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Ongoing symptoms and functional impairment 12 weeks after testing positive for SARS-CoV-2 or influenza in Australia: an observational cohort study

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ABSTRACT

Objective In a highly vaccinated Australian population, we aimed to compare ongoing symptoms and functional impairment 12 weeks after PCR-confirmed COVID-19 infection with PCR-confirmed influenza infection.

Methods and analysis The study commenced on a positive PCR test for either COVID-19 or influenza in June 2022 during concurrent waves of both viruses. Participants were followed up 12 weeks later in September 2022 and self-reported ongoing symptoms and functional impairment. We conducted a multivariate logistic regression analysis, controlling for age, sex, First Nations status, vaccination status and socioeconomic profile.

Results There were 2195 and 951 participants in the COVID-19 and influenza-positive cohorts, respectively. After controlling for potential predictor variables, we found no evidence to suggest that adults with COVID-19 were more likely to have ongoing symptoms (21.4% vs 23.0%, aOR 1.18; 95% CI 0.92 to 1.50) or moderate-to-severe functional impairment (4.1% vs 4.4%, OR 0.81; 95% CI 0.55 to 1.20) at 12 weeks after their diagnosis than adults who had influenza.

Conclusions In a highly vaccinated population exposed to the SARS-CoV-2 Omicron variant, long COVID may manifest as a postviral syndrome of no greater severity than seasonal influenza but differing in terms of the volume of people affected and the potential impact on health systems. This study underscores the importance of long COVID research featuring an appropriate comparator group.

Trial registration number ACTRN12623000041651.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Postacute infection syndromes are associated with a range of illnesses, including COVID-19 and influenza. 'Long COVID' may pose a risk to health systems.

WHAT THIS STUDY ADDS

⇒ In a highly vaccinated population whose primary exposure has been to the Omicron variant, the rates of ongoing symptoms and moderate-to-severe functional impairment at 12 weeks after COVID-19 are no different to influenza.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The public health impact arising from long COVID may not stem from severity, but from volume. We do not dismiss the validity of long COVID but recommend an appropriate comparator group when researching this condition.

INTRODUCTION

Long COVID, now variously described as post-COVID-19 condition, post-COVID-19 syndrome and postacute sequelae of COVID-19,[1] has been described as the pandemic's next challenge to governments and global health systems.[2]

The WHO definition of long COVID includes ongoing symptoms 3 months after infection.[1] Others use different definitions and time periods, or offer refinements to the WHO definition.[3] A diagnosis requires the elimination of other possible explanations and must consider over 200 potential and highly heterogenous symptoms.[4–7] Many of these occur commonly in the general population,[8] and persistent sequelae have been associated with past viral outbreaks and pandemics.[9]

Research has noted the available evidence is frequently low quality, prone to bias and often lacking an appropriate comparator group.[10] While many studies focused on SARS-CoV-2 variants in unvaccinated populations early in the pandemic, relatively few have examined long COVID in vaccinated populations in the Omicron era.[11] As a result, the impact of long COVID in Australia's context remains largely unquantified.

In Australia, the first wave of the Omicron variant commenced in late 2021 when over 90% of the population was double vaccinated

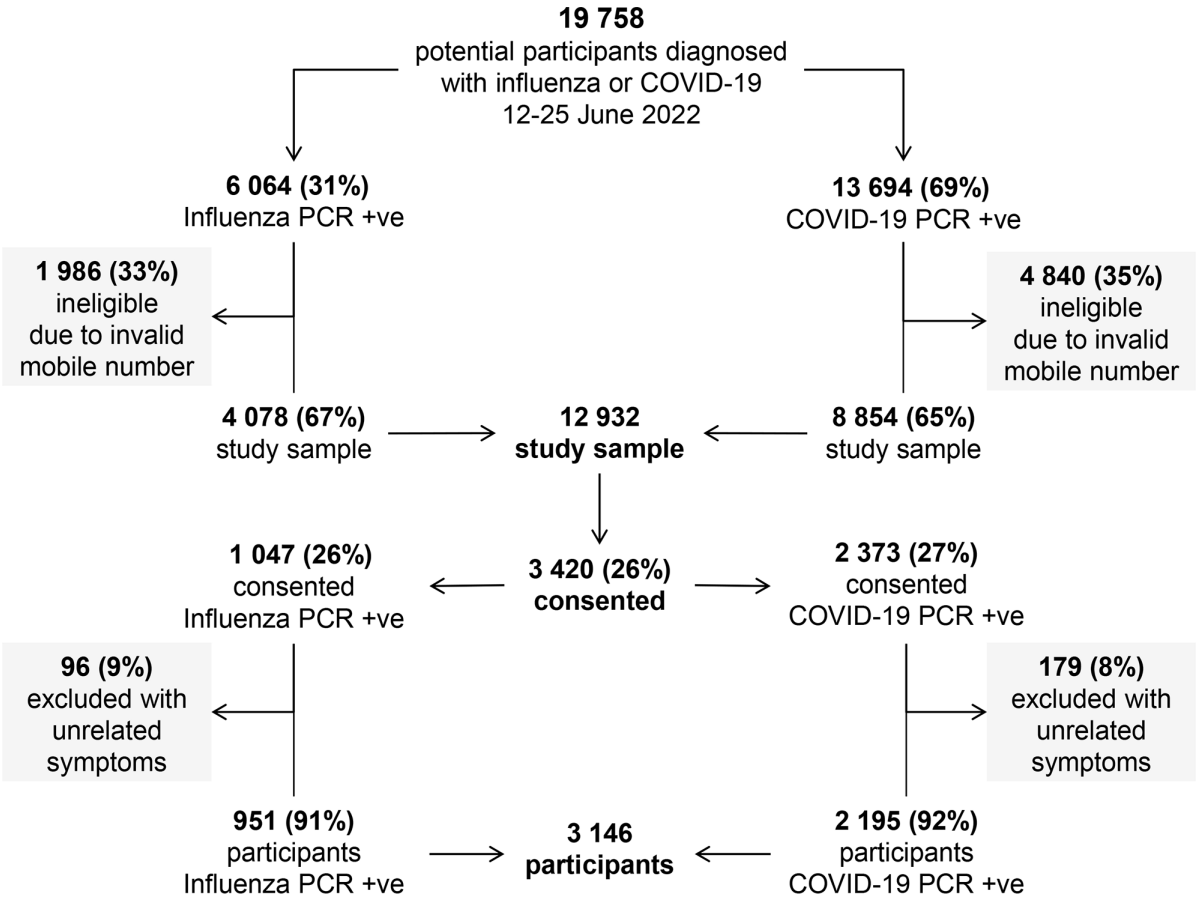

Figure 1 Flow diagram of study sample and participant groups.

against COVID-19.[12] Until that time, the Australian state of Queensland was relatively COVID-19 naïve. This study sought to understand the potential impact of long COVID on the Queensland population and to inform the health system response. Our primary aims were to determine whether a cohort of adults aged 18 years or above who tested reverse transcription (RT)-PCR positive for either COVID-19 or influenza were more likely to have ongoing symptoms or moderate-to-severe functional limitations 12 weeks later if they had COVID-19 (ie, long COVID) in comparison to influenza.

MATERIALS AND METHODS

Study design and participants

We conducted an observational cohort study among individuals aged 18 years and above who tested RT-PCR positive for COVID-19 or influenza between 12 and 25 June 2022 in Queensland. The primary exposure of interest was a diagnosis of COVID-19 versus influenza. Laboratory reporting for these two conditions is mandated on test request under Queensland's public health legislation,[13] with this data recorded in the Queensland Department of Health's Notifiable Conditions System (NoCS). The date range corresponded with the commencement of a COVID-19 wave and the seasonal influenza A peak in Queensland.[14] Our study recruited participants who were PCR positive for either COVID-19 or influenza. The reason for testing was not determined but at the time rapid antigen tests were widely available and recommended for routine screening of asymptomatic individuals. An additional group consisting of individuals who tested RT-PCR negative for both conditions but met all other selection criteria was recruited as a secondary outcome comparator (data not shown here).

The primary outcomes of interest were (a) ongoing symptoms and (b) moderate-to-severe functional limitation. These were assessed through a self-administered questionnaire between 12 and 22 September 2022 (12 weeks post each participant's PCR test result).

Our report conforms with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[15]

Procedures

Each eligible participant's mobile telephone number, first name and date of their PCR test was extracted from NoCS. The data were cleaned, collated and each record was assigned a unique identifier to enable matching with subsequent extraction of relevant predictor variables from NoCS. Participants were sent a text message and the questionnaire using the Whispir communications platform on weeknights between 12 and 22 September 2022. One short reminder text message was sent the

Table 1 Baseline characteristics of participants and non-participants within the eligible cohort groups

	Influenza PCR positive					COVID-19 PCR positive				
	Non-participant (n=3127)		Participants (n=951)			Non-participant (n=6660)		Participants (n=2195)		
Characteristic	n	%	n	%	Diff.	n	%	n	%	Diff.
Female	1857	59.4%	676	71.1%	11.7%	3570	53.6%	1351	61.6%	8.0%
Age at diagnosis										
18–39 years	1794	57.4%	426	44.8%	−12.6%	2674	40.2%	570	26.0%	−14.2%
40–49 years	520	16.6%	171	18.0%	1.4%	1184	17.8%	383	17.5%	−0.3%
≥50 years	810	25.9%	354	37.2%	11.3%	2802	42.1%	1241	56.6%	14.5%
First Nations People	195	6.2%	35	3.7%	−2.5%	228	3.8%	38	1.8%	−2.0%
COVID-19 vaccination										
≥3 doses	1384	44.3%	604	63.5%	19.2%	2689	67.1%	1220	83.2%	16.1%
≥6 months since last dose	1038	39.7%	286	33.4%	−6.3%	1273	31.8%	338	23.1%	−8.7%
Socioeconomic status*										
IRSAD Score=1	225	10.6%	58	8.5%	−2.1%	478	10.0%	102	6.2%	−3.8%
IRSAD Score=2	222	10.5%	39	5.7%	−4.8%	505	10.5%	138	8.3%	−2.2%
IRSAD Score=3	184	8.7%	44	6.5%	−2.2%	486	10.1%	174	10.5%	0.4%
IRSAD Score=4	192	9.1%	68	10.0%	0.9%	373	7.8%	136	8.2%	0.4%
IRSAD Score=5	208	9.8%	62	9.1%	−0.7%	457	9.5%	142	8.6%	−0.9%
IRSAD Score=6	193	9.1%	62	9.1%	0.0%	467	9.7%	181	10.9%	1.2%
IRSAD Score=7	208	9.8%	66	9.7%	−0.1%	431	9.0%	162	9.8%	0.8%
IRSAD Score=8	223	10.5%	77	11.3%	0.8%	540	11.3%	157	9.5%	−1.8%
IRSAD Score=9	211	10.0%	87	12.8%	2.8%	525	10.9%	231	14.0%	3.1%
IRSAD Score=10	250	11.8%	119	17.4%	5.6%	536	11.2%	232	14.0%	2.8%

*IRSAD: Index of Relative Socio-economic Advantage and Disadvantage where IRSAD 1=most disadvantaged and IRSAD 10=most advantaged.

following day. The survey closed 48 hours after the initial text message was sent.

The introductory text was addressed to the individual's first name and indicated the message was from Queensland Health to follow-up a PCR test for COVID-19 or influenza on the relevant date in June 2022.

Respondents were asked if they had ongoing symptoms that related to their initial PCR test, and if so, the degree of functional impairment. The Post-COVID-19 Functional Status (PCFS) tool was used as the basis for grading,[16] because of its demonstrated utility to discriminate between a range of symptoms and functional domains common in postviral syndromes.[17] Modifications were made to provide the brevity and clarity required in a mobile phone-based questionnaire, and to include specific reference to influenza where applicable rather than solely to COVID-19. To maximise engagement across literacy levels using a short text message, the modifications to the PCFS involved simplifying some language and reducing repetition. The questionnaire is provided in online supplemental supporting information.

The grading scores were: no symptoms or no limitations to daily activities (grade 0); ongoing symptoms but no effect on daily activities (grade 1); ongoing symptoms and occasional limitations on daily activities (grade 2); ongoing symptoms that limit all daily activities, with an ability to take care of oneself without assistance (grade 3); and ongoing symptoms resulting in severe limitations in everyday life, and with a dependency on another person for care (grade 4).[16] Consistent with other studies, participants with a PCFS Score of 3 or four were defined as having moderate-to-severe functional limitations.[17]

Potential predictor variables were ascertained from demographic information routinely recorded in NoCS, COVID-19 vaccination records and the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) produced from the Australian Bureau of Statistics.[18] The IRSAD Score is ranked in deciles from 1 to 10 based on economic, educational and social domains, with one being the most disadvantaged and 10 being the most advantaged.

Eligible participants were all those persons recorded on the NoCS system with either condition confirmed from a specimen collected within the specified date range and a valid Australian mobile telephone number. Only one individual was eligible per mobile number. Participants

were excluded from further analyses if they self-reported at the 12 week follow-up that they had symptoms or a new illness that was unrelated to the reasons for their initial PCR test.

Statistical analysis

The primary outcomes (ongoing symptoms, moderate-to-severe functional impairment) and predictor variables were expressed as proportions. We used multivariable logistic regression analysis for each primary outcome as the dependant variable, with the influenza PCR positive individuals as the referent group. Predictor variables assessed for inclusion were age, sex, First Nations status, COVID-19 vaccine dose (<3 doses (referent) vs 3 or more) at the time of testing, vaccine recency at the time of testing (<6 months (referent) vs 6 or more months since last COVID-19 vaccine dose) and the IRSAD Score for the participant's residential address at statistical area 1 with the most disadvantaged quintile as the referent group. Each of the potential predictor variables were assessed against the relevant primary outcome of interest in univariable analysis using χ^2 tests. Those that were significant at the 10% level were included in the multivariable logistic regression model as potential predictors and removed in stepwise fashion if not significant at the 5% level. Adjusted ORs (aORs) and 95% CI were reported.

Study registration

The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12623000041651).

Patient and public involvement

This study was undertaken during a declared public health emergency to urgently ascertain the potential health burden facing a state health system. It was undertaken by the Queensland Government Department of Health under section 83 of the Queensland Public Health Act 2005. Participants were not involved in the design, conduct or reporting of this rapid response research. We aim to engage the public through dissemination of the findings through the Queensland Department of Health.

RESULTS

There were 3146 participants in the study cohort at a ratio of 2.3:1 for individuals diagnosed with COVID-19 compared with influenza (figure 1). Overall, there were 19 758 individuals who had tested PCR positive for either condition during the 2-week eligibility period and 12 932 individuals potentially contactable through a unique valid mobile telephone number. Within each cohort (COVID-19 vs influenza), the eligible proportion (65% vs 67%), the consent rate (27% vs 26%) and postenrolment exclusions (8% vs 9%) were similar. Compared with non-participants for each cohort, there was a relatively higher proportion of women, persons aged ≥50 years, three vaccine dose recipients, recent vaccines and less disadvantaged individuals among the study participants (table 1).

Ongoing symptoms were reported by 21.4% of participants who had been COVID-19 positive when tested 12 weeks earlier and by 23.0% of those who had been influenza positive. After adjusting for all the included covariables (table 2), the aOR was 1.18 (95% CI 0.92 to 1.50). Moderate-to-severe functional impairment was identified among 4.1% of participants who had been COVID-19 positive when tested 12 weeks earlier and by 4.4% of those who had been influenza positive. After adjusting for all the included covariables (table 2), the aOR was 0.81 (95% CI 0.55 to 1.12). Figure 2 shows covariables, referents

Table 2 Proportion of participants with ongoing symptoms and moderate-to-severe functional impairment

Primary outcome	COVID-19 PCR positive	Influenza PCR positive	OR	P>z	95% CI
Ongoing symptoms	21.4% (469/2195)	23.0% (214/951)	1.18	0.19	0.92 to 1.50
Predictor variables		Female	1.65	0.00	1.29 to 2.13
		IRSAD Score=1–2	Referent	Referent	Referent
		IRSAD Score=3–4	0.76	0.17	0.52 to 1.13
		IRSAD Score=5–6	0.66	0.03	0.45 to 0.97
		IRSAD Score=7–8	0.68	0.05	0.47 to 1.00
		IRSAD Score=9–10	0.82	0.25	0.58 to 1.16
		≥3 COVID-19 vaccine doses	0.73	0.02	0.56 to 0.96
		Constant	0.29	0.00	0.19 to 0.43
Moderate-to-severe functional impairment	4.1% (90/2195)	4.4% (42/951)	0.81	0.29	0.55 to 1.20
Predictor variables		Age 18–39 years	Referent	Referent	Referent
		40–49 years	2.01	0.02	1.13 to 3.58
		≥50 years	2.17	0.00	1.35 to 3.50
		First Nations	3.28	0.00	1.52 to 7.06
		Constant	0.03	0.00	0.02 to 0.04

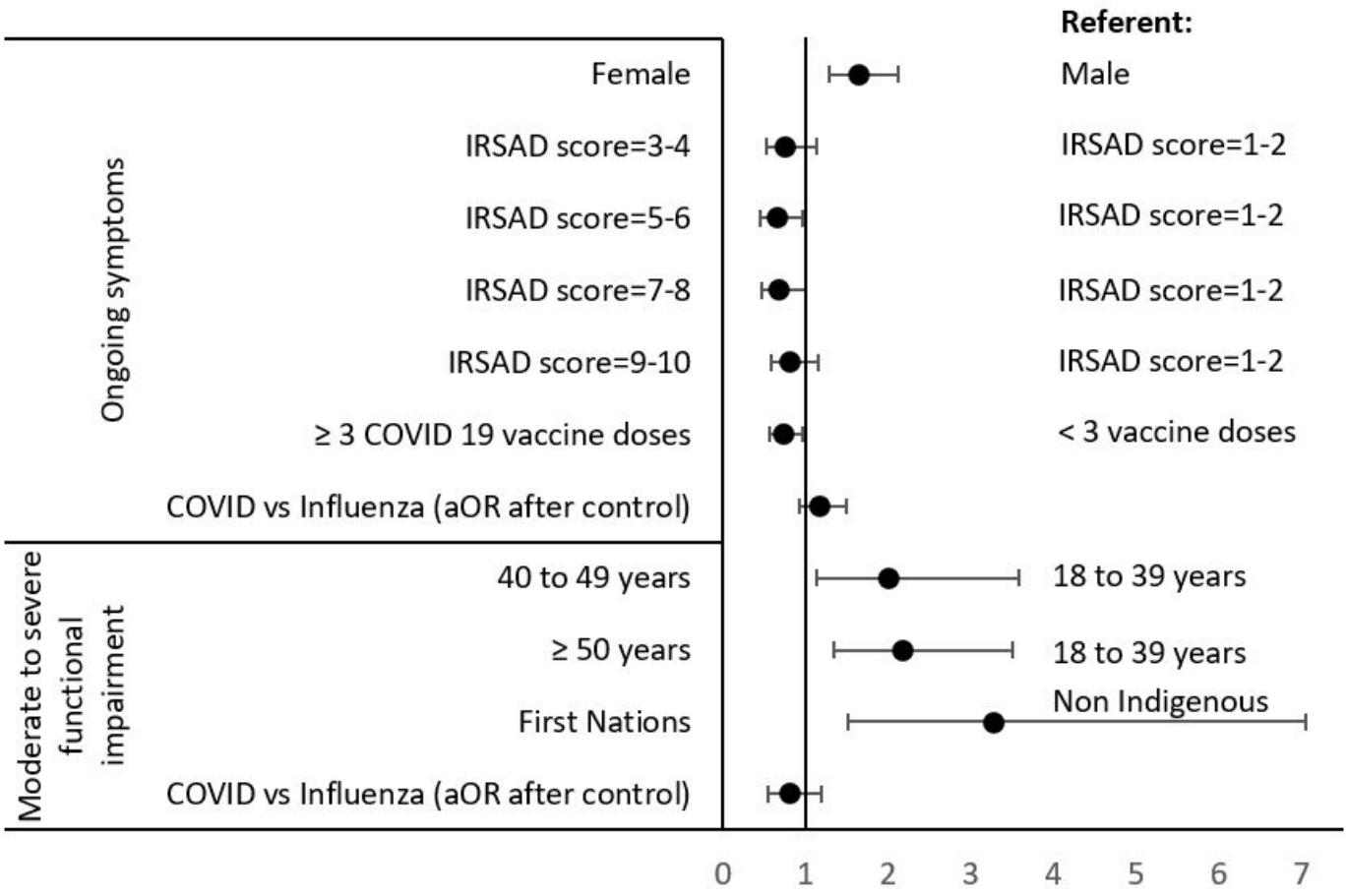

Figure 2 Ongoing symptoms and moderate-to-severe functional impairment—adjusted ORs for COVID-19 compared with influenza.

and aORs for both ongoing symptoms and moderate-to-severe functional impairment. Predictors of self-reported ongoing symptoms at 12 weeks were being female rather than male and being the most disadvantaged on the IRSAD Scale when compared with the midpoint on the IRSAD Scale. Predictors of severe-to-moderate functional impairment were being a First Nations person and being of older age.

DISCUSSION

We found that adults who tested PCR positive for the SARS-CoV-2 Omicron variant were no more likely to have ongoing symptoms at 12 weeks after their test (21.4%) than adults who tested PCR positive for influenza (23.0%, aOR 1.18; 95% CI 0.92 to 1.50). Similarly, we found no evidence to suggest that adults diagnosed with COVID-19 were more likely to have moderate-to-severe functional impairment at 12 weeks after their test (4.1%) than adults who tested PCR positive for influenza (4.4%, OR 0.81; 95% CI 0.55 to 1.20). Being female and socioeconomically disadvantaged were predictors of ongoing symptoms while being a First Nations person and an older person were predictors of moderate-to-severe functional limitations.

To our knowledge, this is the first observational cohort study in a highly vaccinated population that directly compares ongoing symptoms and degree of functional impairment after infection by the SARS-CoV-2 Omicron variant with influenza. Our study was undertaken during the 2022 peak of seasonal influenza in Queensland and at the commencement of a third wave of the Omicron variant when approximately 40% of adults had been vaccinated for influenza and over 93% of adults had received at least two vaccinations for COVID-19.[12 19]

Our findings suggest that, in a highly vaccinated population, the odds of having long COVID arising from the Omicron variant are no greater than the odds of having a postviral illness following seasonal influenza. The finding does not discredit long COVID as a health issue given the significant volume of COVID-19 infections when compared with seasonal influenza, noting that there was a 38-fold difference in reported case numbers (1 606 171 COVID-19 vs 42 338 influenza) between 1 January and 9 September 2022 in Queensland.[14 20] The substantial difference in the incidence of infection with a pandemic virus such as SARS-CoV-2 and an endemic virus such as seasonal influenza may make it appear that postviral syndromes are unusually common with the

novel pathogen, as cases in the community may be high without individual risk being greater.

We acknowledge higher proportions of women, older persons, vaccinees and more advantaged individuals among the study participants, and those who were fully recovered may have been less likely to respond.[21] Approximately one-third of the study population did not have a valid mobile number. Although this rate was similar between the two cohorts (33% for influenza and 35% for COVID-19), we acknowledge the lack of a valid mobile number may be a predictor of disadvantage or another unknown confounder. The lower influenza vaccination coverage (40%) compared with COVID-19's vaccination coverage (93%) may have been a limitation within the study population. Self-reported responses are also a study limitation. Others have shown use of a mobile phone survey when compared with face-to-face data collection increases the adjusted OR for self-reporting long COVID by 30%.[22]

Our study was unable to consider participant's pre-existing health conditions, nor consider the severity of COVID-19 or influenza infection. Participants who were hospitalised or in intensive care were not identifiable within the cohort. Emerging Australian research shows a low prevalence of long COVID in vaccinated adults following Omicron infection, although with a difference between adults who were hospitalised (1.9%) and not hospitalised (0.09%).[23] These rates are lower than those reported in international studies[24] and may be related to the Australian population's high vaccination coverage on exposure to the Omicron variant.

The PCFS tool does not ask respondents to describe specific symptoms so we do not discern if COVID-19 and influenza differ in specific symptom domains, including in areas of functional impact. However, we do discriminate between different levels of fatigue and functional performance, using consistent methods to those used where the PCFS grade 3–4 scale has shown poorer functional outcome, more fatigue and poorer quality of life.[17] We consider the PCFS grades 3–4 scale allows identification of the population of interest when considering the potential for impact on Queensland's health system.

Previous reports have noted the high rate of typical long COVID symptoms among those recovering from influenza.[25] The high number and heterogenous nature of potential long COVID symptoms also underscores the importance of future studies featuring a concurrent control group. Our study supports recent literature suggesting that, in a highly vaccinated population, the SARS-CoV-2 Omicron variant does not result in a significant burden of long COVID.[26] In this context, long COVID manifests at the population level as a postviral syndrome of no greater severity than seasonal influenza but differing in terms of the volume of people affected and the potential impact on health systems.

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Contributors LM, JG and MB conceptualised the study. MB designed the methodology and wrote the protocol and draft manuscript, with input from JG and LM. RA oversaw the data curation and extraction from the Notifiable Conditions System, led the formal analysis and described this in the paper's methodology and results. JM established the data curation protocols for records from the Notifiable Conditions System. TS provided the technical design, development, implementation and collation of the online survey, data cleansing and collation before and after the survey distribution. All authors critically revised and edited the manuscript, confirmed they had full access to all the data in the study and accepted responsibility to submit for publication. MB is the guarantor and accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Metro South Health Research Ethics Committee (HREC/2022/QMS/88587) and the Queensland Office of Precision Medicine and Research (SSA/2022/QHC/88587). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Because of data confidentiality provisions under Queensland public health legislation, individual data from Queensland Health's Notifiable Conditions System will not be shared publicly. We can share the research protocol and survey questions. Requests for deidentified data associated with this research should be sent to the corresponding author (matthew.brown@health.qld.gov.au) after publication of the paper in the form of a formal data request which outlines the proposed use of this data and ensures appropriate attribution to this research.

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