Acta Biomed 2021; Vol. 92, Supplement 6: e2021450 DOI: 10.23750/abm.v92iS6.12217

Safety surveillance after BNT162b2 mRNA COVID-19 vaccination: results from a cross-sectional survey among staff of a large Italian teaching hospital

Giacomo Pietro Vigezzi[1], Alessandra Lume[1], Massimo Minerva[1], Paola Nizzero[2], Anna Biancardi[2], Vincenza Gianfredi[1], Anna Odone[3], Carlo Signorelli[1], Matteo Moro[2]

[1] School of Medicine, Vita-Salute San Raffaele University, Milan, Italy; [2] Infection Control Committee, IRCCS San Raffaele Hospital, Milan, Italy; [3] Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy.

Abstract. *Background and aim:* Comirnaty® was the first COVID-19 vaccine available for the vaccination campaign of healthcare workers in Italy. With the aim of assessing vaccine safety, we conducted a cross-sectional survey administrating a voluntary-based questionnaire on adverse events following immunisation (AEFIs) in San Raffaele Hospital, Milano, Italy. *Methods:* From 4th January 2021 to 27th April 2021, we collected 2,659 questionnaires (response rate: 24,5%). We analyzed data, reporting AEFIs by gender, age, self-reported severity, type, time of insurgence and duration, and estimating relative-risk ratios (RRR) and corresponding 95% confidence intervals (CI). *Results:* The most reported symptoms were injection site pain, fatigue, headache, myalgia, chills, fever, and arthralgia. Severe systemic reactions were more frequent after receiving the second dose (RRR 6.25, 95% CI 4.57-8.55), in women (RRR 3.33, 95% CI 2.30-4.82), and less frequent in individuals aged 60 or more (RRR 0.26, 95% CI 0.14-0.49). In addition, we noted a wide range of adverse events of special interest (AESIs). *Conclusions*: Consistently with clinical trials and pharmacovigilance surveillance, AEFIs were frequent, but severe ones were uncommon, supporting the massive implementation of the COVID-19 vaccination campaign and providing valuable data for a risk profiling of vaccinees. (www.actabiomedica.it)

Key words: vaccine, COVID-19, cross-sectional study, vaccination, pharmacovigilance, adverse drug reaction reporting systems

Introduction

The COVID-19 pandemic is a global crisis with devastating health, societal and economic impacts (1-4). Therefore, the development and rapid global deployment of safe and effective vaccines against COVID-19 are crucial for overcoming this major public health issue (5, 6).

On 21st December 2020, following the European Medicines Agency (EMA) evaluation, the European Commission authorised the first COVID-19 vaccine, Comirnaty®, produced by Pfizer-BioNTech (7, 8). Three other vaccines against SARS-CoV-2 were licensed for use in the European Union in the following months (9). In order to monitor post-marketing vaccine safety, healthcare professionals were required to report to National Pharmacovigilance Network (RNF in Italy) occurring adverse events following immunisation (AEFIs) (10).

The current study aims to describe and evaluate the AEFIs with Pfizer BioNTech vaccine among hospital staff of a large Italian referral teaching hospital. A secondary outcome is the identification of novel side-effects or adverse events of special interest (AESIs) that may not have been reported previously in the clinical trials.

Methods

Setting and study design

San Raffaele Hospital (OSR) is a 2-site tertiary care referral hospital in Milan, Italy, with more than 1,300 beds, hosting a university. OSR Infection Control Committee, with the School of Public Health, during the early phases of the COVID-19 vaccination program, developed a questionnaire to monitor local, systemic, allergic and other reactions after Comirnaty® administration, adopting a cross-sectional study design.

Study population and enrolment

The eligible study population comprised the entire hospital staff (about 7,000 persons), including healthcare professionals, administrative staff, researchers, university employees and training students. The study period started 4th January 2021, few days after the kick-off of hospital staff immunisation in Italy. We ended the study on 27th April 2021, collecting surveys submitted by healthcare workers and other staff vaccinated until 20th April 2021.

Description of the questionnaire

The 11-item questionnaire was set up using SurveyMonkey® and online administered to all OSR staff through the company email (the complete questionnaire is available as Supplementary Table S1). The responders could report if they had or not had any AEFI, and in case possibly detailing the time of insurgence, the duration and the grade of severity of local, systemic, allergic and other symptoms. The intensity of symptoms was self-reported as mild, moderate or severe. We also collected data on sex, age and profession.

Answers were collected on a voluntary and anonymous basis; hence it was not considered necessary to seek ethical approval.

Statistical analysis

We analysed data by gender, age group, AEFI severity and type (local and systemic), time of insurgence and duration, also conducting sub-analysis for those who answered the questionnaire after both doses of vaccine. Percentage comparisons were performed using the χ^2 test for categorical variables and the z test for proportion. In order to evaluate the risk profile of the vaccinees, we estimated relative-risk ratios (RRR) of vaccination and their corresponding 95% confidence intervals (CIs) for AEFIs using multinomial logistic regression models, adjusted for sex, age, profession and vaccine dose. Data were statistically analysed using Excel (Microsoft Corporation, Redmond, WA, USA) and Stata software version 16.0 (Stata Corporation, College Station, Texas, USA).

Results

Between 4th January 2021 and 20th April 2021, 5,668 OSR staff members received the first dose of the Pfizer-BioNTech vaccine; 5,169 of them received the second dose, too. Thus, the total of administered Comirnaty® vaccines was 10,837.

On 27th April 2021, we collected 2,659 answered questionnaires, of which 1,168 referred to the first dose (response rate: 20.6%) and 1,491 to the second one (response rate: 28.8%) with an overall response rate of 24.5%. We observed a significant difference in submitted questionnaires by gender among vaccinees, both after the first and second dose of vaccine [response rate: 33.2% (862/2,600) among women vs 10.0% (306/3,068) among men after the first dose; 46.2% (1,077/2,331) vs 14.6% (414/2,838) after the second one). On the contrary, we observed non-significant differences by age groups [response rate: 20.6% (796/3,870) among 18-49 years, 20.2% (338/1,673) among 50-64, 27.7% (33/119) among 65-74, 16.7% (1/6) among 75-84 after the first dose; 28.2% (994/3,531), 30.4% (462/1,518), 28.9% (33/114), 33.3% (2/6) respectively after the second one).

Overall, 2,105 persons answered the 2,659 questionnaires: 554 gave feedback after the first and second doses.

As reported in Table 1, 1,939 responders were female (72.9% of the total) and 722 males (27.1%); 1,790 responders aged between 18 and 49 years (67.3%), and 800 were more than 50 years old (30.1%). The median vaccinees' age was 42 years old (range 19-76 years). Of all responders, 1,402 defined themselves as healthcare workers (52.7%) and 1,257 as non-healthcare workers (47.3%).

Concerning gender, after receiving the Pfizer-BioNTech COVID-19 vaccine, we observed a difference between women and men (in favour of women) reporting AEFIs, after first and second dose, and for both doses.

About age groups' comparisons, after the first dose, AEFIs were more common among younger responders than no AEFI, and the opposite occurred among older responders. Responders reported similar findings after the second dose of vaccine and for the full sample (see Table 2).

Results from logistic regression models are reported in Table 3. Female gender was associated with a 65% increase in the probability of reporting at least one non-severe systemic AEFI (RRR 1.65, 95% CI 1.37-1.99, p<0.01) and a 233% greater likelihood of reporting at least one severe systemic AEFI (RRR 3.33,

Table 1. Study population: characteristics and reported adverse events following immunization (AEFI) in the full sample.

	COVID-19 vaccine first dose (n=1,168)			**COVID-19 vaccine second dose (n=1,491)**			**COVID-19 vaccine (n=2,659)**		
	N (%) reporting AEFIs	**N (%) not reporting AEFIs**	**Total**	**N (%) reporting AEFIs**	**N (%) not reporting AEFIs**	**Total**	**N (%) reporting AEFIs**	**N (%) not reporting AEFIs**	**Total**
Sex									
Male	110 (35.9)	196 (64.1)	306	266 (64.3)	148 (35.7)	414	376 (52.2)	344 (47.8)	720
Female	442 (51.3)	420 (48.7)	862	844 (78.4)	233 (21.6)	1,077	1,286 (66.3)	653 (33.7)	1,939
χ^2 test	p<0.01			p<0.01			p<0.01		
Age group - years									
18 - 49	402 (50.5)	394 (49.5)	796	794 (79.9)	200 (20.1)	994	1,196 (66.8)	594 (33.2)	1,790
50 - 64	145 (42.9)	193 (57.1)	338	301 (34.8)	161 (65.2)	462	446 (55.8)	354 (44.2)	800
65 - 74	5 (15.2)	28 (84.8)	33	15 (45.5)	18 (54.5)	33	20 (30.3)	46 (69.7)	66
75 - 84	0 (0)	1 (100)	1	0 (0)	2 (100)	2	0 (0)	3 (100)	3
χ^2 test	p<0.01			p<0.01			p<0.01		
Age - years									
Mean (95% CI)	43.5 (42.4-44.6)	40.5 (39.4-41.6)	42.0 (41.3-42.8)	41.8 (41.1-42.5)	47.2 (45.9-48.4)	43.2 (42.6-43.8)	41.4 (40.8-41.9)	44.9 (44.1-45.8)	42.7 (42.2-43.2)
t-test	p<0.01			p<0.01			p<0.01		
Median	41			42			42		
Range	19-76			19-76			19-76		
Profession - n (%)									
Healthcare workers	570 (40.7)			832 (59.3)			1,402		
Non-healthcare workers	598 (47.6)			659 (52.4)			1,257		
AEFI – n (%)									
Mean	2,1			3,7			3,0		
Reporting at least one severe AEFI	63 (5.4)			222 (14.9)			285		
z-test	p<0.01								
Reporting only non-severe AEFIs	489 (41.9)			888 (59.6)			1,377		
z-test	p<0.01								
Reporting only local AEFIs	410 (35.1)			220 (14.8)			630		
z-test	p<0.01								
Reporting no AEFIs	206 (17.6)			161 (10.8)			367		
z-test	p<0.01								

CI: confidence interval

Table 2. Outcomes distribution by selected variables.

Variable	Reporting no AEFIs or only local symptoms	Reporting at least one non-severe systemic AEFI	Reporting at least one severe systemic AEFI
Gender			
Male - n (%)	344 (47.8)	336 (46.7)	40 (5.6)
Female - n (%)	653 (33.7)	1,041 (53.7)	245 (12.6)
Age group			
<60 years old - n (%)	847 (35.3)	1,281 (53.4)	273 (11.4)
≥60 years old - n (%)	150 (58.1)	96 (37.2)	12 (4.7)
Vaccine dose			
First dose - n (%)	616 (52.7)	489 (41.9)	63 (5.4)
Second dose - n (%)	381 (25.6)	888 (59.6)	222 (14.9)
Profession			
Healthcare workers - n (%)	537 (38.3)	706 (50.4)	159 (11.3)
Non-healthcare workers - n (%)	460 (36.6)	671 (53.4)	126 (10.0)

AEFI: adverse events following immunization

Table 3. Relative-risk ratios (RRR) and corresponding 95% CI (confidence interval) from multinomial adjusted logistic regression.

Variable	Reporting at least one non-severe systemic AEFI vs Reporting no AEFIs or only local symptoms	Reporting at least one severe systemic AEFI vs Reporting no AEFIs or only local symptoms
	RRR (95% CI)[a]	**RRR (95% CI)[a]**
Gender		
Male	1.00	1.00
Female	1.65 (1.37-1.99)	3.33 (2.30-4.82)
p-value	<0.01	<0.01
Age group		
<60 years old	1.00	1.00
≥60 years old	0.43 (0.33-0.58)	0.26 (0.14-0.49)
p-value	<0.01	<0.01
Vaccine dose		
First dose	1.00	1.00
Second dose	3.13 (2.64-3.73)	6.25 (4.57-8.55)
p-value	<0.01	<0.01
Profession		
Healthcare workers	1.00	1.00
Non-healthcare workers	1.15 (0.97-1.37)	0.99 (0.75-1.30)
p-value	0.11	0.93

AEFI: adverse events following immunization
[a]adjusted for gender, age group, vaccine dose, profession.

95% CI 2.30-4.82, p<0.01), as compared to males. Subjects aged 60 years old or more had a 57% lower probability of reporting at least one non-severe systemic AEFI (RRR 0.43, 95% CI 0.33-0.58, p<0.01) and a 74% lower probability of reporting at least one severe systemic AEFI (RRR 0.26, 95% CI 0.14-0.49, p<0.01), as compared to individuals younger than 60 years. Subjects who received the second dose reported a greater probability of at least one non-severe systemic AEFI (RRR 3.13, 95% CI 2.64-3.73, p<0.01) and at least one severe systemic AEFI (RRR 6.25, 95% CI 4.57-8.55, p<0.01), as compared to first dose administration. No statistically significant association was found between reported AEFIs and professional category.

Next to the full sample, we separately analysed the subgroup of 554 responders who submitted questionnaires after both the first and second doses in order to exploit the predictable likelihood of using the same severity scale to describe an AEFI by the same person. Results are reported in Supplementary Table S2. We observed an increase in the rate of AEFIs reported after the second dose. In detail, systemic AEFIs (severe and non-severe) reported after the first dose were 239 (43.1%) and 422 (76.2%) after the second. All percentage differences observed were significant.

As summarised in Table 4 and Supplementary Table S3, injection site pain was the most reported AEFI (n = 1,922, 72.3%). In addition, 1,640 responders (93.0% of 1,764) experienced injection site pain in the first 24 hours following the vaccination, and 837 of the 1,720 (48.7%) responders referred that it was resolved within 24 hours.

Systemic AEFIs were frequently reported: among them, fatigue (47.7%), headache (31.3%), myalgia (28.2%), chills (24.2%), fever (23.9%), and arthralgia (21.4%) were the most frequent. We noticed a significant difference in systemic symptoms' rate between the first and second dose: they were more commonly reported after the second dose, as suggested by the increase in the mean of reported AEFIs (from 2.08 after the first dose to 3.44 after the second one) and by the significant proportion difference observed for fever, fatigue, chills, headache, nausea, diarrhoea, myalgia, arthralgia, swollen lymph nodes and dizziness.

Regarding fatigue, among the 1,268 responders who denounced it after vaccination, only 8.6% self-reported it as severe. Of the 1,058 responders reporting the time of insurgence, 77.1% complained of fatigue within the first 24 hours following the vaccination. Among 1,029 responders, who indicated fatigue duration, 52.2% reported a complete resolution within 24 hours.

Likewise, among 633 responders who complained of fever after vaccination, only 10.6% self-reported it as severe. Among 529 responders reporting the time of insurgence, 75.2% had a fever within the first 24 hours following the vaccination. Among 507 responders who reported fever duration, 69.2% reported a complete resolution within 24 hours.

Responders reported few cases of allergic AEFIs, and no cases of anaphylaxis were signalled in the questionnaire. Followed by widespread itch, urticaria was the most common allergic symptom experienced by 11 responders after the first dose and 27 after the second one.

We collected 190 questionnaires that described "other" AEFIs or AESIs, 87 after the first dose and 103 after the second. These symptoms ranged from cardiovascular ones (hypotension, hypertension, bradycardia, palpitations, thoracic pain) and nervous system's events (herpes simplex reactivation, dysgeusia, trigeminal neuralgia, photophobia, tinnitus, sleep disturbances, monolateral hearing loss, vocal cords paralysis) to systemic manifestations (itchiness, sweating).

Conclusions

First of all, in the current study, our findings showed significant differences in the rate of AEFIs experienced by gender, with more women's symptoms, after both doses. Hence, after immunisation with the COVID-19 vaccine, women seemed to experience and report more AEFIs than men (11, 12), supporting the importance of sex-dependent differences in vaccine-induced immunity and explicitly addressing the role of sex as a modulator of humoral immunity (13). Our findings are consistent with the commonly observed sex-based differences in immune function and responses to vaccination: women typically develop higher antibody responses, stronger innate and cellular immunity, and report more adverse immunisation effects than males (14-16). This observed difference should be considered

Table 4. Reported symptoms.

Symptoms	N (% on the responders) COVID-19 vaccine first dose			N (% on the responders) COVID-19 vaccine second dose			N (% on the responders) COVID-19 vaccine	z test (first vs second dose)
	Total	NS	S	Total	NS	S		
Injection site pain	861 (73.7)	817	44	1,061 (71.2)	1,018	43	1,922 (72.3)	p=0.28
Injection site swelling	148 (12.7)	148	0	221 (14.8)	217	4	369 (13.9)	p=0.11
Fever	91 (7.8)	82	9	542 (36.4)	484	58	633 (23.9)	p<0.01
Fatigue	342 (29.3)	328	14	926 (62.1)	831	95	1,268 (47.7)	p<0.01
Chills	144 (12.3)	136	8	499 (33.5)	447	52	643 (24.2)	p<0.01
Headache	233 (19.9)	212	21	598 (40.1)	532	66	831 (31.3)	p<0.01
Nausea	58 (5.0)	58	0	182 (12.2)	174	8	240 (9.0)	p<0.01
Diarrhoea	27 (2.3)	25	2	62 (4.2)	59	3	89 (3.3)	p=0.01
Myalgia	170 (14.6)	160	10	580 (38.9)	514	66	750 (28.2)	p<0.01
Arthralgia	114 (9.8)	104	10	455 (30.5)	397	58	569 (21.4)	p<0.01
Swollen lymph nodes	48 (4.1)	45	3	142 (9.5)	135	7	190 (7.1)	p<0.01
Dizziness	70 (6.0)	64	6	164 (11.0)	157	7	234 (8.8)	p<0.01
Face asymmetry	3 (0.3)	2	1	8 (0.5)	7	1	11 (0.4)	p=0.26
Widespread itch	10 (0.9)	8	2	25 (1.7)	25	0	35 (1.3)	p=0.03
Urticaria	11 (0.9)	10	1	27 (1.8)	27	0	38 (1.4)	p=0.03
Asthma	7 (0.6)	6	1	13 (0.9)	13	0	20 (0.8)	p=0.42
Choking sensation	8 (0.7)	0	8	11 (0.7)	0	11	19 (0.7)	p=0.87
Others	87 (7.4)	82	5	103 (6.9)	87	16	190 (7.1)	p=0.61
Responders	1,168			1,491			2,659	
Total reported symptoms	2,432	2,287	145	5,619	5,124	495	8,051	
Mean of AEFI per responder	2,08	1,96	0,12	3,77	3,44	0,33	3,03	

AEFI: adverse events following immunization; NS: non-severe; S: severe.

in clinical vaccine studies to identify ways to reduce AEFIs in females, increase immune responses in males, and address potential risks and hesitancy in vaccination campaign implementation. Nevertheless, even though we can assume that those who experienced symptoms were more likely to report adverse events and, consequently, more represented among responders, our sample was not representative of the sex distribution of the study population involved.

Secondly, younger vaccinees seemed to suffer more AEFIs than the older ones, maybe due to higher vaccine-induced immunological activation. This result coincides with the observations reported by the Centers for Disease Control and Prevention (CDC) in the USA (12). Concerning age, our responders' sample is representative of the study population, supporting the fact that the lower rate of reported AEFIs is due to the impaired vaccine responses in older individuals for inflammaging and immunosenescence (17-21). Thus, these results are hopefully not related to the vaccine efficacy in older people. In this context, key information on vaccines' safety and efficacy in the elderly need

to be acquired retrospectively through usual pharmacovigilance surveillance systems and epidemiological studies. However, no design could substitute for the information that could have been collected in more inclusive randomised controlled trials (22).

Thirdly, we can state that the second dose was less well tolerated than the first one and produced a higher number of AEFIs per vaccinee. Moreover, our results confirmed that AEFIs in both sexes were more common after the second dose, consistently with the previous findings from clinical trials and national safety surveillance systems (12, 23).

After the second dose, we observed a significantly higher number of systemic AEFIs (fever, fatigue, headache and myalgia, among others) in total and self-reported severe ones. Local symptoms did not have significant variations between the two doses. Allergic symptoms were not often reported and did not vary between the two doses of the vaccine: no cases of anaphylaxis have been reported in the sample, as observed in other populations (24). These observations are unanimous with those of safety reported in the major clinical trials of Comirnaty® (the rate of systemic symptoms was higher after the second dose) and the first published reports of the national surveillance systems after the start of the immunisation campaign (11, 12, 23, 25-27): reported symptoms were as common as expected, and post-vaccine symptoms (both systemic and local) often dissolved in 1-2 days from the injection.

The non-significant association observed between professional category (healthcare workers vs non-healthcare workers) and adverse events supports the biological explanations of the previously discussed findings.

Finally, unusual symptoms signalled and collected as "others" have not been yet reported in clinical trials (11), such as hypotension, hypertension, bradycardia, palpitations, thoracic pain, herpes simplex reactivation, dysgeusia, trigeminal neuralgia, photophobia, tinnitus, sleep disturbances, monolateral hearing loss, vocal cords paralysis, itchiness and sweating.

Our findings highlighted no significant safety issues after Comirnaty® vaccination and endorsed the value of an analytic self-reported infrastructure to support near real-time monitoring of adverse events and safety during rapid vaccine deployment.

Within the study's strengths, our data are grounded on a very large number of observations, particularly compared to the total eligible population (28): our final sample size of more than 2,500 submitted questionnaires covered nearly a fourth of the administered doses (29), and this is quite a unique feature among available evidence on the topic. Moreover, we modelled our questionnaire on the data reported in published clinical trials on the same vaccine. Still, we collected information on a broader range of possible symptoms to explore less frequent manifestations. Furthermore, we could rely upon a study population of healthcare professionals and other hospital or university staff and, therefore, on a significant experience and knowledge in identifying and evaluating symptoms.

It is worthwhile looking at the possible limitations of our study. The study's cross-sectional design and lack of available data on non-responders are the main limitations. Our study employed a voluntary-based electronic questionnaire to collect data instead of a face-to-face questionnaire, resulting in possible bias during the questionnaire's completion. The self-reported nature of suspected side effects in individuals represents another potential limitation, as reporting a medical issue after vaccination does not necessarily imply causality but might have been caused by other health-related problems. Finally, respondents self-reported the symptoms as mild, moderate or severe, without formalised criteria on the severity. This observational study allows us to evaluate only short-term side-effects, and long-term surveillance is required to investigate possible future consequences.

In line with other studies, our results suggested that pain at the injection site was the most common AEFI with the first authorised COVID-19 vaccine. Short-term AEFIs are moderate in frequency, mild in severity and short-lived. AEFIs were more commonly reported after the second dose of vaccine, in women and among younger responders. Some other AEFIs not yet described in the clinical trials were denounced by our responders.

Even if some aspects of vaccine-induced immune responses need to be further explored, our data support the safe implementation of COVID-19 mass vaccination on the field (30). They could be used to predict to vaccinees the likelihood of side-effects on the basis of

their age and sex and allow the risk profiling for each individual in order to build trust and address concerns of vaccine-hesitant people, with the aim of promoting vaccination adherence (31).

Acknowledgements: For their contribution to the successful staff vaccination organisation, we would like to thank all the members of the IRCCS San Raffaele Hospital healthcare directorate (Dr Alberto Ambrosio, Dr Roberts Mazzucconi, Dr Salvatore Mazzitelli, Dr Maria Paola Garancini, Dr Davide Di Napoli, Dr Anna Rossetti, Dr Rosanna Mantecca and Dr Camilla Zandalasini).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Signorelli C, Scognamiglio T, Odone A. COVID-19 in Italy: impact of containment measures and prevalence estimates of infection in the general population. Acta Biomed. 2020;91(3-s):175-9.
2. Amerio A, Aguglia A, Odone A, et al. Covid-19 pandemic impact on mental health of vulnerable populations. Acta Biomed. 2020;91(9-s):95-6.
3. Odone A, Delmonte D, Scognamiglio T, Signorelli C. COVID-19 deaths in Lombardy, Italy: data in context. Lancet Public Health. 2020;5(6):e310.
4. Signorelli C, Odone A, Gianfredi V, et al. COVID-19 mortality rate in nine high-income metropolitan regions. Acta Biomed. 2020;91(9-s):7-18.
5. COVID-19 vaccines 2021 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
6. Burgess RA, Osborne RH, Yongabi KA, et al. The COVID-19 vaccines rush: participatory community engagement matters more than ever. Lancet. 2021;397(10268):8-10.
7. Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT04368728.
8. EMA recommends first COVID-19 vaccine for authorisation in the EU 2021 [Available from: https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu.
9. COVID-19 vaccines: authorised 2021 [Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised#authorised-covid-19-vaccines-section.
10. National Pharmacovigilance Network 2021 [Available from: https://www.aifa.gov.it/en/rete-nazionale-di-farmacovigilanza.
11. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
12. Gee J, Marquez P, Su J, et al. First Month of COVID-19 Vaccine Safety Monitoring - United States, December 14, 2020-January 13, 2021. MMWR Morb Mortal Wkly Rep. 2021;70(8):283-8.
13. Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G. Sex differences in vaccine-induced humoral immunity. Semin Immunopathol. 2019;41(2):239-49.
14. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg. 2015;109(1):9-15.
15. Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. Ann Ist Super Sanita. 2016;52(2) :198-204.
16. Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and Gender Differences in the Outcomes of Vaccination over the Life Course. Annu Rev Cell Dev Biol. 2017;33:577-99.
17. Pinti M, Appay V, Campisi J, et al. Aging of the immune system: Focus on inflammation and vaccination. Eur J Immunol. 2016;46(10):2286-301.
18. Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol. 2014;30(1):16-22.
19. Gustafson CE, Kim C, Weyand CM, Goronzy JJ. Influence of immune aging on vaccine responses. J Allergy Clin Immunol. 2020;145(5):1309-21.
20. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. Semin Immunol. 2018;40:83-94.
21. Crooke SN, Ovsyannikova IG, Poland GA, Kennedy RB. Immunosenescence: A systems-level overview of immune cell biology and strategies for improving vaccine responses. Exp Gerontol. 2019;124:110632.
22. Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age Ageing. 2021;50(2):279-83.
23. Fifth AIFA report on surveillance of COVID-19 vaccines 2021 [Available from: https://www.aifa.gov.it/en/-/quinto-rapporto-aifa-sulla-sorveglianza-dei-vaccini-covid-19.
24. Bardenheier BH, Gravenstein S, Blackman C, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents. Vaccine. 2021.
25. Jęśkowiak I, Wiatrak B, Grosman-Dziewiszek P, Szeląg A. The Incidence and Severity of Post-Vaccination Reactions after Vaccination against COVID-19. Vaccines (Basel). 2021;9(5).
26. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. Jama. 2021;325(11):1101-2.

27. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33(36):4398-405.
28. Menni C, Klaser K, May A, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis. 2021.
29. Djanas D, Yusirwan, Martini RD, et al. Survey data of COVID-19 vaccine side effects among hospital staff in a national referral hospital in Indonesia. Data Brief. 2021;36:107098.
30. Gianfredi V, Pennisi F, Lume A, et al. Challenges and Opportunities of Mass Vaccination Centers in COVID-19 Times: A Rapid Review of Literature. Vaccines. 2021;9(6):574.
31. Rief W. Fear of Adverse Effects and COVID-19 Vaccine Hesitancy: Recommendations of the Treatment Expectation Expert Group. JAMA Health Forum. 2021;2(4):e210804-e.

Correspondence:
Received: 29 August 2021
Accepted: 10 September 2021
Giacomo Pietro Vigezzi, MD
School of Medicine
Vita-Salute San Raffaele University
Via Olgettina, 58
Milan, 20122 Italy
Phone: 0226431
E-mail: gvigezzi@hotmail.com

APPENDIX

Supplementary Table S1. Complete questionnaire administered.

Questions	Possible answers	Severity	Time of insurgence	Duration
1 Date of birth				
2 Sex	Male			
	Female			
3 Working area	Healthcare professionals			
	Administrative staff			
	Researchers			
	University employees			
	Others			
4 Type of vaccine	Comirnarty®			
	Moderna			
5 Vaccine's dose	First			
	Second			
6 Adverse events following immunization	Any adverse event			
	Adverse event			
7 Local adverse events	Injection site pain	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Injection site swelling	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
8 Systemic adverse events	Fever	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Fatigue	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Chills	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	

Questions	Possible answers	Severity	Time of insurgence	Duration
	Headache	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Nausea	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Diarrhoea	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Myalgia	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Arthralgia	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Swollen lymph nodes	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Dizziness	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Face asymmetry	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	

Questions	Possible answers	Severity	Time of insurgence	Duration
9 Allergic adverse	Urticaria anaphylaxis	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Asthma	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Choking sensation	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
	Anaphylaxis	Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
10 Other adverse events 1		Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	
11 Other adverse events 2		Mild	0-30 min	<1 hour
		Moderate	first 24 hours	1-24 hours
		Severe	24-72 hours	24-72 hours
			4-7 days	>72 hours
			>7 days	

Supplementary Table S2. Reported adverse events following immunization (AEFI) by severity and type (systemic or local) in the subsample of 554 responders who answered the questionnaire both after the first and the second dose of vaccine.

	No. (%) COVID-19 vaccine first dose	No. (%) COVID-19 vaccine second dose	No. corresponding COVID-19 vaccine administrations	Z test
Reporting at least one severe systemic AEFI	19 (3.4)	67 (12.1)	86	p<0.01
Reporting only non-severe systemic AEFIs	220 (39.7)	355 (64.1)	575	p<0.01
Reporting only local AEFIs	227 (41.0)	70 (12.6)	297	p<0.01
Reporting no AEFIs	88 (15.9)	62 (11.2)	150	p<0.02
Total	554 (100)	554 (100)	1,108	

Supplementary Table S3. Time of insurgence and duration of reported adverse events following immunization (AEFI).

	COVID-19 vaccine first dose				COVID-19 vaccine second dose			
	Insurgence in the first 24 hours	Insurgence after the first 24 hours	Duration of symptoms 0-24 h	Duration of symptoms >24 h	Insurgence in the first 24 hours	Insurgence after the first 24 hours	Duration of symptoms 0-24 h	Duration of symptoms >24 h
Injection site pain	761	57	375	421	879	67	462	462
Injection site swelling	123	14	69	61	167	22	103	79
Fever	39	34	45	26	359	97	306	130
Fatigue	218	80	161	129	598	162	376	363
Chills	82	36	89	28	316	82	275	110
Headache	131	52	112	71	386	102	287	185
Nausea	33	13	31	17	106	37	97	37
Diarrhoea	10	10	8	12	28	16	31	14
Myalgia	94	42	63	71	361	92	241	202
Joint pain	56	36	39	54	290	72	196	158
Swollen lymph nodes	9	22	4	33	50	62	27	88
Dizziness	41	17	36	19	109	26	74	56
Face asymmetry	0	2	0	2	0	4	0	4
Widespread itch	5	4	2	4	11	8	3	8
Urticaria	3	8	0	10	9	15	2	14
Asthma	4	1	0	1	5	6	0	6
Choking sensation	4	1	2	0	2	5	2	3
Others	54	20	0	14	54	29	0	13