

STI/HIV testing and treatment in all US states and the District of Columbia as of October 2021. Most states also allowed minors to consent independently to STI/HIV prevention, including human papillomavirus vaccination and HIV preexposure and postexposure prophylaxis. However, some states required clinicians to apply specific criteria before minors can consent. Most states neglected or only cursorily addressed confidentiality obligations for clinicians who care for independently consenting minors. In states that permit or require that STI/HIV services be kept confidential from minors' guardians, clinicians will need to identify and implement practices to avoid inadvertent disclosure via insurance billing or electronic health records. Clinicians may need to consult additional state or federal regulations, such as the 21st Century Cures Act, to develop these procedures. This study did not assess municipal or federal law or changes after October 2021.

Minor consent laws are structured to protect clinicians who rely on minors' independent consent when providing STI/HIV services. These statutes therefore benefit both minors and clinicians, allowing minors to obtain STI/HIV services without involving their guardians, and enabling clinicians to provide these services to minors without risking legal sanctions. Due to low levels of knowledge about these laws and a dearth of institutional policies and procedures to support their use, minors often do not receive the services they need.⁶ Trainings, policies, and procedures that support and routinize the application of these statutes may empower clinicians to rely on them more confidently in practice. Ensuring that clinicians, researchers, and minors understand and trust these minor consent laws may expand access to STI/HIV services for youth.

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Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers

Survivors of COVID-19 may present with long-lasting symptoms.¹ Some factors have been associated with the development of post-COVID conditions (also referred to as "long COVID"),² including hospitalization.³ A study of older US veterans showed 15% reduction of long COVID after vaccination; however, study limitations included the low number of women and suboptimal vaccination schedules.⁴



Supplemental content

Methods | The study was approved by the Humanitas Research Hospital institutional review board. Each participant provided written informed consent.

We conducted an observational cohort study from March 2020 to April 2022 in individuals working in 9 Italian health care facilities.^{5,6} Polymerase chain reaction (PCR) tests for SARS-CoV-2 were conducted every week (in COVID wards) or 2 weeks (in other wards) for hospital personnel, or if they developed symptoms or were exposed to cases. All health care workers were required to receive 3 doses of vaccine (BNT162b2), with the first and second doses administered in January-February 2021 and the booster dose in November-December 2021.

Table 1. Characteristics of the Nonhospitalized Study Population of Routinely Tested Health Care Personnel With COVID-19 (N = 739)

	Had long COVID		Did not have long COVID		P value
	No.	% (95% CI) ^a	No.	% (95% CI) ^a	
No.	229	31.0 (27.7-34.5)	510	69.0 (65.5-72.3)	.11 ^b
Women	180	32.7 (28.8-36.8)	371	67.3 (63.2-71.2)	
Men	49	26.1 (19.9-33.0)	139	73.9 (67.0-80.1)	
Age, mean (SD), y	44.3 (10.7)		41.2 (11.4)		<.001 ^c
BMI, mean (SD)	24.3 (4.3)		23.5 (3.7)		.01 ^c
COVID-19 wave ^d					<.001 ^b
1	74	48.1 (39.9-56.2)	80	51.9 (43.8-60.1)	
2	108	35.9 (30.5-41.6)	193	64.1 (58.4-69.5)	
3	47	16.5 (12.4-21.4)	237	83.5 (78.6-87.6)	
Vaccine doses before SARS-CoV-2 infection ^e					<.001 ^b
0	176	41.8 (37.0-46.7)	245	58.2 (53.3-63.0)	
1	3	30.0 (6.7-65.2)	7	70.0 (34.8-93.3)	
2	8	17.4 (7.8-31.4)	38	82.6 (68.6-92.2)	
3	42	16.0 (11.8-21.0)	220	84.0 (79.0-88.2)	
Comorbidities					
Allergies	104	36.5 (30.9-42.4)	181	63.5 (57.6-69.1)	.01 ^b
Heart and cardiovascular diseases	34	40.0 (29.5-51.2)	51	60.0 (48.8-70.5)	.07 ^b
Obstructive lung disease (asthma/COPD/bronchiectasis)	28	46.7 (33.7-60.0)	32	53.3 (40.0-66.3)	.009 ^b
Autoimmune and rheumatic diseases	21	43.8 (29.5-58.8)	27	56.2 (41.2-70.5)	.07 ^b
Metabolic disease	18	34.0 (21.5-48.3)	35	66.0 (51.7-78.5)	.74 ^b
Cancer	5	21.7 (7.5-43.7)	18	78.3 (56.3-92.5)	.46 ^b
Pregnancy or breastfeeding	5	33.3 (11.8-61.6)	10	66.7 (38.4-88.2)	.79 ^b
Anemia/hemoglobinopathies/coagulation disorders	3	23.1 (5.0-53.8)	10	76.9 (46.2-95.0)	.76 ^b
Mental health conditions	3	60.0 (14.7-94.7)	2	40.0 (5.3-85.3)	.18 ^f
IBD	2	40.0 (5.3-85.3)	3	60.0 (14.7-94.7)	.65 ^f
GERD	2	100.0 (15.8-100)	0	0.0 (0-84.2)	.09 ^f

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease.

^a The 95% CIs for the prevalence data were calculated using the Clopper-Pearson method.

^b χ^2 test.

^c Mann-Whitney U test.

^d Wave 1: February-September 2020 (wild-type variant), wave 2, October 2020-July 2021 (Alpha variant), and wave 3, August 2021-March 2022 (Delta and Omicron variants).

^e The average periods of the vaccine administration were January 2021 (first dose), February 2021 (second dose), and November 2021 (third dose).

^f Fisher exact test.

Between February and April 2022, each participant completed a survey including demographics, comorbidities, a list of SARS-CoV-2-related symptoms at the time of infection and their duration (survey in the [Supplement](#)), and vaccination status. We defined long COVID as reporting at least 1 SARS-CoV-2-related symptom with a duration of more than 4 weeks. Hospitalized individuals were excluded to avoid bias related to severe disease, as were individuals with a date of infection less than 28 days before the survey. We included asymptomatic infections in the acute infection group (they could not have long COVID by definition) to avoid overestimating the prevalence of long COVID. The analysis was restricted to health care workers who were tested every 1 or 2 weeks with complete demographic data and a documented positive result for SARS-CoV-2 between March 2020 and March 2022.

By the date of infection, we divided the patients into 3 groups corresponding to the peaks in our data and circulation of variants of concern in Italy (wave 1, February-September 2020 [wild-type variant]; wave 2, October 2020-July 2021 [Alpha]; and wave 3, August 2021-March 2022 [Delta and Omicron]) (eFigure in the [Supplement](#)). A multivariable logistic regression model was used to assess the relationship between long COVID and characteristics, including participant sex, age, SARS-CoV-2 infection, wave, and vaccination status

14 days prior to infection. Time since second vaccination was assessed among vaccinated individuals.

The Clopper-Pearson method was used to calculate 95% CIs and the Mann-Whitney U test or the *t* test for continuous variables and the χ^2 -test for categorical variables to calculate *P* values. The significance threshold was defined as *P* < .05 (2-sided). Analyses were done in Python, version 3.8.3.

Results | Of 2560 participants, 739 individuals (29%) had COVID-19 (89 asymptomatic), of whom 229 (31.0%; 95% CI, 27.7%-34.5%) had long COVID (**Table 1**). The prevalence of long COVID varied across the pandemic waves, from 48.1% (95% CI, 39.9%-56.2%) in wave 1 to 35.9% (95% CI, 30.5%-41.6%) in wave 2 to 16.5% (95% CI, 12.4%-21.4%) in wave 3. The number of vaccine doses was associated with lower long COVID prevalence: 41.8% (95% CI, 37.0%-46.7%) in unvaccinated patients, 30.0% (95% CI, 6.7%-65.2%) with 1 dose, 17.4% (95% CI, 7.8%-31.4%) with 2 doses, and 16.0% (95% CI, 11.8%-21.0%) with 3 doses. Older age, higher body mass index, allergies, and obstructive lung disease were associated with long COVID.

With a reference group of unvaccinated females in wave 1 with no allergies or comorbidities (**Table 2**), male sex (odds ratio [OR], 0.65; 95% CI, 0.44-0.98, *P* = .04), 2 vaccine doses (OR, 0.25; 95% CI, 0.07-0.87, *P* = .03), and 3 vaccine doses (OR, 0.16;

Table 2. Multivariable Logistic Regression Analysis of the Association of Long COVID (N = 229) With Patient Characteristics^a

	OR (95% CI)	P value
Male sex	0.65 (0.44-0.98)	.04
Age ^b	1.23 (1.01-1.49)	.04
BMI ^b	1.10 (0.92-1.31)	.30
Allergies	1.50 (1.06-2.11)	.02
No. of comorbidities ^c	1.32 (1.04-1.68)	.03
COVID-19 wave		
2	0.72 (0.48-1.08)	.11
3	1.34 (0.26-7.01)	.73
Vaccine dose ^d		
1	0.86 (0.21-3.49)	.83
2	0.25 (0.07-0.87)	.03
3	0.16 (0.03-0.84)	.03

Abbreviations: BMI, body mass index; OR, odds ratio.

^a Reference model: women in COVID-19 wave 1 with 0 doses of vaccine, with no allergies and no comorbidities.

^b Age and BMI have been standardized (mean = 0; SD = 1). Age SD = 11.3 years; BMI SD = 3.9.

^c Number of comorbidities is a discrete variable ranging from 0 to 4, where 4 represents 4 or more different comorbidities.

^d At least 14 days prior to infection.

95% CI, 0.03-0.84, $P = .03$) were associated with a lower probability of long COVID. Older age (OR, 1.23; 95% CI, 1.01-1.49, $P = .04$), allergies (OR, 1.50; 95% CI, 1.06-2.11, $P = .02$), and an increasing number of comorbidities (OR, 1.32; 95% CI, 1.04-1.68, $P = .03$) were associated with a higher probability. No statistically significant association with infection wave was found. Among vaccinated individuals ($n = 265$), time between the second vaccination dose and infection was not associated with long COVID (OR, 0.66; 95% CI, 0.34-1.29).

Discussion | In this longitudinal observational study conducted among health care workers with SARS-CoV-2 infections not requiring hospitalization, 2 or 3 doses of vaccine, compared with no vaccination, were associated with lower long COVID prevalence. Study limitations include that symptoms and duration were self-reported, and causality cannot be inferred.

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COMMENT & RESPONSE

Medical Need and Transplant Accessibility

To the Editor A recent Viewpoint¹ discussed inequities in solid organ transplants in the US and presented policy proposals to ameliorate these disparities. However, an additional barrier to transplant accessibility that should be considered is the stigma and ableism faced by individuals with intellectual and developmental disabilities (IDD).



Systematic Review

Effect of COVID-19 Vaccines on Reducing the Risk of Long COVID in the Real World: A Systematic Review and Meta-Analysis

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Abstract: The coronavirus disease 2019 (COVID-19) is still in a global pandemic state. Some studies have reported that COVID-19 vaccines had a protective effect against long COVID. However, the conclusions of the studies on the effect of COVID-19 vaccines on long COVID were not consistent. This study aimed to systematically review relevant studies in the real world, and performed a meta-analysis to explore the relationship between vaccination and long COVID. We systematically searched PubMed, Embase, Web of science, and ScienceDirect from inception to 19 September 2022. The PICO (P: patients; I: intervention; C: comparison; O: outcome) was as follows: patients diagnosed with COVID-19 (P); vaccination with COVID-19 vaccines (I); the patients were divided into vaccinated and unvaccinated groups (C); the outcomes were the occurrence of long COVID, as well as the various symptoms of long COVID (O). A fixed-effect model and random-effects model were chosen based on the heterogeneity between studies in order to pool the effect value. The results showed that the vaccinated group had a 29% lower risk of developing long COVID compared with the unvaccinated group (RR = 0.71, 95% CI: 0.58–0.87, $p < 0.01$). Compared with patients who were not vaccinated, vaccination showed its protective effect in patients vaccinated with two doses (RR = 0.83, 95% CI: 0.74–0.94, $p < 0.01$), but not one dose (RR = 0.83, 95% CI: 0.65–1.07, $p = 0.14$). In addition, vaccination was effective against long COVID in patients either vaccinated before SARS-CoV-2 infection/COVID-19 (RR = 0.82, 95% CI: 0.74–0.91, $p < 0.01$) or vaccinated after SARS-CoV-2 infection/COVID-19 (RR = 0.83, 95% CI: 0.74–0.92, $p < 0.01$). For long COVID symptoms, vaccination reduced the risk of cognitive dysfunction/symptoms, kidney diseases/problems, myalgia, and sleeping disorders/problems sleeping. Our study shows that COVID-19 vaccines had an effect on reducing the risk of long COVID in patients vaccinated before or after SARS-CoV-2 infection/COVID-19. We suggest that the vaccination rate should be improved as soon as possible, especially for a complete vaccination course. There should be more studies to explore the basic mechanisms of the protective effect of COVID-19 vaccines on long COVID in the future.

Keywords: COVID-19 vaccine; long COVID; post COVID-19 condition; systematic review; meta-analysis



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1. Introduction

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still in a global pandemic state. According to the World Health Organization (WHO), there have been 599 million confirmed cases of COVID-19 as of 31 August 2022 [1]. Although patients recover from acute symptoms of COVID-19, it is worrying that certain studies have pointed out that sequelae in some patients (adults and children) may last weeks or even months [2–4]. However, COVID-19 might have detrimental sequelae even after the post-acute phase, depicting a new pathological condition—“post-COVID-19 syndrome (PCS)” or “long COVID” [5]. Long COVID is also known as the post-COVID-19 condition, long-term symptoms following SARS-CoV-2

infection, post-acute COVID-19 syndrome, or post-acute sequelae of SARS-CoV-2 infection, etc. [6,7]. The clinical case definition of long COVID, published by the WHO, is that it occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms, and lasts for at least 2 months, and it cannot be explained by an alternative diagnosis [8]. Long COVID affects multiple organs, and common symptoms include tiredness/fatigue, dyspnea/difficulty breathing, cough, chest pain, diarrhea, headache, impaired balance and gait, insomnia, joint pain, myalgia and weakness, neurocognitive issues, palpitations, pins and needles, rash, and hair loss [9,10].

According to the WHO, a total 12 billion COVID-19 vaccines have been administered as of 23 August 2022 [1]. COVID-19 vaccines could prevent SARS-CoV-2 infection, symptomatic COVID-19, and severe COVID-19, although their effectiveness was found to decline as time went by [11]. COVID-19 vaccines also had a good effectiveness against COVID-19-related hospitalization, admission to the intensive care unit, and death in a real-world setting [12]. The protective effect of COVID-19 vaccines has also been observed among children [13]. However, it is not clear that whether COVID-19 vaccines can prevent long COVID [6]. A cohort study in healthcare personnel with confirmed COVID-19 showed that the prevalence of reporting one or more COVID-like symptom 6 weeks after the onset of illness in the vaccinated group was lower compared with the unvaccinated group [14]. Another study reported that the number of vaccine doses was associated with lower long COVID incidence among healthcare workers who had not required hospitalization [15]. However, one study indicated that the mean number of post-acute sequelae of COVID-19 (PASC) symptoms reported each month during the follow-up period and the odds of full recovery from PASC were comparable between vaccinated and unvaccinated groups [16].

As far as we know, at present, only one preprint [17] and one published article [18] have provided systematic reviews on this topic without a meta-analysis. Therefore, we conducted this systematic review with a meta-analysis to quantitatively explore the effect of COVID-19 vaccines on long COVID, and to provide scientific evidence and suggestions. The PICO (P: patients; I: intervention; C: comparison; O: outcome) was as follows: patients diagnosed as having COVID-19 (P); vaccination with COVID-19 vaccines (I); the patients were divided into vaccinated and unvaccinated groups (C); the outcomes were the occurrence of long COVID, as well as the various symptoms of long COVID (O).

2. Materials and Methods

2.1. Registration and Search Strategy

Our study was registered in Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42022340472). The study process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines strictly. We systematically searched PubMed, Embase, Web of science, and ScienceDirect from inception to 19 September 2022. One part of the search terms was “vaccine” and its synonyms, the other part of the search terms was “long COVID” and its synonyms. The two parts were logically connected by “AND”. The complete search strategy is shown in Table S1 of the Supplementary Materials. In addition, we checked the reference lists of relevant reviews for more studies.

2.2. Study Selection

In this study, no matter how the studies considered defined long COVID, they would be included if they met the inclusion criteria. The inclusion criteria were as follows: (1) studies in extracted data could be extracted on the number of long COVID patients for vaccinated and unvaccinated patients; (2) studies conducted on humans, not on animals or cells; and (3) cohort study design, case-control study, or cross-sectional study. The exclusion criteria were as follows: (1) being irrelevant to this study (animal experiments, basic medical research, using models to evaluate, or participants obviously were vaccinated after long COVID, etc.); (2) study design not needed (clinical trial, review, case series, case report, conference abstract,

or comment); (3) data not available (data were unable to be extracted or unable to be used for quantitative synthesis); and (4) duplicate articles.

EndNote (version 20, Tomson ResearchSoft, Stanford, CA, USA) software was used to exclude duplicates and to manage the results obtained by the search. In order to obtain as much data as possible, during the screening by title and abstract, only studies that obviously met the exclusion criteria were excluded. The rest of the records were selected by reading the full texts. Then, the eligible articles that met the inclusion criteria were finally included. Study selection (as well as data extraction and quality assessment of the included studies below) was done independently by two researchers, and disagreements were resolved through discussion or through a decision by a third researcher.

2.3. Data Extraction

The following information and data of included studies were extracted: (1) basic information, namely first author, title, publication time, and study design; (2) characteristics of the population, namely nationality, age, sample size, and follow-up time; (3) information of vaccination, namely vaccination time, type of vaccine, and number of doses; and (4) information of outcomes, namely outcome, observation period, number of long COVID patients, and number of long COVID symptoms.

2.4. Quality Assessment of Included Studies

For cohort studies and case-control studies, the Newcastle Ottawa scale [19] (NOS) was used to evaluate the risk of bias. The results of NOS include a low risk of bias (7–9 scores), moderate risk of bias (4–7 scores), and high risk of bias (0–3 scores). For cross-sectional studies, the checklist recommended by Agency for Healthcare Research and Quality [20] (AHRQ) was used, and the results include low risk of bias (8–11 scores), moderate risk of bias (4–7 scores), and high risk of bias (0–3 scores).

2.5. Statistical Analysis

In this study, exposure was vaccination with COVID-19 vaccines. We divided the population into vaccinated and unvaccinated groups. Participants who received one or more doses of COVID-19 vaccines were considered to be in the vaccinated group. The outcomes were the occurrence of long COVID (having at least one symptom) and various symptoms of long COVID. The risk ratio (RR) was calculated to assess the risk of developing long COVID in the vaccinated group compared with the unvaccinated group. In addition, we performed a subgroup analysis by age (<60 or ≥60 years), number of vaccine doses (one dose or two doses), vaccination time (before SARS-CoV-2 infection/COVID-19 or after SARS-CoV-2 infection/COVID-19), and definition of long COVID (“presence of symptoms more than 4 weeks after SARS-CoV-2 infection/COVID-19 diagnosis” or “other definitions”). For the primary meta-analysis, a sensitivity analysis was performed to assess the robustness, and the Egger test was conducted to assess the publication bias.

We calculated I^2 statistics to show the heterogeneity between studies. The model used to pool the effect value was chosen based on the heterogeneity. When $I^2 \leq 50$, this showed that the heterogeneity was low to moderate, and a fixed-effect model was used. When $I^2 > 50$, this showed that the heterogeneity was moderate to high, and a random-effects model was used. Statistical analysis was done using Review manager (version 5.4.1, The Cochrane Collaboration, London, UK) and R (version 4.1.0, Robert Gentleman and Ross Ihaka, Auckland, New Zealand) software.

3. Results

3.1. Characteristics of Included Studies

The process of study selection is shown in Figure 1. By searching the databases and checking the reference lists, we obtained 4941 records. A total of 3076 records were screened by reading titles and abstracts after duplicates were removed by the software. Finally, 18 eligible studies were included for quantitative synthesis after reading the full

texts of 145 articles. The main information and the data for the meta-analysis of the included studies are shown in Table 1 and Table S2 of the Supplementary Material, respectively. Among them, 15 articles were accepted or published [15,16,21–33] and 3 articles were preprints [7,34,35]. All of the studies were observational, including 12 cohort studies, 1 case-control study, and 5 cross-sectional studies. Most of the populations were from the USA, UK, and Spain. There were more than 100,000 participants from each of these three countries. Three studies conducted in India, Switzerland, and Saudi Arabia each had a sample size over 1000. The other sample sizes were below 1000. The populations were mainly vaccinated with mRNA vaccines. Part of the populations were vaccinated after they had had SARS-CoV-2 infection or COVID-19. The definition of long COVID varied between studies. Only one study followed the definition published by the WHO (details of definition could be seen in the introduction). Three studies followed the definition published by the National institute for Health and Care Excellence (NICE) (details of the definition can be seen in the footer of Table 1). The definitions of five studies were similar to the NICE definition, because they used “more than 4 weeks” as the cut-off value for the observation time of long COVID-19 symptoms. Eight studies followed other definitions and two studies had no clear definition. In terms of quality assessment, only four studies had moderate risk of bias, and the rest had a low risk of bias. Overall, the quality of the included studies was good. The details of the quality assessment are shown in Table S3 of the Supplementary Material.

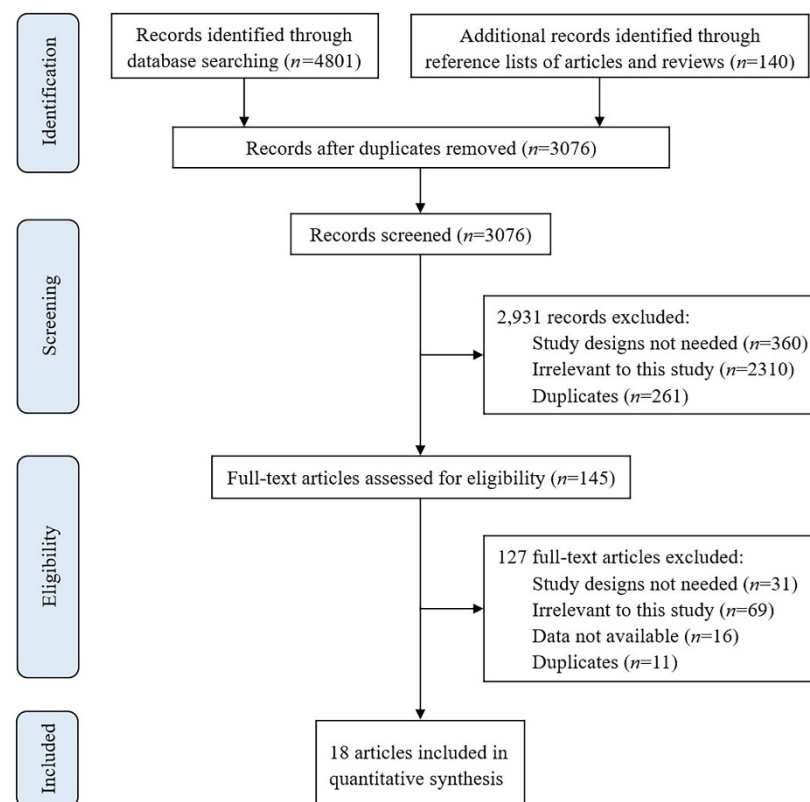


Figure 1. Flowchart of the study selection.

3.2. Primary Meta-Analysis and Sensitivity Analysis

The results of the primary meta-analysis are shown in Figure 2. There was high heterogeneity between studies. Fifteen studies with 185,689 participants in the vaccinated group and 759,987 participants in the unvaccinated group were pooled using a random-effects model. $RR = 0.71$ (95% CI: 0.58–0.87, $p < 0.01$) indicated that the vaccinated group had a lower risk of developing long COVID compared with the unvaccinated group. The funnel plot is shown

in Figure 3. The result of the Egger test ($t = -0.46$, $df = 13$, p -value = 0.65) suggested no publication bias in the primary meta-analysis.

Table 1. Characteristics of the included studies.

Study ID	Study Design	Nationality of Population	Age (Mean \pm SD or Range) (Years)	Vaccination Time	Type of Vaccine	Definition of Long COVID *	Sample Size for Meta-Analysis	Quality Assessment
Nehme 2022 [21]	Cross-sectional study	Switzerland	43.5 \pm 13.7	After SARS-CoV-2 infection	mRNA-1273, BNT162b2	Presence of fatigue, difficulty concentrating or memory loss, loss of or change in smell, loss of or change in taste, shortness of breath, and headache more than 6 months after an infection	1596	Low risk
Ayoubkhani 2022 [7]	Cohort study	UK	18–69	Before SARS-CoV-2 infection	ChAdOx1 nCoV-19, BNT162b2, mRNA-1273	Presence of symptoms more than 4 weeks after the first having COVID-19, that are not explained by something else	6180	Moderate risk
Kuodi 2022 [32]	Cross-sectional study	Israel	≥ 19	Before and after SARS-CoV-2 infection	Mainly BNT162b2	No clear definition	951	Low risk
Alghamdi 2022 [22]	Cross-sectional study	Saudi Arabia	12–70	NA	ChAdOx1 nCoV-19, BNT162b2	No clear definition	2218	Moderate risk
Simon 2021 [34]	Cohort study	USA	NA	Before and after COVID-19 diagnosis	NA	Presence of one or more COVID-associated symptoms between 12 and 20 weeks after the initial COVID-19 diagnosis	240,648	Low risk
Taquet 2022 [24]	Cohort study	USA	57.0 \pm 17.9	Before SARS-CoV-2 infection	BNT162b2, mRNA-1273, Ad26.COV2.S, other COVID-19 vaccines	Presence of chest/throat pain, abnormal breathing, abdominal symptoms, fatigue/malaise, anxiety/depression, pain, headache, cognitive dysfunction, and myalgia between 90 and 120 days after COVID-19 diagnosis	9953	Low risk
Otmani 2022 [23]	Case-control study	Morocco	NA	After contracting the COVID-19 infection	NA	Guideline published by the NICE	118	Low risk
Azzolini 2022 [15]	Cohort study	Italy	44.3 \pm 10.7 (with long COVID); 41.2 \pm 11.4 (without long COVID)	Before SARS-CoV-2 infection	BNT162b2	Presence at least 1 SARS-CoV-2-related symptom with a duration of more than 4 weeks	739	Moderate risk
Wynberg 2022 [16]	Cohort study	Netherlands	53.5 (IQR: 41.0–64.0)	After SARS-CoV-2 infection	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S	Criteria published by the WHO	315	Low risk
Al-Aly 2022 [33]	Cohort study	USA	66.63 \pm 13.84	Before SARS-CoV-2 infection	BNT162b2, mRNA-1273, Ad26.COV2.S	The symptoms starting from 30 days after the first positive SARS-CoV-2 test	147,414	Low risk
Fernández 2022 [25]	Cohort study	Spain	41.0 \pm 16.8	Before or after COVID-19 diagnosis	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S	Presence of symptoms that persisted for more than 3 weeks after the initial infection and cannot be explained by other causes	110,726	Low risk
Messiah 2022 [26]	Cohort study	USA	5–19	NA	NA	Guideline published by the NICE	1748	Low risk
Meza-Torres 2022 [27]	Cohort study	UK	44.5 \pm 21.77	Before or after COVID-19 diagnosis	NA	Presence of fatigue, breathlessness, cognitive dysfunction, and a variety of other symptoms occurring more than 28 days after COVID-19 infection	408,882	Low risk
Peghin 2022 [28]	Cohort study	Italy	≥ 18	After COVID-19 diagnosis	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S	Guideline published by the NICE	479	Low risk

Table 1. *Cont.*

Study ID	Study Design	Nationality of Population	Age (Mean ± SD or Range) (Years)	Vaccination Time	Type of Vaccine	Definition of Long COVID *	Sample Size for Meta-Analysis	Quality Assessment
Pinato 2022 [29]	Cohort study	UK, Italy, Spain	≥18	Before SARS-CoV-2 infection	BNT162b2, mRNA-1273, ChAdOx1 nCoV-19, Ad26.COV2.S	Presence of long-term effects start at least 4 weeks after infection	1228	Low risk
Zisis 2022 [30]	Cohort study	USA	≥18	After COVID-19 diagnosis	NA	Presence of new, continuing, or recurrent symptoms that occur 4 or more weeks after the initial SARS-CoV-2 infection	50,450	Low risk
Budhiraja 2022 [35]	Cross-sectional study	India	<18–≥75	Before COVID-19 diagnosis	ChAdOx1nCoV-19, a whole-virion inactivated vero cell derived vaccine (available as Covaxin in India)	Presence of any symptoms after discharge from the hospital	5529	Low risk
Hajjaji 2022 [31]	Cross-sectional study	France	≥18	NA	NA	Persistent symptoms of SARS-CoV-2 infection lasting more than 6 months	168	Moderate risk

* Definition published by NICE: the term “long COVID” is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) [36].

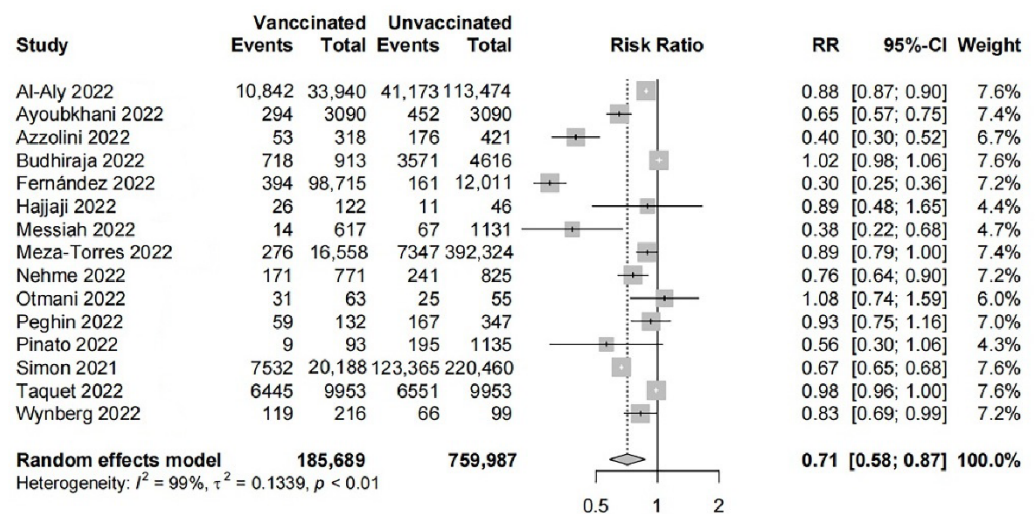


Figure 2. Forest plot of the effect of vaccination on long COVID [7,15,16,21,23–29,31,33–35].

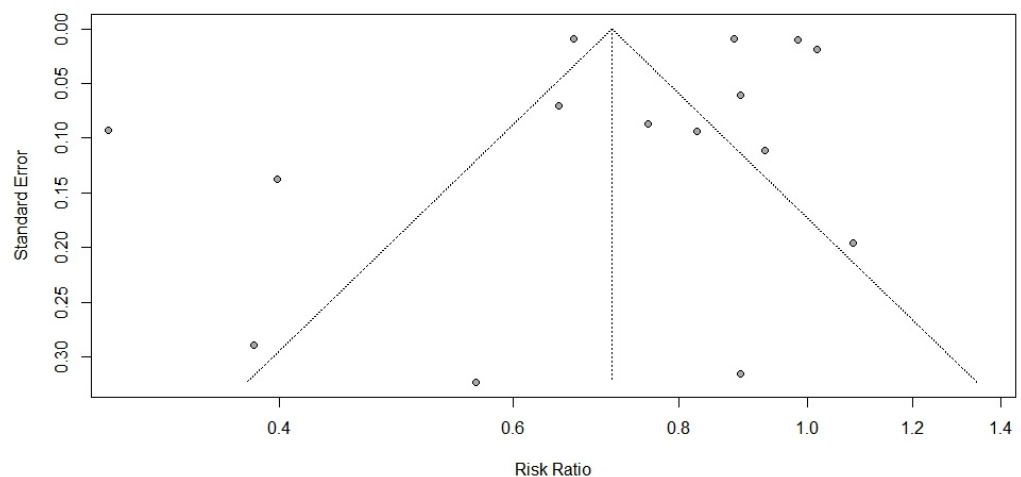


Figure 3. Funnel plot.

All of the participants in the two studies (Pinato 2022 [29] and Hajjaji 2022 [31]) were patients with cancer, and we excluded this study for the sensitivity analysis. The pooled RR = 0.71 (95%CI: 0.57–0.88, $p < 0.01$) with a high heterogeneity ($I^2 = 99\%$) was almost the same as the primary meta-analysis. We excluded preprints (Ayoubkhani 2022 [7], Simon 2021 [34], and Budhiraja 2022 [35]) for the sensitivity analysis. The pooled RR = 0.70 (95%CI: 0.58–0.89, $p < 0.01$) with a high heterogeneity ($I^2 = 96\%$) still indicated that COVID-19 vaccines had a protective effect on long COVID. In addition, regardless of which study was excluded separately, the difference in the incidence of long COVID between two groups still was statistically significant. The RR value ranged from 0.69 to 0.77. More details of the sensitivity analysis are shown in Table S4 of the Supplementary Material.

3.3. Subgroup Analysis

The results of the subgroup analysis are shown in Table 2. For the number of doses, the protective effect of vaccination on long COVID was only found in the population vaccinated with two doses. For age, a protective effect was not found in either subgroup. For vaccination time, vaccination reduced the risk of developing long COVID in both the “before SARS-CoV-2 infection/COVID-19” subgroup and “after SARS-CoV-2 infection/COVID-19” subgroup. For definition, the results of the meta-analysis were both statistically significant.

Table 2. Results of the subgroup analysis of the effect of vaccination on long COVID.

Subgroups	The Number of Studies	The Number of People	I^2 (%)	RR (95% CI)	p Value of Meta-analysis
The number of vaccine doses					
1 dose	6	655,962	99	0.83 (0.65–1.07)	0.14
2 doses	7	420,402	90	0.83 (0.74–0.94)	<0.01
Age					
<60 years	3	12,415	89	0.76 (0.54–1.06)	0.11
≥60 years	2	9509	55	0.87 (0.60–1.24)	0.43
Vaccination time					
Before SARS-CoV-2 infection/COVID-19	6	180,996	97	0.82 (0.74–0.91)	<0.01
After SARS-CoV-2 infection/COVID-19	4	2508	24	0.83 (0.74–0.92)	<0.01
Definition of long COVID					
Presence of symptoms more than 4 weeks after SARS-CoV-2 infection/COVID-19 diagnosis *	7	419,374	87	0.68 (0.53–0.87)	<0.01
Other definitions	8	526,302	99	0.75 (0.64–0.88)	<0.01

* This subgroup contained 3 studies that used the NICE definition.

3.4. Meta-Analysis for Long COVID Symptoms

The results of meta-analysis for long COVID symptoms are shown in Table 3. Compared with the unvaccinated group, the vaccinated group had a lower risk of cognitive dysfunction/symptoms, kidney diseases/problems, myalgia, and sleeping disorders/problems sleeping.

Table 3. Effects of vaccination on long COVID symptoms.

Long COVID Symptom	The Number of Studies	The number of People	I^2 (%)	RR (95% CI)	p Value of Meta-Analysis
Anxiety and/or depression	4	28,604	70	0.83 (0.67–1.03)	0.08
Chest or throat pain	3	26,386	0	1.01 (0.95–1.08)	0.67

Table 3. *Cont.*

Long COVID Symptom	The Number of Studies	The number of People	I ² (%)	RR (95% CI)	p Value of Meta-Analysis
Cognitive dysfunction/symptoms	2	22,124	8	0.89 (0.83–0.96)	<0.01
Fatigue	6	225,478	97	0.77 (0.58–1.02)	0.07
Hair loss	2	6480	50	0.86 (0.62–1.19)	0.37
Headache/migraine	4	76,836	99	0.95 (0.50–1.79)	0.87
Kidney diseases/problems	2	148,365	0	0.68 (0.64–0.73)	<0.01
Loss of concentration	2	6480	71	0.65 (0.35–1.19)	0.16
Loss of smell	3	8698	75	0.67 (0.36–1.26)	0.21
Loss of taste	3	8698	68	0.71 (0.48–1.07)	0.10
Myalgia	2	25,435	15	0.68 (0.62–0.74)	<0.01
Nausea and/or vomiting	2	6480	87	0.80 (0.31–2.02)	0.63
Respiratory symptoms/sequelae	5	78,064	98	0.91 (0.60–1.40)	0.68
Sleeping disorders/problem sleeping	3	8698	25	0.74 (0.64–0.86)	<0.01
Weight loss	2	6480	95	1.24 (0.22–7.05)	0.81

4. Discussion

As far as we know, our study is the first systematic review with a meta-analysis to assess the effect of COVID-19 vaccines on long COVID. A total 18 articles were included. In the primary meta-analysis, vaccination showed the effect of reducing the risk of long COVID. Considering the high heterogeneity between studies, the primary meta-analysis could be unstable, so we performed a sensitivity analysis. Each time a study was excluded for pooled RR evaluation, the protective effect of the vaccine always existed, indicating that the primary meta-analysis was stable. Because there are not many studies examining this topic, we included preprints. However, the preprints have not been peer-reviewed. We performed a sensitivity analysis by excluding three preprints. The result still supported the protective effect of COVID-19 vaccines. In the subgroup analysis, the results showed that people who received one dose vaccine did not acquire protection against long COVID, while those who received two doses did. Based on the data and the results of this paper, we cannot know the exact reason. We consider that it may be related to the higher vaccine effectiveness against symptomatic COVID-19 in people who received two doses of the vaccine. Several previous studies have confirmed this higher effectiveness [37–39]. Based on this, we recommend that people vaccinated with only one dose of COVID-19 vaccines should receive a second dose as soon as possible. Our study also found that the significance of vaccination is not limited to preventing SARS-CoV-2 infection and COVID-19. Vaccination in people who already have been infected with SARS-CoV-2 or COVID-19 is still effective at preventing long COVID. Based on this, we recommend that patients with SARS-CoV-2 infection or COVID-19 could choose to be vaccinated in order to prevent long COVID. The definition of long COVID was different between the included studies. Among the various definitions, more studies used “more than 4 weeks” as the observation period of long COVID symptoms. We divided these studies into one subgroup, and the articles that used other definitions into another subgroup. The results showed that the vaccine had a protective effect against long COVID in both subgroups. However, we believe that the difference in definitions brought an objective problem to our study. In future studies, we recommend that researchers use the NICE or WHO definitions in order to better describe what the outcome (long COVID) is in their articles, especially for review articles.

In this study, the protective effect of COVID-19 vaccines on long COVID symptoms could only be found in cognitive dysfunction/symptoms, kidney diseases/problems, myalgia, and sleeping disorders/problems sleeping. The pooled effect values of the other symptoms were negative. We believe this may be related to the small number of included studies. For most symptoms, only two or three studies were included for calculating the RRs, and most of the data were from three articles (Budhiraja 2022 [35]; Kuodi 2022 [32]; Taquet 2022 [24]). Not only that, in the study by Taquet, the number of patients with outcomes was high. This weight was very high (even higher than 90%) when the effect values were calculated, which had an

impact on the results. The same situation with the small number of included studies also occurred in the subgroup analysis according to age. More original studies are needed to assess the effect of COVID-19 vaccines on these symptoms. In fact, for all of the outcomes, more studies should be included to obtain more reliable results.

The results of some previous studies support our study. One study indicated that COVID-19 vaccination reduced the likelihood of developing long COVID symptoms 12 weeks after infection, and found a sustained improvement over time in people who received two doses of the vaccine [40]. A reduction in the prevalence of one or more of the post-SARS-CoV-2 symptoms (difficulty concentrating or memory loss, fatigue, headache, loss of change in smell, loss of or change in taste, and shortness of breath) was significantly associated with the use of COVID-19 vaccines [21]. In people with SARS-CoV-2 infection, patients who were vaccinated had a significantly lower risk of developing 24 sequelae compared with patients who were not vaccinated [33]. After patients with COVID-19 were discharged from the hospital, persistent symptoms had an impact on their health and reduced their quality of life [41]. In a survey of 2550 people, 32% of participants were unable to live alone without assistance 6 months after onset, and the work of 75% of participants was affected after an average of 7 months into long COVID [42]. A study from Indonesia found that full vaccination improved the health-related quality of life among patients with COVID-19 6 months after hospital discharge, and suggested that COVID-19 survivors be vaccinated [43].

The pathophysiology of long COVID and the mechanism of effect of COVID-19 vaccines on long COVID are not very clear. Varying extents of organ damage, persistence of chronic inflammation, and immune response/auto antibody generation may be the causes of long COVID [9]. In patients with long COVID, persistently elevated inflammatory makers could be observed [44]. A study reported that SARS-CoV-2 damages the neurons, directly or indirectly, involving the central nervous system and the peripheral nervous system, leading to neurological sequelae [45]. Moreover, a hypothesis of persistent and occult virus presence has been proposed after the identification of viral particles in organs after acute infection [46]. Vaccination may decrease the risk of long COVID by increasing antibody titers and potentially eliminating viral reservoirs [47]. This may explain the result (in our subgroup analysis) that vaccination after SARS-CoV-2 infection/COVID-19 is still useful for preventing long COVID. Another mechanism is that vaccines can reduce the severity of acute SARS-CoV-2 infection, thus leading to a lower risk of developing organ or systemic derangements [18]. Severe COVID-19 in the acute phase during hospitalization increased the risk of long COVID [48,49]. This may explain the result (in our subgroup analysis) that vaccination before SARS-CoV-2 infection/COVID-19 has a protective effect on long COVID.

We have four suggestions for future research. First, studies involving long COVID should state the definitions they use. We do not recommend that authors use their own definitions, because this will make it more difficult to summarize the evidence. It is better to use the definitions published by the NICE or WHO. Second, to strengthen the reliability of our results, more studies exploring the effect of vaccines on long COVID are needed in the future. In addition to whether long COVID has occurred, studies should focus on the development of long COVID symptoms. Third, it is important to explore how vaccines can prevent long COVID in basic research. Basic studies have a great reference value for examining the current doubts about mechanisms. Fourth, a large number of people have been vaccinated with inactivated vaccines, and there is an urgent need to assess the effect of inactivated vaccines on long COVID.

This study has two advantages. First, to the best of our knowledge, this is the first systematic review with a meta-analysis to quantifiably assess the effect of COVID-19 vaccines on long COVID. The protective effect of vaccination against long COVID has been found. This study provides evidence-based medical information on this topic. Second, the primary meta-analysis was statistically significant in the sensitivity analysis. The stability of the result was good. This study has four limitations. First, the heterogeneity of the studies was high, which had an impact on the reliability of the results. More studies are

needed in the future to calculate the effect values. Second, the definitions of long COVID are different among the included studies (especially observation time), although the NICE and WHO have both defined long COVID. This problem has also been considered in other studies [50,51]. It may be a source of heterogeneity in our study. Third, the data on some long COVID symptoms were insufficient to perform meta-analyses. For long COVID symptoms with meta-analyses, there were few pooled studies. The concept of fatigue associated with this syndrome is often also underestimated. Fourth, most of the participants were vaccinated with mRNA, and data on inactivated vaccines were lacking.

5. Conclusions

COVID-19 vaccines were found to have an effect on reducing the risk of long COVID. The protective effect was found in participants vaccinated with two doses, but not one dose. Regardless of whether being vaccinated before or after SARS-CoV-2 infection/COVID, vaccination was effective against long COVID. We suggest that the vaccination rate should be improved as soon as possible, especially for a complete vaccination course. It is better to be vaccinated so as to reduce the risk of long COVID, regardless of whether or not a patient has been infected with SARS-CoV-2. There should be more studies done to explore the basic mechanism of the protective effect of COVID-19 vaccines on long COVID in the future.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ijerph191912422/s1>, Table S1: Search strategy. Table S2: Data from the meta-analysis. Table S3: Quality assessment of the studies. Table S4: Sensitivity analysis by excluding one study every time.

Author Contributions: M.L. conceived and designed the study. P.G. carried out the literature searches. P.G. and J.L. selected the studies, extracted the data, assessed the study quality, and wrote the manuscript. P.G. performed the statistical analyses. M.L., J.L. and P.G. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review

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Summary

Background Although COVID-19 vaccination decreases the risk of severe illness, it is unclear whether vaccine administration may impact the prevalence of long-COVID. The aim of this systematic review is to investigate the association between COVID-19 vaccination and long-COVID symptomatology.

Methods MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as medRxiv and bioRxiv preprint servers were searched up to June 20, 2022. Peer-reviewed studies or preprints monitoring multiple symptoms appearing after acute SARS-CoV-2 infection either before or after COVID-19 vaccination collected by personal, telephone or electronic interviews were included. The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale.

Findings From 2584 studies identified, 11 peer-reviewed studies and six preprints were included. The methodological quality of 82% ($n=14/17$) studies was high. Six studies ($n=17,256,654$ individuals) investigated the impact of vaccines before acute SARS-CoV-2 infection (vaccine-infection-long-COVID design). Overall, vaccination was associated with reduced risks or odds of long-COVID, with preliminary evidence suggesting that two doses are more effective than one dose. Eleven studies ($n=36,736$ COVID-19 survivors) investigated changes in long-COVID symptoms after vaccination (infection-long-COVID-vaccine design). Seven articles showed an improvement in long-COVID symptoms at least one dose post-vaccination, while four studies reported no change or worsening in long-COVID symptoms after vaccination.

Interpretation Low level of evidence (grade III, case-controls, cohort studies) suggests that vaccination before SARS-CoV-2 infection could reduce the risk of subsequent long-COVID. The impact of vaccination in people with existing long-COVID symptoms is still controversial, with some data showing changes in symptoms and others did not. These assumptions are limited to those vaccines used in the studies.

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Keywords: Post-COVID syndrome; Long-COVID symptoms; Vaccine; SARS-CoV-2

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Introduction

COVID-19 caused by SARS-CoV-2 is the deadliest communicable healthcare outbreak of the 21st century. COVID-19 vaccines have significantly reduced the risk

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Research in context

Evidence before this study

We searched PubMed and Web of Science databases for studies published until April 1, 2022, using keywords “long-COVID”, OR “post-COVID” AND “vaccine” OR “vaccination”. We identified different studies analyzing the impact of COVID-19 vaccination in long COVID symptoms, but no systematic review was available in the literature.

Added value of this study

This first systematic review evaluating evidence to date about the impact of vaccines on long COVID supports that vaccination before SARS-CoV-2 infection is able to reduce the risk of developing long-COVID. The impact of vaccination in people with long-COVID symptomatology is controversial, with data showing changes in symptoms and others did not.

Implications of all the available evidence

Current results support that COVID-19 vaccines can be used as preventive strategy for decreasing the risk of long-COVID, but data about its effects on people with current long-COVID needs further research. Questions about the impact on hospitalised/non-hospitalised, males/females and the impact of vaccine boosters is clearly needed.

of developing the severe or critical forms of disease, as well as mortality brought by COVID-19.¹ Nonetheless, vaccines seem unable to fully reduce the spread of SARS-CoV-2 variants of concerns (VOCs).²

Following the COVID-19 outbreak, leading to hundreds of millions of acute cases and six million deaths, healthcare professionals are in front of another crisis brought about by development and/or persistence of symptoms after the acute phase of SARS-CoV-2 infection (typically after 3 months), a condition conventionally called long-COVID³ or post-COVID.⁴ More than 100 symptoms can appear after a SARS-CoV-2 acute infection, affecting multiple systems, *e.g.*, cardiovascular, respiratory, musculoskeletal, or neurological.⁵ Several meta-analyses observed that almost 50% of COVID-19 survivors had a lingering plethora of symptoms lasting for weeks or months^{6–8} but also one year^{9,10} after SARS-CoV-2 infection.

As of August 2022, more than 12.4 billion COVID-19 vaccine doses have been administered globally.¹¹ Although vaccination decreases the risk of severe COVID-19, it is unclear whether vaccination before or after an acute infection improves or reduces the prevalence of long-COVID symptoms. In fact, vaccinated people can still be infected and suffer from asymptomatic, mild or moderate COVID-19,

especially when the infection is sustained by VOCs (namely Omicron). Since long-COVID can arise even after a mild or asymptomatic SARS-CoV-2 infection,¹² it is in question what real impact vaccines will have on long-COVID.^{13–16} This review is the first to date to systematically investigate the impact of COVID-19 vaccination on long-COVID symptoms. Therefore, the research question of this review was: “what is the impact of COVID-19 vaccines on the risk of developing long-COVID or on existing long-COVID in COVID-19 survivors?”

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,¹⁷ and was prospectively registered in the Open Science Framework (OSF) database (<https://osf.io/34djr>). No ethical committed is needed for a systematic review.

Search strategy and selection criteria

Electronic literature searches were conducted by two different authors on the following databases: MEDLINE, CINAHL, PubMed, EMBASE, and Web of Science databases, as well as on preprint servers medRxiv and bioRxiv, for studies published until June 20, 2022. Database search strategies were conducted with assistance of an experienced health science librarian. We also screened the reference list of identified papers for capturing black literature. Searches were limited to human studies and English language citations by using the following combinations of terms: “long-COVID”, “long-COVID symptoms”, “long hauler”, “post-COVID-19” OR “post-acute COVID-19 syndrome” OR “post-acute COVID-19 symptoms” OR “COVID-19 sequelae” AND “vaccine” OR “vaccination” OR “COVID-19 vaccines” OR “SARS-CoV-2 vaccine”. The search strategy combined these terms using Boolean operators for the main databases is detailed in Supplementary Table.

The inclusion and exclusion criteria were formulated using the Population, Intervention, Comparison and Outcome (PICO) principle:

Population: Adults (>18 years) infected by SARS-CoV-2 and diagnosed with real-time reverse transcription-polymerase chain reaction (RT-PCR) assay. Individuals could have been hospitalised or not by SARS-CoV-2 acute infection.

Intervention: Any type of COVID-19 vaccine. We included the following types of COVID-19 vaccines: BNT162b2 (“Pfizer/BioNTech”), AZD1222 (“Oxford-AstraZeneca”), mRNA-1273 (“Moderna”), and Ad26.COV2.S (“Janssen”). Vaccine doses can be administered before or after SARS-CoV-2 acute infection.

Comparison: Individuals not receiving any COVID-19 vaccine.

Outcome: Collection of multiple symptoms (post-COVID-19 or long-COVID) developed after a SARS-CoV-2 acute infection (<https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/>) by personal, telephone, or electronic interviews. We included any type of symptom appearing after the infection e.g., physical (fatigue, pain), cognitive (brain fog, memory loss), respiratory (dyspnea, palpitations, cough), gastrointestinal (diarrhoea, stomachache, vomiting) or mental problems (depression, anxiety, sleep disturbances). Due to the different definitions of long-COVID, no specific follow-up period for the presence of symptoms after the acute infection was determined. Studies monitoring solely changes in immunologic or serologic biomarkers without assessment of post-COVID symptoms were excluded.

This review included observational cohort, cross-sectional, and case-control studies where samples of COVID-19 survivors, either hospitalised or non-hospitalised, were followed for presence of symptoms appearing after a SARS-CoV-2 acute infection before or after COVID-19 vaccination. Editorials, opinion, and correspondence articles were excluded.

Two authors reviewed the title and abstract of those publications identified in the databases. Duplicates were then removed. The title and abstract were screened for eligibility and posterior full-read text. Data including authors, country, sample size, setting, vaccination status, type of vaccine, clinical data, and post-COVID symptoms before and after vaccination were extracted from each study. Authors had to reach consensus on data extraction. Discrepancies between reviewers at any stage of screening process were resolved by asking a third author, when necessary.

Data analysis

The methodological quality of the studies was independently assessed by two authors using the Newcastle-Ottawa Scale, a star rating system evaluating the risk of bias of case-control and cohort studies.¹⁸ The Newcastle-Ottawa Scale evaluates the following sections in cohort studies: case selection (*i.e.*, representativeness of the cohort, selection of non-exposed cohort, case definition, outcome of interest), comparability (*i.e.*, proper comparison by controlling for age, gender, or other factors, between-groups) and exposure (*i.e.*, outcome assessment, long enough follow-up, adequate follow-up). Some of these items are adapted if the studies used case-control design. For instance, case selection item includes adequate case definition or selection of controls. In cohort studies using longitudinal design or

case-control studies, a rating of 7 to 9 stars indicates high quality, 5 to 6 medium quality, and less than or equal to 4 is of low quality. In cohort studies using cross-sectional design, a maximum of 3 stars can be awarded. Studies scoring 3 stars are considered of good quality, 2 stars of fair quality, and 1 star of poor quality. Methodological quality was initially evaluated by two authors. If there is disagreement, a third researcher arbitrated a consensus decision.

Meta-analysis was not deemed appropriate due to the high heterogeneity between studies. Accordingly, we conducted a synthesis of the data reported by addressing population, vaccine status related to acute infection, limitations, and methodological quality.

Role of the funding source

The sponsor had no role in the design, collection, management, analysis, or interpretation of the data, draft, review, or approval of the manuscript or its content. The authors were responsible for the decision to submit the manuscript for publication, and the sponsor did not participate in this decision. All authors had access to the data. Kin Israel Notarte and César Fernández-de-las-Peñas verified the data set. All authors were responsible for making the decision to submit this manuscript.

Results

Study selection

The electronic search identified 2584 titles for initial screening. After removing duplicates ($n=138$) and papers not directly related to vaccines and long-COVID ($n=2396$), 50 studies remained for abstract examination. 29 were excluded after abstract examination: not available in English text ($n=3$), case reports and case series studies ($n=5$), review articles ($n=7$), full text not available ($n=4$), and not focused on vaccines and long-COVID ($n=10$).

A total of 13 published and 8 preprint full-text articles were assessed for eligibility^{19–38} (Figure 1). Two articles were excluded because they were government summary reports.^{36,37} One preprint was excluded because it was a study protocol.³⁹ Lastly, one preprint³⁸ was excluded because the same study was previously published in a peer-reviewed journal.²³ Finally, a total of 11 peer-reviewed studies and 6 preprints were included in the systematic review.^{19–35}

Study characteristics

We identified two types of studies according to the relationship between vaccination and acute infection: (1) studies investigating the development of long-COVID symptoms in people who had received COVID-19 vaccine before being infected (vaccine - infection - long COVID); and (2) studies investigating changes in long-

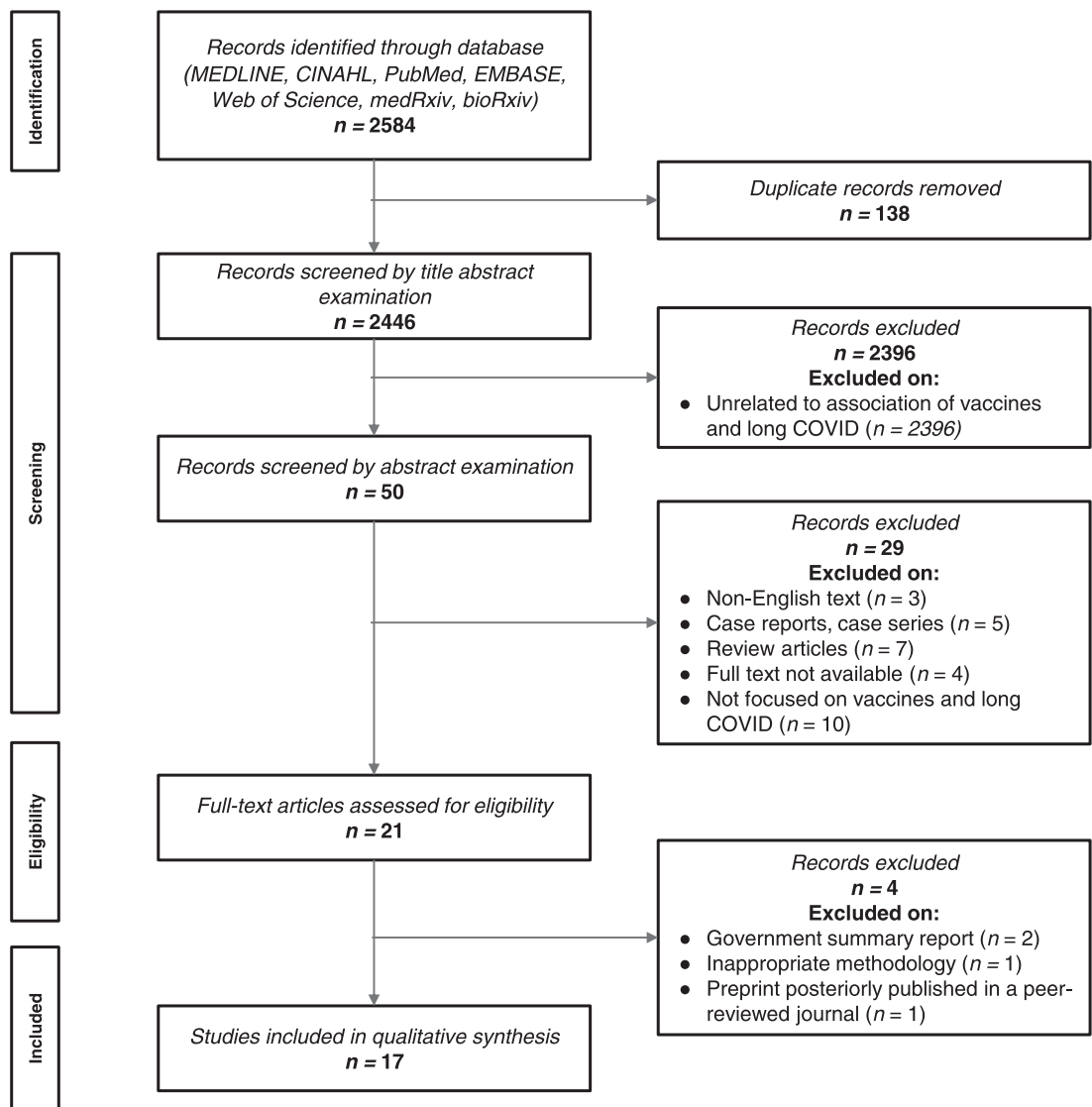


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow diagram.

COVID symptoms in people who had previously been infected, developed long-COVID, and then received vaccine after (infection - long COVID - vaccine).

The characteristics of the 'vaccine - infection - long COVID' studies are shown in [Table 1](#) (total sample $n=17,256,654$ participants). Five^{19,20,22-24} out of six articles provided data on mRNA and vector vaccines while the remaining study²¹ did not list the specific vaccine included. The countries of origin for these studies were the United States of America (USA), United Kingdom (UK), and India. Three papers²⁰⁻²² investigated patients who have had at least 2 doses of vaccine while the remaining three^{19,23,24} papers only required at least one dose of vaccine.

For the 'vaccine - infection - long COVID' studies, the impact of vaccine on long-COVID symptoms was

presented as odds ratio (OR), adjusted odds ratio (aOR), and hazards ratio (HR). Two articles^{23,24} used HR, two^{19,20} used purely OR, one²² used aOR, and another²¹ used both aOR and OR for expressing differences in long-COVID development between vaccinated and non-vaccinate people.

Overall, all six articles¹⁹⁻²⁴ agreed that vaccination before SARS-CoV-2 acute infection was associated with reduced risks or odds of long-COVID. There was high heterogeneity in the time from vaccination to infection, suggesting that people who had been vaccinated a month before being infected has lower risk of developing long-COVID symptoms. Antonelli et al.²⁴ and Taquet et al.²⁴ further posit that two doses could be more effective for reducing the risk of long-COVID than a single dose. Al-Aly et al.²⁴ concluded that

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Simon et al. 2021 ¹⁹ United States of America	Retrospective cohort Study Period: ND	n = 2392 Female = 1504 Hospitalized = 175	0 to >65 year Median age: ND	2392 vaccinated	2392 unvaccinated	Arcadia Data Research	Chest Pain Pallidations Altered mental state Anorexia Chills Fatigue Fever Malaise Loss of sense of smell Loss of sense of taste Nasal congestion Sore throat Abdominal pain Diarrhoea Digestive changes Nausea and/or Vomiting Arthralgia Muscle weakness General weakness Myalgia Headache Cough Dyspnea Fever Persistent cough Loss of smell Fatigue Headache Sore throat Dizziness Chills or shivers Hoarse voice Brain fog Unusual muscle pains Eye soreness Diarrhoea Shortness of breath Chest pain Nausea Tinnitus Abdominal pain Etiache Fatigue Joint pain Muscle pain Hair loss Headache Breathlessness Sleep disturbance Cough ND	Product: BNT162b2, mRNA 1273, Ad26. Dose: at least one Follow-up: 20 weeks Prior to COVID-19 OR 0.22 (0.196–0.245) >1 symptom Prior to COVID-19 OR 0.113 (0.09–0.143)	OR (95%CI) Any symptom Prior to COVID-19 OR 0.22 (0.196–0.245) >1 symptom Prior to COVID-19 OR 0.113 (0.09–0.143)
Antonelli et al. 2022 ²⁰ United Kingdom	Case control December 8, 2020 to July 4, 2021	n = 9462	Mean age: 52.9 years	Individuals with positive COVID-19 test at least 14 days after their first vaccination dose or 7 days after their second vaccination dose and had no positive test before vaccination	Unvaccinated participants reporting a positive SARS-CoV-2 test	COVID-19 Symptom Study App (UK Department of Health and Social Care)		Product: BNT162b2, ChAdOx1 nCoV-19, and mRNA 1273 Dose: Two doses Follow-up: At least 14 days after first dose of vaccination and at least 7 days after second dose of vaccination	OR (p-value) All age groups Symptoms lasting ≥28 day D1: 1.03 (0.78) D2: 0.51 (0.006) Younger adults (18–59 years) Symptoms lasting ≥28 day D1: 1.22 (0.14) D2: 0.37 (0.025) Older adults (60+ years) Symptoms lasting ≥28 day D1: 0.87 (0.29) D2: 0.56 (0.044)
Senjam et al. 2022 ²¹ India	Cross-sectional June 16 to July 28, 2022	n = 773 Female = 337 Male = 436 Hospitalized = 51	Median age: 34 years	366 vaccinated	407 unvaccinated	A semi-structured questionnaire was developed for the study purpose. The questionnaire was digitized using Google forms.		Product: Not reported Dose: Two doses Follow-up: Not reported	aOR (95%CI) Vaccinated: OR 0.65 (0.45–0.96) Unvaccinated: OR 0.55 (0.37–0.85)
Ayoubkhani et al. 2022 ²² United Kingdom	Prospective Cohort Study Period: ND	n = 6180 Female = 3335 Hospitalized = N/A	Mean (SD) Vaccinated: 49.0 (12.0) years Unvaccinated: 46.7 (11.2) years	3090 double vaccinated	3090 unvaccinated	UK COVID-19 Infection Survey		Product: ChAdOx1 nCoV-19, BNT162b2, and mRNA 1273 Dose: Two doses Median follow-up: 96 days Vaccinated: (IQR: 90 to 104) Unvaccinated: 98 days (IQR: 89 to 109)	aOR (95%CI) Long-COVID of any severity: aOR 0.59 (0.50 to 0.69)

Table 1 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Al-Aly et al. 2022 ²³ United States of America	Retrospective cohort March 1, 2020 and January 15, 2021	<i>n</i> = 13,369,073 BTI: <i>n</i> =33,940 Contemporary controls <i>n</i> = 4,983,491 Historical controls <i>n</i> = 5,785,273 Vaccinated controls <i>n</i> = 2,566, 369 Females = 1,300, 744 Hospitalized = 4478	BTI: 66.6 (13.8) years SARS-CoV-2 infection: 57.8 (15.9) years Contemporary control: 63.3 (16.6) years Vaccinated control: 67.7 (14.3) years Historical control: 61.8 (17.3) years	33,940 vaccinated with BTI BNT162b2 <i>n</i> =16,271 mRNA 1273 <i>n</i> =13,726 Ad26.COV2.S <i>n</i> =3943	People with SARS-CoV-2 infection and no prior history of vaccination <i>n</i> = 1,13,474	National healthcare databases of the US Department of Veterans Affairs	Cardiovascular, coagulation and hematologic gastrointestinal kidney mental health metabolic musculoskeletal neurologic disorders	Product: Ad26.COV2.S Dose: One Product: BNT162b2 Dose: Two Product: mRNA 1273 Dose: One Follow-up: within 6 months	BTI: Risk of death HR: 0.66 (0.58–0.74) burden of -10.99 (–13.45 to –8.22) Post-acute sequelae HR = 0.85 (0.82, 0.89) burden of -43.38 (–53.22 to –33.31) **negative values denote reduced burden in BTI relative to SARS-CoV-2 infection
Taquet et al. 2022 ²⁴ United States of America	Retrospective Cohort January 1, 2021 to August 31, 2021	<i>n</i> = 18,958 Female = 11,437 Hospitalized = No Data	Mean (SD), at infection: Vaccinated: 56.5 (18.0) years Unvaccinated: 57.6 (20.6) years	9479 participants vaccinated with COVID-19 vaccine	9479 participants unvaccinated with COVID-19 vaccine but with influenza vaccine at any time	TriNetX Analytics (Federated Network of Linked Electronic Health Records)	Abdominal symptoms Abnormal breathing Anxiety/Depression Chest/Throat Pain Cognitive symptoms Fatigue Headache Myalgia Other pain	Product: BNT162b2, mRNA 1273 Ad26.COV2.S, unspecified subtype Dose: 1-2 Follow-up: within 6 months	Fatigue (HR 0.89, 95% CI 0.81–0.97) Myalgia (HR 0.78, 95% CI 0.67–0.91) Pain (HR 0.90, 95% CI 0.81–0.99) Abnormal breathing (HR 0.89, 95% CI 0.81–0.98) Cognitive symptoms (HR 0.87, 95% CI 0.76–0.99) HR for other symptoms were not reported

Table 1: Summary of results for ‘vaccine - infection - long COVID’ studies.

ND - no data; aOR - adjusted odds ratio; SD - standard deviation; OR - odds ratio; HR - hazard ratio; RR - risk ratio; BTI - breakthrough infections

BNT162b2 (“Pfizer/BioNTech”) and mRNA-1273 (“Moderna”) vaccines were more effective for mitigating the risk of long-COVID compared to Ad26.COV2.S (“Janssen”) vaccine. Five^{19–21,23,24} papers listed specific symptoms, while the remaining²² did not specify any particular post-COVID symptom. The most common post-COVID symptoms analysed in the ‘vaccine-infection-long COVID’ papers were fatigue ($n=5$), muscle and joint pain ($n=5$), abdominal pain ($n=4$), diarrhoea ($n=4$), along with cough ($n=4$). Neurological symptoms and mental health problems including headache ($n=4$), brain fog or memory loss ($n=2$), anxiety ($n=2$), depression ($n=1$), altered mental state ($n=2$), and mood disorder ($n=1$) were also noted.

The characteristics of the ‘infection - long COVID - vaccine’ studies are shown in Table 2, involving 36,736 COVID-19 survivors and encompassing eleven papers.^{25–35} With respect to the geographical distribution, four articles were from the UK, two from the USA, one each from France, Italy, Israel, Japan, and Switzerland. Three out of 11 articles^{26,32,33} gathered data on mRNA vaccines only, seven articles^{25,27,29–31,34,35} on mRNA and viral vector vaccines, while one article²⁸ did not mention the type of vaccine. All studies included patients with at least a single dose of vaccine.

There was heterogeneity in the presentation of results for the ‘infection-long COVID-vaccine’ studies. Six out of the 11 articles^{25–30} made use of percentage in reporting the outcomes, one study³¹ used OR, one³³ aOR, one³⁵ mean difference, one³² risk ratio (RR), and the last one³⁴ all measures: mean difference, HR, and risk difference for the presentation of results. Seven articles^{26,27,30–34} agreed that there was improvement in long-COVID symptoms at least one dose post-vaccination, two of which^{30,32} reported that two doses of vaccines restored the reported symptoms back to baseline. On the contrary, four studies^{25,28,29,35} reported no change of long-COVID symptoms in the majority of participants. Tran et al.³⁴ stated that vaccination doubled the remission rate of long-COVID. On the contrary, Tsuchida et al.²⁸ noted that those participants worsening their long-COVID symptoms were reported to have increased antibody titer ratio resulting from excessive immune response to vaccination.

Seven out of the 11 articles^{28–33,35} listed changes in post-acute symptoms manifested by the patients, while 5 studies^{25–27,30,33} reported improvement, unchanged, or worsening of the long-COVID symptoms. The most common long-COVID symptoms evaluated in the ‘infection-long COVID-vaccine’ papers were fatigue ($n=6$), anosmia ($n=6$), and dysgeusia ($n=4$). Neurological symptoms and mental health problems including headache ($n=5$), anxiety ($n=4$), depression ($n=2$), brain fog ($n=2$), insomnia ($n=2$) and memory loss ($n=1$) were also reported.

Finally, the definition of long-COVID was not consistent. Seven articles described long-COVID in

accordance with the WHO⁴ as having COVID-19 symptoms usually 3 months from the onset of COVID-19 and that lasts for at least 2 months and cannot be explained by an alternative diagnosis.^{19,22,28–32} Two papers defined long-COVID in having persistent symptoms lasting for more than 4 weeks and the lack of an alternative diagnosis,^{20,27} and the remaining articles did not specify a particular definition of long-COVID, doing follow-up periods ranging from 1 month to 6 months after hospital discharge.^{21,23–26,33–38}

Methodological quality

Two studies (11.8%)^{20,27} used a case-control design and were of high (8/9 stars) and medium methodological quality (6/9 stars). The remaining fifteen (88.2%) were cohort studies, with six using a cross-sectional^{21,26,28,30,32,33} ($n=6/17$, 35.3%) and nine a longitudinal^{19,22,24,25,29,31,34,35,38} ($n=9/17$, 52.9%) design. Fourteen were of high methodological quality (3/3 stars or 7/9 stars, as appropriate) and one was of medium quality (6/9 stars). No disagreement between authors was observed. Tables 3–4 present the Newcastle-Ottawa Scale scores for each study and a summary of every item.

Discussion

This is the first systematic review to date aimed at summarising data about the impact of COVID-19 vaccine on long-COVID, to our knowledge. Low level of evidence (grade III, case-controls, cohort studies) suggests that vaccination before SARS-CoV-2 infection could reduce the risk of subsequent long-COVID; however, the influence of vaccination in people with previous long-COVID remains controversial, with evidence reflecting symptoms improving and others not. Our results agree with current opinions questioning the real impact the vaccines may have on current long-COVID symptoms.^{13–16,40}

The first situation is to assess if vaccines prevent long-COVID development. We identified six level III studies of moderate to high methodological quality investigating if vaccination before SARS-CoV-2 acute infection reduces the risk of developing long-COVID after (vaccine-infection-long COVID design). All studies found that vaccines reduced the risk of developing long-COVID in people with mild to moderate COVID-19, supporting the hypothesis that vaccination could be used as a preventive strategy for reducing long-term symptoms. However, most studies assessed the “short-term” effect of vaccines, since most included patients infected from one week to one month after vaccination. Only two studies investigated follow-up periods of six months after vaccination.^{23,24} Further, the definition of long-COVID was inconsistent between studies. Additionally, preliminary data suggest that two doses could

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Arnold et al. 2021 ²⁵ United Kingdom	Prospective observational cohort Patient recruitment: April-May 2020 3-month follow-up: June–July 2020 8-month follow-up: December 2020–January 2021 Vaccination: January–February 2021 Follow-up = 1-month post-vaccination	n = 66 Female = 25 Hospitalized = 66	Vaccinated: 64 (54–73) years Unvaccinated: 55 (47–60) years	44 vaccinated participants	22 unvaccinated participants	Telephone interview of quality of life (SF-36), mental wellbeing (WEMWBS) and ongoing symptoms	Fatigue Breathlessness Insomnia ENT symptoms Brain fog Muscle aches Anosmia Joint pain Cough Headache Palpitations Chest pain Diarrhoea Abdominal pain Nausea	Product: BNT162b2, ChAdOx1 nCoV-19 Dose: One Follow-up: 1 month post-single vaccination	Worsening of symptoms Vaccinated: 9/159 (5.6%) Unvaccinated: 13/91 (14.3%) Unchanged symptoms Vaccinated: 113/59 (71.1%) Unvaccinated: 64/91 (70.3%) Improvement of symptoms Vaccinated: 37/159 (23.2%) Unvaccinated: 14/91 (15.4%) p value = 0.035 Physical Composite Score - Median (IQR) Vaccinated = 41 (27–50) Unvaccinated = 34 (28–48) p value = 0.3 Mental Composite Score Median (IQR) Vaccinated = 48 (37–54) Unvaccinated = 38 (29–48) p value = 0.039 Warwick and Edinburgh Mental Wellbeing scores Median (IQR) Vaccinated 3 month = 51 (40–59) 6 month = 49 (42–57) Post-vaccination = 52 (41–61) Unvaccinated 3 month = 48 (38–54) 6 month = 45 (36–50) Matched post-vaccination = 54 (46–58) Worsening of symptoms 8/67 (12%); 3 with fatigue, 1 with respiratory symptoms, 2 with anxiety, 2 with worsening of other symptoms No change in symptoms 45/67 (67%) Improvement of one or more symptoms 14/67 (21%): 8 improving respiratory symptoms, 4 improving fatigue, 5 improving anxiety, 2 improving other symptoms
Gaber et al. 2021 ²⁶ United Kingdom	ND	n = 67 Females = ND Hospitalized = 67	18–65 years	67 healthcare workers with long-COVID-19	No control group	Survey questionnaire	Fatigue Shortness of breath Anxiety	Product: mRNA COVID-19 vaccine Dose: One dose Follow-up: At least 2 weeks post-single vaccination	

Table 2 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Scherlinger et al. 2021 ²⁷ United States of America	Cross sectional August 3-17, 2021	n = 567 Females = 473 Hospitalized = 25	44 (37-50) years	397 vaccinated with long-COVID-19 (255: 1 dose, 142: 2 doses) Hospitalized: 18	170 unvaccinated with long-COVID-19 Hospitalized: 7	Survey questionnaire	Fever/Chills Fatigue Brain fog Headaches Changing mood/ Impact on morale Sleeping issues Cortical pain Dyspnea Cough Palpitations Muscle aches Joint pain Paresthesia/Tingling Anosmia/Agusia Diarrhea/Vomiting Spontaneous bruises Pruritus	Product: BNT162b2, mRNA 1273, ChAdOx1 nCoV-19, Ad26.COV25, combination of mRNA/vector vaccine Dose: 1-2 Follow-up: Not reported	Improvement of symptoms after vaccination: 83 (21.8%) Anosmia 62% Brain fog 51% Worsening of symptoms after vaccination: 117 (31%) Fever/chills 74% GI symptoms 70% Paresthesia 64% Antralgia 63%
Tsuchida et al. 2022 ²⁸ Japan	Cohort Study period: ND	n = 42 Female = 25 Hospitalization = ND	45 (32-55) years	42 long COVID-19 patients	None	Self-assessments of post-vaccination changes in the main sequelae symptoms were confirmed based on the patient's response as follows: unchanged, relief, and worsened.	Fatigue Joint pain Taste and olfactory abnormality Numbness Sore throat Dizziness Memory impairment Palpitations Cough Headache Chest ache Anxiety	Product: Not reported Dose: One Follow-up: 2 weeks post-single vaccination	n (%) Fatigue Unchanged: 15(55.6) Relief: 5(18.5) Worse: 4(14.8) Joint pain Unchanged: 2(7.4) Worse: 2(7.4) Loss of Taste Unchanged: 5(18.5) Worse: 0(0)

Table 2 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with Long COVID
Peglin et al. 2022 ²⁹ Italy	Prospective cohort 6 months: September–November 2020 12 months: March–May 2021	<i>n</i> = 479 Overall Female: 257 (52.6) Vaccinated Female: 94 (71.2) Unvaccinated Female: 158 (45.5)	<i>n</i> (%) Overall: 18–40: 107 (22.3) 41–60: 205 (42.8) >60: 167 (34.9) Vaccinated: 18–40: 33 (25.0) 41–60: 64 (48.5) >60: 35 (26.5) Unvaccinated: 18–40: 74 (21.3) 41–60: 141 (40.6) >60: 132 (38.0)	132 vaccinated	347 unvaccinated	Telephone interviews	Fatigue Anosmia/dysgeusia Dyspnea Cough Chest pain Headache Rheumatological disorders Gastrointestinal disorders Cutsaneous lesions Hair loss URTl symptoms Ocular symptoms Neurological disorders Psychiatric disorders	Product: BNT162b2, mRNA 1273, ChAdOx1 nCoV-19, Ad26.COV2.S Dose: At least one dose Follow-up: Not reported	Post-COVID symptoms at 12-months compared with 6-months by vaccination Post-COVID-19 syndrome (<i>p</i> =0.209) Vaccinated (<i>n</i> =132) Unchanged: 87 (65.9%) Worsened: 30 (22.7%) Improved: 15 (11.4%) Unvaccinated (<i>n</i> =347) Unchanged: 247 (71.2%) Worsened: 55 (15.8%) Improved: 45 (13.0%) Post-COVID symptoms, <i>n</i> (%) (<i>p</i> =0.604) Vaccinated (<i>n</i> =132) 0: 73 (55.3%) 1: 27 (20.4%) 2: 17 (12.9%) 3: 7 (5.3%) 4: 1 (0.8%) ≥5: 7 (5.3%) Unvaccinated: 0: 180 (51.9) 1: 65 (18.7) 2: 42 (12.1) 3: 27 (7.8) 4: 11 (3.2) >5: 22 (6.3)

Table 2 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Spain et al. 2022 ²⁰ UK, Israel, Russia, India, South Africa	Cross-sectional March 16, 2021 and April 5, 2021	n = 812 Female = 80.6% Short hospital stay = 7.4% Long hospital stay +/- ITU = 3.6%	<20 to >71 years old	812 online Survey respondents	No control group	Survey questionnaire	Fatigue Brain fog Myalgia Shortness of Breath Insomnia Chest Pain Gastrointestinal symptoms Anosmia Autonomic dysfunction Postural Orthostatic Tachycardia Syndrome Persistent Cough Fever Rash (incl COVID-19 toes) Vascular complications	Product: ChAdOx1 nCoV-19, BNT162b2, mRNA 1273 Dose: One dose Follow-up: 1-21 weeks (median 9 weeks) post-single vaccination	57.9% reported overall improvement of symptoms 58% of participants vaccinated with ChAdOx1 nCoV-19 reported overall improvement of symptoms 56% of participants vaccinated with BNT162b2 reported overall improvement of symptoms 66% of participants vaccinated with mRNA 1273 reported overall improvement of symptoms 17.9% reported a worsening of their symptoms 19% of participants vaccinated with ChAdOx1 nCoV-19 reported worsening of their symptoms 18% of participants vaccinated with BNT162b2 reported deterioration of their average symptoms 12% of participants vaccinated with mRNA 1273 reported deterioration of their symptoms 24.2% reported no difference The mRNA 1273 vaccine compared favorably with ChAdOx1 nCoV-19 vaccine for improvements in fatigue (p = 0.009), brain fog (p = 0.01), myalgia (p = 0.006), gastrointestinal symptoms (p = 0.05) and autonomic dysfunction (p = 0.004)

Table 2 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Ayoubhani et al. 2022 ¹ United Kingdom	Prospective cohort February 3 to September 5, 2021	n = 28,356 Female Overall n = 15,760. Standardized difference = -7.1 mRNA vaccine = 7393 Adenovirus vector vaccine = 8367 Hospital admission with COVID-19 = 900. Standardized difference = 4.0 mRNA vaccine = 359 Adenovirus vector vaccine = 541	18–69 years old Mean age: 46 years	Participants with long-COVID symptoms vaccinated with mRNA (n = 12,659) Participants with long-COVID symptoms vaccinated with adenovirus vector (n = 15,497)	ND	COVID-19 Infection Survey UK Government Statistical Office	Loss of smell Loss of taste Trouble sleeping Fatigue Headache Trouble sleeping	Product: ChAdOx1 nCoV-19, BNT162b2, mRNA 1273 Dose: 1 Dose, 2 Doses Follow-up: Median time from first vaccination 141 days (among all participants) Median time from second vaccination 67 days (83.8% of participants)	After dose 1 Loss of smell (OR -12.5%, -21.5% to -2.5%, p=0.02) Loss of taste (OR -9.2%, -19.8% to 2.7%, p=0.13) Trouble sleeping (OR -8.6%, -19.4% to 3.3%, p=0.15) After dose 2 Fatigue (OR -9.7%, -16.5% to -2.4%, p=0.01) Headache (OR -9.0%, -18.1% to 1.0%, p=0.08) Trouble sleeping (OR -9.0%, -18.2% to 1.2%, p=0.08)
Kuodi et al. 2022 ² Israel	Cross-sectional March 2020 to November 2021	n = 3388 No. of participants who filled out 'sex': 750 Female Overall n = 467, p=0.206 Received 1 dose = 175 Received 2 doses = 136 Unvaccinated = 156 Hospitalized Overall n = 85, p = 0.277 Received 1 dose = 35 Received 2 doses = 21 Unvaccinated = 29	≥ 18 years old	Received 1 vaccine dose (n=340) Received 2 vaccine doses (n=294)	Unvaccinated (n=317)	Survey Questionnaire International Severe Acute Respiratory and emerging infection Consortium (ISARIC)	Fatigue Headache Weakness in arms or legs Persistent muscle pain Loss of concentration Hair loss Sleeping problems Dizziness Persistent cough Shortness of breath	Product: BNT162b2 Dose: 1 dose group, 2 doses group Follow-up: Not reported	Fatigue (21.87%) Vaccinated, 1 dose (n=93) RR: 1.057 (0.820–1.364) Vaccinated, 2 doses (n=33) RR: 0.434 (0.299–0.629) p-value: 0.003 Unvaccinated (n=42) Headache (19.98%) Vaccinated, 1 dose (n=110) RR: 1.081 (0.814–1.435) Vaccinated, 2 doses (n=77) RR: 0.641 (0.450–0.911)* Unvaccinated (n=55) Weakness arms/legs (13.5%) Vaccinated, 1 dose (n=127) RR: 1.042 (0.738–1.472) Vaccinated, 2 doses (n=82) RR: 0.423 (0.258–0.692)* Unvaccinated (n=103) Muscle pain (10.3%) Vaccinated, 1 dose (n=106) RR: 1.165 (0.773–1.757) Vaccinated, 2 doses (n=80) RR: 0.509 (0.292–0.886)* Unvaccinated (n=86) Loss of concentration (9.5%)

Table 2 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Nehme et al. 2022 ¹¹ Switzerland	Prospective cohort April 23 to July 27, 2021	n = 1596 Female = 883 Males = 713 all participants are out-patient	Mean age: 43.5 years	771 vaccinated (424 first dose, 347 second dose)	825 unvaccinated	REDCap v11.0.3 and Stata 15.1 (SataCorp)	Fatigue Difficulty concentrat- ing or memory loss Loss or change in smell Loss or change in taste Shortness of breath Headache	Product: BNT1 62b2, mRNA 1273 Dose: 1:2 Vaccination (one or two doses) was associated with decreased preva- lence of the six cardinal post-COVID symptoms [aPR 0.72: 0.56–0.92] Vaccination with 2 doses decreased prevalence of dyspnea [aOR 0.34; 0.14 –0.82] and change in taste [aOR 0.38; 0.18- 0.83] Decreased prevalence of any one symptom [aOR 0.60; 0.43–0.83]	Vaccinated, 1 dose (n=59) RR: 1.243 [0.893–1.901] Vaccinated, 2 doses (n=48) RR: 0.425 [0.228–0.791] * Unvaccinated (n=55) Half loss (9.25%) Vaccinated, 1 dose (n=43) RR: 1.113 [0.735–1.687] Vaccinated, 2 doses (n=9) RR: 0.270 [0.132–0.550] * Unvaccinated (n=36) Sleeping problems (8.94%) Vaccinated, 1 dose (n=42) RR: 1.350 [0.863–2.113] Vaccinated, 2 doses (n=14) RR: 0.521 [0.281–0.965] * Unvaccinated (n=29) Dizziness (7.78%) Vaccinated, 1 dose (n=30) RR: 0.874 [0.544–1.404] Vaccinated, 2 doses (n: 12) RR: 0.404 [0.212–0.770] * Unvaccinated (n=32) Persistent cough (7.36%) Vaccinated, 1 dose (n=26) RR: 1.010 [0.593–1.711] Vaccinated, 2 doses (n=20) RR: 0.899 [0.507–1.592] Unvaccinated (n=26) Shortness of breath (7.15%) Vaccinated, 1 dose (n=29) RR: 1.081 [0.648–1.805] Vaccinated, 2 doses (n=14) RR: 0.604 [0.320–1.139] Unvaccinated (n=25)

Table 2 (Continued)

Author and Country of Origin	Study Design and Study Period	Sample Size	Median Age (Range)	Cases	Controls	Objective Assessment of Symptoms	Post-Acute Symptoms Reported	Vaccine Information (Product, Dose, Follow-up Period)	Impact of Vaccine on Symptoms Associated with long-COVID
Tran et al. 2021 ³⁴ France	Prospective cohort November 2020 to May 2021 (still ongoing)	<i>n</i> = 910 Female = 733 Male = 177 Hospitalized = 81	Mean age: 47 years	445 vaccinated	455 unvaccinated	ComPaRelong-COVID-19 database	COVID-19 ST score (53 symptoms)	Product: BNT162b2, mRNA 1273, ChAdOx1 nCoV-19 Dose: 1–2	Long-COVID was significantly less severe in the vaccination group than in the control group mean (SD) long-COVID ST score 13 (9.4) in the vaccination group and 14.8 (9.8) in the control group Mean Difference: -1.8, 95% CI -2.5 to -1.0 16.6% complete remission from long-COVID 7.5% (control group)
Wisnivesky et al. 2022 ³⁵ United States of America	Prospective Cohort Patient recruitment: July 20, 2020 - February 26, 2021 6-month interview: August 23, 2021	<i>n</i> = 453 Female <i>n</i> = 294 Hospitalized/patients (ER, Inpatient, ICU) <i>n</i> = 264	mean (SD) Vaccinated = 50.1 (13.4) years Unvaccinated = 49.7 (14.1) years	324 vaccinated participants	129 unvaccinated participants	5-point Likert question for anosmia Modified Medical Research Council (mMRC) scale for dyspnea St. George's questionnaire for respiratory symptoms Patient Health Questionnaire-8 (PHQ-8) for depression Generalized Anxiety Disorders-7 (GAD-7) instrument for anxiety PTSD checklist for DSM-5 (PCL-5) for PTSD symptoms Patient-Reported Outcomes Measurement Information System (PROMIS)-29 v2.0 Scale for quality of life	Anosmia Respiratory symptoms Dyspnea Cough Phlegm Wheezing Depression symptoms Anxiety symptoms COVID-19 PTSD symptoms Non-COVID-19 PTSD symptoms Quality of life Physical function Anxiety Depression Fatigue Social roles Sleep Pain	Product: BNT162b2, mRNA 1273, Ad26.COV2.S Dose: at least one dose of vaccine Follow-up: 2 weeks - 6 months post single vaccination	Difference change vaccinated vs. unvaccinated (95% CI) Anosmia -0.26 (-0.54 to -0.03) Respiratory symptoms Dyspnea 0.02 (-0.19 to 0.23) Cough 0.003 (-0.39 to -0.39) Phlegm -0.28 (-0.76 to 0.20) Wheezing 0.41 (-0.27 to 1.1) Depression symptoms 0.32 (-0.88 to -1.53) Anxiety symptoms 1.29 (-0.24 to -2.82) COVID-19 PTSD 3.41 (-1.82 to -8.63) Quality of life Physical function -0.95 (-2.96 to 1.05) Fatigue -1.40 (-3.98 to 1.18) Social role -2.32 (-5.51 to -0.87) Sleep 1.16 (-1.10 to 3.41) Pain -0.84 (-3.19 to 1.52)

Table 2: Summary of results for 'infection - long COVID - vaccine' studies.

ND - no data; aOR - adjusted odds ratio; SD - standard deviation; OR - odds ratio; HR - hazard ratio; RR - risk ratio; BTI - breakthrough infections; ICU - intensive care unit; PTSD - post-traumatic stress disorder; ER - emergency room.

Study	Selection	Comparability	Exposure
	Adequate case definition		
Representativeness of cases Selection of controls Definition of controls Controlled for age Controlled for additional factors Ascertainment of exposure Same method for cases and controls Non-response rate Score Scherlinger et al. 2022 ²⁷ ★★★★★★6/9 Antonelli et al. 2022 ²⁸ ★★★★★★8/9			

Table 3: Newcastle - Ottawa quality assessment scale evaluating methodological quality/risk of bias (case-control studies).

be more effective than one single dose²⁴ and that BNT162b2 (“Pfizer/BioNTech”) or mRNA-1273 (“Moderna”) vaccine could be more effective than Ad26. COV2.S (“Janssen”) vaccine²⁴ for reducing the risk of developing long-COVID, in keeping with previous data showing that the efficacy of mRNA-based vaccines on the risk of developing severe illness may be higher compared to adenoviral vaccines. No study investigated the impact of vaccine boosters on long-COVID.

The mechanisms underlying a potential risk reduction of long-COVID in people previously vaccinated are unknown. Two hypotheses are proposed. First, since vaccines reduce the severity of acute SARS-CoV-2 infection, this may then translate into lower risk of developing organ or systemic derangements, and thus symptoms onset and duration. However, the association of long -COVID with COVID-19 severity remains controversial.⁴¹ A second hypothesis is that vaccines may accelerate clearance of the remaining SARS-CoV-2 virus in the human body (viral remnant hypothesis of long-COVID) or could also reduce the exaggerated inflammatory and/or immune response associated with long-COVID development (immune/inflammatory hypothesis of long-COVID).⁴² Future studies investigating the underlying mechanisms of vaccines on long-COVID would be needed to clarify these issues.

The second topic is to know if COVID-19 vaccines represent a risk for those individuals with ongoing long-COVID symptomatology. We identified eleven level III studies of moderate to high methodological quality investigating the impact of vaccine on individuals who had previously suffered from COVID-19 and developed long-COVID (infection-long COVID-vaccine design). The results here were less consistent, since 63% of the studies ($n=7/11$) found that vaccination improved ongoing symptoms of long-COVID, whereas 36% ($n=4/11$) reported small changes or even worsening in some patients. Again, the definition of long-COVID among the studies was inconsistent. This heterogeneity in the response against vaccines of individuals with long-COVID could be related to the complexity of this condition. For instance, Tsuchida et al.²⁴ identified that people experiencing a worsening of long-COVID symptoms after vaccination are those also showing excessive immune response to vaccination, with higher increased rate of antibody titers. On the contrary, Peghin et al.²⁴ observed that COVID-19 vaccines did not produce an altered humoral response in individuals with current long-COVID. Discrepancies between these studies could be related to the fact that numerous auto-antibodies may be produced after SARS-CoV-2 infection⁴³ and, accordingly, COVID-19 vaccines effects could be dependent on the host immune response. Further, since long-COVID includes a myriad of >100 different multiorgan symptoms,⁵ it is possible that vaccines influence could be related to some specific long-COVID symptoms. Accordingly, COVID-19

Study	Selection		Comparability				Exposure			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest	Controlled for age	Controlled for additional factors	Assessment of outcome	Follow-up long enough	Adequacy of follow-up	Score
Gaber et al. 2020 ²⁶	★			★				★		3/3
Senjam et al. 2021 ²¹	★			★				★		3/3
Nehme et al. 2021 ³³	★			★				★		3/3
Kuodi et al. 2022 ³²	★			★				★		3/3
Tsuchida et al. 2021 ²⁸	★			★				★		3/3
Strain et al. 2022 ³⁰	★			★				★		3/3
Peghin et al. 2022 ²⁹	★		★	★	★			★	★	7/9
Tran et al. 2022 ³⁴	★		★		★		★	★	★	7/9
Ayoubkhani et al. 2022 ³¹	★		★	★	★			★	★	7/9
Ayoubkhani et al. 2022 ²²	★		★		★	★	★	★	★	8/9
Wisnivesky et al. 2022 ³⁵	★		★	★	★			★	★	7/9
Simon et al. 2021 ¹⁹	★		★		★			★	★	6/9
Taquet et al. 2021 ²⁴	★		★		★		★	★	★	7/9
Al-Aly et al. 2022 ²³	★		★	★	★			★	★	7/9
Arnold et al. 2020 ²⁵	★		★	★	★		★	★	★	8/9

Table 4: Newcastle - Ottawa quality assessment scale evaluating methodological quality/risk of bias (cross-sectional or longitudinal descriptive studies and cohort studies).

vaccination may help to reduce long-COVID by eradicating the viral reservoir or by resetting a deregulated immune response to primary acute infection, and this effect could be host-dependent. Overall, although current evidence is inconclusive, available data suggest that COVID-19 vaccines are important factors for further immunological protection against potential reinfections.

The results of this systematic review should be considered according to potential strengths and limitations. Among the strengths, we conducted a deep systematic search of all the available evidence about the impact of vaccines on long-COVID. This led to identification of six non-peer reviewed, preprint articles. Considering the rapid emergence which represents the COVID-19 pandemic, the volume of preprint research could be expected given the need for rapid data dissemination. Second, this is the first time that the methodological quality of published studies is conducted. Interestingly, albeit heterogeneity in the concepts and designs, the quality of most study designs (82%) was high.

Three main limitations should be recognised. First, the effects of vaccines on long-term post-COVID symptoms are scarce, since most studies identified in this review investigated the risk of long-COVID in people infected the first month after being vaccinated. Second, there was no consistent definition of long-COVID in the published literature. In most studies, symptoms were assessed during the first month after the infection, which could not represent the reality of long-COVID, where symptoms can persist during months and years.^{9,10} We included all studies investigating changes in any symptom appearing after a SARS-CoV-2 infection. In fact, just seven studies (41%) used the WHO definition of post-COVID-19 condition.⁴ Future studies including the WHO definition of post-COVID-19 condition⁴ should be conducted to get better stratification of the population. In addition, it should be considered that vaccinated individuals were older than non-vaccinated, probably because worldwide vaccination strategies firstly focused on vulnerable individuals. Third, no study differentiated between hospitalised and non-hospitalised patients or sex-differences between males and females. Similarly, no evidence is available on the SARS-CoV-2 variants that caused acute infections, since no study summarise the VoC included in their population samples; so that a bias on long-COVID burden and characteristics attributable to infection with different VOCs cannot be ruled out. Therefore, studies investigating the impact of COVID-19 vaccines in 1, hospitalised or non-hospitalised patients; 2, males and females; and 3, the different VoC and potential reinfections are now needed. Finally, no study investigated the impact of vaccine boosters in long-COVID symptomatology. Since booster programs have been increasingly implemented in several countries, particularly in vulnerable individuals, the impact of

third or fourth booster dose on long-COVID should be investigated.

In conclusion, low level of evidence suggests that vaccination before SARS-CoV-2 infection could reduce the risk of developing subsequent long-COVID. It seems that two doses of vaccine could be more effective than just one dose, although data are preliminary and based in just two studies. No data on vaccine boosters are still available. The impact of vaccination in people who had been infected, had developed long-COVID symptoms, and, then vaccinated is inconsistent, with both positive and negative impact. This conclusion is based on grade III studies (case-controls, cohort studies). These assumptions are also limited to those vaccines used in the studies. This highlights the need for more studies better defining the participants involved, the inclusion of different SARs-CoV-2 VoC, and a proper definition of long-COVID.

Contributors

All the authors cited in the manuscript had substantial contributions to the concept and design, the execution of the work, or the analysis and interpretation of data; drafting or revising the manuscript and have read and approved the final version of the paper. Kin Israel Notarte: conceptualisation, visualisation, methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing, conceptualisation, formal analysis, data curation, writing-review and editing. Jesus Alfonso Catahay: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Jacqueline Veronica Velasco: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Adriel Pastrana: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Abbygail Therese Ver: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Flos Carmeli Pangilinan: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Princess Juneire Peligro: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Michael Casimiro: methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing. Jonathan Jaime Guerrero: writing-review and editing. Ma. Margarita Leticia Gellaco: writing-review and editing. Giuseppe Lippi: writing—review and editing. Brandon Michael Henry: writing-review and editing. César Fernández-de-las-Peñas: conceptualisation, visualisation, validation, formal analysis, writing-review and editing, and supervision. All authors had access to the data. Kin Israel Notarte and César Fernández-de-las-Peñas verified the data set. All authors were responsible for making the decision to submit this manuscript.

Data Sharing Statement

All data derived from this study are in the article.

Declaration of interests

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101624.

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Long COVID Risk and Pre-COVID Vaccination: An EHR-Based Cohort Study from the RECOVER Program

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Key Points

Question: Does vaccination prior to COVID-19 onset change the risk of long COVID diagnosis?

Findings: Four observational analyses of EHRs showed a statistically significant reduction in long COVID risk associated with pre-COVID vaccination (first cohort: HR, 0.66; 95% CI, 0.55-0.80; OR, 0.69; 95% CI, 0.59-0.82; second cohort: HR, 0.62; 95% CI, 0.56-0.69; OR, 0.70; 95% CI, 0.65-0.75).

Meaning: Vaccination prior to COVID onset has a protective association with long COVID even in the case of breakthrough infections.

Abstract

Importance: Characterizing the effect of vaccination on long COVID allows for better healthcare recommendations.

Objective: To determine if, and to what degree, vaccination prior to COVID-19 is associated with eventual long COVID onset, among those a documented COVID-19 infection.

Design, Settings, and Participants: Retrospective cohort study of adults with evidence of COVID-19 between August 1, 2021 and January 31, 2022 based on electronic health records from eleven healthcare institutions taking part in the NIH Researching COVID to Enhance Recovery (RECOVER) Initiative, a project of the National Covid Cohort Collaborative (N3C).

Exposures: Pre-COVID-19 receipt of a complete vaccine series versus no pre-COVID-19 vaccination.

Main Outcomes and Measures: Two approaches to the identification of long COVID were used. In the clinical diagnosis cohort (n=47,752), ICD-10 diagnosis codes or evidence of a healthcare encounter at a long COVID clinic were used. In the model-based cohort (n=199,498), a computable phenotype was used. The association between pre-COVID vaccination and long COVID was estimated using IPTW-adjusted logistic regression and Cox proportional hazards.

Results: In both cohorts, when adjusting for demographics and medical history, pre-COVID vaccination was associated with a reduced risk of long COVID (clinic-based cohort: HR, 0.66; 95% CI, 0.55-0.80; OR, 0.69; 95% CI, 0.59-0.82; model-based cohort: HR, 0.62; 95% CI, 0.56-0.69; OR, 0.70; 95% CI, 0.65-0.75).

Conclusions and Relevance: Long COVID has become a central concern for public health experts. Prior studies have considered the effect of vaccination on the prevalence of future long COVID symptoms, but ours is the first to thoroughly characterize the association between vaccination and clinically diagnosed or computationally derived long COVID. Our results bolster the growing consensus that vaccines retain protective effects against long COVID even in breakthrough infections.

Introduction

The SARS-CoV-2 virus, and the COVID-19 pandemic it effected, hardly needs introducing more than two years after the WHO first announced evidence of human-to-human transmission in

January of 2020.¹ As of this writing, the WHO states there have been 594 million confirmed cases and more than 6 million deaths attributed to COVID-19 worldwide.² Post-acute sequelae of SARS-CoV-2 infection (PASC) have been widely reported and can include any complication resulting from SARS-CoV-2 infection weeks after infection occurred.^{3–5} Long COVID is a single diagnosis that encapsulates the broad array of ever-shifting symptoms attributed to PASC.

Vaccines have been shown to be safe and effective at dramatically reducing the risk of severe COVID-19.^{6,7} Their impact on long COVID is less understood, with some studies indicating they have a significant protective effect^{8–10} while others reported mixed effects¹¹ or even an anti-protective effect.¹² While some have studied the impact of administering vaccines after the onset of PASC,^{13–15} we attempt to address ambiguity around the association between pre-COVID-19 vaccination and eventual long COVID diagnosis.

To our knowledge, we are the first to consider vaccination with long COVID directly, in the form of clinical diagnoses or a computable phenotype;¹⁶ previous studies have relied on the occurrence of one or two symptoms consistent with long or acute COVID. Ours is also the largest study to leverage time-to-event modeling or control for differences in the vaccinated and unvaccinated populations.

The National Institutes of Health (NIH) created the RECOVER initiative to address the uncertainty surrounding long COVID by coordinating research across hundreds of researchers and more than 30 institutions.¹⁷ The National COVID Cohort Collaborative (N3C),¹⁸ sponsored by NIH's National Center for Advancing Translational Sciences, provides access to harmonized electronic health records (EHRs) through the N3C Data Enclave. More than 75 sites have contributed longitudinal data for over 15.5 million patients with a confirmed SARS-CoV-2 infection, COVID-19 symptoms, or their matched controls.

Methods

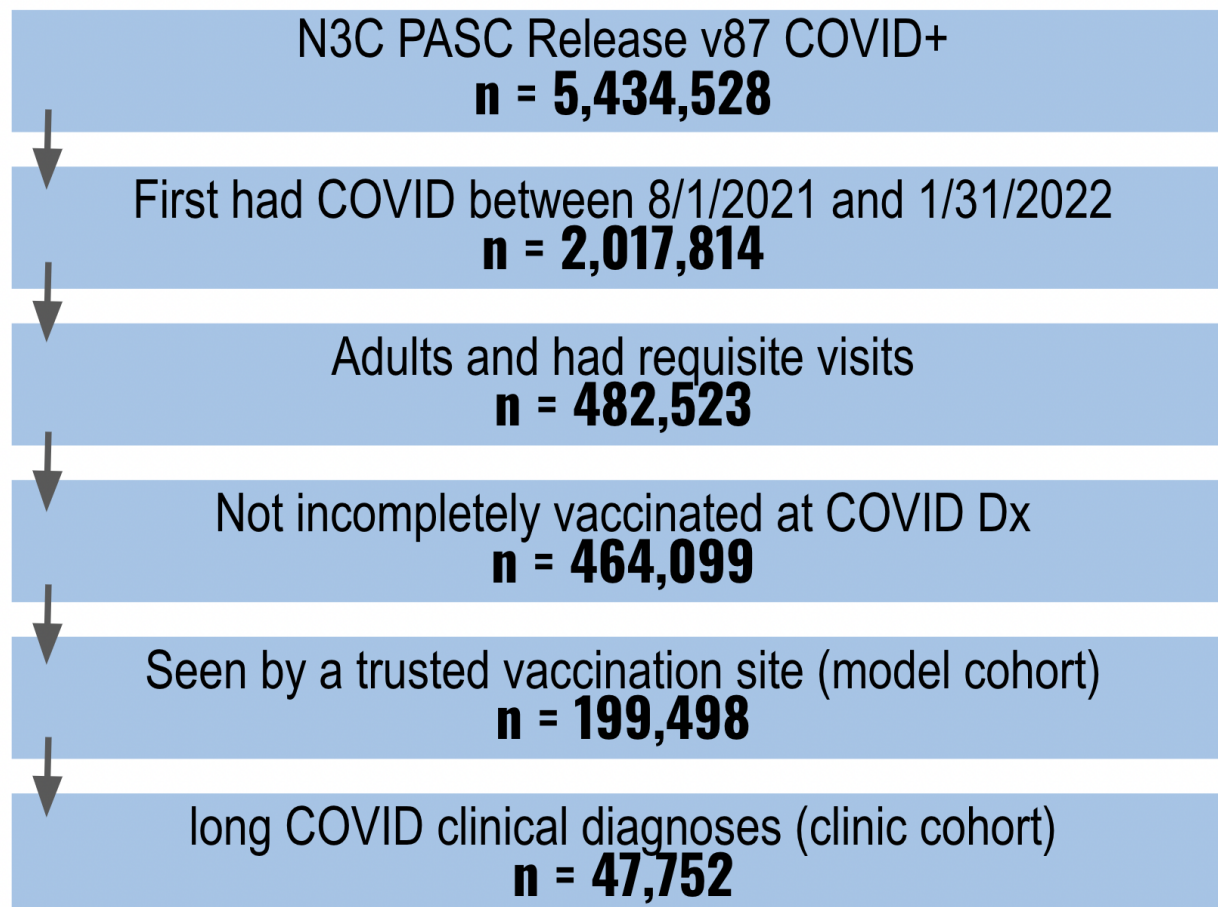
Base Population

This study is part of the NIH Researching COVID to Enhance Recovery (RECOVER) Initiative, which seeks to understand, treat, and prevent PASC. For more information on RECOVER, visit <https://recovercovid.org>. All analyses described here were performed within the secure N3C Data Enclave. N3C's methods for patient identification, data acquisition, ingestion, data quality assessment, and harmonization have been described previously.^{18,19} The study population was drawn from 5,434,528 COVID-19-positive patients available in N3C. A COVID-19 index date (index) was defined as the earliest recorded indication of COVID-19 infection. Individuals who met the following inclusion criteria were eligible: (1) having an International Classification of Diseases-10-Clinical Modification (ICD-10) COVID-19 diagnosis code (U07.1) or a positive SARS-CoV-2 PCR or antigen test between August 1, 2021 and January 31, 2022; (2) having a recorded health care visit between 120 and 300 days after index; (3) having at least two recorded health care visits in the year prior to index; (4) being ≥ 18 years old at index; and (5) having either completed or not started a COVID-19 vaccine regimen at index.

One known limitation of EHR data is that only those healthcare encounters and services provided by the specific health system are available in the data.²⁰ The proportion of patients with a recorded vaccination at a given health care site is driven by two factors: (1) the true rate of vaccination among the population served and (2) how consistently vaccines are captured by the

site. Some sites report no vaccinations, while others sync vaccination records with their state's vaccine registry. There is no explicit indicator of non-vaccination in the N3C Data Enclave, but sites with better vaccination coverage offer more confidence that patients with no recorded vaccine exposure are unvaccinated. We calculated vaccination coverage at each site as the ratio of two statistics: the observed proportion of patients with a vaccination record and an expected vaccination rate derived from CDC reporting²¹ for the population served. Sites with an observed proportion at least two-thirds of their expected vaccination rate were eligible for analysis, leaving 199,498 patients at eleven sites that met our inclusion criteria. A full breakdown of how many patients met our inclusion criteria is shown in Figure 1.

Figure 1. Cohort Definition Flowchart



Exposure Definition

Those who completed their vaccine regimen (2 mRNA or 1 viral vector vaccine) prior to index were considered vaccinated, while those with no recorded vaccines at index were considered unvaccinated. Partially vaccinated patients at index failed to meet the fifth inclusion criterion.

Outcome Definitions

Clinical definition

We considered three clinical indicators of long COVID: (1) an ICD-10 code for post COVID-19 condition (U09.9), (2) an ICD-10 code for sequelae of other specific infectious and parasitic diseases (B94.8), or (3) a visit to a long COVID clinic. Prior to the introduction of U09.9 in October 2021, the CDC endorsed B94.8 to indicate long-term complications of SARS-CoV-2

infection. As with vaccination, not all sites report clinical indicators of long COVID. Six out of eleven sites, comprising 47,752 of 199,498 eligible patients, submitted clinical indicators of long COVID for at least 250 patients. We used patients from these six sites to form a clinic-based cohort of patients, whom we deemed eligible for receiving a clinical long COVID indicator.

Any long COVID clinical indicator was sufficient to label a patient as having had long COVID in the logistic regression. If patients had multiple encounters with a clinical indicator of long COVID, the earliest was used as the event date for purposes of the time-to-event analysis. Death and COVID-19 vaccination after COVID-19 onset were censoring events.

Model-based definition

Long COVID was classified in the model-based cohort using the long COVID cohort identification machine learning model (LC model) described in Pfaff et al, 2022;¹⁶ the model was retrained with U09.9 diagnoses as the target event and without vaccination status as an input. The model calculates a long COVID likelihood score (range 0 to 1) for each patient beginning 100 days after index using only conditions and drugs observed as of that day. New scores are generated in 30-day intervals until 300 days after index or June 1, 2022, whichever comes first. Patients scoring above 0.9 in any interval were labeled as having long COVID. A threshold of 0.9 was chosen as it resulted in a similar prevalence of long COVID across the model-based and clinic-based cohorts. The earliest interval receiving a score above 0.9 was assigned as the event date for purposes of the time-to-event analysis. As in the clinic-based definition, death and COVID-19 vaccination were censoring events.

Any patient meeting our inclusion criteria from any of the eleven sites was eligible for a model-derived indicator of long COVID and was included in the model-based cohort. Therefore, all patients in the clinic-based cohort are also included in the model-based cohort, where they can (and sometimes do) have a different assigned long COVID outcome. This is not unexpected—the LC model was trained using U09.9 as the target, while we include U09.9, B94.8, and long COVID clinic visits as valid clinical diagnoses. Both labels are rare and imperfect; we do not expect one indication to guarantee the other.

Statistical Analysis

Two analyses were carried out to estimate the association between vaccination and long COVID: (1) logistic regression to calculate an overall association while controlling for patient characteristics, and (2) Cox proportional hazards to incorporate potential differences in the time-to-event for long COVID. We do not consider either analysis as primary, as each has weaknesses addressed by the other. Proportional hazards requires a date for long COVID diagnosis and for hazard functions to be proportional over time. Both are difficult to fully validate, and logistic regression requires neither. Logistic regression fails to consider varying times-to-event and vaccinations after COVID-19, which are accounted for in proportional hazards. We present the results of both analyses as a test of the robustness of the association.

Inverse probability of treatment weighting (IPTW) was applied to both logistic regression and proportional hazards to control for differences in patient characteristics across the vaccinated and unvaccinated groups. Logistic regression was used to estimate the propensity score based on demographics, medical history, social determinants of health, and spatial and temporal variables. Our selection of covariates was informed by the literature on important indicators of long COVID and is shown in eTables 1 and 2.^{16,22,23} Covariate balance before and after

weighting was evaluated with standardized mean differences. Covariates with a standardized mean difference less than 0.1 were considered well-balanced. Stabilized treatment weights were calculated as outlined in Robins et al (2000).²⁴ Standard errors in the IPTW-adjusted models were calculated from 200 bootstrapped iterations based on the standard deviation of the estimates.²⁵ Unadjusted associations were also calculated and reported.

For logistic regression models, studentized residuals, leverage scores, Cook's distances, and DFBETAS were examined to identify influential observations. For proportional hazards models, the Lifelines package's *CoxPHFitter.check_assumptions* method was used to test the assumption that each covariate's effect on the hazard rate is constant over time.^{26,27} Interactions with time were added to the model for covariates which did not meet the proportional hazards assumption.

Sensitivity analyses

Sensitivity of the IPTW-adjusted and unadjusted vaccination status coefficients in the logistic regression and proportional hazards models were tested across three dimensions: (1) LC model threshold (0.3 to 0.95), (2) with or without independent features in addition to vaccination, and (3) including or not including post-index vaccinations as a censoring event. The first sensitivity dimension was not relevant in the clinic-based cohort and the third was not relevant for logistic regression analyses.

All analyses were conducted using Python (version 3.6.10) with the Statsmodels (0.12.2) and Lifelines (0.26.4) packages. Study design elements, methods, and results were reported consistent with STROBE guidelines.²⁸

Results

Table 1. Baseline Patient Characteristics

Variable	Model-Based Cohort			Clinic-Based Cohort		
	Overall (N=199498)	Fully Vaccinated (N=87099)	Unvaccinated (N=112399)	Overall (N=47752)	Fully Vaccinated (N=26567)	Unvaccinated (N=21185)
Mean Age	47.22 (100.0)	52.46 (100.0)	43.16 (100.0)	48.17 (100.0)	50.97 (100.0)	44.65 (100.0)
Gender						
Female	128920 (64.6)	56561 (64.9)	72359 (64.4)	31051 (65.0)	17499 (65.9)	13552 (64.0)
Male	70578 (35.4)	30538 (35.1)	40040 (35.6)	16701 (35.0)	9068 (34.1)	7633 (36.0)
Age at COVID Index Date						
18-24	20701 (10.4)	4922 (5.7)	15779 (14.0)	4522 (9.5)	1753 (6.6)	2769 (13.1)
25-34	36729 (18.4)	11382 (13.1)	25347 (22.6)	8557 (17.9)	4078 (15.3)	4479 (21.1)
35-49	53883 (27.0)	21646 (24.9)	32237 (28.7)	12445 (26.1)	6748 (25.4)	5697 (26.9)
50-64	50887 (25.5)	25332 (29.1)	25555 (22.7)	12356 (25.9)	7235 (27.2)	5121 (24.2)
65+	37298 (18.7)	23817 (27.3)	13481 (12.0)	9872 (20.7)	6753 (25.4)	3119 (14.7)
Race / Ethnicity						
Asian Non-Hispanic	3542 (1.8)	2625 (3.0)	917 (0.8)	861 (1.8)	670 (2.5)	191 (0.9)
Black or African American Non-Hispanic	26588 (13.3)	10330 (11.9)	16258 (14.5)	10588 (22.2)	5355 (20.2)	5233 (24.7)
Hispanic or Latino Any Race	18870 (9.5)	9876 (11.3)	8994 (8.0)	3089 (6.5)	1642 (6.2)	1447 (6.8)
NHOPI Non-Hispanic	272 (0.1)	156 (0.2)	116 (0.1)	75 (0.2)	38 (0.1)	37 (0.2)
Other Non-Hispanic	4236 (2.1)	1477 (1.7)	2759 (2.5)	1391 (2.9)	460 (1.7)	931 (4.4)
Unknown	2693 (1.3)	1490 (1.7)	1203 (1.1)	1172 (2.5)	626 (2.4)	546 (2.6)
White Non-Hispanic	143297 (71.8)	61145 (70.2)	82152 (73.1)	30576 (64.0)	17776 (66.9)	12800 (60.4)
Data Partner						
Partner A	9526 (4.8)	5853 (6.7)	3673 (3.3)	9367 (19.6)	5776 (21.7)	3591 (17.0)
Partner B	1746 (0.9)	1162 (1.3)	584 (0.5)			
Partner C	3449 (1.7)	2114 (2.4)	1335 (1.2)	3414 (7.1)	2093 (7.9)	1321 (6.2)
Partner D	1176 (0.6)	754 (0.9)	422 (0.4)	1170 (2.5)	752 (2.8)	418 (2.0)
Partner E	2734 (1.4)	2092 (2.4)	642 (0.6)			
Partner F	27322 (13.7)	14857 (17.1)	12465 (11.1)			
Partner G	6095 (3.1)	3984 (4.6)	2111 (1.9)	6008 (12.6)	3926 (14.8)	2082 (9.8)
Partner H	2136 (1.1)	997 (1.1)	1139 (1.0)			
Partner I	2281 (1.1)	1460 (1.7)	821 (0.7)	2215 (4.6)	1424 (5.4)	791 (3.7)
Partner J	25946 (13.0)	12774 (14.7)	13172 (11.7)	25578 (53.6)	12596 (47.4)	12982 (61.3)
Partner K	117087 (58.7)	41052 (47.1)	76035 (67.6)			
COVID Month						
August 2021	48333 (24.2)	15273 (17.5)	33060 (29.4)	7440 (15.6)	2893 (10.9)	4547 (21.5)
September 2021	45601 (22.9)	16116 (18.5)	29485 (26.2)	7314 (15.3)	3176 (12.0)	4138 (19.5)
October 2021	22949 (11.5)	9382 (10.8)	13567 (12.1)	3482 (7.3)	1705 (6.4)	1777 (8.4)
November 2021	24074 (12.1)	10202 (11.7)	13872 (12.3)	2942 (6.2)	1505 (5.7)	1437 (6.8)
December 2021	23321 (11.7)	12150 (13.9)	11171 (9.9)	7525 (15.8)	4507 (17.0)	3018 (14.2)
January 2022	35220 (17.7)	23976 (27.5)	11244 (10.0)	19049 (39.9)	12781 (48.1)	6268 (29.6)
Health Status						
Immunocompromised	2153 (1.1)	1544 (1.8)	609 (0.5)	1300 (2.7)	1009 (3.8)	291 (1.4)
Diabetes (Complicated)	19805 (9.9)	11412 (13.1)	8393 (7.5)	6715 (14.1)	4293 (16.2)	2422 (11.4)
Diabetes (Uncomplicated)	30550 (15.3)	17044 (19.6)	13506 (12.0)	9833 (20.6)	6106 (23.0)	3727 (17.6)
Kidney Disease	13211 (6.6)	8028 (9.2)	5183 (4.6)	5259 (11.0)	3463 (13.0)	1796 (8.5)
Acute Kidney Injury	7614 (3.8)	4281 (4.9)	3333 (3.0)	3562 (7.5)	2183 (8.2)	1379 (6.5)
Chronic Lung Disease	26652 (13.4)	13964 (16.0)	12688 (11.3)	10261 (21.5)	6089 (22.9)	4172 (19.7)
Tobacco Smoker	8375 (4.2)	3205 (3.7)	5170 (4.6)	5065 (10.6)	2061 (7.8)	3004 (14.2)
Heart Failure	8281 (4.2)	4925 (5.7)	3356 (3.0)	3442 (7.2)	2199 (8.3)	1243 (5.9)
Myocardial Infarction	4950 (2.5)	2726 (3.1)	2224 (2.0)	2225 (4.7)	1314 (4.9)	911 (4.3)
Congestive Heart Failure	6450 (3.2)	3932 (4.5)	2518 (2.2)	2813 (5.9)	1827 (6.9)	986 (4.7)

A summary of patient characteristics for both cohorts is shown in Table 1. The IPTW-adjusted logistic regression and proportional hazards models showed strong, protective associations in both cohorts (Table 2). The full tables of coefficients are provided as eTables 3–6 in the online supplement. There was not a clear association between vaccination status and long COVID in the unadjusted model-based analysis, though an association could still be observed in the clinic-based cohort (Table 2). The IPTW-adjusted Kaplan-Meier curves for the model-based and clinic-based cohorts are shown in Figure 2.

Table 2a. Long COVID by Vaccination Status: Measures of Association

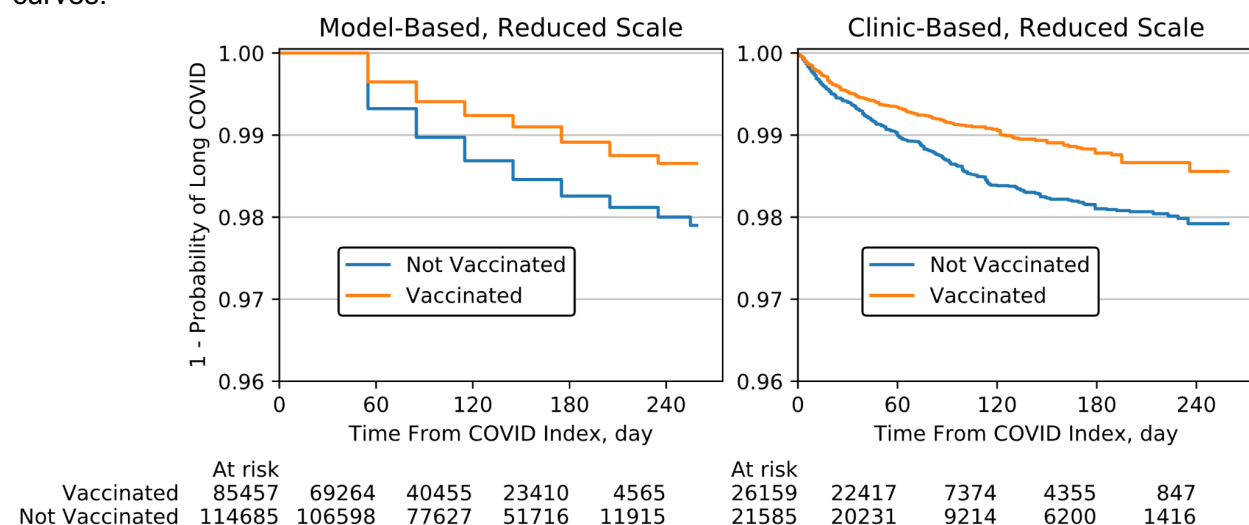
		Logistic Regression OR ^a (95% CI)	Proportional Hazards HR ^b (95% CI)
IPTW-Adjusted	Model-Based Cohort	0.70 (0.65, 0.75)	0.62 (0.56, 0.69)
	Clinic-Based Cohort	0.69 (0.59, 0.82)	0.66 (0.55, 0.80)
Unadjusted	Model-Based Cohort	1.04 (0.97, 1.11)	0.99 (0.90, 1.08)
	Clinic-Based Cohort	0.79 (0.68, 0.92)	0.80 (0.67, 0.95)

^aOR: Odds Ratio, ^bHR: Hazard Ratio

Table 2b. Long COVID by Vaccination Status: Unadjusted Counts

	Model-Based Cohort			Clinic-Based Cohort		
	Overall	With Long COVID	Without Long COVID	Overall	With Long COVID	Without Long COVID
Fully Vaccinated	87,099 (100%)	1,516 (1.7%)	85,583 (98.3%)	26,567 (100%)	352 (1.3%)	26,215 (98.7%)
Unvaccinated	112,399 (100%)	1,889 (1.7%)	110,510 (98.3%)	21,185 (100%)	354 (1.7%)	20,831 (98.3%)

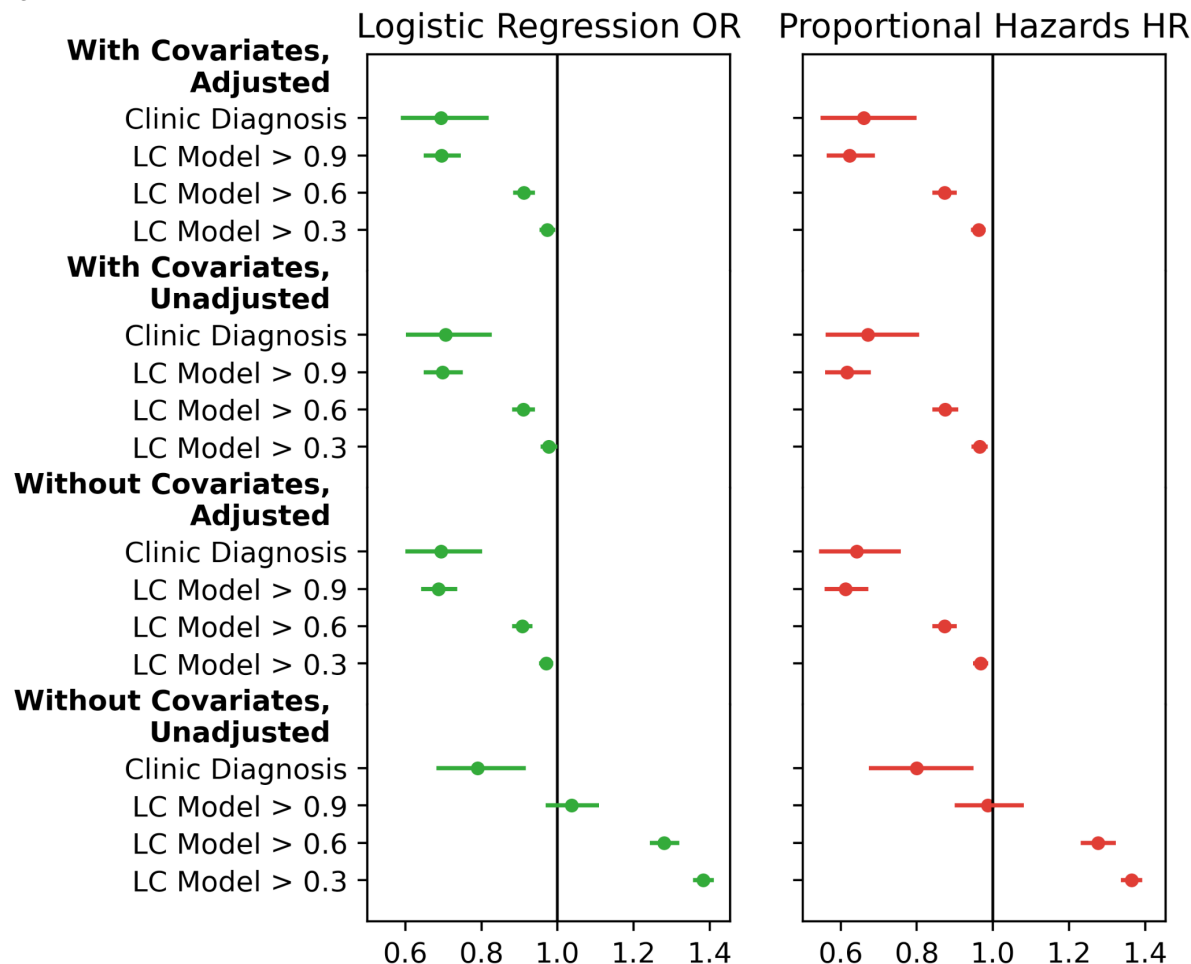
Figure 2. IPTW-Adjusted Kaplan-Meier Curves. Long COVID events can only be observed in the model-based cohort in 30-day increments, resulting in the observed stair-step structure. A reduced scale is used to highlight the differentiation between the vaccinated and unvaccinated curves.



Key results of the sensitivity analysis are summarized in Figure 3. The association between vaccination and long COVID was robust to excluding either IPTW adjustment or non-vaccination covariates, but not both. In the proportional hazards models, the association was robust to not censoring post-COVID-19 vaccination events (uncensored points are not pictured in Figure 3 as they closely overlap the censored points). In the model-based cohort, the association was not

robust to the LC model threshold, with lower thresholds resulting in a progressively weaker protective association.

Figure 3. Sensitivity analysis vaccination coefficients for logistic regression (LR) and proportional hazards (PH). Odds ratios (OR) are shown for LR, hazard ratios (HR) are shown for PH.



After IPTW-adjustment, all covariates were well-balanced (eFigures 1 and 2). Logistic regression diagnostics did not indicate any overly influential observations. Observations with large residuals tended to have low leverage and vice versa. In the model-based cohort, the greatest Cook's distance was < 0.01 and the greatest absolute DFBETA for vaccination status was 0.04. In the clinic-based cohort, the greatest Cook's distance was 0.01 and the greatest absolute DFBETA for vaccination status was 0.08. In the model-based cohort, seven patients had stabilized inverse probability of treatment weights above 20 (max of 33); excluding these patients did not impact vaccination coefficients at the precision reported here. The maximum weight in the clinic-based cohort was nine.

Discussion

Our four analyses yielded consistent results. We see protective associations of vaccination with long COVID onset in both logistic and time-to-event models, and in both clinic-based and

model-based cohorts. While these findings are similar to those of other large observational studies,^{8–10} previous sources have only looked for evidence of COVID-associated symptoms as evidence of long COVID. A major finding of our analysis is that the protective association remains consistent in results where a clinical diagnosis is required, and among those who contracted COVID-19 in a later period that includes Omicron infections. The use of the LC model allowed us to expand our sample from six to eleven sites and 47,752 to 199,498 COVID-positive patients, across which we confirmed consistent results.

Interestingly, the protective association of vaccination with long COVID is weaker or reversed in the unadjusted coefficients and cross tabulations (Table 2, Figure 3). Several features that are associated with a higher likelihood of long COVID (coefficients in eTables 3–6) are also associated with a higher likelihood of vaccination (coefficients in eTables 1–2). The most significant is age: eTable 7 shows how older adults are both more likely to be vaccinated and more likely to contract long COVID in comparison to younger adults. Failing to account for the substantial differences between individuals who were and were not vaccinated prior to COVID-19 could lead one to conclude that vaccination is harmful.

The sensitivity analysis presents other instructive complexities. Reducing the LC model threshold lowers the amount of evidence required to denote someone as having long COVID; it also moderates the protective association of vaccination with long COVID (key results in Figure 3, full range of thresholds in eFigure 3). While we'd expect that including healthy adults in the long COVID population would dilute the observed protective association, individuals with a LC model score between 0.6 and 0.9 are not entirely healthy—they have some evidence of long COVID. If high-confidence and clinically diagnosed long COVID cases are more severe than cases with fewer recorded symptoms, it could suggest that vaccination is most strongly associated with a reduced risk of severe long COVID. More work is needed to validate that conclusion.

Healthcare utilization is one of the most important features in the LC model.¹⁶ If fully vaccinated patients are more likely to utilize the healthcare system, the LC model's marginal predictions may be assigning more fully vaccinated individuals to long COVID because they are more likely to interact with the healthcare system, depressing the observed benefit of vaccination. A known challenge of analyzing EHR data is that they tend to provide more information on individuals who regularly utilize healthcare systems,²⁹ though we attempt to control for this by requiring multiple recorded encounters outside of COVID-19 for inclusion in the study.

It is well-documented that vaccination reduces the risk of developing COVID-19,^{6,7} offering one mechanism for preventing Long COVID. However, there is evidence that widely circulated vaccines are less effective against now-dominant Omicron than earlier SARS-CoV-2 variants,^{30–32} increasing interest in whether or not vaccination reduces the risk of long COVID in breakthrough infections. That is the aim of this study, in which all eligible patients had a COVID-19 diagnosis. As a result, the stated association between vaccination and long COVID will be an underestimate of the effective association in the general population due to the primary prevention of COVID-19 in the first place.

IPTW is often used to estimate causal effects from observational data and is employed here to provide more robust associations. However, we do not interpret these results as causal effects. This is for two reasons: (1) we are unwilling to assume that there are no unmeasured confounders in our treatment model and (2) our causal model includes several latent variables, which obstruct the estimation of treatment effects through covariate adjustment. We explore

each reason in the eDiscussion of the online supplement and provide a directed acyclic graph of confounders in eFigure 4.

Limitations

Our study is limited by its reliance on EHRs and other factors. Those who choose to not seek healthcare, or are unable to do so, are not represented in EHRs. Even among available patients, our sample is biased towards high utilizers and those with hospitalizations. We are forced to assume that those without a recorded condition or symptom do not exhibit it, including potentially unrecorded reinfections of COVID-19. We attempt to mitigate this limitation with respect to vaccination by carefully selecting healthcare sites with reasonably high reported vaccination rates, but some vaccinations remain unreported, likely resulting in a conservative estimate.

We did not distinguish between vaccine types, though previous studies and initial tabulations failed to detect differences in their effectiveness in preventing long COVID.^{9,10}

The ICD10 code for long COVID, U09.9, was not implemented until October 2021, and its full adoption was not immediate. The previously recommended ICD10 code, B94.8, is more general and is used to diagnose long-term complications from any viral infection. We accepted B94.8 as a long COVID diagnosis because use of the code in our data by mid-2021 was 40 times higher than its baseline use in 2018 and 2019.

Finally, the confidence intervals around the LC model-based risk estimates are likely to narrow as there remains residual misclassification of Long COVID outcomes in that cohort not factored into the confidence interval boundaries.

Conclusions

Vaccination is a proven tool in combating onset of COVID-19. We show that benefits of vaccination persist in breakthrough infections through a moderate but consistent protective association against clinically diagnosed long COVID.

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UK Health
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The effectiveness of vaccination against long COVID

A rapid evidence briefing

Key messages

- Fifteen studies were identified that reported on the effectiveness of vaccination against long COVID (search up to **12 January 2022**): 7 studies examined whether vaccination before infection reduced the symptoms or incidence of long COVID, 7 studies examined whether vaccination in people with long COVID reduced or cleared the symptoms of long COVID, and 1 study examined both.
- Six of the 8 studies assessing the effectiveness of vaccination before COVID-19 infection suggested that vaccinated cases (1 or 2 doses) were less likely to develop symptoms of long COVID following infection, in the short term (4 weeks after infection), medium term (12 to 20 weeks after infection) and long term (6 months after infection). As all 8 studies included only participants who had COVID-19, the effect of vaccination on reduced incidence of COVID-19 is not accounted for. This means these studies do not give a total population estimate for the effectiveness of vaccines to prevent long COVID, but rather underestimate it.
- From 2 studies that measured individual long COVID symptoms, fully vaccinated cases were less likely to have the following symptoms in the medium or long term than unvaccinated cases: fatigue, headache, weakness in arms and legs, persistent muscle pain, hair loss, dizziness, shortness of breath, anosmia, interstitial lung disease, myalgia, and other pain.
- In studies examining the effect of vaccination among people with long COVID, 3 of 4 studies comparing long COVID symptoms before and after vaccination suggested that more cases reported an improvement in symptoms after vaccination, either immediately or over several weeks. There were, however, some cases in all studies who reported a worsening in symptoms after vaccination.
- Three studies of people with long COVID who were unvaccinated when they were initially infected, compared people who were subsequently vaccinated and people who remained unvaccinated. All these studies suggested that people with long-COVID were less likely to report long COVID symptoms shortly after vaccination, and over longer periods, than people with long COVID who were not subsequently vaccinated. One study looked at the timing of vaccination after COVID-19 diagnosis, and suggested that cases who were vaccinated sooner rather than later after diagnosis were much less likely to report symptoms of long COVID than cases who remained unvaccinated.
- In 3 of the 5 studies reporting on symptom changes following vaccination of people with long COVID, there was a higher proportion of people with long COVID who reported unchanged symptoms following vaccination (up to 70%) than people whose symptoms improved or worsened.
- All studies were observational, so the results may be from differences other than vaccination, and there was large heterogeneity between studies in the definition of long COVID.

Background

Long COVID, also known as post acute sequelae of a SARS-CoV-2 infection and post COVID-19 syndrome, has several definitions, but typically includes having persistent symptoms of COVID-19, usually for weeks but potentially for months or years (1, 2). Symptoms commonly include fatigue, shortness of breath and a persistent cough, although many other symptoms have been reported (3). As of 6 December 2021, 1.3 million people in the UK (2% of the population) reported experiencing long COVID symptoms for more than 4 weeks after the initial infection (4). Vaccination against COVID-19 reduces the risk of symptomatic COVID-19 infection (5), though vaccination may additionally reduce the risk of long COVID if a vaccinated person is infected with COVID-19 (1, 2). While there is no recommendation against vaccination in people with long COVID (6), it is unclear whether vaccination of previously unvaccinated people with long COVID is more likely to improve or worsen long COVID symptoms (7, 8).

The purpose of this rapid evidence briefing is to provide evidence relating to the effectiveness of vaccination against long COVID, both for vaccinations given before infection with COVID-19 (effectiveness against incidence of long COVID), and for vaccinations given after infection with COVID-19 and development of long COVID symptoms (effectiveness for reducing or eliminating symptoms of long COVID).

Methods

A rapid search was undertaken on **12 January 2022** to identify primary studies related to the effectiveness of vaccination against long COVID. We searched a number of specialist COVID-19 review repositories and ran a broad search using Medline, Embase, NLM COVID portfolio (for preprints), WHO COVID Database and Google. As this work was conducted at pace, data was extracted directly into a narrative summary. The quality criteria checklist (QCC) tool was used to rate the quality of included studies as low, medium, or high quality. Full details of the methods are available in **Appendix A**.

Evidence

Fifteen studies reported on the effectiveness of vaccination against long COVID. Four studies were conducted in the UK (7-10), 4 studies in the US (11-14), 1 study in France (15), 2 studies in India (16, 17), 1 study in Indonesia (18), 1 study in Israel (19), and 2 studies were conducted online with participants from multiple countries (20-22). Seven studies examined whether vaccination before infection reduced the symptoms or incidence of long COVID (9, 11, 12, 16-19), 7 studies examined whether vaccination in people with long COVID reduced or cleared the symptoms of long COVID (7, 8, 10, 14, 15, 20-22), and 1 study examined both (13). **Table 1** shows the characteristics of each included study.

Most studies used different definitions of long COVID, as such these definitions are given in the summaries below. In all studies, fully vaccinated is defined as 2 doses of any 2 dose vaccine or 1 dose of a single dose vaccine, and partially vaccinated is defined as a single dose of a 2 dose vaccine. Where the vaccine brand (e.g. Pfizer, AstraZeneca) is available, this is reported.

Vaccination before infection

Note that all 8 studies included in this section only include participants who had COVID-19, so the effect of vaccination to reduce incidence of COVID-19 is not accounted for. This means all studies will likely underestimate the effectiveness of vaccines to prevent long COVID.

A nested case-control study by Antonelli et al (2022, rated as medium quality) examined whether vaccination for COVID-19 before infection was associated with long duration symptoms of COVID-19 (≥ 28 days) in adults who reported testing positive on RT-PCR or LFD for COVID-19 on the COVID symptom study phone app (ZOE) between 8 December 2020 and 4 July 2021 in the UK (9). In total, 6,030 participants reported a positive test at least 14 days after their first vaccination but before their second (partially vaccinated, tested a median of 67 days after vaccination), and 2,370 at least 7 days after their second vaccine (fully vaccinated, tested a median of 44 days after vaccination). The same number of unvaccinated participants who tested positive were matched with those who were partially and fully vaccinated, accounting for date of positive test, healthcare worker status, sex, body mass index, and age.

- Fully vaccinated participants were about half as likely to have symptoms lasting ≥ 28 days than unvaccinated participants (odds ratio [OR] = 0.51, 95% CI: 0.32 to 0.82, $p=0.005$), whereas partially vaccinated participants were about as likely to have symptoms lasting ≥ 28 days than unvaccinated participants (OR = 1.04, 95% CI: 0.86 to 1.25, $p=0.69$).
- Fully vaccinated younger adults (18 to 59 years) were much less likely to have symptoms lasting ≥ 28 days than younger unvaccinated adults (OR = 0.21, 95% CI: 0.08 to 0.59, $p=0.003$).

A retrospective cohort study by Al-Aly et al (2021, preprint, rated as medium quality) examined whether vaccination for COVID-19 before infection was associated with post-acute sequelae of COVID-19 (symptoms of COVID-19 at 6 months) in adults who had a positive test for COVID-19 in the United States Veterans Health Administration electronic health databases between 1 February and 31 August 2021 in the US (12). Vaccinated cases ($n=16,035$, mean age of 67 years, 71% White race, 91% male) were matched (and weighted) with unvaccinated cases ($n=48,536$, mean age of 56 years, 71% white, 86% male), accounting for age, race, sex, socioeconomic deprivation, smoking status, health conditions and information, data of test and hospital information. Post-acute sequelae of COVID-19 included cardiovascular disorders, coagulation, fatigue, gastrointestinal disorders, kidney disorders, mental health disorders, metabolic disorders, musculoskeletal disorders, neurologic disorders, and pulmonary disorders.

- Vaccinated cases were less likely to have at least 1 post-acute sequelae of COVID-19 at 6 months compared with unvaccinated cases (hazard ratio [HR] = 0.87, 95% confidence interval [CI]: 0.83 to 0.92).

A retrospective cohort study by Arjun et al (2022, preprint, rated as medium quality) examined whether vaccination for COVID-19 before infection (confirmed with RT-PCR) was associated with self-reported long COVID symptoms (including fatigue, cough, loss of taste and smell and cognitive dysfunction 4 weeks from the date of diagnosis) in adults (≥ 18 years) who were diagnosed with COVID-19 between April and September 2021 in India (16). In total, 487 participants who tested positive for COVID-19 in a single hospital responded, with a mean age of 39 years, 41% female, and 59% of participants had 2 doses of a COVID-19 vaccine (the majority had Covaxin), 17% had 1 dose, and 25% were unvaccinated. The analysis was adjusted for age, sex, occupation, body mass index, substance use, past COVID-19 infection, comorbidities, number of COVID-19 symptoms and severity of COVID-19 disease.

- Fully vaccinated participants were more likely to have long COVID symptoms 4 weeks from the date of diagnosis than unvaccinated participants (OR = 2.32, 95% CI: 1.17 to 4.58, $p=0.01$).
- Note that these results are in the opposite direction to all other studies, i.e. that cases who were fully vaccinated had a greater chance of subsequently developing long COVID symptoms, and more analysis is needed to understand why this may be the case.

A retrospective cohort study (POST-COVID) by Herman et al (2022, preprint, rated as medium quality) examined whether vaccination for COVID-19 before infection with COVID-19 (confirmed by RT-PCR, Nucleic Acid Amplification Test [NAAT] or rapid antigen test) was associated with olfactory dysfunction (anosmia or hyposmia) 2 and 4 weeks after the end of infection in cases recruited up to December 2021 in Indonesia (18). Fully vaccinated participants (2 doses, $n=221$, mean age of 32 years, 50% female) more than 14 days before infection were matched with participants who were not fully vaccinated more than 14 days before infection (including unvaccinated and partially vaccinated cases, $n=221$, mean age of 32 years, 50% female), accounting for occupation, education, island, type of living area, living companion, age and hypertension status.

- While fully vaccinated participants were less likely to develop olfactory dysfunction after infection than unvaccinated participants (OR = 0.31, 95% CI: 0.10 to 0.94), there was little evidence for an association between full vaccination and olfactory dysfunction 4 weeks after the end of infection ($p=0.59$)

A cross-sectional study nested in a prospective cohort study by Kuodi et al (2022, preprint, rated as medium quality) examined whether vaccination for COVID-19 before infection was associated with long-term physical, mental, and psychosocial consequences of COVID-19 in adults who tested positive for COVID-19 (RT-PCR) between 15 March 2020 and 15 June 2021 in Israel (19). Study participants ($n=951$, 294 fully vaccinated [2 doses], 340 partially vaccinated [1 dose], 317 unvaccinated), who tested positive for COVID-19 in 1 of 3 government hospitals, completed a survey between 16 July and 18 November 2021 detailing their COVID-19 test results, vaccination status, number of doses, type of vaccine and date of administration, and symptoms experienced at the time of filling out the survey.

In total, 337 of 951 participants (35%) reported not fully recovering from the initial COVID-19 symptoms at follow-up.

- The study suggested that, compared with unvaccinated participants, participants with 2 or 3 doses of vaccine were 54% to 83% less likely to report 7 of the 10 most commonly reported symptoms (see below).
- For most symptoms, the vaccine effectiveness against symptoms reported at follow-up was highest for older participants (>60 years) and lowest for younger participants (19 to 35 years), with the exceptions of hair loss (highest in 36 to 60 year olds), persistent cough (similar in all age groups) and feeling fully recovered from COVID-19 (highest in 19 to 35 year olds).
- The relative risks (RR) of each symptom, comparing participants who received 2 or 3 doses of vaccine with unvaccinated participants (relative risks <1 indicate that fewer vaccinated compared with unvaccinated participants had the symptom at follow-up) were:
 - Fatigue: RR = 0.36 (95% confidence interval (CI): 0.19 to 0.71, p=0.003)
 - Headache: RR = 0.46 (95% CI: 0.26 to 0.83, p=0.01)
 - Weakness in arms and legs: RR = 0.43 (95% CI: 0.20 to 0.94, p=0.03)
 - Persistent muscle pain: RR = 0.32 (95% CI: 0.11 to 0.88, p=0.03)
 - Loss of concentration: RR = 0.59 (95% CI: 0.17 to 2.06, p=0.41)
 - Hair loss: RR = 0.17 (95% CI: 0.06 to 0.60, p=0.005)
 - Sleeping problems: RR = 0.53 (95% CI: 0.18 to 1.61, p=0.26)
 - Dizziness: RR = 0.26 (95% CI: 0.09 to 1.79, p=0.02)
 - Persistent cough: RR = 0.72 (95% CI: 0.28 to 1.83, p=0.48)
 - Shortness of breath: RR = 0.23 (95% CI: 0.07 to 0.84, p=0.03)
 - Feeling fully recovered from COVID-19: RR = 0.98 (95% CI: 0.80 to 1.21, p=0.86)

A cross-sectional study by Senjam et al (2021, preprint, rated as medium quality) examined whether vaccination for COVID-19 before infection was associated with symptoms of long COVID (symptoms present between 4 and 12 weeks [short-term] or beyond 12 weeks [long-term] after a positive RT-PCR or cartridge based NAAT) in adults (≥18 years) who tested positive for COVID-19 between 1 January and 30 April 2021 in India (17). A total of 773 participants, who tested positive in a single hospital, completed a survey between June and July 2021 (median age of 34 years, 56% male, 33% with short-term long COVID symptoms, 13% with long-term long COVID symptoms, 53% unvaccinated, 25% fully vaccinated [2 doses]). The most commonly reported long COVID symptoms were fatigue, pain in the joints and muscle, hair loss, headache, cough, breathlessness, sleep disorders, sore throat and decrease of smell and taste.

- Fully vaccinated (2 doses) participants were less likely to have long COVID symptoms (not stated if these were short-term, long-term or both) than unvaccinated participants (OR = 0.55, 95% CI: 0.37 to 0.85)

A retrospective cohort study by Simon et al (2021, preprint, rated as high quality) examined whether vaccination for COVID-19 before or after infection was associated with long COVID (COVID-19 symptoms present between 12 and 20 weeks after COVID-19 diagnosis) in cases who were diagnosed with, or tested positive for (NAAT or antigen test), COVID-19 between 1 January 2020 and 31 May 2021 in the US (13). In total, 240,648 cases were included, 220,460 (92%) cases were unvaccinated by 12 weeks after their COVID-19 diagnosis, 2,392 (1.0%) cases received 1 dose of vaccine before their diagnosis, and 17,796 (7.4%) cases received 1 dose of vaccine within 12 weeks of their diagnosis. COVID-19 symptoms included: chest pain, palpitations, altered mental state, anorexia, chills, fatigue, fever, malaise, loss of sense of smell, loss of sense of taste, nasal congestion, sore throat, abdominal pain, diarrhoea, digestive changes, nausea, vomiting, arthralgia, muscle weakness, general weakness, myalgia, headache, cough and dyspnoea.

- Cases who were vaccinated before diagnosis were much less likely to have any symptoms of long COVID between 12 and 20 weeks after diagnosis than cases who were unvaccinated up to 12 weeks after their diagnosis (OR = 0.22, 95% CI: 0.20 to 0.25, $p < 0.005$), and even less likely to have more than 1 symptom of long COVID (OR = 0.11, 95% CI: 0.09 to 0.14, $p < 0.005$)

A matched case-control study by Taquet et al (2021, preprint, rated as high quality) examined whether vaccination for COVID-19 before infection (confirmed diagnosis or positive RT-PCR test) was associated with documented consequences of COVID-19 in people in the 6 months after an infection, with infection occurring between 1 January and 31 August 2021, primarily in the US (11). Data was obtained from TriNetX Analytics, which contains data from 59 healthcare organisations and 81 million patients. In total, 9,479 vaccinated cases ($n=2,996$ with 1 dose and $n=6,957$ with 2 doses of any vaccine received at least 14 days before infection during the study) were matched with the same number of unvaccinated cases (who had received an influenza vaccine), accounting for age, sex, ethnicity, obesity, socioeconomic deprivation and specific health conditions, as well as date of infection. The mean age of participants was 57 years, 59% were female, and of those who were vaccinated, 65% had the Pfizer vaccine, 9% the Moderna vaccine, 1.6% the Janssen vaccine, and 24% had an unspecified vaccine. A composite long COVID outcome was defined as having a diagnosis of any of the following symptoms in the 6 months after infection: abdominal symptoms, abnormal bleeding, anxiety/depression, chest/throat pain, cognitive symptoms, fatigue, headache, myalgia and other pain, as well as death (to account for differences in survival between vaccinated and unvaccinated participants).

- The study suggested there was no association between vaccination (comparing participants with 2 doses of vaccine with unvaccinated participants) and the composite long COVID outcome in the 6 months after infection: hazard ratio (HR) = 1.00 (95% CI: 0.95 to 1.06); 64.9% and 65.6% of vaccinated and unvaccinated participants had a long COVID symptom respectively.
- However, participants with 2 doses of vaccine, when compared with unvaccinated participants, were less likely to be diagnosed with:
 - Anosmia: HR = 0.68 (95% CI: 0.55 to 0.84, $p=0.0004$)
 - Fatigue: HR = 0.86 (95% CI: 0.77 to 0.96, $p=0.005$)

- Hair loss: HR = 0.66 (95% CI: 0.54 to 0.81, $p < 0.0001$)
- Interstitial lung disease: HR = 0.74 (95% CI: 0.62 to 0.88, $p = 0.0006$)
- Myalgia: HR = 0.70 (95% CI: 0.59 to 0.84, $p < 0.0001$)
- Other pain: HR = 0.85 (95% CI: 0.76 to 0.96, $p = 0.007$)

Vaccination after infection

A prospective cohort by Arnold et al (2021, preprint, rated as medium quality) examined the effect of vaccination (with Pfizer or AstraZeneca) on long COVID symptoms in previously unvaccinated participants who were hospitalised with COVID-19 in April and May 2020 and either remained unvaccinated or were vaccinated (Pfizer or AstraZeneca) in January or February 2021 in the UK (7). Vaccinated participants ($n=44$, median age 64 years, 64% male, 82% symptomatic 8 months after infection) were matched with unvaccinated participants ($n=22$, median age 55 years, 59% male, 82% symptomatic 8 months after infection), accounting for symptomatology and quality of life at 8 months after infection, and all participants were asked about whether they had symptoms, and whether they had improved, stayed the same, or worsened following vaccination.

- At 1 month after vaccination (or a matched time for unvaccinated cases), more vaccinated participants reported their symptoms improved than unvaccinated participants (23.2% versus 15.4%), and fewer vaccinated participants reported their symptoms worsened than unvaccinated participants (25.6% versus 14.3%, $p=0.035$ for all differences). A similar percentage of vaccinated and unvaccinated participants had unchanged symptoms (71.1% versus 70.3%).

A prospective cohort (the Office of National Statistics COVID-19 infection survey [CIS]) study by Ayoubkhani et al (2021, preprint, rated as high quality) examined the effect of vaccination on long COVID symptoms in previously unvaccinated adults (18 to 69 years) between 3 February and 5 September 2021 in the UK (8). Participants in the CIS were randomly sampled from UK households, and were visited monthly to both provide a swab for RT-PCR testing and to be asked if they would describe themselves as currently experiencing long COVID (in this analysis, symptoms persisting at least 12 weeks from a confirmed or suspected COVID-19 infection that could not be explained by another health condition). All participants had their first vaccine dose by 5 September 2021 ($n=28,356$), 45.7% after 3 February 2021, and 83.8% had their second vaccine dose by 5 September 2021 ($n=23,753$). There were 6,729 participants (23.7%) that reported they had long COVID symptoms, including fever, headache, muscle ache, weakness or tiredness, nausea or vomiting, abdominal pain, diarrhoea, loss of appetite, loss of taste, loss of smell, sore throat, cough, shortness of breath, chest pain, palpitations, vertigo or dizziness, worry or anxiety, low mood or not enjoying anything, trouble sleeping, memory loss or confusion, or difficulty concentrating.

- Both the first and second vaccine doses were associated with reduced odds of reporting long COVID symptoms shortly after vaccination:
 - First vaccine dose: OR = 0.87 (95% CI: 0.81 to 0.93, $p < 0.001$)
 - Second vaccine dose: OR = 0.91 (95% CI: 0.86 to 0.97, $p = 0.003$)

- The second vaccine dose was also associated with a long-term decrease in the odds of reporting long COVID symptoms ($p=0.03$)
- The results were similar for activity limiting long COVID ($n=4,747$ reported activity limiting long COVID):
 - First vaccine dose: OR = 0.88 (95% CI: 0.81 to 0.96, $p=0.003$)
 - Second vaccine dose: OR = 0.91 (95% CI: 0.84 to 0.98, $p=0.01$)
 - The second vaccine dose was also associated with a long-term decrease in the odds of reporting long COVID symptoms ($p=0.03$)
- There was little evidence for differences in results between mRNA and adenovirus vaccine types, and the results suggested that the odds of experiencing most symptoms of long COVID decreased with the first and second doses of vaccine, though these results were relatively imprecise.

A prospective cohort study by Gaber et al (2021, rated as medium quality) asked health care workers in the UK with long COVID whether vaccination between December 2020 and January 2021 changed their long COVID symptoms (10). Of 67 healthcare workers with long COVID receiving the vaccine, 75% had fatigue, 53% had shortness of breath, and 18% had anxiety.

- Several weeks after vaccination, 14 (21%) participants reported an improvement in 1 or more of their symptoms, 8 (12%) participants reported a worsening in symptoms, and 45 (67%) participants reported no change in their symptoms.

An online survey (LongCovidSOS) by Strain et al (2021, preprint, rated as medium quality) asked people in the UK and elsewhere with long COVID (positive RT-PCR or antigen test not required) whether their symptoms improved or worsened following vaccination (21, 22). The survey was completed by 812 respondents (96% above 30 years old, 80% women) in March and April 2021, 41% of participants had a confirmed COVID-19 infection, 50% had the AstraZeneca vaccine, 40% the Pfizer vaccine, 8.6% the Moderna vaccine, 14% had 2 doses of any vaccine, and 40% of participants had at least 30 days between their last vaccine and completing the survey. Long COVID symptoms included fatigue, brain fog, myalgia, shortness of breath, insomnia, chest pain or palpitations, gastrointestinal symptoms, anosmia, autonomic dysfunction, postural orthostatic tachycardia syndrome, persistent cough, fever, rash (including COVID toes) and vascular complications.

- 57% of participants reported an improvement in symptoms after vaccination, 25% of participants reported no change in symptoms, while 19% of participants reported a worsening of symptoms, with Moderna having the most participants report an improvement and least report a deterioration.
- When responses to individual symptoms were grouped together, more participants had all or some of their symptoms improve than worsen:
 - All improved: 11%
 - Some improved: 16%
 - Mixture: 24%
 - No change: 42%

- Some got worse: 3.8%
- All got worse: 2.9%

An online survey by Scherlinger et al (2022, rated as medium quality) asked French-speaking adults with post-acute sequelae of COVID-19 (PASC, persistent symptoms lasting >4 weeks after probable or confirmed COVID-19 infection and no alternative diagnosis to explain the symptoms) whether their symptoms improved or worsened following vaccination (Pfizer [78%], Moderna [16%], AstraZeneca [4%]) (20). The survey was completed by 567 respondents (median age 44 years, 83% women) in August 2021, 64% of participants had a confirmed COVID-19 infection, 25% had one vaccine dose and 45% had 2 vaccine doses. Symptoms of PASC included fever or chills, fatigue, brain fog, headaches, changing mood or impact on morale, sleeping issues, costal pain, dyspnoea, cough, palpitations, muscle aches, joint pain, paraesthesia or tingling, anosmia or ageusia, diarrhoea or vomiting, spontaneous bruises, and pruritus.

- Of the 380 participants who reported long COVID at the time of vaccination, 117 (31%) reported a global worsening of symptoms (including fever/chills [74%], gastro-intestinal symptoms [70%], paraesthesia [64%] and arthralgia [63%]), whereas 83 (21.8%) reported a global improvement in symptoms (including anosmia [62%] and brain fog [51%]), and 179 (47%) reported no change in symptoms following vaccination.
- The symptoms thought to be affected by vaccination persisted for more than 2 weeks after vaccination in 64% of participants reporting a worsening in symptoms, and in 73% of participants reporting an improvement.
- There was little evidence of differences in results between vaccine types ($p=0.60$)

A retrospective cohort study by Simon et al (2021, preprint, rated as high quality), detailed above, examined whether vaccination for COVID-19 before or after infection was associated with long COVID (COVID-19 symptoms present between 12 and 20 weeks after COVID-19 diagnosis) in cases who were diagnosed with, or tested positive for (NAAT or antigen test), COVID-19 between 1 January 2020 and 31 May 2021 in the US (13).

- Cases who were vaccinated 0 to 4 weeks after diagnosis were much less likely to have any symptoms of long COVID between 12 and 20 weeks after diagnosis than cases who were unvaccinated up to 12 weeks after their diagnosis (OR = 0.38, 95% CI: 0.35 to 0.41, $p<0.005$), and even less likely to have more than 1 symptom of long COVID (OR = 0.19, 95% CI: 0.16 to 0.22, $p<0.005$)
- Cases who were vaccinated 4 to 8 weeks after diagnosis were less likely to have any symptoms of long COVID between 12 and 20 weeks after diagnosis than cases who were unvaccinated up to 12 weeks after their diagnosis (OR = 0.54, 95% CI: 0.51 to 0.57, $p<0.005$), and much less likely to have more than 1 symptom of long COVID (OR = 0.32, 95% CI: 0.29 to 0.35, $p<0.005$)
- Cases who were vaccinated 8 to 12 weeks after diagnosis were less likely to have any symptoms of long COVID between 12 and 20 weeks after diagnosis

than cases who were unvaccinated up to 12 weeks after their diagnosis (OR = 0.75, 95% CI: 0.71 to 0.78, $p < 0.005$), and much less likely to have more than 1 symptom of long COVID (OR = 0.46, 95% CI: 0.43 to 0.49, $p < 0.005$)

A prospective cohort (ComPaRe long COVID cohort) study by Tran et al (2021, preprint, rated as high quality) examined the effect of vaccination on long COVID symptoms in adults (≥ 18 years old) who had a COVID-19 infection (confirmed or suspected) and subsequent long COVID symptoms (symptoms persisting > 3 weeks past initial infection) between November 2020 and May 2021 in France (15). Participants ($n=910$, median age of 47 years, 80.5% female, median of 10.7 months of symptoms) were contacted every 60 days and asked about 53 COVID-19 symptoms (to form a COVID ST score, from 0 to 53, representing the number of different symptoms), and every 45 days and asked about vaccination status. Vaccinated ($n=455$) and unvaccinated ($n=455$) participants were matched on sex, age, education, comorbidities, confirmed COVID-19 infection, hospitalisation for COVID-19, time from COVID-19 infection and COVID-19 symptoms.

- Long COVID symptoms were less severe in vaccinated compared with unvaccinated participants 120 days after recruitment (mean difference in COVID ST score = -1.8, 95% CI: -2.5 to -1.0), and more vaccinated than unvaccinated participants had remission of all long COVID symptoms (16.6% versus 7.5%, HR = 1.97, 95% CI: 1.23 to 3.15)
- The impact of long COVID on the lives of vaccinated participants was also less than unvaccinated participants (mean difference in COVID impact score = -3.3, 95% CI: -6.2 to -0.5), and fewer vaccinated participants found their symptoms unacceptable (38.9% versus 46.4%, risk difference = -7.5%, 95% CI: -14.4% to -0.5%)

An online survey conducted by Wanga et al (2021, rated as medium quality) compared long-term symptom changes after receiving a COVID-19 vaccination in adults with and without a previous COVID-19 infection in the US (14). The survey was completed in April 2021 ($n=100$ COVID-19 cases, $n=285$ adults who had always received a negative COVID-19 test result), and long-term symptoms were defined as symptoms lasting longer than 4 weeks after a positive test for COVID-19 cases, and symptoms lasting longer than 4 weeks after they first started for adults who never had COVID-19. The analysis accounted for sex, age, region, race and ethnicity and education. Long-term symptoms included change in mood, change in smell or taste, chest pain or pressure, cough, diarrhoea, difficulty thinking clearly, concentrating, forgetfulness, memory loss or “brain fog”, fatigue, tired, or weakness, fever or chills, hair loss, headache, joint or muscle pain, nausea or vomiting, palpitations (heart racing or pounding), post-exertional malaise (worsening of symptoms after even minor physical, mental, or emotional exertion), problems sleeping, shortness of breath or breathlessness, sore throat, stomach pain, or other symptoms.

- COVID-19 cases were more likely to report that the vaccine improved their long-term symptoms than adults who never tested positive for COVID-19 (28.7% versus 15.7%, $p=0.023$)
- However COVID-19 cases were also more likely to report that their symptoms worsened following the vaccination (although this was not statistically significant,

16.1% versus 11.2%, $p=0.27$), and that their symptoms were gone before receiving the vaccine (28.4% versus 13.1%, $p=0.007$)

- Fewer COVID-19 cases reported that the vaccine did not affect their symptoms at all (26.4% versus 59.2%)

Research in progress

Four additional studies were identified that are still in progress:

- An NIHR funded study by Prieto-Alhambra et al will examine the effect of different COVID-19 vaccines on long COVID in the UK (23).
- A study by Massey et al (Project COVID Recovery: Vaccination Study) will measure the changes in participants' moderate to severe PASC symptoms at 6, 12 and 15 weeks after vaccination in the US (24).
- A study by Premkumar et al (EvaLongCovid, NCT05107271) will measure long haul COVID-19 related symptoms in adults with chronic liver disease in India (25).
- A randomised controlled trial by the Área de Ensayos Clínicos (EUCTR2021-003331-28-ES) will randomise adults with COVID symptoms persisting 3 weeks after the acute phase of COVID-19 in Spain to either the Pfizer vaccine or placebo, and measure the change in frequency and intensity of symptoms (26).

Research Limitations

Most studies included in this report compared people with COVID-19 or long COVID who were vaccinated with people who were not vaccinated. As there are many differences between people who are and are not vaccinated, there is a risk in all these studies that factors other than vaccination status may have influenced the results (in any direction), although some studies accounted for this well (8, 11-13, 15). The selection of participants may also have affected the results, especially for the online surveys, as people may have chosen to take part because they had either good or poor experiences with long COVID and vaccination, and for studies that recruited from hospitals, where participants may have had more severe disease or comorbidities. In studies where participants report on symptom change shortly after vaccination, the results may reflect short-term reactions to vaccination in addition to changes in long-term symptoms.

Long COVID was defined inconsistently across studies, both in terms of the symptoms that would comprise long COVID, but also the time frame in which the symptoms needed to be present (long COVID, or post-COVID syndrome, in the UK is typically defined as COVID-19 symptoms beyond 12 weeks). This is particularly true of the studies where long COVID was defined as a composite of several different symptoms. This increased the heterogeneity between studies, though as the results were still relatively consistent, this may also be considered a strength. The studies were also conducted at different points in the pandemic and in different countries, and notably no studies accounted for, or reported on, the COVID-19 variant in their analyses.

The studies where vaccination occurred before infection only included people who were infected with COVID-19, meaning no effect of vaccination on preventing COVID-19 infection in the first place was included in the results. As such, the total effect of vaccination on prevention of long COVID will have been underestimated.

Review limitations

This summary was produced at pace over several days so formal data extraction was not conducted. Most of the work was completed by one reviewer, although all narrative summaries were checked by a second reviewer.

Conclusion

There is evidence that vaccinated people who are subsequently infected with COVID-19 are less likely to report symptoms of long COVID than unvaccinated people, in the short term (4 weeks after infection), medium term (12 to 20 weeks after infection) and long term (6 months after infection). This is in addition to any benefit of vaccination in preventing COVID-19 infection (5). There is also evidence that unvaccinated people with long COVID who were subsequently vaccinated had, on average, reduced long COVID symptoms (though some people reported worsened symptoms after vaccination). Additionally, there was evidence that unvaccinated people with long COVID who were subsequently vaccinated reported fewer long COVID symptoms than those who remained unvaccinated. However, there is a risk of bias across all studies due to differences in people who were vaccinated and unvaccinated, the measurement of outcomes, and in the selection of participants.

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Table 1: Study characteristics

Study	Country, date	Population	Sample size	Vaccine(s)	Long COVID definition
Vaccination before infection					
Antonelli (9)	UK, Dec 2020 to Jul 2021	Adults with positive COVID-19 test (RT-PCR or LFD) reported to the ZOE app	n=4,740 (2,370 unvaccinated, 2,370 fully vaccinated)	NR	Long duration symptoms of COVID-19 (≥28 days)
Al-Aly (12)	US, Feb to Aug 2021	Adults with positive COVID-19 test recorded in the US VHA database	n=64,571 (48,536 unvaccinated, 16,035 vaccinated)	NR	Post-acute sequelae of COVID-19 (symptoms of COVID-19 at 6 months, including cardiovascular disorders, coagulation, fatigue, gastrointestinal disorders, kidney disorders, mental health disorders, metabolic disorders, musculoskeletal disorders, neurologic disorders, and pulmonary disorders)
Arjun (16)	India, Apr to Sep 2021	Adults with positive COVID-19 test (RT-PCR) from a hospital	n=487 (122 unvaccinated, 287 vaccinated [doses NR])	Covaxin (majority)	Self-reported long COVID symptoms (including fatigue, cough, loss of taste and smell and cognitive dysfunction 4 weeks from the date of diagnosis)
Herman (18)	Indonesia, up to Dec 2021	People (age NR) with positive COVID-19 test (RT-PCR, NAAT or LFD) from across the country	n=442 (221 unvaccinated, 221 fully vaccinated)	NR	Olfactory dysfunction (anosmia or hyposmia) 2 and 4 weeks after the end of infection
Kuodi (19)	Israel, Mar to Jun 2021 (COVID-19 infection), Jul to Nov 2021 (survey completion)	Adults with positive COVID-19 test from a hospital	n=951 (317 unvaccinated, 294 fully vaccinated)	NR	Long-term physical, mental, and psychosocial consequences of COVID-19, including fatigue, headache, weakness in arms and legs, persistent muscle pain, loss of concentration, hair loss, sleeping problems, dizziness, persistent cough, shortness of breath, and feeling fully recovered from COVID-19
Senjam (17)	India, Jan to Apr 2021	Adults with positive COVID-19 test (RT-PCR or NAAT) from a hospital	n=773 (407 unvaccinated, 193 fully vaccinated)	NR	Long COVID symptoms present between 4 and 12 weeks (short-term) or beyond 12 weeks (long-term), including fatigue, pain in the joints and muscle, hair loss, headache, cough, breathlessness, sleep disorders, sore throat and decrease of smell and taste
Simon (13)*	US, Jan 2020 to May 2021	People (any age) with positive COVID-19 test (NAAT or antigen test) from across the country	n=240,648 (220,460 unvaccinated, 17,796 fully vaccinated by 12 weeks after infection)	Pfizer, AstraZeneca, Moderna (all approved for use)	COVID-19 symptoms present between 12 and 20 weeks after COVID-19 diagnosis, including chest pain, palpitations, altered mental state, anorexia, chills, fatigue, fever, malaise, loss of sense of smell, loss of sense of taste, nasal congestion, sore throat, abdominal pain, diarrhoea, digestive changes, nausea, vomiting, arthralgia, muscle weakness, general weakness, myalgia, headache, cough and dyspnoea
Taquet (11)	US, Jan to Aug 2021	People (age NR) with confirmed COVID-19 or positive COVID-19 test (RT-PCR) from across the country	n=18,958 (9479 unvaccinated, 2,996 partially vaccinated, 6,957 fully vaccinated)	Pfizer (65%), Moderna (9%), Janssen (1.6%), unspecified (24%)	Any of the following diagnosed symptoms in the 6 months after infection: abdominal symptoms, abnormal bleeding, anxiety/depression, chest/throat pain, cognitive symptoms, fatigue, headache, myalgia and other pain, and death

Study	Country, date	Population	Sample size	Vaccine(s)	Long COVID definition
Vaccination after infection					
Arnold (7)	UK, Apr to May 2020 (COVID-19 hospitalisation), Jan to Feb 2021 (vaccination)	Adults previously hospitalised with COVID-19	n=66 (22 unvaccinated, 44 partially vaccinated)	Pfizer, AstraZeneca	Persistent symptoms of long COVID, including fatigue, breathlessness, insomnia, ear, nose and throat symptoms, brain fog, muscle aches, anosmia, joint pain, cough, headache, palpitations, chest pain, diarrhoea, abdominal pain and nausea
Ayoubkhani (8)	UK, Feb to Sept 2021	Adults with confirmed COVID-19 (RT-PCR) and long COVID symptoms (self-classified)	n=28,356 (all partially vaccinated by study end, 23,753 fully vaccinated by study end)	mRNA vaccine (45%), adenovirus vector vaccine (55%)	Long duration symptoms of COVID-19 (≥28 days) that could not be explained by another condition, including fever, headache, muscle ache, weakness or tiredness, nausea or vomiting, abdominal pain, diarrhoea, loss of appetite, loss of taste, loss of smell, sore throat, cough, shortness of breath, chest pain, palpitations, vertigo or dizziness, worry or anxiety, low mood or not enjoying anything, trouble sleeping, memory loss or confusion, or difficulty concentrating
Gaber (10)	UK, Dec 2020 to Jan 2021	Healthcare workers with long COVID	n=77 (10 unvaccinated, 67 partially vaccinated)	Pfizer (100%)	Long COVID symptoms, including fatigue, shortness of breath and anxiety
Strain (21)	UK, Mar to Apr 2021	Adults with confirmed (RT-PCR/serology) or suspected COVID-19, and long COVID symptoms	n=812 (698 partially vaccinated, 114 fully vaccinated)	AstraZeneca (50%), Pfizer (40%), Moderna (8.6%)	Current or recent symptoms of long COVID-19, including fatigue, brain fog, myalgia, shortness of breath, insomnia, chest pain or palpitations, gastrointestinal symptoms, anosmia, autonomic dysfunction, postural orthostatic tachycardia syndrome, persistent cough, fever, rash (including COVID toes) and vascular complications.
Scherlinger (20)	France, Aug 2021	Adults with confirmed (RT-PCR/serology) or suspected COVID-19, and long COVID symptoms	n=567 (170 unvaccinated, 255 partially vaccinated, 142 fully vaccinated)	Pfizer (78.1%), Moderna (16.4%), AstraZeneca (4.3%), mRNA/vector vaccine combination (0.5%)	Post-acute sequelae of COVID-19 symptoms (≥28 days) and no alternative diagnosis, with symptoms including fever or chills, fatigue, brain fog, headaches, changing mood or impact on morale, sleeping issues, costal pain, dyspnoea, cough, palpitations, muscle aches, joint pain, paraesthesia or tingling, anosmia or ageusia, diarrhoea or vomiting, spontaneous bruises, and pruritus
Tran (15)	France, Nov 2020 to May 2021	Adults with confirmed or suspected COVID-19, and at least 1 long COVID symptom	n=910 (455 unvaccinated, 455 vaccinated)	Pfizer (78.9%), AstraZeneca (10.5%), Moderna (10.3%), Janssen (0.2%)	Long duration symptoms of COVID-19 (≥3 weeks), including 53 symptoms
Wanga (14)	US, Jan 2020 to Apr 2021 (symptoms), Apr 2021 (survey)	Adults tested for COVID-19 (whether positive or negative)	n=385 ≥1 vaccine dose (100 COVID-19 cases, 285 all prior COVID-19 tests negative)	NR	Long duration symptoms of COVID-19 (≥28 days), including change in mood, change in smell or taste, chest pain or pressure, cough, diarrhoea, difficulty thinking clearly, concentrating, forgetfulness, memory loss or "brain fog", fatigue, tired, or weakness, fever or chills, hair loss, headache, joint or muscle pain, nausea or vomiting, palpitations (heart racing or pounding), post-exertional malaise (worsening of symptoms after even minor physical, mental, or emotional exertion), problems sleeping, shortness of breath or breathlessness, sore throat, stomach pain, or other symptoms
Acronyms: LFD = lateral flow device, NAAT = nucleic acid amplification test, NR = not reported, RT-PCR = reverse transcriptase polymerase chain reaction Fully vaccinated = 2 doses of a 2 dose vaccine or 1 dose of a single dose vaccine; partially vaccinated = 1 dose of a 2 dose vaccine; unvaccinated = no vaccine received *Simon et al looked at vaccination before and after infection					

Appendix A – Methods

This report employed a rapid review approach to address the review question:

Are vaccinations against COVID-19, before or after infection, effective against long COVID?

Our rapid review approach follows streamlined systematic methodologies (27). In particular, title and abstract screening was completed by 1 reviewer, and full text screening and summarisation of the studies were performed by one reviewer and checked by another. Risk of bias was assessed by 1 reviewer, using the quality criteria checklist (QCC) tool (28).

We searched a number of specialist COVID-19 review repositories and ran a broad search using Medline, Embase, NLM COVID portfolio (for preprints), WHO COVID Database and Google. Searches were conducted for papers published between 1 January 2020 and **12 January 2022**. Search terms covered key aspects of the review question. The search strategy for Ovid Medline is presented in **Box A.1**.

Box A.1. Search strategy Ovid Medline

- 1 vaccinat*.tw,kw. (175921)
- 2 vaccine*.tw,kw. (271324)
- 3 previously-vaccin*.tw,kw. (1021)
- 4 post-vaccin*.tw,kw. (5742)
- 5 early-vaccin*.tw,kw. (423)
- 6 late-vaccin*.tw,kw. (84)
- 7 moderna.tw,kw. (618)
- 8 mRNA-1273.tw,kw. (451)
- 9 pfizer.tw,kw. (4091)
- 10 BNT162b2.tw,kw. (1349)
- 11 JNJ-78436735.tw,kw. (5)
- 12 "Johnson & Johnson*".tw,kw. (943)
- 13 Astrazeneca.tw,kw. (1690)
- 14 Oxford-Astrazeneca.tw,kw. (172)
- 15 AZD 1222.tw,kw. (3)
- 16 AZD1222.tw,kw. (165)
- 17 BNT 162b2.tw,kw. (14)
- 18 ChAdOx1.tw,kw. (564)
- 19 Novavax.tw,kw. (38)
- 20 NVX-CoV2373.tw,kw. (24)
- 21 Sputnik V.tw,kw. (57)
- 22 Ad26.tw,kw. (83)
- 23 "Ad26.COVS2".tw,kw. (15)
- 24 Ad5.tw,kw. (2669)
- 25 Janssen.tw,kw. (1173)

26 Sinovac.tw,kw. (77)
 27 sinopharm.tw,kw. (52)
 28 covaxin.tw,kw. (43)
 29 exp Vaccination/ (95675)
 30 COVID-19 Vaccines/ (7849)
 31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 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 (372560)
 32 transmiss*.tw,kw. (426659)
 33 transmit*.tw,kw. (180675)
 34 viral load*.tw,kw. (36428)
 35 viral burden.tw,kw. (1064)
 36 ((severity or severe) adj2 (disease or illness)).tw,kw. (117155)
 37 Viral Load/ (37202)
 38 exp Disease Transmission, Infectious/ (77194)
 39 32 or 33 or 34 or 35 or 36 or 37 or 38 (769168)
 40 exp coronavirus/ (116957)
 41 exp Coronavirus Infections/ (142168)
 42 COVID-19/ (131372)
 43 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. (4131)
 44 (coronavirus* or coronovirus* or coronavirinae* or CoV or HCoV*).ti,ab,kw. (121211)
 45 covid*.nm. (7853)
 46 (2019-nCoV or 2019nCoV or nCoV2019 or nCoV-2019 or COVID-19 or COVID19 or CORVID-19 or
 CORVID19 or WN-CoV or WNCov or HCoV-19 or HCoV19 or 2019 novel* or Ncov or n-cov or SARS-CoV-
 2 or SARSCoV-2 or SARSCoV2 or SARS-CoV2 or SARSCov19 or SARS-Cov19 or SARSCov-19 or SARS-
 Cov-19 or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*
 or SARS2 or SARS-2 or SARScoronavirus2 or SARS-coronavirus-2 or SARScoronavirus 2 or SARS
 coronavirus2 or SARScoronavirus2 or SARS-coronavirus-2 or SARScoronavirus 2 or SARS
 coronavirus2).ti,ab,kw. (204081)
 47 (respiratory* adj2 (symptom* or disease* or illness* or condition*) adj10 (Wuhan* or Hubei* or China*
 or Chinese* or Huanan*)).ti,ab,kw. (700)
 48 ((seafood market* or food market* or pneumonia*) adj10 (Wuhan* or Hubei* or China* or Chinese* or
 Huanan*)).ti,ab,kw. (2159)
 49 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (Wuhan* or Hubei or China* or Chinese* or
 Huanan*)).ti,ab,kw. (465)
 50 or/40-49 (238986)
 51 31 and 39 and 50 (4420)
 52 COVID-19/tm [Transmission] (4367)
 53 31 and 52 (520)
 54 COVID-19 Vaccines/ (7849)
 55 39 and 54 (815)
 56 COVID-19/vi [Virology] (8817)
 57 31 and 56 (1561)
 58 51 or 53 or 55 or 57 (5712)

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59  limit 58 to yr="2020 - 2022" (5195)
60  exp SARS-CoV-2/ (104107)
61  exp COVID-19/ (131372)
62  (corona* adj1 (virus* or viral*)).tw,kw,kf. (4621)
63  (CoV not (Coefficient* or "co-efficen*" or covalent* or Covington* or covariant* or covarianc* or "cut-off
value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or
"central vessel trunk*" or CoVR or CoVS)).tw,kw,kf. (73907)
64  (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or
"SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or
COVID*2).tw,kw,kf. (225343)
65  exp COVID-19 Vaccines/ (7849)
66  exp COVID-19 Testing/ (7905)
67  or/60-66 (231660)
68  ((medium or long-term or long-haul or expanded or extended or recurr* or sustain* or persist* or
prolong* or continu* or debilitating) adj2 (effect* or symptom* or impact* or outcome* or recover* or suffer*
or sequela* or impair*)).ti,ab. (305145)
69  "post acute".tw. (3871)
70  68 or 69 (308748)
71  67 and 70 (3551)
72  ((long* or post) adj4 covid*).tw. (5319)
73  71 or 72 (7953)
74  59 and 73 (166)
75  limit 74 to (english language and yr="2021 - 2022") (141)

```

Article eligibility criteria are summarised in **Table A.1**.

Table A.1. Inclusion and exclusion criteria

	Included	Excluded
Population	All populations	
Settings	All community settings, including households	Healthcare settings
Context	COVID-19 pandemic	Other diseases
Intervention / exposure	Partial or full vaccination against COVID-19; any COVID-19 specific vaccination; vaccination before or after COVID-19 infection	
Outcomes	Incidence or prevalence of long COVID using any definition given by individual studies, including symptoms of COVID-19 >28 days after the initial infection	
Language	English	

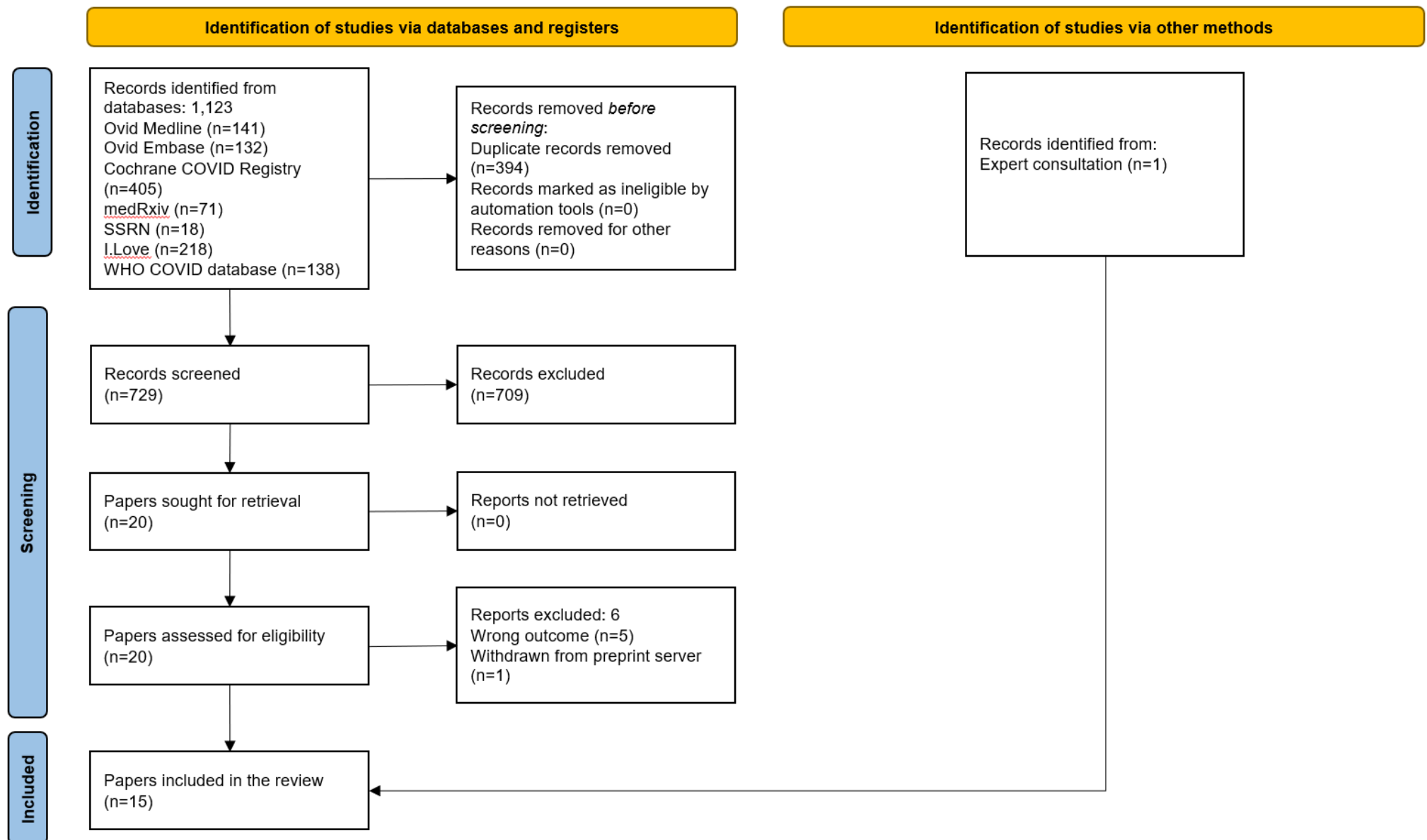
	Included	Excluded
Date of publication	1 January 2020 to 12 January 2022	
Study design	<ul style="list-style-type: none"> • Randomised controlled trials • Cohort studies • Case-control studies 	<ul style="list-style-type: none"> • Systematic or narrative reviews • Other observational studies • Guidelines • Opinion pieces • Outbreak investigations, unless they include an analytical component
Publication type	Published and preprint	

Title and abstract screening was completed by 1 reviewer. Full text screening and study summaries were completed by one reviewer and checked by a second. Only results directly relevant to the review questions were summarised.

Studies were assessed by 1 reviewer, using the QCC for primary research (28). This risk of bias tool can be applied to most study designs (observational and interventional) and is therefore suitable for rapid reviews of mixed type of evidence. It is composed of 10 validity questions based on the criteria and domains identified by the Agency for Healthcare Research and Quality to assess the methodological quality of a study (that is, the extent to which a study has minimised selection, measurement and confounding biases) (29). In the QCC tool, 4 questions are considered critical (on selection bias, group comparability/confounding, interventions/exposure and outcome). A study will be rated as high quality if the answers to the 4 critical questions are 'yes' (and at least one additional 'yes'). The study will be rated as low quality if 2 or more of the critical questions are answered 'no' and/or if $\geq 50\%$ of the remaining questions are answered 'no'. Otherwise, the study will be rated as medium quality. Judgments were made on case by case for questions answered as 'unclear'. To note that we report these ratings as 'quality' ratings for consistency with the name of the tool, although here quality needs to be understood as 'methodological quality' as part of a risk of bias assessment.

The PRISMA diagram showing the flow of citations is provided in **Figure A.1**.

Figure A.1: PRISMA flowchart



About the UK Health Security Agency

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