



# A Cross-Sectional Study of Untoward Reactions Following Homologous and Heterologous COVID-19 Booster Immunizations in Recipients Seventeen Years of Age and Older

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## Abstract

A booster dose after primary COVID-19 vaccination series was considered crucial after the emergence of the B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants. Active surveillance was used to investigate reporting of adverse events post-booster dose of either of the licensed mRNA Comirnaty (Pfizer/BioNTech) or Spikevax (Moderna) vaccines in adult (17 years and older) recipients in central Italy. Eligible participants were enrolled and interviewed via phone using a structured questionnaire. Primary outcomes related to the occurrence of adverse events post-booster were stratified by vaccine, and frequency of local/systemic, mild/moderate/severe events. Of a total of 622 participants interviewed, 554 (89.1%) reported at least one adverse event (88.2% and 92.9% after the Comirnaty or Spikevax vaccine, respectively): 63.4% were female, and 78.5% aged 17 to 64 years, regardless of vaccine. 87.7% and 68.2% of all recipients described at least one local or systemic reaction, respectively: 97.3, 38.6 and 4.7% reported mild, moderate, or severe events, respectively. The most frequent adverse reactions were pain, redness, or swelling at the injection site and fatigue, while malaise and fever significantly occurred after the Comirnaty, and vomiting after the Spikevax booster. Compared to the primary vaccination, lymphadenopathy was more common after the booster ( $p < 0.001$ ), especially after Comirnaty vaccine. The study findings revealed no serious or unexpected adverse events, and are in agreement with data available on booster dose for both mRNA vaccines. The transient, mild to moderate, and common to very common side reactions reported should be used to reassure potential recipients of the lack of safety concerns.

**Keywords** Active surveillance · Adverse reactions · COVID-19 booster vaccination · Comirnaty · Spikevax · Safety

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## Introduction

In November 2021, the U.S. Food and Drug Administration (FDA) amended the emergency use authorizations for mRNA COVID-19 vaccines (BNT162b2, Comirnaty/Pfizer-BioNTech and Spikevax/Moderna) with the use of a single booster dose after the completion of primary vaccination course [1]. In Italy, through the decree law 07 January 2022, n. 1, COVID-19 vaccination (primary course or booster) vaccination was made mandatory by the Italian Minister of Health for all subjects who have reached the age of 50 years. The importance of a booster vaccine dose was strongly recommended after the emergence of the B.1.1.529 (Omicron) SARS-CoV-2 variant in late November 2021 [2], and the rapid surge of cases of infection with this variant globally. A higher neutralization efficiency (by a factor of 100) against Omicron following the booster as compared to after the second dose was demonstrated, although even with three doses, neutralization against this variant was lower (by a factor of 4) than that against the previous Delta variant [3].

In this study, active surveillance of adverse reactions after receiving a booster dose of COVID-19 mRNA vaccines was conducted amongst the general population aged 17 years and above in central Italy, to investigate factors linked to adverse effects and whether reactions were different from the primary course.

## Methods

This was a retrospective study based on data anonymously collected from subjects who had received a booster vaccine dose in the Molise Region, central Italy, between November 2021 and January 2022. Vaccine recipients were contacted at the hospital vaccinal centre and signed an informed consent on the day of vaccination agreeing to the study aims. At least a week later from the booster receipt, trained interviewers contacted recipients by telephone and administered a standard questionnaire, which was based on that used in a previous survey [4] and validated in a pilot study (data not shown). This questionnaire collected sociodemographic data, details of pre-existing diseases and treatment, seasonal flu vaccination, COVID-19 history, primary vaccination course, as well as occurrence/resolution of adverse events after the booster dose. Results were further compared to previous reactions after the primary vaccination. Adverse events following the booster dose of Comirnaty or Spikevax vaccines were categorized as local (injection site pain, redness, or swelling, lymphadenopathy, and pain in a limb other than that injected), and

systemic reactions (malaise, fatigue, asthenia, muscle/joint pain, paraesthesia, headache, fever, chills, diarrhoea, nausea, vomiting, sleep disorders, and rash). The level of severity of post-booster reactions were stratified as previously described [4] as mild (injection site pain, redness, and swelling, fatigue, headache, chills, nausea, sleep disorders, asthenia, general malaise, and fever < 38.5 °C), moderate (lymphadenopathy, muscle/joint pain, rash, vomiting, diarrhoea, and pain in a limb other than that injected), or severe (paraesthesia, and fever > 38.5 °C). The frequency of reported adverse reactions was classified as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to < 1/10), and uncommon ( $\geq 1/1000$  to < 1/100), as reported by the European Medicines Agency for Comirnaty [5] and Spikevax [6]. Data on adverse event frequencies were analysed on these two brands of vaccine through univariate analysis using Chi-square or Fisher's Exact tests (SPSS software, version 28.0) with a level of significance at 0.05. Any association between relevant factors and adverse effects was assessed through logistic regression.

## Results

### Characteristics of the Study Sample

Between November 2021 and the beginning of January 2022, consent to participate was obtained from 876 subjects after receipt of mRNA COVID-19 boosters; however, 254 (29%) were not available for follow-up 7 or more days later. Thus, the study included data from 622 vaccine recipients (71% response rate), mean age 52 years (standard deviation 15.6, median 54, range 17–86 years), of whom 61.9% ( $n = 385$ ) were aged 50 years or above. Sixty-one percent ( $n = 379$ ) of participants were female, 39% ( $n = 243$ ) were attended high school, and 38% ( $n = 235$ ) held graduate or post-graduate qualifications and were professionally employed whilst 19% ( $n = 120$ ) were retired. Of the study participants, 145 (14.5%) suffered from allergies, and 272 (43.7%) from underlying chronic diseases (74.6% and 25.4% with one and  $\geq$  two conditions, respectively). The most frequent underlying chronic diseases were cardiovascular ( $n = 109$ , 17.5%), endocrine ( $n = 40$ , 6.4%), or both ( $n = 28$ , 4.5%). Of the 622 booster recipients, 32.3% ( $n = 201$ ; mean age  $60.6 \pm 14.8$  years; median 65, mode 75 years) had also received seasonal influenza vaccination, 60.2% were female and 51.2% were  $\geq 65$  years of age: in the group  $\geq 65$  years, the mean/median age was 72, and mode 75 years.

### SARS-CoV-2 Infection and COVID-19 Vaccination

Overall, 16 (2.6%) of the booster recipients reported previous SARS-CoV-2 infection. Forty-eight percent ( $n = 300$ )

reported a homologous primary 2-dose mRNA vaccination, with Comirnaty ( $n=242$ , 80.7%) or Spikevax ( $n=58$ , 19.3%) vaccines, followed by 46% ( $n=286$ ) homologous primary viral vector series, with 2-doses of Vaxzevria (AstraZeneca) ( $n=253$ , 88.5%), or one shot of the Janssen ( $n=33$ , 11.5%) vaccine. Furthermore, 21 (3.4%) and 15 (2.4%) recipients received a heterologous primary vaccination or only one dose due to previous COVID-19 history, respectively. Eighty percent ( $n=499$ ) of the 622 recipients reported received their booster dose during December 2021, and 19.5% ( $n=121$ ) during November, with Comirnaty ( $n=510$ , 82.0%) and Spikevax ( $n=112$ , 18%). Compared to the last dose (with mRNA or viral vector vaccine), 53.7% ( $n=334$ ) of subjects had a homologous vaccination receiving the booster shot.

### Adverse Events Reported After the Booster Dose

Following the receipt of the booster vaccination, 554 (89.1%) out of 622 participants reported at least one adverse event (mean  $2.6 \pm 2.3$ , median 2, range 1–13). These were reported more often by female than male subjects (63.4% vs 36.6%,  $p < 0.001$ ), while there was no significant difference between the frequency of adverse reactions amongst recipients younger than 50 years in comparison with those of 50 years or older ( $p=0.194$ ). Irrespectively of the vaccine brand, booster recipients aged below 64 years experienced more frequent adverse reactions than those 65 years and above (78.5% vs 21.5%); this effect was detected following both the Comirnaty (79.3% vs 20.7%) and the Spikevax booster (75.0% vs 25.0%). For 68 (10.9%) of recipients, no post-booster reactions were reported. Significant differences in the reporting of at least one adverse event were observed for homologous and heterologous vaccination in relation to the last dose received (85.9% homologous vs 92.7% heterologous vaccination,  $p=0.007$ ). All except one (93.4%) of the subjects who had a history of COVID-19 infection reported at least one adverse reaction. Among all individuals with an adverse event, 239 (43.1%) had at least one comorbidity but this frequency was not statistically different from those without underlying illnesses ( $p=0.192$ ). Twenty-one percent ( $n=128$ ) of individuals with at least one adverse reaction suffered from allergies, and this was not significantly different compared to those without allergies ( $p=0.727$ ).

Of the 554 recipients reporting post-booster adverse events, 30.8% and 69.1% had or had not received seasonal influenza vaccination and these proportions were significantly different ( $p=0.027$ ). Conversely, there was no significant difference ( $p=0.855$ ) between the 62.1% of individuals who reported adverse events who were undergraduates as compared to the remaining 37.9% with degree or post-degree qualifications ( $p=0.855$ ). Overall, 36 (5.8%) of recipients had received medication before receiving booster,

78% of which was self-prescribed and included paracetamol. Furthermore, 210 (37.9%) out of the 554 recipients who reported adverse reactions received medical treatment post-immunization, which also included the use of paracetamol ( $n=165$ , 78.6%), or non-steroidal anti-inflammatory (NSAIDs) ( $n=25$ , 11.9%), or a combination of paracetamol and NSAIDs ( $n=20$ , 9.5%). After the booster dose, 31 (5.0%) recipients reported adverse reactions to the formal surveillance system, 28 of which to their general practitioners, one to both family physician and pharmacist, and one each to a competent medical doctor and to the national pharmacovigilance passive system.

### Description of Adverse Reactions Reported by Vaccine Recipients

Eighty-one percent ( $n=450$ ) of 554 recipients reported adverse reactions following the Comirnaty vaccine, while 18.8% ( $n=104$ ) after Spikevax booster ( $p=0.156$ ). According to the vaccine received, at least one adverse reaction was reported by 88% of 510 Comirnaty recipients, and injection site pain, redness, or swelling was the most frequent (71.1%) reaction, followed by fatigue (28.6%), muscle/joint pain (24.7%), malaise (22.0%), or headache (21.2%). Additional symptoms were reported in the minority of participants (Table 1). After booster with Spikevax vaccine, 104 (92.8%) of 112 recipients reported at least one adverse reaction, and similarly to Comirnaty, pain, redness or swelling at the injection site was the most frequent ( $n=87$ , 77.7%) reaction, followed by fatigue (34.8%), malaise (33.9%), muscle/joint pain (31.3%), fever (28.6%), headache (27.7%), and chills (25.0%, Table 1). Significant differences between post-booster reactions and vaccine type were observed for malaise and pyrexia ( $p=0.007$ ), and vomiting ( $p < 0.001$ ) (Table 1). Adverse reactions after either Comirnaty or Spikevax boosters were more frequently reported by female subjects.

The side reactions were mainly reported after 4–12 h from receipt of the booster dose, except for rash (Table 2a). Resolution was  $< 12$  h from the onset only for vomiting, while almost all reactions resolved after 12–24 h (Table 2b).

Pain, redness, or swelling at the injection site and fatigue were confirmed as the most frequent adverse reactions after both the primary vaccination series and the booster. Comparing to the primary 2-doses, a significant increase of lymphadenopathy was reported after booster, while malaise, fatigue, asthenia, headache, and fever decreased (Table 3).

Irrespectively of the vaccine manufacturer, among the 554 subjects who reported adverse reactions after the booster, 87.7% ( $n=486$ ) and 68.2% ( $n=378$ ) described at least one local (1 to 3 events) and systemic (1 to 12 events) reaction, respectively, and were more frequently reported by female than male subjects (62.6% and 70.4%,  $p < 0.001$ ).

**Table 1** Adverse events following a booster dose with mRNA COVID-19 vaccines stratified by sex and brand

| Adverse reaction                            | Booster dose of mRNA vaccines (n=622) |              |            | p-value            | Comirnaty<br>booster (n = 510) | Spikevax<br>booster<br>(n = 112) | p-value          |
|---|---------------------------------------|--------------|------------|--------------------|--------------------------------|----------------------------------|------------------|
|   | Total N (%)                           | Female N (%) | Male N (%) |                    | N (%)                          | N (%)                            |                  |
| <i>Mild</i>                                 |                                       |              |            |                    |                                |                                  |                  |
| Injection site pain/redness/swelling        | 472 (75.9)                            | 295 (62.5)   | 177 (37.5) | 0.155              | 385 (75.5)                     | 87 (77.7)                        | 0.624            |
| Malaise                                     | 150 (24.1)                            | 94 (62.7)    | 56 (37.3)  | 0.617              | 112 (22.0)                     | 38 (33.9)                        | <b>0.007</b>     |
| Fatigue                                     | 186 (29.9)                            | 130 (69.9)   | 56 (30.1)  | <b>0.003</b>       | 147 (28.8)                     | 39 (34.8)                        | 0.209            |
| Asthenia                                    | 70 (11.2)                             | 53 (75.7)    | 17 (24.3)  | <b>0.007</b>       | 52 (10.2)                      | 18 (16.1)                        | 0.074            |
| Headache                                    | 139 (22.3)                            | 103 (74.1)   | 36 (25.9)  | <b>&lt;0.001</b>   | 108 (21.2)                     | 31 (27.7)                        | 0.134            |
| Chills                                      | 121 (19.4)                            | 90 (74.4)    | 31 (25.6)  | <b>&lt;0.001</b>   | 93 (18.2)                      | 28 (25.0)                        | 0.101            |
| Nausea                                      | 37 (5.9)                              | 32 (86.5)    | 5 (13.5)   | <b>0.001</b>       | 26 (5.1)                       | 11 (9.8)                         | 0.056            |
| Fever <38.5 °C                              | 121 (19.4)                            | 89 (73.6)    | 32 (26.4)  | <b>0.002</b>       | 89 (17.5)                      | 32 (28.6)                        | <b>0.007</b>     |
| Sleep disorders                             | 47 (7.6)                              | 36 (76.6)    | 11 (23.4)  | <b>0.022</b>       | 34 (6.7)                       | 13 (11.6)                        | 0.073            |
| <i>Moderate</i>                             |                                       |              |            |                    |                                |                                  |                  |
| Muscle/joint pain                           | 161 (25.9)                            | 121 (75.1)   | 40 (24.9)  | <b>&lt;0.001</b>   | 126 (24.7)                     | 35 (31.3)                        | 0.152            |
| Lymphadenopathy                             | 50 (8.0)                              | 38 (76.0)    | 12 (24.0)  | <b>0.023</b>       | 41 (8.0)                       | 9 (8.0)                          | 0.849            |
| Pain in a limb other than site of injection | 24 (3.9)                              | 17 (70.8)    | 7 (29.2)   | 0.311              | 18 (3.5)                       | 6 (5.4)                          | 0.363            |
| Diarrhoea                                   | 19 (3.0)                              | 14 (73.7)    | 5 (26.3)   | 0.247              | 15 (2.9)                       | 4 (3.6)                          | 0.725            |
| Vomiting                                    | 6 (1.0)                               | 5 (83.3)     | 1 (16.7)   | 0.412 <sup>a</sup> | 1 (0.2)                        | 5 (4.5)                          | <b>&lt;0.001</b> |
| Rash  | 10 (1.6)                              | 8 (80.0)     | 2 (20.0)   | 0.330 <sup>a</sup> | 6 (1.2)                        | 4 (3.6)                          | 0.068            |
| <i>Severe</i>                               |                                       |              |            |                    |                                |                                  |                  |
| Paraesthesia                                | 26 (4.2)                              | 21 (80.8)    | 5 (19.2)   | <b>0.034</b>       | 20 (3.9)                       | 6 (5.4)                          | 0.491            |

p-value were calculated using Chi-square test

Significant values for  $p < 0.05$  are reported in bold

<sup>a</sup>Fisher's Exact test

There were no significant differences in the frequency of local ( $p=0.202$ ) and systemic ( $p=0.354$ ) reactions after booster doses either after the Comirnaty or Spikevax.

With respect to the grade of severity, 97.3% of recipients reported mild adverse events, whilst moderate and severe reactions by 38.6% and 4.7% of subjects, respectively. Participants who received a booster dose with Comirnaty mostly reported reactions classified as common, while lymphadenopathy defined as an uncommon event was reported by 41 (8.0%) subjects. After the Spikevax booster, recipients largely reported reactions categorized as very common, and diarrhoea and rash described amongst the common events.

## Discussion

Large-scale vaccination represents the most important and effective public health strategy against COVID-19, and its efficacy strongly relies on protection against the emerging SARS-CoV-2 variants [7]. Indeed, the rapid dissemination of the Delta and then the Omicron variants, characterized by high infectivity and transmissibility, has prompted

vaccination policy to consider and promote the administration of a booster dose [8]. Evidence shows that a booster vaccination significantly increased neutralizing antibody titres against circulating variants of concern [9], because of the waning levels in previously vaccinated or infected subjects [10].

The present study retrospectively explored adverse reactions following the booster dose with mRNA-based vaccines among 622 recipients seventeen years of age and older, who had a complete primary vaccination cycle. Monitoring of reactions to COVID-19 vaccines in the “real world” by an active surveillance approach can provide more detailed information than passive surveillance systems about local and systemic events; furthermore, data related to different vaccine combinations may not be detected through passive pharmacovigilance.

Results obtained through active surveillance on 510 booster recipients who had received Comirnaty revealed that pain at the injection site was the most reported reaction, in line with data from a trial among approximately 300 adults [11]. Therefore, within the top five side events after Comirnaty booster, the surveyed recipients described reactions including pain at the injection site, fatigue, muscle/

**Table 2** Timing of (a) onset and (b) resolution of adverse reactions following the receipt of an additional booster dose of mRNA COVID-19 vaccines

| (a) Onset                                   | < 1 h           | 1–4 h            | 4–12 h            | 12–48 h   | 24–48 h         | > 48 h   | Total |
|---|-----------------|------------------|-------------------|-----------|-----------------|----------|-------|
| <i>Mild</i>                                 |                 |                  |                   |           |                 |          |       |
| Injection site pain/redness/swelling        | 16 (3.4)        | 142 (30.1)       | <b>225 (47.7)</b> | 75 (15.9) | 12 (2.5)        | 2 (0.4)  | 472   |
| Malaise                                     |                 | 23 (15.4)        | <b>62 (41.3)</b>  | 50 (33.3) | 15 (10.0)       |          | 150   |
| Fatigue                                     |                 | 34 (18.3)        | <b>78 (41.9)</b>  | 57 (30.6) | 16 (8.6)        | 1 (0.6)  | 186   |
| Asthenia                                    |                 | 12 (17.1)        | <b>38 (54.3)</b>  | 16 (22.8) | 4 (0.6)         |          | 70    |
| Headache                                    | 2 (1.4)         | 22 (15.8)        | <b>64 (46.0)</b>  | 42 (30.2) | 9 (6.4)         |          | 139   |
| Chills                                      |                 | 14 (11.6)        | <b>65 (53.7)</b>  | 32 (26.4) | 9 (7.4)         | 1 (0.8)  | 121   |
| Nausea                                      |                 | 6 (16.2)         | <b>17 (45.9)</b>  | 11 (29.7) | 3 (8.1)         |          | 37    |
| Fever < 38.5 °C                             |                 | 10 (8.2)         | <b>61 (50.4)</b>  | 40 (33.0) | 9 (7.4)         | 1 (0.8)  | 121   |
| Sleep disorders                             |                 | 5 (10.6)         | <b>24 (51.1)</b>  | 16 (34.1) | 1 (2.1)         | 1 (2.1)  | 47    |
| <i>Moderate</i>                             |                 |                  |                   |           |                 |          |       |
| Muscle/joint pain                           | 1 (0.6)         | 20 (12.4)        | <b>79 (49.0)</b>  | 52 (32.3) | 9 (5.6)         |          | 161   |
| Lymphadenopathy                             | 1 (2.0)         | 1 (2.0)          | <b>18 (36.0)</b>  | 17 (34.0) | 9 (18.0)        | 4 (8.0)  | 50    |
| Pain in a limb other than site of injection |                 | 7 (29.3)         | <b>11 (45.8)</b>  | 2 (8.3)   | 2 (8.3)         | 2 (8.3)  | 24    |
| Diarrhoea                                   | 1 (5.2)         | 2 (10.5)         | <b>7 (36.8)</b>   | 5 (26.3)  | 3 (15.8)        | 1 (5.2)  | 19    |
| Vomiting                                    |                 |                  | <b>5 (83.4)</b>   | 1 (16.6)  |                 |          | 6     |
| Rash  |                 | <b>3 (30.0)</b>  | <b>3 (30.0)</b>   | 1 (10.0)  | 1 (10.0)        | 2 (20.0) | 10    |
| <i>Severe</i>                               |                 |                  |                   |           |                 |          |       |
| Paraesthesia                                | 3 (11.5)        | 5 (19.2)         | <b>9 (34.6)</b>   | 1 (3.8)   | 6 (23.1)        | 2 (7.7)  | 26    |
| (b) Resolution                              | < 12 h          | 12–24 h          | 24–48 h           | 48–72 h   | > 72 h          | Total    |       |
| <i>Mild</i>                                 |                 |                  |                   |           |                 |          |       |
| Injection site pain/redness/swelling        | 29 (6.1)        | 115 (24.4)       | <b>190 (40.2)</b> | 81 (17.2) | 57 (12.1)       | 472      |       |
| Malaise                                     | 10 (6.7)        | 44 (29.3)        | <b>57 (38.0)</b>  | 30 (20.0) | 9 (6.0)         | 150      |       |
| Fatigue                                     | 11 (5.9)        | 49 (26.3)        | <b>75 (40.3)</b>  | 36 (19.4) | 15 (8.1)        | 186      |       |
| Asthenia                                    | 1 (1.4)         | <b>24 (34.3)</b> | 23 (32.9)         | 12 (17.1) | 10 (14.3)       | 70       |       |
| Headache                                    | 20 (14.4)       | <b>48 (34.5)</b> | 41 (29.5)         | 14 (10.1) | 16 (11.5)       | 139      |       |
| Chills                                      | 26 (21.5)       | <b>51 (42.1)</b> | 32 (26.4)         | 9 (7.4)   | 3 (2.5)         | 121      |       |
| Nausea                                      | 1 (2.7)         | <b>13 (35.1)</b> | 9 (24.3)          | 9 (24.3)  | 5 (13.5)        | 37       |       |
| Fever < 38.5 °C                             | 22 (18.2)       | <b>45 (37.2)</b> | 42 (34.7)         | 9 (7.4)   | 3 (2.5)         | 121      |       |
| Sleep disorders                             | 8 (17.0)        | <b>16 (34.0)</b> | 12 (4.2)          | 7 (14.9)  | 4 (8.5)         | 47       |       |
| <i>Moderate</i>                             |                 |                  |                   |           |                 |          |       |
| Muscle/joint pain                           | 13 (8.1)        | 46 (28.6)        | <b>57 (35.4)</b>  | 28 (17.4) | 17 (10.6)       | 161      |       |
| Lymphadenopathy                             | 3 (6.0)         | 16 (32.0)        | <b>17 (34.0)</b>  | 13 (26.0) | 1 (2.0)         | 50       |       |
| Pain in a limb other than site of injection | 1 (4.2)         | 3 (12.5)         | <b>10 (41.7)</b>  | 4 (16.7)  | 6 (25.0)        | 24       |       |
| Diarrhoea                                   | 5 (26.3)        | <b>9 (47.4)</b>  | 3 (15.8)          |           | 2 (10.5)        | 19       |       |
| Vomiting                                    | <b>3 (50.0)</b> | 1 (16.7)         | 1 (16.6)          | 1 (16.7)  |                 | 6        |       |
| Rash  |                 | 1 (10.0)         | 3 (30.0)          | 1 (10.0)  | <b>5 (50.0)</b> | 10       |       |
| <i>Severe</i>                               |                 |                  |                   |           |                 |          |       |
| Paraesthesia                                | 2 (7.7)         | <b>9 (34.6)</b>  | 4 (15.4)          | 4 (15.4)  | 7 (26.9)        | 26       |       |

Most common frequencies are reported in bold

joint pain, headache, and chills, which is consistent with the clinical trial data, although these reactions were found at a lower frequency. Reactions of diarrhoea, vomiting and fever experienced by the study participants were further reported in the trial for the Comirnaty booster, and after the second dose [4]. Recipients also reported reactions that closely reflected the mild or moderate adverse events after

the second Comirnaty dose, as found in a previous study conducted among healthcare workers during the initial phase of the vaccination campaign [4]. However, recipients reported swollen lymph nodes more frequently after the booster than after the second dose of the Comirnaty primary vaccination series (8.0% vs 3.3%). This finding was also supported by a previous study [4] after completion of Comirnaty

**Table 3** Comparison of adverse reactions after the booster dose and previous injections of COVID-19 vaccines

|   | Primary cycle N (%) | Booster dose N (%) | Chi-square test p-value |
|---|---------------------|--------------------|-------------------------|
| <i>Mild</i>                                 |                     |                    |                         |
| Injection site pain/redness/swelling        | 443 (71.2)          | 472 (75.9)         | 0.062                   |
| Malaise                                     | 200 (32.2)          | 150 (24.1)         | <b>0.002</b>            |
| Fatigue                                     | 225 (36.2)          | 186 (29.9)         | <b>0.019</b>            |
| Asthenia                                    | 112 (18.0)          | 70 (11.2)          | <b>&lt; 0.001</b>       |
| Headache                                    | 174 (28.0)          | 139 (22.3)         | <b>0.022</b>            |
| Chills                                      | 141 (22.7)          | 121 (19.5)         | 0.164                   |
| Nausea                                      | 32 (5.1)            | 37 (5.9)           | 0.535                   |
| Fever < 38.5 °C                             | 208 (33.4)          | 121 (19.5)         | <b>&lt; 0.001</b>       |
| Sleep disorders                             | 49 (7.9)            | 47 (7.6)           | 0.832                   |
| <i>Moderate</i>                             |                     |                    |                         |
| Muscle/joint pain                           | 180 (28.9)          | 161 (25.9)         | 0.227                   |
| Lymphadenopathy                             | 17 (2.7)            | 50 (8.0)           | <b>&lt; 0.001</b>       |
| Pain in a limb other than site of injection | 22 (3.5)            | 24 (3.8)           | 0.764                   |
| Diarrhoea                                   | 16 (2.6)            | 19 (3.1)           | 0.607                   |
| Vomiting                                    | 12 (1.9)            | 6 (1.0)            | 0.154                   |
| Rash  | 8 (1.3)             | 10 (1.6)           | 0.635                   |
| <i>Severe</i>                               |                     |                    |                         |
| Paraesthesia                                | 33 (5.3)            | 26 (4.2)           | 0.350                   |

Significant differences for  $p < 0.05$  are reported in bold

vaccination, with cases of lymphadenopathy reported by 2.4% and 6.7% after the first and second dose, respectively, and by data of booster trial with higher rate than the primary series doses (5.2% vs 0.4%) [11].

Pain at the injection site was the most common symptom reported among 112 recipients who received booster dose of Spikevax (77.7%), according to data derived from the clinical trial for booster dose by Moderna (83.8%) [12]. Hence, amongst the top five adverse reactions after Spikevax booster, pain at the injection site, fatigue, muscle/joint pain, and headache were reported by the studied recipients, which were also described among the 167 participants in the booster trial although at higher rates [12]. Indeed, amongst the enrolled recipients all reactions except for fever accounted for significantly lower proportions compared to the clinical trial. Therefore, according to available data [6, 12], the side reactions following booster with Spikevax were similar to those reported in the second injection of the primary vaccination. Lymphadenopathy was reported by 8% of enrolled recipients here, while the reported rate from Spikevax clinical trial was greater (20%), and was most commonly reported among participants aged 18 to 64 years, and increased after the booster dose [12].

According to other data and those collected in the present survey, the rate of reporting of lymphadenopathy after the booster dose of both mRNA vaccines seems to be higher than after the primary vaccination. Indeed, post-anti-COVID-19

vaccine lymphadenopathy was a common event, and both Comirnaty and Spikevax, as well as Vaxzevria vaccine, were reported to induce supraclavicular and axillary lymph nodes, ipsilateral to the injection site, which may mimic pathological lymph nodes [13]. Furthermore, a lymphadenopathy reaction was documented shortly after receiving other vaccines evoking a strong immune system response [14, 15].

In this survey, regardless of vaccine manufacturer, reactions after the booster dose were more frequently reported by women, as found elsewhere [16]. Moreover, adverse reactions in the study population were more frequently reported by recipients of 17 to 64 years compared to those aged 65 years or above, which is consistent with clinical trials for the Comirnaty and Spikevax boosters [11, 12]. For both vaccines, an analogous safety profile was observed from the survey data, as 78% and 78.6% of recipients had local reactions after booster of Comirnaty and Spikevax, respectively, whilst systemic events accounted for 60% and 64.3%. In a preliminary evaluation after a Comirnaty booster in Israel, recipients reported 80% local and 40% systemic reactions [17]. Furthermore, other reports described reactions as milder than previous injections, with increased local but decreased systemic reactions [18]. Although the rate of adverse events after heterologous booster with respect to the last dose received was higher than homologous vaccinations, considering that enrolled recipients had received four different initial vaccine courses (2-doses of Comirnaty,

Spikevax, or Vaxzevria, 1-dose cycle of Janssen or for previous COVID-19 history), both boosting types showed acceptable side-event profiles. These data were consistent with the observations from previous trials demonstrating no safety concerns of homologous or heterologous booster dose [19].

Based on the collected data, the logistic regression did not identify any factors to be associated with the likelihood of adverse reactions following the booster dose. To date, this information is not yet available for booster injections, while vaccine brand, younger age, female sex, and having had COVID-19 before vaccination were associated with greater odds of adverse effects following the primary vaccination cycle [20].

This study was based on active surveillance of reactions to COVID-19 vaccines in a “real world” setting, providing more detailed information about local and systemic reactions than through passive systems. In conclusion, although participant enrolment was voluntary and the study sample may not be representative of the vaccinated population, the study emphasizes the lack of safety concerns related to booster dose for both mRNA vaccines, and is in agreement with data available in the literature. The findings show no unexpected patterns of adverse reactions, even with different combinations of vaccines, which although generally common or very common were transient, mild, or moderate. Furthermore, adverse reactions experienced by booster dose recipients in a routine setting were reported in the minority of subjects and were comparable to that observed in the clinical trials of mRNA booster vaccines. Therefore, these results provide reliable evidence to reassure about the safety profile of COVID-19 boosters and would be useful for risk communication addressing future public health recommendations.

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**Data Availability** The Authors included all the data and material in the study, although they are available for further information whether requested.

**Code Availability** Not applicable.

## Declarations

**Conflict of interest** The Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Ethical Approval** Ethical approval was not requested, as no experimental procedure was applied in this study, and information provided by participants after signing an informed consent were anonymous.

**Consent to Participate** All the study participants signed an informed consent agreeing to provide data and availability for the survey.

**Consent for Publication** The Authors provide the consent for publication data or figure in the manuscript.

## References

1. U.S. Food and Drug Administration. (2021). Coronavirus (COVID-19) Update: FDA expands eligibility for COVID-19 vaccine boosters. U.S. Food and Drug Administration. November 19, 2021. Retrieved December 18, 2021, from <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-covid-19-vaccine-boosters>
2. World Health Organization. (2021). Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern. World Health Organization. November 26, 2021. Retrieved December 7, 2021, from [https://www.who.int/news/item/26-11-2021-classification-of-omicron-\(b.1.1.529\)-sars-cov-2-variant-of-concern](https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern)
3. Nemet, I., Kliker, L., Lustig, Y., Zuckerman, N., Erster, O., Cohen, C., Kreiss, Y., Alroy-Preis, S., Regev-Yochay, G., Mendelson, E., & Mandelboim, M. (2022). Third BNT162b2 vaccination neutralization of SARS-CoV-2 omicron infection. *The New England Journal of Medicine*, 386(5), 492–494. <https://doi.org/10.1056/NEJMc2119358>
4. Ripabelli, G., Tamburro, M., Buccieri, N., Adesso, C., Caggiano, V., Cannizzaro, F., Di Palma, M. A., Mantuano, G., Montemiro, V. G., Natale, A., Rodio, L., & Sammarco, M. L. (2022). Active surveillance of adverse events in healthcare workers recipients after vaccination with COVID-19 BNT162b2 vaccine (Pfizer-BioNTech, Comirnaty): A cross-sectional study. *Journal of Community Health*, 47(2), 211–225. <https://doi.org/10.1007/s10900-021-01039-3>
5. European Medicines Agency. (2022). Comirnaty. Summary of product characteristics. January 12, 2022. Retrieved January 21, 2022, from [https://www.ema.europa.eu/documents/product-information/comirnaty-epar-product-information\\_en.pdf](https://www.ema.europa.eu/documents/product-information/comirnaty-epar-product-information_en.pdf)
6. European Medicines Agency. (2021). Spikevax (previously COVID-19 Vaccine Moderna). Retrieved December 9, 2021, from [https://www.ema.europa.eu/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information\\_en.pdf](https://www.ema.europa.eu/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf)
7. Vasireddy, D., Vanaparthi, R., Mohan, G., Malayala, S. V., & Atluri, P. (2021). Review of COVID-19 variants and COVID-19 vaccine efficacy: What the clinician should know? *Journal of Clinical Medicine Research*, 13(6), 317–325. <https://doi.org/10.14740/jocmr4518>
8. Muik, A., Lui, B. G., Wallisch, A.-K., Bacher, M., Mühl, J., Reinholz, J., Ozhelvacı, O., Beckmann, N., Güimil Garcia, R. C., Poran, A., Shpyro, S., Finlayson, A., Cai, H., Yang, Q., Swanson, K. A., Türeci, Ö., & Şahin, U. (2022). Neutralization of SARS-CoV-2 Omicron by BNT162b2 mRNA vaccine-elicited human

- sera. *Science*, 375(6581), 678–680. <https://doi.org/10.1126/science.abn7591>
9. Wang, X., Zhao, X., Song, J., Wu, J., Zhu, Y., Li, M., Cui, Y., Chen, Y., Yang, L., Liu, J., Zhu, H., Jiang, S., & Wang, P. (2022). Homologous or heterologous booster of inactivated vaccine reduces SARS-CoV-2 Omicron variant escape from neutralizing antibodies. *Emerging Microbes and Infections*, 11(1), 477–481. <https://doi.org/10.1080/22221751.2022.2030200>
  10. Pierobon, A., Dal Zotto, A., Antico, A., De Antoni, M. E., Vianello, L., Gennari, M., Di Caprio, A., Russo, F., Brambilla, G., & Saugo, M. (2022). Outbreak of SARS-CoV-2 B.1.617.2 (Delta) Variant in a nursing home 28 weeks after two doses of mRNA anti-Covid-19 vaccines: Evidence of a waning immunity. *Clinical Microbiology and Infection*, 28(4), 6145.e5-6147.e7. <https://doi.org/10.1016/j.cmi.2021.12.013>
  11. U.S. Food and Drug Administration. (2021). Vaccines and Related Biological Products Advisory Committee meeting. Application for licensure of a booster dose for COMIRNATY (COVID-19 Vaccine, mRNA). November 17, 2021. Retrieved January 10, 2022, from <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine>
  12. U.S. Food and Drug Administration. (2021). Vaccines and related biological products advisory committee meeting. EUA amendment request for a booster dose of the Moderna COVID-19 Vaccine. U.S. Nov 19, 2021. Retrieved Jan 10, 2022, from <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine>
  13. Cocco, G., Delli Pizzi, A., Fabiani, S., Cocco, N., Boccatonda, A., Frisone, A., Scarano, A., & Schiavone, C. (2021). Lymphadenopathy after the anti-COVID-19 Vaccine: Multiparametric ultrasound findings. *Biology (Basel)*, 10(7), 652. <https://doi.org/10.3390/biology10070652>
  14. Studdiford, J., Lamb, K., Horvath, K., Altshuler, M., & Stonehouse, A. (2008). Development of unilateral cervical and supraclavicular lymphadenopathy after human papilloma virus vaccination. *Pharmacotherapy*, 28(9), 1194–1197. <https://doi.org/10.1592/phco.28.9.1194>
  15. Cohen, J., Powderly, W. G., & Opal, S. M. (2017). *Infectious diseases* (4th ed.). Elsevier.
  16. Vassallo, A., Shajahan, S., Harris, K., Hallam, L., Hockham, C., Womersley, K., Woodward, M., & Sheel, M. (2021). Sex and gender in COVID-19 vaccine research: Substantial evidence gaps remain. *Frontiers in Global Women's Health*, 2, 761511. <https://doi.org/10.3389/fgwh.2021.761511>
  17. Gilboa, M., Mandelboim, M., Indenbaum, V., Lustig, Y., Cohen, C., Rahav, G., Asraf, K., Amit, S., Jaber, H., Nemet, I., Kliker, L., Bar-Haim, E., Mendelson, E., Doolman, R., Rubin, C., Regev-Yochay, G., & Kreiss, Y. (2022). Early immunogenicity and safety of the third dose of BNT162b2 mRNA Covid-19 vaccine among adults older than 60 years; real world experience. *Journal of Infectious Diseases*, 225(5), 785–792. <https://doi.org/10.1093/infdis/jiab584>
  18. Rahimi, F., & Bezmin Abadi, A. T. (2021). The third booster vaccination dose against COVID-19: Indication for circulating SARS-CoV-2 variants. *Future Virology*. <https://doi.org/10.2217/fvl-2021-0240>
  19. Munro, A. P. S., Janani, L., Cornelius, V., Aley, P. K., Babbage, G., Baxter, D., Bula, M., Cathie, K., Chatterjee, K., Dodd, K., Enever, Y., Gokani, K., Goodman, A. L., Green, C. A., Harndahl, L., Haughney, J., Hicks, A., van der Klaauw, A. A., Kwok, J., ... COV-BOOST Study Group. (2021). Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): A blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet*, 398(10318), 2258–2276. [https://doi.org/10.1016/S0140-6736\(21\)02717-3](https://doi.org/10.1016/S0140-6736(21)02717-3)
  20. Beatty, A. L., Peyser, N. D., Butcher, X. E., Cocohoba, J. M., Lin, F., Olgin, J. E., Pletcher, M. J., & Marcus, G. M. (2021). Analysis of COVID-19 vaccine type and adverse effects following vaccination. *JAMA Network Open*, 4(12), e2140364. <https://doi.org/10.1001/jamanetworkopen.2021.40364>

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