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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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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 January 31, 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 vaccination within 12 weeks post-infection may reduce the odds of PCC. For those with PCC, vaccination appears safe (4 studies) and may reduce the odds of PCC persistence (pOR 0.73, 95% CI 0.57 – 0.92, I^2 = 15.5%).

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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 eight 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 continues 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-

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infection, post-infection, and post-PCC). The first version of this SR was published with data up to December 13, 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 January 31, 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

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inclusion and exclusion criteria are detailed in the previously published review (21) and protocol. A list of excluded studies is provided in 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 September 21, 2022 and has been updated four times, most recently on January 31, 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

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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-randomised 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 2021). 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

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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, high) was examined for outcomes considered in meta-analysis and reported in 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 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 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 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 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

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studies: 74 peer-reviewed research articles, two preprints, one letter-to-the-editor, and one short communication (Figure 1 and 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 (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 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) (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) 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.

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(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 (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 sub-groups. 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

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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 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

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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 (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, cognitive complaints) at four months post-infection (74), while the other found no significant difference in the

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prevalence of individual symptoms (fatigue, dyspnea, difficulties with a busy environment, memory problems, or brain fog) at three 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 was associated with lower odds of 3+ PCC symptoms at six 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 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 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,

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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) (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

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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 (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).

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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 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 six 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 dyspnea 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

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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 six 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 three to six 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 six 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 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)

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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 two 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.

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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 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 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,

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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 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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Competing Interests

None.

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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References

1. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus. Geneva: World Health Organization, 2021 6 October 2021. Report No.: Contract No.: WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1.
2. National Academies of Sciences E, Medicine. A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences. Fineberg HV, Brown L, Worku T, Goldowitz I, editors. Washington, DC: The National Academies Press; 2024. 186 p.
3. CDC. Clinical Overview of Long COVID 2024 [August 6, 2024]. Available from: https://www.cdc.gov/covid/hcp/clinical-overview/.
4. Government of Canada. Post COVID-19 condition (long COVID) 2022 [cited September 14, 2022]. Available from: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/symptoms/post-covid-19-condition.html.
5. Domingo FR, Waddell LA, Cheung AM, Cooper CL, Belcourt VJ, Zuckermann AME, et al. Prevalence of long-term effects in individuals diagnosed with COVID-19: an updated living systematic review. medRxiv. 2021. Epub June 3, 2021. doi: 10.1101/2021.06.03.21258317.
6. European Centre for Disease Prevention and Control. Prevalence of post COVID-19 condition symptoms: A systematic review and meta-analysis of cohort study data stratified by recruitment setting. ECDC: Stockholm: 2022 https://www.ecdc.europa.eu/en/publications-data/prevalence-post-covid-19-condition-symptoms-systematic-review-and-meta-analysis.
7. Public Health Agency of Canada. COVID-19: Longer-term symptoms among Canadian adults - Second report. Ottawa, Canada: Public Health Agency of Canada, 2023 March 24, 2023. Report No.: https://health-infobase.canada.ca/covid-19/post-covid-condition/spring-2023-report.html.
8. World Health Organization. Coronavirus disease (COVID-19): Post COVID-19 condition 2021 [16 December 2021]. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition#:~:text=Symptoms%20of%20post%20COVID%2D19%20condition%20can%20persist%20from%20the,normal%20recovery%20process%20after%20illness.
9. Taher MK, Salzman T, Banal A, Morissette K, Domingo FR, Cheung AM, et al. Global prevalence of post-COVID-19 condition: a systematic review and meta-analysis of prospective evidence. Health Promotion and Chronic Disease Prevention in Canada. 2025;45(3). doi: https://doi.org/10.24095/hpcdp.45.3.02.
10. Kuang S, Earl S, Clarke J, Zakaria D, Demers A, Aziz S. Experiences of Canadians with long-term symptoms following COVID-19. Statistics Canada, 2023 December 8, 2023. Report No.: https://health-infobase.canada.ca/covid-19/post-covid-condition/fall-2023-report.html.
11. National Center for Health Statistics. U.S. Census Bureau, Household Pulse Survey, 2022–2024. Long COVID.: National Center for Health Statistics; 2024 [cited 2025 March 6]. Available from: https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm.
12. World Health Organization. WHO COVID-19 dashboard: COVID-19 vaccination, World data 2023 [June 3, 2024]. Available from: https://data.who.int/dashboards/covid19/vaccines.
13. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. BMJ Medicine. 2023;2(1):e000385. doi: 10.1136/bmjmed-2022-000385.
14. Gao P, Liu J, Liu M. Effect of COVID-19 vaccines on reducing the risk of long COVID in the real world: A systematic review and meta-analysis. International Journal of Environmental Research and Public Health. 2022;19(29):12422. doi: 10.3390/ijerph191912422.
15. Marra AR, Kobayashi T, Suzuki H, Alsuhaibani M, Hasegawa S, Tholany J, et al. The effectiveness of coronavirus disease 2019 (COVID-19) vaccine in the prevention of post–COVID-19 conditions: A

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

462 systematic literature review and meta-analysis. Antimicrobial Stewardship & Healthcare Epidemiology.
463 2022;2(1):e192. doi: 10.1017/ash.2022.336.
464 16. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of COVID-19
465 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic
466 review. eClinicalMedicine. 2022;53:101624. doi: 10.1016/j.eclinm.2022.101624.
467 17. Marra AR, Kobayashi T, Callado GY, Pardo I, Gutfreund MC, Hsieh MK, et al. The effectiveness of
468 COVID-19 vaccine in the prevention of post-COVID conditions: a systematic literature review and meta-
469 analysis of the latest research. Antimicrobial Stewardship & Healthcare Epidemiology. 2023;3(1). doi:
470 10.1017/ash.2023.447.
471 18. Watanabe A, Iwagami M, Yasuhara J, Takagi H, Kuno T. Protective effect of COVID-19 vaccination
472 against long COVID syndrome: A systematic review and meta-analysis. Vaccine. 2023. Epub 2023/02/12.
473 doi: 10.1016/j.vaccine.2023.02.008. PubMed PMID: 36774332; PubMed Central PMCID: PMC9905096.
474 19. Ceban F, Kulzhabayeva D, Rodrigues NB, Di Vincenzo JD, Gill H, Subramaniapillai M, et al. COVID-
475 19 Vaccination for the Prevention and Treatment of Long COVID: A Systematic Review and Meta-
476 analysis; PMC10067136. Brain, Behavior, and Immunity. 2023;2023/03/30. doi:
477 10.1016/j.bbi.2023.03.022.
478 20. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, et al. Risk Factors
479 Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. JAMA Internal
480 Medicine. 2023;2023/03/24. doi: 10.1001/jamainternmed.2023.0750.
481 21. Jennings S, Corrin T, Waddell L. A systematic review of the evidence on the associations and
482 safety of COVID-19 vaccination and post COVID-19 condition. Epidemiology and Infection.
483 2023;151:e145. Epub 2023/08/18. doi: 10.1017/S0950268823001279.
484 22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA
485 statement for reporting systematic reviews and meta-analyses of studies that evaluate health care
486 interventions: explanation and elaboration. Journal of Clinical Epidemiology. 2009;62:e1-e34. doi:
487 10.1016/j.jclinepi.2009.06.006.
488 23. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page M, Welch V. Cochrane handbook for
489 systematic reviews of interventions version 6.3: Cochrane; 2022 [cited 2022 September]. Available from:
490 www.training.cochrane.org/handbook.
491 24. Corrin T, Ayache D, Baumeister A, Young K, Pussegoda K, Ahmad R, Waddell L. COVID-19
492 literature surveillance—A framework to manage the literature and support evidence-based decision-
493 making on a rapidly evolving public health topic. Canada Communicable Disease Report. 2023;49(1):5-9.
494 doi: 10.14745/ccdr.v49i01a02.
495 25. Fernández-de-las-Peñas C, Notarte KI, Peligro PJ, Velasco JV, Ocampo MJ, Henry BM, et al. Long-
496 COVID Symptoms in Individuals Infected with Different SARS-CoV-2 Variants of Concern: A Systematic
497 Review of the Literature. Viruses. 2022;14(12). doi: 10.3390/v14122629.
498 26. Calabrò GE, Pappalardo C, D'Ambrosio F, Vece M, Lupi C, Lontano A, et al. The Impact of
499 Vaccination on COVID-19 Burden of Disease in the Adult and Elderly Population: A Systematic Review of
500 Italian Evidence. Vaccines (Basel). 2023;11(5). Epub 20230522. doi: 10.3390/vaccines11051011. PubMed
501 PMID: 37243115; PubMed Central PMCID: PMC10222140.
502 27. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta
503 versus omicron variants of SARS-CoV-2. The Lancet. 2022;399(10343):2263-4. doi: 10.1016/S0140-
504 6736(22)00941-2.
505 28. Nehme M, Braillard O, Chappuis F, Courvoisier DS, Kaiser L, Soccal PM, et al. One-year persistent
506 symptoms and functional impairment in SARS-CoV-2 positive and negative individuals. Journal of
507 Internal Medicine. 2022;292(1):103-15. doi: https://doi.org/10.1111/joim.13482.

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

29. Qasmieh SA, Robertson MM, Teasdale CA, Kulkarni SG, Jones HE, McNairy M, et al. The prevalence of SARS-CoV-2 infection and long COVID in U.S. adults during the BA.4/BA.5 surge, June–July 2022. Preventive Medicine. 2023;169:107461. doi: https://doi.org/10.1016/j.ypmed.2023.107461.

30. van der Maaden T, Mutubuki EN, de Bruijn S, Leung KY, Knoop H, Slootweg J, et al. Prevalence and Severity of Symptoms 3 Months After Infection With SARS-CoV-2 Compared to Test-Negative and Population Controls in the Netherlands. The Journal of Infectious Diseases. 2022;227(9):1059-67. doi: 10.1093/infdis/jiac474.

31. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses n.d. [cited September 14, 2022]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

32. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi: 10.1136/bmj.i4919.

33. Ribeiro CM, Beserra BTS, Silva NG, Lima CL, Rocha PRS, Coelho MS, et al. Exposure to endocrine-disrupting chemicals and anthropometric measures of obesity: a systematic review and meta-analysis. BMJ Open. 2020;10:e033509. doi: 10.1136/bmjopen-2019-033509.

34. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. Journal of the American Medical Association. 1998;280:1690-1. doi: 10.1001/jama.280.19.1690.

35. Carazo S, Skowronski DM, Laforce R, Jr., Talbot D, Falcone EL, Laliberté D, et al. Physical, psychological and cognitive profile of post-COVID condition in healthcare workers, Quebec, Canada. Open Forum Infectious Diseases. 2022;9(8):ofac386. doi: 10.1093/ofid/ofac386.

36. George A, Stead TS, Ganti L. What's the Risk: Differentiating Risk Ratios, Odds Ratios, and Hazard Ratios? Cureus. 2020;12(8):e10047. doi: 10.7759/cureus.10047.

37. IntHout J, Ioannidis JPA, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Medical Research Methodology. 2014;14(1):25. doi: 10.1186/1471-2288-14-25.

38. IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open. 2016;6(7):e010247. doi: 10.1136/bmjopen-2015-010247.

39. Schünemann H, Hill S, Guyatt G, Akl EA, Ahmed F. The GRADE approach and Bradford Hill's criteria for causation. Journal of Epidemiology and Community Health. 2011;65:392. doi: 10.1136/jech.2010.119933.

40. Di Fusco M, Sun X, Moran M, Coetzer H, Zamparo J, Alvarez M, et al. Impact of COVID-19 and effects of booster vaccination with BNT162b2 on six-month long COVID symptoms, quality of life, work productivity and activity impairment during Omicron. Journal of Patient-Reported Outcomes. 2023;7(77). doi: 10.1186/s41687-023-00616-5.

41. Mariani F, Morello R, Traini DO, La Rocca A, De Rose C, Valentini P, Buonsenso D. Risk Factors for Persistent Anosmia and Dysgeusia in Children with SARS-CoV-2 Infection: A Retrospective Study. Children (Basel). 2023;10(3). doi: 10.3390/children10030597.

42. Morello R, Mariani F, Mastrantoni L, De Rose C, Zampino G, Munblit D, et al. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. EClinicalMedicine. 2023;59:101961. doi: 10.1016/j.eclinm.2023.101961.

43. Hastie CE, Lowe DJ, McAuley A, Winter AJ, Mills NL, Black C, et al. Outcomes among confirmed cases and a matched comparison group in the Long-COVID in Scotland study. Nature Communications. 2022;13:5663. doi: 10.1038/s41467-022-33415-5.

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

44. Simon MA, Luginbuhl R, Parker R. Reduced incidence of long-COVID symptoms related to administration of COVID-19 vaccines both before COVID-19 diagnosis and up to 12 weeks after. medRxiv. 2021. Epub November 17, 2021. doi: 10.1101/2021.11.17.21263608.
45. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections. Brain, Behavior, and Immunity. 2022;103:154-62. doi: 10.1016/j.bbi.2022.04.013.
46. Nascimento TC, Costa LV, Ruiz AD, Ledo C, Fernandes VPL, Cardoso LF, et al. Vaccination status and long COVID symptoms in patients discharged from hospital. Scientific Reports. 2023;13:2481. doi: 10.1038/s41598-023-28839-y.
47. Ayoubkhani D, Bosworth ML, King S, Pouwels KB, Glickman M, Nafilyan V, et al. Risk of Long COVID in People Infected With Severe Acute Respiratory Syndrome Coronavirus 2 After 2 Doses of a Coronavirus Disease 2019 Vaccine: Community-Based, Matched Cohort Study. Open Forum Infectious Diseases. 2022a;9(9):ofac464. doi: 10.1093/ofid/ofac464.
48. Emecen AN, Keskin S, Turunc O, Suner AF, Siyve N, Basoglu Sensoy E, et al. The presence of symptoms within 6 months after COVID-19: a single-center longitudinal study. Irish Journal of Medical Science. 2022;192(2):741-50. doi: 10.1007/s11845-022-03072-0.
49. Brannock D, Chew R, Preiss A, Hadley E, Redfield S, McMurry J, et al. Long COVID risk and pre-COVID vaccination in an EHR-based cohort study from the RECOVER program. Nature Communications. 2023;14:2914. doi: 10.1038/s41467-023-38388-7.
50. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nature Medicine. 2022;28(7):1461-7. doi: 10.1038/s41591-022-01840-0.
51. Jassat W, Mudara C, Vika C, Welch R, Arendse T, Dryden M, et al. A cohort study of post-COVID-19 condition across the Beta, Delta, and Omicron waves in South Africa: 6-month follow-up of hospitalized and nonhospitalized participants. International Journal of Infectious Diseases. 2023;128:102-11. doi: 10.1016/j.ijid.2022.12.036.
52. Ballouz T, Menges D, Kaufmann M, Amati R, Frei A, von Wyl V, et al. Post COVID-19 condition after Wildtype, Delta, and Omicron SARS-CoV-2 infection and prior vaccination: Pooled analysis of two population-based cohorts. PlosOne. 2023;18(2):e0281429. doi: 10.1371/journal.pone.0281429.
53. Ioannou GN, Baraff A, Fox A, Shahoumian T, Hickok A, O'Hare AM, et al. Rates and Factors Associated with Documentation of Diagnostic Codes for Long COVID in the National Veterans Affairs Health Care System. JAMA Network Open. 2022;5:E2224359. doi: 10.1001/jamanetworkopen.2022.24359.
54. Marra AR, Sampaio VS, Ozahata MC, Lopes R, Brito AF, Bragatte M, et al. Risk factors for long coronavirus disease 2019 (long COVID) among healthcare personnel, Brazil, 2020-2022. Infection Control & Hospital Epidemiology. 2023:1-7. Epub 20230605. doi: 10.1017/ice.2023.95. PubMed PMID: 37272468.
55. Richard SA, Pollett SD, Fries AC, Berjohn CM, Maves RC, Lalani T, et al. Persistent COVID-19 Symptoms at 6 Months After Onset and the Role of Vaccination Before or After SARS-CoV-2 Infection. JAMA Network Open. 2023;6(1):e2251360. doi: 10.1001/jamanetworkopen.2022.51360.
56. Elmazny A, Magdy R, Hussein M, Elsebaie EH, Ali SH, Abdel Fattah AM, et al. Neuropsychiatric post-acute sequelae of COVID-19: prevalence, severity, and impact of vaccination. European Archives of Psychiatry and Clinical Neuroscience. 2023:1-10. Epub 2023/01/28. doi: 10.1007/s00406-023-01557-2. PubMed PMID: 36707454; PubMed Central PMCID: PMC9882743.
57. Wong MC, Huang J, Wong YY, Wong GL, Yip TC, Chan RN, et al. Epidemiology, Symptomatology, and Risk Factors for Long COVID Symptoms: Population-Based, Multicenter Study. JMIR Public Health and Surveillance. 2023;9:e42315. Epub 2023/01/17. doi: 10.2196/42315. PubMed PMID: 36645453.

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

599 58. Abu Hamdh B, Nazzal Z. A prospective cohort study assessing the relationship between long-
600 COVID symptom incidence in COVID-19 patients and COVID-19 vaccination; PMC10039348. Scientific
601 Reports. 2023;13(1):4896. doi: 10.1038/s41598-023-30583-2.
602 59. Angarita-Fonseca A, Torres-Castro R, Benavides-Cordoba V, Chero S, Morales-Satán M,
603 Hernández-López B, et al. Exploring long COVID condition in Latin America: Its impact on patients'
604 activities and associated healthcare use. Frontiers in Medicine. 2023;10. doi:
605 10.3389/fmed.2023.1168628.
606 60. Català M, Mercadé-Besora N, Kolde R, Trinh NTH, Roel E, Burn E, et al. The effectiveness of
607 COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain,
608 and Estonia. The Lancet Respiratory Medicine. 2024. Epub 20240111. doi: 10.1016/s2213-
609 2600(23)00414-9. PubMed PMID: 38219763.
610 61. Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Beiruti Wiegler K, Abu Jabal K, et al. Association
611 between BNT162b2 vaccination and health-related quality of life up to 18 months post-SARS-CoV-2
612 infection in Israel. Scientific Reports. 2023;13(1):15801. Epub 20230922. doi: 10.1038/s41598-023-
613 43058-1. PubMed PMID: 37737268; PubMed Central PMCID: PMC10516916.
614 62. Thaweethai T, Jolley SE, Karlson EW, Levitan EB, Levy B, McComsey GA, et al. Development of a
615 Definition of Postacute Sequelae of SARS-CoV-2 Infection. JAMA. 2023. Epub 20230525. doi:
616 10.1001/jama.2023.8823. PubMed PMID: 37278994.
617 63. Babicki M, Kapusta J, Pieniawska-Śmiech K, Kałuzińska-Kołat Ż, Kołat D, Mastalerz-Migas A, et al.
618 Do COVID-19 Vaccinations Affect the Most Common Post-COVID Symptoms? Initial Data from the STOP-
619 COVID Register–12-Month Follow-Up. Viruses. 2023;15(6). doi: 10.3390/v15061370.
620 64. Diexer S, Klee B, Gottschick C, Xu C, Broda A, Purschke O, et al. Association between Virus
621 Variants, Vaccination, Previous Infections, and Post COVID-19 Risk. International Journal of Infectious
622 Diseases. 2023. Epub 20230825. doi: 10.1016/j.ijid.2023.08.019. PubMed PMID: 37634619.
623 65. Fatima S, Ismail M, Ejaz T, Shah Z, Fatima S, Shahzaib M, Jafri HM. Association between long
624 COVID and vaccination: A 12-month follow-up study in a low- to middle-income country. PLoS One.
625 2023;18(11):e0294780. Epub 20231122. doi: 10.1371/journal.pone.0294780. PubMed PMID: 37992084;
626 PubMed Central PMCID: PMC10664948.
627 66. de Bruijn S, van Hoek AJ, Mutubuki E, Knoop H, Slootweg J, Tulen A, et al. Lower prevalence of
628 post-Covid-19 Condition following Omicron SARS-CoV-2 infection. Heliyon. 2024;10(7):e28941. doi:
629 10.1016/j.heliyon.2024.e28941.
630 67. Antonelli M, Penfold RS, Canas LDS, Sudre C, Rjoob K, Murray B, et al. SARS-CoV-2 infection
631 following booster vaccination: illness and symptom profile in a prospective, observational community-
632 based case-control study. Journal of Infection. 2023. Epub 20230928. doi: 10.1016/j.jinf.2023.08.009.
633 PubMed PMID: 37777159.
634 68. Atchison CJ, Whitaker M, Donnelly CA, Chadeau-Hyam M, Riley S, Darzi A, et al. Characteristics
635 and predictors of persistent symptoms post-COVID-19 in children and young people: a large community
636 cross-sectional study in England. Archives of Disease in Childhood. 2023. Epub 2023/03/03. doi:
637 10.1136/archdischild-2022-325152. PubMed PMID: 36863848.
638 69. Getsuwan S, Boonsathorn S, Chaisavaneeyakorn S, Butsriphum N, Tanpowpong P,
639 Lertudomphonwanit C, Treepongkaruna S. Clinical manifestations and outcomes of coronavirus disease
640 2019 among pediatric liver transplant recipients in the delta and omicron variant pandemic: A
641 retrospective study. Medicine. 2023;102(41):e35537. doi: 10.1097/md.0000000000035537. PubMed
642 PMID: 37832076; PubMed Central PMCID: PMC10578722.
643 70. Li J, Nadua K, Chong CY, Yung CF. Long COVID prevalence, risk factors and impact of vaccination
644 in the paediatric population: A survey study in Singapore. Annals of the Academy of Medicine Singapore.
645 2023;52(10):522-32. doi: 10.47102/annals-acadmedsg.2023238.

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

71. Mizrahi B, Sudry T, Flaks-Manov N, Yehezkelli Y, Kalkstein N, Akiva P, et al. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. BMJ. 2023;380:e072529. Epub 2023/01/12. doi: 10.1136/bmj-2022-072529. PubMed PMID: 36631153; PubMed Central PMCID: PMC9832503.
72. Fernández-de-las-Peñas C, Ortega-Santiago R, Fuensalida-Novo S, Martín-Guerrero JD, Pellicer-Valero OJ, Torres-Macho J. Differences in Long-COVID Symptoms between Vaccinated and Non-Vaccinated (BNT162b2 Vaccine) Hospitalized COVID-19 Survivors Infected with the Delta Variant. Vaccines. 2022;10. doi: 10.3390/vaccines10091481.
73. Mitrović-Ajtić O, Stanisavljević D, Miljatović S, Dragojević T, Živković E, Šabanović M, Čokić VP. Quality of Life in Post-COVID-19 Patients after Hospitalization. Healthcare (Basel). 2022;10. doi: 10.3390/healthcare10091666.
74. Spiliopoulos L, Sørensen AIV, Bager P, Nielsen NM, Vinsløv Hansen J, Koch A, et al. Post-acute symptoms 4 months after SARS-CoV-2 infection during the Omicron period: a nationwide Danish questionnaire study. American Journal of Epidemiology. 2023. Epub November 17, 2023. doi: 10.1093/aje/kwad225.
75. Kahlert CR, Strahm C, Güsewell S, Cusini A, Brucher A, Goppel S, et al. Post-acute Sequelae After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection by Viral Variant and Vaccination Status: A Multicenter Cross-sectional Study. Clinical Infectious Diseases. 2023:ciad143. doi: 10.1093/cid/ciad143.
76. Hernández-Aceituno A, García-Hernández A, Larumbe-Zabala E. COVID-19 long-term sequelae: Omicron versus Alpha and Delta variants. Infectious Diseases Now. 2023:104688. Epub 2023/03/02. doi: 10.1016/j.idnow.2023.104688. PubMed PMID: 36858287; PubMed Central PMCID: PMC9970656.
77. Diez-Cirarda M, Yus M, Gomez-Ruiz N, Polidura C, Gil-Martinez L, Delgado-Alonso C, et al. Multimodal neuroimaging in post-COVID syndrome and correlation with cognition. Brain. 2023;146(5):2142-52. doi: 10.1093/brain/awac384.
78. Arnold DT, Milne A, Samms E, Stadon L, Maskell NA, Hamilton FW. Are vaccines safe in patients with Long COVID? A prospective observational study. medRxiv. 2021. Epub March 11, 2021. doi: 10.1101/2021.03.11.21253225.
79. Peghin M, De Martino M, Palese A, Gerussi V, Bontempo G, Graziano E, et al. Post-COVID-19 syndrome and humoral response association after 1 year in vaccinated and unvaccinated patients. Clinical Microbiology and Infection. 2022;28:1140-8. doi: 10.1016/j.cmi.2022.03.016.
80. Salmon D, Slama D, Linard F, Dumesges N, Lebaut V, Hakim F, et al. Long COVID patients continue to experience significant symptoms at 12 months and factors associated with improvement: a prospective cohort study in France (PERSICOR). International Journal of Infectious Diseases. 2023. Epub 20231221. doi: 10.1016/j.ijid.2023.11.038. PubMed PMID: 38141960.
81. Krishna BA, Lim EY, Metaxaki M, Jackson S, Mactavous L, BioResource N, et al. Spontaneous, persistent, T cell–dependent IFN-γ release in patients who progress to Long Covid. Science Advances. 2024;10(8):eadi9379. doi: 10.1126/sciadv.adi9379.
82. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, Rossman J. The impact of COVID vaccination on symptoms of long COVID: an international survey of people with lived experience of long COVID. Vaccines. 2022;10(5):652. doi: 10.3390/vaccines10050652.
83. Fong SW, Goh YS, Torres-Ruesta A, Chang ZW, Chan YH, Neo VK, et al. Prolonged inflammation in patients hospitalized for coronavirus disease 2019 (COVID-19) resolves 2 years after infection. Journal of Medical Virology. 2023;95(5). doi: 10.1002/jmv.28774.
84. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. BMJ. 2022b;377:e069676. doi: 10.1136/bmj-2021-069676.

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

85. Nakagawara K, Morita A, Namkoong H, Terai H, Chubachi S, Asakura T, et al. Longitudinal long COVID symptoms in Japanese patients after COVID-19 vaccinations. Vaccine: X. 2023;15. doi: 10.1016/j.jvacx.2023.100381.
86. Malesevic S, Sievi NA, Schmidt D, Vallelian F, Jelcic I, Kohler M, Clarenbach CF. Physical Health-Related Quality of Life Improves over Time in Post-COVID-19 Patients: An Exploratory Prospective Study. Journal of Clinical Medicine. 2023;12(12). Epub 20230615. doi: 10.3390/jcm12124077. PubMed PMID: 37373770.
87. Romero-Rodríguez E, Perula-de-Torres LÁ, González-Lama J, Castro-Jiménez RÁ, Jiménez-García C, Priego-Pérez C, et al. Long COVID Symptomatology and Associated Factors in Primary Care Patients: The EPICOVID-AP21 Study. Healthcare (Basel). 2023;11(2). doi: 10.3390/healthcare11020218.
88. Gerhards C, Kittel M, Ast V, Bugert P, Froelich MF, Hetjens M, et al. Humoral SARS-CoV-2 Immune Response in COVID-19 Recovered Vaccinated and Unvaccinated Individuals Related to Post-COVID-Syndrome. Viruses. 2023;15(2). doi: 10.3390/v15020454.
89. da Silva NS, de Araújo NK, dos Santos KA, de Souza KSC, de Araújo JNG, Cruz MS, et al. Post-Covid condition and clinic characteristics associated with SARS-CoV-2 infection: a 2-year follow-up to Brazilian cases. Scientific Reports. 2023;13. doi: 10.1038/s41598-023-40586-8.
90. Wisnivesky JP, Govindarajulu U, Bagiella E, Goswami R, Kale M, Campbell KN, et al. Association of vaccination with the persistence of post-COVID symptoms. Journal of General Internal Medicine. 2022;37(3):1748-53. doi: 10.1007/s11606-022-07465-w.
91. Augustin M, Stecher M, Wüstenberg H, Di Cristanziano V, Sandaradura de Silva U, Picard LK, et al. 15-month post-COVID syndrome in outpatients: Attributes, risk factors, outcomes, and vaccination status - longitudinal, observational, case-control study. Frontiers in Immunology. 2023;14. doi: 10.3389/fimmu.2023.1226622.
92. Nehme M, Braillard O, Salamun J, Jacquerioz F, Courvoisier DS, Spechbach H, Guessous I. Symptoms after COVID-19 vaccination in patients with post-acute sequelae of SARS-CoV-2. Journal of General Internal Medicine. 2022;37(6):1585-8. doi: 10.1007/s11606-022-07443-2.
93. Yin Y, Guo Y, Xiao M, Chen Q, Long P, Wang X, et al. Health Consequences Among COVID-19 Convalescent Patients 30 Months Post-Infection in China. Zoonoses. 2024;4(1). doi: 10.15212/ZOONOSES-2023-0014.
94. Kim Y, Bae S, Chang HH, Kim SW. Characteristics of long COVID and the impact of COVID-19 vaccination on long COVID 2 years following COVID-19 infection: prospective cohort study. Scientific Reports. 2024;14(1):854. Epub 20240109. doi: 10.1038/s41598-023-50024-4. PubMed PMID: 38191556; PubMed Central PMCID: PMC10774352.
95. Bostanci A, Gazi U, Tosun O, Suer K, Unal Evren E, Evren H, Sanlidag T. Long-COVID-19 in Asymptomatic, Non-Hospitalized, and Hospitalized Populations: A Cross-Sectional Study. Journal of Clinical Medicine. 2023;12(7). doi: 10.3390/jcm12072613.
96. Adly HM, Saleh SAK, Garout MA, Abdulkhaliq AA, Khafagy AA, Saati AA, et al. Post COVID-19 Symptoms Among Infected Vaccinated Individuals: A Cross-Sectional Study in Saudi Arabia. Journal of Epidemiology and Global Health. 2023. Epub 20230904. doi: 10.1007/s44197-023-00146-9. PubMed PMID: 37665505.
97. Raw RK, Kelly C, Rees J, Wroe C, Chadwick D. Previous COVID-19 infection, but not Long-COVID, is associated with increased adverse events following BNT162b2/Pfizer vaccination. Journal of Infection. 2021;83(3):381-412. doi: 10.1016/j.jinf.2021.05.035.
98. Tran V-T, Perrodeau E, Saldanha J, Pane I, Ravaud P. Efficacy of first dose of covid-19 vaccine versus no vaccination on symptoms of patients with long covid: target trial emulation based on ComPaRe e-cohort. BMJ Medicine. 2023;2:e000229. doi: 10.1136/bmjmed-2022-000229.

https://doi.org/10.1017/S0950268825000378 Published online by Cambridge University Press

739 99. Gaber TAZK, Ashish A, Unsworth A, Martindale J. Are mRNA covid 19 vaccines safe in long covid
740 patients? A health care workers perspective. British Journal of Medical Practitioners. 2021;14(1):a008.
741 100. Reme BA, Gjesvik J, Magnusson K. Predictors of the post-COVID condition following mild SARS-
742 CoV-2 infection. Nature Communications. 2023;14(1):5839. Epub 20230920. doi: 10.1038/s41467-023-
743 41541-x. PubMed PMID: 37730740; PubMed Central PMCID: PMC10511472.
744 101. Wynberg E, Han AX, Boyd A, van Willigen HDG, Verveen A, Lebbink R, et al. The effect of SARS-
745 CoV-2 vaccination on post-acute sequelae of COVID-19 (PASC): A prospective cohort study. Vaccine.
746 2022;40:4424-31. doi: 10.1016/j.vaccine.2022.05.090.
747 102. Kim Y, Bae S, Chang HH, Kim SW. Long COVID prevalence and impact on quality of life 2 years
748 after acute COVID-19. Scientific Reports. 2023;13(1):11207. Epub 20230711. doi: 10.1038/s41598-023-
749 36995-4. PubMed PMID: 37433819.
750 103. Funk AL, Kuppermann N, Florin TA, Tancredi DJ, Xie J, Kim K, et al. Post–COVID-19 Conditions
751 Among Children 90 Days After SARS-CoV-2 Infection. JAMA Network Open. 2022;5(7):e2223253-e. doi:
752 10.1001/jamanetworkopen.2022.23253.

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754 **Table 1:** General characteristics of the 78 included primary research publications on post-COVID-19

755 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,	9	0	8	0

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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)
Singapore, Pakistan, Saudi Arabia, Thailand, South Korea, Japan, Palestine, Israel)				
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
Veterans or military health system beneficiaries (active duty, dependents, and retirees)	4	0	1	0

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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)**
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.

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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

Exposure	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)			Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Baseline without vaccine	Corresponding risk with vaccine	Risk difference				
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)	333033 (8 non-randomised 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)	888111 (2 non-randomised 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).

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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)	336982 (13 non-randomised 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)	409123 (4 non-randomised 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-randomised 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)	1588 (1 non-randomised 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)	19421 (5 non-randomised 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).

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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)	3331 (1 non-randomised 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)	6180 (1 non-randomised 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)	1029533 (2 non-randomised 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).

Footnotes: 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 August 31, 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).

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761 **Table 3:** Summary of findings table for the main outcomes of PCC development or persistence in
762 individuals vaccinated after COVID-19 or after PCC, compared to unvaccinated. The illustrative example
763 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

Exposure	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)			Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Baseline without vaccine	Corresponding risk with vaccine	Risk difference				
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)	238256 (1 non-randomised 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							

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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-randomised 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)	1331 (4 non-randomised 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).

Footnotes: 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 August 31, 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.

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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

Exposure	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)			Relative effect (95% CI) (OR/HR/IRR)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Baseline with vaccine before infection	Corresponding risk with vaccine after infection	Risk difference				
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-randomised 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)	2950 (1 non-randomised 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-randomised 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).

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Footnotes: 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 August 31, 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).

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770 **Table 5:** Summary of findings table for the main outcome of PCC development, in individuals who

771 received a booster dose versus only primary series. The illustrative example is based on a PCC

772 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)	34247 (3 non-randomised 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).

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Footnotes: 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 August 31, 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

Exposure	Illustrative comparative in cases of PCC per 100 COVID-19 cases (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Baseline without vaccine	Corresponding risk with vaccine	Risk difference				
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)	6886 (1 non-randomised 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).

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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)	1275 (3 non-randomised 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).

Footnotes: 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.

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779 **Figure 1.** PRISMA flow diagram of articles through the systematic review process, including studies from

780 the previous version and new studies in this update.

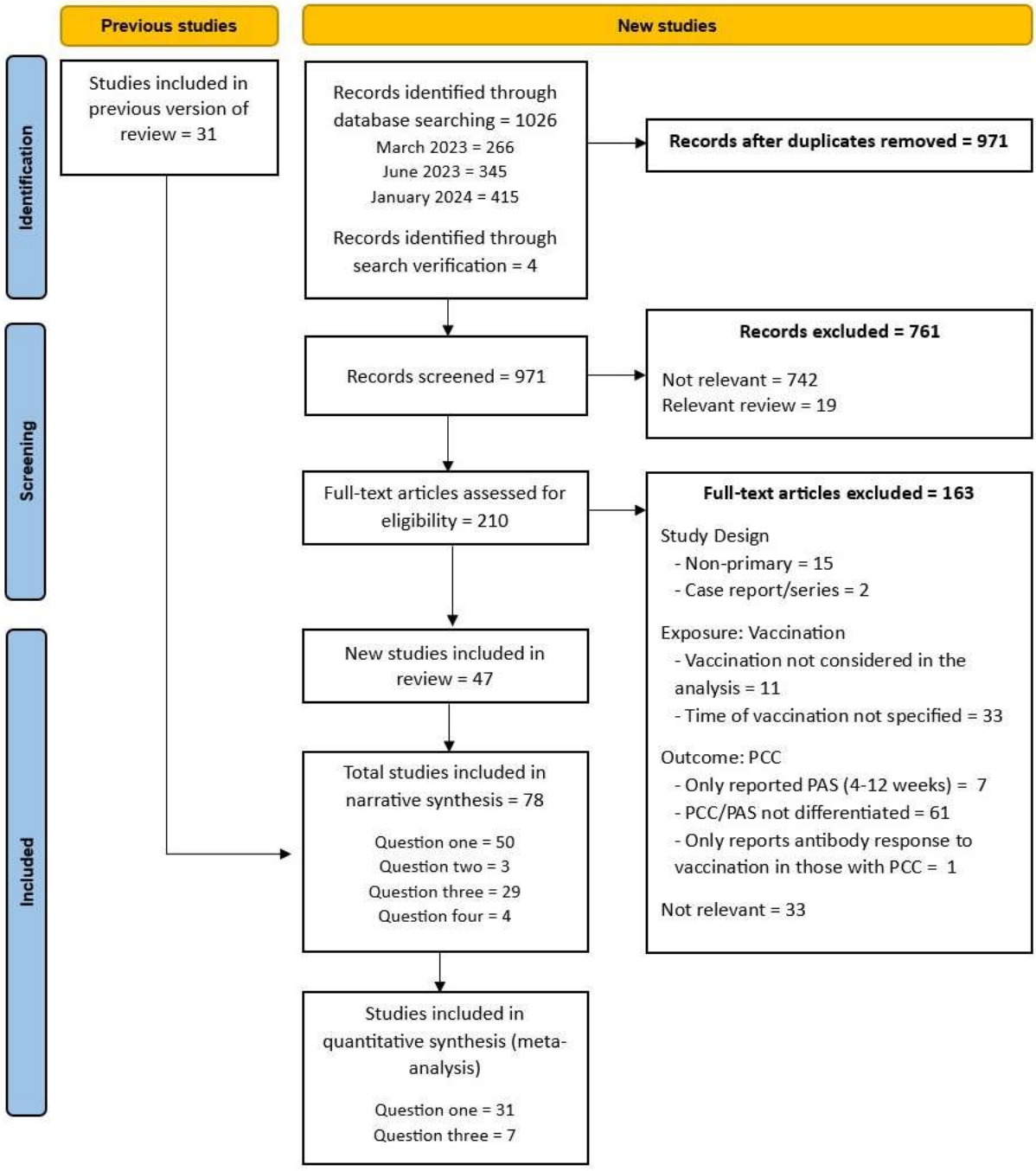

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Figure 2. Meta-analysis of the effect of vaccination prior to COVID-19 compared to unvaccinated on the odds of developing PCC, stratified by number of doses.

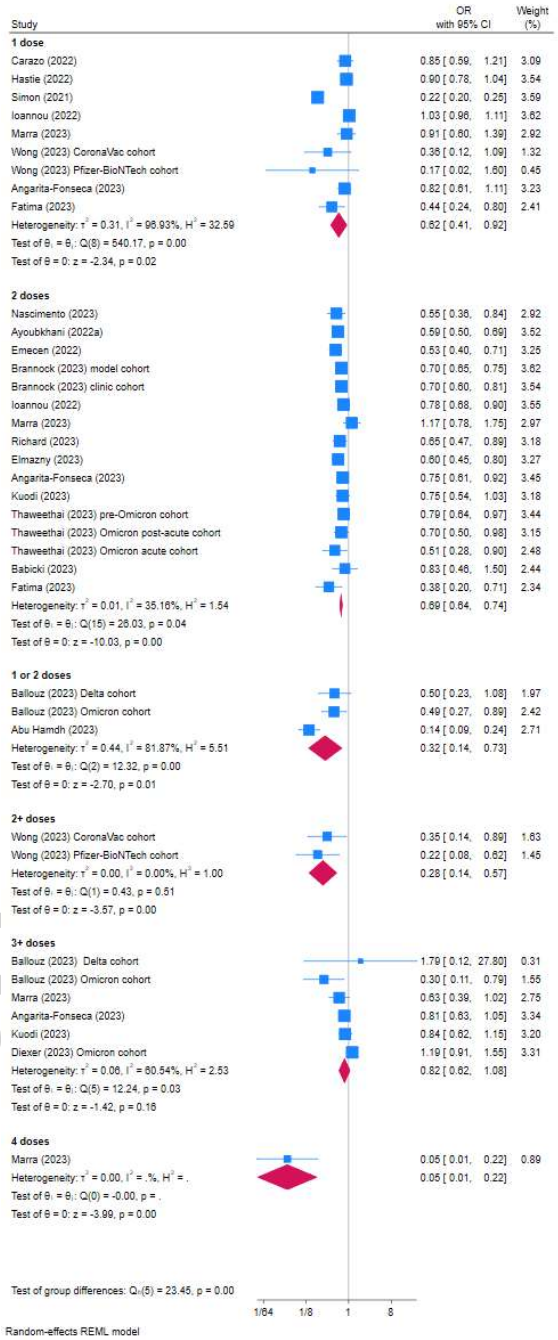

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Figure 3. Meta-analysis of the hazard ratios for developing PCC in those vaccinated prior to COVID-19 compared to unvaccinated, stratified by number of doses.

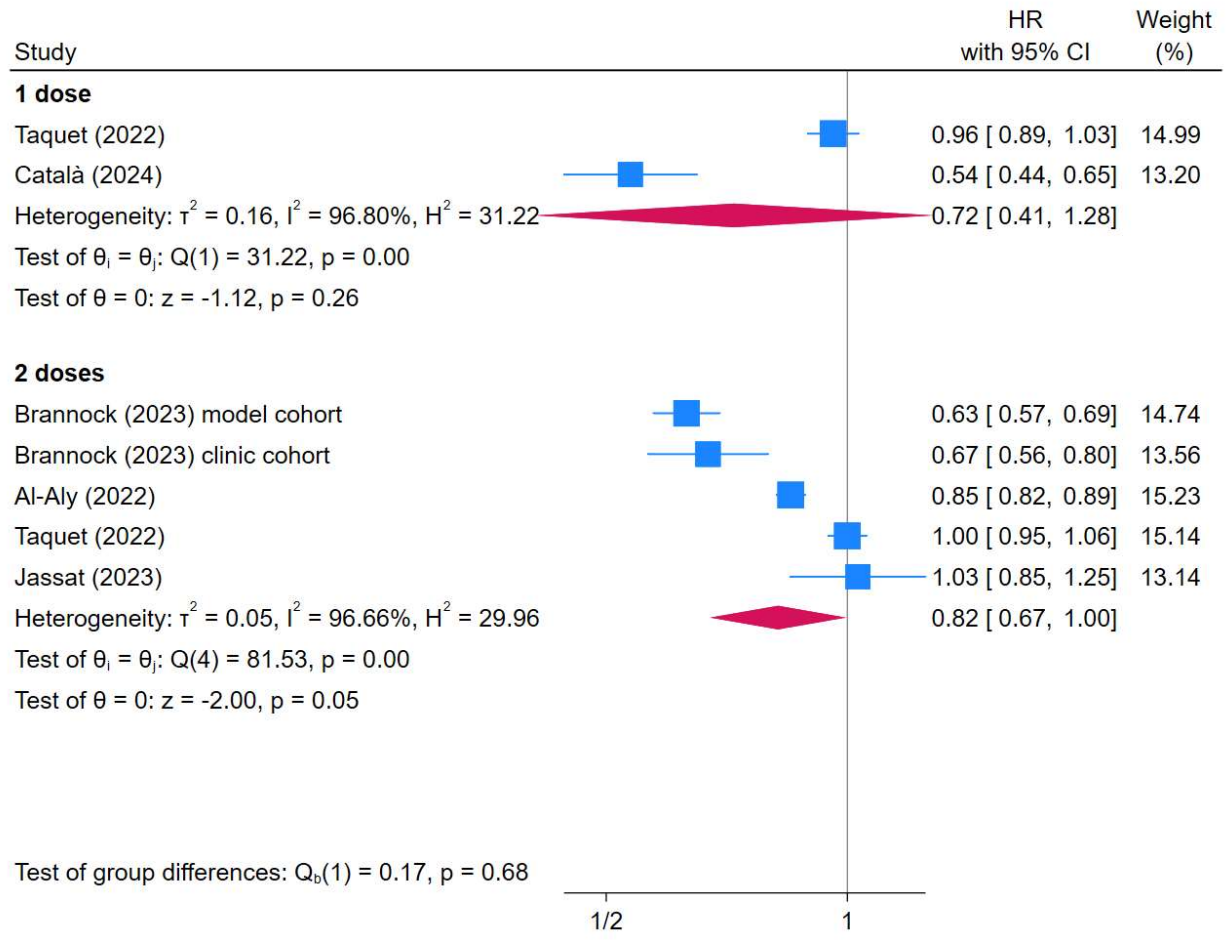

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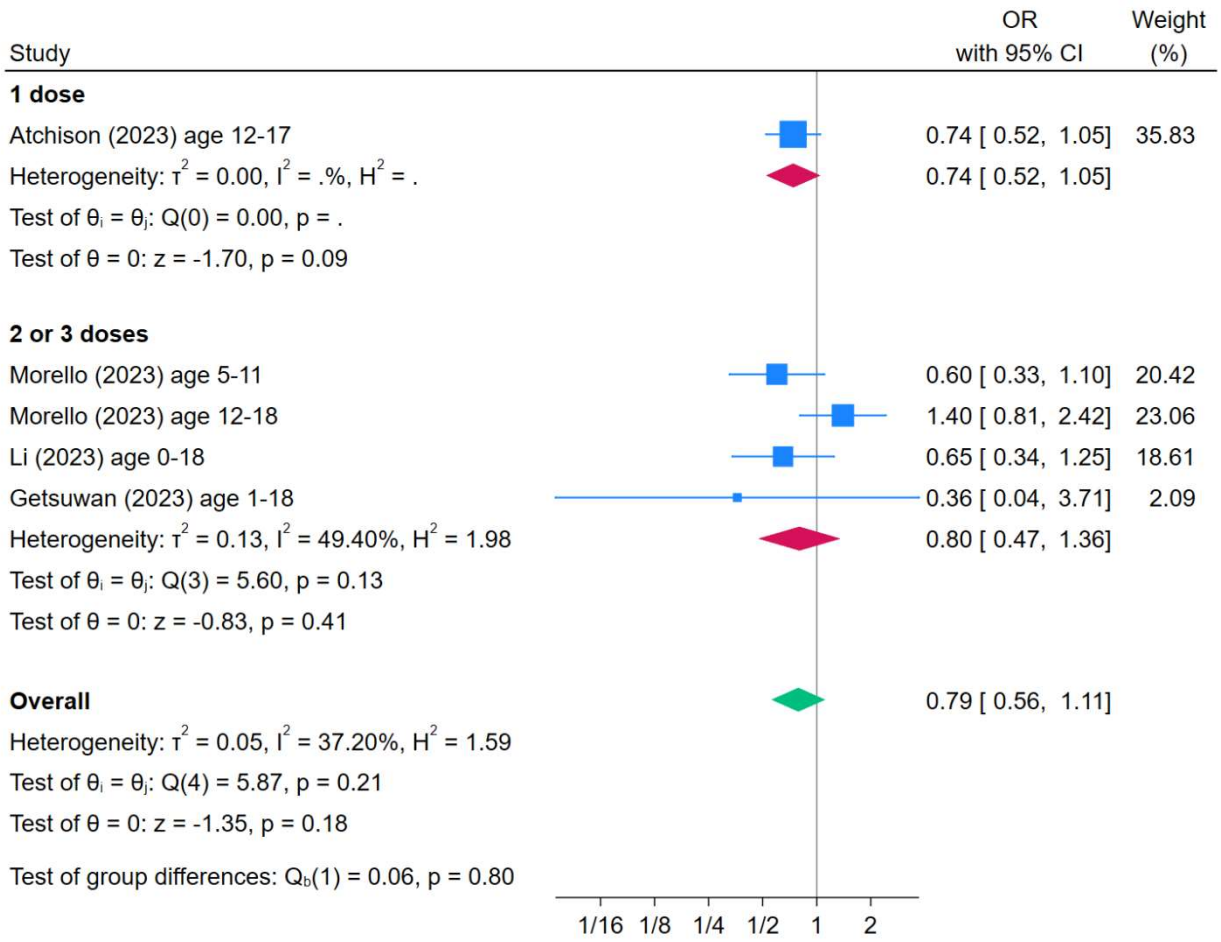
Figure 4. Meta-analysis of the effect of vaccination prior to COVID-19 compared to unvaccinated on the odds of developing PCC in children up to 18 years old, stratified by number of doses.



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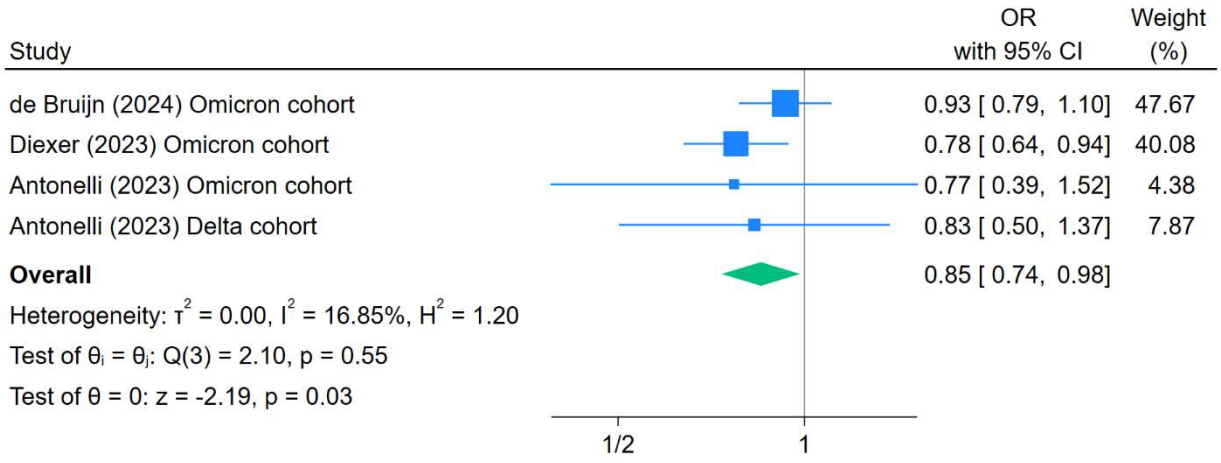
795 **Figure 5.** Meta-analysis of the effect of booster vaccination prior to COVID-19 compared to only a

796 primary series on the odds of developing PCC.



797 Random-effects REML model

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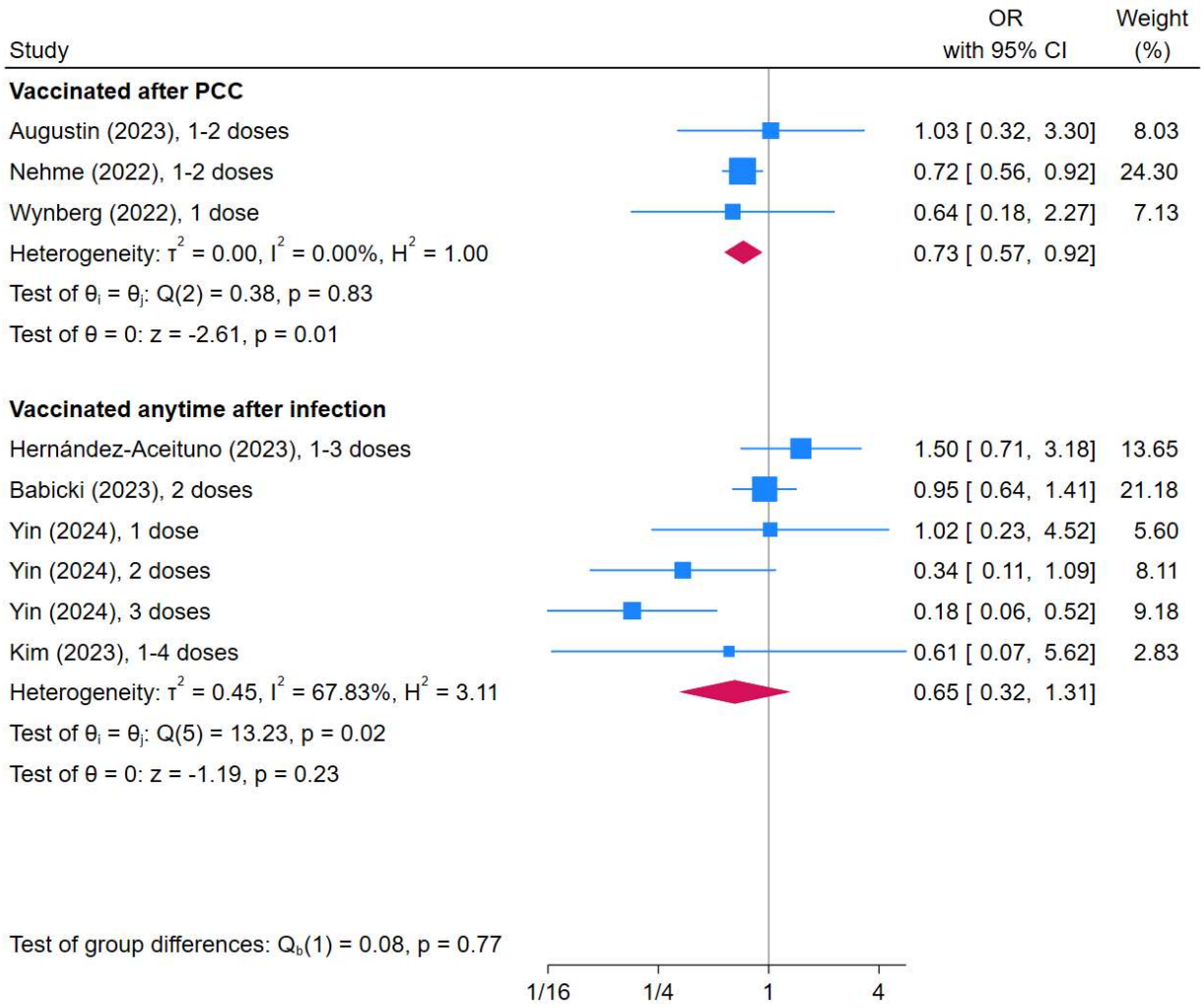
799 **Figure 6.** Meta-analysis of the effect of vaccination after COVID-19 compared to unvaccinated on the
800 odds of developing PCC or persistent PCC, stratified by vaccination after established PCC and vaccination
801 anytime after COVID-19 infection.



802 Random-effects REML model

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