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MONITORING

Does COVID-19 vaccination reduce the risk and duration of post-COVID-19 condition?

Rapid systematic literature review

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This review was commissioned by the European Centre for Disease Prevention and Control (ECDC) under Framework Contract ECDC/2023/024 - Lot 2: Rapid reviews from Amaris Consulting. The commissioning and production of this review was coordinated by Ajibola Omokanye (ECDC).

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Abbreviations

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CIS	UK Coronavirus (COVID-19) Infection Survey
COVID-19	Coronavirus disease 2019
CVID	Common variable immunodeficiency
DALY	Disability-adjusted life year
DOR	Diagnostic odds ratio
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
FE	Fixed-effect
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HIV	Human immunodeficiency virus
HR	Hazard Ratio
ICD	International Classification of Disease
ICU	Intensive care unit
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
JBI	Joanna Briggs Institute
MNS	Major neuropsychological symptoms
MPS	Major physical symptoms
mRNA	Messenger Ribonucleic Acid
NA	Not applicable
NCBI	National Center for Biotechnology Information
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NOS	Newcastle-Ottawa scale
NR	Not reported
OR	Odds ratio
PCC	Post-COVID-19 condition
PHEIC	Public Health Emergency of International Concern
PICOS	Population, Intervention, Comparator, Outcome, Study type
PLHIV	People living with human immunodeficiency virus infection
PTE	Pulmonary thromboembolism
PR	Prevalence ratio
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RE	Random-effect
ROB	Risk of bias
RR	Risk ratio
RT-PCR	Reverse transcription polymerase chain reaction
RWE	Real-world evidence
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SLR	Systematic literature review
VA	Veterans Affairs
WHO	World Health Organization

Executive summary

Whilst it is well established that COVID-19 vaccination protects against severe outcomes of acute SARS-CoV-2 infection, such as hospitalisation and death [1,2], there is still uncertainty as to whether vaccination also reduces the risk and/or duration of a wide range of post-acute COVID-19 symptoms, commonly referred to as 'long COVID'. Assessment of evidence is complicated by the wide range of qualifying symptoms, minimum symptom durations and time-since-infection criteria used to define 'long COVID' in observational studies. In response, the World Health Organization (WHO) has established consolidated clinical case definitions for post-acute COVID-19 symptoms in adults [3] and children/adolescents [4], applying the specific terminology 'post COVID-19 condition' (PCC), to support harmonised reporting on post-acute COVID-19 outcomes. Determining whether COVID-19 vaccination reduces the risk and/or duration of PCC may critically inform decision-making on public health interventions to reduce the burden of COVID-19 disease.

This rapid review addressed the following research questions:

1. Does COVID-19 vaccination reduce the risk of developing PCC?
2. Does COVID-19 vaccination reduce the duration of PCC?

The review was conducted in accordance with Cochrane methods guidance for rapid reviews of effectiveness [5], applying the following restrictions to scope: i) limiting the population to individuals who experienced PCC as defined by WHO [3,4]; ii) focusing on studies taking place in Europe or comparable contexts; iii) limiting to vaccines authorised by the European Medicines Agency (EMA) at any point in time; iv) focusing only on comparisons of full course vaccination prior to SARS-CoV-2 infection with no vaccination; v) restricting the timing of publications to after October 2021, to align with the timing of the WHO PCC case definition; and vi) focusing only on published articles and articles-in-press.

Electronic databases (EMBASE, MEDLINE, PubMed, MEDLINE In-Process and the Cochrane Database of Systematic Reviews [CDSR]) were searched for relevant publications. Additional searches were also carried out, including Google Scholar, reference lists of previously published systematic literature reviews (SLRs), relevant literature repositories, and websites of selected organisations. Data extraction was completed for relevant articles identified via title and abstract screening, and subsequent full-text review of articles to assess adherence to predefined inclusion and exclusion criteria. Risk of bias (ROB) scores were derived for included studies, applying the Newcastle-Ottawa scale (NOS) to assess the quality of cohort and case control studies, and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies. ROB scores resulted in the following possible classifications: 'low', 'medium' or 'high'.[1]

A total of 4 303 records were identified through electronic database searches, with 3 342 of these records screened at the title and abstract stage following removal of duplicates. This resulted in 179 publications being assessed for eligibility based on their full texts, of which 171 were excluded. In addition, 227 potentially relevant records were identified via other search methods, and upon further review, 223 of these publications were excluded. Taken together, a total of 12 studies addressing the two research questions of interest were included. Eleven studies assessed whether COVID-19 vaccination reduces the risk of PCC, and one study assessed whether COVID-19 vaccination reduces both the risk and duration of PCC.

Of the 12 studies assessing whether COVID-19 vaccination reduces the risk of PCC, nine assessed risk for general adult populations (ROB: low 7, medium 1, high 1), two assessed risk for immunocompromised adult populations (ROB: low 1, high 1) and one assessed risk for a general child/adolescent population (ROB: high). For general adult populations, six studies assessed as having low ROB found that full vaccination prior to infection had a statistically significant effect on reducing PCC compared to no vaccination. These studies represented a range of recruitment settings (including both community and hospital settings), time period of infection (and consequently SARS-CoV-2 variant), as well as acute COVID-19 disease severity. For immunocompromised populations, one community-based study of adults living with HIV was assessed as having low ROB and reported no statistically significant difference between risk of developing PCC symptoms between vaccinated and unvaccinated groups. For child/adolescent populations, no studies were assessed as having a low ROB. Factors affecting the interpretation of studies assessed as having medium or high ROB included: i) comparability of cohorts in studies, specifically that results were not adjusting for confounding factors that may have affected the outcomes reported; and ii) reporting of follow-up – that some studies did not specify whether any of the participants initially selected were lost to follow-up. In addition, two of the three studies which did not find that vaccination reduced PCC had small sample sizes, particularly where symptoms were assessed in sub-group analyses. Furthermore, timing of vaccination prior to SARS-CoV-2 infection was not reported across all studies.

A meta-analysis of comparable studies assessing whether COVID-19 vaccination reduces the risk of PCC for general adult populations was conducted to generate a pooled effect estimate. Four studies of sufficient quality (ROB: low)

[1] For the purposes of this rapid review and to align with ECDC terminology, the report has adopted the term 'risk of bias' and categorised studies as 'low,' 'medium', and 'high'. These criteria align with the NOS recommended wording of 'good', 'fair', and 'poor' respectively. For JBI, these criteria align with the overall appraisal scoring of 'include', 'exclude' and 'seek further information'.

were included. Using a random-effects model, the pooled adjusted odds ratio (OR) was 0.73 (95% CI: 0.62–0.85), suggesting that full vaccination prior to acute infection could reduce the risk of PCC by 27% relative to no vaccination for general adult populations.

With regard to duration, no longitudinal studies were identified that evaluated the persistence of PCC symptoms in a defined PCC cohort at multiple time points (e.g. at 6, 12, 18 and 24+ months). However, one study (ROB: low), sampling from an adult hospitalised population, which categorised PCC to major physical symptoms (MPS) or major neuropsychological symptoms (MNS), evaluated persistence of PCC symptoms at 12- and 18-months post discharge. While results indicated that vaccination may reduce the duration of MPS, no effect was found for MNS. However, interpretation of these findings is challenging due to limited sample size.

In conclusion, a review of available literature indicates that, in general adult populations of mixed disease severity, vaccination offers some degree of protection against PCC onset, aligning with findings from previous reviews into this area of research. This indicates that vaccination offers additional benefits beyond protecting against severe acute outcomes of SARS-CoV-2 infection for this population. There were insufficient well-designed studies to draw specific conclusions as to whether COVID-19 vaccination reduces the risk of PCC for general child/adolescent or immunocompromised populations. Furthermore, there were insufficient well-designed studies to assess if vaccination reduces PCC symptom duration. This review highlights the ongoing need for further studies evaluating PCC that consistently apply the WHO case definitions.

1. Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronavirus that causes coronavirus disease 2019 (COVID-19). The most common symptoms of acute COVID-19 are fever, chills, a sore throat, loss of smell (anosmia) or taste (ageusia), and shortness of breath, although the disease is characterised by a range of symptoms, which can make it difficult to distinguish COVID-19 from other respiratory illnesses [6]. Although most individuals experience mild symptoms that do not require medical attention, COVID-19 can cause serious illness and death, particularly in people over 60 years, pregnant women, and individuals with underlying health conditions, including obesity and diabetes, individuals with compromised immune systems, and heart disease [7,8].

SARS-CoV-2 was first identified in late 2019 and spread quickly across the globe before being declared a global pandemic by the World Health Organization (WHO) on 11 March 2020 [9]. Following its rapid spread, SARS-CoV-2 caused widespread global disruption in the form of travel and trade restrictions, national lockdowns, widespread prevention measures such as social distancing and requirements to wear personal protective equipment in public settings, and disruptions to a range of everyday activities. As of February 2025, over 777 million confirmed cases and more than 7 million confirmed deaths globally due to COVID-19 had been reported to WHO. In Europe alone, there were over 281 million cases and over 2 million deaths reported — although it is widely accepted that the true number of cases and deaths is far higher than reported [10,11]. International efforts to control the pandemic led to the development of vaccines that have been effective in protecting people from severe illness, and widespread vaccination helped countries to lift their non-pharmaceutical prevention measures, with an estimated 13.8 billion doses administered globally as of June 2024 [12].

The global deployment of COVID-19 vaccines, and their impact on reducing deaths and the burden of the disease on health systems, contributed to the decision to end classification of COVID-19 as Public Health Emergency of International Concern (PHEIC) by WHO on 5 May 2023 [13]. However, despite this declaration, circulation of SARS-CoV-2 has continued, and COVID-19 remains a key public health concern, and it is expected to remain so for the foreseeable future. In its declaration, WHO warned that the disease continues to cause epidemics of acute illness, and that millions of people continue to experience debilitating effects from post-COVID-19 condition (PCC) [13].

A wide range of long-term effects have been reported following infection with SARS-CoV-2, including a myriad of symptoms and syndromes, often referred to as 'long COVID' [14]. In September 2020, WHO established International Classification of Disease (ICD) codes to facilitate documentation of clinical sequalae following SARS-CoV-2 infection [15]. In response to the wide range of symptom constellations included in varying definitions for 'long COVID' [14], WHO established a Delphi consensus process, engaging an international panel of 265 patients, clinicians, researchers and WHO staff to develop a consolidated clinical case definition in October 2021, applying the specific terminology 'post COVID-19 condition':

> 'Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, **usually 3 months from the diagnosis of COVID-19 with symptoms that last for at least 2 months** and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children [3].'

Following a systematic literature review (SLR) and expert consensus consisting of 27 participants, WHO subsequently published a PCC definition for children and adolescents in February 2023:

> 'Post COVID-19 condition in children and adolescents occurs in individuals with a **history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19.** Current evidence suggests that symptoms more frequently reported in children and adolescents with post-COVID-19 condition compared with controls are **fatigue, altered smell/anosmia and anxiety.** Other symptoms have also been reported.[2] Symptoms generally have an impact on everyday functioning such as changes in eating habits, physical activity, behaviour, academic performance, social functions (interactions with friends, peers, family) and developmental milestones. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. They may also fluctuate or relapse over time [4].'

While the terms PCC and 'long COVID' may be used interchangeably in the media and scientific literature, 'long COVID' is much more variable, with a wide range of qualifying symptoms, minimum symptom durations and time-since-infection criteria used. Critically, the WHO clinical case definitions for PCC offer a clear distinction from symptoms typical of post-viral fatigue, which occur following infection with a wide range of viral pathogens and typically resolve within three months [3,4,16].

[2] These symptoms could include chest pain, cognitive difficulties, cough, diarrhoea, dizziness, dyspnoea, earache/ringing in ears, fever, headache, insomnia, joint pain or swelling, light sensitivity, loss of appetite, mood swings, myalgia, nausea, palpitations, postural symptoms, rash, stomach aches, and sore eyes or throat.

Estimates of the proportion of people who develop post COVID-19 condition can differ substantially between studies because of varying study designs and populations [17]. While most patients with COVID-19 return to their prior health state after acute infection, approximately 5–20% of people are estimated to experience persistent or new onset symptoms after three months following SARS-CoV-2 infection [17–20]. Although the protection offered by COVID-19 vaccines in protecting individuals from serious acute illness and death is well understood, further insight is required into the extent to which COVID-19 vaccines protect against PCC.

2. Methodology

2.1 Research questions and PICOS

This rapid review addressed the following research questions:

1. Does COVID-19 vaccination reduce the risk of developing PCC?
2. Does COVID-19 vaccination reduce the duration of PCC?

The rapid review was conducted in accordance with Cochrane methods guidance for rapid reviews of effectiveness [5], applying the following restrictions to scope:

- Limiting the population to individuals who had experienced PCC that aligned strictly with the WHO case definition, to ensure both comparability between studies and to remove studies that potentially categorised prolonged acute COVID-19 symptoms as PCC;
- Focusing primarily on studies conducted in European or comparable settings, as well as on vaccines that were authorised by the EMA, to ensure that only studies applicable to geographies of interest to ECDC were included;
- Ensuring only completion of at least primary course vaccination (e.g. two doses of a two-dose regimen), or 'full vaccination', prior to SARS-CoV-2 infection was compared with no vaccination, to focus on the specific role that vaccination prior to infection could have in protecting against PCC. Therefore, for this review, results reported for intervention and control groups that had been partially vaccinated, and those where vaccination took place after the acute infection, were excluded;
- Restriction of the timing of publications from October 2021 to August 2024, to align with the timing of the publication of the WHO PCC case definition in October 2021; and
- Focusing only on published articles and articles-in-press to ensure that only results that had been peer-reviewed were included in the final analysis.

Elements of the research question are presented in the PICOS framework in Table 1. Further details on the specific inclusion and exclusion criteria can be found in Annex A.

Table 1 PICOS Framework for the rapid review

PICOS	Criteria
Population	Humans (all ages) with confirmed SARS-CoV-2 diagnosis*, with and without PCC, as defined by the WHO case definition. Stratification by age, sex and COVID-19 disease severity (where available).
Intervention	Full COVID-19 vaccination prior to acute infection with vaccines approved by the European Medicines Agency (EMA) at any point in time, and/or booster COVID-19 vaccinations following a full course of COVID-19 vaccination of vaccines approved by the EMA.
Comparator	No COVID-19 vaccination (excluding partial vaccination)
Outcomes	Diagnosis of PCC; duration of PCC.
Study type	Prospective and retrospective population-based cohort study designs; analytical cross-sectional studies; case-control studies. Animal studies, individual case studies, non-peer-reviewed studies were excluded.
Time frame	October 2021 to August 2024
Language	No restriction.
Geography	Studies reporting from European and comparable settings (Australia, Canada, New Zealand, and the United States).

**Focus on individuals at least three months after confirmed (PCR or rapid antigen test) SARS-CoV-2 infection and with symptoms persisting or recurring for at least two months, as per the WHO clinical case definitions for post-COVID-19 condition.*

2.2 Sources of evidence

The following electronic databases were searched:

- EMBASE (via EMBASE.com [Elsevier])
- MEDLINE (via EMBASE.com)
- MEDLINE/PubMed (via PubMed [US National Library of Medicine])
- MEDLINE In-Process (via PubMed)
- Cochrane Database of Systematic Reviews (CDSR; via Cochrane Library)

Electronic database search strategies were validated according to the PRESS Peer Review of Electronic Search Strategies guideline statement [21]. Details of the search strategies used in this review can be found in Annex B. In addition to searches of the electronic databases, searches of additional sources were conducted, including Google Scholar, reference lists of systematic literature reviews (SLRs), relevant literature repositories, and websites of selected organisations. The citation index Google Scholar was searched using combinations of terms relating to post-COVID condition, COVID-19 vaccine terms, and relevant outcome terms with, in each case, the first 25 records retrieved screened and details of each search documented.

Specialised COVID-19 and vaccine literature repositories were searched, as listed in Table 2, and materials from websites of relevant organisations were searched, as shown in Table 3.

Table 2. Specialised COVID and vaccine literature repositories searched

Website name and organisation	URL	Search terms and/or filters applied	No. of records	Date searched
COVID-19 Living Overview of Evidence (COVID-19 L·OVE) repository – Advanced search Epistemonikos Foundation	https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d/advanced-search	('long covid' OR 'post-covid condition' OR pcc) AND (vaccine OR vaccination OR immunization OR immunize) AND (duration OR 'duration of illness' OR incidence)	103	21 August 2024
COVID-END Inventory of Evidence Syntheses McMaster Health Forum	https://www.mcmasterforum.org/networks/covid-end/covid-end-inventory	Search terms: 'long COVID' OR 'post-COVID condition' OR PCC Filter: Search all syntheses	17	16 August 2024
iSearch COVID portfolio National Institutes of Health (NIH)	https://icite.od.nih.gov/covid19/search/	Search terms: 'post-COVID condition' AND incidence AND (vaccine OR vaccination OR immuniz*) Filters: Observational study	26	21 August 2024
VIEW-Hub International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health	https://view-hub.org/vaccine/covid/effectiveness-studies?field_outcomes_table=65711	Filters: Vaccine effectiveness studies; long COVID filter	2	16 August 2024

Table 3. Organisation websites searched

Organisation or website name	URL	Search terms and/or filters applied	No of records	Date searched
COVID-END McMaster University	https://www.mcmasterforum.org/networks/covid-end/covid-end-evidence-syntheses/scan-evidence-products	List of evidence products was screened	4	23 August 2024
RECOVER COVID Initiative	https://recovercovid.org/publications	List of publications was screened	2	23 August 2024

2.3 Screening of the literature

A bibliographic database of all retrieved citations was constructed using Zotero® reference management software. Duplicate publications were identified and removed. Only studies summarised in published articles or in articles-in-press were included, while pre-prints, conference abstracts, editorials and letters were not included in the review.

A single reviewer screened articles at the title/abstract and full-text screening steps. A second reviewer validated screening results by reviewing 20% of screened articles, selected at random. Any discrepancy between the reviewers was resolved through discussion. No language restrictions were applied.

2.4 Extraction of studies and quality assessment

Once the screening of titles and abstracts, and the full-text review of articles was completed, data extraction was undertaken using a pre-defined Excel® template. Extraction was performed by a single reviewer, with 20% of extracted articles validated by a second reviewer. Disagreements were resolved with a third reviewer.

The following quality assessment tools were used to assess risk of bias (ROB):[3]

- The Newcastle-Ottawa scale (NOS) was used for retrospective and prospective cohort studies, as well as case control studies [22].
- The Joanna Briggs Institute (JBI) Critical Appraisal checklist was used for cross-sectional studies [23].

ROB scores resulted in the following possible classifications: 'low, 'medium' or 'high'.

2.5 Meta-analysis

Following extraction and quality assessment, a feasibility assessment was conducted to assess the extent to which results from the included studies could be pooled to provide an overall estimate of the role of COVID-19 vaccination on PCC. More specifically, each study population and outcome measure was reviewed to identify alignment across studies (Annex E). Regarding outcome measures, both the measurement of PCC (including definition and timing) and the measurement used to conduct the comparator analysis (e.g. OR or HR, adjusted or univariate) were assessed. The intervention, comparators, and geography were not considered to be differentiating factors between studies, as they were assumed to be sufficiently comparable, given the review eligibility criteria.

For the included results, pooled results were produced using standard frequentist meta-analyses methods, with both fixed- (FE) and random-effect (RE) models being fitted. The meta-analyses were performed using the *meta* R package, approved by Cochrane [24,25]. Further details of the methodology used for the meta-analysis is provided in Annex E.

[3] For the purposes of this rapid review and to align with ECDC terminology, the report has adopted the term 'risk of bias' and categorised studies as 'low,' 'medium', and 'high'. These criteria align with the NOS recommended wording of 'good', 'fair', and 'poor' respectively. For JBI, these criteria align with the overall appraisal scoring of 'include', 'exclude' and 'seek further information'.

3 Results

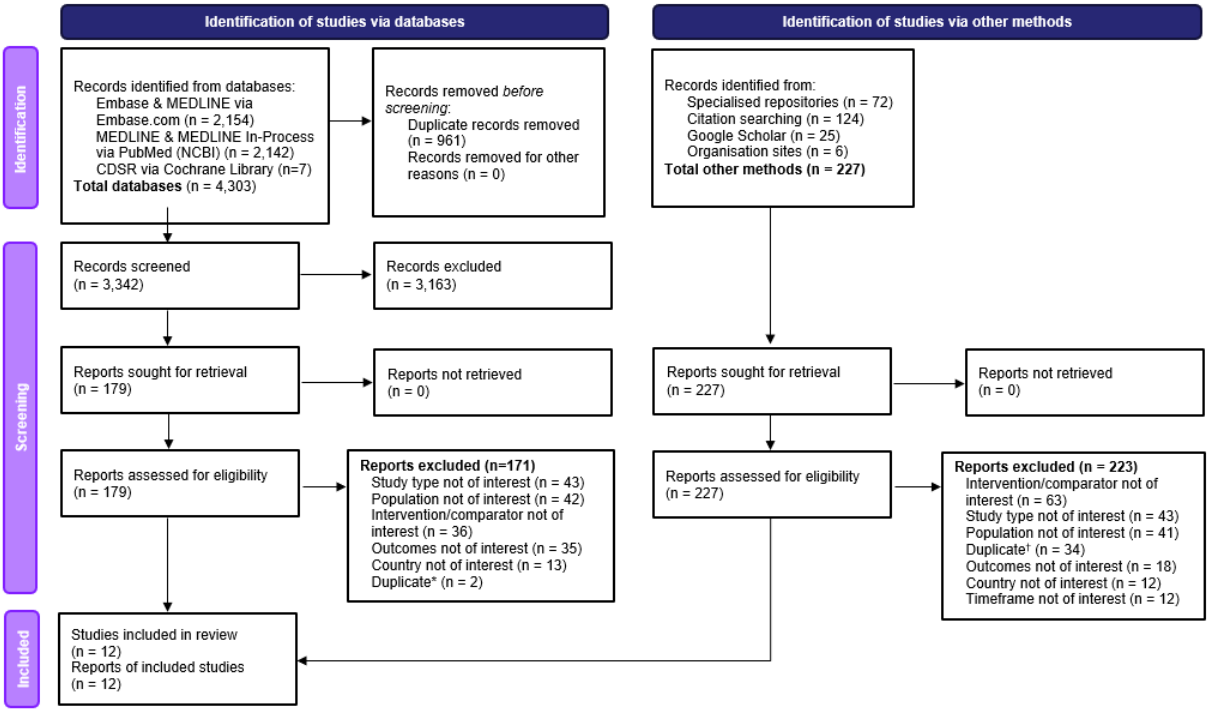
3.1 Identification of included studies

A PRISMA diagram showing the flow of records through each stage of the literature identification and selection process is presented in Figure 1.

A total of 4 303 records were identified through electronic database searches. Following de-duplication, 3 342 unique records were screened at the title and abstract stage according to pre-specified eligibility criteria. This resulted in 179 publications being assessed for eligibility at the full-text review stage, of which 171 were excluded. The most common reasons for exclusion were study type not of interest (n=43), population not of interest (n=42) and intervention/comparator not of interest (n=36) (Annex C). Two publications were excluded as duplicates, as they had already been identified and screened as part of the additional searches via other methods. There were eight studies (from eight reports) included from the electronic database searches.

In addition, 227 potentially relevant records were identified via other search methods of specialised repositories, organisation sites, screening of reference lists from previous reviews, and Google Scholar. Upon further review of the full texts, 223 publications were excluded, mainly due to the intervention/comparator not being of interest (n=63), study type not of interest (n=43) and population not of interest (n=41). There were three studies (from three reports) included from additional searches. Taken together, this rapid review included a total of 12 studies that addressed the two research questions of interest.

Figure 1. PRISMA flow diagram



Abbreviations: CDSR: Cochrane Database of Systematic Reviews; NCBI: National Center for Biotechnology Information.

**Screening of records from electronic databases and other search methods occurred in parallel. For database screening, duplicate records refer to those that had been screened as part of the other search methods.*

***Screening of records from electronic databases and other search methods occurred in parallel. For screening of records identified through other methods, duplicate records refer to those that had been screened as part of the electronic database screening or those previously identified in other search methods.*

Among the publications that were excluded because the reported population did not meet the eligibility criteria (n=83, including 42 from database searches and 41 from additional searches), 78 studies were excluded due to misalignment with the WHO definition of PCC (see Annex C for full list of excluded studies). In addition, there were 99 studies excluded because the reported intervention or comparator did not meet the eligibility criteria (36 from database searches and 63 from additional searches). Further details regarding reasons for exclusion are provided in Table 4.

Table 4. Summary of exclusions by population and intervention/comparator criteria

Overall reason for exclusion, per PICO		Detailed reason for exclusion			
PICO	**No. of studies***	**Category**	**No. of studies**	**Detail**	**No. of studies**
Population not of interest	83 (Databases search: 43 Other search methods: 41)	PCC definition in the study did not align with the WHO definition	78	Different timepoint after infection used	44
				Did not include information on the duration of symptoms	26
				Symptoms persisted for less than two months	2
				Study did not define PCC	6
		Other	5	Not all patients had COVID-19	4
				Patients did not have confirmed COVID-19	1
Intervention/ comparator not of interest	99 (Databases search: 36 Other search methods: 63)	Incomplete reporting of vaccination status	37	No information reported on vaccination status	29
				Number of doses in the intervention group unclear	6
				Number of doses in the comparator group unclear	2
		Partial vaccination status	31	Intervention group included those with partial vaccination	24
				Comparator group included those with partial vaccination	7
		Vaccination timing relative to infection did not align	23	Some or all participants were vaccinated after infection	18
				Unclear whether vaccination occurred prior to infection	5
		Other	8	Total cohort unvaccinated	3
				Total cohort vaccinated	2
				Ineligible vaccine	2
				Dietary supplement as intervention, not vaccine.	1

**The reported number of studies includes those identified through both electronic database searches and other search methods.*
Abbreviations: COVID-19: coronavirus disease 2019; No.: number; PCC: post-COVID-19 condition; PICO: Population, Intervention, Comparator, Outcomes; WHO: World Health Organization.

3.2 Summary of study, participant characteristics and intervention characteristics

3.2.1 Study characteristics

The rapid review included 11 studies that assessed whether COVID-19 vaccination reduces the risk of PCC, and one study that assessed whether COVID-19 vaccination reduces both the risk and duration of PCC.

Studies that used a retrospective design were the most common (n=6) [26–31], followed by prospective studies (n=5) [32–36], while one study [37] used a cross-sectional design. Study locations varied, and included Italy (n=4), the USA (n=3), Poland (n=2), Norway (n=1), Greece (n=1), and the UK (n=1). Data sources included COVID-19 surveys (n=4), hospital cohorts (n=3), regional health databases (n=1), COVID-19 registries (n=1), real-world evidence (RWE) databases (n=1), data from a COVID-19 surveillance study (n=1), and disease-based cohorts (n=1). Study durations varied from seven to 39 months. Specific variants circulating at the time of infection included the ancestral strain of the SARS-CoV-2 virus (n=4), Delta (n=6), and Omicron (n=7), with two studies [27,36] assessing differences in the role of vaccines on PCC, based on the period during which specific variants were in circulation. Details of the study characteristics for the studies included are presented in Annex D.

3.2.2 Participant characteristics

Across the 12 included studies, a total of 94 834 participants were included in the analyses, comprising 10 638 in the intervention (fully vaccinated prior to infection) arms and 70 633 in the control (unvaccinated) arms. The participant groups assessed primarily consisted of adults with confirmed diagnoses of COVID-19. Only one study by Morello et al. (2023) focused specifically on paediatric participants [34]. For the studies in the adult populations, ages of included participants ranged from younger adults (e.g. Perlis et al. 2022, mean age 40.5 years) to elderly participants, (specifically Ranucci et al. (2023), mean age 66.3 years) [33,37]. Two studies conducted by Villa et al. (2024) and Degli Antoni et al. (2024) assessed immunocompromised populations, focusing on people with common variable immunodeficiency (CVID) and people living with human immunodeficiency virus (HIV) infection (PLHIV) respectively [29,31]. While only five studies explicitly cited the WHO definitions for PCC, all included studies provided data for COVID-19 symptoms persistent after a minimum of three months post-infection, with several extending beyond this. For example, Brunvoll et al. (2023) included individuals 3–15 months post-infection, and Ranucci et al. (2023) reported results after 12 and 18 months following initial SARS-CoV-2 infection [32,33]. Participants were generally excluded based on missing data (for example, missing vaccination data or incomplete follow-up), reinfection with SARS-CoV-2 or multiple positive tests during the study period, or pre-existing or unclear PCC symptoms.

Details of the participant characteristics for included studies are presented in Annex D.

3.2.3 Intervention characteristics

Among the 12 included studies, seven explicitly stated the vaccine name and/or vaccine type:

- In Ayoubkhani et al. (2022), participants were vaccinated with two doses at least 14 days prior to first test-confirmed infection and stratified by the type of vaccine: 2 287 participants were vaccinated with ChAdOx1 nCoV-19 (74%), 788 participants with BNT162b2 (25.5%) and 15 participants with mRNA-1273 (0.5%) [26].
- In Ioannou et al. (2022), 2 447 (3.6%) of participants in the study were vaccinated with two doses of BNT162b2 and mRNA-1273 before the date of infection. The authors excluded a small proportion of vaccine recipients (0.6%) who received the Ad26.COV2.S vaccine [30].
- In Brunvoll et al. (2023), participants received two or more doses of BNT162b2 and mRNA-1273 and were considered fully vaccinated 14 days after the second dose. Specific vaccines used within the sample were not reported, but they noted that 97% of vaccines administered in Norway were mRNA vaccines [32].
- In Morello et al. (2023), 146 children (89.6%) vaccinated with two doses of mRNA vaccine before SARS-CoV-2 infection, while 17 children (10.4%) vaccinated with three doses [34].
- In Degli Antoni et al. (2024), 52 PLHIV and diagnosed with PCC (35.9%) were fully vaccinated, having received three doses of the vaccines (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S) [29]. The vaccine ChAdOx1 nCoV-19 was exclusively used for the first and the second doses. In cases where Ad26.COV2.S was administered as the first dose, the second dose was considered as a booster. Therefore individuals in this group were considered fully vaccinated following the administration of the second dose.
- In MacCallum-Bridges et al. (2024), a study conducted in the USA, 1 311 respondents (27.9%) completed the initial vaccination 14 days after receiving their second dose. Respondents were vaccinated with ChAdOx1 nCoV-19, Ad26.COV2.S, mRNA-1273, BNT162b2, and/or CoronaVac vaccines (with the latter assumed to be low given its lack of authorisation in the USA). However, the number or proportion of participants receiving each vaccine was not provided [36]. For the Ad26.COV2.S vaccine, the series was considered complete 14 days after the first dose.
- In Villa et al. (2024), 59 participants with PCC (51.3%) received three doses of BNT162b2 at first infection and 17 participants (14.8%) received four doses [31].

For five studies that did not report the vaccine name and type, three only reported the vaccination status and sample size, while two reported the number of vaccine doses, vaccination status, and sample size. However, given the location of these studies and the vaccines approved in the countries, it was assumed that these would sufficiently align with EMA-approved vaccine to warrant inclusion in this review.

Detailed intervention characteristics of the included studies are presented in Annex D.

3.3. Quality assessment of studies

The quality of six retrospective cohort studies and five prospective cohort studies were assessed using the NOS [22]. The results of the quality assessment are summarised in Table 5 below.

Of the 11 studies evaluated using the NOS, seven were assessed to be of low ROB [26,27,29,30,33,35,36], one was medium ROB [32], and three were high ROB [28,31,34]. The main reason for the high ROB in Morello et al. (2023) was the use of univariate analysis for the OR of PCC, and, as a result, confounding factors were not accounted for in the analysis [34]. In Babicki et al. (2023), those vaccinated prior to infection and unvaccinated cohorts were compared to identify significant differences using basic descriptive statistics, but confounding factors were not adjusted for [28]. In Villa et al. (2024), the number of patients with PCC is reported, but it is unclear whether the OR uses the unvaccinated group as the reference group, and their analysis of whether vaccination reduces the risk of PCC does not control for potential confounding factors. In addition, the total sample size and the individual sub-sample sizes of the above groups were not equal [31]. For Brunvoll et al. (2023, which was rated as medium ROB, there was no statement provided on the adequacy of follow-up, selection of exposed cohorts from specific groups, and reliance on self-reported data [32]. Most studies (n= 9) [26−29, 31−33,35,36] assessed outcomes through self-reported assessments of symptoms, with only two studies using independent blind assessment and record linkage [30,34].

In addition, one cross-sectional study was assessed using the JBI Critical Appraisal checklist [23]. Perlis et al. (2022) used a non-probability sampling method, applying representative quotas to balance important factors [37]. They addressed the potential bias in the study's design, implementation and analysis by providing a detailed description of subjects and setting, ensuring valid exposure measurement, and implementing strategies for dealing with confounding factors (for example, through use of an adjusted OR to control for the effects of age, sex, predominant variant, and other key factors that may have affected the observed results). Overall, it was concluded that the study applied a rigorous methodology and thorough consideration of potential biases, meeting all of the checklist's criteria for low ROB research (Table 5).

Table 5. Quality assessment for included studies

First author & year	Selection	Comparability	Outcome/ exposure	Risk of bias
Cohort studies analysing vaccine effectiveness on reducing PCC diagnosis only				
Ayoubkhani 2022 [26]	★★★	★★	★★	Low
Ioannou 2022 [30]	★★★	★★	★★★	Low
Babicki 2024 [27]	★★★	★★	★★	Low
Degli Antoni 2024 [29]	★★★	★★	★★	Low
MacCallum-Bridges 2024 [36]	★★★	★★	★★	Low
Petrakis 2024 [35]	★★★	★★	★★	Low
Brunvoll 2023 [32]	★★★	★★	★	Medium
Villa 2024 [31]	★★	—	★★	High
Babicki 2023 [28]	★★★	—	★★	High
Morello 2023 [34]	★★★★	—	★★★	High
Cohort studies analysing vaccine effectiveness on reducing PCC diagnosis and duration				
Ranucci 2023 [33]	★★★	★★	★★	Low
Cross sectional studies analysing vaccine effectiveness on reducing PCC diagnosis only				
Perlis 2022 [37]	NA	NA	NA	Low

Abbreviations: NA: not applicable.

Note: In the NOS quality assessment, stars are used to rate the ROB of non-randomised studies based on three main categories: selection, comparability and outcome/exposure. A dash indicates that studies were assessed but did not receive any stars. For Perils et al. *(2022), outcomes were described as not applicable since the quality was assessed using the JBI.*

3.4 Summary of key study outcomes

3.4.1 Role of vaccination in reducing risk of developing PCC

A summary of the results from the studies assessing the role of vaccination on reducing PCC diagnosis and/or symptom onset is provided in Tables 6, 7 and 8 below. The proportions of participants in the sub-samples categorised as having some form of PCC ranged from 8.3% (122 of 1 311 participants) in the vaccinated cohort of MacCallum-Bridges et al. (2024), to 94% (90 of 96 participants) of the unvaccinated cohort in Ranucci et al. (2023) [33,36]. The variations in the proportions of participants with PCC between studies are probably driven by the specific populations being studied. For example, in studies of adults who had been hospitalised for acute COVID-19 (Ranucci et al. (2023) and Petrakis et al. [2024]) or immunocompromised individuals (Villa et al. (2024) and Degli Antoni et al. [2024]), proportions of participants suffering from PCC were typically higher than studies of broader populations from the community (i.e. with different levels of acute COVID-19 severity in the sample) [29,31,33,35].

Of the 12 studies that were included:

- Nine assessed risk of PCC in the general adult population (see Table 6), of which:
  - seven were assessed to have low ROB, six of which found that full vaccination prior to infection had a statistically significant effect on reducing PCC compared to no vaccination, while one found an adjusted odds ratio (OR) of less than one, but the value was not statistically significant [26,27,30,33, 35–37];
  - one study by Brunvoll et al. (2023) was assessed to have medium ROB, and reported inconclusive results on whether full vaccination reduced the risk of PCC, with results varying by the sub-set of symptoms analysed (see Table 6) [32]; and
  - one study by Babicki et al. (2023) was assessed to have high ROB and found no relationship between vaccination prior to acute infection and risk of at least one symptom of PCC. However, it should be noted that this study did find that vaccination prior to acute infection reduced the risk of headache (26.7% in vaccinated versus 29.4% in unvaccinated participants, p<0.001) and arthralgia (22.7% in vaccinated versus 10.3% in unvaccinated, p=0.03) [28].
- Two studies assessed the risk of PCC in the immunocompromised adult population, of which, one (Degli Antoni et al. [2024]) was assessed to have low ROB and one (Villa et al. (2024) was assessed to have high ROB. While the adjusted OR in Degli Antoni et al. (2024) and the univariate OR calculated by the authors of this review for Villa et al. (2024) are both less than one, neither of these studies show a statistically significant effect of full vaccination prior to acute infection on PCC (see Table 7).
- One study (Morello et al. [2023]) assessed the risk of PCC in children and was found to have a high ROB. In the sub-analysis from the study where different age cohorts were compared to unvaccinated cohorts, no statistically significant relationship was found in either of the analyses (see Table 8).

Regarding the studies in the general adult population that found a statistically significant effect of full vaccination on reducing PCC compared to unvaccinated controls, four reported these results based on adjusted ORs, one used adjusted hazard ratios (HRs) and one study assessed differences between groups using prevalence ratios (PRs). The number of participants with PCC in the vaccinated cohorts ranged from just six participants (24% of total sub-sample) after 18 months in Ranucci et al. (2023) to 321 (64.1% of total sub-sample) vaccinated participants with PCC in Petrakis et al. (2024), while the number of unvaccinated participants with some form of PCC ranged from 31 in one of the sub-samples of Ranucci et al. (2023) that assessed vaccine effectiveness against major neuropsychological symptoms (MNS), to 6 811 unvaccinated individuals in Ioannou et al. (2022) [30,33,35]. Adjusted ORs in the studies ranged from 0.59 (95% CI: 0.5–0.69) in Ayoubkhani et al. (2022) to 0.78 (95% CI: 0.68–0.90) in Ioannou et al. (2022) [26,30].

The results in most studies did not vary in additional analyses carried out, including analysing results by vaccine types, specific sub-samples or in univariate analyses. The only exception to this was in Ioannou et al. (2022), where the univariate analysis OR had a 95% CI that could not confirm a significant effect existed (OR 0.92; 95% CI: 0.81–1.05) [30]. In Ranucci et al. (2023), HRs for both major physical and major neuropsychological symptoms were 0.30 (95% CI: 0.16–0.56) and 0.21 (0.11–0.39) respectively, suggesting that full vaccinations significantly reduced the risk of PCC 12 to 18 months after acute infection [33]. In MacCallum-Bridges et al. (2024), the full analysis of the sample suggested a PR of 0.43 (0.34–0.54) when comparing individuals vaccinated prior to infection with those that were unvaccinated, and these results also aligned with the comparator analysis of sub-samples, as well as the univariate analyses [36]. In addition, when including individuals vaccinated after the initial infection in the reference group, vaccination prior to infection was shown to have a protective effect (PR 0.42, 95% CI: 0.34-0.53).

For the three studies in the general adult population that found inconclusive results or no relationship between full vaccination and PCC, two reported adjusted ORs and one reported size effects based on the chi-squared statistic. The number of vaccinated participants with PCC across these studies varied from 40 (11.% of total sub-sample) in the Brunvoll et al. (2023) analysis of individuals with dyspnoea to 962 (60.5% of total sub-sample) in Babicki et al. (2024) [27,32]. For the unvaccinated cohorts, participants with PCC ranged from 127 (12% of total sub-sample) in the Brunvoll et al. (2023) analysis of participants with dyspnoea to 320 (30.2% of total sub-sample) in the same study's analysis of participants with fatigue [32]. The adjusted ORs ranged from 0.88 (95% CI: 0.69–1.14, p=0.34) in the

Babicki et al. (2024) study that analysed PCC symptoms for at least three months after initial infection to 1.91 (95% CI: 1.07–3.34, p=0.03) for the analysis reported in Brunvoll et al. (2023) of persistent memory problems at least three months after initial infection [27,32]. In the latter study, the vaccinated cohort was included as the reference group, meaning that the base case analysis of memory problems suggested that vaccination had a positive effect on reducing symptoms. However, this was only observed when hospitalised individuals were included in the analysis; when excluding individuals that were hospitalised during the acute phase of COVID-19, the adjusted OR for persistent memory problems was no longer significant (OR 1.5, 95% CI: 0.83−2.84) [32]. No significant differences between these groups were observed for the other symptoms assessed. In Babicki et al. (2023) differences between the vaccinated group prior to infection, vaccinated after infection, and unvaccinated groups were not found when the authors used the definition of at least one symptom being present 12 months after acute infection. In addition, no significant relationships were found for individual symptoms, with the exception of differences in the proportions of headache (26.7% versus 29.4% in vaccinated versus unvaccinated participants, p<0.001) and arthralgia (22.7% in vaccinated versus 10.3% in unvaccinated, p=0.03) [28]. In Babicki et al. (2024), the overall results did not change when considering only the pre-Omicron or Omicron dominance period [27].

Two studies analysed immunocompromised cohorts (one including participants with HIV, one including participants with CVID) [29,31]. Sample sizes for vaccinated individuals with PCC varied from 17 (58.6% of total sub-sample vaccinated with four doses) in Villa et al. to 59 (65.5% of total sub-sample) in the sub-sample vaccinated with three doses in the same study [31]. For the unvaccinated cohorts, sample sizes ranged from 31 (72.1% of the total sub-sample) in Villa et al. (2024) to 89 (37.7% of the total sub-sample) in Degli Antoni et al. (2024) [29,31]. Regarding the comparator analysis in Degli Antoni et al. (2024), the base case adjusted OR was 0.92 (95% CI: 0.6−1.42, p=0.72), suggesting that although the adjusted OR was less than one, the relationship was not found to be statistically significant [29]. The results in this study did not differ between the univariate analysis and the adjusted analysis. In Villa et al. (2024), the proportion of individuals with CVID that suffered from PCC was lower in the cohorts that were vaccinated with three (n=59, 65.5%) or four (n=17, 58.6%) doses compared to the unvaccinated group (n=31, 72.1%) [31]. However, in the comparator analysis in this study, the unvaccinated group was not set as the reference group when determining whether vaccination reduced PCC. Instead, univariate ORs were calculated that compared each individual sub-group with those not included in that sub-group. For example, the three dose sub-group was compared with those that did not receive three doses, which included unvaccinated groups as well as other individuals who received a different number of doses.

Given that the total sample size and the individual sub-sample sizes of the above groups were not equal, it is possible that individuals vaccinated with one or two doses were also included in the study. Because of these factors, it was not possible to conclude from the study that the comparator analysis matched this review's research question.[4] Using the reported sub-samples in each of the cohorts in the study, the authors of this rapid review have included the univariate analysis in Table 7 below, which suggests that while the ORs are lower than one for the analyses of both the three dose and four dose sub-groups, no statistically significant relationship could be found in either analysis. Similar conclusions were also drawn when combining both the three and four-dose vaccinated groups together (OR: 0.68, 95% CI: 0.32-1.47, p=0.33, not reported in the table). However, given that this analysis does not adjust for any potential confounding factors, it is difficult to draw definitive conclusions from these results.

Finally, in the Morello et al. (2023) study that analysed the role of full vaccination prior to acute infection in children, neither analysis of children aged 5–11 years (OR 0.6, 95% CI: 0.33–1.11, p=0.58) nor children aged 12-18 years (OR 1.4, 95% CI: 0.81–2.43, p=0.22) found the effect to be statistically significant [31]. However, given that neither analysis adjusts for any potential confounding factors, it is difficult to draw definitive conclusions from these results.

[4] For the analyses that were conducted in the study, the univariate analyses reported for each of the three above groups did not find that vaccination offered protection against overall PCC. The only significant relationship that was found was that four vaccines doses offered a protection against fatigue (OR 0.39, 95% CI: 0.17-0.92, p=0.03).

Table 6. PCC diagnosis by vaccination status across included studies assessing general adult populations (significant values indicated in bold)[5]

First author, year, overall population & variant(s)	Sub-group	Sample size – N	PCC		Comparator analysis			
			Definition	n (%)	Comparator metric	Factors adjusted	Value (95% CI)	p-value
Studies finding that full vaccination reduced key PCC symptoms relative to no vaccination in primary analysis								
Ranucci 2023 [33]* Population: Adults who had been hospitalised for acute COVID-19 Variant(s): NR ROB: *Low*	Vacc., total cohort	25	MPS (at least one of fatigue, fever, cough or dyspnoea) persisting 12 months after discharge. MPS	13 (50.0)	HR for the persistence of MPS after 12-18 months	Sex, BMI, hospital stay, ICU admission, obesity, comorbidities and treatment	**0.30 (0.16–0.56)**	**0.001**
	Unvacc., total cohort	96		88 (92.0)				
	Vacc., total cohort	25	MPS persisting 18 months after discharge.	6 (22.0)				
	Unvacc., total cohort	96		48 (50.0)				
	Vacc., total cohort	25	MNS (at least one of anxiety, new or worsening depression, memory dysfunction or 'brain fog') persisting 12 months after discharge. MPS	6 (24.0)	HR for the persistence of MNS after 12-18 months	Sex, BMI, hospital stay, ICU admission, obesity, comorbidities and treatment	**0.21 (0.11–0.39)**	**0.001**
	Unvacc., total cohort	96		90 (94.0)				
	Vacc., total cohort	25	MNS persisting 18 months after discharge.	6 (24)				
	Unvacc., total cohort	96		31 (32.0)				
MacCallum-Bridges 2024 [36] Population: Community-dwelling adults with mixed disease severity Variant(s): 96% of the vaccinated group, 18% of the full comparison group, 0% of the historical comparison group, and 56% of the concurrent comparison group were positive for COVID-19 during Delta and Omicron variant periods† ROB: *Low*	Vacc.	1 311	Persistent symptoms ≥three months after COVID-19 diagnosis.	122 (8.3)	IPTW adjusted prevalence ratio (PR) of prevalence of 90-day PCC	IPTWs to account for differences in age, sex, race and ethnicity, education level, employment status, health insurance coverage at time of illness, and residential rurality/urbanicity.	**0.43 (0.34–0.54)**	NR
	Unvacc. full comparison group	2 595		745 (28.7)				

[5] Values from the comparator analyses of less than one with a p-value of less than 0.05 suggest favourable outcomes to the intervention group (i.e. full vaccination) compared to the comparator group (no vaccination), with the exception of Brunvoll et al. (2023) where the vaccinated group was used as the reference group, meaning a value of greater than one and a p-value of less than 0.05 suggest favourable outcomes to the fully vaccinated group compared to the unvaccinated group.

First author, year, overall population & variant(s)	Sub-group	Sample size – N	PCC		Comparator analysis			
			Definition	n (%)	Comparator metric	Factors adjusted	Value (95% CI)	p-value
Ayoubkhani 2022 [26] Population: Community-dwelling adults with mixed disease severity Variant(s): For vaccinated participants, 98.9% were infected during the Delta period, while for the unvaccinated population 99.7% were infected by prior variants. ROB: *Low*	Vacc.	3 090	Symptoms of any severity at least three months after acute infection	294 (9.5)	Adjusted OR of PCC of any severity	Age, sex, ethnicity, country/ region of residence, area deprivation, pre-existing health/ disability status, time from infection to follow-up for PCC	**0.59 (0.5–0.69)**	NR
	Unvacc.	3 090		452 (14.6)				
Petrakis 2024 [35] Population: Adults who had been hospitalised for acute COVID-19 Variant(s): 54.6% and 45.4% of participants with PCC were infected with the Delta and Omicron variants respectively compared to 32.2% and 67.8% of patients without PCC. ROB: *Low*	Vacc., total cohort	523	Persistence of symptoms 6, 12 and 18 months after COVID-19 symptoms diagnosis and hospital discharge.	321 (64.1)	Adjusted OR of persistent PCC symptoms after 18 months	Age, sex, comorbidities, treatment and Omicron variant infection	**0.67 (0.35–0.99)**	**<0.001**
	Unvacc., total cohort	288		247 (85.8)				
Perlis 2022 [37] Population: Community-dwelling adults with mixed disease severity Variant(s): Ancestral: 57.0%; Delta: 17.6%; Omicron: 10.4%; Epsilon: 8.7%; Alpha: 6.2%. ROB: *Low*	Vacc., total cohort	2 243	Continued COVID-19 symptoms two months after initial first month of symptoms	249 (11.1)	Adjusted OR for PCC diagnosis	Age, sex, income, education, race, urbanicity, region and predominant variant	**0.72 (0.6–0.86)**	**<0.001**
	Unvacc., total cohort	13 434		2 052 (15.3)				
Ioannou 2022 [30] Population: Community-dwelling adults with mixed disease severity (Veterans) Variant(s): 65.0% of participants were infected during the third wave/Alpha variant ROB: *Low*	Vacc., total cohort	2 447	COVID-19 ICD-10 codes documented ≥three months after infection	263 (10.7)	Adjusted OR for documented PCC according to ICD-10 codes	Age, sex, race, ethnicity, urban vs rural residence, comorbidity, VA service, time of infection, no. of care encounters prior to infection	**0.78 (0.68–0.90)**	NR
	Unvacc., total cohort	58 693		6 811 (11.6)				

First author, year, overall population & variant(s)	Sub-group	Sample size – N	PCC		Comparator analysis			
			Definition	n (%)	Comparator metric	Factors adjusted	Value (95% CI)	p-value
Studies finding inconclusive results or no relationship between vaccination and PCC symptoms in primary analysis								
Babicki 2024 [27] Population: adults who had visited a medical centre due to COVID-19 symptoms with mixed disease severity Variant(s): 66.9% of participants infected during the pre-Omicron period ROB: *Low*	Vacc., whole period	1 590	Persistent PCC symptoms at least three months after initial infection	962 (60.5)	Adjusted OR	Age, sex, BMI, chronic disease, severity and Omicron period	0.88 (0.69–1.14)	0.34
	Unvacc., whole period	376		227 (60.4)				
Brunvoll 2023 [32] Population: Community-dwelling adults with mixed disease severity Variant(s): NR ROB: *Medium*	Vacc.	360	Persistent memory problems, reported at least three months after initial infection	43 (11.9)	Adjusted OR for memory problems	Age, sex, BMI, chronic disease and days since COVID-19	**1.91 (1.07–3.34)**	**0.03**
	Unvacc.	1 060		183 (17.3)				
	Vacc.	360	Persistent dyspnoea, reported at least three months after initial infection	40 (11.1)	Adjusted OR for dyspnoea	Age, sex, BMI, chronic disease and days since COVID-19	1.48 (0.77–2.85)	0.24
	Unvacc.	1 060		127 (12)				
	Vacc.	360	Persistent fatigue, reported at least three months after initial infection	110 (30.6)	Adjusted OR for fatigue	Age, sex, BMI, chronic disease and days since COVID-19	0.9 (0.56–1.43)	0.65
	Unvacc.	1 060		320 (30.2)				
	Vacc.	360	Persistent concentration problems, reported at least three months after initial infection	63 (17.5)	Adjusted OR for concentration problems	Age, sex, BMI, chronic disease and days since COVID-19	1.23 (0.72–2.1)	0.45
	Unvacc.	1 060		231 (21.8)				
Babicki 2023 [28]** Population: Adults who had visited a medical centre due to COVID-19 symptoms with mixed disease severity Variant(s): NR ROB: *High*	Vacc. prior to acute infection	75	Participants reporting at least one symptom 12 months after initial infection	47 (62.7)	Size effect based on chi-squared statistic, and including comparison between all three groups in study (vaccination prior to, after acute infection, and unvaccinated).	NA	0.022	0.82
	Unvacc.	136		91 (66.9)				

Abbreviations: BMI: body mass index; COVID-19: coronavirus disease 2019; HR: hazard ratio; ICD-10: International Classification of Diseases, 10th Revision; ICU: intensive care unit; IPTW: inverse probability of treatment weighting; MNS: major neuropsychological symptoms; MPS: major physical symptoms; N: number of participants; NR: not reported; OR: odds ratio; PCC: post-COVID-19 condition; PLHIV: people living with HIV; PTE: pulmonary thromboembolism; HIV; ROB: risk of bias; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VA: Veterans Affairs; Vacc: vaccinated; Unvacc: unvaccinated.

**In Ranucci et al. (2023), only percentages of participants with MPS and MNS were reported. However, these percentages do not align with the total sample size numbers, for example, see the vaccinated cohort percentage for PCC (50%) and the corresponding calculated absolute number of participants (13).*

***In Babicki et al. (2023), a chi-squared test was first performed to analyse whether there were differences in both the overall measurement of PCC (at least one persistent symptom reported after 12 months), and individual symptoms for the three groups (vaccinated prior to acute COVID-19, vaccinated after acute COVID-19, and unvaccinated). For those where a significant difference was found, a post-hoc analysis using the Bonferroni test was applied to assess whether significant pairwise differences existed between the groups (for example, vaccination prior to acute COVID-19 and unvaccinated only). Since no significant relationship was found for the overall PCC definition, a post-hoc analysis was not conducted.*

[7]This variant status refers to the entire comparator group (n=3 384), including respondents who received a COVID-19 vaccine after their COVID-19 onset. However, in the outcomes, the study restricted the analysis to comparator groups that only included respondents who never received a COVID-19 vaccine (n=2 595) to report that full vaccination reduced key PCC symptoms relative to no vaccination.

Table 7. PCC diagnosis by vaccination status across included studies assessing immunocompromised adults[6]

First author, year, overall population & variant(s)	Sub-group	Sample size – N	PCC		Comparator analysis			
			Definition	n (%)	Comparator metric	Factors adjusted	Value (95% CI)	p-value
Studies finding that full vaccination reduced key PCC symptoms relative to no vaccination in primary analysis								
No included studies								
Studies finding inconclusive results or no relationship between vaccination and PCC symptoms in primary analysis								
Degli Antoni 2024 [29] Population: Community-dwelling adults with HIV, with mixed disease severity Variant(s): 38.6% of participants infected during the pre-Omicron period; 61.4% infected during the Omicron period ROB: *Low*	Vacc. PLHIV	145	Persistent symptoms at least three months after initial infection	52 (35.9)	Adjusted OR	Age, sex, years of HIV infection, comorbidities, SARS-CoV-2 infection period, hospitalisation for COVID-19 and immune status	0.92 (0.6–1.42)	0.72
	Unvacc. PLHIV	236		89 (37.7)				
Villa 2024 [31] Population: Community-dwelling adults common variable immunodeficiency (CVID) with mixed disease severity Variant(s): 72.2% of participants were infected during the Omicron period ROB: *High*	Vacc. with 3 doses	90	Any persistent symptoms at least three months after initial infection	59 (65.5)	OR for vacc. (3 doses) vs. unvacc.	NA	0.74 (0.33-1.63)*	0.45
	Unvacc.	43		31 (72.1)				
	Vacc. With 4 doses	29		17 (58.6)	OR for vacc. (4 doses) vs. unvacc.		0.55 (0.20-1.48)*	0.24
	Unvacc.	43		31 (72.1)				

[6] Values from the comparator analyses of less than one with a p-value of less than 0.05 suggest favourable outcomes for the intervention group (i.e. full vaccination) compared to the comparator group (no vaccination).

Table 8. PCC diagnosis by vaccination status across included studies assessing children and adolescents[7]

First author, year, overall population & variant(s)	Sub-group	Sample size – N	PCC		Comparator analysis			
			Definition	n (%)	Comparator metric	Factors adjusted	Value (95% CI)	p-value
Studies finding that full vaccination reduced key PCC symptoms relative to no vaccination in primary analysis								
No included studies								
Studies finding inconclusive results or no relationship between vaccination and PCC symptoms in primary analysis								
Morello 2023 [34]* Population: Children and adolescents with mixed disease severity. Variant(s): Omicron: 57.8%; Delta: 22.1%; Alpha: 12.9%; Original: 7.1% ROB: *High*	Vacc., 5–11 years	82	Persistence of symptoms for at least three months after initial infection, which had a negative impact on daily life, and other possible diagnoses excluded	14 (9.4)	Odds ratio of PCC (at least three months, 2 or more doses v. unvaccinated)	NA	0.6 (0.33–1.11)	0.58
	Vacc., 12–18 years	76		40 (35.7)	Odds ratio of PCC (at least three months, 2 or more doses v. unvaccinated)		1.4 (0.81–2.43)	0.22

Abbreviations:
COVID-19: coronavirus disease 2019; HR: hazard ratio; N: number of participants; NR: not reported; OR: odds ratio; PCC: post-COVID-19 condition; ROB: risk of bias; Vacc: vaccinated; Unvacc: unvaccinated.

**In Morello et al. (2023), the number of unvaccinated individuals in each sub-group was not reported, and it was not possible to calculate these numbers based on the information provided in the study.*

[7] Values from the comparator analyses of less than one with a p-value of less than 0.05 suggest favourable outcomes for the intervention group (i.e. full vaccination) compared to the comparator group (no vaccination).

3.4.2 Role of vaccination in reducing duration of PCC

With regard to PCC duration, no longitudinal studies were identified that evaluated the persistence of PCC symptoms in a defined PCC cohort at multiple time points (for example, at 6, 12, 18 and 24+ months). Of the 12 studies included in the review, only one reported the duration of PCC according to vaccination status. The data from this study is presented in Table 9. More specifically, Ranucci et al. (2023) conducted a study in Italy using a cohort of 121 adult participants who had been hospitalised for acute COVID-19, comprising 96 unvaccinated (79.3%) and 25 vaccinated participants (20.7%) [33]. They followed the participants for 12 and 18 months after hospital discharge to evaluate the persistence of major physical symptoms (MPS) — a combination of fatigue, fever, cough, or dyspnoea, defined by the presence of one or more symptoms — and major neuropsychological symptoms (MNS), which included one or more of the following: anxiety, depression (new symptoms or worsening during hospitalisation), memory dysfunction, and brain fog. After 12 months of follow-up, a smaller proportion of vaccinated participants showed persistent MPS and MNS compared to unvaccinated participants (MPS: 52% versus 91.7%, MNS: 24% versus 93.8%). Similarly, at 18 months post-discharge, vaccinated participants experienced fewer MPS and MNS (MPS: 24% versus 50%, MNS: 24% versus 32.3%).

A specific comparator analysis was not conducted by the study authors to assess whether differences between groups were statistically significant [33]. To assess differences between groups, univariate ORs for both MPS and MNS at the different time points were calculated and are summarised in Table 9 below. As shown in the table, the differences between both groups for MPS were significant at 12 and 18 months, although the OR was higher at 18 months, suggesting that protection persisted to this time point, but was lower than at 12 months. For MNS, the OR was only significant at 12 months, while at 18 months no significant difference was found for the OR. This suggests that vaccination offered protection against MNS up to 12 months, but this protection did not continue up to 18 months. However, it is important to note that this analysis does not account for potential confounding factors, and that sample sizes were very low, particularly for the vaccinated populations. Consequently, results should be interpreted with caution.

Table 9. Duration of PCC by vaccination status

First author, year and overall population	PCC definition	Sub-group	N (%)	Univariate OR (95% CI)	P-value
Ranucci 2023 [33] **Population:** adults who had been hospitalised for acute COVID-19. **Variant: NR**	Persistence of MPS 12 months after hospital discharge	Vaccinated	13 (52)	0.1 (0.04–0.28)	<0.001
		Unvaccinated	88 (91.7)		
	Persistence of MPS 18 months after hospital discharge	Vaccinated	6 (24)	0.32 (0.12–0.86)	0.02
		Unvaccinated	48 (50)		
	Persistence of MNS 12 months after hospital discharge	Vaccinated	6 (24)	0.02 (0.01–0.07)	<0.001
		Unvaccinated	90 (93.8)		
	Persistence of MNS 18 months after hospital discharge.	Vaccinated	6 (24)	0.66 (0.24–1.82)	0.42
		Unvaccinated	31 (32.3)		

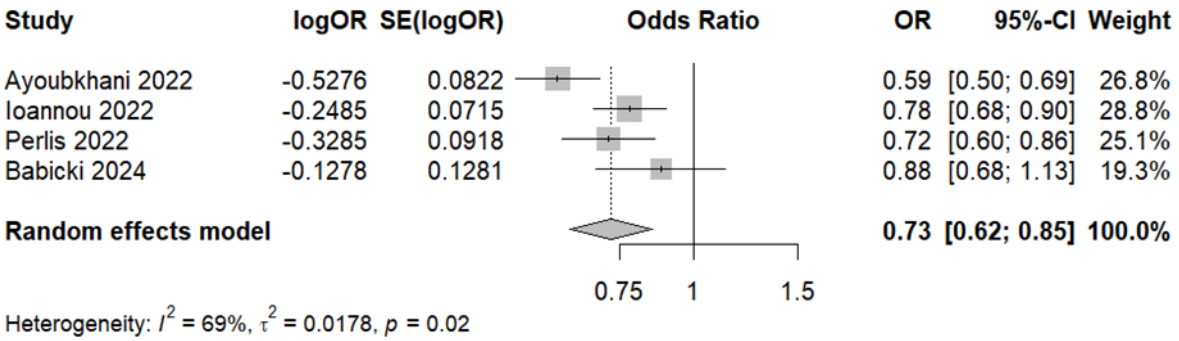
Abbreviations: CI: confidence interval; MNS: major neuropsychological symptoms; MPS: major physical symptoms; N: number of participants; NR: not reported; OR: odds ratio; PCC: post-COVID-19 condition.

3.5 Meta-analysis

A feasibility assessment was conducted to determine if it was appropriate to pool results from the included studies to derive a pooled estimate for the extent to which full vaccination prior to infection offers protection against PCC. Full details of the methodology can be found in Annex E. Based on the feasibility assessment, it was concluded that results from four studies could be pooled. Broad reasons for exclusion included misalignment on the outcome used (n=7), and misalignment on the population included (n=4), with some studies being excluded for multiple reasons. The studies that have been included are community-based studies, analysing the role of vaccination for reducing PCC lasting at least three months, with participants experiencing mixed severity of acute disease. All of these studies were assessed to be of sufficient quality (ROB: low), according to the NOS or JBI Critical Appraisal checklist. Three of these studies concluded that vaccination significantly reduced the risk of PCC and one did not find a significant relationship.

The summary of the base-case meta-analysis is provided in Figure 2 below. Given the relatively high heterogeneity observed between study results (as demonstrated by an I^2 statistic of 69%), the random effects approach was considered for this analysis. Based on this model, the meta-analysis provided a pooled adjusted OR of 0.73 (95% CI: 0.62–0.85), suggesting that full vaccination prior to acute infection could reduce the risk of PCC by 27% relative to no vaccination. When removing the Ioannou et al. (2022) study, which used ICD-10 codes to identify PCC as opposed to self-reported symptoms, the overall pooled results did not differ noticeably from the base case (see Annex E for further details).

Figure 2. **Forest plot of meta-analysis of adjusted ORs**



4. Discussion and conclusions

The objective of this review was to determine whether vaccination against COVID-19 prior to SARS-CoV-2 infection reduces the risk and duration of PCC, and ultimately support decision-making related to public health interventions to reduce the burden of COVID-19. By strictly applying the WHO clinical case definitions, the review sought to identify studies where overall findings could be interpreted appropriately, and avoid the challenges associated with interpreting previous reviews on the topic where a wide range of qualifying symptoms, minimum symptom durations and time-since-infection criteria are used (Table 22, Annex F) [38–42].

Of the 12 studies assessing whether COVID-19 vaccination reduces the risk of PCC, nine assessed risk for general adult populations (ROB: low 7, medium 1, high 1), two assessed risk for immunocompromised adult populations (ROB: low 1, high 1) and one assessed risk for a general child/adolescent population (ROB: high).

For general adult populations, six studies assessed as having low ROB found that full vaccination prior to infection had a statistically significant effect on reducing PCC compared to no vaccination. These studies represented a range of recruitment settings (including both community and hospital settings), time period of infection (and consequently SARS-CoV-2 variant), as well as acute COVID-19 disease severity. One study assessed as having low ROB, Babicki et al. (2024), did not find a statistically significant association. For the remaining two studies, one was assessed to have medium ROB and one was assessed to have high ROB, with these studies having either inconclusive results or finding no effect of vaccination on reducing PCC risk.

The findings from the studies of the general adult population that concluded that vaccination does reduce the risk of PCC are broadly aligned with the findings from seven previous SLRs, summarised in Table 22, Annex F. Of the seven reviews identified, two stated that they applied the WHO case definitions for PCC, although some of the studies included in these two reviews did not strictly adhere to this definition, while the remaining reviews applied a range of 'long COVID' definitions. However, all seven identified reviews concluded that full vaccination prior to contracting COVID-19 reduced the risk of subsequent post-acute COVID-19 symptoms. In addition, the findings from this review's base case meta-analysis of a sub-set of included studies (adjusted OR 0.73, 95% CI: 0.62–0.85) fall within the range of point estimates for ORs calculated in these previous reviews (see Annex F for further details).

For the two studies that assessed the role of vaccination in immunocompromised populations, one (Degli Antoni et al. (2024)) was assessed to have low ROB and one (Villa et al. (2024)) was assessed to have high ROB. In Degli Antoni et al. (2024), the authors found no statistically significant effect of vaccination on reducing the risk of PCC. However, the adjusted OR in this study was reported to be in favour of vaccination, and consequently had there been a larger sample, a statistically significant relationship may have been found. For Villa et al. (2024), the limitations in the study's reporting and lack of control for confounding factors make it difficult to draw definitive conclusions. Similarly, the one study in children/adolescents was assessed as having high ROB due to the lack of control for confounding factors. This, coupled with the small sub-samples included, means that it is not possible to conclude whether vaccination reduces PCC in this population.

With regard to PCC duration, no longitudinal studies were identified that evaluated the persistence of PCC symptoms in a defined PCC cohort at multiple sequential time points. One study included an assessment of whether PCC persisted between two time points, specifically Ranucci et al. (2023), which was assessed to have low ROB. This study found the proportion of patients suffering from both MPS and MNS was lower in the vaccinated group at 12 and 18 months. Based on the univariate analysis calculated by the authors of this review, the protection offered by vaccination against MPS persisted at both 12 and 18 months, while for MNS the protection was only significant at 12 months. Such findings should be interpreted with caution, given the low sample sizes and that the analysis does not account for potential confounding factors.

A key strength of this review is the employment of strict inclusion and exclusion criteria. All studies used the WHO definition of PCC and analysed the role a full course of EMA-approved COVID-19 vaccination prior to SARS-CoV-2 infection. This allowed the role of vaccination to be evaluated according to a consistently applied PCC definition. This differs from the SLRs that have previously been conducted, in which heterogeneity in the PCC definition makes it difficult to determine whether studies are analysing the same outcomes. In addition, the review includes a meta-analysis of a sub-set of the studies that were determined to be comparable. Key limitations include implementation of a rapid review — with restrictions to scope applied to increase relevance to the EU/EEA context — as opposed to an SLR. However, given the comprehensiveness of the search strategy within this specified scope, it is unlikely that potentially relevant studies for the EU/EEA context were not included.

In conclusion, this review has highlighted that, in general adult populations of mixed disease severity, vaccination offers some degree of protection against PCC onset, with an estimated 27% reduction in PCC risk compared to no vaccination. However, it is not possible to conclude that the same relationship applies to immunocompromised populations, or children and adolescents, due to a lack of data. Further research using the WHO PCC case definition for these populations and controlling for potential confounding factors would be beneficial to definitively conclude the role of vaccination in these groups. Additional studies to understand how COVID-19 vaccination prior to SARS-CoV-2 infection may reduce the duration of PCC are also warranted.

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Annex A. Inclusion and exclusion criteria

Table 10. Criteria for selection of eligible publications

Category	Inclusion criteria	Exclusion criteria
Population	Individuals of any age with confirmed diagnosis of SARS-CoV-2, with and without PCC as defined by the WHO case definition.	Individuals without a PCR or rapid antigen test confirmation of SARS-CoV-2. Individuals with PCC not defined using the WHO case definition.
Intervention	COVID-19 vaccinations that have received EU EMA approval at any point in time, where full course and/or full course with booster(s) has been received prior to SARS-CoV-2 infection	Partial COVID-19 vaccination, any non-vaccine intervention, or non-COVID-19 vaccination, full COVID-19 vaccination course not received prior to SARS-CoV-2 infection, COVID-19 vaccination with vaccines other than those that received EMA marketing approval in the EU
Comparator	No COVID-19 vaccination	COVID-19 vaccination
Outcomes	• Diagnosis of post COVID-19 condition • Duration of post COVID-19 condition.	Any other outcomes
Study type	• Prospective and retrospective population-based cohort studies • Analytical cross-sectional studies • Case-control studies.	• Animal studies • Individual case studies • Non-peer-reviewed studies.
Language	No restriction	
Timeframe	Publication date 1 October 2021 to present.	Any studies published prior to 1 October 2021.

Annex B. Search strategy

Search terms for EMBASE and MEDLINE via the Elsevier Embase platform (http://www.embase.com) are provided in Table 11. The search was conducted on 16 August 2024.

Table 11. Search terms and results from EMBASE and MEDLINE, searched using Embase.com

Search facets	No.	Query	Results
PCC terms	#1	'post covid condition' OR 'long covid'/exp OR 'long covid*' OR 'long hauler*' OR 'post covid disease' OR 'post-acute covid-19 syndrome' OR 'long covid symptoms' OR 'post-covid-19' OR 'post-acute covid-19 symptoms' OR 'covid-19 sequelae' OR 'covid sequelae' OR 'post covid*' OR 'post-acute sequelae of covid-19' OR 'post-acute sequelae of sars-cov-2 infection' OR 'long haul covid' OR 'chronic covid*' OR pc19s	21594
Symptom duration	#2	'duration of symptoms' OR 'remission of symptoms' OR 'course of symptoms' OR 'disappearance of symptoms' OR 'persistence of symptoms' OR 'symptom duration' OR 'symptom remission' OR 'symptom disappearance' OR 'symptom persistence' OR 'persistent symptom*' OR 'duration of illness' OR 'length of illness'	48060
	#3	'disease course' OR 'illness trajectory' OR 'disease clearance' OR 'duration, disease' OR 'disease duration'	751281
	#4	('long-term' OR continu* OR sustain* OR persist* OR extended) NEAR/2 symptom*	37035
	#5	'disease duration'/exp	211811
	#6	'illness trajectory'/exp	3347
	#7	'disease clearance'/exp	32207
	#8	'symptom'/de	173357
	#9	'complication'/de	411108
Symptom duration terms combined	#10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	1391808
PCC & symptom duration	#11	#1 AND #10	5144
COVID-19 vaccination terms	#12	'sars-cov-2 vaccine'/exp OR 'sars-cov-2 immuni*' OR 'sars-cov-2 vaccin*' OR 'covid-19 vaccin*' OR 'covid19 vaccin*' OR 'covid vaccin*' OR 'sars-cov2 vaccin*'	60890
	#13	(covid OR 'sars cov 2' OR 'sars cov2' OR '2019 ncov' OR 'coronavirus disease 2019' OR 'hcov 19' OR 'human coronavirus 2019' OR 'ncov 2019' OR 'novel 2019 coronavirus' OR 'sars coronavirus 2' OR sars2 OR 'severe acute respiratory syndrome 2') AND (vaccine OR vaccines OR vaccination OR vaccinations OR immunize OR immunization OR immunise OR immunisation)	99859
	#14	'mrna 1273' OR 'chadox1 s' OR 'chadox1 ncov-19' OR azd1222 OR ad26covs1 OR 'jnj 78436735' OR 'nvx cov2373' OR azd2816 OR vat00002 OR vat00008 OR novavax OR bnt162b2 OR spikevax OR comirnaty OR nuvaxovid OR covovax OR ad26.cov2.s OR 'vidprevtyn beta' OR 'vla2001' OR valneva OR vaxzevria OR jcovden OR bimervax OR vidprevtyn	17938
COVID-19 vaccination terms combined	#15	#12 OR #13 OR #14	101648
PCC & COVID-19 vaccination	#16	#1 AND #15	3730
PCC & symptom duration/PCC & COVID-19 vaccination	#17	#11 OR #16	7984
Observational & epidemiological study terms [43]*	#18	('cross sectional' NEAR/1 (study OR studies)):ti,ab	383141
	#19	(epidemiologic$ NEAR/1 (study OR studies)):ti,ab	36850
	#20	(observational NEAR/1 (study OR studies)):ti,ab	282882

Search facets	No.	Query	Results
	#21	('follow up' NEAR/1 (study OR studies)):ti,ab	83110
	#22	('case control' NEAR/1 (study OR studies)):ti,ab	177702
	#23	(cohort NEAR/1 (study OR studies)):ti,ab,kw	558490
	#24	'cohort analysis'/de	1200227
	#25	'prospective study'/de	931360
	#26	'retrospective study'/de	1660833
	#27	'longitudinal study'/de	218538
	#28	'family study'/de	26447
	#29	'case control study'	270946
	#30	'clinical study'/de	167956
	#31	'register'/exp OR registr*:ti,ab	582320
	#32	real NEAR/3 world	166173
	#33	'real world' NEAR/2 (data OR evidence OR research OR study OR studies OR trial*)	58786
	#34	hospital NEAR/3 record*	35626
	#35	claim* NEAR/3 (medical OR database*)	25637
	#36	'incidence'/de OR incidence:ti,ab OR incidences:ti,ab	1605041
	#37	'epidemiology'/de OR epidemiology:ti,ab OR epidemiologic:ti,ab OR epidemiological:ti,ab	820686
Observational & epidemiological terms combined	#38	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	6335474
PCC & symptom duration/PCC & COVID-19 vaccination - observational/epidemiological studies	#39	#17 AND #38	3844
Removal of non-human studies [44]	#40	#39 NOT ([animals]/lim NOT [humans]/lim)	3842
Date publication limit	#41	#40 AND [01-10-2021]/sd	3701
Restrict to articles or articles-in-press	#42	#41 AND ('article'/it OR 'article in press'/it)	2154

**Adapted from cited filter.*

Search terms for MEDLINE and MEDLINE In-Process (via PubMed; NCBI) are shown below in Table 12. The search was conducted on 16 August 2024.

Table 12. Search terms and results from MEDLINE and MEDLINE In-process, searched using PubMed

Search facets	No.	Query	Results
PCC terms	#1	("post-acute covid-19 syndrome"[MeSH] OR "post-covid syndrome" OR "long covid*" OR "long hauler*" OR "post covid disease" OR "post-acute covid-19 syndrome" OR "long covid symptoms" OR "post-covid-19" OR "post-acute covid-19 symptoms" OR "covid-19 sequelae" OR "covid sequelae" OR "post-acute sequelae of covid-19" OR "post-acute sequelae of SARS-CoV-2 infection" OR "long haul covid" OR "post covid*" OR "chronic covid*" OR PC19S)	16 128
Symptom duration terms	#2	("duration of symptoms" OR "remission of symptoms" OR "course of symptoms" OR "disappearance of symptoms" OR "persistence of symptoms" OR "symptom duration" OR "symptom remission" OR "symptom disappearance" OR "symptom persistence" OR "persistent symptom*" OR "duration of illness" OR "length of illness")	567 274
	#3	("disease course" OR "illness trajectory" OR "disease clearance" OR "duration, disease" OR "disease duration")	48 140
	#4	(("long-term" OR continu* OR sustain* OR persist* OR extended) AND symptom*)	288 272
	#5	"symptoms" OR "complications"	4 424 267
Symptom duration terms combined	#6	#2 OR #3 OR #4 OR #5	4 825 362
PCC and symptom duration	#7	#1 AND #6	8 419
COVID-19 vaccination terms	#8	"COVID-19 Vaccines"[MeSH Terms] OR "covid-19 vaccin*" OR "covid19 vaccin*" OR "covid vaccin*" OR "sars-cov2 vaccin*" OR "sars-cov-2 immuni*" OR "sars-cov-2 vaccin*"	41 775
	#9	(covid OR "sars cov 2" OR "sars cov2" OR "2019 ncov" OR "coronavirus disease 2019" or "hcov 19" OR "human coronavirus 2019" or "ncov 2019" OR "novel 2019 coronavirus" OR "sars coronavirus 2" OR sars2 OR "severe acute respiratory syndrome 2") AND (vaccine OR vaccines OR vaccination OR vaccinations OR immunize OR immunization OR immunise OR immunisation)	99 410
	#10	("mrna-1273" OR "chadox1 s" OR "chadox1 ncov-19" OR "azd1222" OR "jnj 78436735" OR "ad26.cov2.s" OR "ad26covs1" OR "bnt162b2" OR "nvx-cov2373" OR "azd2816" OR "vat00002" OR "vat00008" OR "novavax" OR "spikevax" OR "comirnaty" OR "nuvaxovid" OR "covovax" OR "vidprevtyn beta" OR "vla2001" OR "valneva" OR "vaxzevria" OR "jcovden" OR "bimervax" OR "vidprevtyn")	9 621
COVID-19 vaccination terms combined	#11	#8 OR #9 OR #10	100 592
PCC & COVID-19 vaccination	#12	#1 AND #11	3 543
PCC & symptom duration/PCC & COVID-19 vaccination	#13	#7 OR #12	9 893
Observational & epidemiological study terms [43]*	#14	"cross sectional study"[tiab:~1]	323 424
	#15	"cross sectional studies"[tiab:~1]	20 150
	#16	"epidemiologic study"[tiab:~1]	8 107
	#17	"epidemiologic studies"[tiab:~1]	23 802
	#18	"observational study"[tiab:~1]	170 058
	#19	"observational studies"[tiab:~1]	53 532
	#20	"follow up study"[tiab:~1]	55 383
	#21	"follow up studies"[tiab:~1]	19 918
	#22	"case control study"[tiab:~1]	121 540
	#23	"case control studies"[tiab:~1]	25 203
	#24	"cohort study"[tiab:~1]	355 670
	#25	"cohort studies"[tiab:~1]	45 217
	#26	"cohort studies"[mh:noexp]	345 313
	#27	"prospective studies"[mh:noexp]	694 443
	#28	"retrospective studies"[mh:noexp]	1 221 886
	#29	"longitudinal studies"[mh:noexp]	174 473
	#30	"case-control studies"[mh]	1 527 894
	#31	"registries"[mh] OR registries[tiab] OR registry[tiab]	248 126
	#32	"real world"[tiab:~3]	98 245
	#33	"hospital record"[tiab:~3]	2 565
	#34	"hospital records"[tiab:~3]	19 781
	#35	"claims medical"[tiab:~3]	4 623
	#36	"claims database"[tiab:~3]	7 906
	#37	"incidence"[mh:noexp] OR incidence[tiab] OR incidences[tiab]	1 108 544

Search facets	No.	Query	Results
	#38	"epidemiologic studies"[mh:noexp]	9 568
	#39	epidemiology[tiab] OR epidemiologic[tiab] OR epidemiological[tiab]	533 301
Observational & epidemiological study terms combined	#40	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	3 759 913
PCC & symptom duration/PCC & COVID-19 vaccination - observational/epidemiological studies	#41	#13 AND #40	2 329
	#42	editorial[pt]	700 428
	#43	letter[pt]	1 265 687
	#44	#42 OR #43	1 964 487
Remove editorials & letters	#45	#41 NOT #44	2 288
Remove non-human studies [44]	#46	#45 NOT ("animals"[mh] NOT "humans"[mh])	2 287
Date of publication limit	#47	#46 AND 2021/10/01:2024/12[dp]	2 117

**Adapted from cited filter.*

Search terms for the Cochrane Database of Systematic Reviews (CDSR), as searched within the Cochrane Library platform are provided below in Table 13. The search was conducted on 16 August 2024.

Table 13. Search terms and results from CDSR, searched using the Cochrane Library

Search facets	No.	Query	Results
PCC terms	#1	MeSH descriptor: [Post-Acute COVID-19 Syndrome] explode all trees	255
	#2	('post covid condition' OR 'long covid' OR 'long covid' OR 'long hauler' OR 'post covid disease' OR 'post-acute covid-19 syndrome' OR 'long covid symptoms' OR 'post-covid-19' OR 'post-acute covid-19 symptoms' OR 'covid-19 sequelae' OR 'covid sequelae' OR 'post covid' OR 'post-acute sequelae of covid-19' OR 'post-acute sequelae of SARS-CoV-2 infection' OR 'long haul covid' OR 'chronic covid' OR PC19S):ti,ab,kw	6 407
	#3	('long covid*' or 'post covid*'):ti,ab,kw	5 502
PCC terms combined	#4	#1 OR #2 OR #3	6 556
COVID-19 vaccination terms	#5	MeSH descriptor: [COVID-19 Vaccines] explode all trees	730
	#6	(covid OR 'sars cov 2' OR 'sars cov2' OR '2019 ncov' OR 'coronavirus disease 2019' or 'hcov 19' OR 'human coronavirus 2019' or 'ncov 2019' OR 'novel 2019 coronavirus' OR 'sars coronavirus 2' OR sars2 OR 'severe acute respiratory syndrome 2') AND (vaccine OR vaccines OR vaccination OR vaccinations OR immunize OR immunization OR immunise OR immunisation):ti,ab,kw	3 380
	#7	('mrna 1273' OR 'chadox1 s' OR 'chadox1 ncov-19' OR azd1222 OR ad26covs1 OR 'jnj 78436735' OR bnt162b2 OR 'nvx cov2373' OR azd2816 OR vat00002 OR vat00008 OR novavax OR bnt162b2 OR spikevax OR comirnaty OR nuvaxovid OR covovax OR ad26.cov2.s OR 'vidprevtyn beta' OR 'vla2001' OR valneva OR vaxzevria OR jcovden OR bimervax OR vidprevtyn):ti,ab,kw	701
COVID-19 vaccination terms combined	#8	#5 OR #6 OR #7	3 460
PCC & COVID-19 vaccination terms in CDSR	#9	#4 AND #8 in Cochrane Reviews	7

Annex C. List of excluded studies and reasons for exclusion

The link below provides a list of the studies excluded and reasons for their exclusion from the literature review.

https://www.ecdc.europa.eu/sites/default/files/documents/excluded-studies.xlsx

Annex D. Detailed results

Study characteristics

Table 14. Summary of study characteristics

First author & year	Study design	Overall objective	Data source used	Country	Study duration & start and end date of analysis	SARS-CoV-2 variants circulating at time of study	Overall study conclusions
Studies analysing vaccine effectiveness on reducing PCC diagnosis only							
Ayoubkhani 2022 [26]	Retrospective cohort	To describe self-reported PCC symptoms, including memory and concentration problems, changes in smell and taste, fatigue, and dyspnoea, persisting 3–15 months after a positive test in SARS-CoV-2 unvaccinated and vaccinated participants with a breakthrough infection.	COVID-19 survey	UK	19 months April 2020 – November 2021	Delta (intervention group); variants prior to Delta (control group)	Vaccination offered protection against PCC symptoms.
Ioannou 2022 [30]	Retrospective cohort	To determine the rates, clinical setting, and factors associated with documented receipt of COVID-19–related care three or more months after acute infection.	RWE database	USA	23 months February 2020 – December 2021	Period of infection: Alpha, first wave and second wave	Vaccination offered protection against PCC symptom onset.
Perlis 2022 [37]	Cross-sectional	To estimate the prevalence of and sociodemographic factors associated with PCC and to identify whether the predominant variant at the time of infection and prior vaccination status are associated with differential risk.	COVID-19 survey	USA	17 months February 2021 – July 2022	Ancestral (54.2%), Delta (17.6%), Omicron (10.4%), Alpha (6.2%), Epsilon (8.7%)	Vaccination offered protection against PCC symptom onset.
Babicki 2023 [28]	Retrospective cohort	To assess whether COVID-19 vaccinations affect the most common post-COVID symptoms.	COVID-19 survey	Poland	12 months NR	NR	Vaccination did not offer protection against PCC symptom onset, but offered protection against specific PCC symptoms.
Brunvoll 2023 **[32]**	Prospective cohort	To describe PCC related symptoms 3-15 months after a positive test in SARS-CoV-2 unvaccinated and vaccinated participants with a breakthrough infection.	COVID-19 survey	Norway	15 months November 2020 – January 2022	NR	Vaccination offered protection against some symptoms but not all of them.
Morello 2023 [34]	Prospective cohort	To investigate the long-term duration of persisting symptoms and risk factors for developing of PCC in a large cohort of children using in-clinic assessments.	Disease-based cohort	Italy	34 months February 2020 – October 2022	Omicron (70.8%), Delta (19.9%), Alpha (6%), Wild (3.3%)	Vaccination offered protection against PCC symptom onset but results were not significant.
Babicki 2024 [27]	Retrospective cohort	To compare the course of COVID-19 in the periods before and during the dominance of the Omicron variant.	COVID-19 registry	Poland	36 months January 2020 – December 2022	Period of infection: Pre-Omicron and Omicron dominance	Vaccination did not offer protection against PCC symptom onset.
Degli Antoni 2024 [29]	Retrospective cohort	To investigate the prevalence, clinical symptoms, and risk factors for PCCs among PLHIV in a province of northern Italy highly affected by COVID-19.	Database	Italy	25 months February 2020 – May 2022	Period of infection: Pre-Omicron and Omicron	Vaccination did not offer protection against PCC symptom onset.

First author & year	Study design	Overall objective	Data source used	Country	Study duration & start and end date of analysis	SARS-CoV-2 variants circulating at time of study	Overall study conclusions
MacCallum-Bridges 2024 [36]	Prospective cohort	To use a population-based probability sample of adults with COVID-19 to evaluate whether vaccination status at the time of COVID-19 diagnosis was associated with prevalence of PCC.	COVID-19 Surveillance	USA	25 months June 2020 – July 2022	Period of infection (SARS-CoV-2 variant proxy): Wuhan + Alpha (21.7%), Delta (6.1%), Omicron (72.2%) in PCC group	Vaccination offered protection against PCC symptom onset.
Petrakis 2024 [35]	Prospective cohort	The aim of the study is the estimation of prevalence of PCC and identification of possible risk factors.	Hospital cohort	Greece	18 months January 2021 – July 2022	Delta (54.6%) and Omicron (45.4%) in PCC group	Vaccination offered protection against PCC symptoms.
Villa 2024 [31]	Retrospective cohort	To assess the risk of PCC in an Italian cohort of people with COVID.	Hospital cohort	Italy	39 months March 2020 – June 2023	Period of infection (SARS-CoV-2 variant proxy): Wild, Alpha, Delta and Omicron	Vaccination did not offer protection against PCC symptoms.
Studies analysing vaccine effectiveness on reducing PCC diagnosis and duration							
Ranucci 2023 [33]	Prospective cohort	To address the persistence of a wide spectrum of symptoms after hospital discharge of patients with COVID-19, and the association between factors related to the acute phase of the disease and the presence of residual symptoms after 12 months or longer from hospitalisation.	Hospital cohort	Italy	22 months January 2021 – November 2022	NR	Vaccination offered protection against PCC symptoms and reduced the duration of PCC.

Abbreviations: COVID-19: coronavirus disease; CVID: common variable immunodeficiency; PCC: post-COVID-19 condition; PLHIV: people living with HIV; RWE: real-world evidence.

Participant characteristics

Table 15. Summary of overall participant characteristics

First author and year	Overview of population	Inclusion criteria	Exclusion criteria	COVID-19 severities included in study (ECDC definition)	WHO PCC definition used?	Specific PCC definition
Studies analysing vaccine effectiveness on reducing PCC diagnosis only						
Ayoubkhani 2022 [26]	Participants randomly selected from the UK community population*	CIS participants aged 18–69 years who tested positive for SARS-CoV-2	Participants who reported suspected COVID-19 or tested positive for antibodies >2 weeks before their first positive swab; reported PCC symptoms at any time before their first positive swab; had never responded to the survey question on PCC; did not have ≥three months of postinfection follow-up; or were single-vaccinated when infected.	Various severity groupings (asymptomatic, symptomatic, non-hospitalised, and/or hospitalised)	No	Respondents reporting persistent symptoms after SARS-CoV-2 infection not explained by something else, with answers to question taken from surveys conducted ≥three months after their first test-confirmed infection.
Ioannou 2022 [30]	USA VA health system participants who tested positive for SARS-CoV-2.	Persons in the database with a positive SARS-CoV-2 test between 1st February 2020, and 30th April 2021	Individuals who died within three months of testing positive or who had reinfection (a second positive test 3 or more months after the first).	Various severity groupings	No	Documentation of PCC care based on the presence of certain ICD-10 codes (U07.1, Z86.16, U09.9, J12.82) at least three months post-infection.
Perlis 2022 [37]	USA adults with confirmed COVID-19	Individuals aged ≥18 years	NR	NR	Yes	Participants whose symptoms persisted two months following the initial month after positive test.
Babicki 2023 [28]	Polish adults who had contracted COVID-19	Individuals aged ≥18 years with prior positive diagnosis for SARS-CoV-2	NR	Various severity groupings)	Yes	Symptoms persisting for at least three months post-infection, as per WHO definition.
Brunvoll 2023 [32]	Participants of the Norwegian COVID-19 cohort who had received a positive SARS-CoV-2 test	Individuals with laboratory-confirmed positive SARS-CoV-2 test 3-15 months prior to study	Individuals with only one vaccine dose, second COVID-19 diagnosis, or COVID-19 diagnosis less than three months before follow-up.	Various severity groupings	No	Self-reported symptoms persisting for 3-15 months after positive test.
Morello 2023 [34]	Children referred to a paediatric post-COVID clinic in Rome, Italy	Individuals aged <19 years with laboratory confirmed SARS-CoV-2 infection	Individuals ≥19 years, with ≥1 SARS-CoV-2 infection, those without lab-confirmed infection, or those with ongoing acute infection.	Various severity groupings	No	Persistence of otherwise unexplained symptoms for at least three months after infection, negatively impacting daily activities.
Babicki 2024 [27]	Polish participants with confirmed COVID-19	Individuals aged ≥18 years with a confirmed SARS-CoV-2 infection (via antigen or RT-PCR test)	Individuals without follow-up visit three months post-infection, or those with incomplete medical data.	Various severity groupings	Yes	Participants whose symptoms persisted for at least three months post infection.
Degli Antoni 2024 [29]	People living with HIV in Northern Italy diagnosed with COVID-19	Individuals aged ≥18 years with positive RT-PCR diagnosis for SARS-CoV-2	NR	Various severity groupings	No	Persistence of self-reported symptoms evaluated after three months.

First author and year	Overview of population	Inclusion criteria	Exclusion criteria	COVID-19 severities included in study (ECDC definition)	WHO PCC definition used?	Specific PCC definition
MacCallum-Bridges 2024 [36]	Non-institutionalised adults from Michigan diagnosed with COVID-19	Individuals aged ≥18 years with RT-PCR-confirmed SARS-CoV-2 infection	Respondents with missing information regarding the outcome or exposure, incomplete vaccination data, or missing covariates.	NR	Yes	Persistent symptoms lasting ≥30 days or ≥90 days post-infection.
Petrakis 2024 [35]	Hospitalised patients with COVID-19 at the University General Hospital of Alexandroupolis, Greece	Individuals aged ≥18 years with confirmed COVID-19, hospitalised between January 2021 and May 2022	Individuals who died before follow-up, those living in nursing homes, or those with mental disorders or dementia preventing participation in follow-up visits.	Hospitalised - ICU	No	Persistence of at least one symptom 6-, 12-, and 18-months post-hospitalisation.
Villa 2024 [31]	Individuals with CVID in Italy who experienced SARS-CoV-2 infection	Individuals aged ≥18 years with a diagnosis of CVID, documented SARS-CoV-2 infection, and follow-up ≥six months after infection	NR	Various severity groupings	Yes	Signs and symptoms persisting for more than three months after SARS-CoV-2 infection.
Studies analysing vaccine effectiveness on reducing PCC diagnosis and duration						
Ranucci 2023 [33]	Italian patients hospitalised during the acute phase of SARS-CoV-2 infection	Individuals aged ≥18 years hospitalised for COVID-19 at IRCCS San Donato, Milan with a diagnosis between January 2021 and July 2022.	Age >90 years, or cognitive impairment.	Hospitalised - ICU	No	Persistence of symptoms after 12–18 months from the diagnosis of infection and hospitalisation.

Abbreviations: CIS: UK Coronavirus (COVID-19) Infection Survey; COVID-19: coronavirus disease 2019; CVID: common variable immunodeficiency; ECDC: European Centre for Disease Prevention and Control; ICD-10: International Classification of Diseases, 10th Revision; ICU: intensive unit care; IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico; NR: not reported; PCC: post-COVID-19 condition; RT-PCR: reverse transcription polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; VA: veterans affairs; WHO: World Health Organization.

**Excluding communal establishments such as hospitals, care homes, halls of residence and prisons.*

Table 16. Number of participants in studies

First author & year	Total participants included	Participants included in intervention arm (vaccinated)	Participants included in control arm (unvaccinated)
Studies analysing vaccine effectiveness on reducing PCC diagnosis only			
Ayoubkhani 2022 [26]	6 180	3 090	3 090
Ioannou 2022 [30]	61 140	2,447	58 693
Perlis 2022 [37]	15 677	249	2 052
Babicki 2023 [28]	801	665	136
Brunvoll 2023 [32]	1 420	360	1 060
Morello 2023 [34]	1 243	163	1 001
Babicki 2024 [27]	1 966	1 590	376
Degli Antoni 2024 [29]	381	145	236
MacCallum-Bridges 2024 [36]	4 695	1 311	3 384
Petrakis 2024 [35]	995	517	478
Villa 2024 [31]	215	76	31
Studies analysing vaccine effectiveness on reducing PCC diagnosis and duration			
Ranucci 2023 [33]	121	25	96
Total (all studies)	**94 834**	**10 638**	**70 633**

Table 17. Summary of participant baseline characteristics

First author & year	Population/sub-group	Sample size	Age – mean (SD)	Male – n (%)	Follow-up time since acute SARS-CoV-2 infection		Differences in intervention and comparator arms	
					Definition	Value	Details	
Studies analysing vaccine effectiveness on reducing PCC diagnosis only								
Ayoubkhani 2022 [26]	Double vaccinated group, post-matching	3 090	49 (12)	1 414 (45.8)	Median days (IQR) follow-up after infection	96 (90-104)	• Variant at time of circulation different between vaccinated (Delta) and unvaccinated (variants prior to Delta) groups. • Age was slightly higher in vaccinated than unvaccinated group (absolute standardised difference of 19.6%).	
	Unvaccinated group, post-matching	3 090	46.7 (11.2)	1 431 (46.3)	Median days (IQR) follow-up after infection	96 (89-109)		
Ioannou 2022 [30]	Total cohort	198 601	60.4 (17.7)	176 942 (89.1)	Mean follow-up time following infection, months	13.5 (3.6)	NA	
	Cohort without PCC (3 or more months after initial infection)	171 856	NR	152 895 (89)	NR	NR		
	Cohort with PCC (3 or more months after initial infection)	26 745	NR	24 047 (89.9)	NR	NR		
Perlis 2022 [37]	Total cohort	16 091	40.5 (15.2)	6 016 (37.4)	NR	NR	NA	
Babicki 2023 [28]	Vaccinated before COVID-19 group	75	55.9 (14.1)	16 (5.8)	For outcomes of interest, study followed up with participants for 12 months.	NR	NA	
	Unvaccinated group	136	53.9 (12.6)	49 (17.7)	NR	NR	NA	
Brunvoll 2023 [32]	Vaccinated group	360	48.3 (11.4)	97 (26.9)	Median days since COVID-19	110 (25)	Median of the days since COVID-19 was far higher in the unvaccinated group compared to the vaccinated group, although logistic regression did adjust for this.	
	Unvaccinated group	1 060	45.7 (12.3)	310 (29.2)	Median days since COVID-19	293.5 (85)		
Morello 2023 [34]	Total cohort (any follow up)	1 243	NR	668 (53.7)	Study reports proportion of participants with 3, 6, 12, and 18 months follow up since the date of initial infection. 1234 children (99.3%) had three months follow-up, 1171 (94.2%) had six months, 167 (13.4%) had 12 months, and 77 (6.2%) had 18 months follow-up.	NA	NA	
	Cohort with PCC (at three months follow up)	294	NR	146 (49.7)	Follow-up timepoint (months)	3		
	Cohort without PCC (at three months follow up)	940	NR	518 (55.1)	Follow-up timepoint (months)	3		
Babicki 2024 [27]	Total cohort	1 967	55.1 (13.5)	675 (34.3)	Participants were with follow-up visit three months after their infection	NR	NA	

First author & year	Population/sub-group	Sample size	Age – mean (SD)	Male – n (%)	Follow-up time since acute SARS-CoV-2 infection	Differences in intervention and comparator arms	
					Definition	Value	Details
Degli Antoni 2024 [29]	Total cohort	510	52.6 (10.81)	359 (70.4)	For outcomes of interest, study conducted telephone-administered questionnaire three months after SARS-CoV-2 infection	NR	NA
MacCallum-Bridges 2024 [36]	Vaccinated cohort	1 311	NR	547 (46.5)	NR	NR	NA
	Full comparison group	3 384	NR	1 378 (45.8)	NR	NR	
	Historic comparison group (with COVID-19 diagnosis before 1st March 2021)	2 294	NR	941 (46.1)	NR	NR	
	Concurrent comparison group (who had COVID-19 onset on or after 1st March 2021)	1 090	NR	437 (45.1)	NR	NR	
Petrakis 2024 [35]	Total cohort	995	44 (67)	567 (57)	For outcomes of interest, study followed up with participants for 18 months	NR	NA
Villa 2024 [31]	PCC cohort	115	NR	41 (35.7)	The median interval of time of follow-up since SARS-CoV-2 infection to the date of completion of the CDC survey	13 (11-16)	NR
	Non-PCC cohort	60	NR	32 (53.3)	The median interval of time of follow-up since SARS-CoV-2 infection to the date of completion of the CDC survey	13 (11-16)	NR
Studies analysing vaccine effectiveness on reducing PCC diagnosis and duration							
Ranucci 2023 [33]	Mild group (no oxygen therapy)	19	59.5 (15.3)	12 (63.2)	Median follow-up time after discharge from the hospital	12 (8-17)	NR
	Moderate group (nasal oxygen or oxygen mask)	68	66.3 (11.6)	46 (67.6)	Median follow-up time after discharge from the hospital	17 (12-18)	NR
	Severe group (non-invasive or invasive ventilation)	34	63.6 (14.6)	22 (64.7)	Median follow-up time after discharge from the hospital	17 (14-19)	NR

Abbreviations:

CDC: US Centers for Disease Control and Prevention; COVID-19: coronavirus disease 2019; IQR: interquartile range; N: number of participants; NA: not applicable; NR: not reported; PCC: post-COVID-19 condition; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation.

Intervention characteristics

Table 18. Summary of intervention characteristics

First author & year	Population/sub-group	Intervention					Comparator	
		Vaccine name (manufacturer)	Vaccine type	Number of doses	Vaccination status	Sample size – n (%)	Name	Details
Studies analysing vaccine effectiveness on reducing PCC diagnosis only								
Ayoubkhani 2022 [26]	Vaccinated with ChAdOx1 nCoV-19	ChAdOx1 nCoV-19 (Oxford University/AstraZeneca)	Adenovirus vector	Two doses	Vaccinated at least 14 days prior to first test-confirmed infection	2 287 (74)	No vaccination	Unvaccinated matched controls
	Vaccinated with BNT162b2	BNT162b2 (Pfizer/BioNtech)	mRNA	Two doses		788 (25.5)	No vaccination	Unvaccinated matched controls
	Vaccinated with mRNA-1273	mRNA-1273 (Moderna)	mRNA	Two doses		15 (0.5)	No vaccination	Unvaccinated matched controls
Ioannou 2022 [30]	Fully vaccinated population	BNT161b2 (Pfizer/BioNtech) and mRNA-1273 (Moderna)	mRNA	Two doses	Two vaccines received at the time of infection	2 447 (100)	No vaccination	Vaccinated controls
Perlis 2022 [37]	PCC cohort	NR	NR	NR	Completion of the primary vaccination (2 vaccinations) series occurring prior to the first month of illness	249 (10.6)	No vaccination	Unvaccinated controls
Babicki 2023 [28]	Vaccinated before SARS-CoV-2 infection	NR	NR	Two or more doses	Received at least the basic vaccination schedule	75 (9.4)	No vaccination	Unvaccinated controls
Brunvoll 2023 [32]	Total cohort	BNT161b2 (Pfizer/BioNtech) and mRNA-1273 (Moderna)	mRNA	Two or more doses	Vaccinated with two doses with 14 days passing since last vaccination	NR	No vaccination	Unvaccinated controls
Morello 2023 [34]	Total cohort	BNT161b2 (Pfizer/BioNtech) and mRNA-1273 (Moderna)	mRNA	Two doses	Vaccinated (mRNA vaccine) with 2 doses before SARS-CoV-2 infection	146 (89.6)	No vaccination	Children without vaccination (0 doses)
	Total cohort	BNT161b2 (Pfizer/BioNtech) and mRNA-1273 (Moderna)	mRNA	Three doses	Vaccinated (mRNA vaccine) with 3 doses before SARS-CoV-2 infection	17 (10.4)	No vaccination	Children without vaccination (0 doses)
Babicki 2024 [27]	PCC cohort (including pre-Omicron and Omicron)	NR	NR	NR	Every participant who completed at least the basic vaccination regimen	962 (60.5)	No vaccination	Unvaccinated controls
Degli Antoni 2024 [29]	Total cohort	BNT161b2 (Pfizer/BioNtech), mRNA-1273 (Moderna),	mRNA and adenovirus vector	Three doses	Fully vaccinated participants were those that had received 3 doses of the vaccines*	145 (100)	No vaccination	Unvaccinated controls

First author & year	Population/sub-group	Intervention					Comparator	
		Vaccine name (manufacturer)	Vaccine type	Number of doses	Vaccination status	Sample size – n (%)	Name	Details
		ChAdOx1 nCoV-19 (Oxford University/AstraZeneca), Ad26.COV2.S (JnJ)						
	PLHIV with PCC	BNT161b2 (Pfizer/BioNtech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford University/AstraZeneca), Ad26.COV2.S (JnJ)	mRNA and adenovirus vector	Three doses		52 (35.9)	No vaccination	Unvaccinated controls
	PLHIV without PCC	BNT161b2 (Pfizer/BioNtech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford University/AstraZeneca), Ad26.COV2.S (JnJ)	mRNA and adenovirus vector	Three doses		93 (64.1)	No vaccination	Unvaccinated controls
MacCallum-Bridges 2024 [36]	Vaccinated cohort	BNT161b2 (Pfizer/BioNtech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford University/AstraZeneca), Ad26.COV2.S (JnJ), and/or CoronaVac (Sinovac)	NR	NR	Initial series was completed 14 days after the second dose was received	1 311 (27.9)	No vaccination	Unvaccinated controls
Petrakis 2024 [35]	Total cohort	NR	NR	NR	Complete vaccination scheme and one booster dose	517 (52)	No vaccination	Unvaccinated controls
	PCC cohort	NR	NR	NR		321 (44.9)	No vaccination	Unvaccinated controls
Villa 2024 [31]	PCC cohort	BNT161b2 (Pfizer/BioNtech)	mRNA	Three doses	Vaccinated (mRNA vaccine) with 3 doses at first infection	59 (51.3)	No vaccination	Unvaccinated controls
	Non-PCC cohort	BNT161b2 (Pfizer/BioNtech)	mRNA			31 (51.7)	No vaccination	Unvaccinated controls

First author & year	Population/sub-group	Intervention					Comparator	
		Vaccine name (manufacturer)	Vaccine type	Number of doses	Vaccination status	Sample size – n (%)	Name	Details
	PCC cohort	BNT161b2 (Pfizer/BioNtech)	mRNA	Four doses	Vaccinated (mRNA vaccine) with 4 doses at first infection	17 (14.8)	No vaccination	Unvaccinated controls
	Non-PCC cohort	BNT161b2 (Pfizer/BioNtech)	mRNA			12 (20)	No vaccination	Unvaccinated controls
Studies analysing vaccine effectiveness on reducing PCC diagnosis and duration								
Ranucci 2023 [33]	Total cohort	NR	NR	Two doses	Vaccinated at the time of hospital admission (2 doses)	25 (20.7)	No vaccination	Unvaccinated controls

*Abbreviations: COVID: coronavirus disease; mRNA: messenger Ribonucleic Acid; NR: not reported; PCC: post-COVID-19 condition; PLHIV: people living with HIV; SARS-CoV-2: Severe acute respiratory syndrome coronavirus. *In cases where the Ad26.COV2.S vaccine was administered as first dose, the second one was considered as a booster dose. Therefore individuals in this group were considered fully vaccinated following the administration of the second dose.*

Annex E: Meta-analysis methods and results

This section summarises the methods and results of the meta-analysis conducted on the results identified in the rapid review related to the role of vaccination on reducing PCC.

Feasibility assessment

Prior to conducting the analysis, the included studies were reviewed to determine the extent to which each study could be included based primarily on the following:

- Population – Did the study populations align between studies sufficiently to pool the results together, or were differences between the individual studies and others included significant enough for pooling not to be appropriate?
- Outcomes – were outcomes comparable between studies, both in terms of their measurement of PCC (including definition and timing) and the measurement used to conduct the comparator analysis, to mean that pooling could be possible?

Given the PICO review, it was assumed that the interventions and comparators for these studies would be sufficiently comparable that exclusion would not take place based on this. The geography of the individual studies was also not considered to be a key differentiating factor between studies, since the idea of the original review was to include studies conducted either in Europe or in comparable settings.

The results of this feasibility assessment are summarised in Table 19 below. Four studies were determined to be suitable for inclusion in the meta-analysis, while eight studies were excluded. Broad reasons for exclusion included misalignment on the outcome used (n=7), and misalignment on the population included (n=4, with some studies being excluded for multiple reasons).

Table 19. Summary of feasibility assessment for meta-analysis

Study author and year	Population	PCC outcome	Comparator metric used	Quality assessment score	Include in meta-analysis	Reasons for exclusion
Ayoubkhani 2022	Community-dwelling adults with mixed disease severity and infected with Delta (vaccinated) and pre-Delta (unvaccinated) variants.	Self-reported symptoms of any severity more at least three months after acute infection.	Adjusted OR	Good	**Yes**	NA
Ioannou 2022	Community-dwelling adults (veterans) with mixed disease severity, of which 65% were infected during the period when the Alpha variant was dominant.	COVID-19 ICD-10 codes documented ≥3 months after infection.	Adjusted OR	Good	**Yes**	NA
Perlis 2022	Community-dwelling adults with mixed disease severity, of which 57% were infected during the period when the Ancestral variant was dominant.	Self-reported persistent COVID-19 symptoms two months after initial first month of symptoms.	Adjusted OR	Good	**Yes**	NA
Babicki 2024	Adults who had visited a medical centre for COVID-19 symptoms with mixed severity, with 66.9% infected during the pre-Omicron period.	Self-reported persistent symptoms at least three months after initial infection.	Adjusted OR	Good	**Yes**	NA
Babicki 2023	Adults who had visited a medical centre for COVID-19 symptoms with mixed severity, timing of infections according to dominant variant period not reported.	Self-reporting of at least one symptom 12 months after initial infection.	Size effect based on chi-squared statistic	Poor	**No**	Timing of PCC analysis differs from other studies, outcomes differ, no adjustment carried out
Brunvoll 2023	Community-dwelling adults with mixed disease severity, timing of infections according to dominant variant period not reported.	Self-reported persistent specific PCC symptoms reported at least three months after initial infection.	Adjusted OR, with vaccinated group as reference	Fair	**No**	Different outcome measures (specific PCC symptoms, not overall PCC)
Morello 2023	Community-dwelling paediatric population with mixed disease severity, of which 57.8% were infected during the Omicron period.	Persistence of symptoms for at least three months after initial infection, which had a negative impact on daily life, and other possible diagnoses excluded by medical professional.	OR	Poor	**No**	Different population (children), no adjustment carried out
Ranucci 2023	Adults hospitalised for acute COVID-19, timing of infections according to dominant variant period not reported.	Self-reported MPS and MNS at 12 and 18 months after hospital discharge.	Adjusted HR	Good	**No**	Timing of PCC analysis differs from other studies, outcomes differ

Study author and year	Population	PCC outcome	Comparator metric used	Quality assessment score	Include in meta-analysis	Reasons for exclusion
Degli Antoni 2024	Immunocompromised, community-dwelling adults with mixed disease severity, with 61.4% infected during Omicron period.	Self-reported persistent symptoms at least three months after initial infection.	Adjusted OR	Good	**No**	Different population (PLHIV)
MacCallum-Bridges 2024	Community-dwelling adults with mixed disease severity, with 96% of vaccinated participants primarily vaccinated during the Delta and Omicron periods, while 18% of the full comparison group were infected during these periods.	Self-reported symptoms ≥3 months after COVID-19 diagnosis.	IPTW adjusted prevalence ratio (PR)	Good	**No**	Different outcome measurement (IPTW adjusted PR, not OR). Not clear how weighting has been done.
Petrakis 2024	Adults hospitalised for acute COVID-19, infected during the Delta and Omicron periods, with 54.6% with PCC infected during the Delta period compared to 32.2% without PCC.	Self-reported persistent symptoms reported 6, 12 and 18 months after COVID-19 diagnosis and hospital discharge.	Adjusted OR	Good	**No**	Different population (hospitalised adults), different time periods measured for outcomes
Villa 2024	Immunocompromised, community-dwelling adults with mixed disease severity, with 72.2% infected during Omicron period.	Self-reported persistent symptoms at least three months after initial infection.	Not reported for outcomes of interest	Poor	**No**	Different population (immunocompromised), unclear if unvaccinated group reference group in outcomes

Meta-analysis methods

The adjusted ORs were used to summarise the relative binary outcomes from the studies. These ORs do not follow a normal distribution; therefore, a log transformation was used before pooling the results to ensure asymptomatic normality of effect sizes:

$$Log_{OR} = log_e(OR)$$

The standard error of Log_{OR} ($SE_{\log OR}$) can be expressed as follows:

$$SE_{\log OR} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

Results were back transformed using exponential function for a better interpretability.

Pooled estimates were produced using standard frequentist meta-analyses methods, with both fixed- (FE) and random-effect (RE) models being fitted. The meta-analyses were performed using the *meta* R package, approved by Cochrane [24,25].

The estimations of the effect sizes were obtained by the weighted average method:

$$\hat{O} = \frac{\sum_{k=1}^{K} \hat{o}_k w_k}{\sum_{k=1}^{K} w_k}$$

Where:

- K is the number of the included studies in the meta-analysis.
- $\hat{o}_k$ is the estimated effect size of study k.
- w_k is the weight assigned to study k.

The calculation of the weights (w_k) differs between the two modelling options, as shown below in Table 20.

Table 20. Weight calculation based on the type of the model

Model	Weight calculation
Fixed-effect model	$w_k = \frac{1}{s_k^2}$
Random-effects model	$w_k = \frac{1}{s_k^2 + \gamma^2}$

Where:

- w_k is the assigned weight for study k.
- s_k^2 is the effect size's variance for the study k.
- γ^2 is the between-studies variance.

Results

Base case

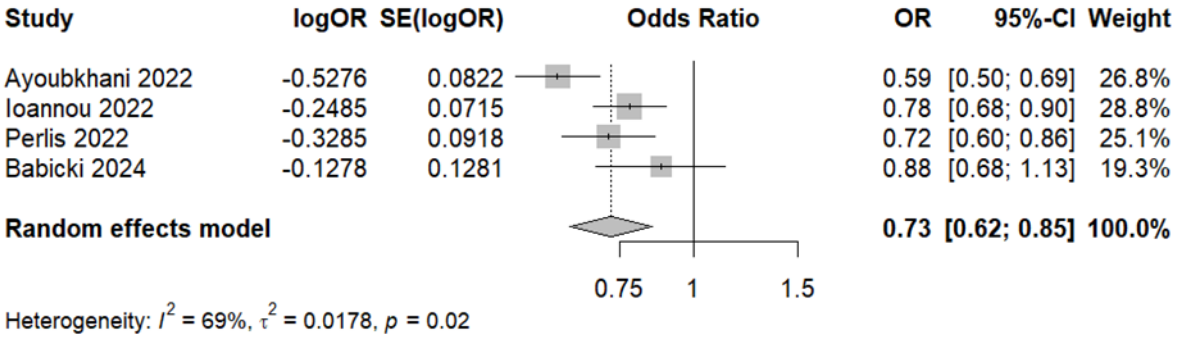
To overcome imbalances between cohorts within studies, adjusted OR were used, as presented in Table 21.

Table 21. Data inputs used for the meta-analysis

Study	Vaccinated		Not Vaccinated		Adjusted OR [95% CI]	Variables used in adjustment
	N	Number of events	N	Number of events		
Ayoubkhani 2022 [26]	3 090	294	3 090	452	0.59 [0.50, 0.69]	Age, sex, ethnicity, country/ region of residence, area deprivation, pre-existing health/ disability status, time from infection to follow-up for PCC
Ioannou 2022 [30]	2 447	263	58 693	6 811	0.78 [0.68, 0.90]	Age, sex, race, ethnicity, urban vs rural residence, comorbidity, VA service, time of infection, no. of care encounters prior to infection
Perlis 2022 [37]	2 243	249	13 434	2 052	0.72 [0.60, 0.86]	Age, sex, income, education, race, urbanicity, region and predominant variant
Babicki 2024 [27]	1 590	962	376	227	0.88 [0.69, 1.14]	Age, sex, BMI, chronic disease, severity and Omicron period

The results from the meta-analysis are presented in Figure 3. Based on moderate statistical heterogeneity observed (I^2=69%) and clinical heterogeneity between studies, it is recommended that random-effect meta-analysis results are used. Based on using the random effects model, vaccination is associated with significant reduction in PCC, with a pooled OR of 0.73 (95% CI: 0.62–0.85).

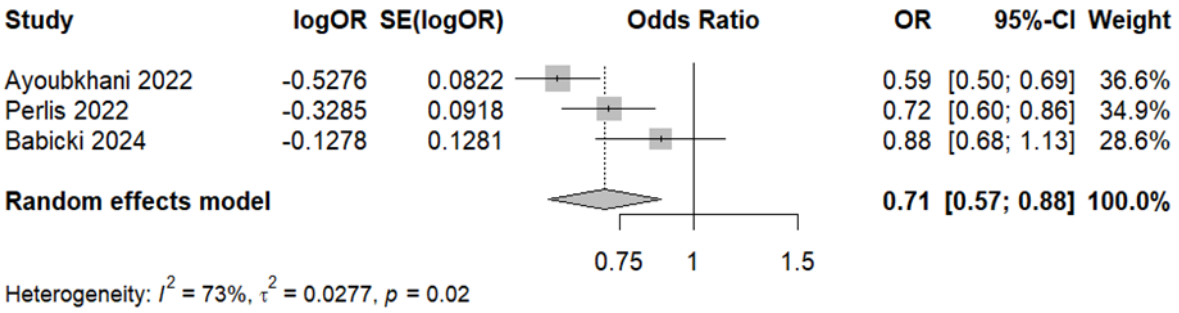
Figure 3. Forest plot of meta-analysis of OR



Analysis without Ioannou et al. (2022)

In addition to the above analysis, an analysis that excluding Ioannou et al. (2022) was also conducted, given that the study outcome definition differed from other studies (ICD-10 coding vs. self-reported symptoms). As shown in Figure 4 below, the exclusion of this study did not significantly affect the overall conclusion from the meta-analysis.

Figure 4. Forest plot of sensitivity meta-analysis of OR



Annex F. Summary of findings from previous SLRs assessing whether vaccination prior to SARS-CoV-2 infection reduces the risk of PCC

Table 22. Summary of SLRs identified via databases and other methods

First author & year, review type	No. studies	Population	Intervention	Vaccination timing relative to infection	Comparator	Geography	Used WHO PCC Definition?	Conclusion
Gao (2022) [38] SLR and meta-analysis	18†	Participants diagnosed with COVID-19	Vaccination with one or more doses of COVID-19 vaccines (mainly mRNA vaccines, but not specified).	• Before (n=6) • After (n=5) • Before/after (n=4)	Unvaccinated individuals.	Global, including 11 countries in total, of which six in Europe	No (pre-defined PCC restriction used).	COVID-19 vaccines reduced the risk of PCC in patients vaccinated before or after SARS-CoV-2 infection (vaccination before RR: 0.82, 95% CI: 0.74–0.91, p <0.01; vaccination after RR: 0.83, 95% CI: 0.74–0.92, p<0.01), but one study did not align with this finding.
Notarte (2022) [39] SLR	17	Adults (>18 years) infected by SARS-CoV-2 and diagnosed with RT-PCR	Any dose of BNT162b2 (Pfizer/BioNTech), ChAdOx1 nCoV-19 (Oxford/AstraZeneca), mRNA-1273 (Moderna), and Ad26.COV2.S (JnJ).	• Before (n=6) • After (n=11)	Unvaccinated individuals.	Global, including 10 countries in total, of which four in Europe	No (pre-defined PCC restriction used).	Low strength of evidence according to NOS score suggests that vaccination before SARS-CoV-2 infection could reduce the risk of subsequent PCC.
Byambasuren (2023) [45] SLR	16	All ages who were eligible to receive a COVID-19 vaccine	Any dose of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (Oxford/AstraZeneca), and Ad26.COV2.S (JnJ).	• Before (n=11) • After (n=4)* • Before/after (n=1)	No vaccination, an active non-COVID-19 vaccine control (e.g., influenza vaccine), or placebo.	Global, including five countries in total, of which four in Europe	Yes (SLR used the WHO definition, but not all of the included studies aligned with it††).	Two or more doses of vaccine given before infection with the SARS-CoV-2 virus were associated with significant reductions in the rates of PCC, but two studies did not align with this finding.
Jennings (2023) [46] SLR and meta-analysis	31**	All age groups who have experienced COVID-19	Any dose of BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (JnJ).	• Before (n=18) • After (n=3)	Unvaccinated individuals who had COVID-19 or comparison between doses of COVID-19 vaccination among those who had COVID-19.	Global, including 17 countries in total, of which 10 in Europe	Yes (SLR used the WHO definition, but not all of the included studies aligned with it†††).	Two doses of vaccine prior to COVID-19 likely reduced the odds of developing PCC compared to unvaccinated individuals (pooled OR: 0.67, 95% CI: 0.60–0.74). All studies aligned with this finding.

First author & year, review type	No. studies	Population	Intervention	Vaccination timing relative to infection	Comparator	Geography	Used WHO PCC Definition?	Conclusion
Marra (2023) [40]	32***	Adults who have experienced COVID-19.	Fully vaccinated (at least two doses of COVID-19 vaccines [mRNA, or vectorial or inactivated viral vaccine], with exception of one dose for Ad26.COV2.S [JnJ]).	• Before (n=20) • After (n=3) • Before/after (n=4)	Unvaccinated individuals	Global, including 16 countries in total, of which eight in Europe	No (A wide range of health symptoms that are present four or more weeks after SARS-CoV-2 infection)	Receiving a complete COVID-19 vaccination prior to contracting the virus resulted in a significant reduction in PCC (pooled DOR: 0.63, 95% CI: 0.52–0.77); one study did not align with this finding.
Watanabe (2023) [41] SLR and meta-analysis	12	Participants of any age diagnosed with COVID-19 either by RT-PCR, serum antibody test, or the development of clinical symptoms after close contact with proven cases.	Any dose of CoronaVac (Sinovac), BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), Ad26.COV2.S (JnJ), and ChAdOx1 nCoV-19 (Oxford/AstraZeneca) before or after acute SARS-CoV-2 infections.	• Before (n=6) • After (n=6)	Unvaccinated individuals (patients vaccinated before infection); no comparator (patients vaccinated after infection)	Global, including 7 countries in total, of which four in Europe	No (Persistent or new-onset symptoms and/or conditions four weeks after the acute SARS-CoV-2 infection)	Full COVID-19 vaccination before SARS-CoV-2 infection was associated with a lower risk of PCC (pooled OR: 0.64, 95% CI: 0.45–0.92), while most of those with ongoing PCC did not experience symptomatic changes following vaccination. All included studies comparing full vaccination to no vaccination were aligned with this finding.
Man (2024) [42] SLR and meta-analysis	13	All ages with PCC.	Assessing the vaccination status and timing relative to SARS-CoV-2 infection for any dose of Ad26.COV2.S (JnJ), mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNTech), and CoronaVac (Sinovac).	Before (n=13)	Unvaccinated individuals	Global, including six countries in total, of which four in Europe	No (No pre-defined PCC restriction used)	A pre-infection COVID-19 vaccination was associated with a significant reduction in the risk and severity of PCC (pooled OR: 0.77, 95% CI: 0.75–0.79), but one study did not align with this finding.

Abbreviations: CI: confidence interval; COVID-19: coronavirus disease 2019; DOR: diagnostic odds ratio; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; PCC: post-COVID-19 condition; NA: not applicable; n: number of studies; NOS: Newcastle-Ottawa Scale; OR: odds ratio; RR: risk ratio; RT-PCR: reverse transcription; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SLR: systematic literature review; WHO: World Health Organization.

**Four studies assessed vaccine effectiveness after infection and a diagnosis of PCC.*

***This SLR also included studies that reported the effect of vaccination administered to previously unvaccinated individuals already experiencing PCC (n=10) and adverse events post-vaccination among those with PCC (n=3). Some studies were counted more than once due to multiple outcomes being reported.*

****Five studies evaluated vaccine effectiveness but did not specify the timing of vaccination.*

†Three studies did not clarify the vaccination timing.

††Some studies defined the PCC as reporting at least one SARS-CoV-2–related symptom with a duration of more than 4 weeks or experiencing constitutional or systemic symptoms beyond 28-day post-infection period.

†††Some studies did not specify how long the symptoms lasted or whether the symptoms started from the initial SARS-CoV-2 infection.

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