Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

UNIVERSITÀ DEGLI STUDI DI MILANO

Precedente infezione da SARS CoV-2 e sintomi post vaccinazione con mRNA BNT162b2: dati di 3078 lavoratori dell'ASST Santi Paolo e Carlo

Alessandro Tavelli

CONVEGNO
VIRTUAL EDITION
7-8 Giugno 2021

EClinicalMedicine 36 (2021) 100914

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Association between previous infection with SARS CoV-2 and the risk of self-reported symptoms after mRNA BNT162b2 vaccination: Data from 3,078 health care workers

Antonella d'Arminio Monforte[a,*], Alessandro Tavelli[a], Pier Mario Perrone[b], Alessandro Za[c], Katia Razzini[c], Daniele Tomasoni[a], Vittorio Bordoni[d], Luisa Romanò[b], Nicola Orfeo[c], Giulia Marchetti[a], Claudio Colosio[d]

[a] *Unit of Infectious Diseases, ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy*
[b] *Department of Biomedical Sciences for Health, University of Milan, Milan, Italy*
[c] *Medical Direction, ASST Santi Paolo e Carlo, Milan, Italy*
[d] *Occupational Health Unit, International Centre for Rural Health, Department of Health Sciences, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy*

Background

- Health care workers (HCWs) are a particularly at risk of get infected by SARS CoV-2: in Italy 124,003 (4.2%) COVID-19 have been reported in this population
- BNT162b2 first mRNA vaccine approved (Dec-21 EMA):
  - 95% efficacy
  - low incidence of moderate adverse events

- A worldwide vaccination campaign was launched (prioritizing HCWs) to achieve the goal of creating the herd immunity but some questions remain open on reactogenicity to vaccine:

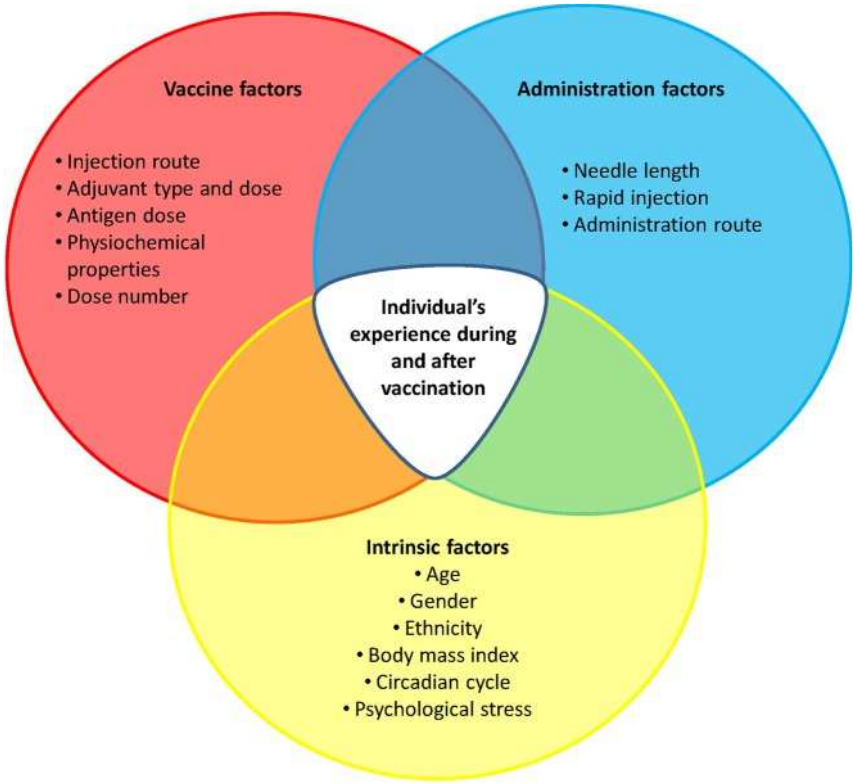
1) Safety in real-world setting is comparable to RCT data?
2) Is there a higher risk of AE in subjects who have already experienced SARS CoV-2 infection?
3) Time between SARS CoV-2 infection and vaccination and the severity diseases affect the risk of AE?
4) Demographic parameters associated with differences in vulnerability to risk?

Polack FP, Thomas SJ, Kitchin N, et al.N Engl J Med 2020.

Background

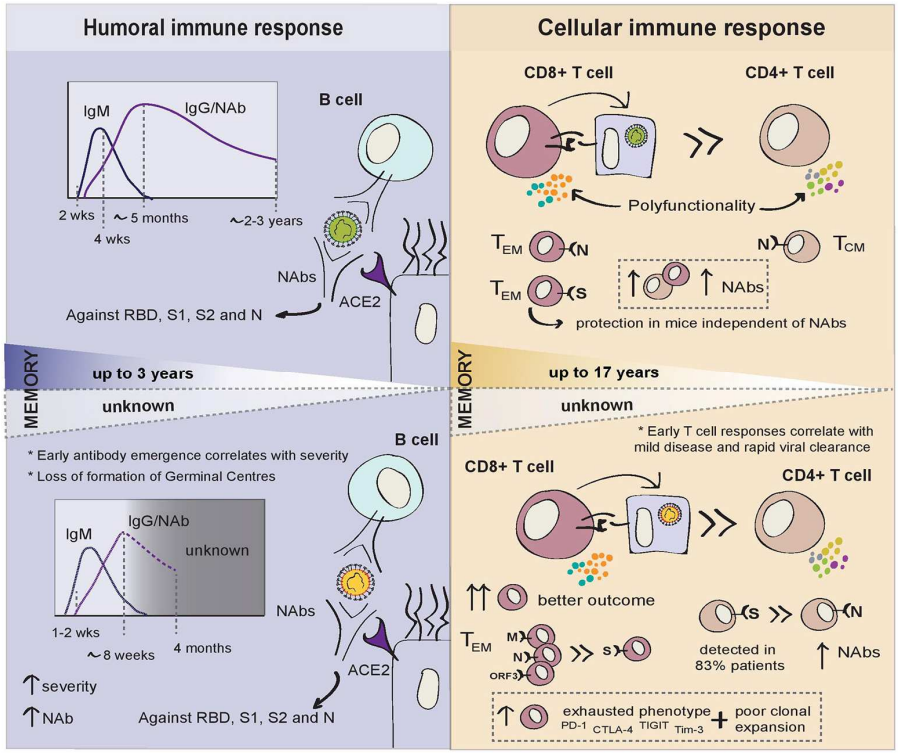
Hervé C, Laupèze B, Del Giudice G, et al. NPJ Vaccines. 2019;
Kim DS, Rowland-Jones S, Gea-Mallorquí E. Front Immunol. 2020

Reactogenicity



Physical manifestation of the inflammatory response to vaccination

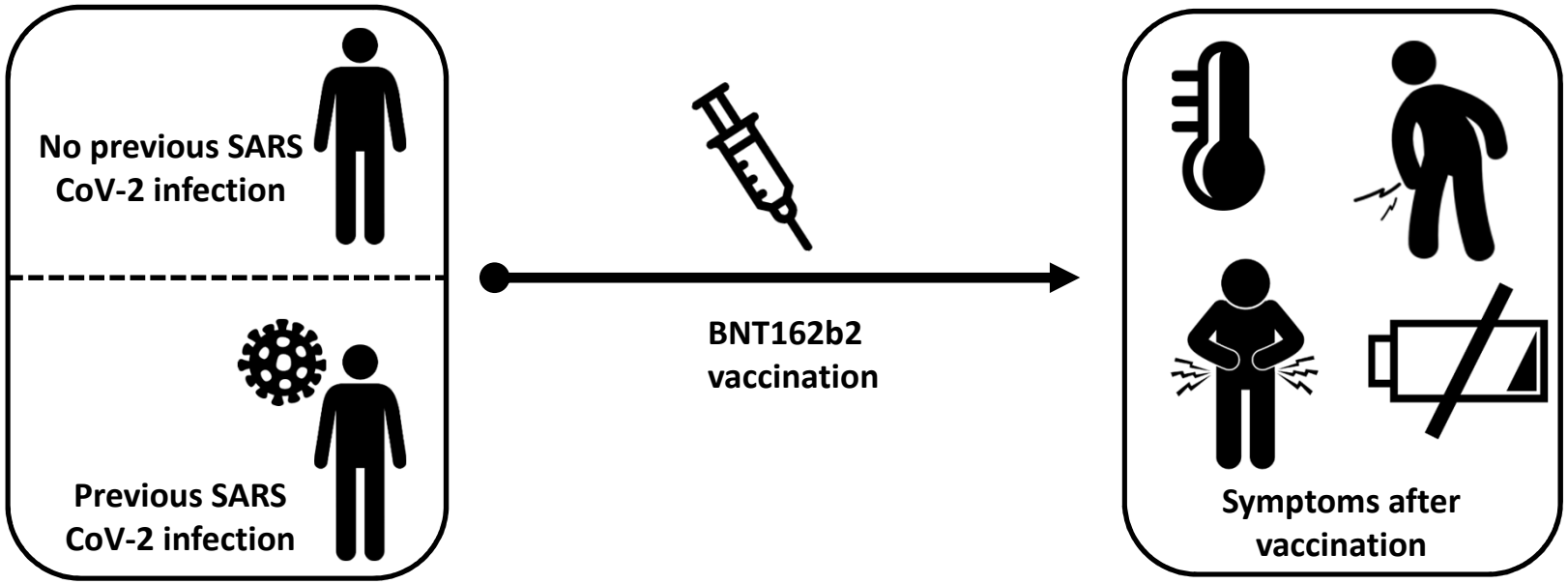
Immunogenicity



Ability of a vaccine to induce an immune response (antibody- and/or cell-mediated)

Study aims

Primary: Verify whether a previous SARS CoV-2 infection or COVID-19 brings about an increased risk of suffering local or systemic symptoms upon anti-SARS CoV-2 vaccination.



Secondary: Establishing whether other variables affect the risk of adverse reactions to vaccine.

Study Design

Study population: HCWs of ASST S.Paolo e Carlo vaccinated with mRNA BNT162b2 between January 4th and February 9th 2021 and responded to an online questionnaire, from the occupational medicine service.

Online questionnaire: 3 sessions

1. Demographic session and COVID-19 anamnesis
2. Adverse events to the first dose of BNT162b2 vaccine
3. Adverse events to the second dose of BNT162b2 vaccine.

Subjects were asked type of symptoms and whether interfered with daily activities or resulted in time-off work.

Exposure: Data from the hospital occupational medicine service on the occurrence of asymptomatic or symptomatic SARS CoV-2 infection, as well as timing and severity of disease were also collected.

Only subjects with a known positive SARS CoV-2 NP swab has been classified as previously infected to SARS CoV-2 (both subjects with COVID-19 and asymptomatic SARS CoV-2 infection)

Endpoints:

- Moderate systemic symptoms (MSS): symptoms interfering with daily activities or resulting in time-off work occurring after either the first or the second dose of vaccine (corresponding to Grade 3 FDA Guidance),
- Severe systemic symptoms (SSS): those requiring hospitalization or death (Grade 4, FDA)

US DHHS FDA Guidance for Industry. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials.

Statistical Analysis

- Descriptive statistics and Chi-square or Kruskal Wallis test, for the comparison of subjects with and without a previous SARS CoV-2 infection.
- Univariate and multivariable logistic regression models to evaluate the association between a previous SARS CoV-2 infection (and other variables) and the occurrence of MSS:

  i) after the first dose

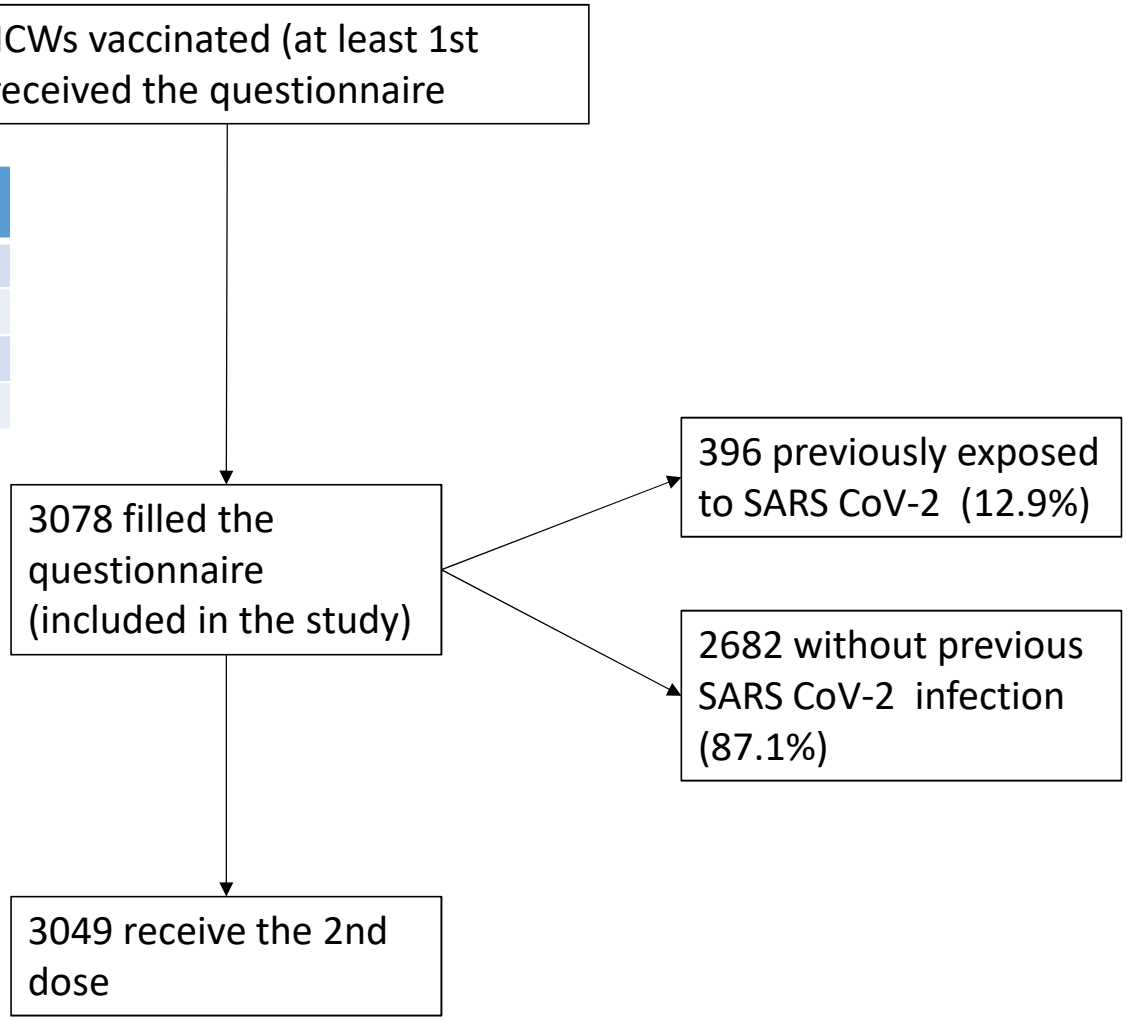
  ii) after the second dose

  iii) after either the first or second dose.

- A separate analysis only in the patients with previous SARS CoV-2 infection to evaluate the association of MSS with:
  - time from SARS CoV-2 infection to vaccination
  - severity of COVID-19

Flowchart – Enrollment

	HCWs vaccinated (n=5562)	Survey respondents (n=3078)	p-value
Gender, Female, n(%)	3483 (61·9%)	1980 (64·3%)	0·028
Age, years, median (IQR)	47 (35-56)	47 (34-56)	0·785
Italian, Yes, n(%)	5139 (91·4%)	2856 (92·8%)	0·001
Previous COVID-19, n(%)	677 (12·2%)	396 (12·9%)	0·349



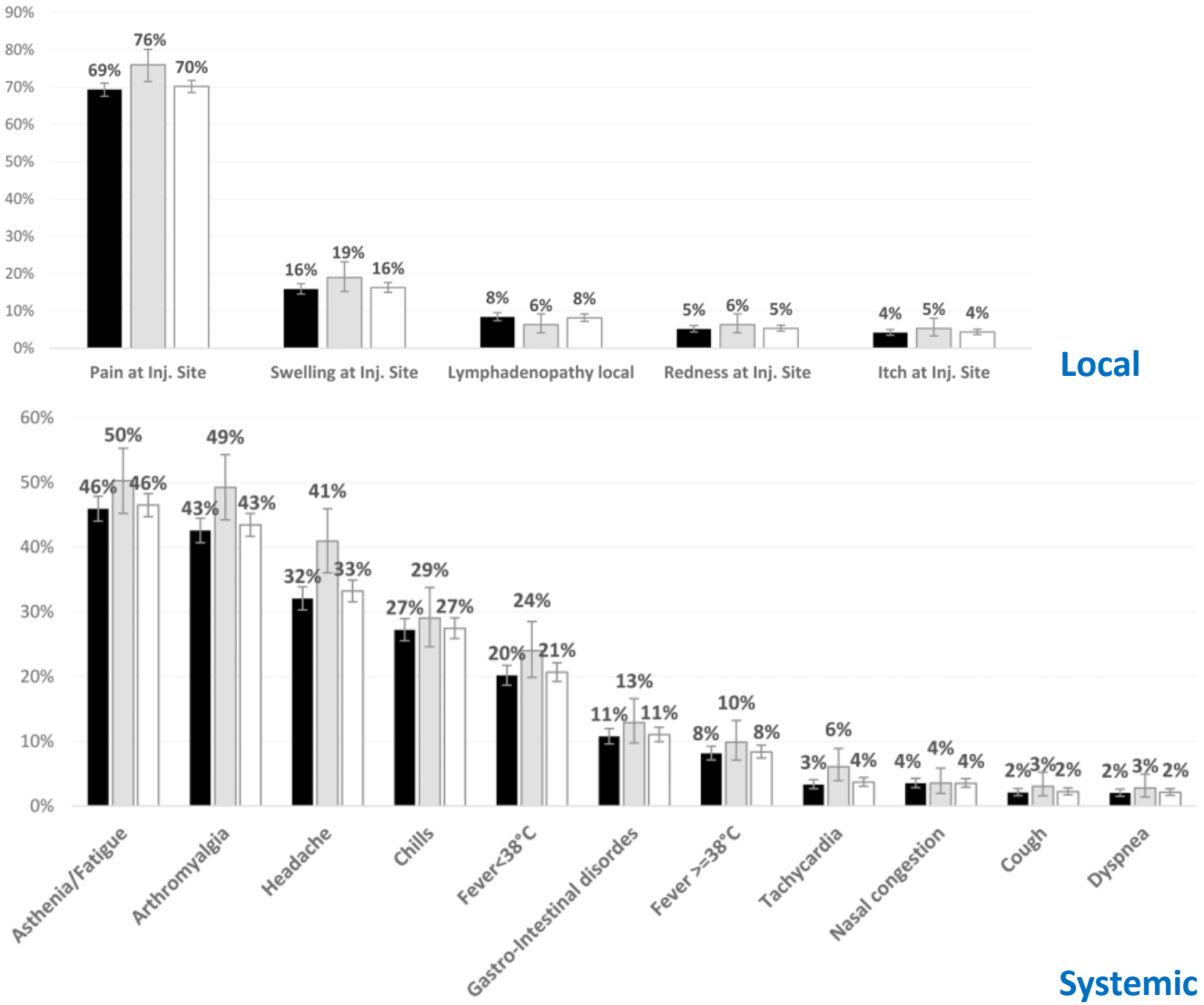
Characteristics of the study group

characteristics of the 3078 included subjects according to previous COVID-19.

Characteristics	No previous COVID-19 (*n*=2682; 87.1%)	Previous COVID-19 (*n*=396; 12.9%)	Total (*n*=3078; 100.0%)	*p*-value*
Females, n (%)	1,710 (63.8)	270 (68.2)	1980 (64.3)	0.086
Age, years median (IQR)	48 (35–56)	45 (30–54)	47 (34–56)	<0.001
Age strata, years, n (%)				<0.001
<30	393 (14.6)	95 (24.0)	488 (15.8)	
30–39	493 (18.4)	69 (17.4)	562 (18.3)	
40–49	599 (22.3)	84 (21.2)	683 (22.2)	
50–59	801 (29.9)	112 (28.3)	913 (29.7)	
>=60	396 (14.8)	36 (9.1)	432 (14.0)	
Italians, n (%)	2495 (93.0)	361 (91.2)	2856 (92.8)	0.231
Occupation, n (%)				<0.001
Healthcare professionals	2062 (76.9)	344 (86.9)	2406 (78.2)	
Technicians	367 (13.7)	30 (7.5)	397 (12.9)	
Clerks	253 (9.4)	22 (5.6)	275 (8.9)	
Months from COVID-19 to first dose of vaccine:				
median (IQR)	..	2.9 (1.9–9.8)	..	..
n (%)	..	..	..	..
1–3	..	206 (52.0)	..	..
3–6	..	17 (4.3)	..	..
>6	..	173 (43.7)	..	..
Severity of COVID-19, n (%)				
Asymptomatic	..	72 (18.3)	..	..
Paucisymptomatic	..	183 (46.2)	..	..
Symptomatic not hospitalized	..	129 (32.7)	..	..
Symptomatic hospitalized	..	12 (3.0)	..	..

Prevalence of previous COVID-19 infection at vaccination: 14% among healthcare personnel, 7.5% among technicians and 8.0% among clerks

Symptoms (≥2%, 1st or 2nd dose)



Symptoms either 1st or 2nd dose	
No Symptoms	609 (19.8%)
Only local	365 (11.8%)
Systemic Mild	1,161 (37.7%)
Systemic Moderate	943 (30.6%)
Systemic Severe	0 (0.0%)

544 HCWs (17.6%) missed at least 1 day work
399 (13.0%) symptoms limited daily activity (not missing work)

Median duration of symptoms was of 24 h

Uncommon (<2%) symptoms (1st or 2nd dose)

	No previous COVID-19	Previous COVID-19	Total
Mild allergic reaction (rash/itch/edema)	39 (1.5%)	9 (2.3%)	48 (1.6%)
Paresthesie (not local)	34 (1.3%)	6 (1.5%)	40 (1.3%)
Anosmia dysgeusia	18 (0.7%)	15 (3.8%)	33 (1.1%)
Lymphadenopathy (not local)	24 (0.9%)	3 (0.8%)	27 (0.9%)
Hypotension/hypertension	17 (0.6%)	6 (1.5%)	23 (0.7%)
Vertigo/dizziness	16 (0.6%)	4 (1.0%)	20 (0.6%)
Sleeping disorders	15 (0.6%)	1 (0.3%)	16 (0.5%)
Pharyngodynia	9 (0.3%)	2 (0.5%)	11 (0.4%)
Chest pain	7 (0.3%)	1 (0.3%)	8 (0.3%)
Herps simplex, labial	6 (0.2%)	1 (0.3%)	7 (0.2%)
Conjunctivitis	5 (0.2%)	1 (0.3%)	6 (0.2%)
Diplopia	2 (0.1%)	2 (0.5%)	4 (0.1%)
Flushing	3 (0.1%)	0 (0.0%)	3 (0.1%)
Tinnitus	2 (0.1%)	1 (0.3%)	3 (0.1%)
Otalgia	2 (0.1%)	0 (0.0%)	2 (0.1%)

Severity of symptoms after the 1st or 2nd dose

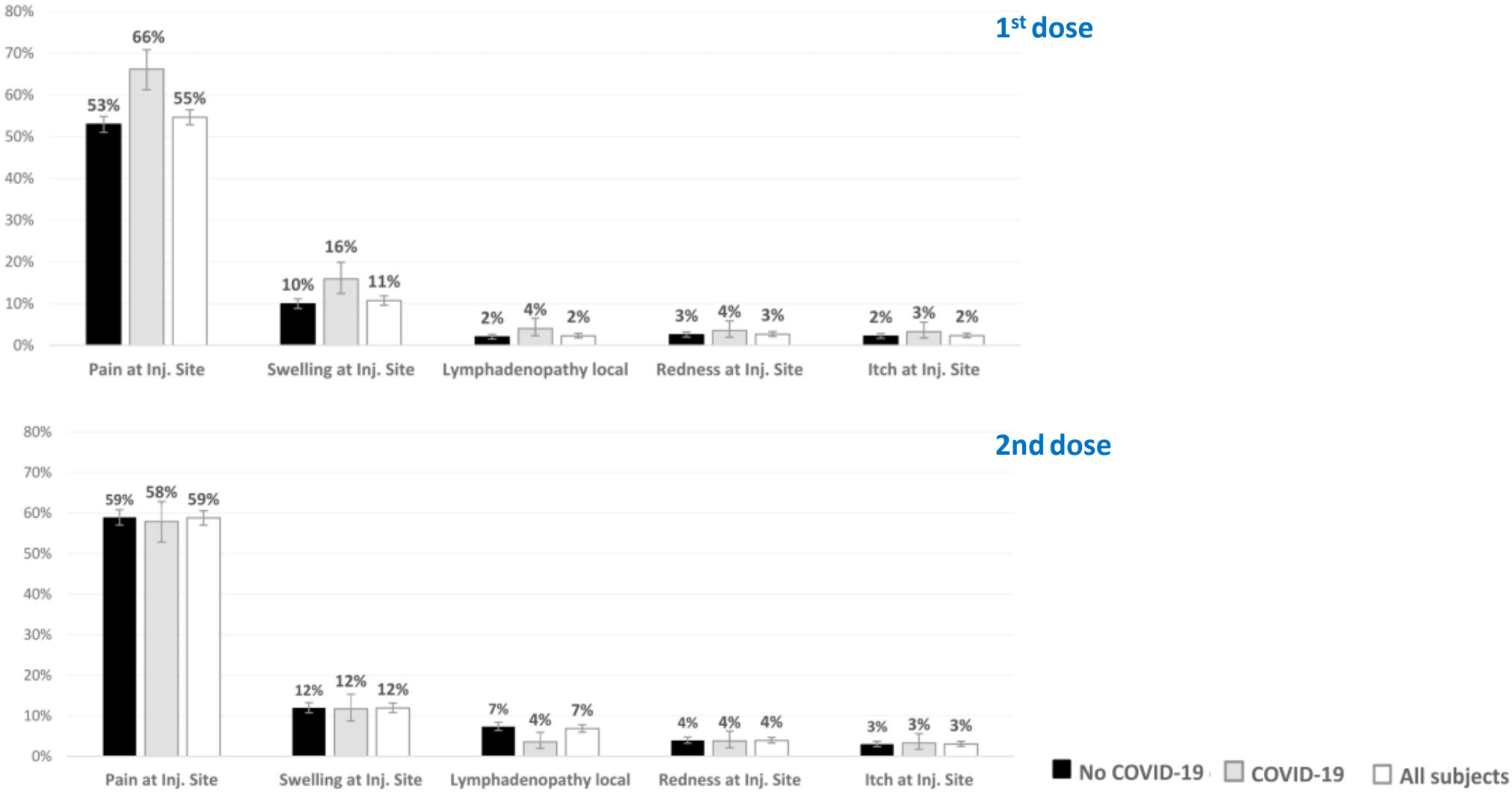
1st dose

Characteristics	No previous COVID-19 (*n*=2682; 87.1%)	Previous COVID-19 (*n*=396; 12.9%)	Total (*n*=3078; 100.0%)	*p*-value*
Local or systemic symptoms, 1st dose, n (%)	1549 (57.8)	287 (72.5)	1836 (59.6)	<0.001
Local symptoms, 1st dose, n (%)	1481 (55.2)	274 (69.2)	1755 (57.0)	<0.001
Systemic symptoms, 1st dose, n (%)	789 (29.4)	206 (52.0)	995 (32.3)	<0.001
Time from vaccination to symptoms, 1st dose, hours, median (IQR)	6 (3–12)	8 (4–12)	6 (3–12)	0.020
Symptoms duration, 1st dose, hours, median (IQR)	24 (24–48)	24 (14–48)	24 (24–48)	0.453
Local or systemic symptoms resulting in time off-work, n (%)	60 (3.9)	27 (9.4)	87 (4.7)	<0.001
Local or systemic symptoms interfering with daily activities, n (%)	152 (9.8)	61 (21.2)	213 (11.6)	<0.001
Moderate Systemic symptoms, n (%)	138 (5.1)	57 (14.4)	195 (6.3)	<0.001
Symptoms severity, n (%)				<0.001
no symptoms	1133 (42.2)	109 (27.5)	1242 (40.4)	
only local	760 (28.3)	81 (20.5)	841 (27.3)	
systemic mild	651 (24.3)	149 (37.6)	800 (26.0)	
systemic moderate	138 (5.1)	57 (14.4)	195 (6.3)	
systemic severe	0 (0.0)	0 (0.0)	0 (0.0)	

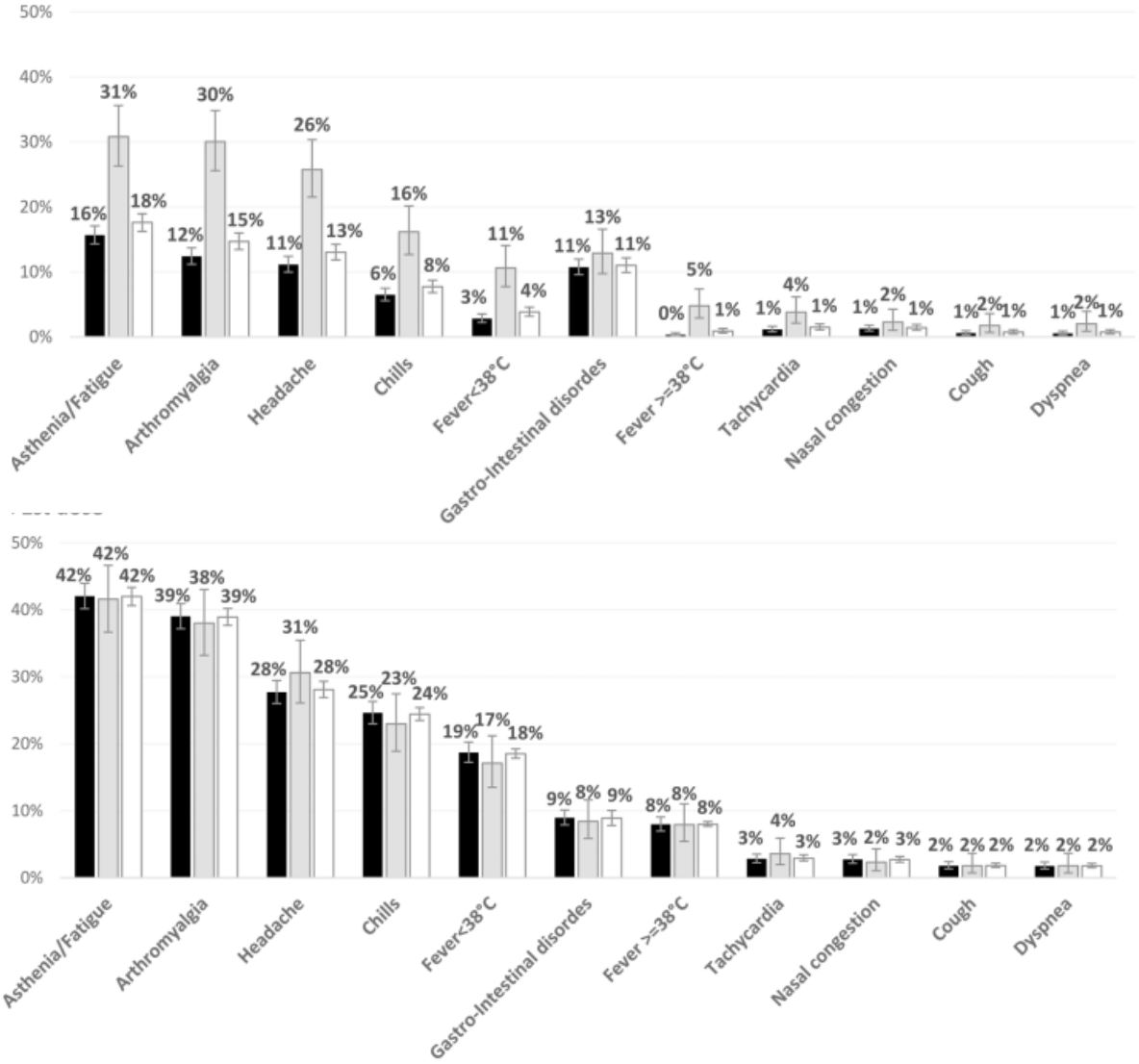
2nd dose

Characteristics	No previous COVID-19 (*n*=2657; 87.1%)	Previous COVID-19 (*n*=392; 12.9%)	Total (*n*=3049; 100.0%)	*p*-value*
Local or systemic symptoms, 2nd dose, n (%)	1962 (73.8)	276 (70.4)	2238 (73.4)	0.151
Local symptoms, 2nd dose, n (%)	1675 (63.0)	240 (61.2)	1915 (62.8)	0.479
Systemic symptoms, 2nd dose, n (%)	1643 (61.8)	242 (61.7)	1885 (61.8)	0.955
Time from vaccination to symptoms, 2nd dose, hours, median (IQR)	10 (4–14)	8 (4–12)	10 (4–14)	0.113
Symptoms duration, 2nd dose, hours, median (IQR)	24 (18–48)	24 (12–48)	24 (18–48)	0.049
Local or systemic symptoms resulting in time off-work, n (%)	454 (23.1)	50 (18.1)	504 (22.5)	0.061
Local or systemic symptoms interfering with daily activities, n (%)	777 (39.6)	98 (35.5)	875 (39.1)	0.192
Moderate Systemic symptoms, n (%)	773 (29.1)	97 (24.7)	870 (28.5)	0.075
Symptoms severity, n (%)				0.032
no symptoms	696 (26.2)	116 (29.6)	812(26.6)	
only local	318 (12.0)	34 (8.7)	352 (11.5)	
systemic mild	870 (32.7)	145 (37.0)	1015 (33.3)	
systemic moderate	773 (29.1)	97 (24.7)	870 (28.5)	
systemic severe	0 (0.0)	0 (0.0)	0 (0.0)	

Local symptoms observed (1st and 2nd dose)



Systemic symptoms observed (1st and 2nd dose)



Reasons for not administering the second dose of vaccine

A total of **29 subjects** did not receive the second dose of vaccine due to occurrence of:

- Moderate symptoms resulting in 2nd dose refusal (N=5),
- Travel abroad (N=1):
- Quarantine due to household contacts (N=2)
- COVID-19 pauci-symptomatic disease (N=21)

- Symptoms appeared median 7 days after 1st vaccine administration (6-9), but in one case the latency was of 17 days.

Predictors of the occurrence of MSS (N=2682)

Factors associated with moderate systemic symptoms to different doses of anti-SARS CoV-2 mRNA BNT162b2 vaccine by univariate and multivariable logistic regression.

	OR	95%CI		p	AOR*	95%CI		p
Either first or second dose anti-SARS CoV-2 mRNA BNT162b2 vaccine among 3078 HCWs								
Age, per 10 years older	0.79	0.74	0.84	<0.001	0.78	0.74	0.83	<0.001
Sex, Female (vs Male)	2.37	1.99	2.82	<0.001	2.35	1.97	2.81	<0.001
Natives-italian (vs expatriated)	0.93	0.66	1.31	0.663	0.93	0.66	1.33	0.704
Previous COVID-19 (vs no)	0.98	0.88	1.24	0.878	0.89	0.70	1.13	0.328
First dose anti-SARS CoV-2 mRNA BNT162b2 vaccine among 3078 HCWs								
	OR	95%CI		p	AOR*	95%CI		p
Age, per 10 years older	1.09	0.97	1.22	0.147	1.14	1.01	1.29	0.028
Sex, Female (vs Male)	2.17	1.53	3.09	<0.001	2.15	1.50	3.06	<0.001
Natives-Italian (vs expatriated)	0.56	0.33	0.97	0.037	0.59	0.34	1.01	0.056
Previous COVID-19 (vs no)	3.10	2.23	4.31	<0.001	3.14	2.25	4.38	<0.001
Second dose anti-SARS CoV-2 mRNA BNT162b2 vaccine among 3048 HCWs								
	OR	95%CI		p	AOR*	95%CI		p
Age, per 10 years older	0.78	0.73	0.83	<0.001	0.77	0.72	0.82	<0.001
Sex, Female (vs Male)	2.34	1.95	2.80	<0.001	2.34	1.95	2.80	<0.001
Natives-Italian (vs expatriated)	1.00	0.70	1.43	0.998	1.00	0.70	1.45	0.987
Previous COVID-19 (vs no)	0.80	0.63	1.02	0.076	0.71	0.55	0.92	0.008

* Adjusted for all the factors showed.

Predictors of the occurrence of MSS in HCW previously exposed to SARS CoV-2 (N=396)

Factors associated to the occurrence of MSS in subjects with previous COVID-19, by univariate and multivariable logistic regression analysis.

	OR	95%CI		p	AOR*	95%CI		p
Age, per 10 years older	0.98	0.83	1.15	0.765	0.89	0.75	1.07	0.217
Sex, Female (vs Male)	1.64	0.99	259	0.056	1.64	1.00	2.68	0.050
Italian (vs expatriated)	0.95	0.38	2.40	0.916	1.09	0.42	2.81	0.860
Months from COVID-19 diagnosis to vaccination								
1–3 months	1.00				1.00			
3–6 months	1.06	0.36	3.5	0.912	1.05	0.35	3.19	0.930
>6 months	1.25	0.81	1.94	0.312	1.23	0.78	1.92	0.374
COVID-19 severity								
Asymptomatic/ Pauci-symptomatic	1.00				1.00			
Symptomatic	1.87	1.20	2.90	0.005	1.95	1.2	3.09	0.005

* Adjusted for all the factors showed in table.

Summary of results

- In this real-world scenario the safety of BNT162b2 vaccine is confirmed:

- 59.6% after the 1st dose and 73.4% after the 2nd reported local or syst. symptoms (mostly mild).

- MSS occurred in 6% and 28% of subjects after the first and second dose, respectively.

- No serious AE leading to hospitalization or death

- COVID-19 do not suffer from more serious AE after a complete cycle of SARS CoV-2 vaccination compared to SARS CoV-2 naïve subjects.
- 3-fold higher risk of MSS after the 1st dose of vaccine
- 30% lower after the 2nd dose

- MSS risk not affected by the time from COVID-19 diagnosis to vaccination, but by the severity of COVID-19

- Higher risk in females, and in younger individuals.

Limitations

- Selection bias: Half of the invited HCWs have filled the online questionnaire (more woman)
- Recall bias: those filling the questionnaire might be those experiencing symptoms more frequently
- Fear of side effects might be more frequent in our real-word cohort compared to the close monitoring schedule as in RCT, thus reporting even minimal symptoms
- Persons who experienced COVID-19 might be more anxious on possible side effects of vaccination and this could have affected their reporting.
- Information on comorbidities and BMI are lacking in our study, thus we might have missed a possible confounding factor predictive of post-vaccination symptoms occurrence

Discussion

Previous COVID-19

An already primed immune system might explain the higher risk of MSS at the first dose, reactogenicity was sustained at the first dose, and lost by the second dose (compared to SARS CoV-2 naïve)

Female

- Better prognosis of females in the acute phase → higher level of IgG Ab in the early phase
- Association between female and "long COVID", part of gender differences in the immune responses
- Women's awareness of symptoms, higher attention in their health conditions
- In other settings (e.g. HIV) women show higher frequency of AE often leading to TD

Younger

Post vaccine higher titer of anti-SARS CoV-2 neutralizing Ab in younger people; suggesting that immune mediated mechanisms resulting in increased reactogenicity responsible of symptoms

Mussini C et al. Clin Microbiol Infect 2021; Zeng F et al. J Med Virol 2020; Bai F C et al. under review; Abu Jabal K et al. Eurosurveillance 2021

Grazie a tutti per l'attenzione

Marina Allegrini
Matteo Augello
Francesca Bai
Diletta Barbanotti
Tomaso Beringheli
Lorenzo Biasioli
Teresa Bini
Valeria Bono
Roberto Castoldi
Andrea Cona
Alessandro Copes
Antonella d'Arminio Monforte
Anna De Bona
Camilla Falcinella
Paolo Franchina
Nicole Gemignani
Mohamad Hadla
Giulia Marchetti
Francesco Molà
Debora Mondatore
Giovanni Mulè
Sofia Pettenuzzo
Alessandra Rodanò
Roberta Rovito
Matteo Sala
Elisa Suardi
Gianmarco Tagliaferri
Daniele Tesoro
Camilla Tincati
Daniele Tomasoni
Benedetta Varisco
Ottavia Viganò
Claudio Colosio
Piermario Perrone
Vittorio Bordoni

Alessandro Za'
Luisa Romano'
Nicola Orfeo
Katia Razzini

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

UNIVERSITÀ DEGLI STUDI DI MILANO