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

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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 $\chi^2$ 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, 95% CI 2.53–4.41, p<0.01).

### 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 (%) reporting AEFIs       | N (%) reporting AEFIs       |
|                                       | N (%) not reporting AEFIs            | Total                       | N (%) not reporting AEFIs   | Total                       | N (%) not reporting AEFIs |
| 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                        |
| χ² test                               | 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                             |
| χ² test                               | 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                       |                             |                             |
| 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

*aadjusted 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    | 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 AEFIIs 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 AEFIIs 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 AEFIIs 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).

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**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            | >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.

| Reporting at least one severe systemic AEFI | No. (%) COVID-19 vaccine first dose | No. (%) COVID-19 vaccine second dose | No. corresponding COVID-19 vaccine administrations | Z test |
|--------------------------------------------|-------------------------------------|--------------------------------------|---------------------------------------------------|--------|
| 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                         | 16                           | 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                         |