European Review for Medical and Pharmacological Sciences 2021; 25: 7985-7996

Host factors and history of SARS-CoV-2 infection impact the reactogenicity of BNT162b2 mRNA vaccine: results from a cross-sectional survey on 7,014 workers in healthcare

N. UGHI[1], F. DEL GAUDIO[2], A. DICUONZO[2], M. ORSO[3], G. MICHELONI[4], M. PUOTI[5], A. PANI[6,7], F. SCAGLIONE[6,7], L. ZOPPINI[8], C. ROSSETTI[2], O.M. EPIS[1], G. BELLAVIA[8], S. GIROLDI[8], M. MORENO[8], M. BOSIO[8]

[1]Multispecialist Medical Department, Division of Rheumatology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[2]Functional Department for Higher Education, Research, and Development, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[3]Vaccination Centre, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[4]Division of Occupational Medicine, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[5]Multispecialist Medical Department, Division of Infectious Disease, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[6]Department of Laboratory Medicine, Division of Chemical-Clinical and Microbiological Analyses, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
[7]Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy
[8]Hospital Direction, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Abstract. – OBJECTIVE: This study aimed to improve the post-marketing surveillance on mRNA anti-SARS-CoV-2 vaccines, characterizing the adverse events (AEs) after the first dose of mRNA BNT162b vaccine. The associations between the AEs and individuals' characteristics were explored.

PATIENTS AND METHODS: All adult healthcare workers at Niguarda Hospital (Milan, Italy) who were referred for the first dose of vaccine were offered to participate in a cross-sectional survey during the second-dose administration, between 18 January and 7 February 2021. All participants completed a questionnaire about age, gender, weight, height, medical history, concurrent therapies, employment status, previous diagnosis/testing for SARS-CoV-2 infection, and a list of 24 AEs (solicited AEs). The development of at least one solicited AEs was the main outcome. AEs were stratified by the presence of injection-site symptoms, systemic symptoms or both, and the differences between strata were assessed as a secondary outcome. Biometric data and reports of a previous diagnosis of SARS-CoV-2 infection were also explored, as predictors of the main outcome.

RESULTS: 7,014 healthcare workers were included. An incidence of 3 per 10.000 persons for serious AEs following the first administration of the mRNA BNT162b vaccine was found. An association between the development of non-serious AEs with young age, female gender, low body mass index, and previous history of SARS-CoV-2 was described.

CONCLUSIONS: This real-life study supported data on the safety profile of the BNT162b2 mRNA vaccine. Our findings on the associations between the development of non-serious AEs with some individual characteristics may help physicians and patients make educated and informed medical decisions towards anti-COVID-19 vaccination.

Key Words:
mRNA anti-SARS-CoV-2 vaccines, Anti-COVID-19 vaccination, Post-marketing surveillance, Healthcare workers, Adverse events.

Introduction

In response to the urgency of the pandemic, a growing number of vaccines for the prevention of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have been developed with unprecedented promptness[1]. By the end of 2020, SARS-CoV-2 vaccines based on mRNA technology were among the first whose safety and efficacy were proved by phase III trials[2,3] and

Corresponding Author: Nicola Ughi, MD; e-mail: nicola.ughi@ospedaleniguarda.it

emergency use authorization was issued by drug regulatory authorities worldwide, given the benefit of immediate availability despite the risk from less comprehensive data than normally required. The high efficacy of the protection of mRNA vaccines against the deadly COVID-19 disease greatly outweighs the risk of serious reactions, as supported by clinical trial data and the first large reports from post-marketing surveillance after the anti-SARS-CoV-2 vaccination campaign started. Anaphylaxis following these vaccinations is exceedingly rare and the frequency of this event ranges from 0.025/10,000 vaccinations from the US national passive surveillance of 17,524,676 doses of mRNA vaccines administered through 18 January 2021[4] to 2.47/10,000 vaccinations in a prospective cohort of 64,900 US healthcare employees[5]. These 82 cases were all non-fatal and mostly occurred in people known for a history of anaphylaxis. With regards to non-serious adverse events, such as injection site reactions or systemic symptoms (e.g., fever, headache), safety monitoring systems based on passive spontaneous reporting methods may be less accurate than clinical trials reporting of adverse events, where frequencies of non-serious events up to 80% were recorded[3]. However, clinical trial data are limited, particularly in special populations, such as immunocompromised patients excluded from trials, and additional monitoring is mandatory for mRNA SARS-CoV-2 vaccines whose use is still under conditional marketing authorization in a number of countries, such as those in Europe[6].

Therefore, in this rush, the clinical evidence base is suboptimal for helping both healthcare professionals and patients to make informed decisions, and real-life data about the safety of mRNA vaccines are a medical unmet need.

This real-life study aimed to improve the post-marketing surveillance on anti-SARS-CoV-2 vaccines by documenting, recording and quantifying the frequency of the suspected treatment-associated adverse events after the administration of mRNA BNT162b during the first vaccination campaign among the healthcare workers. Moreover, the association between the reactogenicity and the characteristics of the individuals was explored.

Patients and Methods

Study Design, Setting and Participants

This study was designed as a cross-sectional survey to retrospectively collect and describe the suspicion of adverse events after the administration of the first dose of BNT162b vaccine in healthcare workers during the first anti-SARS-CoV-2 vaccination campaign between 27 December 2020 and 17 January 2021 at Niguarda Hospital in Milan (Italy). Niguarda is one of the largest general hospitals in the north of Milan within a metropolitan area, having a population of 3,279,944 people (January 2020). It is equipped with a vaccination center and hosts all medical and surgical disciplines for adults and children, including 2,198,074 outpatient visits, 1,167 beds, a 24-hour Emergency Department with 66,727 visits, and 27,230 in hospital admissions covering every intensity of care in 2020. In this context, all adults (≥18 years old) who were referred for the first dose of vaccine were offered to participate in the study during the second dose administration, carried out between 18 January and 7 February 2021.

This study was conformed to Helsinki's Declaration and was approved by the Ethics Committee Milano Area 3 (register number 16-14012021). The reporting of adverse events was managed in compliance with the requirements of the Italian Medicines Agency National Pharmacovigilance Network, which is connected to EudraVigilance, and both serious adverse events (SAEs) and important medical events (IMEs) were notified to the responsible for pharmacovigilance of Niguarda Hospital and reported by using the VigiFarmaco website (https://www.vigifarmaco.it/). This safety signaling was not meant to replace nor was in contrast with the spontaneous reports from all healthcare professionals and citizens as required by European pharmacovigilance legislation. Written informed consent was obtained from all individual participants included in the study.

Data Collection

All the eligible subjects were asked to fill in an *ad hoc* questionnaire about age, gender, weight, height, medical history, concurrent therapies, employment status, previous diagnosis and testing for SARS-CoV-2 infection either by serology test or nasopharyngeal (NF) swab (molecular or antigen tests), and a list of 24 adverse events (hereafter termed solicited adverse events), including both injection site reactions (5 items) and systemic symptoms (19 items). The reporting of other suspected adverse events (hereafter termed unsolicited adverse events) was also encouraged with two open questions about further symptoms and free comments. The identification of SAEs was based on the

occurrence of hospitalization, permanent or severe disability, life-threatening events, death or a birth defect. The definition of IMEs was in accordance with the last criteria developed by the European Medicine Agency (update 11 September 2020). Data were also collected about the features of the adverse events in terms of duration, time to the onset, impact on quality of life (from 0 = none to 10=highest on a Likert Scale), the need for medications, and the outcome (i.e., completely resolved, resolved with unserious consequences, ongoing but improved, or ongoing and stable). Absence from work in the days after the administration was also investigated and the opinion about the possible relation with the vaccine was sought.

Study Outcomes

Only the solicited adverse events were considered for the analyses to overcome the reporting bias from the spontaneous signaling method of the unsolicited reports, which were only described. The presence of at least one among the solicited adverse events was the main outcome. Then, reported solicited adverse events were stratified by the presence of injection site symptoms only, systemic symptoms only or both, and the differences between strata were assessed as a secondary outcome. Biometric data and reports of a previous diagnosis of SARS-CoV-2 infection based on either NF swab or serology testing were also explored, as predictors of the main outcome.

Statistical Analysis

The response rate was calculated in compliance with the requirements of the American Association for Public Opinion Research[7] and complete plus partial interviews were the numerator and eligible cases that were not interviewed (non-respondents) with cases of unknown eligibility were included in the denominator.

The distributions of the outcomes and the other variables were described by absolute and relative frequencies, mean and standard deviation (SD), and median and interquartile range (IQR) for categorical, un-skewed and skewed continuous variables, respectively. The Pearson χ^2 statistic was used to test the hypothesis that the rows and columns in the two-way table of categorical variables were independent and the Student's *t*-test was used to test the hypothesis of difference between means of two independent samples in case of continuous variables unless otherwise stated. Univariable and multivariable logistic regression models for the binary outcome of reporting of adverse events were used to explore the associations with age, gender, body mass index (BMI) and SARS-CoV-2 status as predictors and the point estimate of odds ratios (OR) along with 95% confidence intervals (CIs) were reported as association measures. Main effects models with the categorization of age and BMI into the level of interest (decades and WHO classification of nutritional status, respectively) were assessed for the principal analyses. Wald tests of linear hypotheses were used to test the equality of coefficients between equations and Sidak's method for adjusting p-values was considered in case of multiple testing. Then, first-order interaction effects and non-linear relations between the dependent and the independent variables were explored in separate models as well. Complete case analyses were performed after checking that non-missing data were still representative of the target population and the proportion could be judged negligible in relation to the sample size. Nonetheless, analysis by multiple imputations with chained equations was also performed to compare parameter estimates with the complete case analysis. Finally, a sensitivity analysis was performed by comparing logistic regression, log-binomial regression, and Poisson regression with robust (Huber-White sandwich) estimator of the variance[8] to assess model parameters when the incidence of the outcome is large.

The primary endpoint of the study was to estimate the frequency of the main outcome in the population of the 7679 candidates who were expected to be referred to Niguarda Hospital for the vaccination. After assuming up to 10% of lost cases due to the lack of either the first or the second administration for any reason or refusal to participate in the study, for a prevalence of the main outcome of 80% as reported in the clinical trials, a sample size of 6920 subjects was calculated to be needed to detect a difference of 1.5% with a type I error of 0.05 and a statistical power of 90% by using a one-sample two-sided Wald test of proportions.

All the analyses were performed using Stata Statistical Software Release 15 (StataCorp. 2017, StataCorp LLC; College Station, TX, USA).

Results

Participants

Out of 7,619 subjects who received the first dose of the BNT162b2 mRNA anti-COVID-19 vaccine, 7,460 (98%) presented themselves for the second dose, and 7,014 (response rate: 93%) filled in the questionnaire about the suspected adverse events at this time. The flow of the participants in the study and their characteristics are shown in Figure 1 and Table I, respectively. Almost two out of five were overweight or obese (39%). A history of SARS-CoV-2 infection based on either NF swab or serology test was reported by 1078 subjects (15%).

Incidence of Suspected Adverse Events

The overall incidence of any adverse event independently of the severity was 66% (4602/7014) in the 21 days following the first dose of the anti-COVID-19 vaccine. The number of SAEs and IMEs was 2/7,014 and 2/7,014, with an observed incidence of 3 per 10,000 persons in both cases. Among the 7,654 vaccinees who received the first dose, no additional SAEs or IMEs, including ana-

Table I. Characteristics of the participants (n=7,014).

Characteristics	n (%)*
Time between doses (days), mean (SD)	21 (0.04)
Age (years), mean (SD):	45 (12)
• <30 years	1115 (16)
• 30-39 years	1349 (19)
• 40-49 years	1445 (21)
• 50-59 years	2113 (30)
• >60 years	898 (13)
Gender (female):	4263 (61)
• Current breast feeding	33 (0.7)
BMI (kg/m^2), mean (SD):	24.5 (4.4)
• <18.5 kg/m^2, mean (SD)	258 (4.1)
• 18.5-24.9 kg/m^2, mean (SD)	3621 (57.2)
• 25-29.9 kg/m^2, mean (SD)	1728 (27.3)
• ≥30 kg/m^2, mean (SD)	720 (11.3)
Workplace, n (%):	
• Niguarda Hospital	4466 (64)
• Other†	2469 (36)
Professional role in healthcare, n (%):	
• Physician	1103 (16)
• Nurse	1406 (20)
• Allied health workers	1439 (21)
• Unspecified health workers	974 (14)
• Non-healthcare workers	1967 (28)
Reported diagnosis of SARS-CoV-2 by NF swab	
• Yes	829 (12)
• No	5162 (74)
• Unknown	1023 (14)
Reported NF swab testing for SARS-CoV-2 in the previous 30 days:	
• Yes, positive	29 (0.4)
• Yes, negative	1734 (25)
• No	4176 (59)
• Unknown	1075 (15)
Reported SARS-CoV-2 serology test:	
• Yes, positive	527 (7)
• Yes, negative	3912 (56)
• No	1615 (23)
• Unknown	960 (14)
Immunocompromised subjects‡	33 (5)

*Unless otherwise specified.†Local emergency medical service and territorial health assistance referred to Niguarda Hospital. ‡Status defined by concurrent one or more immunomodulatory therapies. SD, standard deviation; NF, nasopharyngeal; BMI, body mass index.

Table II. Main features of the suspected adverse events reported after the first dose of anti-COVID-19 vaccine.

Features	n (%)†
Suspect of adverse event (at least one):	4602 (66)
• Solicited	4596 (98)
• Unsolicited	144 (2)
Serious adverse events:	2 (0.04)
• Hospitalization^	2 (100)
• Life-threatening	0
• Permanent or severe disability	0
• Death	0
Other important medical events	2 (0.04)
• Acute pancreatitis§	1 (50)
• Miscarriage*	1 (50)
Impact on quality of life (0 = none, 10 = highest):	
• Median (IQR)	0 (0-1)
• Mean (SD)	1.02 (1.78)
Time to the onset (days):	
• Median (IQR)	0 (0-1)
• Mean (SD)	0.83 (1.80)
Duration of the suspected adverse event,	
• Median (IQR)	0 (0-2)
• Mean (SD)	1.11 (2.49)
Outcome of the suspected adverse event:	
• Completely resolved	4357 (97)
• Resolved with unserious consequences	4 (0.1)
• Ongoing, but improved	60 (1)
• Ongoing and stable	31 (0.7)
• Cannot answer	17 (0.4)
• Need for medication	544 (12)
Second dose not administered:	7 (0.1)
• Reason for interruption of vaccination:	
Headache	2 (29)
Injection site reaction	1 (14)
Flu-like symptoms	1 (14)
Low back pain	1 (14)
Unknown	2 (29)
Absence from work:	
• No	5904 (96)
• Yes	260 (4)
Related to vaccine	123 (47)
Unrelated to vaccine	127 (49)
Unknown	10 (4)
Duration (days)	
• Median (IQR)	2 (1-5)
• Mean (SD)	3.6 (3.9)

^1 pneumothorax, 1 dark urine and dysuria referred to Emergency Department. §2 days after the vaccination, completely resolved without hospitalization. *Miscarriage at 5 weeks (unaware of pregnancy), without hospitalization. The relation with the vaccination was defined possible for the miscarriage by the Regional Centre of Pharmacovigilance of Lombardy according to the WHO classification for the causality assessment of an adverse event following immunization, while the other assessments were undetermined or unrelated. †Unless otherwise specified.

phylaxis further to those collected in this study were notified in the safety-monitoring system based on spontaneous reporting, as verified by the pharmacovigilance service of Niguarda Hospital. The features of the reported SAEs and IMEs are detailed in Table II and all these occurrences resolved without any sequelae.

Most of the reported events occurred within the day after the vaccination and lasted 2 days, with no or minimal impact on quality of life and the need for medication was reported in 12% of cases (Table II). Absence from work in the days following the vaccination was reported by 260 respondents (4%) of which 123

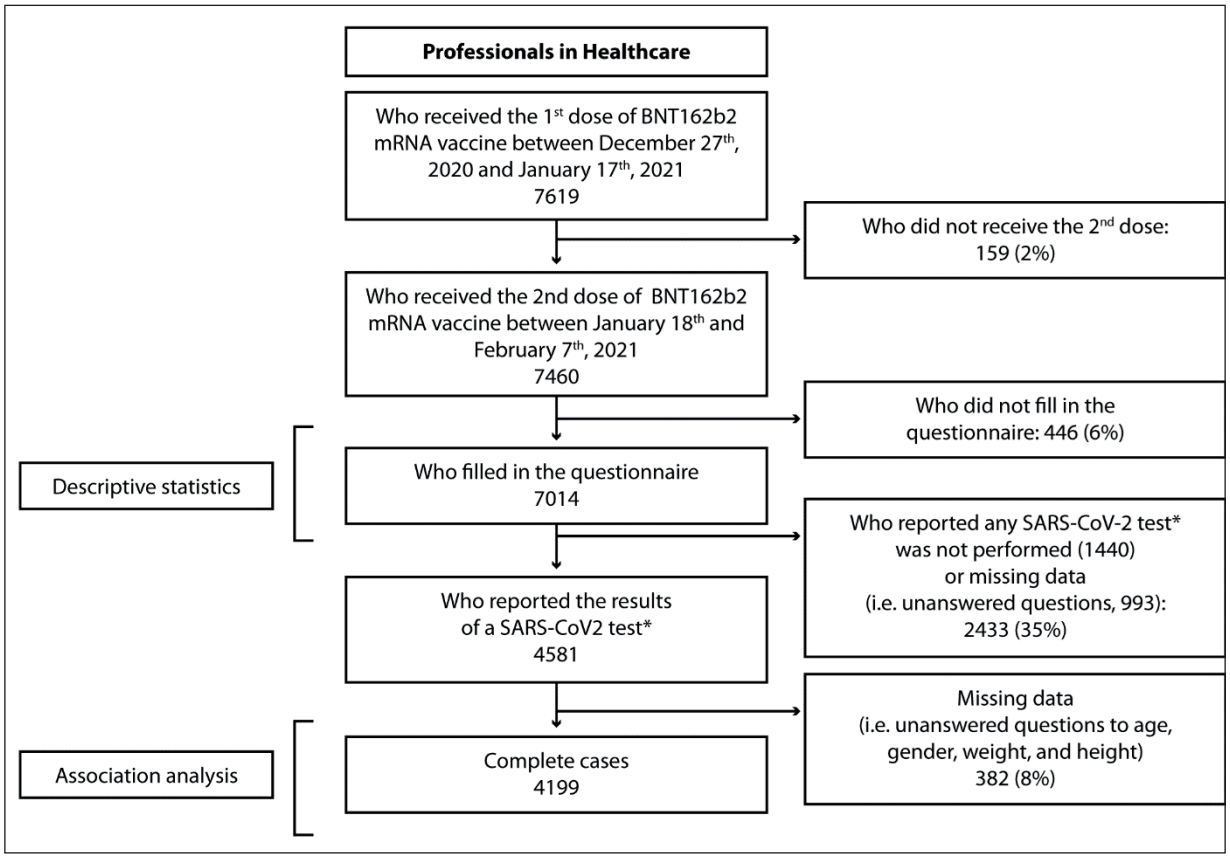

Figure 1. Flow chart of the participants in the study. *Either serology assay or nasopharyngeal swab (molecular or antigen test). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(47%) judged the absence to be related to the suspected adverse events after the vaccination.

Secondary Outcomes

Stratification of the suspected adverse events

The prevalence of the non-serious solicited and unsolicited adverse events is reported in Figure 2 and their features are detailed in **Supplementary Table I**.

The reactions at the site of injection were the most frequent (58%), which represented 88% of the whole reporting of solicited adverse events. Two out of five respondents reported systemic reactions, mainly including myalgia (48%), unusual fatigue (48%), headache (35%), limb pain (33%), joint pain (26%), malaise (26%), and shivers (20%), while the other symptoms were below 10%.

Frequency of the suspected adverse events across subgroups

Those who reported at least one solicited adverse event after the first dose of vaccine were younger, had a lower BMI and were more frequently female with a history of positivity to SARS-CoV-2 tests compared to those who had no symptoms (Table III and Figure 3). Among those who reported any adverse effect, the majority had both injection site and systemic symptoms (53%) and those who had injection site reactions only and systemic symptoms only were significantly older (mean [SD]: 43[12] and 48 [11] years, respectively) and less frequently female (64% and 64%, respectively) compared with having both symptoms as reference (mean [SD]: 42 [12] years and 73% of female, $p \leq 0.001$ for all tests). The BMI was significantly lower in the subgroup of injection site reaction only (mean [SD]: 23.8 [4.1] kg/m^2) and higher in one of systemic symptoms only (mean [SD]: 25.1 [4.7] kg/m^2) than in those who reported both symptoms (mean [SD]: 24.2 [4.4] kg/m^2, $p = 0.019$ and $p < 0.001$, respectively).

Conversely, a previous SARS-CoV-2-positive test was more frequently reported in those who had both symptoms compared with injection-site only reactions (19% *vs.* 11%, $p = 0.027$ with NF swab, and 16%

and 9%, p <0.001 with serology), but this difference was not statistically significant when compared with those who reported systemic symptoms only.

Finally, 33 subjects reported being on one or more current immunomodulatory treatment, including TNF inhibitors (4 adalimumab, 2 etanercept, 2 golimumab, and 1 infliximab), methotrexate (7), mycophenolic acid preparations (6), azathioprine (5), cyclosporine (2), anti-interleukin 12/23 (2), sulfasalazine (1), anti-interleukin 5 (1), anti-interleukin 6 (sarilumab 1), and glucocorticoids (1) for several chronic inflammatory diseases (16 autoimmune inflammatory rheumatic diseases, 8 inflammatory bowel diseases, 2 organ transplant recipients, 2 autoimmune hepatitis, and other 3 diseases were reported). In this special group, the proportion of reports of any solicited adverse event was higher (76%, 95% CI: 58-89) compared to those who did not report an immunomodulatory treatment (65%, 95% CI: 64-67, n=6,981), but the difference was not statistically significant (Fisher's exact test p=0.271).

Associations between the characteristics of the individual vaccinee and the adverse events

The associations between the outcome and the independent variables (age, gender, BMI and his-

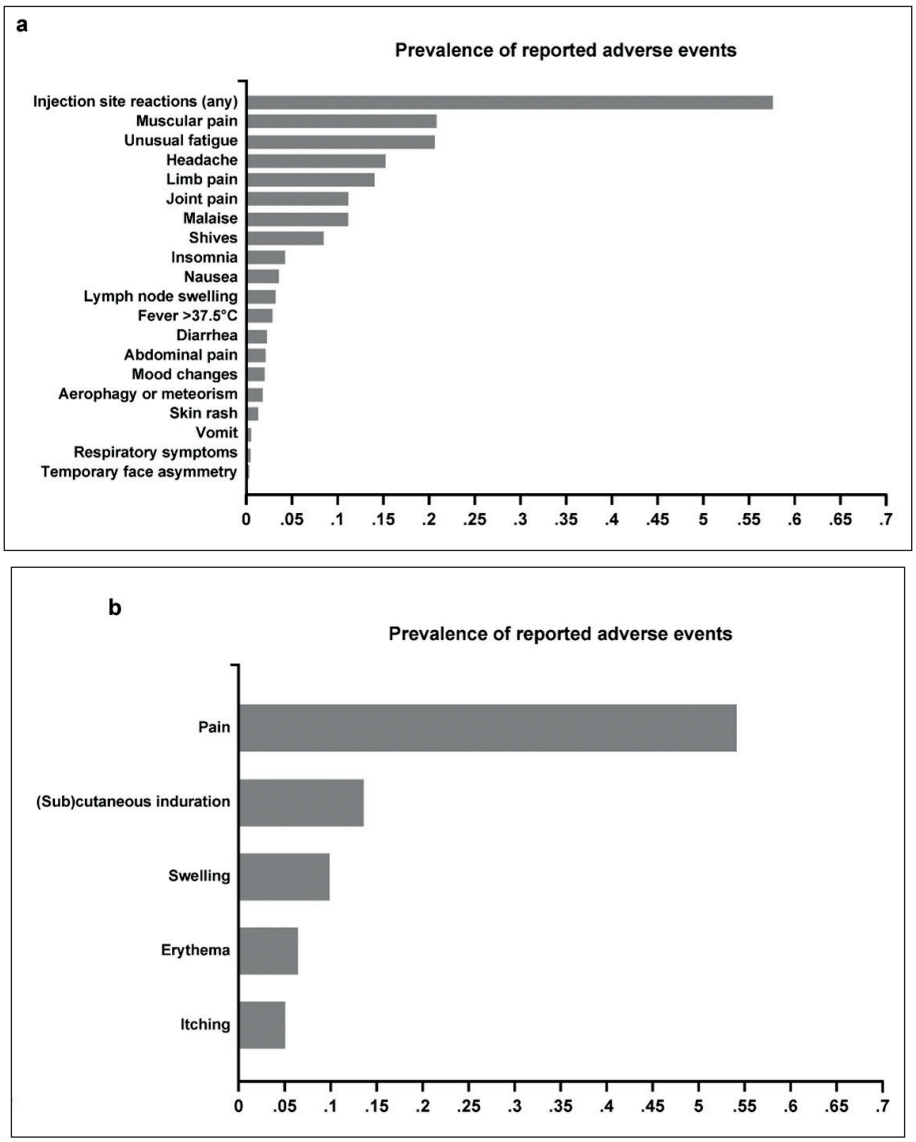

Figure 2. Distributions of the solicited adverse events (**a**) and the features of the injection-site reactions (**b**) after the first dose of the BNT162b2 mRNA anti-COVID-19 vaccine.

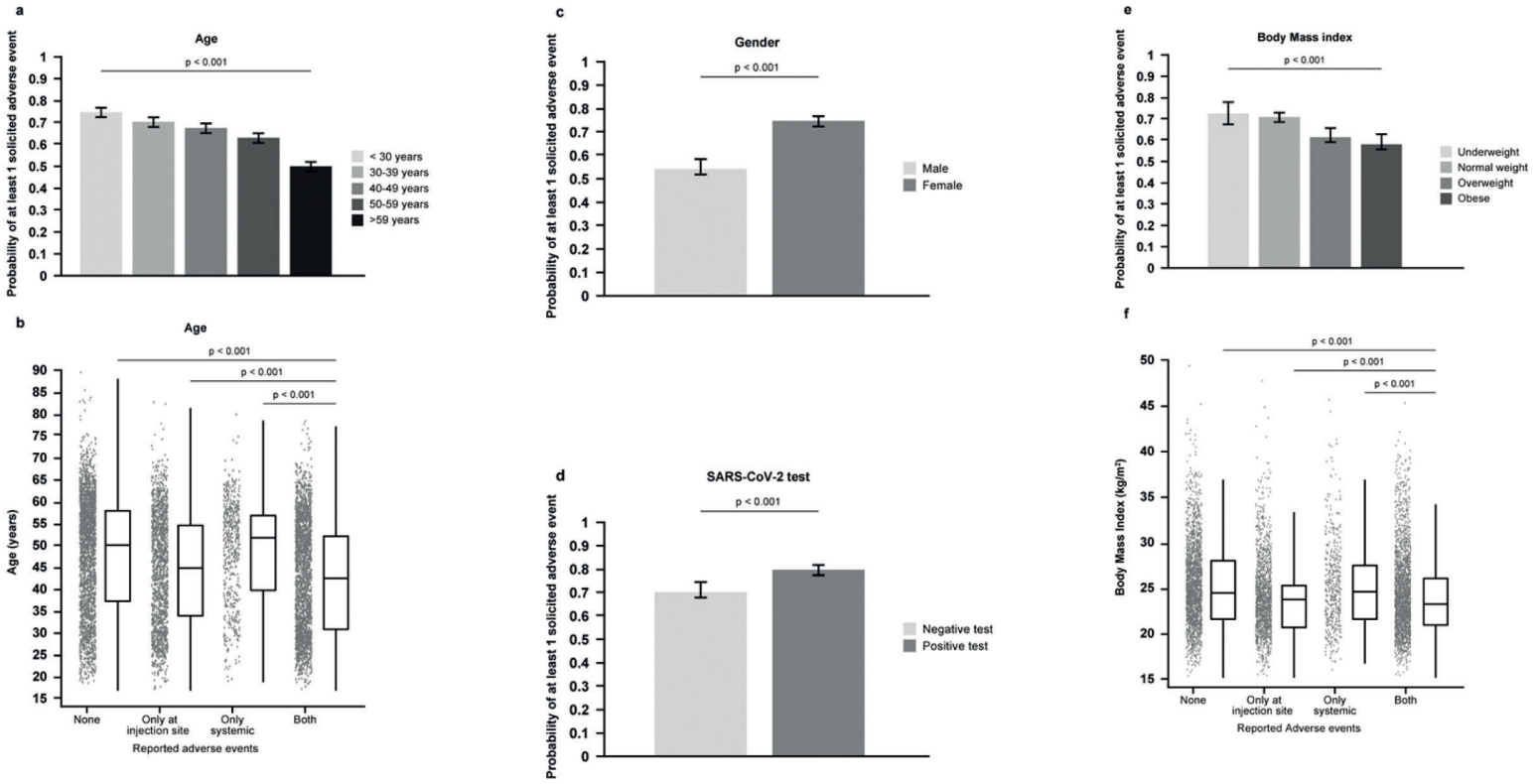

Figure 3. Distribution of the solicited adverse events after the first dose of BNT162b2 mRNA anti-COVID -19 vaccine within age (**a-b**), gender (**c**), history of positivity to SARS-CoV-2 tests (**d**), and body mass index (**e-f**). Boxes show medians and interquartile ranges. Bars are 95% confidence intervals.

Table III. Comparisons between vaccinees who reported adverse events and who did not.

Feature	No symptoms, n (%)	Symptoms						
		Overall, n (%)	*p*-value	Both (reference), n (%)	Injection-site only, n (%)	*p*-value	Systemic only, n (%)	*p*-value
	n=2372	***n=4548***		***n=2437***	***n=1567***		***n=544***	
Age (years), mean (SD)	47 (13)	44 (12)	<0.001	42 (12)	44 (12)	0.001	48 (11)	<0.001
<30 years	278 (12)	837 (18)	<0.001	509 (21)	286 (18)	0.002	42 (8)	<0.001
30–39 years	387 (16)	962 (20)		555 (23)	314 (20)		93 (17)	
40–49 years	465 (20)	980 (21)		507 (21)	375 (24)		98 (18)	
50–59 years	788 (33)	1325 (29)		667 (27)	426 (27)		232 (43)	
>60 years	454 (19)	444 (10)		199 (8)	166 (11)		79 (14)	
	n=2381	***n=4564***		***n=2446***	***n=1569***		***n=549***	
Female	1112 (47)	3151 (69)	<0.001	1792 (73)	1007 (64)	<0.001	352 (64)	<0.001
	n=2108	***n=4219***		***n=2274***	***n=1462***		***n=483***	
BMI (kg/m^2), mean (SD)	25.27 (4.49)	24.20 (4)	<0.001	24.22 (4.39)	23.88 (4.06)	0.019	25.11 (4.73)	<0.001
<18.5 kg/m^2	71 (3)	187 (4)	<0.001	99 (4)	66 (4)	0.053	22 (5)	<0.001
18.5–24.9 kg/m^2	1055 (50)	2566 (61)		1380 (61)	943 (64)		243 (50)	
25–29.9 kg/m^2	681 (32)	1047 (24)		565 (25)	336 (23)		146 (30)	
≥30 kg/m^2	301 (15)	419 (11)		230 (10)	117 (9)		72 (15)	
	n=1737	***n=4254***		***n=2318***	***n=1449***		***n=487***	
Reported diagnosis of SARS-CoV-2 (NF swab) – yes	156 (9)	673 (16)	<0.001	439 (19)	165 (11)	0.027	69 (14)	0.341
	n=497	***n=1266***		***n=686***	***n=430***		***n=150***	
Reported NF swab testing for SARS-CoV-2 in the previous 30 days (yes, positive)	7 (1)	22 (1)	0.625	12 (1)	5 (1)	0.850	5 (3)	0.222
	n=1212	**n=3227**		**n=1754**	**n=1134**		**n=339**	
Reported SARS-CoV-2 Serology test (ever) – yes, positive	102 (8)	425 (13)	<0.001	280 (16)	102 (9)	<0.001	43 (12)	0.126

NF, nasopharyngeal; BMI, body mass index.

tory of SARS-CoV-2 infection) were explored in the 4,199 complete cases of the 4,581 respondents who reported to be tested by either NF swab or serology assay. Comparisons between complete cases and subjects with missing data are reported in **Supplementary Table II**.

Age groups, gender, BMI classification and history of SARS-CoV-2 infection were significantly

Table IV. Associations between the presence of adverse events after the first dose of anti-COVID-19 vaccine and the independent variables (age, gender, body mass index, and history of SARS-CoV-2 infection), n = 4199.

	Univariable		Multivariable	Pseudo R^2=0.0605
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Positive NF swab or serology testing for SARS-CoV-2 (no as reference)	1.70 (1.42-2.02)	<0.001	1.77 (1.47-2.12)	<0.001
Age (<30 years as reference)				
30-39 years	0.67 (0.52-0.85)	0.001	0.76 (0.59-0.98)	0.032
40-49 years	0.60 (0.47-0.77)	<0.001	0.68 (0.53-0.87)	0.002
50-59 years	0.56 (0.44-0.71)	<0.001	0.61 (0.48-0.78)	<0.001
≥60 years	0.31 (0.23-0.40)	<0.001	0.38 (0.29-0.51)	<0.001
Gender (male as reference)	2.68 (2.32-3.09)	<0.001	2.58 (2.22-2.99)	<0.001
BMI (kg/m^2), 18.5-24.9 as reference				
<18.5 kg/m^2	1.30 (0.87-1.95)	0.197	1.00 (0.66-1.50)	1.000
25-29.9 kg/m^2	0.68 (0.57-0.78)	<0.001	0.89 (0.75-1.06)	0.189
≥30 kg/m^2	0.62 (0.49-0.77)	<0.001	0.77 (0.61-0.97)	0.027

OR, odds ratio; CI, confidence interval; NF, nasopharyngeal; BMI, body mass index.

associated with reporting of adverse events in the univariable and multivariable analysis (Table IV). In particular, a previous positive NF swab or serology test for SARS-CoV-2 was associated with the adverse events when adjusted for age, sex and BMI (OR 1.77, 95% CI: 1.47-2.12). Moreover, age <30 years and ≥60 years were associated with a higher and lower risk of adverse events compared to the other age groups, respectively, even after adjustment for multiple comparisons (**Supplementary Table II**). Similarly, a BMI ≥30 kg/m^2 was consistently associated with a lower risk of adverse events (OR 0.77, 95% CI: 0.61-0.97) in comparison to another weight status (**Supplementary Table III**). Then, when non-linear relations between the dependent and the independent variables and first-order interactions were explored, the effect of BMI showed to be higher in males than in females (OR 1.04, 95% CI 1.01-1.08) as shown in **Supplementary Table IV** and **Supplementary Figure 1**. This analysis on multiple imputed datasets yielded results comparable with that based on complete cases only (**Supplementary Table V**). Finally, the results of sensitivity analyses showed that large incidence of the main outcome (73%) may have an effect on the parameters estimates with overestimation of the risk when the log-binomial model and the Poisson model with robust standard errors were used to calculate the relative risks (**Supplementary Table VI**).

Discussion

On 27 December 2020, a vaccination campaign against COVID-19 started in all countries of the EU and the Niguarda Hospital was identified as one of the vaccination centers within the metropolitan area of Milan for the dispensation of the BNT162b2 mRNA vaccine and the first administrations to the healthcare professionals.

In this context, a cross-sectional survey was performed among healthcare professionals at the time of the second dose of vaccine and the results from this real-life study confirmed the overall safety profile reported in the pre-marketing clinical-trial data.

The favorable safety profile was comparable to those reported among BNT162b2 recipients in phase I[9,10] and phase II/III clinical trials[2], which was similar to that of other viral vaccines, particularly in terms of SAEs and IMEs. No deaths occurred among the study subjects in the time between the two doses and the absence of observed anaphylactic reactions to BNT162b2 mRNA vaccine in the sample study was in line with the rarity of this event, as reported by the continued safety monitoring systems in the USA (4.7 cases/million doses and in Italy (4.3 cases/million doses)[11] and similar to the other mRNA-1273 anti-COVID -19 vaccine (2.5 cases/million doses in the USA)[4].

The observed frequency of solicited non-SAEs either local or systemic, after the first dose, was significantly lower (65%) than reported in phase II/III trials on mRNA anti-COVID-19 vaccines (up to 83% for BNT162b2[2] and 84% for mRNA-1273[3]), but comparable to a real-life report performed on healthcare workers[12] and to the results from an active surveillance system on 1,659,724 people[13]. Despite this difference, a mild-to-moderate severity, onset and complete resolution within 2–3 days after vaccination and the distributions of local (mostly pain) and systemic reactogenicity (mostly fatigue, headache, and myalgia) were similar.

In this study, an association between the reporting of solicited adverse events and age, gender, BMI, and history of SARS-CoV-2 infection was observed. Particularly, female gender and previous SARS-CoV-2 infection were independently associated with the risk of development of suspected adverse events, while older age, high BMI, particularly in males, showed to be protective. Lower reactogenicity has been already reported among older participants (i.e., >55–65 years of age) than among younger participants in subgroup analyses of phase II/III trials on mRNA anti-COVID-19 vaccines[2,3], as well as in a report from a large post-marketing surveillance[13]. Moreover, these results are consistent with the preliminary data on a cohort of healthcare workers who reported a high rate of suspected adverse events in association with a history of SARS-CoV-2 infection[12,14], whilst such association was reported to be inconclusive in the BNT162b2 mRNA vaccine phase II/III trial[2].

To our knowledge, data about the role of gender and BMI on the reactogenicity of the BNT162b2 mRNA vaccine are lacking. With regards to its immunogenicity, in a preliminary publication on 248 healthcare workers[15], antibody titer in response to mRNA vaccines was found to be higher in young and female participants and lower in obese participants[12]. Further data are available for other viral vaccines, especially for the influenza virus. Host factors including age, gender and BMI may play roles as modifiers of the response to influenza virus vaccines, with high rates of reporting of adverse events in young and female vaccinees[16] and age-dependent early response[17]. However, the relation between immunogenicity and reactogenicity in response to the anti-COVID -19 vaccine is unknown and extrapolations from other viral vaccines should be considered with caution.

Finally, immunocompromised patients were excluded from pre-marketing trials and data on these special populations are limited. Our findings are consistent with the only study performed on 26 patients with chronic inflammatory diseases whose reporting of adverse events was comparable to 42 healthy controls who received anti-SARS-CoV-2 mRNA vaccines[18].

However, further investigations in large samples are needed to unravel safety differences, which may be related to concurrent immunosuppressant therapies.

This study has some limitations. First, these data represent the response to the first dose of a two-dose series and data on the second dose for which a higher rate of adverse events is expected than for the first dose were not assessed[5,13]. Secondly, the sample size and the follow-up time were insufficient to capture rare and delayed events, whose incidence will be properly described by the national continue monitoring systems. However, the high survey response rate and the level of details on solicited adverse events may help widen the knowledge in the phase of pharmacovigilance to overcome the reporting bias of the spontaneous signaling methods.

Finally, the effect sizes of the multivariable model for the prediction of adverse events are highly significant, but the goodness-of-fit and the proportion of the total variability in the dependent variable explained by this model are low (6%). These findings suggest that further investigations are needed to identify the additional factors associated with the development of adverse events after the BNT162b2 mRNA vaccination.

Conclusions

Real-life data on the safety of mRNA anti-COVID-19 vaccine are largely lacking but rapidly growing and this study confirms the safety profile of the BNT162b2 mRNA vaccine supported by clinical-trial data. Moreover, our findings on the associations between the development of non-serious adverse events with young age, female gender, low BMI, and previous history of SARS-CoV-2 infection may help physicians and patients make education and informed medical decisions towards anti-COVID-19 vaccination.

Conflicts of interest

The authors declare no conflicts of interest.

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