1-1-2023

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10.1016/j.jiph.2022.12.004

Wang, Y., Zhang, Y., Zhang, M., Zhang, X., Li, H., Wang, Y., ... & Zheng, D. (2023). The prevalence of adverse reactions among individuals with three-dose COVID-19 vaccination. Journal of Infection and Public Health, 16(1), 125-132. https://doi.org/10.1016/j.jiph.2022.12.004

Journal of Infection and Public Health 16 (2023) 125–132

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

# The prevalence of adverse reactions among individuals with three-dose COVID-19 vaccination

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ARTICLE INFO

*Article history:*
Received 14 September 2022
Received in revised form 17 November 2022
Accepted 5 December 2022

*Keywords:*
COVID-19 vaccine
SARS-CoV-2
Special populations
Booster dose
Adverse reactions

ABSTRACT

*Background:* Considering the adverse reactions to vaccination against coronavirus disease 2019 (COVID-19), some people, particularly the elderly and those with underlying medical conditions, are hesitant to be vaccinated. This study aimed to explore the prevalence of adverse reactions and provide direct evidence of vaccine safety, mainly for the elderly and people with underlying medical conditions, to receive COVID-19 vaccination.

*Methods:* From 1st March to 30th April 2022, we conducted an online survey of people who had completed three doses of COVID-19 vaccination by convenience sampling. Adverse reaction rates and 95% confidence intervals were calculated. In addition, conditional logistic regression was used to compare the differences in adverse reactions among the elderly and those with underlying medical conditions with the general population.

*Results:* A total of 3339 individuals were included in this study, of which 2335 (69.9%) were female, with an average age of 32.1 ± 11.4 years. The prevalence of adverse reactions after the first dose of inactivated vaccine was 24.6% (23.1–26.2%), 19.2% (17.8–20.7%) for the second dose, and 19.1% (17.7–20.6%) for the booster dose; among individuals using messenger RNA vaccines, the prevalence was 42.7% (32.3–53.6%) for the first dose, 47.2% (36.5–58.1%) for the second dose, and 46.1% (35.4–57.0%) for the booster dose. Compared with the general population, the prevalence of adverse events did not differ in individuals with underlying medical conditions and those aged 60 and above.

*Conclusions:* For individuals with underlying medical conditions and those aged 60 and above, the prevalence of adverse reactions is similar to that of the general population, which provides a scientific basis regarding vaccination safety for these populations.



## Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the presenting symptoms of most infected people typically include fever, cough, dyspnea, myalgia or fatigue [1]. More than 603 million people worldwide were infected with SARS-CoV-2 until September 2022 [2,3], while the infected cases in China were more than 6 million [4]. Currently, there is no effective treatment for COVID-19, and vaccination is still one of the most efficient control programs [5,6]. Safe vaccines are available to provide effective

*Abbreviations:* COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mRNA, messenger RNA; CI, confidence interval; RBD-subunit vaccine, receptor-binding domain subunit vaccine

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https://doi.org/10.1016/j.jiph.2022.12.004

protection against serious disease and death [7]. Several vaccines that differ in form and effectiveness have been approved for vaccination. In general, these vaccines are based on inactivation technology, such as Sinopharm (BBIBP-CorV) and Sinovac (CoronaVac), or new messenger RNA (mRNA) technology, such as Pfizer-BioNTech (BNT162b2 [equivalent to Fosun-BioNTech]) and Moderna (Spikevax mRNA-1273). Others, such as Anhui Zhifei Longcom (ZF2001), are RBD-subunit vaccines [8–12]. In China, the two inactivated vaccines described above are generally accepted [13].

Previous research suggests that older adults aged 60 and above are at high risk of COVID-19 [14,15]. Additionally, individuals with underlying medical conditions, such as hypertension and coronary heart disease, are at an increased risk of infection with COVID-19 and mortality [14,16]. Vaccination is the most effective way to prevent the development of severe disease and death due to COVID-19 [6,17]. Several studies suggest that the elderly and people with underlying medical conditions should be vaccinated as soon as possible, but some are still hesitant to vaccinate [18,19]. The Strategic Advisory Group of Experts on Immunization of WHO defines vaccine hesitancy as "a delay in acceptance or refusal of vaccines despite the availability of vaccination services" [20,21]. In China, the elderly and people with underlying medical conditions are more prone to vaccine hesitancy, and their vaccination rate is lower than that of the general population. In Shanghai, the overall vaccination rate is now over 90%, but only 62% of people aged over 60 years have received the vaccination, and only 38% have received a booster dose [19]. The main reason for vaccine hesitancy may be concerns about vaccine safety, i.e., the risk of adverse reactions [22,23].

Thus, it is important to have concrete evidence regarding vaccine safety in different populations, which could serve as the basis for reducing vaccine hesitancy [19,23]. V-safe, a voluntary, smartphone-based safety surveillance system, was established in 2020 to monitor mRNA vaccine safety in the USA and provide information on adverse reactions after vaccination [24,25]. However, most vaccines used in China are inactivated, thus, the V-safe report cannot be generalized to Chinese citizens [13]. In addition, few studies have focused on the adverse reactions to inactivated vaccines in China, particularly for individuals who received three doses of the vaccine.

Therefore, we conducted an online survey of adults who had completed three doses of COVID-19 vaccination using convenience sampling. Three types of vaccines were involved in our survey, including inactivated vaccines (Sinopharm and Sinovac), mRNA vaccines (Pfizer-BioNTech, Fosun-BioNTech and Moderna), and RBD-subunit vaccines (Anhui Zhifei Longcom). This study aimed to explore (1) the overall prevalence of injection site and systemic adverse reactions after vaccination, (2) whether the prevalence of adverse reactions varies by vaccine type or dose, and (3) whether the prevalence is higher among the elderly or people with underlying medical conditions compared with the general population.

## Methods

### *Participants*

This is a cross-sectional study. We conducted an online questionnaire survey on a convenience sample of adults who completed three doses of the COVID-19 vaccination. All respondents were recruited online. This study conformed to the requirements of medical ethics which was approved by the ethics committee of the study institution, and the questionnaire did not involve personal information, such as name, which conforms to the requirements of relevant laws and regulations. Participants provided online informed consent. Each IP address can only answer once to avoid duplicate answers. In total, 3467 respondents filled out and submitted the online questionnaire. Among these, 128 invalid questionnaires were excluded. Finally, 3339 participants were included in the analysis, with an effective response rate of 96.31%.

### *Measures*

Data were collected using a self-made questionnaire comprising four parts [25] (Additional file 1). The first part included socio-demographic information, including sex, age, height, weight, education, underlying medical conditions, BMI (calculated from self-reported weight and height, BMI [in $kg/m^2$] = weight [in kg]/ height$^2$ [in $m^2$]), and the frequency of dizziness and headache within 1 year before injection.

The second part was the type of vaccine received for each of the three doses: Sinopharm, Sinovac, Pfizer-BioNTech, Fosun-BioNTech, Moderna, and Anhui Zhifei Longcom.

The third part included adverse reactions after each dose of the vaccine, including injection site adverse reactions (itching, pain, swelling, induration, and redness), systemic adverse reactions (headache, dizziness, fever, fatigue, myalgia, joint pain, cough, nausea and vomiting, diarrhea, palpitations, insomnia, drowsiness, anaphylaxis, and others), and health impacts (needed medical care, unable to perform normal daily activities, and unable to work or attend school). Anaphylaxis included angioneurotic edema, Henoch-Schonlein purpura, and anaphylactic shock.

The fourth part was the time of occurrence and duration of each adverse reaction. The occurrence times were as follows: < 30 min, 30 min to < 1 day, 1–2 days, 3–4 days, 5–7 days, and > 7 days. The duration included < 1 day, 1–2 days, 3–5 days, > 5 days, and non-remission until the survey.

### *Outcome*

The outcome of this study was adverse reactions, including injection site and systemic adverse reactions. We then combined the injection site and systemic adverse reactions into one new group (any adverse reactions) as another outcome.

### *Statistical analysis*

The prevalence of adverse reactions was defined as the ratio of individuals with one or more adverse reactions to the total number of participants. Categorical variables were presented as counts (%) and continuous variables as means ± standard deviation (mean ± SD). The $\chi^2$ or Fisher's exact test was used to compare the proportions in different subgroups.

Based on the number of responses, the occurrence time was consolidated into < 1 day, 1–4 days, and > 4 days, and the duration was consolidated into < 1 day, 1–2 days, 3–5 days, and > 5 days.

To explore whether the adverse reaction was associated with age, we selected participants aged 60 and above as the exposure group, matched with those younger than 60 years based on sex, education, and experience of any adverse reaction. To study the association between underlying medical conditions and adverse reactions, we selected individuals with medical conditions as the exposure group and matched those without medical conditions based on age ( ± 5 years), sex, education, and experience of adverse reactions. Additionally, we explored whether the subsequent adverse reactions (such as reactions after the second or booster dose) could be affected by the previous reactions, either in the first or second doses. The study participants were matched based on age ( ± 5 years), sex, education, underlying medical conditions, and dizziness or headache. Conditional logistic regression analysis was used to explore the association between these characteristics and adverse reactions.

The analyses were performed using R (version 4.1.3) and SPSS (version 25.0). Graphing was performed using GraphPad Prism

**Table 1**
Characteristics and prevalence of adverse reactions (N = 3339).

| Demographics | Total (n = 3339) | | | Male (n = 1004) | | | Female (n = 2335) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total, n | Adverse reactions, n (%) | *P* value | Total, n | Adverse reactions, n (%) | *P* value | Total, n | Adverse reactions, n (%) | *P* value |
| **Age group (yrs)** | | | **< 0.001** | | | 0.261 | | | **< 0.001** |
| 18–29 | 1782 | 632 (35.47%) | | 510 | 145 (28.43%) | | 1272 | 487 (38.29%) | |
| 30–39 | 693 | 276 (39.83%) | | 217 | 63 (29.03%) | | 476 | 213 (44.75%) | |
| 40–49 | 520 | 243 (46.73%) | | 156 | 53 (33.97%) | | 364 | 190 (52.20%) | |
| 50–59 | 288 | 108 (37.50%) | | 96 | 21 (21.88%) | | 192 | 87 (45.31%) | |
| ≥ 60 | 56 | 19 (33.93%) | | 25 | 5 (20.00%) | | 31 | 14 (45.16%) | |
| **BMI** | | | 0.327 | | | **0.029** | | | 0.229 |
| < 18.5 | 322 | 110 (34.16%) | | 53 | 9 (16.98%) | | 269 | 101 (37.55%) | |
| 18.5–23.9 | 1976 | 777 (39.32%) | | 475 | 127 (26.74%) | | 1501 | 650 (43.30%) | |
| 24–27.9 | 714 | 268 (37.54%) | | 316 | 93 (29.43%) | | 398 | 175 (43.97%) | |
| ≥ 28 | 327 | 123 (37.61%) | | 160 | 58 (36.25%) | | 167 | 65 (38.92%) | |
| **Education** | | | **< 0.001** | | | **< 0.001** | | | **< 0.001** |
| Junior and below | 91 | 10 (10.99%) | | 57 | 4 (7.02%) | | 34 | 6 (17.65%) | |
| Senior | 137 | 32 (23.36%) | | 53 | 9 (16.98%) | | 84 | 23 (27.38%) | |
| College | 1805 | 647 (35.84%) | | 494 | 121 (24.49%) | | 1311 | 526 (40.12%) | |
| Postgraduate | 1306 | 589 (45.10%) | | 400 | 153 (38.25%) | | 906 | 436 (48.12%) | |
| **Underlying medical conditions**[a] | | | 0.584 | | | 0.424 | | | **0.027** |
| CVD and CVA | 152 | 67 (44.08%) | | 76 | 25 (32.89%) | | 76 | 42 (55.26%) | |
| Dyslipoproteinemia | 71 | 27 (38.03%) | | 33 | 9 (27.27%) | | 38 | 18 (47.37%) | |
| Endocrine disease | 136 | 45 (33.09%) | | 43 | 7 (16.28%) | | 92 | 38 (41.30%) | |
| Autoimmune disease | 22 | 7 (31.82%) | | 11 | 3 (27.27%) | | 11 | 4 (36.36%) | |
| Others | 101 | 48 (47.52%) | | 43 | 13 (30.23%) | | 58 | 35 (60.34%) | |

Adverse reaction: Any adverse reaction was defined as the occurrence of any injection site adverse reaction or systemic adverse reaction.
CVD and CVA: hypertension, stroke, heart disease (angina pectoris, heart failure, congenital cardiovascular disease, myocarditis, pulmonary hypertension).
Endocrine disease: diabetes mellitus, thyroid disorder (hyperthyroidism, hypothyroidism).
Autoimmune disease: HIV, rheumatoid arthritis, systemic lupus erythematosus, vasculitis, ankylosing spondylitis.
Others: chronic lung disease (chronic obstructive pulmonary disease, emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, pulmonary tuberculosis, bronchial asthma), liver disease (hepatitis, liver cirrhosis), hyperuricemia, uterine myoma, epilepsy, etc.
Bold indicates statistically significant < 0.05.
[a] The *P* value of the underlying medical conditions was used to indicate whether there was a statistically significant difference between groups (general population, male, female) with or without underlying medical conditions

(version 8.4.2). A two-tailed *P*-value < 0.05 was considered statistically significant.

## Results

A total of 3339 valid questionnaires were collected, including 1004 males (30.07%) and 2335 females (69.93%) (Table 1). The mean age was 32.1 ± 11.4 years. As shown in Table 1, 1278 participants had one or more adverse reactions, and the prevalence (95% confidence interval [CI]) was 38.27% (36.62–39.95%). The prevalence of adverse reactions was different between both sexes ($P < 0.001$) and was generally higher in females than in males. The highest prevalence was noted among individuals aged 40–49 years, which was 46.73% (42.38–51.12%). We also found a significant difference among individuals with different educational levels ($P < 0.001$); the prevalence was higher among people with postgraduate education, which was 45.10% (42.38–47.84%). There was no significant association between individuals with or without underlying medical conditions ($P = 0.584$), and the prevalence was 39.57% (34.58–44.73%) and 38.11% (36.36–39.89%), respectively. The comparison of the prevalence of underlying medical conditions among three different types of vaccines in age wise criteria was shown in Table S1 (Additional file 2: Table S1).

Table 2 shows the prevalence of adverse reactions in participants who received three doses of inactivated, mRNA, or RBD-subunit vaccines. We found that vaccine types were significantly associated with any adverse reactions in each dose (all $P < 0.001$). The prevalence (95% CI) of any adverse reaction in different types were as follows: first doses 24.58% (23.06–26.15%), 42.70% (32.26–53.63%), and 19.70% (10.93–31.32%) in the inactivated, mRNA, and RBD-subunit vaccines, respectively; second doses 19.22% (17.83–20.66%), 47.19% (36.51–58.06%), and 18.18% (9.76–29.61%), respectively; booster doses 19.12% (17.73–20.56%), 46.07% (35.44–56.96%), and 18.18% (9.76–29.61%), respectively. The pain was the most common injection site adverse reaction for both inactivated and mRNA vaccines, whereas itching was most frequently reported for RBD-subunit vaccines. The most common systemic adverse reactions for those who received inactivated vaccines were fatigue, myalgia, and drowsiness, whereas fatigue, myalgia, and fever were more common in those who received mRNA vaccines. Only two participants who received RBD-subunit vaccines had systemic adverse reactions (2/66). Among all the participants, the prevalence (95% CI) of any adverse reaction, any injection site reaction, and any systemic reaction that appeared in all three doses were 8.39% (7.43–9.43%), 4.87% (4.13–5.70%) and 2.07% (1.60–2.64%) for inactivated vaccine, respectively; being 31.46% (22.03–42.17%), 14.61% (8.01–23.68%) and 11.24% (5.52–19.69%), respectively, for mRNA vaccine; being 9.09% (3.41–18.74%), 4.55% (0.95–12.71%) and 1.52% (0.04–8.16%), respectively, for RBD-subunit vaccine.

We then analyzed the prevalence of adverse reactions in two age groups (18–59 and above). We found that in the age group of 18–59, the prevalence of any adverse reactions was significantly associated with vaccine types in each dose (all $P < 0.001$), and it was generally higher in mRNA vaccines than in others (Additional file 3: Table S2). As in the age group of 60 and above, most participants received three dose of inactivated vaccines (55/56), we only compared the adverse reactions to inactivated vaccines in three doses and found that there was no significant difference between three vaccinations (all $P > 0.05$) (Additional file 4: Table S3).

The prevalence of any adverse reactions to the inactivated vaccine decreased with each injection (total $P < 0.001$), whereas the prevalence of any adverse reactions to the mRNA or RBD-subunit vaccine was not different among the three vaccinations (Additional file 5: Fig. S1a).

**Table 2**
Prevalence of adverse reactions to different types of vaccines in three doses.

| Adverse reaction | Dose 1 | | | | Dose 2 | | | | Dose 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | INACT VAC (n = 3039) | mRNA VAC (n = 89) | RBD-SU VAC (n = 66) | *p* value | INACT VAC (n = 3039) | mRNA VAC (n = 89) | RBD-SU VAC (n = 66) | *p* value | INACT VAC (n = 3039) | mRNA VAC (n = 89) | RBD-SU VAC (n = 66) | *p* value |
| **Any adverse reaction (%)** | 24.58 | 42.70 | 19.70 | **< 0.001** | 19.22 | 47.19 | 18.18 | **< 0.001** | 19.12 | 46.07 | 18.18 | **< 0.001** |
| **Any injection site reaction (%)** | 14.41 | 32.58 | 13.64 | **< 0.001** | 12.47 | 25.84 | 13.64 | **< 0.001** | 13.33 | 20.22 | 13.64 | 0.172 |
| Itching (%) | 1.55 | 3.37 | 6.06 | | 1.25 | 1.12 | 9.09 | | 1.61 | 3.37 | 10.61 | |
| Pain (%) | 12.60 | 30.34 | 7.58 | | 10.66 | 23.60 | 7.58 | | 11.62 | 16.85 | 4.55 | |
| Swelling (%) | 3.78 | 7.87 | 6.06 | | 2.44 | 4.49 | 7.58 | | 2.50 | 5.62 | 7.58 | |
| Induration (%) | 2.11 | 3.37 | 3.03 | | 1.74 | 2.25 | 6.06 | | 2.20 | 2.25 | 10.61 | |
| Redness (%) | 0.46 | 1.12 | 1.52 | | 0.30 | 1.12 | 7.58 | | 0.49 | 2.25 | 10.61 | |
| **Any systemic reaction (%)** | 11.48 | 17.98 | 3.03 | **0.016** | 7.04 | 31.46 | 3.03 | **< 0.001** | 6.42 | 39.33 | 1.52 | **< 0.001** |
| Headache (%) | 2.11 | 8.99 | 0.00 | | 0.92 | 13.48 | 1.52 | | 0.86 | 17.98 | 0.00 | |
| Dizziness (%) | 2.67 | 6.74 | 0.00 | | 1.45 | 11.24 | 1.52 | | 1.22 | 11.24 | 0.00 | |
| Fever (%) | 1.45 | 11.24 | 0.00 | | 0.79 | 25.84 | 0.00 | | 0.86 | 29.21 | 0.00 | |
| Fatigue (%) | 7.01 | 11.24 | 1.52 | | 3.49 | 21.35 | 3.03 | | 3.09 | 24.72 | 1.52 | |
| Myalgia (%) | 3.55 | 8.99 | 0.00 | | 1.78 | 21.35 | 1.52 | | 2.14 | 15.73 | 0.00 | |
| Joint pain (%) | 0.36 | 1.12 | 0.00 | | 0.16 | 5.62 | 1.52 | | 0.26 | 3.37 | 0.00 | |
| Cough (%) | 0.23 | 1.12 | 0.00 | | 0.30 | 0.00 | 0.00 | | 0.26 | 0.00 | 0.00 | |
| Nausea and Vomiting (%) | 0.49 | 0.00 | 0.00 | | 0.39 | 0.00 | 0.00 | | 0.46 | 1.12 | 0.00 | |
| Diarrhea (%) | 0.43 | 0.00 | 0.00 | | 0.10 | 0.00 | 0.00 | | 0.20 | 0.00 | 0.00 | |
| Palpitation (%) | 0.16 | 2.25 | 0.00 | | 0.26 | 1.12 | 1.52 | | 0.13 | 1.12 | 0.00 | |
| Insomnia (%) | 0.13 | 0.00 | 0.00 | | 0.10 | 1.12 | 0.00 | | 0.20 | 2.25 | 0.00 | |
| Drowsiness (%) | 4.48 | 4.49 | 3.03 | | 2.44 | 6.74 | 1.52 | | 1.71 | 6.74 | 1.52 | |
| Anaphylaxis (%) | 0.33 | 1.12 | 0.00 | | 0.16 | 1.12 | 0.00 | | 0.36 | 0.00 | 0.00 | |
| Mild allergy (%) | 0.13 | 0.00 | 0.00 | | 0.13 | 0.00 | 0.00 | | 0.13 | 0.00 | 0.00 | |
| Menoxenia (%) | 0.23 | 0.00 | 0.00 | | 0.23 | 0.00 | 0.00 | | 0.13 | 0.00 | 0.00 | |
| Hearing loss (%) | 0.03 | 0.00 | 0.00 | | 0.07 | 0.00 | 0.00 | | 0.03 | 0.00 | 0.00 | |
| Tinnitus (%) | 0.00 | 0.00 | 0.00 | | 0.00 | 0.00 | 0.00 | | 0.07 | 0.00 | 0.00 | |
| **Any health impact (%)** | 1.02 | 4.49 | 0.00 | **0.027** | 1.25 | 14.61 | 1.52 | **< 0.001** | 1.41 | 14.61 | 0.00 | **< 0.001** |
| Needed medical care (%) | 0.53 | 2.25 | 0.00 | | 0.95 | 5.62 | 0.00 | | 0.95 | 4.49 | 0.00 | |
| Unable to perform normal daily activities (%) | 0.33 | 1.12 | 0.00 | | 0.20 | 5.62 | 1.52 | | 0.39 | 6.74 | 0.00 | |
| Unable to work or attend school (%) | 0.33 | 1.12 | 0.00 | | 0.13 | 5.62 | 1.52 | | 0.13 | 5.62 | 0.00 | |
| **Others (%)** | 0.86 | 0.00 | 3.03 | | 0.59 | 1.12 | 3.03 | | 0.53 | 0.00 | 3.03 | |

INACT VAC Inactivated vaccine, mRNA VAC mRNA vaccine, RBD-SU VAC Receptor-binding domain subunit vaccine.
Others: herpes zoster, chest pain, astigmatism, immunologic conjunctivitis, etc.

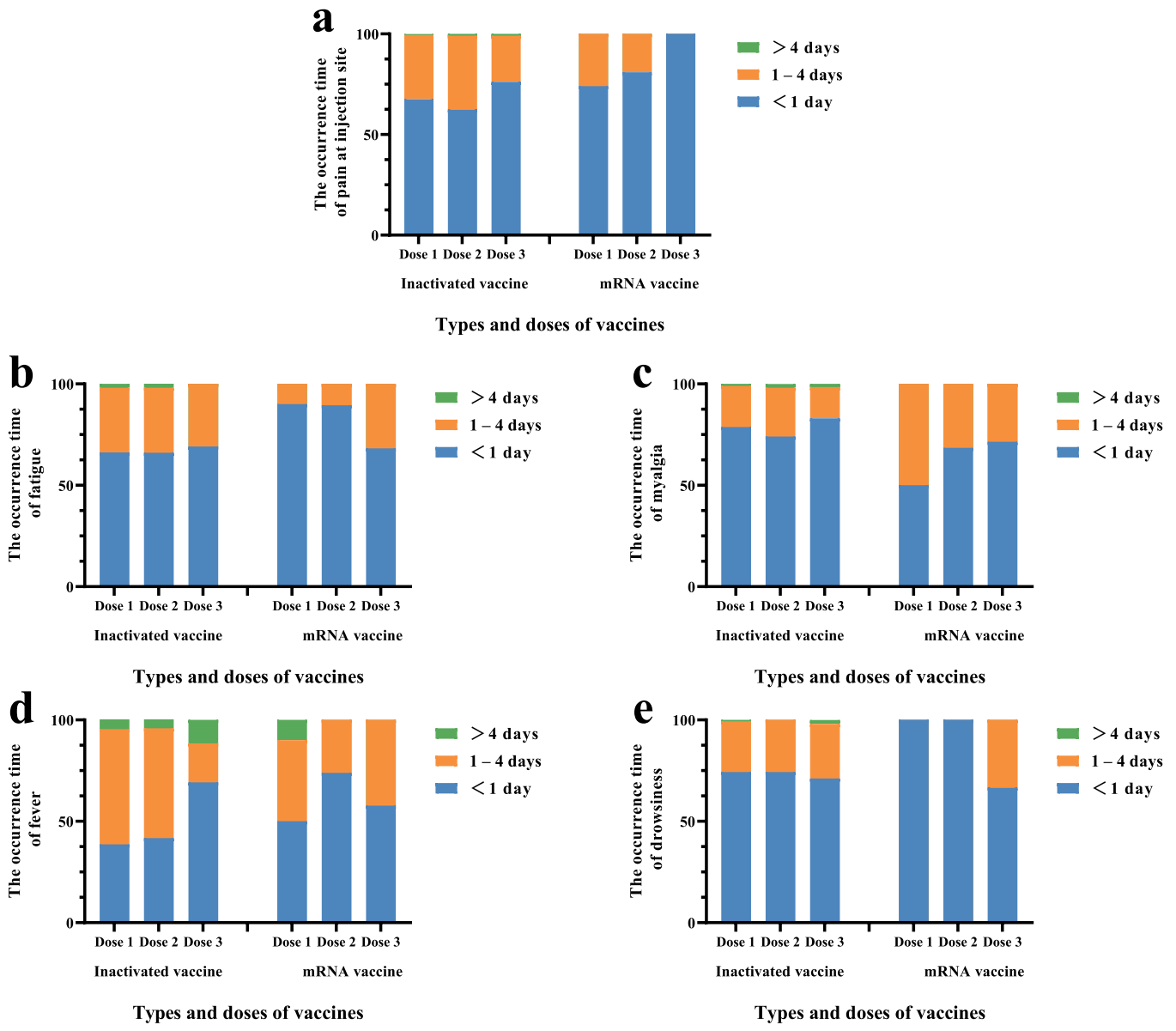


**Fig. 1.** The occurrence time of common adverse reactions of inactivated vaccine and mRNA vaccine.

The most prevalent injection site adverse reaction for both inactivated and mRNA vaccines was pain (Additional file 6: Fig. S2a). The prevalence of fatigue decreased with each dose of inactivated vaccine (total $P < 0.001$), whereas it increased with each dose of mRNA vaccine (total $P = 0.022$) (Additional file 6: Fig. S2b).

Some common adverse reactions (pain at the injection site, fatigue, myalgia, and drowsiness) of the three doses of inactivated vaccines mainly occurred in less than 1-day post-vaccination (62.50–83.08%) (Fig. 1a, b, c, e), and the duration was usually < 1 day (13.84–37.84%) or 1–2 days (33.78–55.09%) (Additional file 7: Fig. S3a, b, c, e). Meanwhile, some common adverse reactions of the three doses of mRNA vaccines (pain at the injection site, fatigue, myalgia, and fever) mainly occurred in < 1 day (50.00–100.00%) (Fig. 1a, b, c, d), and the duration was usually < 2 days (52.38–92.31%) (Additional file 7: Fig. S3a, b, c, d). Because only two participants had systemic reactions to the RBD-subunit vaccines, the occurrence time and duration were not analyzed.

We also analyzed the association between the different types of booster vaccines and adverse reactions after the booster dose (Fig. 2). For those who received inactivated vaccine for the first two

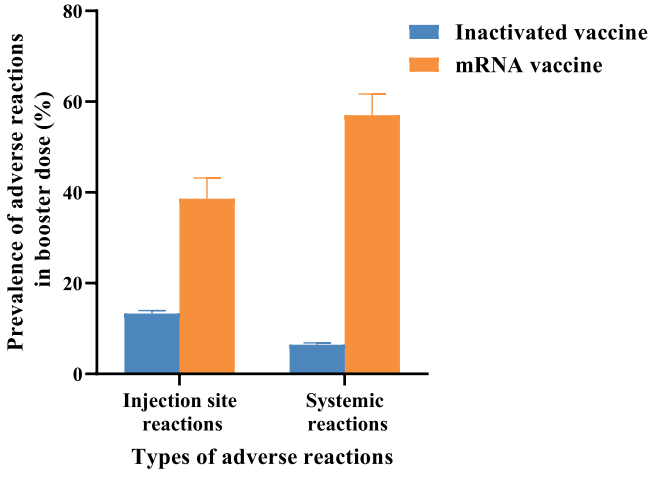


**Fig. 2.** The association between different types of booster vaccines and adverse reactions after the booster dose.

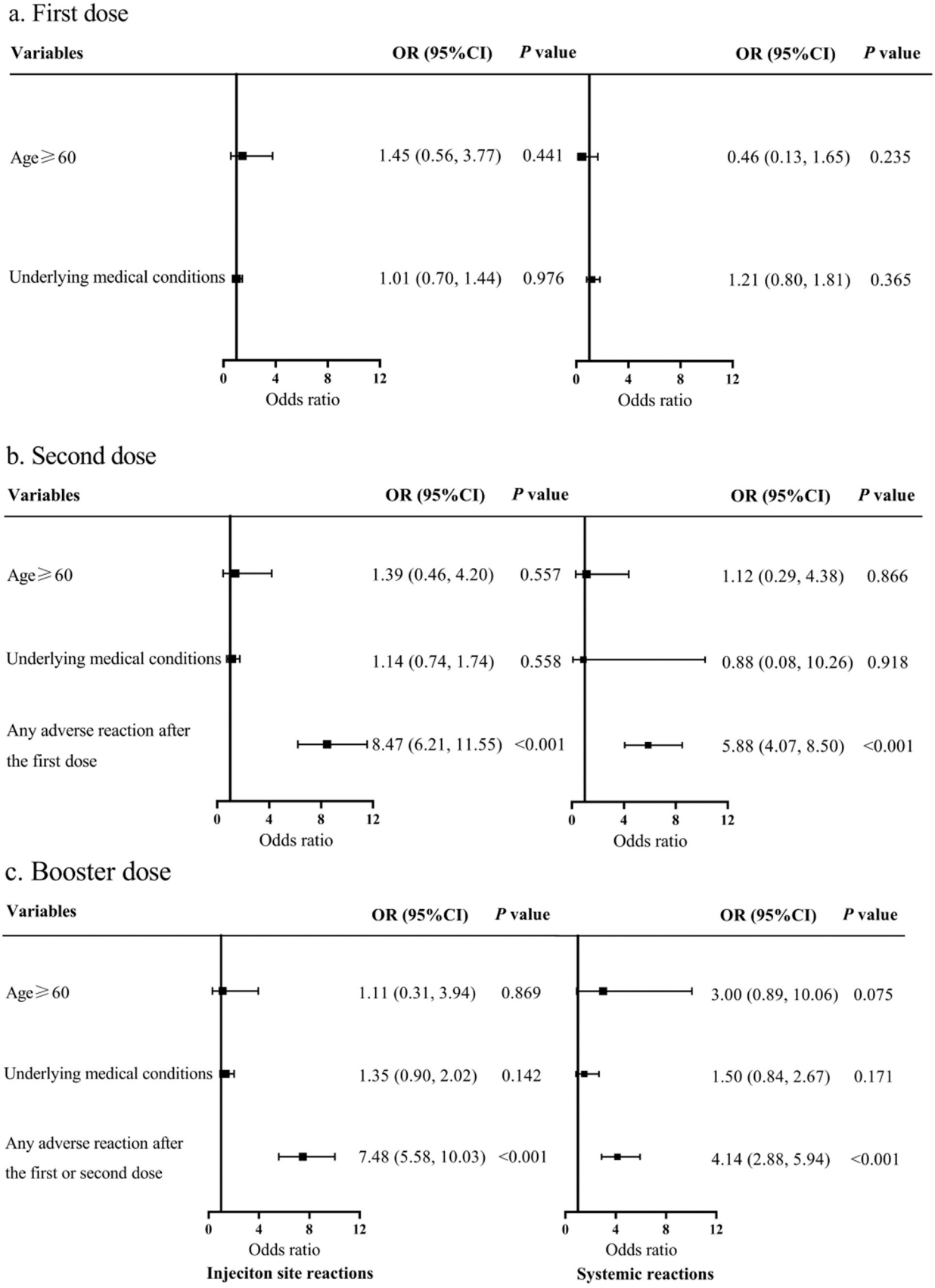


**Fig. 3.** Associations of age, underlying medical conditions, and experience of reactions with adverse reactions. OR: odds ratio; CI: confidence interval.

doses, the prevalence of injection site adverse reactions was 13.33% (12.14–14.59%) and 38.60% (29.63–48.17%), respectively, for a booster dose with inactivated or mRNA vaccine; systemic adverse reactions were 6.42% (5.57–7.35%) and 57.02% (47.41–66.25%), respectively.

As shown in Fig. 3, age and underlying medical conditions were not significantly associated with injection site or systemic reactions for all three doses (Fig. 3). Individuals with any adverse reaction after the first dose had an increased risk of injection site (OR=8.47, 95% CI, 6.21–11.55, Fig. 3b) and systemic reactions (OR=5.88, 95% CI, 4.07–8.50, Fig. 3b) for the second dose. In addition, those who developed adverse reactions in the first two doses had a higher risk of injection site reactions (OR=7.48, 95% CI, 5.58–10.03, Fig. 3c) and systemic adverse reactions (OR=4.14, 95% CI, 2.88–5.94, Fig. 3c) after receiving the booster dose.

## Discussion

In this cross-sectional study, we identified 3339 participants who had completed three doses of the COVID-19 vaccination. The most common injection site adverse reaction of both inactivated and mRNA vaccines was pain, whereas itching was the most common for RBD-subunit vaccines. Fatigue and myalgia were the most common systemic adverse reactions to inactivated and mRNA vaccines, respectively. Age and underlying medical conditions were not significantly associated with injection site or systemic reactions. People who developed adverse reactions during the first two doses had a higher risk of adverse reactions after the booster dose.

Compared with previous studies on adverse reactions in China [26], the prevalence of adverse reactions in our study was higher (15.60% vs. 24.58% in the first dose and 14.60% vs. 19.22% in the second dose). This may be due to the detailed adverse reactions and higher education levels of the participants in our study. Individuals with higher education levels may pay more attention to their physical condition and be more sensitive to adverse reactions [27]. The prevalence (95% CI) of anaphylaxis or hospitalization with the three doses was 0.39% (0.21–0.66%), 0.24% (0.10–0.47%), and 0.33% (0.16–0.59%) in our study, which was similar to previous studies [25,28,29]. Fever, as a measurable objective indicator, is often a concern after vaccination. In our study, the prevalence of fever after mRNA vaccination was 11.24% and 25.84% in the first and second doses, respectively, which was similar to 9.5% and 29.6% in the US study [30]. However, fever was uncommon after the inactivated vaccine, with a prevalence of 2% and 1%, respectively, for the first and second dose in a clinical trial done by India and less than 1% in the booster dose in Brazil, similar to our study (1.45% in the first dose, 0.79% in the second dose and 0.86% in the booster dose) [31,32]. The prevalence of adverse reactions in our study was higher in females than in males, and these findings align with that of previous studies which showed that females typically developed higher antibody responses and were more sensitive [33,34].

The WHO reported that COVID-19 vaccines are safe and effective for people with underlying medical conditions such as hypertension and diabetes [17]. Previous studies also showed that the prevalence of injection site and systemic adverse reactions to inactivated vaccines was relatively low [35,36], and few serious adverse reactions were reported [26], which were similar to the results of our study.

Our study showed that patients with adverse reactions to the first or second dose had a higher risk of adverse reactions to the booster dose. Participants who had an adverse reaction to the first two doses may have had an immunocompromised immune system [37] or a stronger antibody-mediated hypersensitivity to the COVID-19 vaccine [38]. In addition, multiple patterns of protective immunity may exist after vaccination, and antigen-specific CD4 and CD8 T-cell reactions may be associated with additional adverse reactions [39,40]. Thus, these patients may be more prone to adverse reactions after a booster dose.

In our study, individuals who received a booster dose of mRNA vaccine had a higher risk of injection site and systemic reactions than those who received the inactivated vaccine, suggesting the necessity for adverse reaction monitoring and seeking medical care in cases of severe reactions after vaccination with a booster dose of mRNA vaccine.

### *Strengths*

This study has several strengths. First, we were the first to collect and analyze data on adverse reactions in participants who had completed three doses of vaccination, which can provide scientific evidence for the safety of vaccination, particularly for booster doses. Second, our questionnaire included some adverse reactions with a low tendency to report (such as fatigue and drowsiness), which were rarely mentioned in previous studies, as well as detailed information on the occurrence time and duration of each adverse reaction analyzed. Moreover, we compared the difference in adverse reactions between the general population and the elderly or people with underlying medical conditions, providing scientific evidence for these populations.

### *Limitations*

First, since we conducted an online questionnaire survey using convenience sampling and not a random sampling, the results were unlikely to be generalizable to all vaccinated populations. Second, adverse reactions were collected using a self-reported questionnaire, which probably led to a high reporting rate and bias. Third, the power for comparing the difference between inactivated and RBD-subunit vaccines was relatively lower (< 80%) due to the relatively small samples of RBD-subunit vaccination and the similar prevalence of the adverse reactions, suggesting that a larger sample size for the RBD-subunit vaccine is needed to get more accurate and comparable results in the future study. However, the power of detecting the difference of adverse reactions between the inactivated and mRNA vaccination was relatively high (0.96), suggesting that the results from our study might be relatively stable and reasonable.

## Conclusions

Among those who received three doses of the COVID-19 vaccine, the most common injection site adverse reaction was pain, whereas fatigue and drowsiness were the most common systemic adverse reactions. The prevalence of anaphylaxis and hospitalization was low. Participants aged 60 and above and those with underlying medical conditions were not at a higher risk for adverse reactions, which provides a scientific basis for strengthening vaccination safety for the elderly and individuals with underlying medical conditions.

## Funding

This work was supported by grants from the Beijing Municipal Health System Special Funds of High-Level Medical Personnel Construction (grant number 2022-3-042) and the China Scholarship Council (grant number 202008110060). The founder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Ethical approval

The study was approved by the Ethics Committee of Capital Medical University.

## Author contributions

DZ, LW, JJ, and YW contributed to the study concept and design. YW, YZ, and MZ performed statistical analysis. XZ, HL, YW, and WW contributed to the interpretation of the results. All authors contributed to drafting or revising the manuscript. DZ and LW are the guarantor of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Availability of data and material

Data and survey materials will be made available from the corresponding author on reasonable request.

## Competing interests

All authors declare that they have no competing interests.

## Acknowledgements

We thank all the participants and staff for their efforts in conducting and collecting data throughout this investigation.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.12.004.

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