RESEARCH LETTER

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.

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.

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		
	No.	% (95% CI)[a]	No.	% (95% CI)[a]	*P* value
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.

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.

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; 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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Conflict of Interest Disclosures: Dr Mantovani reported receiving personal fees for lectures from Ventana, Novartis, and Roche; consulting fees from Pierre Fabre, Verily, AbbVie, AstraZeneca, Third Rock Venture, and Merck; serving on the advisory board for Verseau Therapeutics, Myeloid Therapeutics, Imcheck Therapeutics, Ellipses, Olatec Therapeutics, Macrophage Pharma, Biovelocita,

Principia, and Biolegend; grants from Novartis; and royalties for sale of reagents from Biolegend Royalties, Cedarlane Laboratories, HyCult Biotechnology, eBioscience Royalties, ABCAM Plc, Novus Biologicals, Enzo Life, and Affymetric. Dr Mantovani also reported having a patent for antihuman migration stimulating factor (MSF), a patent for NK or T cells and uses thereof, a patent for "use of SAP for the treatment of *Euromycetes fungi* infections," and a patent for PTX3 as prognostic marker in COVID-19 licensed to Diasorin (prospective trial in sepsis underway). Dr Rescigno reported serving on the advisory board (with compensation) for MillBo and receiving grants from AlfaSigma, Gelesis, and Diasorin outside the submitted work. No other disclosures were reported.

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