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

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ARTICLE INFO

Article History:
Received 17 March 2021
Revised 3 May 2021
Accepted 4 May 2021
Available online xxx

Keywords:
anti-SARS CoV-2 mRNA BNT162b2 vaccination
health care workers
self-reported symptoms

ABSTRACT

Background: Health care workers (HCWs) are at high risk of contracting an infection by SARS CoV-2 and thus they are a priority for vaccination. We hereby aim to investigate whether the risk of severe and moderate systemic symptoms (MSS) after vaccination is higher in HCWs with a history of previous COVID-19.
Methods: An online questionnaire was offered to the cohort all HCWs undergoing anti-SARS CoV-2 mRNA BNT162b2 vaccination between January 4th and February 9th 2021 in two large tertiary hospitals (ASST Santi Paolo and Carlo) in Milan, Italy. Previous SARS-CoV-2 infection/COVID-19 was recorded. Local and systemic symptoms after each of the two doses were reported. MSS were those either interfering with daily activities or resulting in time off-work. Factors associated to MSS were identified by logistic regression.
Findings: 3,078 HCW were included. Previous SARS-CoV-2 infection/COVID-19 occurred in 396 subjects (12·9%). 59·6% suffered from ≥1 local or systemic symptom after the first and 73·4% after the second dose. MSS occurred in 6·3% of cases (14·4% with previous vs 5·1% with no COVID-19 $p<0·001$) and in 28·3% (24·5% in COVID-19 vs 28·3% no COVID, $p = 0·074$) after the first and second dose, respectively. Subjects already experiencing COVID-19 had an independent 3-fold higher risk of MSS after the first and a 30% lower risk after the second dose. No severe adverse events were reported.
Interpretation: Our data confirm in a real-world setting, the lack of severe adverse events and the short duration of reactogenicity in already infected HCWs. Possible differences in immune reactivity are drivers of MSS among this group of HCWs, as well as among females and younger individuals.
Funding: None.

1. Introduction

Health care workers (HCWs) are a group particularly at risk of get infected by SARS CoV-2 virus: in Italy, among a total number of 2953,120 COVID-19 cases since the beginning of the pandemic, 124,003 (4·2%) have been reported in this population [1]. These workers are indicated as a priority for Occupational Health Interventions in the COVID-19 pandemic by World Health Organization (WHO) and International Labour Organization (ILO) [2] and thus they are in any corner of the world the first category of candidates for vaccination.

Due to the spread of pandemic, a number of pharmaceutical companies has been involved in the development of a safe and efficient vaccine, and research is still in progress.

The first vaccine approved by the U.S. National Institute of Health (NIH) and by the European Medicines Agency (EMA) was the mRNA vaccine, concomitantly, developed by BioNTech and Pfizer, the BNT162b2. Data on efficacy and safety are reported by randomized clinical trials [3,4], showing 95% efficacy in preventing COVID-19 and low incidence of moderate adverse events among 21,720 subjects receiving the vaccine. Similar data are reported by the trial on the mRNA-1273 Moderna vaccine [5].

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https://doi.org/10.1016/j.eclinm.2021.100914

Research in context

Evidence before this study

Anti-SARS CoV-2 mRNA BNT162b2 is a novel vaccine in use to vaccinate millions of subjects all over the world based on a genetically engineered RNA able to generate in the treated subjects a protein that prompts an immune response, thus conferring immunity against SARS CoV-2 in vaccinated subjects. Premarketing trials demonstrate its efficacy and safety, but the incidence and severity of adverse reactions in the real-world data are missing, as well as the identification of groups at risk of developing adverse reactions.

Added value of this study

In the setting of health care workers (HCWs), this study has clarified that the vaccination with anti-SARS CoV-2 mRNA BNT162b2 brings about a frequency of symptoms comparable with the one observed in the trials. In subjects already infected with SARS CoV-2, the consequent reactivation of the immune system might explain an increased risk of moderate systemic symptoms at the first dose of vaccine as compared to individuals naives to the virus. This effect is lost by the second dose, indicating a short-lasting reactogenicity.

Implications of all the available evidence

This study offers new data to practitioners to face the problem of adverse reactions consequent to anti-SARS CoV-2 mRNA BNT162b2 vaccination. The findings of this research might suggest that, when a second dose is needed in subjects previously SARS CoV-2 infected, it can be administered without fear of severe side events. To note, the duration of immune reactivity and the proper policy on frequency of vaccination according to previous infection with SARS CoV-2 goes beyond the scope of this research.

After the introduction of vaccines against SARS CoV-2 infection, a worldwide vaccination campaign was launched, aimed at achieving the goal of creating the herd immunity necessary for ending the pandemic. Whilst the campaign is ongoing some questions remain open. Among them, the incidence of adverse events to vaccination. The main observed local symptoms are pain, redness, and swelling, whilst the most commonly observed systemic symptoms are fever, fatigue, headache, and muscle and joint pain [6]. Also, the incidence of allergic reactions seems limited: anaphylactic reactions occurred only in 21 out of 1800,000 first doses, with an incidence of 11·1 cases per million and no fatalities [7]. In the frame of the vaccination campaign, a further problem is under discussion, that is: is it necessary to vaccinate subjects who have already suffered from the disease or from asymptomatic SARS CoV-2 infection? If so, should a full vaccination cycle be practiced or is a single administration sufficient? WHO recommends to offer vaccination to people who had COVID-19 in the past [8]. Nonetheless, at the basis of the decision on the advisability of vaccinating subjects who already experienced COVID-19, there is not only the need for saving doses in a period of limited availability of vaccines, but also the possibility that the administration of the vaccine to subjects who have already experienced the infection may lead to an increased risk of adverse events. The topic has not yet been addressed extensively; however, it deserves attention in order to define the most appropriate vaccination strategies. The hinges on which to focus attention are the following: 1) is there a higher risk of adverse events following the administration of the vaccine in subjects who have already experienced SARS CoV-2 infection? 2) Does the time between infection and vaccination affect the risk of adverse events? 3) Are sex, age or other demographic parameters associated with differences in vulnerability to risk?

HCWs represent an ideal group for the purposes of the study because in the working age and reasonably affected by few comorbidities that could bring about symptoms similar to the post vaccination ones. Therefore, we addressed our study on a group of over 3000 HCWs undergoing anti-SARS CoV-2 mRNA BNT162b2 vaccination in our University Hospitals.

The main aim of the study was to verify whether a previous SARS CoV-2 infection or disease brings about an increased risk of suffering local or systemic symptoms upon anti-SARS CoV-2 vaccination. A further objective was establishing whether other variables affect the risk of adverse reactions to vaccine.

2. Methods

2.1. Study design

We included in the present survey study all the subjects working in two large tertiary hospitals in Milan, who had scheduled the two doses of anti-SARS CoV-2 mRNA BNT162b2 vaccine between January 4th and February 9th 2021 and responded to an online questionnaire, whose link was offered by email from the hospital occupational medicine service, as routine monitoring program. Occupational medicine service is responsible for occupational health surveillance of all HCWs and periodically promotes SARS CoV-2 screening by PCR or antigenic tests on naso-pharyngeal swabs; further, all symptomatic SARS CoV-2 infections among HCWs are checked and followed-up by the service also to identify close contacts.

HCWs were recommended to fill the questionnaire twice, i.e. at the first one just before the second dose, and the second one within two weeks after the second dose. We included under the category of HCWs both healthcare personnel directly engaged in health care provision (i.e.: physicians, nurses, auxiliary staff), and technicians and clerks, all working in the hospital.

The online questionnaire consisted in three main sessions; the first one was a demographic session, asking for age, sex, country of birth, and occupation. Second and third sessions were identical and concerned possible adverse events to the first and to the second dose of vaccine. Subjects were asked at what time after the dose of vaccine the events occurred and how long they lasted (See Supplementary Table 1). Adverse events were divided into local (pain, swelling, reddening and itch at site of injection, enlargement of axillary nodes, others) and systemic symptoms (fatigue, arthro-myalgias, headache, chills, fever <38 °C, fever ≥ 38 °C, gastrointestinal disorders, tachycardia, cough, dyspnea, nasal congestion, dysgeusia, anosmia, allergic reaction, other). Subjects were also asked whether systemic symptoms interfered with daily activities and whether resulted in time-off work. 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. Asymptomatic SARS CoV-2 infection was diagnosed with naso-pharyngeal swab positivity for SARS CoV-2 by PCR in the absence of symptoms, COVID-19 in case of minor or major symptoms in subjects with positive SARS CoV-2 by PCR. To simplify we used the term COVID-19 in this paper, for both asymptomatic and symptomatic SARS CoV-2 infection.

We defined moderate systemic symptoms (MSS) those either 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 on toxicity grading scale in subjects enrolled in preventive vaccine trials [9]), and severe systemic

symptoms those requiring hospitalization or death (Grade 4, FDA) [9]. All the other symptoms were defined as mild. We also evaluated possible predictors of experiencing MSS in our cohort, aiming in particular at ascertaining whether vaccination of individuals with former previous COVID-19 resulted in higher risk. Further, in the subgroup of HCWs already experiencing COVID-19, we evaluated whether there was an association between time elapsing from COVID-19 to vaccination and the severity of disease with the occurrence of MSS.

2.2. Statistical analysis

Statistical analyses included descriptive statistics as absolute and relative frequencies for categorical factors and median with interquartile range (IQR) for continuous variables; Chi-square or Kruskal–Wallis test, were used, as appropriate, to compare characteristics of subjects with and without a previous COVID-19 diagnosis. Local and systemic symptoms were presented as counts, percentages, and associated 95% confidence intervals (95% CI). Univariate and multivariable logistic regression models were used to evaluate the association between a previous COVID-19 and the occurrence of MSS i) after the first dose, ii) after the second dose and iii) after either the first or second dose.

We also evaluated the possible association of other variables including age, sex and country of birth (native-Italian versus expatriated) with the occurrence of MSS.

A separate analysis only in the patients with previous COVID-19 was performed to investigate the association of MSS with the time from COVID-19 to vaccination and with the severity of COVID-19 (asymptomatic and pauci-symptomatic vs symptomatic SARS-CoV2 infection).

All statistical analyses were performed using Stata (version 14, StataCorp LP, TX, USA). All p–values presented are two sided and a p–value < 0·05 indicated conventional statistical significance.

The protocol was approved by the Ethic Committee Area 1, Milan (Supplemental Material 1); all HCWs signed the informed consent.

2.3. Role of the funding source

The was no funding for this study.

3. Results

3.1. Characteristics of the study group

A total of 3078 out of 5662 (54·4%) subjects filled the questionnaire. Compared to all the HCWs vaccinated that received the questionnaire, those filling it were more frequently females (64·3% vs 61·9%, p = 0·028) and more frequently native-Italian (92·8% vs 91·4%, p<0·001) with no difference in median age (p = 0·785). Previous COVID-19 occurred in 12·2% of all HCWs vaccinated vs 12·9% of those filling the questionnaire, p = 0·349) (See Supplementary Table 2).

Table 1 shows the characteristics of the included subjects according to previous COVID-19. Younger people were those more frequently affected by COVID-19 among this cohort of subjects undergoing SARS CoV-2 vaccination, with a median age of 45 years (IQR 30-54) compared to 48 years (IQR 35-56) for the group without previous COVID-19 (p<0·001).

Healthcare personnel were the major group with previous COVID-19 (344 out of 396, 86·9%). Actually, the prevalence of previous COVID-19 at vaccination was 14·3% among healthcare personnel, 7·5% among technicians and 8·0% among clerks working in the hospital (p<0·001).

A total of 52% of the subjects with previous COVID-19 underwent vaccination 1 to 3 months after the disease, 4% between 1 and 3 months, and 44% after more than 6 months from the disease.

3.2. Local and systemic symptoms after the first dose

A total of 1836 subjects (59·6%) suffered from at least one mild or moderate local or systemic symptoms after the first dose of vaccine. The occurrence of either local or systemic symptoms was more frequent in individuals with previous COVID-19 (no symptoms in 27·5% with previous COVID-19 vs 42·2% of subjects without, p<0·001). MSS occurred only in a minority of cases (6·3% of the total) but were more frequent in subjects with previous COVID-19 compared to those without (14·4% vs 5·1%, p<0·001). Severe systemic symptoms, as well as severe allergic reactions did not occur at all (Table 2).

Table 1
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)	..	..

* Chi-square or Kruskal-Wallis test, as appropriate.

Table 2
Frequency of local or systemic symptoms after the first dose of anti-SARS CoV-2 mRNA BNT162b2 vaccine 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*
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)	

* Chi-square or Kruskal–Wallis test as appropriate.

3.3. 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: COVID-19 pauci-symptomatic disease (21 cases, 0·7%), moderate symptoms resulting in vaccine refusal (5 cases, 0·2%), or other reasons (3 cases, 0·1%: travel abroad in 1, quarantine due to household contacts in 2). In the 21 COVID-19 subjects, symptoms appeared 7 days after vaccine administration (median value, IQR 6-9), but in one case the latency was of 17 days.

3.4. Local and systemic symptoms after the second dose

A high percentage of subjects (73·4%) suffered from at least one local or systemic symptom after the second dose of vaccine, in most cases at mild severity. The occurrence of either local or systemic symptoms was similar in individuals with and without previous COVID-19 (no symptoms in 29·7% of subjects with previous COVID-19 vs 26·2% of subjects without, $p = 0{\cdot}151$).

MSS occurred in less than one third of subjects (28·5%), with no statistically significant difference according to previous COVID-19 (24·7% vs 29·1% no COVID, $p = 0{\cdot}074$). Severe systemic symptoms and severe allergic reactions did not occur at all following the second dose of vaccine too (Table 3).

3.5. Details on symptoms observed after anti-SARS CoV-2 vaccination

After both the first and the second dose the median duration of symptoms was of 24 h. Symptoms started earlier after the first dose than after the second one (a median of 6 h vs 10 h later, $p<0{\cdot}001$). Globally, the second dose of vaccine resulted in a higher frequency of any symptoms as compared with the first dose (1st vs 2nd dose: 59·6% vs 73·4%, $p<0{\cdot}001$); the second dose resulted also in a higher percentage of MSS (6·3% vs 28·5%, $p<0{\cdot}001$).

Looking in detail at different symptoms, considering overall their frequency either after the first or the second dose, pain at the site of injection was the most frequent one, occurring in 76% of COVID-19 and 69% of non COVID-19 subjects ($p = 0{\cdot}007$). Among systemic symptoms, fatigue, arthro-myalgias and headache were the most common, occurring in 30–50% of subjects. Chills, fever <38 °C and gastrointestinal symptoms occurred in around 10 to 25% of subjects; all the other symptoms occurred in less than 10% (Fig. 1a).

Overall, 544 HCWs (17·7%) missed at least 1 day work and 399 (13·0%) had symptoms resulting in limited daily activity. High grade fever (>38 °C) was more frequent among HCWs missing work (32·5% vs 15·8%, $p<0{\cdot}001$).

Symptoms occurring in less than 2% of cases are listed in Table 4. Mild allergic reactions, paresthesia, anosmia/dysgeusia, systemic lymphadenopathy, hypo- or hypertension, dizziness, sleeping disorders and pharyngodinia were the most frequent ones, occurring in more than 10 cases each. To note, 7 cases of herpes simplex and 6 cases of conjunctivitis were reported.

Both all the local and the systemic symptoms were more frequently reported by the COVID-19 group after the first dose of vaccine, while symptoms following the second dose were reported with the same frequency in the two groups of subjects (Fig. 1b and c).

Table 3
Frequency of local or systemic symptoms after the second dose of anti-SARS CoV-2 mRNA BNT162b2 vaccine according to previous COVID-19.

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)	

* Chi-square or Kruskal-Wallis test, as appropriate.

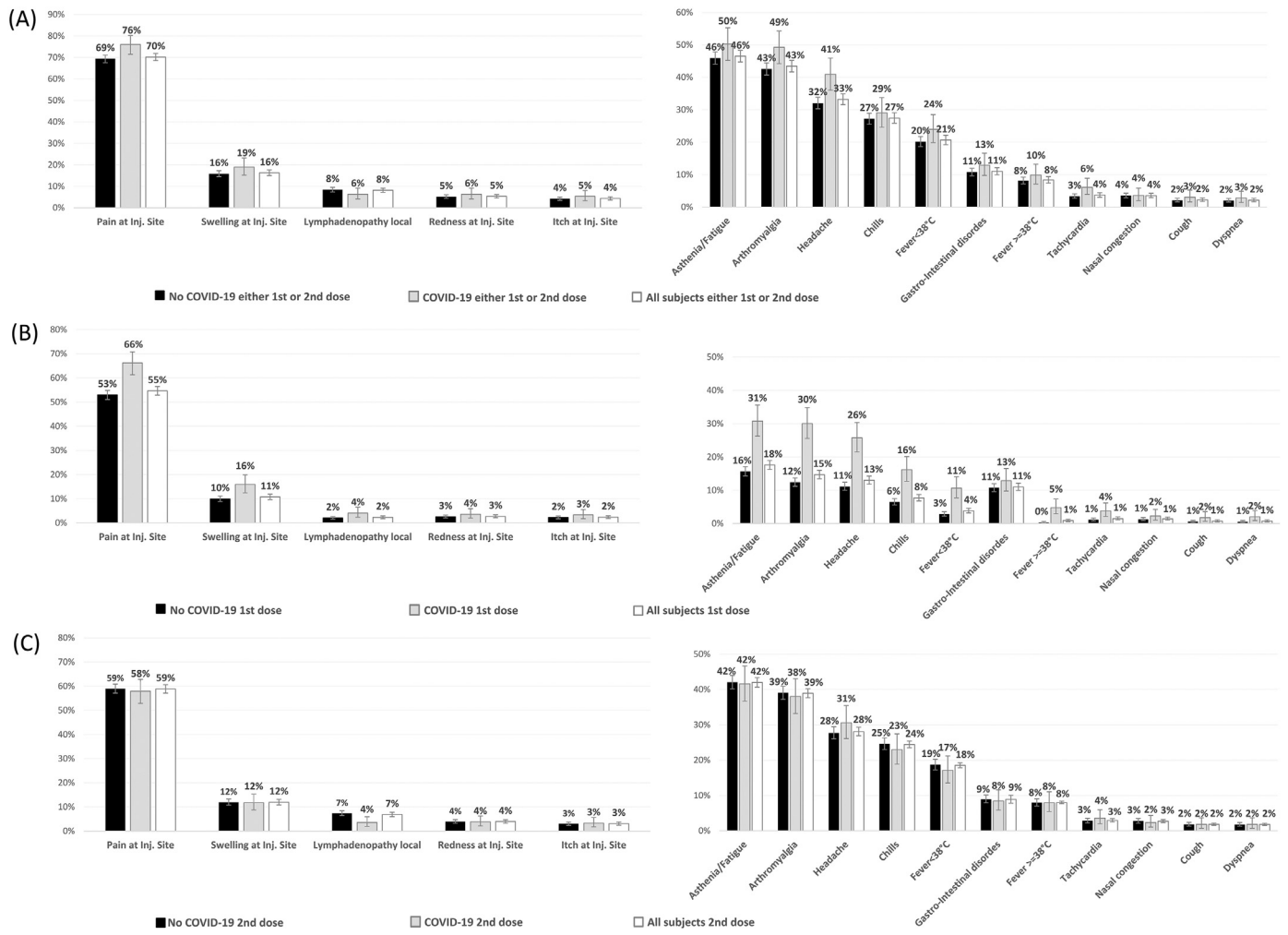

Fig. 1. prevalence of local and systemic symptoms after SARS CoV-2 mRNA BNT162b2vaccine, (A) either after the first or the second dose, (B) after the first dose and (C) after the second dose. The vertical bars indicate 95% Confidence Interval.

3.6. Predictors of the occurrence of MSS

Factors predictive of MSS to any of the two doses of vaccine, to the first dose and to the second dose, by univariate and multivariate logistic regression analyses, are shown in Table 5.

Subjects already experiencing COVID-19 had a 3-fold higher risk of MSS after the first dose and a 30% lower risk after the second dose of vaccine, as compared with subjects without previous COVID-19, after adjusting for sex, age, country of birth.

Moreover, at any increase of 10 years of age corresponded a 30% lower risk of suffering from MSS after any of the two doses of vaccine, after adjusting for sex, country at birth (native-Italian vs expatriates) and previous COVID-19; females had a double risk of MSS compared to males at any of the two doses, independently from other variables.

By analyzing only subjects with previous COVID-19, females were confirmed to be at higher risk of experiencing MSS. No differences in risk were found according to the time elapsed from COVID-19 to vaccination. Severity of previous COVID-19 was associated with a double risk of experiencing MSS in symptomatic as compared to asymptomatic/pauci-symptomatic HCWs with SARS CoV-2 infection, after adjustment for confounding variables (Table 6).

4. Discussion

During the vaccination campaign, a discussion arose regarding the need to vaccinate subjects who already experienced COVID-19. Among the reasons reported against this option there was a supposed increase of the risk of adverse reactions, even though this aspect has not been explored in literature.

All together our findings suggest that individuals having experienced COVID-19 do not suffer from more serious adverse events after a complete cycle of SARS CoV-2 vaccination, as compared to SARS CoV-2 naïve subjects.

Interestingly, we observed a 3-fold higher risk of moderate symptoms after the first dose of vaccine in individuals with previous COVID-19, with higher risk in females, and in younger individuals. On the contrary, at the second dose the probability of symptoms was 30% lower in these subjects compared with those who did not experience a previous SARS CoV-2 infection. The risk was not affected by the time elapsed from COVID-19 diagnosis, but was double in those who had experienced a symptomatic infection versus those who were infected without any relevant symptoms.

Having in mind the typical mode of action of a mRNA vaccine, we may argue that the first contact with the SARS CoV-2 or its antigens might create a hyperactivity which results in a higher frequency of symptoms at the next contact, after this the condition reaches a steady state. Data on animal models undergoing different vaccines revealed elevated circulating levels of CCL2 and CXCL10 as potential biomarkers of vaccine-elicited adverse inflammation [10]. The detailed description of the immune signatures behind the different reactogenicity of BNT162b2 mRNA vaccine according to previous history of COVID-19 needs to be better investigated as it might inform

Table 4
Symptoms occurring with less than 2% frequency either after the first or the second dose of anti-SARS CoV-2 mRNA BNT162b2 vaccine.

	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%)

on vaccination strategies. Because an excessive inflammation has been shown to feature symptomatic/severe forms of COVID-19 [11,12], a detailed investigation of the possible pre-vaccine hyperactivated immune status in patients with previous COVID-19 is advisable.

Other observations can be obtained by our study: also in a real-world scenario the safety of vaccine is confirmed. Actually, among 3078 HCWs the proportion of those who reported local or systemic symptoms after the administration of SARS CoV-2 mRNA BNT162b2 vaccine was 59·6% after the first dose and 73·4% after the second one. In most cases reported symptoms were mild in intensity; moderate systemic symptoms, i.e. those interfering with daily activity or resulting in time-off work, occurred in 6% and 28% of subjects after the first and second dose, respectively. No serious adverse events leading to hospitalization or death and no serious allergic reactions were reported. These results are in line with the data published by Polack et al.[4] and confirm the safety of this vaccine.

Looking in detail to self-reported symptoms, local symptoms, represented mainly by pain at the site of injection, were reported with a frequency comparable to the BNT162b2 trial [4], ranging from 50 to 75% of subjects. Similar to the BNT162b2 trial, systemic symptoms occurred more frequently after the second dose of vaccine and more frequently in younger than in older people. The most frequent symptoms, fatigue and headache, occurred less frequently in our cohort than in the trial: fatigue occurred in 45−50% of our cohort and 51 to 59% of the trial's older and younger than 55 year participants; headache in 30−40% of our cohort and 39−52% of the trial participants. Of note, fatigue occurred less frequently after the BNT162b2 vaccine than after other viral vaccines [13].

In our setting, the risk of experiencing post-vaccination symptoms was higher among females. This observation goes in parallel with the finding of a better prognosis of females in the acute phase of the disease [14], possibly attributable to a higher level of IgG antibodies production in females in the early phase of the disease [15]. Also, the finding of the association between female sex and the so called "long COVID", a frequent syndrome including long-lasting symptoms after the acute phase of COVID-19 is part of this sex differences in the immune responses [16,17].

Another possible explanation might be a difference in women's awareness of symptoms, attributable to the higher attention paid to any change in their health conditions possibly related to their childbearing potential. Actually, MSS were reported more frequently by women aging less than 50 years (39% vs 33%, p = 0·003, data not shown). Also in other settings women show higher frequency of adverse events often leading to discontinuation of the ongoing treatment [18,19].

The association between age and symptoms goes in parallel with the finding of a post-vaccine higher titer of anti-SARS CoV-2 neutralizing antibodies in younger people [20]; suggesting that immune-mediated mechanisms resulting in increased reactogenicity responsible of symptoms might be present.

A lateral consideration relates to the high frequency of previous COVID-19, 13%, among HCWs, mostly belonging to healthcare personnel, i.e. doctors and nurses at direct contact with the patients. HCWs have paid an important tribute to deaths in Italy as well as in other parts of the world and vaccine campaigns have correctly started with this category worldwide [8]; actually, 21 cases of COVID-19 occurred in the time frame between the two doses, when protective effect of vaccine was still lacking.

Our research has several limitations: first, only half of the invited HCWs have filled the online questionnaire; thus, there might have

Table 5
Factors associated with moderate systemic symptoms to different doses of anti-SARS CoV-2 mRNA BNT162b2 vaccine by univariate and multivariable logistic regression.

Either first or second dose anti-SARS CoV-2 mRNA BNT162b2 vaccine among 3078 HCWs								
	OR	95%CI		p	AOR*	95%CI		p
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.

Table 6
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.

been a recall bias, as those filling the questionnaire might be those experiencing symptoms more frequently. Second, even if the way to collect the symptoms was by self-reporting in both the trial participants and HCWs of our study, we could suppose that fear of side effects might be more frequent in our cohort, as not included in a close monitoring schedule as in RCT, thus reporting even minimal symptoms. Further, persons who experienced COVID-19 might be more anxious on possible side effects of vaccination and this could have affected their reporting. Third, 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.

In conclusion: in the real-world setting of individuals aging less than 70, without any known severe chronic diseases preventing job activities, anti-SARS CoV-2 mRNA BNT162b2 vaccine results in a high prevalence of mild symptoms, lasting a median of 24 h, indicating local and systemic reactogenicity. An already primed immune system might explain the higher risk of systemic symptoms as early as the first dose of vaccine in subjects with previous COVID-19; in these subjects, reactogenicity was sustained mainly at the first dose, and no severe reactions were detected, thus confirming the safety of BNT162b2 vaccine also in subjects previously exposed to the virus. The findings of this research might suggest that, when a second dose is needed in subjects previously SARS CoV-2 infected, it can be administered without fear of severe side events. The question regarding the durability of vaccine efficacy both in those with previous SARS CoV-2 infection/disease and in naïve subjects remains open and goes beyond the findings of this research.

Funding

None

Authors' contribution

AdM and CC: conceptualization, investigation, coordination, writing - original draft. ; AT formal analysis; AT, PMP and GM: investigation; writing - review & editing; DT and VB: data curation; AZ, KR and NO: investigation, project administration ; LR: writing - review & editing. AdM, CC, PMP and AT had full access to the data.

Data sharing statement

All the data generated during the study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

None of the authors have any conflicts of interest to disclose

Acknowledgment

We thank L.A. Messina, G. Ria, E. Cocchi and S. Barzaghi for technical assistance and all the colleagues that participated to the study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.100914.

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