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RESEARCH PAPER

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Self-Reported adverse events among Chinese healthcare workers immunized with COVID-19 vaccines composed of inactivated SARS-CoV-2

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ABSTRACT

Mass vaccination is critical to control the pandemic of coronavirus disease 2019 (COVID-19). Fear of adverse events (AEs) after COVID-19 vaccination is a main factor associated with vaccination hesitancy. We aimed to analyze AEs in healthcare workers (HCWs) vaccinated with COVID-19 vaccines (Aikewei or CoronaVac) composed of inactivated virus. We used a structured self-administered questionnaire to conduct two surveys on COVID-19 vaccination among HCWs in perinatal medicine and obstetrics/gynecology from April 5 to April 21, 2021. In total, 1392 HCWs who had received at least one vaccine dose were included. Of them, 1264 (90.8%) were females and 1047 (75.2%) received two doses. The overall incidence of any AEs after the first and second dose was 38.2% (532/1392) and 31.0% (325/1047) respectively ($\chi 2$ = 13.506, P = .0002). Female and HCWs aged 18–30 y were more likely to report AEs. The most common AEs were local reaction, accounting for 48.1% and 67.4% of all AEs after the first and second dose respectively. The systemic AEs were mainly neurological (9.8% and 4.8% after the first and second injection respectively) and flu-like symptoms (6.3% and 3.2%). Overall, most of AEs were mild, only 5.1% (after the first dose) and 2.8% (after the second dose) of individuals with AEs received symptomatic treatment or sick leaves, and none of them required hospitalization. Our data added more evidence that inactivated COVID-19 vaccines are highly safe. The data are valuable to overcome vaccine hesitancy associated with concerns about the safety of COVID-19 vaccines.

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Introduction

Coronavirus disease 2019 (COVID-19) has lead to global healthcare crisis because its causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been transmitted to all over the world and COVID-19 has a high fatality rate.[1,2] In addition, COVID-19 has caused adverse effects in patients with other diseases and in those who may be immunocompromised.[3–6] Universal vaccination in all populations should be the most effective way to control the pandemic of COVID-19. Since December 2020, several kinds of COVID-19 vaccines, including mRNA-based vaccine, non-replicating viral vector vaccine, inactivated virus, or protein subunit, have been developed, licensed, and recommended for use in human.[7–11] However, the real-world COVID-19 vaccination coverage in general populations as well as in healthcare workers (HCWs) was not as high as expected.[12–16] The reasons for the suboptimal coverage of COVID-19 vaccination are complicated, and an important one appears the concern about the safety of COVID-19 vaccines,[15,16] although clinical trials demonstrated that the vaccines are highly safe.[17–20] Therefore, more safety data from the real-world applications of COVID-19 vaccines are critical to increase the coverage of COVID-19 vaccination. In the current study, we presented the self-reported adverse events (AEs) in Chinese HCWs who were vaccinated with COVID-19 vaccine (Aikewei or CoronaVac) composed of inactivated SARS-CoV-2.

Subjects and methods

Participants

The China Health Authority issued the first licensed COVID-19 vaccine (Aikewei, Beijing Institute of Biological Products/Sinopharm, Beijing, China) composed of inactivated SARS-CoV-2 for emergency use in adult populations (at 18–60 y age) at risk for infection on December 30, 2020, and issued the second licensed inactivated COVID-19 vaccine (CoronaVac, Sinovac Life Sciences, Beijing, China) on February 5, 2021. The recommended full vaccination requires two injections at an interval 2–4 weeks. The COVID-19 vaccination was compulsory for all persons employed in hospitals as well as other populations at high risk for infection of SARS-CoV-2 during the initial period of the vaccination campaign. It was planned to complete the COVID-19 vaccination in all HCWs between January 1 and March 31, 2021. Each hospital made every effort to have all staff to receive COVID-19 vaccination.

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The present study was the detailed analysis of self-reported AEs in HCWs who were included in two cross-sectional surveys to investigate the actual acceptance of COVID-19 vaccination during the first three months period of the vaccination campaign among HCWs in the field of perinatal medicine and obstetrics/gynecology in China.[15,16] One survey was conducted among HCWs who participated in a nation-wide symposium on the perinatal medicine held Taiyuan city, April 16–18, 2021, and the survey was conducted by an online platform from April 9–21, 2021. The questionnaires contained the detailed questions in Chinese about AEs after the first and second dose of COVID-19 vaccination (Supplementary Material). In total, 1087 HCWs participated in the survey. Of them, 36 (3.3%) who provided incomplete responses were excluded, and 1051 (96.7%) who completed the survey were included in the analysis. Of these 1051 eligible participants, 86.2% (906) received at least one dose of COVID-19 vaccine.[15]

Another survey was conducted in Jiangsu province, involving HCWs who participated in a Jiangsu provincial symposium in perinatal medicine held in Nanjing city, April 10–11, 2021, and HCWs in the Department of Obstetrics and Gynecology, Nanjing Drum Tower Hospital, April 5–11. The questionnaire form used in this survey was same as that used in the above nation-wide symposium in Taiyuan city except that ethnic minority and religion were deleted, because 99.5% of the population in Jiangsu province is Han nationality. This survey was performed by distributing questionnaire form on-site so that we were able to directly communicate with the participants to exclude those who were planning to participate in the nation-wide symposium in Taiyuan city and those who were employed in Nanjing Drum Tower Hospital. Among the 269 participants in the symposium, 250 questionnaire forms were distributed, because 8 HCWs declined and 11 HCWs were not eligible. Of them, 22 did not submit the forms and 2 submitted the incomplete forms, and finally 226 (90.4%) forms were included in the analysis. Among all 422 HCWs in Obstetrics and Gynecology, Nanjing Drum Tower Hospital, 412 questionnaire forms were distributed, because 6 HCWs were not accessible and 4 HCWs were not eligible. Of them, 19 did not submit the forms and 1 submitted an incomplete form, and finally 392 (95.1%) forms were included in the analysis. Therefore, a total of 618 HCWs were included, and 79.0% (488) of them were vaccinated with at least one dose of COVID-19 vaccine.[16] These two surveys were approved by the Ethics Committee of the Nanjing Drum Tower Hospital (2021-138-01).

COVID-19 vaccines

The COVID-19 vaccines initially used in China were mainly composed of inactivated SARS-CoV-2 adsorbed on aluminum hydroxide adjuvant (Aikewei, Beijing Institute of Biological Products/Sinopharm, or CoronaVac, Sinovac Life Sciences, Beijing, China).[21,22] This study only included HCWs who received these two types of inactivated COVID-19 vaccines. The vaccine was intramuscularly injected in the deltoid muscle (usually left arm).

Survey contents about AEs after vaccination

In addition to questions on the demographic characteristics in the questionnaire form, we prepared a question of whether any AEs occurred after the first or second vaccine dose. If any AEs occurred, nine categories of questions about the detailed AEs were provided and the severity of AEs was included. The questionnaire form was in Chinese, which is presented in the Supplementary Material with English translation.

Statistical analyses

Categorical variables were reported as number and percentage. We used chi-squared test or the chi-squared test with Yates' correction for continuity to compare the rates between participants with reported AE and those without reported AE. $P < .05$ was considered statistically significant. Multivariable logistic regression analysis was performed to explore the risk factors associated with AEs after COVID-19 vaccination. All statistical analysis was performed using the R software (R version 4.04).

Results

Participant characteristics and the incidence of AEs in HCWs vaccinated with the first and second COVID-19 vaccine

In total, 1394 HCWs received COVID-19 vaccination. All, except for two who received the recombinant adenovirus vaccine, were vaccinated with inactivated SARS-CoV-2 vaccines (Aikewei or CoronaVac). Thus, 1392 HCWs were included in this study. The demographic characteristics, educational levels, and professional roles of HCWs who accepted the first COVID-19 vaccination are summarized in Table 1. Of them, 860 (61.8%) reported no any AEs, and 532 (38.2%) reported one or more AEs, including local pain at the injection site. The comparison of demographic characteristics between those with and without AEs showed that females, younger individuals, and those with junior profession titles were more likely to have AEs after the first vaccination, while other parameters, such as roles in hospital, hospital levels and university hospitals, were not associated with the occurrence of AEs (Table 1).

As of the completion of the survey, of the 1392 HCWs who accepted the first vaccine dose, 1047 (75.2%) received the second dose and 345 (24.8%) did not yet receive the second dose due to the shorter interval (less than 2 weeks), temporary lack of vaccine, catching cold, acute toothache, or other reasons. Of those vaccinated with the second dose, 722 (69.0%) reported no any AEs and 325 (31.0%) reported one or more AEs, including local pain at the injection site (Table 2). The overall incidence of any AEs after the second dose was significantly lower than the incidence of 38.2% after the first vaccine dose ($\chi 2 = 13.506$, $P = .0002$). The comparison of demographic characteristics between those with and without AEs after the second vaccination showed that female HCWs were more likely to have AEs, whereas other parameters, such as ages, educational levels, professional titles, roles in hospital, hospital levels and university hospitals, were not associated with the occurrence of AEs (Table 2).

Table 1. Comparison of demographic characteristics between vaccinees with and without adverse events (AEs) after the 1st dose of inactivated COVID-19 vaccine.

Variable	Total, N = 1392	Vaccinees without AEs, n = 860 (%)	Vaccinees with AEs, n = 532 (%)	Statistics	*P*
Gender				$\chi2 = 11.701$	.0006
Male	128	97 (75.8)	31 (24.2)		
Female	1264	763 (60.4)	501 (39.6)		
Age (years)				$\chi2 = 18.720$	.0003
18–30	301	178 (59.1)	123 (40.9)		
31–40	511	287 (56.2)	224 (43.8)		
41–50	360	239 (66.4)	121 (33.6)		
51–60	220	156 (70.1)	64 (29.1)		
Education				$\chi2 = 9.991$	.0186
Doctorial degree	127	86 (67.7)	41 (32.3)		
Master	355	220 (62.0)	135 (38.0)		
University (Bachelor)	817	485 (59.4)	332 (40.6)		
Below University	93	69 (74.2)	24 (25.8)		
Departments				$\chi2 = 4.961$	.0837
Obstetrics/Gynecology	1143	700 (61.2)	443 (38.8)		
Pediatric	142	99 (69.7)	43 (30.3)		
Others	107	61 (57.0)	46 (43.0)		
Roles				$\chi2 = 6.480$	.0905
Physician	845	544 (64.4)	301 (35.6)		
Nurse/midwife	429	245 (57.1)	184 (42.9)		
Laboratory technician	82	52 (63.4)	30 (36.6)		
Others	36	20 (55.6)	16 (44.4)		
Professional title				$\chi2 = 9.144$	.0274
High (senior)	202	139 (68.8)	63 (31.2)		
High (junior)	282	184 (65.2)	98 (34.8)		
Middle	449	259 (57.7)	190 (42.3)		
Primary	459	278 (60.6)	181 (39.4)		
Hospital level				$\chi2 = 2.146$	.3421
High	1136	696 (61.3)	440 (38.7)		
Middle	219	137 (62.6)	82 (37.4)		
Low	37	27 (73.0)	10 (27.0)		
University hospital				$\chi2 = 2.039$	.1533
Yes	955	578 (60.5)	377 (39.5)		
No	437	282 (64.5)	155 (35.5)		

Table 2. Comparison of demographic characteristics between vaccinees with and without adverse events (AEs) after the 2nd dose of inactivated COVID-19 vaccine.

Variable	Total, N = 1047	Vaccinees without AEs, n = 722 (%)	Vaccinees with AEs, n = 325 (%)	Statistics	*P*
Gender				$\chi2 = 5.003$	.0253
Male	103	81 (78.6)	22 (21.4)		
Female	944	641 (67.9)	303 (32.1)		
Age (years)				$\chi2 = 1.099$	.7773
18–30	223	150 (67.3)	73 (32.7)		
31–40	378	260 (68.8)	118 (31.2)		
41–50	264	181 (68.6)	83 (31.4)		
51–60	182	131 (72.0)	51 (28.0)		
Education				$\chi2 = 1.561$	.6683
Doctorial degree	100	70 (70.0)	30 (30.0)		
Master	251	172 (68.5)	79 (31.5)		
University (Bachelor)	634	433 (68.3)	201 (31.7)		
Below University	62	47 (75.8)	15 (24.2)		
Departments				$\chi2 = 0.527$	.7685
Obstetrics/Gynecology	904	624 (69.0)	280 (31.0)		
Pediatric	98	69 (70.4)	29 (29.6)		
Others	45	29 (64.4)	16 (35.6)		
Roles				$\chi2 = 3.486$	.3226
Physician	660	463 (70.2)	197 (29.8)		
Nurse/midwife	308	202 (65.6)	106 (34.4)		
Laboratory technician	57	43 (75.4)	14 (24.6)		
Others	22	14 (63.6)	8 (36.4)		
Professional title				$\chi2 = 0.504$	.9181
High (senior)	162	115 (71.0)	47 (29.0)		
High (junior)	219	150 (68.5)	69 (31.5)		
Middle	332	230 (69.3)	102 (30.7)		
Primary	334	227 (68.0)	107 (32.0)		
Hospital level				$\chi2 = 3.543$	.1700
High	828	560 (67.6)	268 (32.4)		
Middle	183	134 (73.2)	49 (26.8)		
Low	36	28 (77.8)	8 (22.2)		
University hospital				$\chi2 = 2.645$	.1039
Yes	681	458 (67.3)	223 (32.7)		
No	366	264 (72.1)	102 (27.9)		

Detailed AEs in vaccinees

The detailed AEs in the HCWs after the first and second vaccine dose are listed in Table 3. The most common self-reported AEs were local pain, redness, swelling, or itch at the injection site in the absence of any other AEs, which accounted for 48.1% and 67.4% of all AEs after the first and second vaccine dose, respectively (Table 3). The second and third most common AEs were neurological (9.8% and 4.8% after the first and second dose respectively) and flu-like (6.3% and 3.2%) symptoms respectively. The other AEs included fever (2.15% and 0.9%), gastroenterological (3.1% and 1.1%) and respiratory (1.1% and 0.7%) symptoms and allergic reactions (1.4% and 0.8%). Notably, 22 and 10 had menstrual disorders after the first and second vaccine dose respectively.

Table 3 also shows that, of the 532 HCWs with AEs after the first vaccine dose, 505 (94.9%) just had mild symptoms and required no treatment, 27 (5.1%) received symptomatic treatment or took sick leaves, and none (0%) required hospitalization. Of the 325 HCWs with AEs after the second vaccine dose, 316 (97.2%) required no treatment, 9 (2.8%) received the treatment, and none (0%) needed hospitalization (Table 3).

Incidence of AEs after the second vaccine dose in HCWs with or without AEs after the first dose

Of the 532 HCWs who had AEs and the 860 HCWs who had no AEs after the first vaccination, 381 (71.6%) and 666 (77.4%) received the second vaccination respectively. The incidence of AEs in these HCWs after the second vaccination is presented in Figure 1. Following the second vaccination, those who had AEs after the first vaccination reported higher frequencies of AEs than those who did not have AEs after the first vaccination (61.9% vs 13.7%, $\chi^2 = 263.012$, $P < .0001$).

Comparison of incidence of AEs after the first and second vaccine doses in HCWs

In total, 1047 HCWs were fully vaccinated with two doses of inactivated COVID-19 vaccine. We compared the incidences of AEs after the first and second vaccine doses (Table 4). The results showed that the incidence of AEs after the second vaccine dose was significantly lower than that after the first vaccine dose (31.0% vs. 36.7%, $\chi^2 = 14.565$, $P = .0001$).

Risk factors associated with AEs after COVID-19 vaccination

Table 5 presents the risk factors associated with AEs after the first and second vaccine dose determined with the binary logistic regression analysis. Compared with male subjects, female subjects appeared to have reported more AEs. In addition, compared to those aged 18–30 y, subjects aged 51–60 y were less likely to have AEs after the first vaccination.

Table 3. The incidence and proportion of adverse events (AEs) in vaccinees after the 1st and 2nd dose of inactivated vaccine.

	After the 1st dose, N = 1392			After the 2nd dose, N = 1047		
Type of AEs	No of vaccinees	Incidence (%)	Proportion (%)	No of vaccinees	Incidence (%)	Proportion (%)
Total No of Any AEs	532	38.2	100	325	31.0	100.0
Local AEs*	398	28.6	74.8	272	26.0	83.7
With no other AEs	256	18.4	48.1	219	20.9	67.4
With other AEs	142	10.2	26.7	53	5.1	16.3
Headache, dizziness, insomnia	137	9.8	25.8	50	4.8	15.4
With no other event	79	5.7	14.9	31	3.0	9.5
With any other event	58	4.2	10.9	19	1.8	5.9
Flu-like events	87	6.3	16.4	34	3.2	10.5
Fever (°C)	30	2.15	5.64	9	0.9	2.8
≥39.0	1	0.07	0.19	0	0	0
38–38.9	2	0.14	0.38	1	0.1	0.3
<38	27	1.94	5.07	8	0.8	2.5
Loss of appetite, nausea, vomiting, abdominal pain, or diarrhea	43	3.1	8.1	11	1.1	3.4
With no other event	22	1.6	4.1	4	0.4	1.2
With any other event	21	1.5	4.0	7	0.7	2.2
Cough, sputum, shortness of breath	16	1.1	3.0	7	0.7	2.2
With no other event	9	0.6	1.7	4	0.4	1.2
With any other event	7	0.5	1.3	3	0.3	1.0
Skin allergic events	19	1.4	3.6	8	0.8	2.5
With no other event	8	0.6	1.5	6	0.6	1.9
With any other event	11	0.8	2.1	2	0.2	0.6
Menstrual changes	22	2.1†	4.1	10	1.0†	3.1
Menstruation delay	15	1.4	2.8	6	0.6	1.9
Early menstruation	4	0.4	0.7	3	0.3	0.9
Menorrhagia	2	0.2	0.4	1	0.1	0.3
Prolonged period	1	0.1	0.2	0	0.0	0.0
Severity of AEs						
Mild	505	36.3	94.9	316	30.2	97.2
Moderate	27	1.9	5.1	9	0.9	2.8
Severe	0	0	0	0	0	0

*Pain, erythema, swelling, or itch on injection site. †The denominators were those women at the age of ≤50 y who were assumed to still have menstruation as the average age of menopause in China is around 50 y. 1073 and 943 women with the age ≤50 y accepted the 1st and 2nd vaccination respectively.

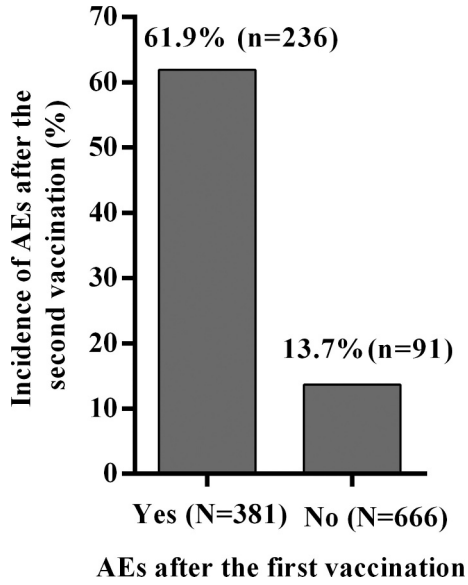

Figure 1. Incidence of adverse events (AEs) after the second vaccination in those with or without AEs following the first vaccination. the difference was statistically significant ($\chi 2$ = 263.012, P <.0001).

Table 4. The incidence of adverse events (AEs) after the 1st and 2nd vaccine dose in 1047 subjects who received the full vaccination*.

	After the 1st dose		
	AEs	No AEs	Total
After the 2nd dose			
AEs	235	90	325 (31.0%)
No AEs	149	573	722
Total	384 (36.7%)	663	1047

*The incidence of AEs after the 1st and 2nd vaccination was statistically significant ($\chi 2$ = 14.565, P = .0001) by McNemar test.

Table 5. Risk factors of adverse events after the 1st and 2nd vaccine dose analyzed with binary logistic regression.

Covariates	*B*	*SE*	*OR*	*OR* 95% *CI*	Wald $\chi 2$	*P*
After the 1st vaccination						
Sex (Female:Male)	0.6945	0.2157	2.003	1.31–3.06	10.364	.0013
Age (51–60:18–30)	−0.4822	0.1901	0.617	0.43–0.90	6.433	.0112
Age (41–50:18–30)	−0.2951	0.1624	0.744	0.54–1.02	3.301	.0692
Age (31–40:18–30)	0.1414	0.1479	1.152	0.86–1.54	0.914	.3391
Constant	−1.0240	0.2361	–	–	18.813	<.0001
After the 2nd vaccination						
Sex (Male:Female)	0.5058	0.2463	1.658	1.02–2.69	4.217	.0400
Constant	−1.2584	0.2362	–	–	28.377	<.0001

Discussion

In the present study, we revealed that AEs occurred in 38.2% and 31.0% of HCWs after the first and second dose of inactivated COVID-19 vaccines respectively, and the local reactions accounted for 48.1% and 67.4% of all AEs respectively. The most systemic AEs were headache (9.8% and 4.8%) and flu-like symptoms (6.3% and 3.2%). Only 5.1% and 2.8% of HCWs who had AEs after the first and second vaccination respectively received symptomatic treatment or sick leave, and none of them required hospitalization. These data indicate that the COVID-19 vaccines composed on inactivated SARS-CoV-2 are highly safe in the real-world application.

In the phase 1/2 clinical trials, any AEs occurred in 15.0% (36/240) to 29.0% (42/144) of the Chinese subjects injected with the inactivated COVID-19 vaccines (CoronaVac and Aikewei).[21–23] In the phase 3 clinical trials of these inactivated COVID-19 vaccines, the United Arab Emirates reported any AEs in 41.7% (5623/13471) to 44.2% (5957/13464) of the participants,[17] and Turkey reported any AEs in 18.9% (1259/6646) of the CoronaVac recipients.[24] The considerably varied incidence of AEs after the vaccination was also observed in clinical trials of other types of COVID-19 vaccines.[25] In our present survey, the incidence (38.2% after the 1st dose and 31.0% after the 2nd dose) of self-reported AEs appeared to be within the range reported in clinical trials. Other investigators reported a wide range of the incidence (from fewer than 3% to 82.6%) of any AEs following inactivated COVID-19 vaccination in the actual application.[26–31] The substantial difference in the reported incidence of AEs after the vaccination might be related with different populations and different definitions of AEs.

In the present study, the vaccinees who had AEs after the first vaccine dose were much more likely to have AEs after the second dose (Figure 1), which is in agreement with the findings reported by Zhang et al.[27] This suggests that some individuals are prone to have AEs. The binary logistic regression analysis showed that females and young subjects were more likely to experience AEs (Table 5), which have been observed in individuals injected with mRNA or adenovirus-vector COVID-19 vaccines and other vaccines.[28,29,31–34]

Notably, the data in clinical trials and real-world applications showed that, among those who were injected with mRNA or adenovirus-vectored vaccines against COVID-19, any AEs occurred in as high as more than 70% to 95% of the recipients and the systemic SEs were observed in more than 47% to 85.9%.[13–37–39] Studies showed that inactivated COVID-19 vaccines have the lowest reported AEs.[31,40] On the other hand, mRNA vaccines appear to have higher antibody response and better protection against COVID-19 than inactivated vaccines.[41,42] These results suggest that the occurrence of AEs may be related to the strength of the immune response; the higher the immune responses, the more frequency of AEs.

In addition to the local and systemic AEs, we found that 2.1% and 1.0% of women aged 18–50 y reported menstrual changes after the first and second COVID-19 vaccination respectively (Table 3). Irregular menstrual changes have also been observed in women vaccinated with other types of COVID-19 vaccines.[38,43] Whether the irregular menstrual change was associated with COVID-19 vaccination or was a co-incident event requires further investigation.

Of interesting, we revealed that AEs occurred less frequently after injection of the second dose of inactivated COVID-19 vaccine (Table 3), which was also observed in Jordanian population,[31] or in Indian population vaccinated with different inactivated COVID-19 vaccine.[44] These findings are practically useful. In the real-world practice, some individuals were reluctant to receive second vaccine dose because of the AEs occurred after the first vaccination. The finding of the lower incidence of AEs after the second dose can be used by health providers to encourage those who had AEs after the first dose to receive the second dose.

This study has several limitations. First, because HCWs in the present study were from perinatal medicine and obstetrics and gynecology, the female subjects accounted for more than 90% of total participants, which may over-estimated the incidence of AEs, since females are more likely to have AEs after vaccination.[28,29,31–34] Second, since the participants were vaccinated in the first period of the vaccination campaign, during which those who had chronic diseases were mostly not vaccinated, whether those with chronic diseases may have more AEs is unknown. Third, since the vaccinated subjects were at the age of 18–60 y, the incidence of AEs in those who are older than 60 y or younger than 18 y is still unknown. Fourth, we did not compare the frequency of AEs between the two types of inactivated COVID-19 vaccines. Fifth, we did not follow up the long-term AEs after COVID-19 vaccination.

In conclusion, the present study showed that AEs after the first and second dose of COVID-19 vaccines composed of inactivated SARS-CoV-2 are mostly local reactions, and the systemic AEs are generally mild and well tolerated. Female and young individuals are more likely to have AEs after COVID-19 vaccination. The real-world evidence of COVID-19 vaccine safety should be valuable to overcome the vaccine hesitancy.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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