25	8 (3.5 to 18.3)	17 fewer PCC cases (6.7 to 21.5 fewer)	pOR 0.32 (0.14 to 0.73)	2060 (2 non-randomized studies)	⨁⨁◯◯ Low	One or two vaccine doses prior to COVID-19 may reduce the odds of developing PCC [52, 58].
PCC – 2 or more doses, OR	25	7 (3.5 to 14.3)	18 fewer PCC cases (10.7 to 21.5 fewer)	pOR 0.28 (0.14 to 0.57)	1,588 (1 non-randomized study)	⨁◯◯◯ Very low	Two or more vaccine doses before COVID-19 may reduce the odds of developing PCC; however, a single study is considered uncertain evidence [57].
PCC – 3 or more doses, OR	25	20.5 (15.5 to 27)	4.5 fewer PCC cases (9.5 fewer to 2 more)	pOR 0.82 (0.62 to 1.08)	19,421 (5 non-randomized studies)	⨁⨁◯◯ Low	Three or more vaccine doses before COVID-19 may have little to no effect on the odds of developing PCC. Moderate heterogeneity (I^2 = 60.5%) and 95% prediction interval (0.37–1.80) suggest the results are imprecise [52, 54, 59, 61, 64].

(*Continued*)

Table 2. (*Continued*)

Patient or population: general population who had COVID-19
Setting: any
Intervention: COVID-19 vaccination before infection, stratified by number of doses
Comparison: unvaccinated before infection or vaccinated with different vaccine brand specified in the question

	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)						
Exposure	Baseline without vaccine	Corresponding risk with vaccine	Risk difference	Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
PCC – 4 doses, OR	25	1.3 (0.3 to 4.8)	23.7 fewer PCC cases (20.2 to 24.7 fewer)	OR 0.05 (0.01 to 0.19)	3,331 (1 non-randomized study)	⨁◯◯◯ Very low	Four vaccine doses before COVID-19 may reduce the odds of developing PCC, however a single study is considered uncertain evidence [54].
Q1: the risk of developing PCC in those vaccinated with mRNA vs. adenovirus vaccines before COVID-19							
PCC – 2 doses mRNA vs. adenovirus vaccines, OR	25	12.5 (9.3 to 17.3) vs. 15.5 (12.8 to 18.8)	12.5 (7.7 to 15.7) vs. 9.5 (6.2 to 12.2) fewer PCC cases	mRNA: OR 0.50 (0.37–0.69) vs. adenovirus: OR 0.62 (0.51–0.75)	6,180 (1 non-randomized study)	⨁◯◯◯ 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 [47].
PCC – 1 or 2 doses mRNA vs. adenovirus vaccines, HR	25	2 doses BNT162b2/mRNA–1273 vs. Ad26.COV2.S: 22.3 (20.3 to 24.3) 1 dose BNT162b2 vs. ChAdOx1: 21 (18.8 to 23.5)	2 doses BNT162b2/mRNA–1273 vs. Ad26.COV2.S: 2.7 fewer PCC cases (0.7 to 4.7 fewer) 1 dose BNT162b2 vs. ChAdOx1: 4 fewer PCC cases (1.5 to 6.2 fewer)	2 doses BNT162b2/mRNA–1273 vs. Ad26.COV2.S: HR 0.89 (0.81–0.97) 1 dose BNT162b2 vs. ChAdOx1: aHR 0.84 (0.75–0.94)	1,029,533 (2 non-randomized studies)	⨁⨁◯◯ Low	Receiving an mRNA vaccine (BNT162b2/mRNA–1273) compared to adenovirus vaccine (Ad26.COV2.S/ChAdOx1-S) prior to COVID-19 may further reduce the hazard of developing PCC [50, 60].

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 S2a.
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, 13.2% (11.3–15.3) for those with two doses of COVID-19 vaccine before infection and 12.2% (9.2–15.7) for those with three doses before infection up to 31 August 2022 in the Canadian COVID-19 Antibody and Health Survey [7]. 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 that the effect estimate is close to the true effect) to * (very low confidence in the effect estimate, the true effect is likely to be substantially different).

Table 3. Summary of findings table for the main outcomes of PCC development or persistence in individuals vaccinated after COVID-19 or after PCC, compared to unvaccinated. The illustrative example is based on a PCC prevalence of 25% in the unvaccinated population

Patient or population: general population who had COVID-19
Setting: any
Intervention: COVID-19 vaccination after infection
Comparison: unvaccinated

	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)						
Exposure	Baseline without vaccine	Corresponding risk with vaccine	Risk difference	Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Q2: the risk of developing PCC in those vaccinated with one dose after COVID-19 by time from infection to vaccination							
PCC – 1 dose	25	0–4 weeks: 9.5 (8.8–10.3) 4–8 weeks: 13.5 (12.8–14.3) 8–12 weeks: 18.8 (17.8–19.5)	0–4 weeks: 15.5 fewer PCC cases (14.7 to 16.2 fewer) 4–8 weeks: 11.5 fewer PCC cases (10.7 to 12.2 fewer) 8–12 weeks: 6.2 fewer PCC cases (5.5 to 7.2 fewer)	0–4 weeks: aOR 0.38 (0.35 to 0.41) 4–8 weeks: aOR 0.54 (0.51 to 0.57) 8–12 weeks: aOR 0.75 (0.71 to 0.78)	238,256 (1 non-randomized study)	⨁◯◯◯ Very low	One vaccine dose 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 [44].
Q3: the risk of persistent PCC among those vaccinated after PCC, and the risk of developing PCC or persistent PCC among those vaccinated anytime after COVID-19, compared to unvaccinated							
Persistence of PCC – Vaccinated after PCC	25	18.3 (14.3 to 23)	6.7 fewer PCC cases (2 to 10.7 fewer)	pOR 0.73 (0.57 to 0.92)	1749 (3 non-randomized studies)	⨁⨁◯◯ Low	Vaccination among those with PCC may reduce the odds of persistent PCC [91, 92, 101]. Low heterogeneity (I^2 = 0.00%), however 95% prediction interval (0.16–3.42) suggests results are imprecise.
PCC – Vaccinated anytime after COVID-19	25	16.3 (8 to 32.8)	8.7 fewer PCC cases (17 fewer to 7.8 more)	pOR 0.65 (0.32 to 1.31)	1,331 (4 non-randomized studies)	⨁⨁◯◯ Low	There was no association between receiving a vaccine anytime after COVID-19 and odds of PCC. Moderate heterogeneity (I^2 = 67.8%) and 95% prediction interval (0.08–5.40) suggest the results are imprecise [63, 76, 93, 102].

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 S2b.
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, 13.2% (11.3–15.3) for those with two doses of COVID-19 vaccine before infection and 12.2% (9.2–15.7) for those with three doses before infection up to 31 August 2022 in the Canadian COVID-19 Antibody and Health Survey [7]. 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 that the effect estimate is close to the true effect) to * (very low confidence in the effect estimate, the true effect is likely to be substantially different).

Table 4. Summary of findings table for the main outcome of PCC development in individuals vaccinated after COVID-19 versus vaccinated before COVID-19. The illustrative examples are based on a PCC prevalence of 13.2% for those with two doses before infection and 12.2% for those with three doses before infection

Patient or population: general population who had COVID-19
Setting: any
Intervention: COVID-19 vaccination after infection, stratified by number of doses
Comparison: vaccinated before infection

	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)						
Exposure	Baseline with vaccine before infection	Corresponding risk with vaccine after infection	Risk difference	Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Q3: the risk of developing PCC in those vaccinated after COVID-19 vs. before COVID-19							
PCC – primary series, OR	13.2 (2 doses)	12.3 (4.9 to 30.8)	0.9 fewer PCC cases (8.3 fewer to 17.6 more)	OR 0.93 (0.37 to 2.33)	80 (1 non-randomized study)	⨁◯◯◯ Very low	No difference in the odds of developing PCC between those vaccinated with a primary series after vs. before COVID-19; however, the evidence is very uncertain [95].
PCC – primary series, IRR	13.2 (2 doses)	12 (9.9 to 14.5)	1.2 fewer PCC cases (3.3 fewer to 1.3 more)	IRR 0.91 (0.75 to 1.10)	2,950 (1 non-randomized study)	⨁◯◯◯ Very low	There was no association with the timing of vaccination, primary series after vs. before COVID-19; however, the evidence is very uncertain [51].
PCC – 2 or 3 doses, OR	12.2 (3 doses)	3–6 months post-infection: 32.9 (19.5 to 54.9) >6 months: 3.2 (1.7 to 5.9)	3–6 months post-infection: 20.7 more PCC cases (7.3 to 42.7 more) >6 months: 9 fewer PCC cases (6.3 to 10.5 fewer)	3–6 months: OR 2.7 (1.6 to 4.5) >6 months: OR 0.26 (0.14 to 0.48)	339 (1 non-randomized study)	⨁◯◯◯ Very low	Those vaccinated with two or three doses after COVID-19 had higher odds of PCC at 3–6 months post-infection, but lower odds at >6 months, compared to those vaccinated with three doses before COVID-19; however, the evidence is very uncertain [96].

Note: The illustrative example is based on a PCC prevalence of 13.2% for those with two doses before infection and 12.2% for those with three doses before infection. For explanations see the GRADE data in Supplementary Table S2c.
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, 13.2% (11.3–15.3) for those with two doses of COVID-19 vaccine before infection and 12.2% (9.2–15.7) for those with three doses before infection up to 31 August 2022 in the Canadian COVID-19 Antibody and Health Survey [7]. 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 that the effect estimate is close to the true effect) to * (very low confidence in the effect estimate, the true effect is likely to be substantially different).

Table 5. Summary of findings table for the main outcome of PCC development, in individuals who received a booster dose versus only primary series. The illustrative example is based on a PCC prevalence of 13.2% in the primary series population

Patient or population: general population who had COVID-19
Setting: any
Intervention: COVID-19 booster vaccine dose (additional dose after primary series) before infection
Comparison: COVID-19 vaccine primary series before infection

	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)						
Exposure	Baseline with primary series only	Corresponding risk with booster dose	Risk difference	Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Q1: the risk of developing PCC in those vaccinated with a booster dose before COVID–19 compared to only primary series before COVID-19							
PCC – Booster vs. primary	13.2	11.2 (9.8 to 12.9)	2 fewer PCC cases (0.3 to 3.4 fewer)	pOR 0.85 (0.74 to 0.98)	34,247 (3 non-randomized studies)	⨁⨁◯◯ Low	A booster dose before COVID-19 may reduce the odds of developing PCC compared to those who received only a primary series. Low heterogeneity (I^2 = 16.85%), however the 95% prediction interval (0.56–1.3) suggests results are imprecise [64, 66, 67].

Note: The illustrative example is based on a PCC prevalence of 13.2% for those with two doses before infection. For explanations see the GRADE data in Supplementary Table S2d.
Abbreviations: CI: confidence interval; GRADE: grade of evidence; pOR: pooled odds ratio.
*The basis for the *assumed risk* was a base rate of 13.2% (95%CI 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 [7]. 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.

Table 6. Summary of findings table for the main outcome of PCC development in children up to 18 years old. Separated by number of vaccine doses. The illustrative example is based on a PCC prevalence of 5.8% in the unvaccinated children population

Patient or population: children up to 18 years old who had COVID-19
Setting: any
Intervention: vaccination before COVID-19 infection
Comparison: unvaccinated

	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)						
Exposure	Baseline without vaccine	Corresponding risk with vaccine	Risk difference	Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Q1: the risk of developing PCC in children vaccinated before COVID-19 compared to unvaccinated							
PCC – 1 dose	5.8	4.3 (3.0 to 6.0)	1.5 fewer PCC cases (2.8 fewer to 0.2 more)	OR 0.74 (0.52 to 1.04)	6,886 (1 non-randomized study)	⨁◯◯◯ Very low	Among children aged 12–17, one vaccine dose before COVID-19 may have little to no effect on the odds of developing PCC; however, the evidence is very uncertain [68].
PCC – 2 or 3 doses	5.8	5.1 (3.9 to 6.7)	0.7 fewer PCC cases (1.9 fewer to 0.9 more)	pOR 0.88 (0.67 to 1.15)	1,275 (3 non-randomized studies)	⨁⨁◯◯ Low	Among children up to 18 years old, two or three vaccine doses may have little to no effect on the odds of developing PCC. Moderate heterogeneity (I^2 = 49.4%) and 95% prediction interval (0.12–5.6) suggest the results are imprecise [42, 69, 70].

Note: The illustrative example is based on a PCC prevalence of 5.8% in the unvaccinated children population. For explanations see the GRADE data in Supplementary Table S2e.
Abbreviations: CI: confidence interval; GRADE: grade of evidence; pOR: pooled odds ratio.
*The basis for the *assumed risk* was a base rate of 5.8% reported by unvaccinated children under 18 years old in eight countries (Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the United States) [103]. 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.

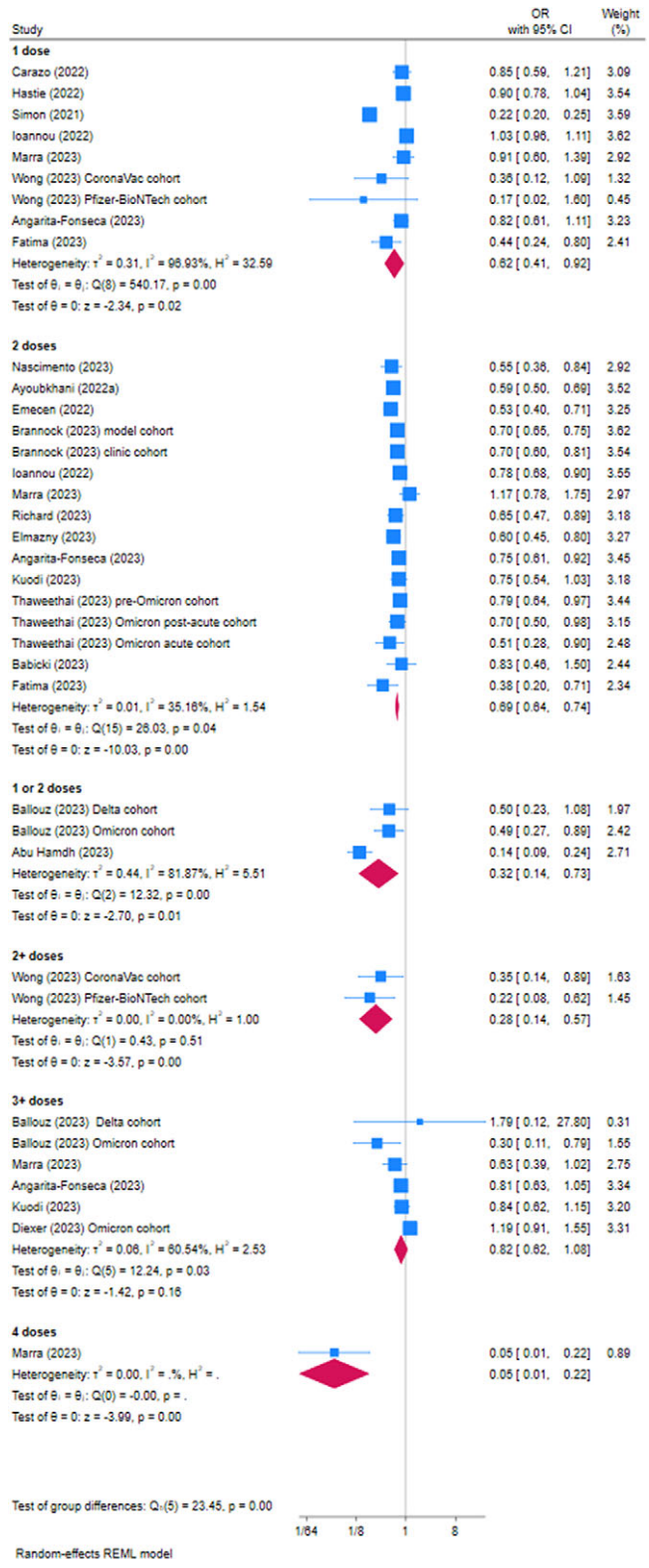

Figure 2. Meta-analysis of the effect of vaccination prior to COVID-19 compared to unvaccinated on the odds of developing PCC, stratified by number of doses.

on the odds of developing PCC compared to unvaccinated before infection (aOR 0.05, 95% CI 0.01–0.19) [54].

Among children (≤18) with one or more doses prior to COVID-19, the overall meta-analytic estimate indicated no association (pOR 0.79, 95% CI 0.56–1.11, I^2 = 37.2%, four studies) with the odds of developing PCC compared to unvaccinated before infection, and no difference between one versus two or three doses (p = 0.80) (Figure 4). In the two or three doses subgroup, Morello et al. reported an OR > 1 for 12–18 year olds, which was the main source of heterogeneity and pulled the pooled estimate towards the null [42]. For those who received one to three doses in Morello et al., the estimates were similar to those who received two or three doses for both 5–11 year olds and 12–18 year olds [42]. All studies were evaluated as high ROB.

A booster dose before Delta or Omicron infection may reduce the odds of developing PCC compared to those with only a primary series (pOR 0.85, 95% CI 0.74–0.98, I^2 = 16.85%, three studies) (Figure 5). All three studies were high ROB and did not specify the length of time between vaccination and infection.

Impact of vaccination before infection on individual PCC symptoms

Twenty-three studies reported on differences in individual PCC symptoms in those vaccinated before COVID-19. Among studies reporting an effect estimate for vaccinated versus unvaccinated, vaccination was associated with a protective effect for the most common PCC symptoms, including fatigue in 5/7 studies, anxiety/depression in 3/5 studies, dyspnea in 4/7 studies, pain in 3/6 studies, insomnia in 1/2 studies, and cognitive impairment in 3/8 studies (Supplementary Table S3). Only one study reported that vaccination was associated with a higher risk of individual symptoms (concentration and memory impairment, voice disorder) compared to unvaccinated; however, when excluding those vaccinated >3 months before COVID-19, there was no association with concentration/memory impairment [71]. Seven studies reported on the prevalence of individual PCC symptoms in vaccinated versus unvaccinated without an effect estimate [30, 40, 41, 46, 61, 63, 72, 73]; one of these examined children (≤18) and found no significant differences in anosmia or dysgeusia [41]. Two studies reported on individuals with a booster versus primary series before Omicron infection. One found that those with a booster had reduced incidence rates of specific PCC symptoms (physical symptoms, depression, anxiety, fatigue, and cognitive complaints) at 4 months post-infection [74], while the other found no significant difference in the prevalence of individual symptoms (fatigue, dyspnoea, difficulties with a busy environment, memory problems, or brain fog) at 3 months post-infection [66].

There was no association with one to three doses before infection and the number of PCC symptoms compared to unvaccinated, with a rate ratio of 1.27 (95% CI 0.82–1.94) adjusted for variant among other variables; this represents the multiplicative effect of vaccination on the number of symptoms [75]. Among those infected during Omicron dominance, 3+ doses before infection were associated with lower odds of 3+ PCC symptoms at 6 months post-infection compared to unvaccinated (aOR 0.36, 95% CI 0.15–0.87, p = 0.019), while no association was found with two doses [40].

Differences between vaccine products

Three studies addressed differences between vaccine products and 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) [50]. Similarly, another study found that BNT162b2 resulted in a reduced hazard of PCC compared to ChAdOx1 (AstraZeneca) (aHR 0.84, 95% CI 0.75–0.94) and some individual symptoms [60]. A third study found no significant

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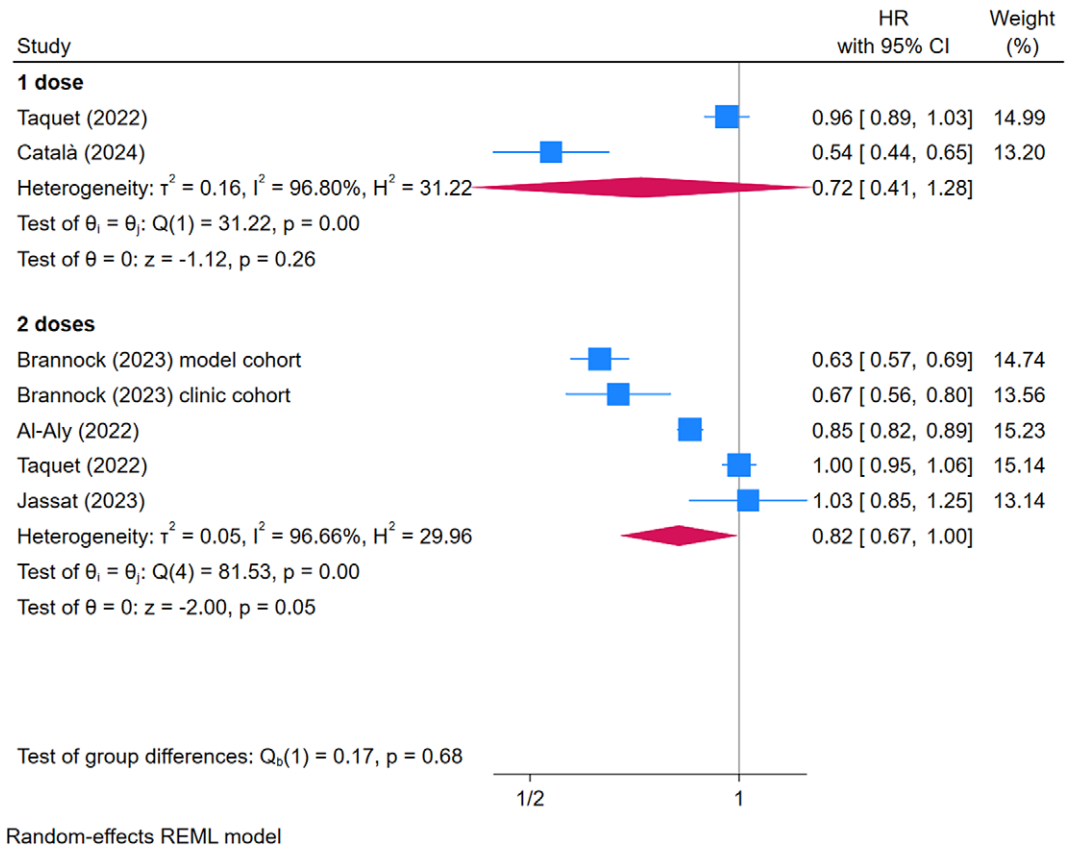

Figure 3. Meta-analysis of the hazard ratios for developing PCC in those vaccinated prior to COVID-19 compared to unvaccinated, stratified by number of doses.

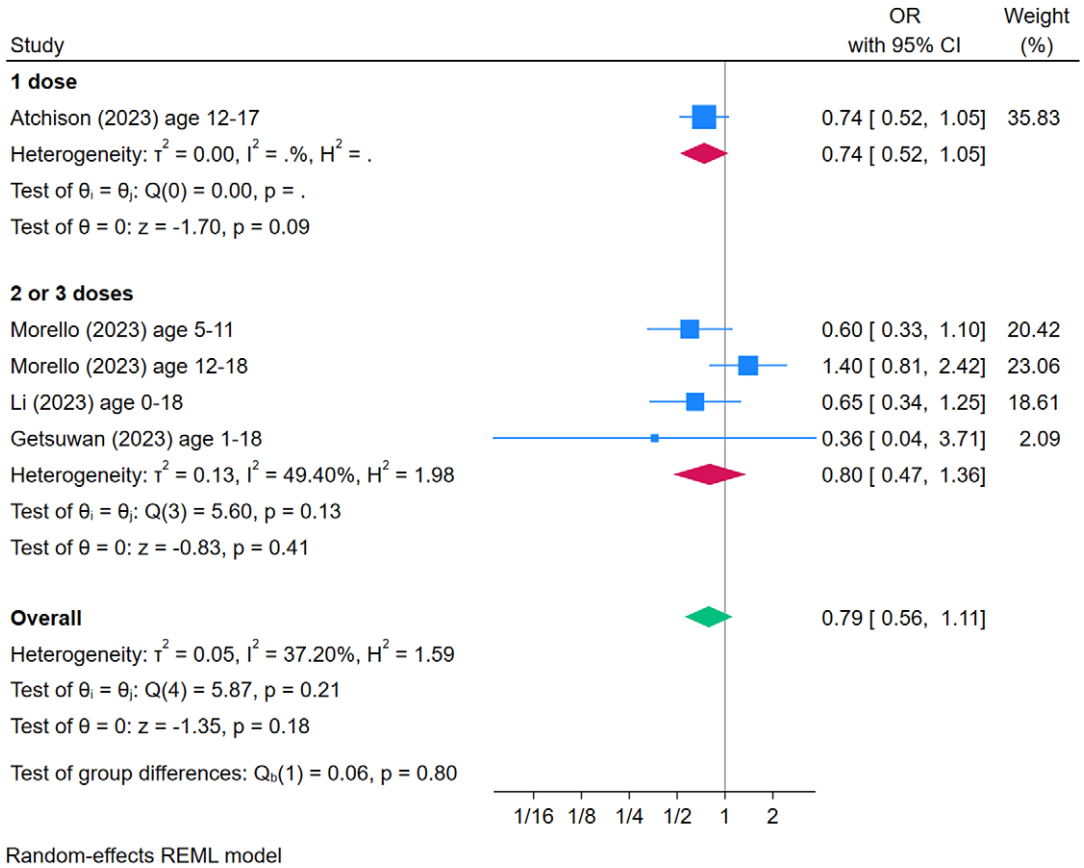

Figure 4. Meta-analysis of the effect of vaccination prior to COVID-19 compared to unvaccinated on the odds of developing PCC in children up to 18 years old, stratified by number of doses.

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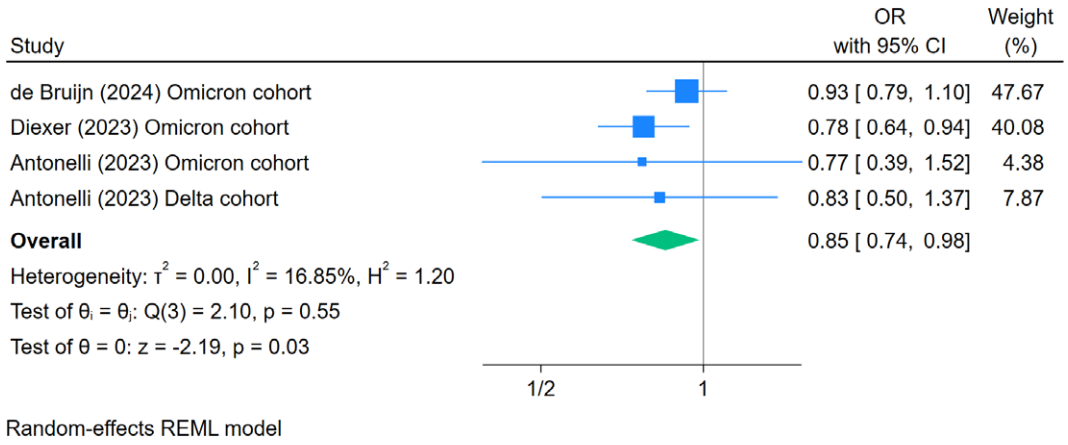

Figure 5. Meta-analysis of the effect of booster vaccination prior to COVID-19 compared to only a primary series on the odds of developing PCC.

difference between mRNA, viral vector, or inactivated vaccines for protection against developing 'neuropsychiatric PCC' (various neurological and mental health symptoms) [56].

Timing of vaccination before infection

One study found that vaccination (one to three doses) within 6 months before Omicron infection was associated with a lower odds of PCC compared to vaccination more than 6 months before infection [52]. Another study found that vaccination (three doses) within 3 months before Omicron infection was associated with higher odds of PCC compared to vaccination 4–6 months before, which may be explained by a limited number of PCC cases [67]. A third study found that vaccination (one to three doses) before infection with mostly Omicron was not associated with PCC compared to unvaccinated, regardless of the timing of last dose (>6 months, 3–6 months, or < 3 months before infection) [76]. There was no association between timing of vaccination (up to three doses) before Delta infection and the odds of developing PCC in two studies [52, 67].

Differences by age and sex

One study suggested older adults (≥60 years), who received a third dose at 4–6 months prior to Omicron infection had significantly lower odds of PCC compared to those who received a third dose within 3 months, and this association was not found in the 18–59 age group [67]. Another study found no association between vaccination with one or two doses and the hazard of developing PCC in either the <60 age group or ≥ 60 age group [45]. A third study found no association between vaccination with one to three doses and the odds of PCC in either younger (5–11 years old) or older (12–18 years old) children [42]. None of the studies examined differences by sex regarding the association between vaccination prior to COVID-19 and risk of developing PCC.

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

Two studies assessed the association between PCC and vaccination post-infection (up to 12 weeks), including one retrospective cohort study with moderate ROB [44] and one cross-sectional study with high ROB [77] (Supplementary Table S4). The GRADE Summary of Findings is provided in Table 3.

In the retrospective cohort study, the protective effect against PCC development was stronger when one dose 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 unvaccinated (Table 3) [44].

The cross-sectional study found no significant difference in cognition and neuroimaging results (grey matter volume, white matter hyperintensities, functional connectivity) between those with one or two doses versus unvaccinated; however, vaccinated individuals performed better on Visual Object and Space Perception Battery discrimination [77].

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

Nineteen studies examined the effect of COVID-19 vaccination on individuals with established PCC, and ten studies examined individuals where it was unclear if vaccination occurred after developing PCC or within 12 weeks of infection. These 29 studies included 18 prospective cohorts, eight cross-sectional, two retrospective cohorts, and one case-control (Supplementary Table S5).

Seven studies contributed to the meta-analysis on the odds of PCC persistence among vaccinated individuals compared to unvaccinated, stratified by two subgroups: vaccinated after PCC and vaccinated anytime after COVID-19 infection (Figure 6). The certainty of evidence was evaluated for each subgroup and the GRADE Summary of Findings is provided in Table 3. Among those vaccinated after PCC, vaccination may reduce the odds of PCC persistence compared to unvaccinated (pOR 0.73, 95% CI 0.57–0.92, I^2 = 15.5%, three studies). When stratified by ROB, a pooled protective effect was found for the high ROB studies (n = 2), while there was no association for the moderate ROB study. Among those vaccinated anytime after infection, there may be little to no effect on the odds of PCC development or persistence compared to unvaccinated (pOR 0.65, 95% CI 0.32–1.31, I^2 = 67.8%, four studies). These four studies were high ROB.

Findings were inconsistent regarding symptom improvement, worsening, or no change for vaccinated versus unvaccinated individuals with established PCC across three studies. One study found a significantly higher proportion of vaccinated had improved symptoms (23.3% vs. 15.4%, p = 0.035) [78], while two studies found no significant difference by vaccination in PCC symptom improvement [79, 80].

Across nine studies that compared PCC symptoms pre- and post-vaccination in the same individuals, symptoms tended to improve or remain the same following vaccination, rather than

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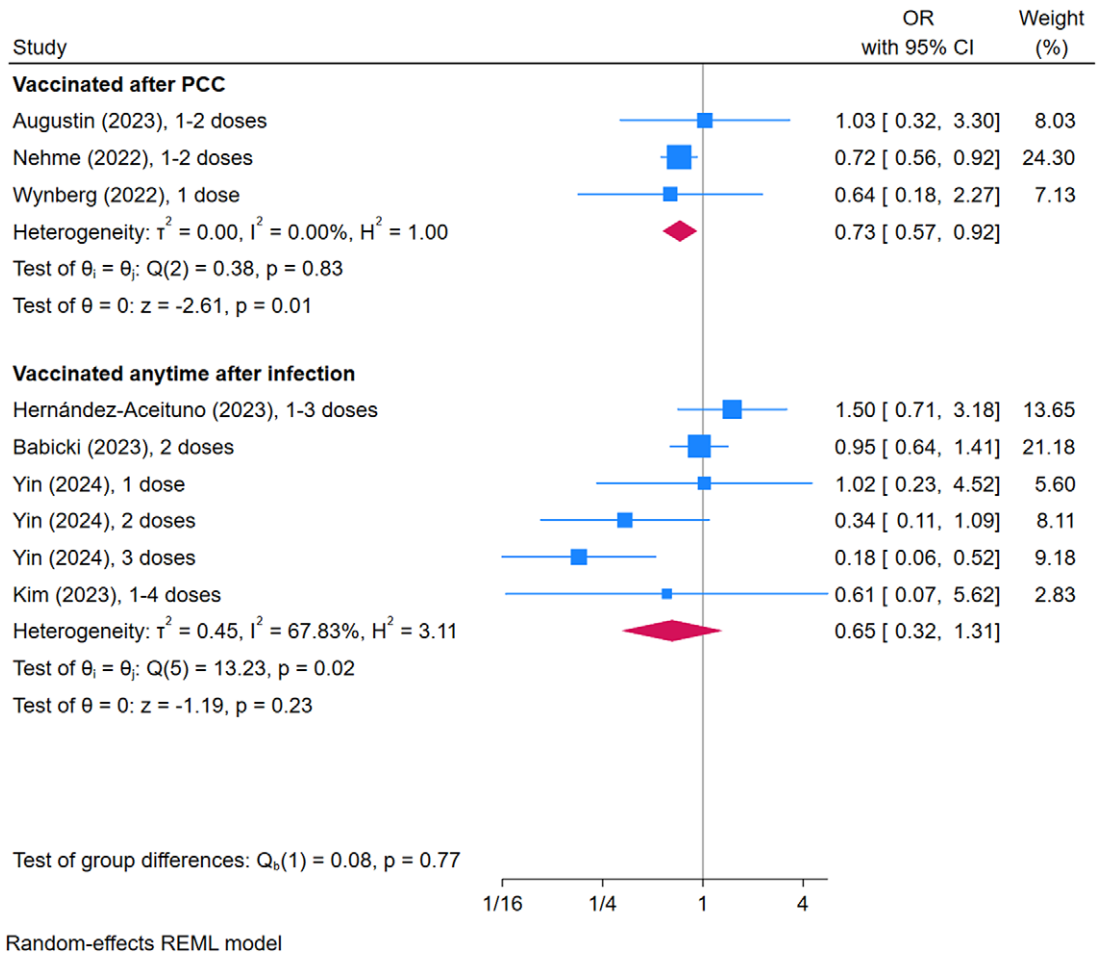

Figure 6. Meta-analysis of the effect of vaccination after COVID-19 compared to unvaccinated on the odds of developing PCC or persistent PCC, stratified by vaccination after established PCC and vaccination anytime after COVID-19 infection.

worsen. Across four studies, one dose resulted in symptom improvement [81, 82], a reduction in the proportion of those with more than one PCC symptom [83], and a slightly reduced odds of on-going PCC 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) [84]. Three studies examined one to three doses post-infection; two studies reported a greater proportion of PCC cases had symptom improvement post-vaccination compared to worsening [85, 86], while a third reported the opposite (12.7% improved vs. 20% worsened) [87]. The other studies on one to two doses post-infection [88] and two or more doses [89] found no significant change in PCC symptoms post-vaccination.

Nine studies reported on individual PCC symptoms: one pre-post study [84], five comparing those vaccinated after PCC versus unvaccinated [78, 79, 90–92], and three comparing those vaccinated anytime after infection versus unvaccinated [63, 93, 94], with follow-up ranging from 6 to 30 months post-infection. One study did not have extractable data [78] and three studies did not find a significant difference for any symptoms [90, 91, 94]. Four studies found significant differences in PCC symptoms between vaccinated versus unvaccinated. Fatigue was less prevalent for those with three doses [93], as well as headache and arthralgia for those with two doses [63]. Worsening ocular symptoms were less prevalent [79] and dyspnoea and change in taste were lower [92] in those with one or two doses. More vaccinated individuals (one to two doses) reported persistent hair loss in one study [79]. The pre–post-study found individuals with PCC had significantly lower odds of fatigue after two doses and loss of smell after one dose but not two [84].

Vaccination anytime after COVID-19 versus vaccination before COVID-19

Three studies compared individuals vaccinated anytime after infection versus individuals vaccinated before infection. The GRADE Summary of Findings is provided in Table 4. Two studies compared those who received a primary series after infection versus before infection: one found no significant difference in the odds of developing PCC [95], and the other found no difference in the rate of PCC at 6 months follow-up (aIRR 0.91, 95% CI 0.75–1.10) [51]. A third study found that a significantly higher proportion of individuals vaccinated (two to three doses) after infection reported PCC symptoms at 3 to 6 months compared to those vaccinated (three doses) before infection (74.5% vs. 51.9%, $p < 0.001$), but significantly fewer reported symptoms at more than 6 months (13.7% vs. 38%, $p < 0.001$) [96].

Differences between vaccine products

Three studies found no significant differences between mRNA vaccines (BNT162b2 or mRNA-1273) and adenoviral vector vaccines (ChAdOx1 or Ad26.COV2.S) [78, 79, 84]. However, a fourth study suggested those who received mRNA-1273 after PCC experienced

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improvement in certain symptoms significantly more than those who received ChAdOx1, including fatigue, brain fog, myalgia, gastro-intestinal symptoms, and autonomic dysfunction [82].

Differences by age and sex

One study found that only individuals ≥60 years who received two doses post-infection had significantly lower odds of persistent PCC compared to unvaccinated, and there was no association with sex [92]. Worsening PCC symptoms after one to three doses was significantly higher among individuals aged 14–40 compared to older individuals (aged 41–76) and among males compared to females [87].

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

Four studies reported on the safety or adverse events among those with PCC following COVID-19 vaccination, including three cross-sectional and one prospective cohort, all of which were high ROB (Table S6). Only one study included a vaccinated comparator group with no previous COVID-19 and found no significant difference in the number or type of side effects following one dose (BNT162b2) among those with PCC (n = 30) compared to controls [97]. Previous COVID-19 infection, but not PCC, was associated with an increased risk of adverse events post-vaccination. Another study found that only 5.7% (n = 26/455) of participants with PCC reported adverse events after one dose (various brands) [98]. However, the control group was unvaccinated individuals with PCC; therefore, this study does not show if the effects of vaccination were like those without PCC. In a survey of 67 healthcare workers with PCC, 72% reported immediate but self-limiting side effects at 2 weeks after one dose (BNT162b2) [99]. A fourth study found that the most common adverse effects after one to three doses (various brands) in those with PCC were pain at the injection site (90.8%), tiredness or fatigue (76.7%), and muscle pain (68.3%) [87]. A significantly higher proportion of those aged 14–40 reported dizziness post-vaccination ($p = 0.017$); otherwise, there were no significant differences in adverse effects by age or gender [87].

Discussion

The results of this updated living SR are aligned with the previous version and other evidence syntheses, which suggest that vaccination before COVID-19 provides protection against the risk of developing PCC [13–17]. There was moderate confidence that two vaccine doses before COVID-19 decreased the odds of developing PCC by 31%, compared to unvaccinated. Vaccination within 12 weeks after COVID-19 may offer additional protection against developing PCC compared to unvaccinated, but the evidence was very uncertain from only one study. There was low confidence that vaccination after PCC may reduce the odds of PCC persistence. Preliminary evidence suggested that a booster dose before infection may offer additional protection against PCC compared to only primary series [64, 66, 67]. Among children up to 18 years old, vaccination may have little to no effect on the odds of developing PCC [42, 68–70].

More recent studies examining the effect of three or more vaccine doses before infection on PCC frequently reported no association compared to unvaccinated [52, 54, 59, 61, 64]. There are several explanations for the association with vaccination becoming less clear than earlier in the pandemic. Population immunity has become more complex, with most people having hybrid immunity. Furthermore, the risk of PCC has changed over time as different variants have become dominant [62, 64, 100], and there are likely some differences in virulence between variants. The potential impact of variants was seen in a couple of studies where a significant association between vaccination and PCC was found in univariate analysis; however, after controlling for variant in multivariate analysis, the association became non-significant [54, 100]. Finally, individuals becoming vaccinated during the follow-up period may also impact the development or persistence of PCC but this was not accounted for in analyses; this would bias the estimated association between vaccination before infection and PCC towards the null. Overall, it has become increasingly more complex to measure the impact of vaccination on PCC.

Vaccination for those with PCC was safe across four studies, and there is low confidence that vaccination may reduce odds of PCC persistence. Although most studies suggested there was an improvement or resolution of PCC following vaccination, some suggested that PCC worsened or remained unchanged. Some of this heterogeneity in results may be due to recall bias in the self-reported PCC assessments. Improvement in PCC symptoms post-vaccination may also be conflated with natural recovery over time. Some studies did not specify whether individuals were vaccinated before PCC (<12 weeks post-infection) or after PCC (>12 weeks), so it was unclear whether the outcome was PCC development or persistence. Only one study reported results on the association between vaccination and PCC stratified by re-infection status [100]. Clear reporting on the timing of vaccination and re-infections after the infection that resulted in PCC would be useful in future studies.

Only a few studies examined differences in the association between vaccination and PCC by sociodemographic variables. However, many studies controlled for potential confounding variables, such as sex, age, and severity of initial COVID-19, which have been reported as risk factors for PCC [43, 46, 48]. Any differences by sociodemographic variables would be important to consider when developing recommendations for treatment and equitable resource allocation.

Across studies, there were various methodological differences in how PCC was defined and measured. Prospective studies often assessed PCC using self-reported surveys, while retrospective studies examined ICD-10 codes in health records; both of which could have resulted in the misclassification of PCC due to sequelae that are related to other conditions. Using a consistent PCC definition and developing validated PCC diagnostic tools in future research will help improve our understanding of this condition.

Limitations to this SR process include using the NOS tool for risk of bias assessments, which has not been validated, and a modified version of the tool to assess cross-sectional studies [33]. Furthermore, even though updated searches were conducted, the findings of this SR may change with emerging evidence on this evolving topic.

Conclusion

This updated SR indicates that there is moderate confidence that two vaccine doses before COVID-19 reduces the odds of developing PCC. For those with PCC, getting a COVID-19 vaccine appears to be safe, and there is low confidence that vaccination may reduce the odds of PCC persistence. Understanding the impact of vaccination on PCC, in the context of booster doses and re-infections, is important for informing public health recommendations.

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Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0950268825000378.

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

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Competing interests. The authors declare none.

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