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Short communication

Preventive effect of vaccination on long COVID in adolescents with SARS-CoV-2 infection

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ABSTRACT

Purpose: In adolescents (12–17 years), it is unknown whether COVID-19 vaccination reduces progression from COVID-19 to Long COVID (LC) beyond preventing SARS-CoV-2 infection. We assessed the effect of vaccination among SARS-CoV-2 infected adolescents.

Methods and results: Participants were recruited from over 60 US healthcare and community settings. The exposure was any COVID-19 vaccination 6 months prior to infection. The outcome was LC defined using the LC research index. Vaccinated (n = 724) and unvaccinated (n = 507) adolescents were matched on sex, infection date, and enrollment date. The risk of LC was 36 % lower (95 % CI, 17 %, 50 %) in vaccinated compared to unvaccinated participants.

Conclusions: Vaccination reduces the risk of LC. Given the profound impact LC can have on the health and well-being of adolescents and the limited availability of treatments during this developmental stage, this supports vaccination as a strategy for preventing LC by demonstrating an important secondary prevention effect.

1. Introduction

Long COVID (LC) is a chronic condition occurring after SARS-CoV-2 infection that can affect multiple organ systems. LC is a significant public health problem for children and adolescents, with health, educational, familial, and economic costs [1,2]. While LC can affect people of all ages, it is understudied in children, and adolescents may be at the highest risk [3]. Treatment and prevention strategies for LC are limited.

Vaccination against COVID-19 can reduce the risk of LC in three ways (Fig. 1). First, vaccination prevents infection [4], indirectly preventing LC. Second, vaccination decreases infection severity [5], and more severe COVID-19 is associated with higher risk of LC [6]. Third, vaccination may mitigate the longer-term pathophysiologic response to infection [7]. Distinguishing these pathways is crucial for better understanding the underlying biological mechanisms leading to LC and the broader public health impact of vaccination.

Studies have shown vaccination to be protective against LC in adults [8], but evidence in pediatric populations is limited and conflicting. Most studies are electronic health records (EHR)-based [9,10] or only include patients from post-covid clinics [11]. Research from a large, diverse community-based cohort is needed.

We sought to assess the impact of COVID-19 vaccination prior to SARS-CoV-2 infection on preventing LC among adolescents with history of SARS-CoV-2 infection in the NIH-funded Researching COVID to Enhance Recovery (RECOVER) Initiative [12].

2. Methods

2.1. Study design

RECOVER-Pediatrics is an observational cohort study of LC in children, adolescents, and young adults, including participants recruited from the Adolescent Brain and Cognitive Development (ABCD) study [13]. These analyses focused on adolescents (12–17 years) and used caregiver-reported survey data to conduct a retrospective analysis to determine associations between vaccination status and LC in adolescents infected with SARS-CoV-2. Participants were enrolled between February 7, 2022 and November 14, 2024. The NYU Grossman School of Medicine and the UC San Diego Human Research Protections Program (ABCD) institutional review boards provided approval with reliance from other institutions. Participants reporting SARS-CoV-2 infection at least 90 days prior to enrollment (at which time LC was assessed) were included. Participants enrolled within 30 days after an infection and participants with history of Multisystem Inflammatory Syndrome in Children were excluded.

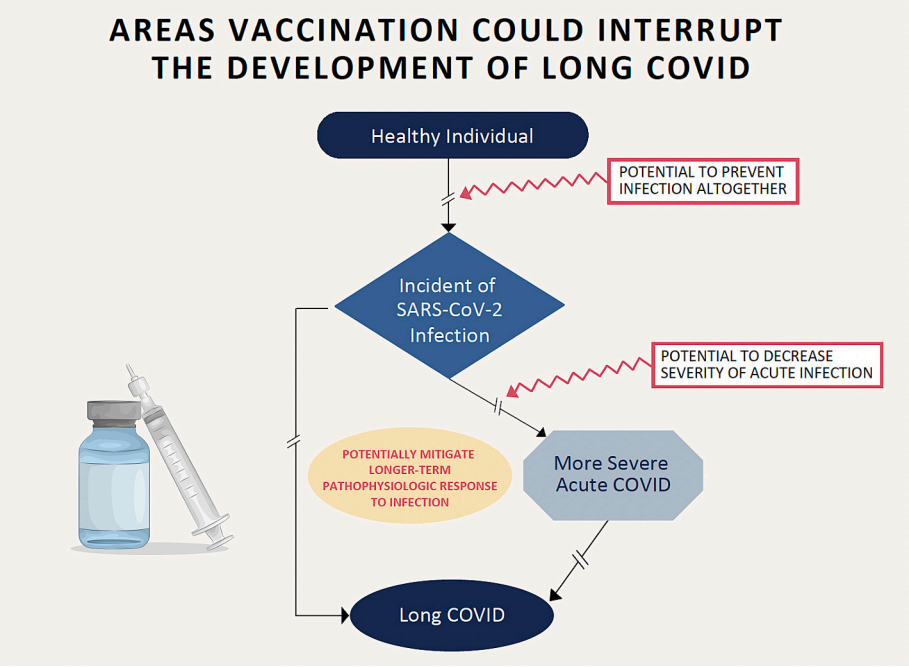

Fig. 1. Areas vaccination could interrupt the development of Long COVID.

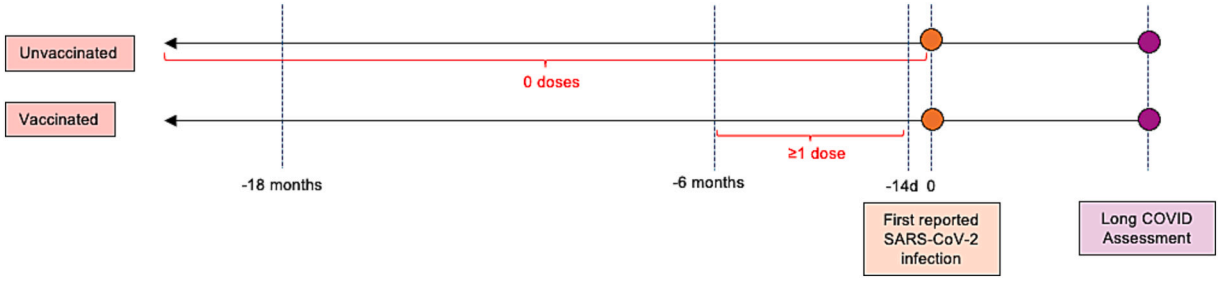

Fig. 2. Study design for matched analysis.
Caption: First reported SARS-Cov-2 infection is "time zero" above, and the enrollment date is some time (denoted t) at least 90 days after enrollment. Up to two vaccinated participants were matched to each unvaccinated participant within age cohort by sex assigned at birth (exact match), calendar time of first infection (within 45 days) and calendar time of enrollment/long COVID assessment (within 90 days). Time periods with brackets are those for which inclusion/exclusion criteria were applied with regards to the number of vaccination doses reported during that period.

2.2. Study endpoints

The primary endpoint was the presence of LC at enrollment, defined using the LC research index for adolescents, a weighted summary measure of 8 LC-associated symptoms: loss of smell/taste, body/joint pain, fatigue, post-exertional malaise, back/neck pain, cognitive difficulties, headache and lightheadedness [14]. A symptom was counted if it was present for at least 4 weeks since first infection and at enrollment (at least 90 days after infection). Each symptom was assigned a score of 0.5–12, with a threshold of 5 or greater indicating LC.

The secondary endpoint was severe LC, defined as having a LC symptom profile consistent with the previously published cluster with the highest symptom burden and worst overall health, quality of life, and physical health (Cluster 1) [14].

2.3. Statistical analysis

Exposure was any COVID-19 vaccine dose within 6 months and 14 days prior to first reported SARS-CoV-2 infection ("first infection") (Fig. 2). Six months was selected due to waning immunity after vaccination [15]. Vaccinated participants whose only vaccine dose(s) were $>$ 6 months or $<$ 14 days prior to first infection were excluded. Demographic, vaccine, and infection-related characteristics were reported. Race/ethnicity was included to better characterize vaccination across subgroups. Unvaccinated participants (never vaccinated) were matched to 1 or 2 vaccinated participants based on sex (exact matching), first infection date (45-day window), and enrollment date (90-day window). Participants who did not provide symptom data, sex, or vaccination history, or whose reported vaccination history was implausible (e.g., vaccinated for COVID-19 prior to 2020), were excluded. The relative risk (RR) for the association between vaccination and LC/severe LC was estimated using a log-binomial model and cluster-robust standard errors. [16] In sensitivity analyses, models were adjusted for SARS-CoV-2 variant, caregiver education, and residence in a medically underserved area, with multiple imputation (25 imputations) to address missingness in caregiver education after matching. Analyses were performed using the *MatchIt* [17] and *mice* [18] packages in R (Version 4.4.1) [19].

3. Results

Overall, 2353 participants (1425 never vaccinated prior to first infection, 928 vaccinated within 6 months prior to first infection) were eligible and 1231 were selected in the matched cohort (507 unvaccinated, 724 vaccinated, eFigure 1; Supplement). Demographic characteristics are provided in Table 1 and eTable 1 (Supplement). Most (86 %) vaccinated participants reported $\geq$2 doses within 18 months before first infection.

For infected adolescents, the risk of LC was 20.7 % in unvaccinated participants and 13.3 % in vaccinated participants [RR 0.64 (95 % CI: 0.50, 0.83)] (Table 2). The risks of severe LC were 6.1 % and 4.7 % in unvaccinated and vaccinated participants, respectively [RR 0.77 (95 % CI: 0.48, 1.26)]. In sensitivity analyses, the adjusted RR was slightly attenuated [RR 0.74 (95 % CI: 0.56, 0.97) for LC, 0.87 (95 % CI: 0.52, 1.45) for severe LC].

4. Discussion

In this study of adolescents with SARS-CoV-2 infection, vaccination in the 6 months prior to first infection reduced the risk of LC by 36 %. The estimated risk reduction was slightly attenuated to 26 % after adjusting for potential confounding. The COVID-19 vaccine is relatively unique in having this effect on progression to a chronic condition, despite infection. This highlights that even if infection occurs, recent vaccination still has a protective effect on LC risk.

This is the first study to assess the preventive effect of vaccination against LC beyond infection prevention among adolescents drawn from both community and medical settings. Of prior EHR-based studies, only two (using data from the same cohort) analyzed adolescents and younger children separately [9,10]. While estimated overall relative risk reduction ranged from 50 to 95 %, estimates of the effect of vaccination on LC beyond preventing SARS-CoV-2 infection were imprecise, with wide 95 % confidence intervals (CI; relative risk estimates of 0.75–1.55 for the Delta variant and 0.69–1.19 for the Omicron variant) [10]. A meta-analysis of cross-sectional and prospective studies [6] and a survey-based study [20] showed no effect.

This estimate of vaccine effectiveness beyond infection prevention may be conservative. Our analysis focused on prolonged LC present at enrollment and does not consider intermittent LC. Additionally, adolescents with subclinical LC may be asymptomatic and not meet the research index threshold [21]. This estimate of vaccine effectiveness also does not account for infection that is prevented altogether through vaccination.

There are several strengths of this study. RECOVER-Pediatrics is geographically, racially, and ethnically diverse [12]. We recruited from community settings, allowing inclusion of those not captured in EHR cohorts or LC clinics, who are predominately from academic medical settings. We used a LC research index that did not rely on self-identified or clinician-diagnosed LC and is more robust than other, less specific definitions. Finally, the analytic approach ensured that comparisons between vaccinated and unvaccinated participants accounted for SARS-CoV-2 variant.

This study is subject to some limitations. Vaccinations were caregiver-reported, potentially introducing recall bias. However, correlation between reported vs. EHR-documented COVID-19 vaccinations is high [2,22]. Since individuals infected during pre-Delta and Delta waves were generally not vaccine-eligible, they could not be matched to vaccinated individuals who were contemporaneously infected, and were excluded. Only vaccination prior to first infection was assessed, and

Table 1
Characteristics of matched cohort.

	Vaccinated[a] ($N = 724$)	Vaccinated, after reweighting to match to those not vaccinated[b]	Not vaccinated[c] ($N = 507$)
Age at enrollment (years)			
Median (IQR)	15 (14, 16)	15 (14, 16)	15 (14, 16)
Sex			
Male	370 (51 %)	51 %	257 (51 %)
Female/Intersex	354 (49 %)	49 %	250 (49 %)
Race/ethnicity			
White/non-Hispanic	428 (59 %)	60 %	245 (48 %)
Hispanic	134 (19 %)	19 %	144 (28 %)
Black/non-Hispanic	50 (7 %)	7 %	58 (11 %)
Asian/non-Hispanic	19 (3 %)	2 %	9 (2 %)
Mixed/Other/Missing	93 (13 %)	12 %	51 (10 %)
BMI (kg/m^2)	21 (19, 24)	21 (19, 25)	22 (19, 24)
Variant era[d]			
Delta & earlier (before Nov. 30, 2021)	113 (16 %)	22 %	147 (29 %)
Delta-Omicron (Dec. 1–31, 2021)	172 (24 %)	24 %	103 (20 %)
Omicron (Jan. 1, 2022 onwards)	439 (61 %)	54 %	257 (51 %)
Time from most recent pre-infection vaccination to first infection (days)			
Median (IQR)	112 (56, 157)	109 (55, 155)	
Time from first infection to enrollment/Long COVID assessment (days)			
Median (IQR)	459 (337, 583)	491 (362, 614)	504 (384, 666)
Number of vaccine doses during 18 months before first infection			
1	116 (16 %)	18 %	
2	373 (52 %)	56 %	
3	219 (30 %)	24 %	
4+	16 (2 %)	2 %	
Number of vaccine doses between first infection and enrollment/Long COVID assessment			
1	276 (74 %)	72 %	53 (35 %)
2	87 (23 %)	25 %	74 (49 %)
3	8 (2 %)	2 %	21 (14 %)
4+	3 (1 %)	1 %	4 (3 %)
Caregiver educational attainment			
College or higher	512 (75 %)	73 %	213 (47 %)
Less than college	171 (25 %)	27 %	240 (53 %)
Missing	41		54
Resides in a medically underserved area			
Yes	175 (24 %)	25 %	150 (30 %)
No	549 (76 %)	75 %	357 (70 %)

All numbers are count (%) unless otherwise specified. First infection refers to first reported SARS-CoV-2 infection.

[a] Vaccinated refers to participants who received at least 1 dose in the 6 months to 14 days prior to first infection.

[b] Because more than 1 vaccinated participant may be matched to a single unvaccinated participant, the distribution of demographic factors must be reweighted to account for the matching scheme for the purposes of comparison to the unvaccinated cohort. A sample size is not provided due to reweighting.

[c] Unvaccinated refers to participants who received 0 doses prior to first infection.

[d] Because most participants were not enrolled during acute COVID-19, biospecimens were not collected that would allow identification of the exact SARS-CoV-2 strain with which each participant was infected. Therefore, variant is defined by the reported time of first infection and is categorized into three variant eras.

participants were not followed prospectively from first vaccination. Specific dose effects were not assessed given that most had multiple doses prior to first infection. Finally, the study was likely underpowered to evaluate the rare outcome of severe LC.

Table 2
Estimated relative risk of Long COVID, comparing vaccinated to not vaccinated, after matching.

	Vaccinated[(a)]	Not vaccinated[(b)]	Relative risk, unadjusted (95 % CI)[(c)]	Relative risk, adjusted (95 % CI)[(d)]
Count	724	507		
Long COVID	13.3 %	20.7 %	0.64 (0.50, 0.83)	0.74 (0.56, 0.97)
Severe Long COVID	4.7 %	6.1 %	0.77 (0.48, 1.26)	0.87 (0.52, 1.45)

Abbreviation: CI = Confidence Interval.

[a] At least 1 dose between 6 months (180 days) and 14 days before first infection.

[b] No doses reported prior to and including day of first infection.

[c] Unadjusted analysis is performed after matching on sex, first infection date, and enrollment date.

[d] Adjusted analysis includes additional adjustment for SARS-CoV-2 variant (Delta & earlier, Delta-Omicron, Omicron), residence in a medically underserved area (yes, no), and caregiver education level (college or higher, less than college).

5. Conclusions

We demonstrated that COVID-19 vaccination has an important secondary prevention effect by limiting progression to LC by 36 %, despite infection. Given the profound impact LC can have on the health and well-being of adolescents and the lack of available treatments, these findings support vaccination as an effective and meaningful prevention strategy for LC.

Additional Contributions

We would like to thank the National Community Engagement Group, all patient, caregiver, and community representatives, and all the participants enrolled in the RECOVER Initiative.

Data Sharing Statement

An overview of the availability of RECOVER observational cohort data for researchers is available (https://recovercovid.org/data). Because the study is ongoing, data are dynamically updated and have been available as of 2023. To analyze de-identified individual participant data from the RECOVER observational cohort studies, researchers must receive authorization for access for a specified purpose with a signed data access agreement. This authorization is required to maintain the integrity of the data and protect participant privacy. Authorized researchers can access RECOVER observational cohort study data from BioData Catalyst (https://biodatacatalyst.nhlbi.nih.gov). Additional information about how to access RECOVER data can be found here: https://bdcatalyst.gitbook.io/biodata-catalyst-documentation/written-documentation/nih-recover-release-notes. Specifically, the post dated October 2024 ("RECOVER Pediatric Observational Cohort Study") has links to the data dictionary/REDCap codebooks for the various substudies within RECOVER.

CRediT authorship contribution statement

Tanayott Thaweethai: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Rachel S. Gross:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Deepti B. Pant:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Kyung E. Rhee:** Writing – review & editing, Investigation. **Terry L. Jernigan:** Writing – review & editing,

Investigation. **Lawrence C. Kleinman:** Writing – review & editing, Investigation. **Jessica N. Snowden:** Writing – review & editing, Investigation. **Amy L. Salisbury:** Writing – review & editing, Investigation. **Patricia A. Kinser:** Writing – review & editing, Investigation. **Joshua D. Milner:** Writing – review & editing, Investigation. **Kelan Tantisira:** Writing – review & editing, Investigation. **David Warburton:** Writing – review & editing, Investigation. **Sindhu Mohandas:** Writing – review & editing, Investigation. **John C. Wood:** Writing – review & editing, Investigation. **Megan L. Fitzgerald:** Writing – review & editing, Investigation. **Megan Carmilani:** Writing – review & editing, Investigation. **Aparna Krishnamoorthy:** Writing – review & editing, Validation, Formal analysis. **Harrison T. Reeder:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Andrea S. Foulkes:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization. **Melissa S. Stockwell:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Disclaimer

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127907.

Data availability

There is a data availability statement provided in the manuscript which describes how to access the data in the study.

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