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SYNTHESIS

Published: March 2022

Impact of Vaccination on Post-Acute COVID-19 Syndrome (PACS) – What We Know So Far

Introduction

Public Health Ontario (PHO) is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

Key Findings

- We identified three studies that examined whether the receipt of a Coronavirus Disease 2019 (COVID-19) vaccine prior to severe acute respiratory syndrome 2 (SARS-CoV-2) infection reduces the risk or prevalence of persistent post-acute COVID-19 symptoms (referred to as post-acute COVID-19 syndrome or PACS). Two studies demonstrated a 50-80% lower odds of developing post-acute symptoms in vaccinated individuals, when compared to unvaccinated individuals. One study observed no significant difference in the prevalence of post-acute symptoms between vaccinated and unvaccinated individuals.

- Evidence was mixed regarding the impact of COVID-19 vaccines administered after acute SARS-CoV-2 infection on the improvement of post-acute symptoms. Four studies demonstrated that individuals who experience persistent PACS reported improvement of post-acute symptoms after COVID-19 vaccination. However, five studies demonstrated no significant change in PACS after vaccination.

- In addition to the known benefits of COVID-19 vaccination (i.e., preventing symptomatic infection, hospitalization, death), vaccines may reduce the risk of PACS among those vaccinated prior to acquiring an acute SARS-CoV-2 infection. While the available evidence on the improvement of PACS after COVID-19 vaccination is limited, findings suggest that COVID-19 vaccination is not significantly associated with the worsening of PACS.

- The available evidence summarized in this synthesis represents a period early in the vaccination roll out, prior to booster availability, and prior to the emergence of Omicron; and therefore, may have limited applicability to the current pandemic context.

Background

There are still discussions and research into what constitutes post-acute COVID-19 syndrome (PACS) and how to define it. For the purposes of this synthesis, we consider persistent symptoms (sequelae) as those that develop or last beyond three weeks or 21 days since symptom-onset. The three-week period is consistent with evidence that live or viable virus is rarely detected past 10 days in mild to moderate cases and rarely detected past 20 days in severe cases.[1] Terminology varies across existing literature, with some patients that have experienced persistent symptoms being referred to as "long-haulers" or having a condition called "long COVID".[2,3] Others have described a "post-acute" phase of the disease with symptoms persisting three to four weeks after symptom-onset (or after discharge from inpatient care), or a "chronic" phase with symptoms persisting past 12 weeks.[4-6] There are no agreed-upon definitions for these time points after initial infection.[6-8] The term post-acute COVID-19 syndrome (PACS) will be used throughout this synthesis to refer to these persistent post-acute symptoms.

Recent evidence on prevalence and risk factors for PACS is synthesized in elsewhere, in *Post-Acute COVID-19 Syndrome (PACS) in Adults – What We Know So Far*.[9] Available literature demonstrates that approximately 50% of COVID-19 patients experience PACS. The most commonly reported sequelae affected most organ groups (i.e., neurological, respiratory, cardiovascular) and contributed to a decreased quality of life, noting that the results were highly heterogeneous.[9]

Vaccine efficacy and vaccine effectiveness measure the proportionate reduction in cases among vaccinated persons compared to those not vaccinated.[10] Vaccine efficacy refers to the reduction in disease incidence when a study is carried out under ideal conditions (e.g., clinical trial), whereas vaccine effectiveness refers to a vaccine's ability to prevent illness in people vaccinated in the real world setting. Both vaccine efficacy and effectiveness are determined by calculating the risk of disease among vaccinated and unvaccinated persons, and determining the percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons.[10] Due to the lack of clinical trial data, this synthesis will focus on available evidence of vaccine effectiveness, that is, evidence from a real world setting.

In September 2021, the Ontario Science Table estimated that 57,000 to 78,000 Ontarians have, or had, PACS.[11] Based on this available data, it is expected that PACS will impact the physical and mental health of a substantial proportion of Ontario's population as well as impact healthcare system resources in the coming years. Therefore, it is important to understand PACS and whether COVID-19 vaccination before or after acute infection improves or reduces the prevalence of these symptoms. The purpose of this document is to examine what is known about the impact COVID-19 vaccination has on post-acute COVID-19 syndrome (referred to herein as PACS).

Methods

In considering feasibility, scope, and a need for responsiveness, we chose a rapid review as an appropriate approach to understanding the persistent symptoms of post-acute COVID-19. A rapid review is a knowledge synthesis where certain steps of the systematic review process are omitted (e.g., quality assessment) in order to be timely.

Public Health Ontario (PHO) Library Services conducted searches in in MEDLINE (February 11, 2022), National Institutes of Health COVID-19 Portfolio (Pre-prints) (February 11, 2022), Embase (February 15, 2022) and Global Health/Scopus (February 15, 2022). The search was informed by a previous search strategy utilized for the *Persistent Symptoms and Post-Acute COVID-19 in Adults – What We Know So Far*, with the addition of updated SARS-CoV-2 variant of concern (VOC) and COVID-19 vaccination search

terms to ensure up to date relevant concepts were captured (search strategies available upon request). PubMed and Google Scholar were also searched for additional articles of interest up to March 10, 2022.

English-language peer-reviewed and non-peer-reviewed records that described the impact of vaccination on PACS were included. We restricted the search to articles published after the previous search (March 1, 2021). This rapid review attempted to concentrate on evidence from systematic reviews and meta-analyses, supplemented by primary literature where appropriate and necessary.

This synthesis does not examine evidence on VE against SARS-CoV-2 infection, hospitalization or death, nor does it examine the general prevalence of PACS after acute COVID-19 infection. Refer to previous PHO syntheses for evidence on real-world VE,[10] VE over time,[12] and post-acute COVID-19 among adults,[9] and pediatric PACS and Multisystem Inflammatory Syndrome in Children (MIS-C).[13]

Search Results

There were 7,263 articles identified from database searches that were screened for inclusion: MEDLINE (n=2,893 articles), Embase and Global Health (n=3,223), Scopus (n=756), and National Institutes of Health COVID-19 Portfolio (Pre-prints) (n=391). After screening and full-text review we included one rapid review and 14 primary research articles. Four of the 14 primary articles (28%) were non-peer-reviewed pre-prints.

The included rapid review examined patients from multiple countries. Six of the 14 single studies examined patients from the United Kingdom (UK), four included patients from the United States (US), two examined patients from France, and two examined patients from Switzerland. Seven studies included an objective assessment of post-acute COVID-19 symptoms. Twelve single studies focused on adult populations and two focused on pediatric and adolescent populations. Please refer to Appendix A for additional details on each included study.

Findings

This section summarizes the results from one rapid review, followed by a summary of 14 primary research articles identified through the PHO Library Services search organized below by sub-topic.

A recent rapid review from the UK Health Security Agency (UKHSA) examined 15 primary studies published in peer-reviewed and pre-print literature up to January 2022. Overall, the review found that people with acute COVID-19 who received two doses of the Pfizer, AstraZeneca, or Moderna vaccines or one dose of the Janssen vaccine, were about half as likely to develop post-acute COVID-19 symptoms lasting more than 28 days when compared to people who received one dose or were unvaccinated.[14] The VE against most PACS in adults was highest among people aged 60 years and over and lowest for younger participants (aged 19 to 35 years).[15] Six of the eight studies in the UKHSA review that assessed the impact of vaccination prior to SARS-CoV-2 infection demonstrated that vaccinated individuals (one or two doses) were less likely to experience PACS following infection in the short term (four weeks after infection), medium term (12 to 20 weeks after infection) and long term (six months after infection).[15] Among the rapid review's studies that examined PACS before and after vaccination, three studies of people with PACS who were unvaccinated at the time of initial infection were less likely to report post-acute symptoms shortly after vaccination, and over longer periods, when compared to people with PACS who were not subsequently vaccinated. There were, however, some cases in all studies included in the UKHSA rapid review who reported no improvements in post-acute symptoms after vaccination during study follow-up periods.[15]

Vaccination before acute SARS-CoV-2 infection

This section summarizes three studies that examined the impact of COVID-19 vaccination administered before SARS-CoV-2 infection on the development of post-acute symptoms.[16-18] Two studies found that receiving COVID-19 vaccination before an acute SARS-CoV-2 infection reduced the risk of developing PACS,[16,18] and one study found no significant difference in the risk of developing PACS between vaccinated and unvaccinated individuals with subsequent SARS-CoV-2 infection.[17]

A pre-print of a US retrospective cohort study reported that people who received one or more doses of the COVID-19 vaccine before acute SARS-CoV-2 infection (n=2,392) were less likely to develop any PACS between 12 and 20 weeks after acute infection (odds ratio [OR] 0.22, 95% CI: 0.20-0.25) compared to unvaccinated patients with COVID-19.[16] The results of this study suggest that one or more doses of a COVID-19 vaccine had a protective effect (relative to unvaccinated individuals) against PACS.

A case-control study from the UK examined 8,400 people who received either one dose (n= 6,030) or two doses (n=2,370) of the COVID-19 vaccine prior to acute SARS-CoV-2 infection.[18] Fully vaccinated (two doses) participants were about half as likely to have PACS lasting for 28 days or longer compared to unvaccinated participants (OR = 0.51, 95% CI: 0.32 to 0.82, p=0.006). There was no significant difference in the experience of PACS lasting 28 days or longer according to age (age 60 and older OR = 0.56 [95% CI: 0.31-0.98, p=0.044]; age 18-59: OR = 0.37 [95% CI: 0.16-0.88, p=0.025]).

A matched case-control pre-print study from the US compared individuals who were vaccinated (one or two doses) prior to acute SARS-CoV-2 infection (n=9,479) to those with an acute infection that have not received a COVID-19 vaccine.[17] The authors found no significant difference between the two groups in their risk of developing post-acute COVID-19 outcomes in the six months following SARS-CoV-2 infection (hazard ratio [HR] = 1.02, 95% CI: 0.97-1.07, p=0.43).

Vaccination after acute SARS-CoV-2 infection

This section summarizes the nine studies that examined the impact of COVID-19 vaccination administered after SARS-CoV-2 infection on post-acute symptoms. Four studies demonstrated that patients who received one or two doses of a COVID-19 vaccine after an acute SARS-CoV-2 infection reported an improvement of post-acute symptoms.[16,19-21] Five demonstrated no significant difference in the prevalence of PACS.[22-26]

A US retrospective cohort study examined the individuals with PACS who were vaccinated at different time periods following acute SARS-CoV-2 infection.[16] Results demonstrate the earlier individuals receive their first dose of a COVID-19 vaccine after acute infection, the less likely they are to develop PACS symptoms between 12 and 20 weeks post-acute COVID-19 diagnosis, when compared to those that remain unvaccinated at 12 weeks post-diagnosis: at 0 to 4 weeks (OR = 0.38, 95% CI: 0.35 to 0.41, $p<0.005$), 4 to 8 weeks (OR = 0.54, 95% CI: 0.51 to 0.57, $p<0.005$) and 8 to 12 weeks (OR = 0.75, 95% CI: 0.71 to 0.78, $p<0.005$). The author noted that their results show vaccination status consistently and substantially had a larger effect on developing PACS than any other factors measured in the study (i.e., demographic factors, pre-existing chronic conditions), with a larger effect observed the earlier vaccination occurred following acute infection.

A cohort study from the UK followed up with 28,356 adults with prior SARS-CoV-2 infection and self-reported PACS at study follow-up after their first vaccine dose (follow-up was at median 141 days after first dose) and after their second vaccine dose (median 67 days after second dose).[19] PACS of any severity were reported by 6,729 participants (23.7%) at least once during follow-up, and PACS that resulted in the limitation of daily activities were reported by 4,747 participants (16.7%) at least once during follow-up. The study demonstrated that the likelihood of post-acute symptoms reduced after COVID-19 vaccination, and the improvement was sustained over the follow-up period after the second dose.

- The first dose was associated with an initial 12.8% decrease (95% CI: -18.6% to -6.6%) odds of experiencing PACS, followed by an increase of 0.3% (0.6% to +1.2%) per week until receiving the second dose. The first dose was also associated with an initial 12.3% decrease (-19.5% to -4.5%) in the odds of activity-limiting PACS, followed by an increase of 0.9% (-0.2% to +1.9%) per week until receiving the second dose.

- The second dose of the vaccine was associated with an initial 8.8% decrease (95% CI: -14.1% to -3.1%) in the odds, followed by a decrease of 0.8% (-1.2% to -0.4%) per week, and an initial 9.1% decrease (-15.6% to -2.1%) in the odds of activity-limiting PACS, followed by a decrease of 0.5% (-1.0% to +0.05%) per week.

In Switzerland, adults with a previous SARS-CoV-2 infection completed a survey 250 days (standard deviation [SD] 72) after acute infection.[20] Of the 2,094 respondents, 1,596 reported developing PACS and 47.1% of those individuals also reported receiving vaccination (one or two doses) after acute infection (survey answered on average 40 days [SD 29 days] after vaccination). Vaccinated individuals reported their symptoms disappeared (30.8%) or improved (4.7%), while 28.7% reported their symptoms were stable and 3.3% had worsened. The authors noted that the symptom changes occurred within five days of vaccination among 69.6% of individuals that reported improvement and 82.3% that reported worsening. Of note, “other” was selected for 29.0% of cases and 2.6% preferred not to answer the question. Those vaccinated with two doses (20.5% of participants) reported a decreased prevalence of dyspnea (aOR 0.34; 0.14–0.82), change in taste (0.38; 0.18–0.83) and of at least one post-acute symptom (aOR 0.60; 0.43–0.83).

A pre-print describing a matched cohort study conducted in France found that being vaccinated with one dose after having an acute SARS-CoV-2 infection improved the severity and impact of PACS.[21] A validated tool called the Long COVID Symptoms Tool was used to examine how many of the 53 included symptoms individuals had at 120 days after baseline (i.e. inclusion in the study) resulted in scores of 13.0 (SD 9.4) for vaccinated (one-dose) individuals and 14.8 (SD 9.8) for unvaccinated individuals (mean difference: -1.8, 95% CI -2.5 to -1.0). In addition, 16.6% of vaccinated (one-dose) individuals reported that all of their PACS had resolved compared to 7.5% of unvaccinated individuals (HR: 1.97, 95% CI 1.23 to 3.15). The impact of PACS on individuals’ lives was also examined using a validated tool called the COVID-19 impact tool which examined six dimensions of individuals’ lives possibly affected post SARS-CoV-2 infection. Those who were vaccinated reported a COVID-19 impact tool mean of 24.3 (SD 16.7) compared to 27.6 (SD 16.7) for unvaccinated individuals (mean difference: -3.3, 95% CI -6.2 to -0.5). Authors also found that vaccination significantly decreased the percentage of individuals reporting an unacceptable symptom state by 7.5% (vaccinated 38.9%; unvaccinated 46.4%; risk difference -7.5%, 95% CI -14.4 to -0.5).

A survey study of adults in France with confirmed PACS demonstrated mixed effects of COVID-19 vaccination on PACS.[26] Among the 380 patients who reported PACS at the time of vaccination (64% received a complete vaccination scheme), 21.8% (n=83) reported symptom improvement driven by improvements to anosmia (62%) and brain fog (51%). The frequency of PACS improvement following vaccination was similar between virologically-confirmed and non-virologically-confirmed PACS patients (20.2% [48/238] vs. 24.3% [34/140], p = 0.35). Conversely, a worsening of PACS severity was reported by 31% of vaccinated PACS patients (n=117), mostly represented by fever/chills (74%), gastrointestinal symptoms (70%); however, authors of this study note these symptoms are also commonly reported following vaccination in the general population who do not experience PACS.

Two prospective cohort studies with small sample sizes demonstrated that after vaccination, post-acute symptoms remained unchanged among a majority of participants (67-71%), with some participants reporting symptom improvements (21-23%). One UK cohort study followed-up with individuals (n=36) previously hospitalized with COVID-19 who continued to experience at least one persistent symptom and received one dose of the COVID-19 vaccine.[24] Upon follow-up (eight months post-hospitalization, 30 days post-first dose) there was a high burden of PACS with a median of 4 (IQR 2 to 5) symptoms per patient and a total of 159 symptoms overall. Among the 159 symptoms reported before vaccination, 37 symptoms (23.2% of symptoms) improved, 9 (5.6%) worsened, and 113 (71.1%) were unchanged. According to validated assessment tools, there was no significant worsening in quality-of-life or mental well-being metrics after vaccination. Another UK cohort study of healthcare workers with PACS (n=67) reported that several weeks after receiving one dose of the COVID-19 vaccine, a majority of participants (67%, n=45) reported no change in post-acute symptoms, 14 (21%) participants reported an improvement in one or more symptom, and 8 (12%) reported a worsening of post-acute symptoms.[25]

Two survey studies demonstrated no significant difference in PACS following COVID-19 vaccination. A survey of health-care workers in Switzerland (n=3,334) found that SARS-CoV-2 vaccination (administered after SARS-CoV-2 infection in the large majority of participants) did not reduce the number of post-acute symptoms.[22] Another survey study conducted in the US recruited patients with a previous acute SARS-CoV-2 infection who had either one or two doses of a COVID-19 vaccine and at least one PACS symptom.[23] On average, there were no significant differences in changes to a variety of PACS symptom (i.e., anosmia, respiratory symptoms, depression, anxiety, COVID-19 related post-traumatic stress disorder, fatigue, sleep, pain) between vaccinated (one or two doses) and unvaccinated individuals. Further analyses examined vaccinated participants that had one dose and two doses of vaccine, and found no significant difference in the measured outcomes of one dose or two dose vaccinated participants when compared to unvaccinated participants.[23]

Multisystem Inflammatory Syndrome in Children (MIS-C)

One case-control study from the US conducted during the dominance of Delta VOC (July 1 to December 9, 2021) examined VE against multisystem inflammatory syndrome in children (MIS-C). MIS-C is a severe post-infectious hyper-inflammatory condition, which generally occurs two to six weeks after a typically mild or asymptomatic infection with SARS-CoV-2.[13] The study compared children age 12-18 hospitalized with MIS-C (n=102) to hospitalized controls age 12-18 (n=181). The authors used two control groups; a symptomatic but SARS-CoV-2 test-negative group and a non-symptomatic group. Results demonstrate that 4.9% of MIS-C case patients were vaccinated compared to 35.9% of controls, giving an adjusted VE of two doses of the Pfizer-BioNTech vaccine against MIS-C of 91% (95% CI = 78%–97%).[27]

Modelling the Impact of vaccination

Two modelling studies from the UK modelled the effect of COVID-19 vaccination on PACS at a population-level.[28,29] One UK modelling study demonstrated that as vaccination coverage increases across the population, the risk of PACS decreases.[29] Another UK modelling study demonstrated that by extending the UK vaccination program to all adolescents over the age of 12, there would be a potential 27% reduction in the prevalence of PACS. If the vaccination eligibility was further extended to children over the age of five, the benefit would be expanded to a 75% reduction in cases of PACS.[28] However, authors acknowledge that most of this benefit is not realized in adolescents and children receiving the vaccine, but largely in older individuals.

Limitations

Four of the 14 (28%) primary research articles included in this synthesis were non-peer-reviewed, pre-print articles. Considering the rapid emergence of the COVID-19 pandemic, the volume of pre-print research is expected given the need for rapid dissemination of data. Furthermore, all but one article included in this synthesis were primary research articles, with the exception of a rapid review identified in the grey literature for which we presented high-level findings. Due to a lack meta-analysis in the included UKHSA rapid review, we included primary research articles identified through the PHO Library Services search that also appeared in the rapid review.

Another limitation of this synthesis is that among the study participants across the 14 primary research articles we included, symptoms at baseline or before acute SARS-CoV-2 infection were unknown. Without pre-COVID-19 clinical assessments, it is difficult to attribute post-acute symptoms solely to COVID-19. Furthermore, there was no consistent definition of persistent post-acute symptoms. In most studies, it was not possible to determine the proportion of cases that had persistent symptoms but who had completely recovered, in contrast to those with ongoing symptoms from a lack of complete recovery from infection.

Furthermore, in studies where there is no comparison in symptoms between vaccinated and unvaccinated, it is difficult to determine whether the change in symptoms is associated with vaccination or due to the passage of time. Additionally, some studies did not adequately describe the timing between the onset of acute SARS-CoV-2 infection and vaccination, to help evaluate the possible impact.

The included studies involved a range of sample sizes, with some involving a very small number of participants. The patient populations of the included studies also tended to over represent older populations (i.e., 50 years or older). This overrepresentation of older adults may be explained in part by the time period that these studies were conducted in, which coincided with early stages in global COVID-19 vaccination programs in which older adults and healthcare workers were among the only populations eligible for vaccination.

Among the studies that examined vaccination after an acute SARS-CoV-2 infection, it was difficult to garner whether vaccinated study participants who had received one dose of a COVID-19 vaccine had done so on the recommendation of public health agencies at the time due to their previous infection. The study period of most included articles coincides with a period in which there were various recommendations from public health agencies regarding the number of COVID-19 vaccine doses that should be administered among previously infected individuals (i.e., whether “fully vaccinated” was defined as one or two doses post-acute infection). For example, Switzerland recommended only one vaccine dose for previously infected individuals and France recommended a three month wait after infection before vaccination.[20,21] Thus, individuals with one dose of a COVID-19 vaccine may have been considered fully vaccinated in some of the included primary studies.

Conclusions and Public Health Implications

We identified two studies which demonstrated a 50-80% lower odds of vaccinated individuals developing PACS when compared to unvaccinated controls, while one study observed no significant difference in the prevalence of PACS. Evidence was mixed regarding the impact of COVID-19 vaccination administered after acute infection on the improvement of PACS. Four studies demonstrated improvement of PACS among individuals who were vaccinated after developing PACS, and five studies demonstrated no significant differences in PACS before and after vaccination. While the evidence of improvement of PACS after vaccination is mixed, these findings provide reassurance that COVID-19 vaccination is not significantly associated with worsening of PACS.

Some findings in this synthesis suggest greater protection against PACS among those who receive vaccination earlier following infection. However, the National Advisory Committee on Immunization (NACI) recommends longer intervals between infection and vaccination, due to evidence that time allows for the immune response to mature in breadth and strength and for circulating antibodies to decrease, thus providing a greater immune response and avoiding immune interference when the vaccine is administered.[30] NACI recommends individuals five years of age and older who are not immunocompromised and have not initiated their primary vaccination series should delay vaccination until eight weeks following symptom onset or positive test confirming acute infection. For those who experienced infection after their primary vaccine series but before their booster dose, NACI recommends a delaying receipt of their booster dose until three months after symptom onset or positive test (if asymptomatic), provided it is at least six months from primary series completion.[30]

Some studies hypothesized possible mechanisms of action underlying the impact of vaccination on PACS. Hypotheses included the potential correction of dysregulated immune or inflammatory responses after vaccination,[16,31] and the possible acceleration of the clearance of the remaining SARS-CoV-2 viral reservoirs and/or viral fragments from specific organ systems following vaccination.[16,20,21] However, more research is needed to understand the mechanism of impact of vaccination on PACS.

The prevalence and risk for developing PACS following acute infection with Omicron is unknown. Available evidence on the severity of Omicron infection indicates that infection with the Omicron variant causes less severe disease compared to the Delta variant.[32] However, at this time, there is insufficient data on Omicron hospitalization outcomes, mortality, or long-term COVID-19 outcomes such as PACS.[32]

The studies included in this synthesis represent a period of the pandemic prior to widespread availability of booster vaccination and before the emergence and circulation of the currently dominant Omicron variant. Two and three COVID-19 vaccine doses have high VE against severe outcomes from Omicron, however, given the lower VE against mild infection, when compared to VE against wild-type and other variants,[32] findings from the available evidence may have limited applicability to the current context in which Omicron is the dominant SARS-CoV-2 lineage in Ontario. While three doses of a COVID-19 vaccine provides greater protection against Omicron variant infection compared to two doses, evidence continues to suggest third dose VE against symptomatic infection wanes over time.[32]

Based on available data from the Ontario Science Table, it is expected that PACS will impact the physical and mental health of a substantial proportion of Ontario's population as well as impact healthcare system resources in the coming years.[11] In addition to the known benefits of COVID-19 vaccination (i.e., preventing symptomatic infection, hospitalization, death), existing evidence suggests a possible protective effect of vaccination against persistent post-acute COVID-19 symptoms. Ongoing monitoring of the literature on this topic is warranted.

Appendix A: Characteristics of included studies

Table 1. Summary of characteristics of included studies

First author (study design)	Study country	Study period	Study population	Patient age	% female patients	Objective assessment of symptoms	Post-acute symptoms assessed or reported	Vaccine information (product, dose) and follow-up period
UKHSA (rapid review)[15]	Various	Search Jan 2022	Various	Various	41-81%	Various	Various	Varied across the 15 included studies
Antonelli (nested case-control)[18]	UK	Dec 2020-July 2021	N = 8,400	Mean 50-52 (SD 13.5-14.1)	61-63%	No, self-report	Not specified	Dose: One dose (n=6,030), two doses (n=2,370) Follow-up: 14 days after testing positive Vaccine: AstraZeneca, Pfizer, Moderna, some not specified
Arnold (case series)[24]	UK	Follow-up one month after vaccination received Jan-Feb 2021	N = 36	Median 64 (IQR 53-73)	42%	Yes, validated questionnaire	Symptoms assessed: Fatigue, Breathlessness, Insomnia, Ear Nose Throat symptoms, Brain fog, Muscle aches, Anosmia, Joint pain, Cough,	Dose: One dose (n=36) Follow-up: Median of 30 days after first dose (IQR, 26 to 36 days) Vaccine: AstraZeneca, Pfizer

First author (study design)	Study country	Study period	Study population	Patient age	% female patients	Objective assessment of symptoms	Post-acute symptoms assessed or reported	Vaccine information (product, dose) and follow-up period
							Headache, Palpitations, Chest pain, Diarrhea, Abdominal pain, Nausea	
Ayoubkhani (prospective cohort)[19]	UK	Feb-Sept 2021	N = 28,356	Mean 46 (SD: 14)	56%	No, self-report	Loss of taste, loss of smell, fatigue, sleep	Dose: One dose (100% of participants), two doses (84% of participants) Follow-up: Median follow-up was 141 days from first dose vaccination and 67 days from second dose vaccination Vaccine: mRNA 45%, adenovirus 55%
Gaber (cohort)[25]	UK	Dec 2020-Jan 2021	N = 77	Range 18-56	91%	No	Anxiety, shortness of breath, fatigue	Dose: One dose Follow-up: Follow-up at two weeks post-first dose Vaccine: Pfizer
Nehme (survey)[20]	Switzerland	April-July, 2021	N = 1,596	Mean 43.5 (SD 13.7)	55%	No, self-report in survey	Fatigue, difficulty concentrating or memory	Dose: One dose (n=424), two doses (n=347)

First author (study design)	Study country	Study period	Study population	Patient age	% female patients	Objective assessment of symptoms	Post-acute symptoms assessed or reported	Vaccine information (product, dose) and follow-up period
							loss, loss of or change in smell, loss of or change in taste, shortness of breath, and headache.	Follow-up: Average 40.3, SD 29.2 days after vaccination (IQR 19–57). Vaccine: Pfizer, Moderna
Scherlinger (survey)[26]	France	Aug 2021	N = 567	Median 44 (IQR 37-50)	83%	Yes, satisfied Ministry of Health's case definition	Anosmia, brain fog, headache, fever, fatigue, changing mood, sleep, joint pain, muscle aches, tingling, Costal pain, dyspnea, cough, palpitations, bruising, diarrhea, vomiting, pruritus/itchy skin	Dose: 396 received at least one dose after a median of 357 (198–431) days following SARS-CoV-2 infection. 255 of 396 (64.4%) had a complete vaccination scheme. Follow-up: Up to 12 weeks post COVID-19 diagnosis (all participants diagnosed post-vaccination) Vaccine: Majority received mRNA, two patients received a mix of

First author (study design)	Study country	Study period	Study population	Patient age	% female patients	Objective assessment of symptoms	Post-acute symptoms assessed or reported	Vaccine information (product, dose) and follow-up period
								mRNA and viral vector.
Shiri 1 (model)[29]	UK	Not reported (NR)	NR	NR	NR	NR	No specific symptoms or organ systems	Modelled the effect following primary series or booster over a three-month period
Shiri 2 (model)[28]	UK	NR	NR	Under 18	NR	NR	No specific symptoms or organ systems	Modelled the effect following primary series
Simon (retrospective cohort)[16]	US	Jan 2020-May 2021	N = 240,648	NR	60%	Yes, analyzed administrative data (via Arcadia Data Research electronic health records network containing records of 150 million people)	No specific symptoms or organ systems	Dose: One dose before infection (n=2,392), one dose within 12 weeks after infection (n=17,796) Follow-up: Varied, outcomes were examined between 12 and 20 weeks after SARS-CoV-2 infection in participants' medical history Vaccine: Pfizer, AstraZeneca, Moderna

First author (study design)	Study country	Study period	Study population	Patient age	% female patients	Objective assessment of symptoms	Post-acute symptoms assessed or reported	Vaccine information (product, dose) and follow-up period
Strahm, (survey)[22]	Switzerland	Jan 2021	N = 3,334	Median 41	80%	No	No specific symptoms or organ systems	Dose: Not specified Follow-up: Not specified Vaccine: Not specified
Taquet (matched case-control)[17]	US	Jan-Aug 2021	N = 18,958 (9,479 vaccinated with PACS, 9,479 unvaccinated with PACS)	Mean 57 (SD: 18)	59%	Yes, analyzed administrative data (via TriNetX electronic health records network containing records of 81 million people)	Anosmia, abdominal symptoms, anxiety/depression, chest or throat pain, cognitive symptoms, fatigue, interstitial lung disease, hair loss, myalgia, other pain	Dose: One or two doses Follow-up: Received one dose minimum two weeks before SARS-CoV-2 infection, outcomes measured within six months of infection Vaccine: Pfizer, Moderna, Janssen, unspecified
Tran (matched cohort study)	France	May 2021	N = 910	Median 47 (IQR 40-54)	80%	Yes, validated tool	Validated patient-reported instruments assessed 53 post-acute symptoms and 6 dimensions of patients' lives	Dose: One dose (n=455) Follow-up: Varied, median of 38 days (IQR 24-53) between baseline questionnaire and first vaccine dose, study results from

First author (study design)	Study country	Study period	Study population	Patient age	% female patients	Objective assessment of symptoms	Post-acute symptoms assessed or reported	Vaccine information (product, dose) and follow-up period
							affected by the disease	day 120 from baseline Vaccine: Pfizer, AstraZeneca, Moderna, Janssen
Wisnivesky (cohort)[23]	US	July 2020-Feb 2021	N = 453	Vaccinated: mean 50.1 (SD 13.4) Unvaccinated: mean 49.7 (SD 14.1)	65%	Yes, multiple validated questionnaires and assessment tools	Anosmia, dyspnea, other respiratory symptoms, depression, anxiety, post-traumatic stress disorder (PTSD)	Dose: One or two doses Follow-up: Varied, vaccination occurred after baseline survey and minimum two weeks before six month survey Vaccine: Pfizer, Moderna, Janssen
Zambrano (case-control)[27]	US	July 1-Dec 9, 2021	N = 283 (102 MIS-C, 181 controls)	Range 12-18	NR	Yes, clinically diagnosed MIS-C	MIS-C involving cardiovascular, gastrointestinal, and hematologic systems	Dose: Two doses (n=5 MIS-C patients) Follow-up: N/A. Patient population was inpatient. Vaccinated MIS-C patients received two doses ≥28 days before hospitalization Vaccine: Pfizer

References

1. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 overview of the period of communicability – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2021 [cited 2022 Mar 07]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/03/wwksf-period-of-communicability-overview.pdf?la=en#:~:text=The%20specific%20period%20of%20communicability,symptom%2Donset%20in%20index%20cases

2. Butler M, Pollak TA, Rooney AG, Michael BD, Nicholson TR. Neuropsychiatric complications of covid-19. BMJ. 2020;371:m3871. Available from: https://doi.org/10.1136/bmj.m3871

3. Baker HA, Safavynia SA, Evered LA. The 'third wave': impending cognitive and functional decline in COVID-19 survivors. Br J Anaesth. 2021;126(1):44-7. Available from: https://doi.org/10.1016/j.bja.2020.09.045

4. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026. Available from: https://doi.org/10.1136/bmj.m3026

5. Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: an overview and approach to classification. Open Forum Infect Dis. 2020;7(12):ofaa509. Available from: https://doi.org/10.1093/ofid/ofaa509

6. Baig AM. Chronic COVID syndrome: need for an appropriate medical terminology for long-COVID and COVID long-haulers. J Med Virol. 2020;23(5):23. Available from: https://doi.org/10.1002/jmv.26624

7. Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. JAMA. 2020;324(17):05. Available from: https://doi.org/10.1001/jama.2020.19719

8. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. BMJ. 2021;372:n136. Available from: https://doi.org/10.1136/bmj.n136

9. Ontario Agency for Health Protection and Promotion (Public health Ontario). Post-acute COVID-19 syndrome (PACS) in adults – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2022. Forthcoming.

10. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 real-world vaccine effectiveness – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2021 [cited 2022 Mar 07]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/04/wwksf-vaccine-effectiveness.pdf?sc_lang=en

11. Razak F, Katz GM, Cheung AM, Herridge MS, Slutsky AS, Allen U, et al. Understanding the post COVID-19 condition (long COVID) and the expected burden for Ontario [Internet]. Science Briefs of the Ontario COVID-19 Science Advisory Table. 2021;2(44). Available from: https://doi.org/10.47326/ocsat.2021.02.44.1.0

12. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 vaccine effectiveness over time – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2021 [cited 2022 Mar 11]. Available from: https://www.publichealthontario.ca/-/media/Documents/nCoV/COVID-WWKSF/2021/11/wwksf-vaccine-effectiveness-over-time.pdf?sc_lang=en

13. Ontario Agency for Health Protection and Promotion (Public Health Ontario). Pediatric post-acute COVID-19 and multisystem inflammatory syndrome in children (MIS-C) – what we know so far [Internet]. Toronto, ON: Queen's Printer for Ontario; 2021 [cited 2022 Mar 29]. Available from: https://www.publichealthontario.ca/-/media/Documents/nCoV/COVID-WWKSF/2021/05/wwksf-children-long-term-sequelae.pdf?sc_lang=en

14. UK Health Security Agency. UKHSA review shows vaccinated less likely to have long COVID than unvaccinated [Internet]. London: Crown Copyright; 2022 [cited 2022 Mar 11]. Available from: https://www.gov.uk/government/news/ukhsa-review-shows-vaccinated-less-likely-to-have-long-covid-than-unvaccinated

15. UK Health Security Agency. The effectiveness of vaccination against long COVID: A rapid evidence briefing [Internet]. London: Crown Copyright; 2022 [cited 2022 Mar 11]. Available from: https://ukhsa.koha-ptfs.co.uk/cgi-bin/koha/opac-retrieve-file.pl?id=fe4f10cd3cd509fe045ad4f72ae0dfff

16. Simon MA, Luginbuhl RD, Parker R. Reduced incidence of long-COVID symptoms related to administration of COVID-19 vaccines both before COVID-19 diagnosis and up to 12 weeks after. medRxiv 21263608 [Preprint]. 2021 Nov 18 [cited 2022 Mar 29]. Available from: https://doi.org/10.1101/2021.11.17.21263608

17. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. medRxiv 21265508 [Preprint]. 2021 Nov 8 [cited 2022 Mar 29]. Available from: https://doi.org/10.1101/2021.10.26.21265508

18. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis. 2022;22(1):43-55. Available from: https://doi.org/10.1016/S1473-3099(21)00460-6

19. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. Changes in the trajectory of Long Covid symptoms following COVID-19 vaccination: community-based cohort study. medRxiv 21267516 [Preprint]. 2021 Dec 9 [cited 2022 Mar 29]. Available from: https://doi.org/10.1101/2021.12.09.21267516

20. Nehme M, Braillard O, Salamun J, Jacquerioz F, Courvoisier DS, Spechbach H, et al. Symptoms after COVID-19 vaccination in patients with post-acute sequelae of SARS-CoV-2. J Gen Intern Med. 2022 Feb 22 [Epub ahead of print]. Available from: https://doi.org/10.1007/s11606-022-07443-2

21. Tran V, Perrodeau E, Saldanha J, Pane I, Ravaud P. Efficacy of COVID-19 vaccination on the symptoms of patients with long COVID: a target trial emulation using data from the ComPaRe e-cohort in France. SSRN. 2021 Sep 29 [cited 2022 Mar 29]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3932953

22. Strahm C, Seneghini M, Güsewell S, Egger T, Leal O, Brucher A, et al. Symptoms compatible with long-COVID in healthcare workers with and without SARS-CoV-2 infection – results of a prospective multicenter cohort. Clin Infect Dis. 2022 Jan 28 [Epub ahead of print]. Available from: https://doi.org/10.1093/cid/ciac054

23. Wisnivesky JP, Govindarajulu U, Bagiella E, Goswami R, Kale M, Campbell KN, et al. Association of vaccination with the persistence of post-COVID symptoms. J Gen Intern Med. 2022 Mar 9 [Epub ahead of print]. Available from: https://doi.org/10.1007/s11606-022-07465-w

24. Arnold D, Milne A, Samms E, Stadon L, Maskell N, Hamilton F. Are vaccines safe in patients with Long COVID? A prospective observational study. medRxiv 21253225 [Preprint]. 2021 Mar 24 [cited 2022 Mar 29]. Available from: https://doi.org/10.1101/2021.03.11.21253225

25. Gaber TA-ZK, Ashish A, Unsworth A, Martindale J. Are mRNA covid 19 vaccines safe in long covid patients? A health care workers perspective. BJMP. 2021;14(1):a008. Available from: https://www.bjmp.org/content/are-mrna-covid-19-vaccines-safe-long-covid-patients-health-care-workers-perspective

26. Scherlinger M, Pijnenburg L, Chatelus E, Arnaud L, Gottenberg J-E, Sibilia J, et al. Effect of SARS-CoV-2 vaccination on symptoms from post-acute sequelae of COVID-19: results from the nationwide VAXILONG study. Vaccines. 2022;10(1):46. Available from: https://doi.org/10.3390/vaccines10010046

27. Zambrano LD, Newhams MM, Olson SM, Halasa NB, Price AM, Boom JA, et al. Effectiveness of BNT162b2 (Pfizer-BioNTech) mRNA vaccination against multisystem inflammatory syndrome in children among persons aged 12–18 years — United States, July–December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(2):52-8. Available from: http://dx.doi.org/10.15585/mmwr.mm7102e1

28. Shiri T, Evans M, Talarico CA, Morgan AR, Mussad M, Buck PO, et al. Vaccinating adolescents and children significantly reduces COVID-19 morbidity and mortality across all ages: a population-based modeling study using the UK as an example. Vaccines. 2021;9(10):1180. Available from: https://doi.org/10.3390/vaccines9101180

29. Shiri T, Evans M, Talarico CA, Morgan AR, Mussad M, Buck PO, et al. The population-wide risk-benefit profile of extending the primary COVID-19 vaccine course compared with an mRNA booster dose program. Vaccines. 2022;10(2):140. Available from: https://doi.org/10.3390/vaccines10020140

30. National Advisory Committee on Immunization. NACI rapid response: updated guidance on COVID-19 vaccination timing for individuals previously infected with SARS-CoV-2 [Internet]. Ottawa, ON: Government of Canada; 2022 [cited 2022 Mar 15]. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/rapid-response-guidance-covid-19-vaccination-timing-individuals-previously-infected-sars-cov-2.html

31. Greif R, Bhanji F, Bigham BL, Bray J, Breckwoldt J, Cheng A, Duff JP, et al. Education, implementation, and teams: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation. 2020;142(16_suppl_1):S222-S83. Available from: https://doi.org/10.1161/CIR.0000000000000896

32. Ontario Agency for Health Protection and Promotion (Public Health Ontario). COVID-19 variant of concern Omicron (B.1.1.529): risk assessment, February 23, 2022 [Internet]. Toronto, ON: Queen's Printer for Ontario; 2022 [cited 2022 Mar 11]. Available from: https://www.publichealthontario.ca/-/media/Documents/nCoV/voc/covid-19-omicron-b11529-risk-assessment.pdf?sc_lang=en

Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Impact of vaccination on post-acute COVID-19 syndrome (PACS) – what we know so far. Toronto, ON: Queen's Printer for Ontario; 2022.

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