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Original Article

Adverse reactions to the first and second doses of Pfizer-BioNTech COVID-19 vaccine among healthcare workers

Ayano Maruyama a, *,1, Teiji Sawa b,1, Satoshi Teramukai c, Norito Katoh a

a Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine Kajiicho 465, Kawaramachi-Hirokoji, Kamigyo, Kyoto, 602-8566, Japan
b Medical Safety Promotion Division of the University Hospital, and Department of Anesthesiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine Kajiicho 465, Kawaramachi-Hirokoji, Kamigyo, Kyoto, 602-8566, Japan
c Department of Biostatistics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine Kajiicho 465, Kawaramachi-Hirokoji, Kamigyo, Kyoto, 602-8566, Japan

ARTICLE INFO

Keywords:
mRNA vaccine
COVID-19
SARS-CoV2
Adverse reaction
Healthcare worker
Sex
Age group
Public health

ABSTRACT

Introduction: In the current coronavirus infection 2019 (COVID-19) pandemic, the messenger RNA vaccines have been shown to help protect high-risk groups from COVID-19. Among healthcare workers vaccinated with Pfizer-BioNTech COVID-19 vaccine, a survey was conducted to analyze the relationship between the incidence and severity of adverse reactions after vaccination.

Methods: We conducted a prospective self-reported survey of adverse reactions among healthcare workers vaccinated with the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®) in Japan. After the first and second dose of vaccine, local and systemic reactions for 8 days after vaccination were reported by volunteer participants using a website. After receiving vaccination, 374 respondents participated in this matched-pair study.

Results: Both the incidence and severity of adverse reactions tended to be higher after the second vaccine dose than after the first dose. However, the incidence and numeric rating scale (NRS) score of muscle and skin pain were nearly the same after the first and second doses. In a comparison by sex, women had significantly higher incidence and NRS scores for adverse reactions such as headache, skin pain, erythema, and itching. The results also showed that younger age groups had higher incidence rates and NRS scores for all adverse reactions investigated, except for muscle pain, compared with older age groups.

Conclusion: Some adverse reactions to the Pfizer-BioNTech Comirnaty® COVID-19 vaccine showed gender and age differences. However, generally speaking, all side reactions disappear within a week. Therefore, these side reactions are not a significant concern in recommending vaccination.

1. Introduction

The pandemic of coronavirus infection 2019 (COVID-19), which has spread to countries worldwide since the beginning of 2020, shows no sign of resolution as of the beginning of 2022. The messenger RNA (mRNA) vaccines, such as the Pfizer-BioNTech COVID-19 vaccine (Comirnaty®) and Moderna mRNA-1273 COVID-19 vaccine (Spikevax®), have received emergency authorization for clinical use and have been shown to help protect high-risk groups from COVID-19 infection. Since February 2021, healthcare workers in Japan have been given first priority for vaccination with the Comirnaty® vaccine. The target population was then expanded to people aged 65 years and over. Large-scale vaccination is currently underway for all citizens over the age of 12 in the national plan of Japan. However, in Japan as well as other countries, vaccination tends to be avoided by young people. As a result, younger people who become infected can spread the infection and thereby constitute an important factor in perpetuating the pandemic. Because the vaccination campaign began very quickly, a lack of accurate information regarding adverse reactions is also linked to the tendency of younger people to refrain from vaccination.

* Corresponding author. Department of Dermatology, Kyoto Prefectural University of Medicine Kajiicho 465, Kawaramachi-Hirokoji, Kamigyo, Kyoto, 602-8566, Japan.
E-mail addresses: maruchan@koto.kpu-m.ac.jp (A. Maruyama), anesth@koto.kpu-m.ac.jp (T. Sawa), steramu@koto.kpu-m.ac.jp (S. Teramukai), nkatoh@koto.kpu-m.ac.jp (N. Katoh).
1 These authors contributed equally to this work.

https://doi.org/10.1016/j.jiac.2022.03.015
Received 19 December 2021; Received in revised form 22 February 2022; Accepted 22 March 2022
Available online 25 March 2022
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The prevalence and spread of COVID-19 vary greatly among ethnic groups, and the effects of and adverse reactions to the COVID-19 vaccines may also differ among ethnic groups [1–8]. There are few detailed reports from Japan regarding the actual symptoms and frequency of vaccine adverse effects [9,10]. Additionally, no reports have compared or examined data for the same vaccinee after repeated inoculations. Therefore, it is important to more accurately evaluate the changes and characteristics of adverse reactions by comparing the incidence and severity of adverse reactions after each vaccination in the same vaccinee. During mass COVID-19 vaccination conducted at the Kyoto Prefectural University of Medicine Hospital, we administered a survey regarding adverse reactions occurring after the first and second vaccinations, and examined the relationship between the incidence and severity of adverse reactions after COVID-19 vaccination according to sex and age.

2. Materials and methods

2.1. Study design and participants

During the 4 months from March 8 to July 9, 2021, medical workers, medical students, and nursing students involved in healthcare at the Hospital of Kyoto Prefectural University of Medicine were vaccinated with the Comirnaty®. A total of 4,503 individuals were vaccinated with the first dose, and 4,473 received a second dose. According to the manufacturer’s recommendations for administration of the vaccine, one frozen multidose vial was thawed at room temperature, diluted with 1.8 mL saline, and dispensed into six doses of 0.3 mL each in one 1-mL syringe per inoculation. Two injections were administered intramuscularly at intervals of 21 days ± 2 days in the deltoid muscle of the upper arm using a 25G needle. The study participants were individuals aged 18 years or older who were vaccinated and who voluntarily agreed to participate in the survey. Individuals who agreed to participate in the study were asked to report daily regarding the presence and severity of any adverse reactions (local reactions such as muscle pain, erythema, skin pain, itching, and headache; systemic reactions such as fever, general fatigue, chills, joint pain, and diarrhea) for a total of 8 days from skin pain, itching, and headache; systemic reactions such as fever, general fatigue, chills, joint pain, and diarrhea; for a total of 8 days from injection. Reporting was conducted via a website using a computer or mobile terminal. A 10-step numeric rating scale (NRS) was used (zero was set to indicate no reaction). For fever, the actual body temperature measurement was categorized using the NRS (score of 4 or higher indicated a body temperature of 37 °C or higher).

2.2. Sample size calculation and statistical analysis

After receiving the first dose, 595 (13.2%) participants voluntarily responded to the survey, with 584 valid surveys. After receiving the second dose, 442 (9.9%) participants responded to the survey, with 438 valid surveys (Table 1). The incidence of vaccine adverse reactions is presented as number and percentage or mean and standard deviation. We used the $\chi^2$-test to compare the incidence of various side effects between the first and second doses. Paired $t$-tests were used for NRS comparison of adverse reactions using matched paired data for the first and second dose. The unpaired $t$-test was used for NRS comparisons by sex. Analysis of variance (ANOVA) was applied for NRS comparisons by age group, and repeated measures ANOVA was used for NRS comparisons by time-course. With a significant difference at $p < 0.05$ in ANOVA, the Student–Newman–Keuls multiple comparisons test was added as a post-hoc test for intergroup NRS comparison. R version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) and Rstudio (ver. 1.4, Integrated Development for R, Rstudio, PBC, Boston, MA, USA) were used for the Cochran–Armitage trend test to evaluate the linear trend between the incidence of adverse reactions among age groups. Python version 3.8 (Python Software Foundation, https://www.python.org) with the Seaborn visualization library version 0.11.2 was used for linear regression analysis, graphing, and kernel density estimation (KDE) plots; InStat (GraphPad Software, San Diego, CA, USA) and Microsoft Excel for Mac ver. 16.53 (Microsoft Co., Redmond, WA, USA) was also used for statistical analysis.

3. Results

3.1. Study population

We analyzed adverse reactions after receipt of the first and second doses of the Comirnaty® as paired data for 374 participants who completed our survey (Table 2). The 374 participants comprised doctors, nurses, other medical workers, students, and non-medical staff. Among them, there was a slightly higher proportion of female respondents (39.8% men, 60.2% women), but there were no statistically significant differences in the average age between men and women ($p = 0.935$). The 374 respondents in the paired data ranged in age from 18 to 74 years old. Participants were divided into five age groups: 18–29 (76, 20.3%), 30–39 (69, 18.4%), 40–49 (101, 27.0%), 50–59 (96, 25.7%), 60–69 (37, 9.8%), 70–74 (3, 0.7%).

Table 1

| Characteristics of participants vaccinated with Pfizer-BioNTech Comirnaty® COVID-19 vaccine at Kyoto Prefectural University of Medicine Hospital. |
|---|
| vaccinated, n 4,503 4,473 |
| survey participants, n (%) 595 (13.2) 442 (9.9) |
| valid answer, n (%) 584 (13.0) 438 (9.8) |
| sex: male, female, n (%) 237 (40.6), 347 (59.4) 169 (38.6), 269 (61.4) |
| age: mean ± SD 40.08 ± 13.23 41.90 ± 12.76 |
| generations, n (%) 18–19 18 (3.1) 11 (2.5) 20–29 144 (24.7) 88 (20.0) 30–39 113 (19.3) 80 (18.3) 40–49 144 (24.7) 118 (26.9) 50–59 125 (21.4) 105 (24.0) 60–69 37 (6.3) 35 (8.0) 70–74 3 (0.5) 1 (0.2) |
| occupation, n (%) doctors 185 (31.7) 133 (30.4) nurses 140 (24.0) 117 (26.7) other medical workers 83 (14.2) 63 (14.4) students 96 (16.4) 58 (13.2) non-medical staff and others 80 (13.7) 67 (15.3) |
| SD, standard deviation. |

(https://seaborn.pydata.org/#) was used for linear regression analysis, graphing, and kernel density estimation (KDE) plots; InStat (GraphPad Software, San Diego, CA, USA) and Microsoft Excel for Mac ver. 16.53 (Microsoft Co., Redmond, WA, USA) was also used for statistical analysis.

Table 2

| Characteristics of study participants (matched pairs) vaccinated with Pfizer-BioNTech Comirnaty® COVID-19 vaccine. |
|---|
| age, generation sex total |
| male | female | total |
| age: mean ± SD | age: mean ± SD | age: mean ± SD |
| 18–29 | 42.38 ± 13.35 | 42.49 ± 12.30 | 42.44 ± 12.71 |
| 30–39 | 28 (18.8) | 38 (16.9) | 66 (17.6) |
| 40–49 | 27 (18.1) | 42 (18.7) | 69 (18.4) |
| 50–59 | 38 (25.5) | 63 (28.0) | 101 (27.0) |
| 60–69 | 33 (22.1) | 63 (28.0) | 96 (25.7) |
| 70–74 | 17 (11.4) | 14 (6.2) | 31 (8.3) |
| n (%) | 149 (39.8) | 225 (60.2) | 374 (100.0) |
| generations, n (%) | 18–19 | 5 (3.4) | 5 (2.2) | 10 (2.7) |
| | 20–29 | 28 (18.8) | 38 (16.9) | 66 (17.6) |
| | 30–39 | 27 (18.1) | 42 (18.7) | 69 (18.4) |
| | 40–49 | 38 (25.5) | 63 (28.0) | 101 (27.0) |
| | 50–59 | 33 (22.1) | 63 (28.0) | 96 (25.7) |
| | 60–69 | 17 (11.4) | 14 (6.2) | 31 (8.3) |
| | 70–74 | 1 (0.7) | 0 (0.0) | 1 (0.3) |
| occupation, n (%) | doctors | 84 (56.4) | 36 (16.0) | 120 (32.1) |
| | nurses | 3 (2.0) | 91 (40.4) | 94 (25.1) |
| | other medical workers | 17 (11.4) | 36 (16.0) | 53 (14.2) |
| | students | 24 (16.1) | 23 (10.2) | 47 (12.6) |
| | non-medical staff and others | 21 (14.1) | 39 (17.3) | 60 (16.0) |
| SD, standard deviation. |
and 60–74 years old (32, 8.6%). There was no significant difference in the proportion of men and women in each age group from 18 to 74 years (p = 0.375) (Table 2).

3.2. Incidence and NRS of adverse reactions between first and second vaccination

For the 10 types of adverse reaction investigated in this study, the time-course of incidence and severity (NRS) was examined for up to 8 days after inoculation, including the day of vaccination (day 0) (Fig. 1a and b). For the first dose, the incidence of muscle pain exceeded 70%–90% on days 0 and 1. The incidence of general fatigue, skin pain, and headache were approximately 10%–30% and peaked on day 1. For the second dose, the incidence of most adverse reactions, including fever, general fatigue, chills, headache, joint pain, and erythema, and diarrhea, also increased and peaked on day 1. This indicated a general tendency for a higher incidence and NRS score for most adverse reactions after the second dose, with longer duration and greater severity than reactions after the first dose (Fig. 1a and b). For example, the NRS score for general fatigue, headache, muscle pain, erythema, and itching showed a significant increase on the day after receiving the second dose of vaccine, and these increases continued for several days after day 2 (p < 0.001 to 0.01) (Fig. 1b).

3.3. Sex differences in the incidence and NRS of adverse reactions

For headache, skin pain, erythema, and itching, the incidence and NRS values in women after the second dose were significantly higher for several days than those in men (p < 0.05) (Fig. 2a and b). For incidence of fever after the first dose, there was no significant increase and no difference by sex (Supplementary Fig. S1a). The degree of fever was slightly higher in women on day 0 (p = 0.024) and day 1 (p = 0.015), but this was not a large difference (Supplementary Fig. S1b). After the second dose, significant increases in the incidence and NRS scores of fever in women were observed on days 1 and 2 (p < 0.05) (Supplementary Figs. S1a and S1b). Regarding incidence of general fatigue, chills, muscle pain and joint pain, significantly higher incidences were detected in women than men on day 1 and/or day 2 (p < 0.05) (Supplementary Fig. S1a). Regarding muscle pain, NRS scores were significantly higher in women than in men for 3–6 days after the first and second injections (p < 0.05) (Supplementary Fig. S1b).
3.4. Age differences in the incidence and NRS of adverse reactions

We investigated the incidence of adverse reactions by age group (Fig. 3 and Supplementary Fig. S2a). Muscle pain, general fatigue, headache, fever, joint pain, and chills were the most frequent adverse reactions overall; except for muscle pain, the incidence of these reactions was significantly higher after the second dose than after the first dose in all age groups (p < 0.05). In the comparison of the incidence of adverse reactions among age groups, after the 1st dose, a statistically significant difference was detected in fever at day 1, general fatigue from day 0 to day 4, chills from day 1 to day 2, and muscle pain from day 0 to day 1 (p < 0.05) (Fig. 3). After the 2nd dose, a statistically significant difference among age groups was detected in fever on day 1, general fatigue on day 0, headache from day 0 to day 1, muscle pain on day 1, skin pain from day 5 to day 6, and itching on day 6 (p < 0.05) (Fig. 3 and Supplementary Fig. S2a). In the adverse reactions that showed statistically significant differences in the age group comparison, the younger age cohorts generally tended to show a higher incidence than the older age groups.

We used the Cochran–Armitage trend test to analyze the linear trend for the incidence of adverse reactions by age group (Fig. 3).
between age groups and the incidence of adverse reactions on day 1 (Table 3). The incidence of fever and general fatigue was more elevated in younger age groups after the first and second doses, with statistical significance. The same linear trend was observed for muscle and joint pain only after the first dose, and for headache only after the second dose.

Next, we compared NRS values for adverse reactions among age groups (Fig. 4 and Supplementary S2b). The NRS scores for fever, general fatigue, and headache were significantly higher in younger age groups than those in older participants on day 1 to day 2 after the second dose (p < 0.05) (Fig. 4).

3.5. NRS correlation after first and second vaccination

Focusing on the paired data of the 374 survey respondents after receiving both vaccine doses, NRS values after the first and second doses were plotted on an XY diagram with a KDE plot with linear regression (Fig. 5 and Supplementary S3). For all adverse reactions, the correlations expressed by the coefficient of determination $R^2$ between the first-time and the second-time NRS were low, and the 95% confidence intervals for linear regression were widespread along the lines, except for NRS of day 0–2 in fever, fatigue and muscle pain. Among frequently occurring adverse reactions, such as fever and muscle pain, the KDE plot color-graded contour lines were distributed evenly along the XY axes; the same NRS score for severity tended to occur after both the first and second doses. However, for general fatigue, chills, headache, and joint pain, the KDE contour lines tended to extend in the positive direction of NRS values after the second dose, owing to higher NRS scores at earlier time points after receiving the second dose in comparison with those after the first dose (Fig. 5). The KDE plot contour lines of local adverse reactions such as skin pain, erythema, and itching, which occurred less frequently, also showed axially biased distributions of NRS values after the second dose (Supplementary Fig. S3).

4. Discussion

The characteristics and severity of adverse reactions of Comirnaty® may differ considerably between the first and second doses, even in the
same vaccinee. In this study, we compared data from the same vaccinee to evaluate the incidence and severity of adverse reactions between the first and second doses to more accurately evaluate various adverse reactions after each inoculation. As a whole, the incidence of adverse reactions was reported to be higher after the second dose than after the first dose for nearly all items. Specifically, muscle pain (93.0%), general fatigue (38.0%), and headache (50.3%) were significantly increased and diminished 7 days after injection. The NRS score for severity tended to be higher after the second dose than after the first dose.

Table 3

| adverse reaction | dose | Incidence among genders (%) | Cochran-Armitage trend test |
|------------------|------|----------------------------|---------------------------|
|                  | 18-29 | 30-39 | 40-49 | 50-59 | 60-74 | χ²-value | p-value |
| fever            |       |       |       |       |       |           |         |
| 1st              | 13.2  | 8.7   | 5.9   | 1.0   | 0.0   | 13.326    | 0.000262 |
| 2nd              | 75.0  | 58.0  | 55.4  | 50.0  | 45.5  | 11.605    | 0.000658 |
| general fatigue  |       |       |       |       |       |           |         |
| 1st              | 39.5  | 34.8  | 31.7  | 13.5  | 25.0  | 11.758    | 0.000606 |
| 2nd              | 86.8  | 82.6  | 77.2  | 70.8  | 71.9  | 7.457     | 0.00632  |
| chills           |       |       |       |       |       |           |         |
| 1st              | 2.6   | 10.1  | 7.9   | 0.0   | 0.0   | 2.657     | 0.103    |
| 2nd              | 42.1  | 44.9  | 39.6  | 30.2  | 31.3  | 3.773     | 0.0521   |
| headache         |       |       |       |       |       |           |         |
| 1st              | 11.6  | 11.6  | 15.8  | 9.4   | 9.4   | 0.216     | 0.642    |
| 2nd              | 55.8  | 42.0  | 48.5  | 52.1  | 31.3  | 5.471     | 0.0193   |
| muscle pain      |       |       |       |       |       |           |         |
| 1st              | 97.4  | 95.7  | 94.1  | 90.6  | 81.3  | 8.76      | 0.00308  |
| 2nd              | 92.1  | 94.2  | 92.1  | 91.7  | 81.3  | 1.85      | 0.174    |
| joint pain       |       |       |       |       |       |           |         |
| 1st              | 13.2  | 7.2   | 9.9   | 2.1   | 6.3   | 4.850     | 0.0277   |
| 2nd              | 47.4  | 37.7  | 40.6  | 39.6  | 21.9  | 3.404     | 0.0650   |
| skin pain        |       |       |       |       |       |           |         |
| 1st              | 15.8  | 20.3  | 16.8  | 21.9  | 21.9  | 0.815     | 0.367    |
| 2nd              | 18.4  | 23.2  | 17.8  | 19.8  | 15.6  | 0.116     | 0.733    |
| erythema         |       |       |       |       |       |           |         |
| 1st              | 3.9   | 7.2   | 5.9   | 7.3   | 3.1   | 0.0776    | 0.781    |
| 2nd              | 15.6  | 10.1  | 11.9  | 14.6  | 6.3   | 0.441     | 0.507    |
| itching          |       |       |       |       |       |           |         |
| 1st              | 9.2   | 4.3   | 3.0   | 5.2   | 3.1   | 1.682     | 0.195    |
| 2nd              | 10.5  | 10.1  | 7.9   | 10.4  | 12.5  | 0.0205    | 0.886    |
| diarrhea         |       |       |       |       |       |           |         |
| 1st              | 0.0   | 2.9   | 5.0   | 2.1   | 3.1   | 0.863     | 0.353    |
| 2nd              | 3.9   | 5.8   | 5.9   | 5.2   | 9.4   | 0.629     | 0.428    |

The comparison by age group showed an increased incidence and NRS of adverse reactions in younger age groups, especially for systemic adverse reactions such as fever and general fatigue. A large population-based study in the US found that participants over the age of 65 years had a lower incidence of adverse reactions than participants under the age of 65 years [1], consistent with our study. Several relevant reports have shown a high incidence and severity of adverse reactions with COVID-19 vaccines in younger age groups. Along with the production of neutralizing antibodies, release of inflammatory cytokines from activated specific T cells occurs with vaccination [15]; thus, the increase in interferon-γ concentration among young adults is greater after COVID-19 vaccination than after COVID-19 infection [16]. The fact that COVID-19 infection is less severe in young people and less severe in women than men may have an association with strong adverse effects after vaccination. In other words, the effective immune response in vaccination may cause strong adverse effects but produce effective protective immunity against the pathogens. It has become clear that the immunity to SARS-CoV2 acquired by the COVID-19 vaccination significantly prevents the aggravation of COVID-19 [17]. However, there are no reports on whether neutralizing antibodies are more likely to be produced in young people and women, although it has been reported that, in various vaccines, vaccine efficacy and the intensity of adverse reactions are correlated among age and sex [11–14]. Because strong adverse reactions may not always match the degree of neutralizing antibody production, further investigation is required to examine the association between adverse responses and protective immunity. A unique feature in our study is that we analyzed changes in NRS levels after the first and second doses in the same vaccinee. We also visually assessed the relationship between severity after the first and second doses. In general, systemic adverse reactions such as fever and general fatigue were more frequent in younger age groups and women and significantly more severe after the second dose than after the first dose. Muscle pain at the injection site was the most frequent complaint and occurred with the same severity after the first and second doses. Local reactions such as skin pain, erythema, and itching were less frequent but had a longer duration in older age groups. However, as a whole, it is important to understand that all adverse reactions were relieved within a week.

This survey has several limitations in interpreting the incidence and averaged intensity of adverse reactions. The vaccinees themselves voluntarily reported the occurrence and intensity of adverse reactions, and only 13.2% of vaccinees in the first dose and 8.9% of vaccinees in the second dose participated in this survey. The observed high incidence
of adverse reactions may be because vaccinees without strong adverse reactions may not have actively participated in this study. Therefore, comparing the incidence rates of each country must be undertaken with care. Also, because this survey included medical students and healthcare professionals, the complaints of non-healthcare workers may differ from those of professionals. We hope that enlightening the public about vaccines may fill these gaps.

5. Conclusions

Some of the adverse reactions of the Pfizer-BioNTech Comirnaty® COVID-19 vaccine have gender and age differences. However, nearly all adverse reactions disappear within a week. Therefore, these side effects are not a significant concern in recommending vaccination. Regarding vaccination with Comirnaty®, providing appropriate information concerning the incidence and extent of adverse reactions by age and sex are important for correct understanding among the public to increase the uptake of COVID-19 vaccination and help to control the COVID-19 pandemic.

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki. The survey (data collection and management) was performed with the approval (ERB-C-1968) of the research ethics committee of Kyoto Prefectural University of Medicine. Informed consent was obtained online from all participants via the study website before the survey start.

Declaration of competing interest

The authors declare that they have no conflicts of interests.
Funding
This research received no external funding.

Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions
Ayano Maruyama, Teiji Sawa and Norito Katoh contributed to the design of the study, carried out the experiment and drafted the manuscript. Satoshi Teramukai participated in the statistical verification. All authors met JCMJE authorship criteria and have read and agreed to the published version of the manuscript.

Acknowledgements
We thank Analisa Avila, MPH, ELS, of Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.03.015.

Fig. 5. Correlation of numeric rating scale (NRS) scores after the first and second doses of Pfizer-BioNTech Comirnaty® COVID-19 vaccine. Six major adverse reactions (fever, general fatigue, chills, headache, muscle pain, and joint pain). Paired NRS data of the 374 survey respondents after receiving both vaccine doses were plotted on an XY diagram with a kernel density estimation (KDE) plot, linear regression, and marginal histograms with density curves on the marginal axes. The KDE contour lines were color-graded at 11 levels between 0% and 100%. Dark blue line shows a linear regression of NRS values between doses, and light blue area represents the 95% confidence interval of linear regression. \( R^2 \): the coefficient of determination.

References
[1] Chapin-Bardales J, Gee J, Myers T. Reactogenicity following receipt of mRNA-based COVID-19 vaccines. JAMA 2021;325:2201–2. https://doi.org/10.1001/jama.2021.5374.
[2] Powell AA, Power L, Westrop S, McOwat K, Campbell H, Simmons R, et al. Real-world data shows increased reactogenicity in adults after heterologous compared to homologous prime-boost COVID-19 vaccination, March-June 2021, England. Euro Surveill 2021;26:2100634. https://doi.org/10.2807/1560-7917.ES.2021.26.28.2100634.
[3] Almohaya AM, Qari F, Zohaidi GA, Alnajim N, Moustafa K, Alshabi MM, et al. Early solicited adverse events following the BNT162b2 mRNA vaccination, a population survey from Saudi Arabia. Prev Med Rep 2021;24:101595. https://doi.org/10.1016/j.pmedr.2021.101595.
[4] Bae S, Lee YW, Lim SY, Lee J-H, Lim JS, Lee S, et al. Adverse reactions following the first dose of ChAdOx1 nCoV-19 vaccine and BNT162b2 vaccine for healthcare workers in South Korea. J Kor Med Sci 2021;36:e115. https://doi.org/10.3346/jkms.2021.36.e115.
[5] Ossato A, Tessari R, Trabucchi C, Zuppini T, Realdon N, Marchesini F. Comparison of medium-term adverse reactions induced by the first and second dose of mRNA BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine: a post-marketing Italian study conducted between 1 January and 28 February 2021. Eur J Hosp Pharm 2021;1-6. https://doi.org/10.1136/ejpharm-2021-002933. 0.
[6] Klugar M, Riad A, Mekhemar M, Conrad J, Buchbender M, Howaldt H-P, et al. Side effects of mRNA-based and viral vector-based COVID-19 vaccines among German healthcare workers. Biology 2021;10:752. https://doi.org/10.1159/0000556.
[7] Riad A, Pokorná A, Attia S, Klugarová J, Košick M, Klugar M. Prevalence of COVID-19 vaccine side effects among healthcare workers in the Czech Republic. J Clin Med 2021;10:1428. https://doi.org/10.3390/jcm10071428.

[8] El-Shitany NA, Harakeh S, Badr-Eldin SM, Bagher AM, Eid B, Almukadi H, et al. Minor to moderate side effects of Pfizer-BioNTech COVID-19 vaccine among Saudi residents: a retrospective cross-sectional study. Int J Gen Med 2021;14:1389–401. https://doi.org/10.2147/IGM.S316497.

[9] Saita M, Yan Y, Ito K, Sasano H, Seyama K, Niato T. Reactogenicity following two doses of the BNT162b2 mRNA COVID-19 vaccine: real-world evidence from healthcare workers in Japan. J Infect Chemother 2022;28:116–9. https://doi.org/10.1016/j.jiac.2021.09.009.

[10] Otani J, Ohta R, Sano C. Association between immunoglobulin G levels and adverse effects following vaccination with the BNT162b2 vaccine among Japanese healthcare workers. Vaccines 2021;9:1149. https://doi.org/10.3390/vaccines9101149.

[11] Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. Trans R Soc Trop Med Hyg 2015;109:9–15. https://doi.org/10.1093/trstmh/tru167.16. 10.1093/trstmh/tru167.

[12] Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626–38. https://doi.org/10.1038/nri.2016.90.

[13] Ruggieri A, Anticoli S, D’Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. Ann Ist Super Sanita 2016;52:198–204. https://doi.org/10.4415/ANN_16_02_11.

[14] Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and gender differences in the outcomes of vaccination over the life course. Annu Rev Cell Dev Biol 2017;33:577–99. https://doi.org/10.1146/annurev-cellbio-100616-060716.

[15] King C, Sprent J. The dual nature of type I interferons in SARS-CoV-2 induced inflammation. Trends Immunol 2021;42:312–22. https://doi.org/10.1016/j.it.2021.02.003.

[16] Spagnolo PA, Manson JE, Joffie H. Sex and gender differences in health: what the COVID-19 pandemic can teach us. Ann Intern Med 2020;173:385–6. https://doi.org/10.7326/m20-1941.

[17] Self WH, Tenforde MW, Rhoads JP, Gaglani M, Ginde AA, Douin DJ, et al. Comparative effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions - United States, March-August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1337–43. https://doi.org/10.15585/mmwr.mm7038e1.