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COVID-19 vaccines safety tracking (CoVaST): Part I

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Published in
Frontiers in Public Health
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-83251-879-3
DOI 10.3389/978-2-83251-879-3

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COVID-19 vaccines safety tracking (CoVaST): Part I

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Citation

Riad, A., Klugar, M., Marc, J., Pérez-Gaxiola, G., Attia, S., Peričić, T. P., eds. (2023). *COVID-19 vaccines safety tracking (CoVaST): Part I*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-879-3

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frontiers | Frontiers in Public Health

TYPE Editorial
PUBLISHED 24 February 2023
DOI 10.3389/fpubh.2023.1154500

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Infectious Diseases: Epidemiology and Prevention, a section of the journal Frontiers in Public Health

RECEIVED 30 January 2023
ACCEPTED 08 February 2023
PUBLISHED 24 February 2023

CITATION
Klugar M, Attia S, Pérez-Gaxiola G, Poklepović Peričić T, Marc J and Riad A (2023) Editorial: COVID-19 Vaccines Safety Tracking (CoVaST): Part I. *Front. Public Health* 11:1154500. doi: 10.3389/fpubh.2023.1154500

Editorial: COVID-19 Vaccines Safety Tracking (CoVaST): Part I

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KEYWORDS

COVID-19, side effects, vaccination, cross-sectional study, VAERS, Vaccine Adverse Event Reporting System, systematic review

Editorial on the Research Topic
COVID-19 Vaccines Safety Tracking (CoVaST): Part I

Acceleration of coronavirus disease (COVID-19) mass vaccination has been a chief priority for health systems globally since the first emergency approvals of COVID-19 vaccines in late 2020. Nevertheless, vaccine hesitancy (VH), which is nourished by misinformation about vaccines' effectiveness and safety, remains as a serious threat for vaccination strategies worldwide. Aversion to post-vaccination side effects, the lack of trust of pharmaceutical industry, and the lack of knowledge about vaccines' safety are among the VH drivers; therefore independent (non-sponsored) and active surveillance of COVID-19 vaccines safety is of utmost importance for suppressing VH.

This was a motivation for our team to initiate a global study which will be focused on the COVID-19 Vaccines Safety Tracking (CoVaST). We registered this study as the first of its kind with the US National Library of Medicine registry (ClinicalTrials.gov, accessed on 9 May 2021), with the identifier NCT04834869 and published the "*Protocol of a Multi-Center Prospective Cohort Study for Active Surveillance of COVID-19 Vaccines' Side Effects*" (1) together with our international partners from 24 institutions worldwide.

Our next logical step was the registration of the Research Topic with a prestigious, highly impactful journal focused on public health. The overarching aim of this Research Topic was to synthesize a collection of studies that evaluate the short-term side effects of different types of COVID-19 vaccines; i.e., mRNA-based, viral vector-based, inactivated virus-based, and protein subunit-based vaccines in various countries worldwide. The post-vaccination side effects can be evaluated either using the data of passive surveillance systems; e.g., VAERS, DAEN, EudraVigilance, etc., or through active surveillance (epidemiological) studies; e.g., cohort, cross-sectional studies, etc., and we were open also to research synthesis study designs.

We received 22 relevant submissions and accepted 15 articles after rigorous peer review and editorial process. Most of the accepted articles are epidemiological "active surveillance" studies, although three passive surveillance studies were included as well, together with two systematic reviews and two literature reviews (one with case series).

All included studies reported the good safety of all included vaccines against COVID-19. The prevalence of local and systemic side effects was modest. Most of the symptoms disappeared after 3 days. The risk-benefit ratio of vaccination remains positive compared to potential SARS-CoV-2 infection. Although all included studies except one systematic review, which meta-analyzed six randomized controlled trials with 6,427 participants in the observation group and 3,535 participants in the control group that reported safety data, are limited by their descriptive observational nature.

The mentioned systematic review from Du et al., evaluated the safety, immunogenicity, and efficacy of COVID-19 vaccines in adolescents, children and infants (0–17 years). Compared with mRNA vaccines and adenovirus vector vaccines, inactivated vaccines have a more satisfactory safety profile, both after the initial (RR 1.40, 95% CI 1.04–1.90) and booster (RR 1.84, 95% CI 1.20–2.81) vaccination. The risk of adverse events statistically significantly increased after the first and second doses, but there was no statistically significant difference between the first two doses (RR 1.00, 95% CI 0.99–1.02). Nevertheless, the two-dose regimen is obviously superior to the single-dose schedule for immunogenicity and efficacy. After booster vaccination, both neutralizing antibodies (RR 144.80, 95% CI 44.97–466.24) and RBD-binding antibodies (RR 101.50, 95% CI 6.44–1,600.76) reached optimal levels, but the cellular immune response did not appear to be further enhanced.

All descriptive cross-sectional studies of self-reported side effects consistently report local and systemic side effects with nuances coming from different types of vaccines, different age, and population groups. From Mexico Moll et al., (n = 4,024) at dose 1, ChAdOx1 was the vaccine with the highest rate of at least one side effect (85%) followed by Gam-COVID-Vac (80%). Both were associated with greater extension (adjusted OR 2.53, 95% CI 2.16, 2.96 and adjusted OR 2.41, 95% CI 1.76, 3.29, respectively) and severity of side effects (adjusted OR 4.32, 95% CI 3.73, 5.00, and adjusted OR 3.00, 95% CI 2.28, 3.94, respectively). Young age (<50 years), female sex, comorbidity, and history of allergies were associated with greater extension and severity, independent of the type of vaccine and potential confounders. From 721 Algerian healthcare workers, Lounis et al., self-reported post-vaccination side effects of inactivated (BBIBP-CorV and CoronaVac) and adenoviral vector-based (AZD1222, Gam-COVID-Vac, and Ad26.COV2.S) vaccines. Less than half (49.1%) of the respondents reported at least one local side effect, while 53.8% reported at least one systemic side effect. These side effects were more prevalent among viral vector vaccinees than inactivated virus vaccinees. The side effects appeared earlier among inactivated virus vaccines recipients and generally lasted for 2–3 days for the two vaccinated groups. The risk factors associated with a higher prevalence of side effects included female gender, allergic individuals and individuals with regular medication. Data from Saudi Arabia on 1058 participants from the general population Al-Hanawi et al. observed that the most common vaccine side effects reported were tiredness/fatigue (52.6%), swelling (38%), fever (31.3%), headache (29.1%), and muscle pain (22.2%). In multivariable analyses, the odds of experiencing severe side effects were significantly higher among males [adjusted odds ratio (aOR) = 2.76, 95% confidence interval (CI) = 1.71–4.45, $p < 0.01$], those aged 40–49 years (aOR = 3.10, 95% CI = 1.10–8.72, $p < 0.1$), and Saudi nationals (aOR = 3.64, 95% CI = 1.58–8.38, $p < 0.05$) compared to their counterparts. Among those who had received two doses, a higher proportion had received Pfizer-BioNTech (54.2%) than AstraZeneca/Oxford (33.1%). Data from Ethiopia on a sample of 346 healthcare workers Yesuf et al., reported after the Oxford AstraZeneca COVID-19 vaccine prevalence of at least one local- and systemic-side effect was 50.6 and 44.5%, respectively. The most frequent local- and systemic- side effects were injection site pain and headache, respectively. Both types of side effects mostly subsided in the first 3 days. These data are consistent with other studies which used similar standardized tools as Yesuf et al. and Lounis et al. (2–6).

Another observational study among a population with stroke risk was reported on 1,747 participants from China Wu et al. the incidence of adverse events after the first and second dose was 16.6 and 13.7%, respectively. There was no difference in the incidence of adverse reactions among different risk groups. Sex, vaccine type, sleep quality, worry of adverse events, age, and education level were statistically significantly related to adverse reactions to vaccination.

One small observational study from Italy Reschini et al. on a sample of 106 men tested a hypothesis rather popular amongst conspirative theories regarding the impact of immunization on future fertility. The study concluded that no difference was observed even after considering different types of vaccines (viral vector or mRNA). The vaccination did not affect sperm quality and fertilization capacity of men undergoing assisted reproduction technology attempts.

Wound healing and scar formation were reported on small case series n = 31 to be not affected by the COVID-19 vaccination Dong et al. Case reports of four patients with myocarditis early after mRNA vaccination demonstrated the need for multimodal diagnostics, Nunn et al., however with certain limitations, authors concluded the risk-benefit ration of vaccination remains positive.

Three of included studies in our Research Topic were reporting the passive surveillance data based on the analyses of the Vaccine Adverse Event Reporting System (VAERS) co-managed by the United States Food and Drug Administration and the Centers for Diseases Control and Prevention. Analyses from Zou et al. showed that the most commonly reported adverse events of COVID-19 vaccines were mild. Cases with mortality outcomes tended to occur in older adults. However, the World Health Organization international database study did not identify significant safety concerns regarding mRNA vaccination in real-world settings. The authors reported an overall lower risk of serious adverse events following mRNA vaccines when compared to influenza vaccines. There were 103 (0.5%) deaths out of 18,755 COVID-19 vaccine-related AEs and 104 (0.4%) deaths out of 27,895 influenza vaccine-related AE (7). Bian et al. analyzed VAERS data from the perspective of allergic reactions after the COVID-19 vaccination and concluded that female predominance in allergic reaction cases after the receipt of COVID-19 vaccines was observed. Previous histories of allergies, asthma, or anaphylaxis

were risk factors for anaphylaxis post-vaccination. Riad et al., focused their VAERS analyses on the oral adverse events following COVID-19 vaccination and reported that COVID-19 vaccines were found to be associated with rare oral adverse events that are predominantly similar to those emerging following seasonal influenza vaccines.

All included studies brought the best available evidence about short-term vaccine safety, which seems not to differ significantly from influenza vaccines. More evidence of the safety of COVID-19 vaccines is still needed to help make informed public decisions about their benefits, as there are newly developed booster doses of vaccines, and the virus is still mutating. It is important and challenging to collect longitudinal data about the safety of the COVID-19 vaccines.

Author contributions

MK: drafted the manuscript. SA, GP-G, TP, JM, and AR: reviewed, edited, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
published: 02 February 2022
doi: 10.3389/fpubh.2022.839967

COVID-19 Vaccination Does Not Affect Reproductive Health Parameters in Men

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: *20 December 2021*
Accepted: *10 January 2022*
Published: *02 February 2022*

Citation:
Reschini M, Pagliardini L, Boeri L, Piazzini F, Bandini V, Fornelli G, Dolci C, Cermisoni GC, Viganò P, Somigliana E, Coccia ME and Papaleo E (2022) COVID-19 Vaccination Does Not Affect Reproductive Health Parameters in Men. Front. Public Health 10:839967. doi: 10.3389/fpubh.2022.839967

With the implementation of COVID-19 vaccine up-take, doubts regarding the impact of immunization on future fertility have begun to emerge. We have examined vaccine safety on male reproductive health. We set up a multicentre (three infertility centers), retrospective study in order to assess semen parameters and fertilization rate of one hundred-six men in a pairwise comparison between the first and second assisted reproduction technology (ART) attempt, performed respectively before and after COVID-19 vaccination. Median time (range) between the first vaccine dose and the second ART cycle was 75 days (39–112). Semen parameters did not change before and after the exposure. Fertilization rate was also similar before and after vaccination. Twenty-five patients (24%) were oligozoospermic before the vaccination while 26 (25%) after the exposure ($P = 0.87$). Severe asthenozoospermia were present in 11 patients before as well as after the exposure. No difference was observed even after considering different types of vaccines (mRNA or viral vector). COVID-19 vaccination did not affect sperm quality and fertilization capacity of men undergoing ART treatments and should be considered safe for men's reproductive health.

Keywords: reproduction, COVID-19 vaccine, infertility, fertilization rate, semen, sperm, fertilization

INTRODUCTION

Both types of COVID-10 vaccines, the messenger RNA (mRNA) vaccines and the vaccines utilizing a viral vector, have been shown to reduce COVID-19 infections, transmissions, hospitalizations and deaths in randomized controlled trials and real-world effectiveness studies (1). Evidence of the short- to medium-term safety of these vaccines is accumulating. Besides the common and usually mild side effects, such as the low-grade fever and the pain at the injection site, some major, but thankfully, uncommon, adverse reactions have been reported during the post marketing surveillance phase (2–4). The identification of other adverse events is now a global scientific priority.

Despite the high efficacy found in clinical trials, a sizeable minority of people in civilized countries does not plan to get a COVID-19 vaccine. The speed and urgency at which the vaccines were initially created and authorized caused some concern. With the implementation of the vaccine up-take, questions regarding the impact of the vaccine on future reproductive health have begun to emerge. Headlines have appeared across multiple social media platforms questioning the effects of the newly authorized vaccines on fertility, with little or no scientific evidence supporting the claims. In this regard, recent studies have shown that both BNT162b2 and mRNA-1273 vaccinations have no influence on sperm parameters of 45 young volunteers (5, 6). However, the impact of the vaccine on gamete functional competence has not been assessed. Moreover, in this selected young population, the overall presence of semen parameters within the normal ranges may have hidden subtle differences potentially attributed to the vaccine. Therefore, in a larger sample of patients undergoing infertility treatments for pregnancy seeking, we have evaluated semen parameters in a pairwise comparison between the first and second assisted reproduction technology (ART) attempt, performed respectively before and after COVID-19 vaccination. Fertilization rate as an indicator of sperm developmental competence has also been measured before and after the exposition to the vaccine (7). The potential effects of the two different vaccine-types were also considered.

METHODS

Study Design

The study design was developed to examine vaccine safety. We compared (for each case) the parameters of interest after the exposure (after vaccination) with those observed in the unexposed period (baseline). The study was restricted to men who met the following eligibility criteria: (i) age $>$ 18 years; (ii) have undergone two cycles of intrauterine insemination (IUI) or *in vitro* fertilization (conventional IVF or ICSI) before and after vaccination in the context of the couple's infertility management; (iii) evaluation of basal semen parameters before and after the exposure in the context of the infertility management. Those with COVID-19 symptoms or a positive test result within 90 days were excluded. None of the patients received any fertility-based medical treatments or surgical interventions between the unexposed and exposed periods. Men provided semen samples after 2 to 4 days of abstinence. IUI and IVF were standardized and performed as previously described (8–10). For IVF, oocyte collection was performed 36 h after triggering of ovulation. After 2–3 h incubation, oocytes were allocated to conventional *in vitro* fertilization or ICSI based on the semen characteristics. For ICSI, denudation of the cumulus oophorus was performed as previously described (11). Inseminated or injected oocyte were cultured in microdrops of specific medium under oil. Sixteen-eighteen hours after insemination or ICSI, all oocytes were checked for fertilization (two pronuclei) as previously described (12).

Outcome Measures

Semen evaluation was performed before and after vaccination on the days of oocyte retrieval for IVF or on the same days of IUI. The analysis was done in the andrology laboratory, located nearby the embryology laboratory by trained embryologists. All semen parameters were assessed according to the 2010 World Health Organization (WHO) guideline laboratory manual for the examination and processing of human semen as previously described (13). The following variables were taken into consideration: volume (mL), sperm concentration (Number/mL), motility (%) and morphology (%). Sperm motility was graded into total (progressive + non-progressive motility) and progressive motility. Total sperm count (volume $\times$ sperm concentration) and total number of progressively motile sperm (%) were also calculated. Both internal and external quality control programmes have been established in the laboratories in order to control random and systematic errors and interlaboratory differences. Fertilization rate was calculated by dividing the number of fertilized oocytes by the total number of metaphase II oocytes retrieved on the basis of the recommendations of the Vienna Consensus (14).

Statistical Analysis and Sample Size Calculation

A sample size of 90 patients was calculated on the basis of a 25% incidence of oligozoospermia (sperm concentration $<$ 15 million/ml) reported in a population of men attending an infertility center, setting type 1 and 2 errors at 0.05 and 0.20, respectively and considering as clinically relevant an increase in frequency of 15% after the vaccination (25 vs. 40% after the vaccination).

Statistical analyses were performed using Statistical Package for Social Science (SPSS) for Windows, Version 26.0 (SPSS Inc., Chicago, IL). Reference values of semen analyses were based on WHO parameters. Data are presented as number (%) mean $\pm$ Standard Deviation (SD), or median [Interquartile range–IQR] A binomial exact distribution model was used to estimate the 95% Confidence Interval (95%CI) of proportions.

RESULTS

One hundred and six men were ultimately included. Baseline characteristics are shown in **Table 1**. The median [IQR] age was 39 [36–42] years. All the subjects underwent a semen analysis before and after vaccination in the context of the infertility treatments. Eighty-two men received two vaccine doses between the two infertility treatments while twenty-two received a single dose. Frequency of the various types of vaccine received and time occurred between the vaccine exposure and the following semen analysis is reported in **Table 1**. Forty-five percent of the patients reported mild, self-resolving adverse events after the vaccine including pain at injection site, fever, fatigue, nausea, muscle pain, diarrhea and lymphadenopathy.

Of the included subjects, 89 (84%) underwent two attempts of IVF while IUI procedures were performed in 17 patients.

TABLE 1 | Baseline characteristics of the ART population analysed.

Characteristics	Number (%) or median [IQR]
Number of cases	106
Age	39 [36–42]
Technique	
IUI	17 (16%)
IVF	89 (84%)
COVID-19 Vaccines	
Pfizer-BioNTech	73 (69%)
Moderna	20 (19%)
Oxford/AstraZeneca	10 (9%)
Johnson & Johnson's Janssen	1 (1%)
Mixed vaccines	2 (2%)
(AstraZeneca + Moderna and Pfitzer + AstraZeneca)	
Time between first vaccine dose and subsequent ART cycle (days)	75 [39–112]
Time between second dose and subsequent ART cycle[a] (days)	59 [28–100]

[a] *82 patients received the vaccine second dose.*

The latter population was used only for the evaluation of semen parameters.

Pairwise comparisons of fertilization rates and semen parameters before and after the exposure for the entire cohort are summarized in **Table 2**. Fertilization rate was similar before and after vaccination. Similarly, the various semen parameters did not change before and after the exposure. Twenty-five patients (24%) were oligozoospermic before the vaccination while 26 (25%) after the exposure ($P = 0.87$). Severe asthenozoospermia were present in 11 patients (10%) before as well as after the exposure. None of the patients was azoospermic after the vaccination nor one had a severe deterioration of the semen parameter.

Even considering only the cohort of patients who received two doses ($n = 82$), results were similar. Median [IQR] rate of fertilization of partner's oocyte was 75 [50–100] before and 80 [50–100] after the exposure ($P = 0.87$). The median [IQR] sperm concentration/ml was 41 [14–70] before and 36 [14–66] post vaccination ($P = 0.90$) and the median [IQR] total number of spermatozoa was 86 [30–150] before and 81 [24–150] after ($P = 0.33$). Percentages of progressive motility [median (range) 41 (30–55) before and 40 (30–50) after the vaccine; $P = 0.15$] and total motility [median (range) 52 (40–62) before and 50 (40–60) after the vaccine; $P = 0.23$] did not change as well after the vaccination. Median [IQR] percentage of morphologically normal forms were 4 [2–6] before the exposure and 4 [3–6] following the vaccine, $P = 0.09$. Finally, the total number of progressively motile spermatozoa/ml was similar in the pre- and post-exposure period [median (range) 34.4 (9.0–70.2) before and 32.9 (8.9–67.9) after the vaccine; $P = 0.55$].

No difference was observed for any of the outcome considered in the pairwise comparisons before and after the vaccine exposure as divided according to the vaccine type (**Supplementary Table 1**).

Finally, no difference was observed for any of the outcome considered in the pairwise comparisons before and after the vaccine exposure in the subgroup of patients that reported vaccine-associated symptoms (data not shown).

DISCUSSION

This study was specifically designed to investigate the impact of COVID-19 vaccination on semen parameters in a cohort of infertile men belonging to couples undergoing ART programs at three tertiary referral centers in Italy. Of clinical importance, we found that COVID-19 vaccination had no impact on fertilization rate and sperm parameters. This was even true after considering different types of vaccines (mRNA or viral vector).

The study was motivated by the substantial lack of data, and the related public uncertainties, regarding the potential negative impact of COVID-19 vaccination on men's reproductive health. Particularly, little is known about the effect of COVID-19 vaccination on sperm function and quality and, because of this, one of the reported reasons for vaccine hesitancy is the potential negative effect on fertility (15).

Previous studies have demonstrated that COVID-19 infection negatively affects men's reproductive health. In terms of serum hormones, an independent association between SARS-CoV-2 infection status and secondary hypogonadism was observed, with lower testosterone levels predicting the most severe clinical outcomes (16). Furthermore, more than half of men who recovered from the disease still had circulating testosterone levels suggestive for a condition of hypogonadism after several month (17).

It is known that SARS-CoV-2 infects host cells through angiotensin-converting enzyme 2 (ACE2) receptors and that transmembrane serine protease 2 (TMPRSS2) also plays a major role in the entry of SARS-CoV-2 into the cell (18). ACE2 and TMPRSS have been shown to be highly expressed in spermatogonia and Sertoli and Leydig cells, thus suggesting that SARS-CoV-2 infection may affect the testis and lead to possible harmful effects on spermatogenesis (19). Duarte-Neto et al. described the pathological findings in testes from fatal cases of COVID-19, including the detection of viral particles and antigens and inflammatory cell subsets (20). By using post-mortem testicular samples by percutaneous puncture from 11 deceased men, Authors found decreased Leydig and Sertoli cells with reduced spermatogenesis in all cases. Immunohistochemistry detected SARS-Cov-2 antigen in Leydig cells, Sertoli cells and spermatogonia; electron microscopy detected viral particles in the cytoplasm of fibroblasts, endothelium, Sertoli and Leydig cells, spermatids, and epithelial cells of the rete testis in four cases, while RT-PCR detected SARS-CoV-2 RNA in three cases (20). Nonetheless, the presence of the virus in semen of COVID-19 patients was found to be poor. He et al. (21) analyzed the presence of SARS-CoV-2 in semen, testis, and prostatic fluid as well as the effects of COVID-19 on male reproductive function. Among the 15 semen studies in their review (290

TABLE 2 | Fertilization rate and semen parameters as evaluated in a pairwise comparison between the first and second ART attempt, performed respectively before and after COVID-19 vaccination.

Variables	Pre-vaccination	Post-vaccination	*p*-value
Volume (ml)	2.5 [1.5–3.0]	2.5 [1.8–3.0]	0.77
Concentration (M/ml)	41 [15–70]	35 [16–66]	0.82
Total N. spermatozoa (M)	94.5 [30.0–175.3]	81.3 [30.9–150.0]	0.99
Progressive motility (%)	43 [30–55]	40 [30–50]	0.14
Total motility (%)	53 [40–62]	50 [40–60]	0.21
Morphologically normal forms (%)	4 [2–6]	4 [3–6]	0.21
Total number of progressively motile spermatozoa (M)	39.0 [9.0–81.8]	32.9 [10.5–69.1]	0.77
Fertilization rate (%)	75 [50–100]	80 [50–100]	0.64

patients considered), only one showed detection of SARS-CoV-2 in semen (6 men; 2%). Authors found that semen quality of patients with moderate infection was lower than that of patients with mild infection and healthy controls suggesting that spermatogenic dysfunction could be related to immune or inflammatory reactions (22). Similarly, Erbay et al. (22) analyzed data from 69 patients aged 20–45 years with a history of a positive test result for SARS-CoV-2 and divided the cohort into two groups according to their COVID-19 symptoms being mild or moderate. Semen samples taken before and after COVID-19 were compared between groups. Patients with moderate symptoms had worsening sperm parameters after infection compared to baseline (22). Overall, these results corroborated previous evidence suggesting that COVID-19 negatively affects sperm parameters at short-term.

Little is known about the long-term effect of COVID-19 on sperm quality. Guo et al. (23) analyzed data from 41 reproductive-aged male patients who had recovered from COVID-19 and 50 matched controls; semen parameters were considered at a median time of 56 days after hospital discharge and a second sampling was conducted for 22 patients at 84.0 (IQR: 74.0–89.0) days after hospital discharge. Compared with healthy controls, sperm concentration and progressive motility were lower in COVID-19 patients at first sampling. Of note, total sperm count, sperm concentration and motile sperm count at the second sampling significantly improved. Therefore, COVID-19 might exert adverse but potentially reversible effects on sperm quality.

Several pathophysiological mechanisms have been proposed to elucidate the negative impact of COVID-19 infection on semen quality. Oxidative stress and increased apoptosis, altered ACE2 signaling pathways and the synergistic negative contribute of air pollution were among the most frequently reported mechanism of sperm impairment by COVID-19 (24–26).

Prompted by the previous evidence of impaired reproductive function after COVID-19 infection, public concerns emerged regarding the association between SARS-CoV-2 vaccine and infertility. In this context, it was found that internet search queries in Google related to the COVID-19 vaccine and fertility significantly increased in the 48 days following Emergency Use Authorization (27). This increase in search volume suggests a desire for information about the vaccine's impact on fertility potential which could be influencing public concern and hesitancy for vaccine uptake.

Only few studies have investigated the real-life impact of COVID-19 vaccine on semen quality. Gonzalez et al. collected semen samples from 45 healthy volunteers (with no underlying fertility issues) prior to receiving the first mRNA vaccine dose and approximately 70 days after the second (5). Authors found no significant decreases in any sperm parameter after vaccination in their cohort.

In a similar study, Lifshitz et al. collected semen samples from 75 fertile men 1–2 months following the second dose of Pfizer's COVID-19 vaccine (6). The semen parameters were compared with the WHO reference ranges. Of note, only one patient (1.3%) showed sperm parameters suggestive for oligozoospermia and asthenozoospermia (6). Lastly, Orvieto et al. investigated the influence of mRNA SARS-CoV-2 vaccine on 36 couples undergoing ART treatments (28). By comparing pre/post vaccination data, Authors found no differences in the number of oocytes and mature oocytes retrieved, fertilization rate and pregnancy rate (30% per transfer). Additionally, sperm parameters from the male partner did not change after vaccination (28).

Our study corroborates theses previous findings since we showed that COVID-19 vaccination did not affect sperm quality of men undergoing ART treatments. These results were confirmed for both mRNA and viral vector vaccines. Notably, our data also indicate that COVID-19 vaccination does not impact on fertilization rate which is a critical fertility parameter because it expresses a fundamental aspect of both oocyte and sperm developmental competence. The regulatory mechanisms required for fertilization are believed to influence the development and health of the conceptus (7). Overall, our data are of utmost clinical and sociological importance since we revealed that COVID-19 vaccines are safe for men's reproductive health and they should be recommended to men seeking fertility treatment.

There are several strengths of our study. First, this is the largest multicenter study specifically designed to investigate pre

vs. post COVID-19 vaccination difference in fertilization rate and sperm parameters in infertile men. Conversely, other Authors have analyzed fertile men or did not include a pre-vaccination examination, thus limiting the validity of their findings (5, 27, 28). In fact, infertile men are those who most would benefit from the lack of sperm impairment from vaccination. Second, only mRNA vaccines have been considered in previous publication (27, 28). Third, previous reports did not include the evaluation of the functional properties of the sperm. Forth, the design of the study evaluating the same cohort of men undergoing the same ART procedure before and after vaccination in a pairwise comparison allows to exclude potential biases that may derive from a case-control study.

Likewise, the study is not devoid of limitations. A selection bias might be claimed in terms of subjects who, knowing about their poor semen parameters, were particularly afraid of the vaccine consequences and refused the immunization. However, this issue is very unlikely as in Italy, about 85% of adults accepted the vaccination and this was not different in our population of patients. This rate was even higher in the Lombardy area where two of the study centers are located. As a matter of fact, we did not have a significant proportion of patients who refused to be vaccinated. On the other hand, despite being the largest series published in this topic, our results deserve external validation with an independent, larger and more diverse sample and this should be one of the recommendations of the study. In addition, results should be confirmed in long-term studies mostly because mRNA technology will be increasingly frequent in the design of new vaccines to manage various pathologies of importance in public health. Additionally, we lack data on serum hormones and patient's clinical characteristics that might affect sperm quality. Nonetheless, it is unlikely that those would change between ART cycles.

CONCLUSION

Both COVID-10 vaccines, the messenger RNA (mRNA) vaccines and the vaccines utilizing a viral vector did not affect sperm quality of men undergoing ART treatments and should be considered safe for men's reproductive health.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico Milano Area B, N. 1083_2021; IRCCS San Raffaele Scientific Institute, ID BC-GINEOS, and Ospedale Careggi, Firenze N. 18111, 20/05/2021. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MR and PV conceived the study. VB, GF, CD, FP, and GCC collected the data. LP and MR analyzed the data. PV, LB, and ES wrote the first draft. MEC and EP revised the manuscript. All authors discussed the results and contributed to the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.839967/full#supplementary-material

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frontiers in Medicine

CASE REPORT
published: 14 February 2022
doi: 10.3389/fmed.2022.836620

Case Report: Myocarditis After COVID-19 Vaccination – Case Series and Literature Review

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OPEN ACCESS

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Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Medicine

Received: 15 December 2021
Accepted: 20 January 2022
Published: 14 February 2022

Citation:
Nunn S, Kersten J, Tadic M, Wolf A, Gonska B, Hüll E, Dietenberger H, Rottbauer W and Buckert D (2022) Case Report: Myocarditis After COVID-19 Vaccination – Case Series and Literature Review. Front. Med. 9:836620. doi: 10.3389/fmed.2022.836620

Background: The ongoing COVID-19 pandemic demands a series of measures and, above all, the vaccination of a substantial proportion of the population. Acute myocarditis is a rare complication of the widely used mRNA-based vaccines.

Case Presentation: We present a case series of four patients (three men and one woman, 16 to 47 years old) with acute pericarditis/myocarditis 3 to 17 days after mRNA vaccination. They presented with chest pain, fever, and flu-like symptoms. Diagnosis was made based on the synopsis of clinical presentation, elevated levels of troponin T and NT-proBNP, impaired systolic function on echocardiography, and findings in non-invasive tissue characterization by cardiovascular magnetic resonance imaging. Two patients also underwent endomyocardial biopsies. As none of the patients showed signs of cardiogenic shock, they were discharged from ward care only a few days after their initial presentations.

Conclusions: Our data are consistent with other case reports of myocarditis early after mRNA vaccination and demonstrate the need for multimodal diagnostics. In view of its rarity and mild course, the risk–benefit ratio of vaccination remains positive compared to potential SARS-CoV-2 infection.

Keywords: SARS-CoV-2, myocarditis, mRNA vaccines, echocardiography, cardiovascular magnetic resonance (CMR), endomyocardial biopsy (EMB), speckle tracking

INTRODUCTION

The ongoing COVID-19 pandemic is an acute medical, social, political, and economic problem (1, 2). Tremendous effort has gone into developing vaccines to prevent SARS-CoV-2 infection. To date, several mRNA-based vaccines and vaccines with adenoviruses as vectors have been approved. Since these mRNA based vaccines have not been used so broadly before, little is known about adverse events. The most common systemic adverse effects of mRNA-based vaccines are fatigue, headaches, chills, muscle pain, and fever. The initial registration studies described no cases of myocardial injury (3, 4). However, increasing evidence of myocarditis in the context of vaccination has been reported in the subsequent literature (5). This has attracted media interest due to the ongoing pandemic and has resulted in a fear of vaccination in parts of society.

Myocarditis is an inflammatory disease of the myocardium that can be caused by various infectious agents, systemic diseases, drugs, and toxins. The current guidelines of the European Society of Cardiology (ESC) also mention that non-COVID-19 vaccines can cause myocarditis (6). Myocarditis has been described to be more common in young adults and men (7). Furthermore, there is an increased risk of myocarditis within 1 week after vaccination (8). We present three cases of acute myocarditis and one case of pericarditis potentially caused by mRNA vaccines and discuss them in the context of the current literature. All patients were managed in our tertiary university care center and provided written informed consent.

CASE REPORTS

Case 1

A 31-year-old woman with no preexisting diseases or cardiovascular risk factors presented in May 2021 with a shivering attack, intensifying stabbing chest and back pain, and dyspnea after moderate physical activity (NYHA II). Seventeen days previously, she had been vaccinated for the first time against COVID-19 with Comirnaty® (BioNTech/Pfizer). The following day, she registered flu-like symptoms, which quickly resolved. In the period between her vaccination and presentation, she engaged in physical activity that involved riding a bicycle for 15 km.

The initial physical examination showed normal blood pressure and mild tachycardia, with no signs of cardiac congestion. The initial laboratory tests showed increased levels of high-sensitivity troponin T (hsTnT) and NT-pro B-type natriuretic peptide (NT-proBNP). Transthoracic speckle-tracking echocardiography showed a mildly reduced left ventricular ejection fraction (51%) and wall motion abnormalities in the inferolateral region (**Figure 1**). The global left ventricular longitudinal strain was reduced to −11.0% (normal <-18.0%). Cardiovascular magnetic resonance (CMR) imaging showed increased values in parametric mapping, with a global native T1 of 1,183 ms (normal 955 ± 23 ms), T2 of 81 ms (normal <60 ms), and an extracellular volume (ECV) of 35% (normal 25.3 ± 3.5%). A subepicardial scar in the basal inferolateral region was seen in late gadolinium enhancement (LGE) sequences (**Figure 2**). Left heart catheterization and endomyocardial biopsy (EMB) confirmed the diagnosis of acute myocarditis (**Figure 3**). Polymerase chain reaction (PCR) analysis did not detect cardiotropic viruses, so there was no pathohistological evidence of a cause of myocarditis. Because of the limited ejection fraction, medical therapy with beta blocker and AT1 antagonist was initiated.

A follow-up examination after seven weeks revealed that the patient had developed movement-dependent thoracic pain but presented with no angina, dyspnea, palpitations, dizziness, or syncope. Transthoracic echocardiography showed normal left ventricular function, with no preexisting regional wall motion abnormalities. The longitudinal strain improved significantly, as shown in **Figure 1**. Repeat mRNA-based vaccination is not recommended.

Case 2

A 47-year-old man with Sjogren syndrome and a history of perimyocarditis (2018) presented with a recurrence of myocarditis, with breath-dependent thoracic pressure and a fever of 38.8°C. Six days before presentation, the patient had received the second dose of Comirnaty® (BioNTech/Pfizer). The symptoms developed shortly after vaccination.

The initial presentation revealed normal blood pressure and a normal sinus rhythm. Myocardial injury was confirmed by elevated hsTnT and NT-proBNP levels. An echocardiographic examination detected no regional wall motion abnormalities. Pericarditis was confirmed by CMR because of LGE in the basal and midventricular pericardium. No LGE was detected in the myocardium. Furthermore, T1 and T2 mapping and feature-tracking strain analysis showed normal values, which is why EMB was not performed. Consistent with Sjogren's syndrome, Ro-52, SSA and SSB parameters are elevated.

Case 3

A 16-year-old male with a family history of myocardial infarction presented with a fever and head, limb, and chest pain after receiving the second dose of Comirnaty® (BioNTech/Pfizer) 3 days previously. He reported self-medication with ibuprofen, which had improved his symptoms.

As in the other three cases, there was no indication of cardiogenic shock or congestion. The patient had the highest hsTnT values of all described cases, with a maximum of 1,361 ng/ml upon admission (normal < 14 ng/ml). His heart rate was normal, with elevations in the inferior and anterior leads (II, III, aVF, V3–V6) on an initial 12-lead electrocardiogram (ECG). Echo showed a midrange reduction in the left ventricular ejection fraction. Due to the ECG changes, left heart catheterization and EMB were performed soon after admission. No evidence of coronary artery disease was found. EMB showed fibrosis but no clear evidence of myocarditis. Moreover, there were no giant cells or signs of amyloidosis. Testing for viruses by PCR is unremarkable, so that no viral genesis of the myocarditis can be assumed. Accordingly, CMR showed a subepicardial focal scar in the basal anteroseptal region in LGE. T2 and ECV were elevated in the anteroseptal region (T2: 63 ms; ECV: 32%). The patient was hospitalized and observed for 4 days. In addition, a strain analysis was performed at the beginning and end of the inpatient stay, which showed a significant improvement of the global longitudinal strain within the few days (**Figure 4**).

Three months later, a follow-up examination was performed. The patient had good cardiopulmonary exercise capacity without angina, dyspnea, syncope, dizziness or palpitations. Echocardiography showed normalized ejection fraction, so heart failure therapy was discontinued. Speckle tracking analysis showed a fully recovered longitudinal strain compared with the two echocardiographic studies previously (**Figure 4**). Based on the findings and a period of 3 months after the acute event, there is no reason for further abstinence from sports.

Case 4

A 24-year-old man who had received the second dose of the Moderna COVID-19 vaccine 4 days previously initially presented

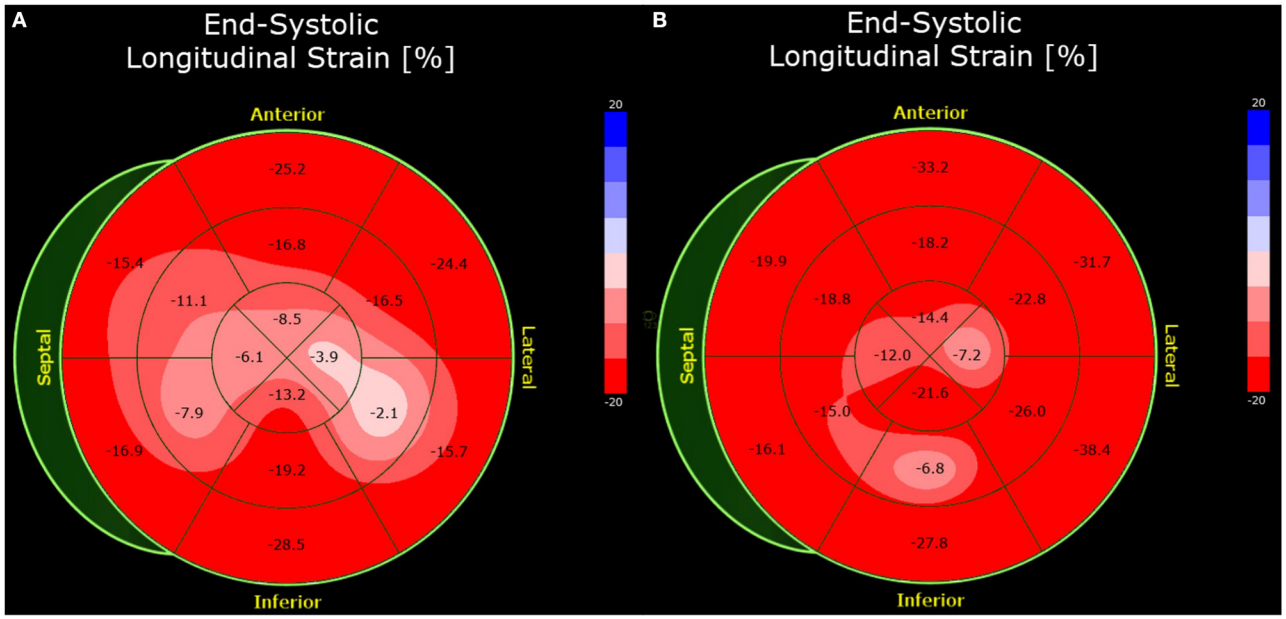

FIGURE 1 | Bull's eye plot of the speckle-tracking analysis of Case 1. The global longitudinal strain was impaired by −13.4% (normal <- 18.0%) at presentation **(A)**. At 7-week follow-up, the strain analysis was normal **(B)**.

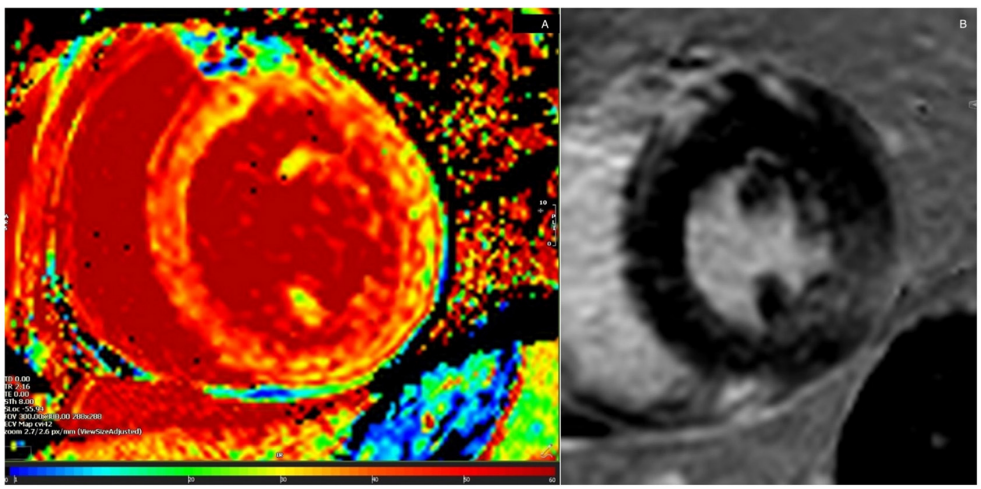

FIGURE 2 | Global extracellular volume by cardiovascular magnetic resonance imaging of Case 1. Pathological values were obtained from the entire left ventricular circumference **(A)**. Focal conspicuities were shown in late gadolinium enhancement (LGE) sequences. This showed inferolateral LGE consistent with regional wall motion abnormalities on echocardiography **(B)**.

to a general practitioner, who referred him to the hospital with suspected myocarditis because of a high fever (40.5°C) and non-significant elevations on a lead V2–V4 ECG. He reported retrosternal pain in association with deep inspiration, as well as a sore throat and cough. Self-medication with ibuprofen provided no relief.

Elevated hsTnT and NT-proBNP levels indicated myocardial injury. The patient's blood pressure and heart rate were normal. An ECG showed a sinus rhythm with preexisting ST changes. CMR showed normal left ventricular function with LGE in the basal and inferior pericardium. These findings suggested acute perimyocarditis. In the presence of normal left ventricular ejection fraction and absent LGE, EMB was not performed because of lack of therapeutic consequence. The patient was discharged 2 days later.

An overview of the laboratory and imaging data of all four patients is presented in **Table 1**.

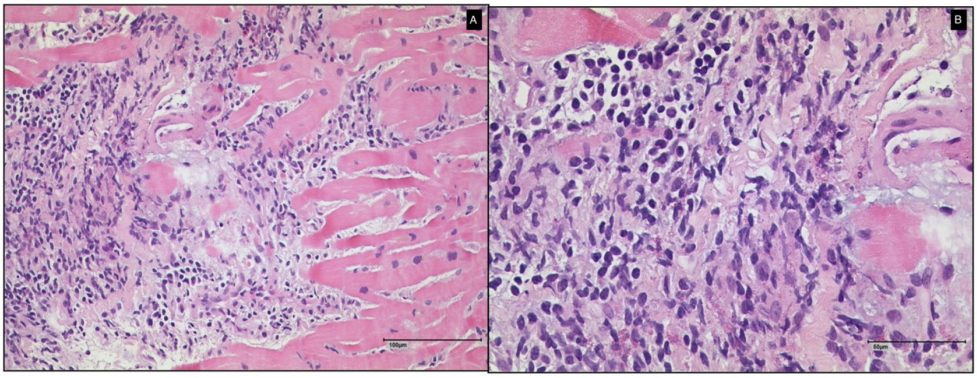

FIGURE 3 | Histological findings of endomyocardial biopsy of Case 1 (**A**: 100 μm and **B**: 50 μm). A diagnosis of myocarditis without giant cells was made.

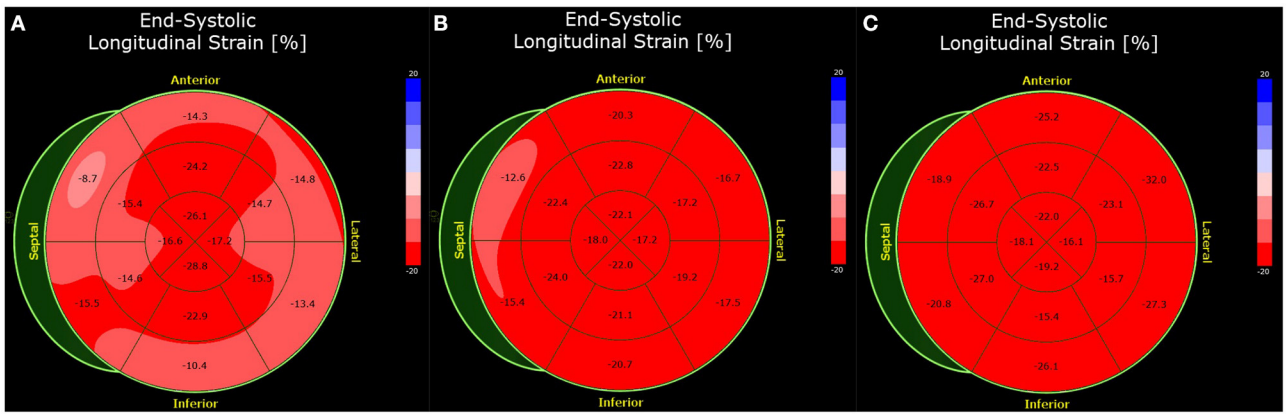

FIGURE 4 | Bull's eye plot of the speckle-tracking analysis of Case 3. The global longitudinal strain was impaired by −17.1% (normal <-18.0%) at presentation **(A)**. Before discharge 4 days later, the strain analysis is improved (-19.1%) **(B)**. At 3 months follow-up, the strain analysis was normal (-21.8%) **(C)**.

DISCUSSION AND LITERATURE REVIEW

Myocarditis has already been identified as an adverse event of mRNA vaccines. There were justified clinical suspicions that the presented myocarditis cases were caused by vaccination, although a causal relationship could not be fully established in all cases. Case 2 presented a challenge in the differential diagnosis between myocarditis and preexisting rheumatic disease. We included this case to show that underlying conditions may also induce cardiac involvement.

The diagnosis of myocarditis is challenging regardless of the causative agent and should be performed by an experienced clinician based on a synopsis of symptoms, laboratory data, imaging results, and histopathological findings (9–11). The clinical symptoms are broad with low specificity and include chest pain, acute or subacute shortness of breath, acute or chronic heart failure, palpitations, arrhythmia, and unexplained cardiogenic shock (11). There is no specific blood test, but biomarkers of cardiac injury such as troponin or NT-proBNP can be elevated (6, 11, 12). The ESC recommends that in all patients with clinically suspected myocarditis should be considered for selective coronary angiography and EMB (6). It is used to confirm the diagnosis of myocarditis and to identify the underlying etiology. Furthermore, the analysis provides key information on the treatment strategy and prognosis (6, 11–13). The most scientific statements about EMB are based on the classical histopathological Dallas criteria, which do not include methods established after that time such as immunohistochemistry or viral genome analysis (10, 14). EMB has a high false negative rate due to its susceptibility to sampling errors (15, 16). The AHA and ESC statements are based on consensus recommendations in the absence of large clinical trials to clarify the role of EMB for further management and cause-specific therapy (13). Therefore, EMB was not performed in cases 2 and 4 in the presence of normal ejection fraction and absence of LGE. In Case 3, this was also a potential cause of the negative EMB in the presence of otherwise undoubtful diagnostics. EMB is recommended in the case of a new onset of a reduced ejection fraction within 2 weeks and hemodynamic compromise, such as cardiogenic shock (17).

To describe the myocardial deformation, echo strain analysis based on speckle tracking is a reliable and feasible tool (18). Deformation imaging is useful to detect subclinical

TABLE 1 | Overview of clinical, laboratory, and imaging data of the four cases.

Characteristic	Case 1	Case 2	Case 3	Case 4
Age	31	47	16	24
Sex	Female	Male	Male	Male
Vaccine	1st dose of BioNTech/Pfizer	2nd dose of BioNTech/Pfizer	2nd dose of BioNTech/Pfizer	2nd dose of Moderna
Time from vaccination to admission (days)	17	6	3	4
Relevant preexisting conditions	–	Sjogren syndrome, perimyocarditis (2018)	Family disposition	
Time from admission to discharge (days)	4	7	4	2
Biomarkers				
hsTnT (ng/l, normal < 14)				
First admission	223	43	1,361	412
Peak value	549	202	2,170	412
NT-proBNP (pg/ml, normal < 130)				
First admission	2325.0	579.0	1245.0	550.0
Peak value	2325.0	579.0	1245.0	550.0
CRP (mg/l, normal < 5)				
First admission	12.0	97.8	7.1	52.0
Peak value	12.0	97.8	43.5	52.0
Left and right ventricular volumetry by cardiovascular magnetic resonance imaging				
LVEDV (ml)	155	178	180	156
LVEDVI (ml/m^2)	80	77	89	78
LVEF (%)	52	53	50	69
SV (ml)	81	92	90	108
RVEDV (ml)	128	194	185	154
RVEDVI (ml/m^2)	66	84	92	77
RVEF (%)	70	53	46	64
Tissue characterization by cardiovascular magnetic resonance imaging				
LGE	Basal inferolateral subepicardial	Basal and mid-ventricular pericardium	Basal anteroseptal subepicardial	Basal anterior and inferior pericardium
Native T1 (ms, normal 955 ± 23)	1,183	970	1,107	992
T2 (ms, normal < 60)	81	53	• 61 (anterolateral) • 63 (anteroseptal)	50
ECV (%, normal 25.3 ± 3.5)	35	27	• 28 (basal) 31 (anterolateral) 32 (anteroseptal)	26

hsTNT, high sensitivity troponin T; NT-proBNP, NT-pro B-type natriuretic peptide; CRP, C-reactive protein; LVEDV, left ventricular end diastolic volume; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; SV, stroke volume; RVEDV, right ventricular end diastolic volume; RVEDVI, right ventricular end diastolic volume index; RVEF, right ventricular ejection fraction; LGE, late gadolinium enhancement; ECV, extracellular volume.

systolic or diastolic functional impairment (19). Left ventricular strain and strain rate analyses appears to be a good prognostic tool in patients with reduced and normal left ventricular ejection fraction (20). With normalized left ventricular ejection fraction and strain measurement at follow-up as described in Case 1, a repeat MRI was not performed because there was no therapeutic consequence. Furthermore, it could be shown in case 3 that the speckle tracking analysis can describe an improvement of global longitudinal strain within a few days indicating good short term prognosis.

CMR is also widely used due to its safety and plays a key role in the diagnosis of inflammatory myocardial diseases. Optimal results are obtained by combining a T1-based criterion (LGE, native T1, or ECV) with a T2-based criterion (Updated Lake Louise Criteria) (21, 22). Although CMR characterizes the tissue, EMB cannot be replaced (6). CMR guidance to enhance the diagnostic accuracy of EMB is possible but should not delay EMB in life-threatening presentations (6, 10).

A central role of the therapy of myocarditis is the optimal treatment of possible arrhythmias as well as heart failure. In hemodynamically stable patients, the classic agents for the

treatment of heart failure are used (6, 23). In pericardial involvement, NSAIDs should be used and colchicine is also recommended as an adjunct to aspirin and NSAID therapy (23, 24). In the described cases, medical therapy for heart failure was initiated. In addition, following the AHA and ESC guidelines, abstinence from sports was recommended for 6 months or until follow-up (6, 13). The guidelines make clear that the few studies primarily address competitive sports, but the Task Force of the ESC believes that the recommendations should also be applied as expert opinion to amateur sports (6).

In the case of myocarditis due to mRNA vaccination, repeat mRNA-based vaccination was not recommended to our patients, although no study data are available until now. As shown in Case 1, vaccination with the Johnson & Johnson vaccine was performed without complications, so that the switch to a vector-based vaccine seems reasonable. A third vaccination in myocarditis due to mRNA vaccine should be performed as well with a different vaccination technology such as vector vaccines.

The most common symptoms of COVID-19 are fever, cough, and dyspnea, which are also known symptoms of pneumonia (2). The virus can enter human cells that express ACE-2, such as those in the lungs, heart, and renal and gastrointestinal tracts, with the help of its spike protein. A "cytokine storm" occurring after 7 to 14 days can lead to severe disease (25, 26). The probability of severe disease depends, among other factors, on comorbidities. Given that a cytokine storm may play a key role in the severity of the disease, the question that arises is whether it can also be triggered by mRNA vaccination.

The Israeli Ministry of Health initiated an active surveillance program for 6 month from December 2020 through May 2021 to monitor the adverse events of COVID-19 vaccines. Among 5.1 million fully vaccinated individuals, 136 were diagnosed with myocarditis. Most (95%) cases had a mild course. Compared with the pre-pandemic incidence of myocarditis obtained from the Israel National Hospital Discharge Database from 2017 to 2019, the second dose of mRNA vaccination resulted in a standardized incidence ratio of 5.3 (27). Young males were the most likely to suffer this adverse event in the first week after receiving the second dose (27). These data are in line with the myocarditis frequency of 1 to 17,000 after the second dose reported by the vaccination committee of the German Robert Koch Institute in August 2021 (28). Cohort studies in China have reported rates of myocardial injury, such as myocarditis, ranging from 7 to 17% among hospitalized COVID-19 patients. The percentage rose to 22% for patients requiring intensive care and to 59% for deceased patients (29). In a case series of 150 patients, 7% of the 68 deaths were due to myocarditis with subsequent circulatory failure. Another 22 deaths (33%) were associated with myocarditis and respiratory failure. Consequently, a definite cause of death could not be determined (30). Conversely, no cases of fatal myocarditis have been reported in the context of mRNA vaccination. Barda et al. (31) reported that vaccination increased the risk of myocarditis by a factor of 3.2. The risk difference calculated by 100,000 persons is 2.7 (CI 1.0 to 4.6). To put this risk in context, 240,000 SARS-CoV-2 infections were studied to compare the incidences of the same complications. This showed an 11.0 myocarditis per 100,000 persons (31). Data from the Premier Healthcare Database Special COVID-19 Release, which is a large US hospital-based database, showed an overall adjusted myocarditis risk ratio of 15.7 in COVID-19 patients. The risk difference is higher in male than female. The highest risk ratio in terms of age was in the group under 16. The second peak was reached after a reduction until the age of 40 with a subsequent increase in the group of patients over 75 years (risk ratio 31.6, CI 25.9–37.2) (32). Therefore, the question arises as to how the risk ratio regarding myocarditis relates between infection and vaccination in young people or children. A preliminary publication by Singer et al. examined that in the highest risk group, consisting of adolescents between 12 and 17 years old, the risk of myocarditis was 5.9-fold higher with infection compared with mRNA vaccination (33). In line with this, a British study of more than 38 million vaccinated persons shows that although the risk of myocarditis increases after vaccination, this is significantly lower compared with myocarditis after SARS-CoV-2 infection (1–10 vs. 40 extra events per 1,000,000 persons) (8). It is not yet known whether abstaining from intense physical activity for a few days after vaccination can reduce the risk of myocardial involvement, as has been recommended in myocarditis of other causes (6). Fear of this cause of myocarditis may have led to vaccine hesitancy in parts of society, which has been stoked by some media. In view of the ongoing pandemic and this rather rare adverse side effect, which mostly shows a mild clinical course, this should not be supported for rational reasons.

CONCLUSION

Myocarditis may be an exceptionally rare complication after vaccination against SARS-CoV-2. The clinical course of the cases described herein was mild. The performed diagnostics conformed to current guidelines and substantiated the suspicion of myocardial involvement. Based on the currently available knowledge, the benefits of vaccination outweigh its potential risks. Therefore, broad vaccination is recommended. Nevertheless, we recommend further investigation into the adverse effects of the new mRNA vaccine technology, which may be used for most vaccines in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SN and JK: concept and writing of the manuscript. MT, AW, BG, and EH: interpretation of the sources and patient acquisition. MT and HD: image example. WR and DB: supervision and concept. Each author has read and approved the final draft. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Public Health

ORIGINAL RESEARCH
published: 14 March 2022
doi: 10.3389/fpubh.2022.834744

Extension and Severity of Self-Reported Side Effects of Seven COVID-19 Vaccines in Mexican Population

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A few studies examined the comparative side effects of Coronavirus Disease-19 (COVID-19) vaccines. We compared the extension and severity of self-reported side effects of seven COVID-19 vaccines [BNT162b2 (Pfizer-BioNTech), ChAdOx1 (AstraZeneca), mRNA-1273 (Moderna), CoronaVac (Sinovac Life Sciences), Gam-COVID-Vac (Gamaleya's Sputnik V), Ad5-nCoV (CanSinoBIO), and Ad26.CoV2.S (Johnson & Johnson/Janssen)] in the Mexican population. We also evaluated the association of type of vaccine, sex, age, comorbidity, and history of allergies to the extent and severity of side effects. This was a cross-sectional study carried out online between August 12 and September 3, 2021 in Mexico. The first inclusion criterion was to receive a COVID-19 vaccine and the second, being at least 18 years old. The survey link was distributed *via* multiple social media platforms. We questioned about the type of vaccine and symptoms based on short-term side effects reported in the literature. Side effect extension was classified as local, systemic, or both. We asked about the need to take medicine, stop activities/miss work, or seek medical attention. Then, a severity index was constructed based on responses. Descriptive and stepwise multivariate logistic ordinal regression analyses were used to calculate odds ratio (OR) and 95% CI for each outcome adjusted by potential confounders. The mean age was 38.9 ± 11.0 years (n = 4,024). Prevalence of at least one side effect varied between vaccines and by a number of doses. At dose 1, ChAdOx1 was the vaccine with the highest rate of at least one side effect (85%) followed by Gam-COVID-Vac (80%). Both were associated to greater extension (adjusted OR 2.53, 95% CI 2.16, 2.96 and adjusted OR 2.41, 95% CI 1.76, 3.29, respectively) and severity of side effects (adjusted OR 4.32, 95% CI 3.73, 5.00 and adjusted OR 3.00, 95% CI 2.28, 3.94, respectively). Young age (<50 years), female sex, comorbidity, and history of allergies were associated with greater extension and severity, independent of the type of vaccine and potential confounders. At dose 2,

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Edited by:
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Reviewed by:
Shyh Poh Teo, Raja Isteri Pengiran Anak Saleha Hospital, Brunei
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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: *13 December 2021*
Accepted: *07 February 2022*
Published: *14 March 2022*

Citation:
Camacho Moll ME, Salinas Martínez AM, Tovar Cisneros B, García Onofre JI, Navarrete Floriano G and Bermúdez de León M (2022) Extension and Severity of Self-Reported Side Effects of Seven COVID-19 Vaccines in Mexican Population. Front. Public Health 10:834744. doi: 10.3389/fpubh.2022.834744

mRNA-1273 was the vaccine with the highest rate of side effects (88%) and the only vaccine associated to greater extension (adjusted OR 2.88, 95% CI 1.59, 5.21) and severity of symptoms (adjusted OR 3.14, 95% CI 1.82, 5.43). Continuous studies are necessary to acknowledge more post-vaccine symptoms in different populations.

Keywords: COVID-19, SARS-CoV-2, side effects, local effects, systemic effects, vaccination, vaccine

INTRODUCTION

By January 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that originated in Wuhan, China had already spread to Europe and by March 2020, it had already spread to the whole world (1–4). The number of people infected was rapidly reached stunning figures given its high transmissibility. The health services collapsed, and the loss of life was alarming in the absence of a specific treatment. Fortunately, Coronavirus Disease-19 (COVID-19) vaccines emerged in record time. Clinical trials began to show the efficacy and safety of vaccines, such as the mRNA-1273 vaccine (Moderna) (5), the BNT162b2 vaccine (Pfizer-BioNTech), and the Gam-COVID-Vac (Gamaleya's Sputnik V) (6). Therefore, regulatory agencies began authorizing their emergency use. Starting date and requirements for the public to receive the vaccine varied by region. In Mexico, vaccination started in December 2020 and the administration was in stages according to priority groups with vaccines varying in type upon availability (**Figure 1**) (7). Additionally, some Mexicans sought to receive a vaccine abroad, mainly the United States, where mRNA-1273 (Moderna), Ad26.CoV2.S (Johnson & Johnson/Janssen), and BNT162b2 (Pfizer-BioNTech) were available. Vaccine acceptability is key to the success of any vaccination program. Two nationally representative surveys on COVID-19 vaccination are available in Mexico. One, conducted from August to November 2020, identified 62.3% acceptance, 28.2% refusal, and 9.5% hesitancy (8). The second, conducted in November 2020, reported 82% acceptance. Although unlike the first, this study combined a doubtful answer with a definitive one (9). Reports on the progress of coverage of the vaccination strategy in the country showed 20% of the target population fully vaccinated by August 2021 (beginning of the data collection of the present study), and 59% by the end of January 2022 (10, 11).

Despite having proven their safety, COVID-19 vaccines are not exempt from adverse effects. Adverse reactions have been reported in more than 1 in 10 people in BNT162b2 (Pfizer-BioNTech), ChAdOx1 (AstraZeneca), and mRNA-1273 vaccine (Moderna) clinical trials. They usually happen shortly after the vaccination and are not associated with a serious or lasting illness (12–17). Moreover, some factors, such as young age, female sex, and prior COVID-19 infection, may increase the frequency of side effects (18–24). Pharmacovigilance activities

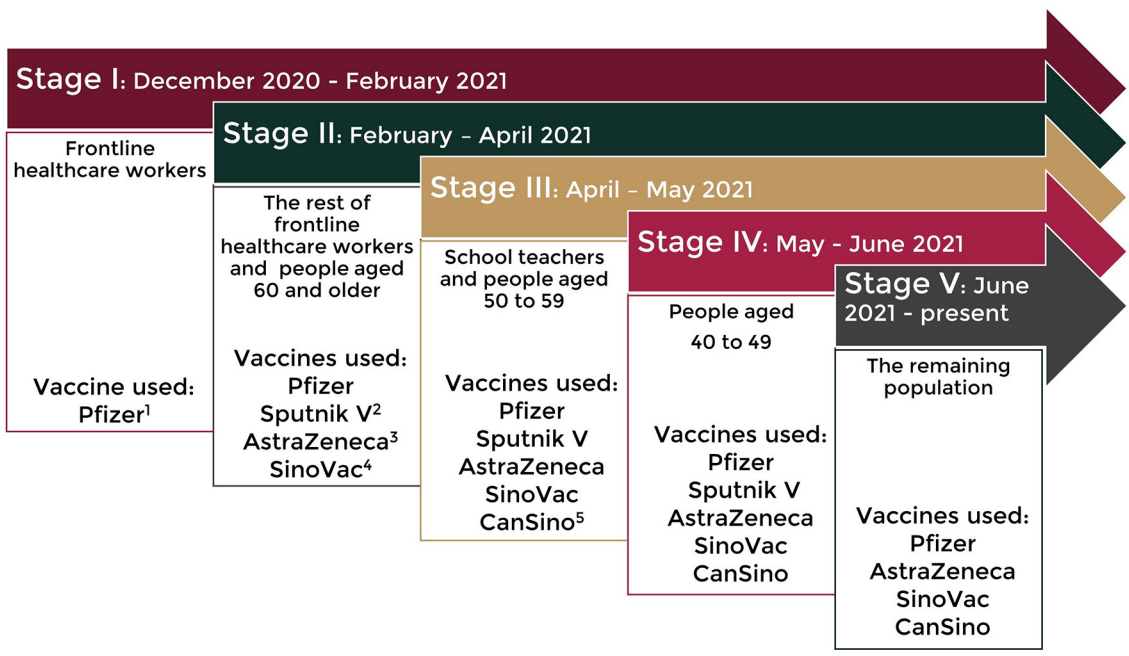

FIGURE 1 | Vaccination strategy in Mexico. [1]BNT162b2 (Pfizer-BioNTech), [2]Gam-COVID-Vac (Gamaleya's Sputnik V), [3]ChAdOx1 (AstraZeneca), [4]CoronaVac (Sinovac Life Sciences), and [5]Ad5-nCoV (CanSinoBIO).

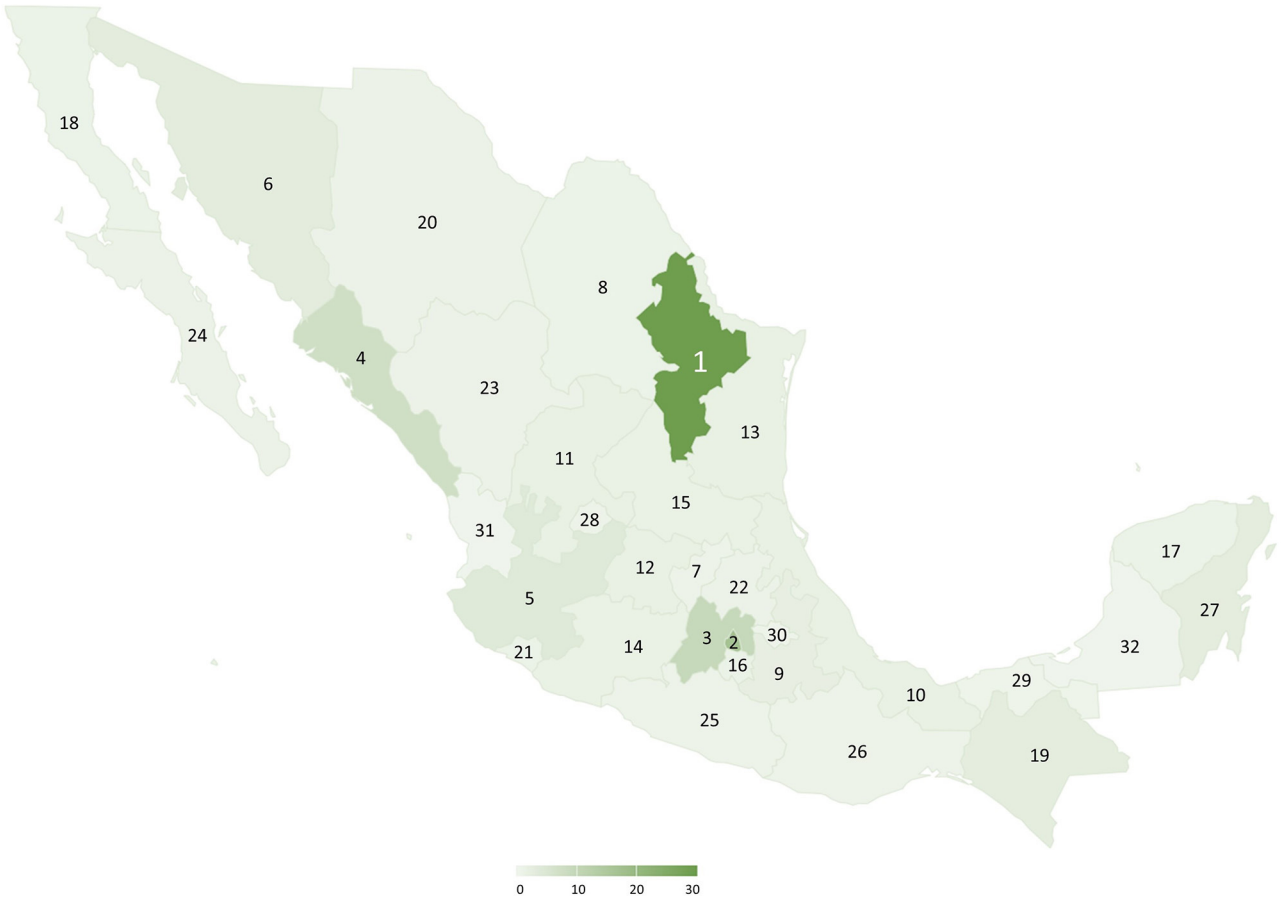

FIGURE 2 | Geographical origin of participants and percentage of participation per state: 1. Nuevo León 29.2%, 2. Mexico City 16.7%, 3. State of Mexico 9.5%, 4. Sinaloa 7.4%, and 5–32. Rest of the country 0–5%. Study of Coronavirus Disease-2019 (COVID-19) vaccines' side effects in the Mexican population, August to September 2021.

are essential in any country. In Mexico, a web page is available for registration of vaccines' adverse effects directly by the public (25). However, there is no promotion of its use and much of the general population is unaware of its existence. Post-vaccination surveillance studies are needed worldwide because it is important to understand the frequency and regional variation of side effects and its potential impact on daily life, so that the public can successfully anticipate appropriate actions. A few studies examined the comparative side effects of COVID-19 vaccines (18, 21, 26) and the reactogenicity of more than three different types of vaccines has not been assessed on the same survey.

The objective of the present study was to compare the extension and severity of self-reported side effects of seven COVID-19 vaccines [BNT162b2 (Pfizer-BioNTech), ChAdOx1 (AstraZeneca), mRNA-1273 (Moderna), CoronaVac (Sinovac Life Sciences), Gam-COVID-Vac (Gamaleya's Sputnik V), Ad5-nCoV (CanSinoBIO), and Ad26.CoV2.S (Johnson & Johnson/Janssen)] in the Mexican population. A second objective was to evaluate the association of type of vaccine, sex, age, comorbidity, and history of allergies to the extent and severity of side effects.

MATERIALS AND METHODS

Study Design

This was a cross-sectional study carried out online between August 12 and September 3, 2021 in Mexico (two months after the vaccination was opened to all population groups). Nuevo Leon and Mexico City were the locations with more participants (**Figure 2**). The first inclusion criterion was to receive a COVID-19 vaccine and the second, being at least 18 years old. Those who did not sign the informed consent were excluded and there was no need to eliminate any registry due to lack of information on vaccine adverse effects. Non-random sampling based on the snowballing technique was used for recruiting potential participants who were invited through social media groups and word-of-mouth campaigns with no proportional quotas by sociodemographic variables or by type of vaccine.

TABLE 1 | Severity categorization.

Severity	Took medicine to relieve symptom	Suspended daily activity or missed work	Sought medical attention
Mild	Yes	No	No
Moderate	Yes	Yes	No
Severe	Yes or No	Yes or No	Yes, regardless of the need to take medication or suspend activities/miss work

Study on self-reported side effects of Coronavirus Disease-19 (COVID-19) vaccines in the Mexican population, August to September 2021.

The survey link was distributed *via* multiple media platforms, such as Facebook and WhatsApp. Participants did not receive any kind of financial reward. Two sample sizes were estimated. One is based on the expected frequency of at least one local side effect between 48.9 and 85.8% reported in the literature (22, 27). The second is based on the expected frequency of at least one systemic side effect between 52.6 and 70.5% (22, 27). Both, with a margin of error of 3% and a CI of 95%. The minimum *n* required varied from 514 to 1,067 for estimates of local effects and between 879 and 1,064 for estimates of systemic effects. However, there were 4,024 participants. Such a sample size provided determinations with a precision of <2% and confidence level >95% given the frequencies obtained in the study of 67 and 65% for local and systemic side effects after the 1st dose (28). The protocol was approved by the Committees of Ethics and Health Research (R2021-1909-106). The study followed the Declaration of Helsinki for research on human subjects' guidelines (29). All the participants had to give their informed consent digitally before filling in the questionnaire. Participation was entirely voluntary, and withdrawal was allowed at any time without the need to justify the decision. There was no personal data collected that might enable the retrospective identification of the participant.

Study Variables

Vaccine Information

Participants were asked about the type of vaccine received (multiple choice), vaccine combination (yes, no; if yes, type of combination), and the number of doses. Moreover, about the use of pre-vaccination medication to prevent symptoms (yes, no). For side effects evaluation, the participant chose all the symptoms that he/she had presented from a list made with short-term side effects reported in the literature (12–17). Then, the extension was classified as local, systemic, or both. To simplify the questionnaire as much as possible, the time of onset and duration for each side effect were not included. The side effects of dose 1 and dose 2 were questioned in separate sections. For severity evaluation, three questions were asked for first or single dose: need to take medicine, stop activities/miss work, or seek medical attention (went to a doctor, went to an emergency room, or was hospitalized). Then, an index was constructed based on negative and affirmative responses obtaining 3 categories: mild, moderate, and severe (**Table 1**). One question was used for the second dose: notice any difference in symptomatology between the first and second doses (felt better, felt the same, or felt worse).

Comorbidity, Sociodemographic, and Other Characteristics

One question filtered the history of any comorbidity. Those who answered affirmatively were asked about a previous diagnosis of prediabetes, diabetes, hypertension, chronic renal failure, chronic obstructive lung disease, asthma, immune disease, cancer, cerebrovascular disease, others. Moreover, about the history of allergies and COVID-19 infection (had symptoms consistent with COVID-19 disease and was positive to PCR or rapid nasal swab antigen test). Sex, age, schooling, occupation, place of residence, smoking, pregnancy, and breastfeeding at the time of vaccination were identified too. Nutritional status was assessed using a validated body mass index-body size pictorial method that indicated low weight (shape 1), normal weight (shapes 2 and 3), overweight (shape 4), and obesity (shapes 5–10) (30).

Study Procedures

The self-applied electronic survey was designed in Spanish with the software tool QuestionPro (Survey Analytics LLC, San Francisco, CA, USA) and Google Forms (Google, Mountain View, CA, USA). The survey took an average of 5 min to complete. It was divided into the following sections: privacy policy (statements about voluntary participation and confidentiality), vaccine data, post-vaccination side effects, COVID-19 prior infection, and comorbidity data; sociodemographic and other information of interest. The items were developed by the authors after a thorough review of the literature on side effects reported by the different vaccines. These were submitted to a panel of experts (an epidemiologist medical doctor and 2 full-time medical researchers) who reviewed the pertinence and relevance of the content. Moreover, they checked if writing was clear, concise, and unambiguous and verified the absence of technical language. The proposed questionnaire was pre-tested among colleagues, then it was tested in a pilot study with participants of sociodemographic characteristics similar to the target population. Some adjustments were made on section skipping according to filter questions. The final version is available in **Supplementary Materials S1**.

Statistical Analysis

Frequencies were obtained for the categorical variables, as were means and SDs for the non-categorical variables. Point prevalence and 95% CIs were estimated. The association of sociodemographic, comorbidity, and history of allergies to extension and severity of side effects was evaluated through the chi-square tests. Then, stepwise multivariate logistic ordinal regression models were run to calculate adjusted odds ratio (OR) and 95% CI for each outcome of interest. One model included an extension of side effects as dependent variable (coded as absent, local, systemic, both) and type of vaccine, sex, age, comorbidity, allergies, and smoking as independent variables; use of pre-vaccination medication to prevent symptoms and

TABLE 2 | Sociodemographic, comorbidity, and other characteristics.

		Type of vaccine							
	Total *n* = 4,024	**Pfizer[a]** *n* =1,579	**AstraZeneca[b]** *n* =1,193	**Moderna[c]** *n* =52	**SinoVac[d]** *n* =299	**Sputnik V[e]** *n* =202	**Cansino[f]** *n* =598	**J & J[g]** *n* =97	**Chi-square** *p*-value
Female	79.7%	79.4%	79.3%	76.9%	78.9%	84.2%	80.4%	79.4%	0.778
Age group (years)									
<29	18.8%	16.2%	19.5%	21.2%	27.2%	24.8%	17.1%	23.7%	
30–39	41.9%	36.7%	47.8%	28.8%	30.9%	49.0%	46.9%	50.5%	
40–49	21.2%	24.0%	20.1%	30.8%	16.8%	1.0%	25.6%	12.4%	
50 a 59	12.3%	16.3%	6.2%	11.5%	13.8%	19.8%	10.2%	13.4%	
≥60	5.8%	6.8%	6.4%	7.7%	11.4%	5.4%	0.2%	0.0%	0.0001
Schooling									
Middle school	3.0%	3.3%	4.0%	0.0%	5.0%	1.5%	0.3%	2.1%	
High school	11.3%	11.4%	14.9%	3.8%	19.1%	9.4%	2.2%	6.2%	
Bachelor's degree	50.1%	48.7%	52.1%	53.8%	53.5%	54.0%	44.8%	61.9%	
Postgraduate	35.5%	36.6%	28.9%	42.3%	22.4%	35.1%	52.7%	29.9%	0.0001
Occupation									
Employed/self-employed	71.6%	75.0%	63.5%	75.0%	59.2%	57.9%	90.1%	66.0%	
Housewife	12.1%	11.0%	16.2%	17.3%	15.7%	14.4%	1.7%	23.7%	
Retired/unemployed	7.7%	7.7%	9.3%	1.9%	11.4%	13.4%	2.3%	1.0%	
Student	8.6%	6.2%	11.1%	5.8%	13.7%	14.4%	5.9%	9.3%	0.0001
Smoking	13.1%	13.5%	14.6%	15.4%	13.7%	8.9%	10.5%	8.2%	0.075
Comorbidity (any)	19.3%	22.9%	16.3%	15.4%	18.4%	18.3%	18.9%	7.2%	0.0001
Hypertension	7.4%	9.4%	6.4%	9.6%	7.0%	6.4%	5.7%	2.1%	0.006
Prediabetes or diabetes	4.8%	6.2%	4.1%	1.9%	4.0%	3.0%	4.2%	1.0%	0.025
Allergies	30.9%	30.8%	30.9%	32.7%	28.4%	23.3%	34.8%	27.8%	0.085
COVID-19 before 1st dose	17.4%	22.0%	15.6%	17.3%	17.4%	11.9%	12.4%	7.2%	0.0001
Overweight/obese	54.7%	56.3%	53.5%	51.9%	54.8%	44.1%	57.9%	46.4%	0.010

Study on self-reported side effects of Coronavirus Disease-19 (COVID-19) vaccines in the Mexican population, August to September 2021 (n = 4,024).
[a]BNT162b2 (Pfizer-BioNTech).
[b]ChAdOx1 (AstraZeneca).
[c]mRNA-1273 (Moderna).
[d]CoronaVac (Sinovac Life Sciences).
[e]Gam-COVID-Vac (Gamaleya's Sputnik V).
[f]Ad5-nCoV (CanSinoBIO).
[g]Ad26.CoV2.S (Johnson & Johnson/Janssen).

history of confirmed COVID-19 infection were used as control variables. The model for analyzing severity included severity index (coded as absent, mild, moderate, and severe) or difference in symptomatology between first and second doses (coded as felt better, felt the same, or felt worse) as dependent variables. Outcomes were analyzed for dose 1 and dose 2, separately. Due to the small sample size, 4 records were removed from inferential statistical analysis, 1 BBIBP-CorV (Sinopharm, Beijing, China) registry, and 3 CureVac registries. Analyses were done using SPSS for Windows version 22.

RESULTS

The mean age was 38.9 ± 11.0 years, 3.6% were pregnant and 9.9% were breastfeeding when they got the vaccine. The female sex, the bachelor's school degree, and being employed or self-employed were characteristics that predominated in the study population. Some characteristics differed by type of vaccine. There were more participants between 30 and 39 years with ChAdOx1 (AstraZeneca), Gam-COVID-Vac (Gamaleya's Sputnik V), Ad5-nCoV (CanSinoBIO), and Ad26.CoV2.S (Johnson & Johnson/Janssen). Moreover, more participants with higher schooling and employed/self-employed with Ad5-nCoV (CanSinoBIO). **Table 2** shows these and other detailed results. A very low percentage of combined vaccines (2%) and 67.4% had a complete scheme (two doses or one for single-shot vaccines). Less than 7% of participants used medication to prevent symptoms before the first or second vaccinations (6.9 and 6.5%, respectively, $p = 0.549$).

Extension of Side Effects

Prevalence of side effects varied by type of vaccines and number of doses. ChAdOx1 (AstraZeneca) was the vaccine with the highest prevalence of at least one side effect at dose 1 and mRNA-1273 (Moderna), at dose 2 (**Figure 3**). Stratification by

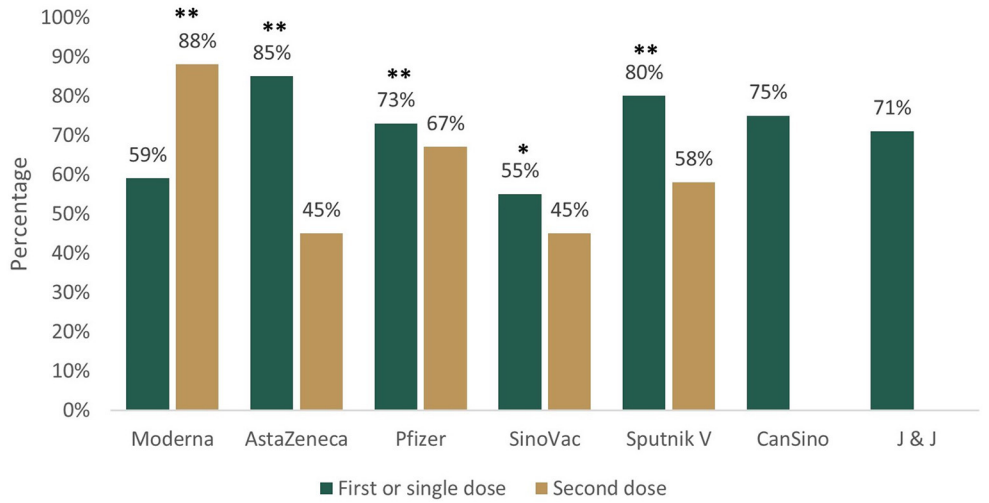

FIGURE 3 | Prevalence of at least one side effect after first/single and second dose of Coronavirus Disease-2019 (COVID-19) vaccines in Mexican population, August to September 2021. *$p \leq 0.05$, **$p < 0.001$ Z-tests for analyzing the difference between two proportions. Moderna (mRNA-1273), AstraZeneca (ChAdOx1), Pfizer (BNT162b2), Sinovac (CoronaVac), Sputnik V (Gam-COVID-Vac), CanSino (Ad5-nCoV), and J & J (Johnson & Johnson, Ad26.CoV2.S).

local and systemic effects showed the prevalence of 67% (95% CI 65.1, 68.0) and 65% (95% CI 63.3, 66.2) after the first vaccination, respectively. The classification by extension showed that the combination of local and systemic effects was the most frequent category after the first dose, which exceeded that of the second dose. Arm/injection site pain was the most common local symptom and headache was the most common systemic symptom regardless of the number of doses (**Table 3**). Side effects categorized by organ system and the number of doses are provided in **Supplementary Table S2**. Side effects categorized by organ system and type of vaccine are provided in **Supplementary Tables S3, S4**.

Severity of Side Effects

After dose 1, 62.6% needed to take medicine for relieving symptoms, 31.3% suspended daily activities or missed work, and 5.3% sought medical attention. The severity index showed 28% had mild, 21% moderate, and 4% severe effects; the rest did not experience symptoms, did not take medication, stopped activities, or sought medical attention (47%). The severity of side effects differed by type of vaccine. At dose 1, there were more respondents suspending activities/missing work and taking medicine for relieving symptoms with ChAdOx1 (AstraZeneca) and more seeking medical attention with Ad5-nCoV (CanSinoBIO) (**Table 4**).

Factors Associated to Extension of Side Effects

At dose 1, participants with ChAdOx1 (AstraZeneca) and Gam-COVID-Vac (Gamaleya's Sputnik V) were more likely to have local and systemic side effects than BNT162b2 (Pfizer-BioNTech). In contrast, participants with CoronaVac (Sinovac Life Sciences) were less likely to have such an outcome. At dose 2, mRNA-1273 (Moderna) increased the odds of greater side effects extension, while ChAdOx1 (AstraZeneca) and CoronaVac (Sinovac Life Sciences) decreased them. Factors, such as female sex, age under 50, and history of allergies, increased the possibilities of greater extension at doses 1 and 2, regardless of comorbidity, smoking, pre-vaccination medication to prevent symptoms, and history of confirmed COVID-19 infection (**Table 5**).

Factors Associated to Severity of Side Effects

At dose 1, four vaccines were associated to greater severity: ChAdOx1 (AstraZeneca), Ad5-nCoV (CanSinoBIO), Gam-COVID-Vac (Gamaleya's Sputnik V), and Ad26.CoV2.S (Johnson & Johnson/Janssen). Female sex, age <50 years, comorbidity, and allergies were also associated factors, independent of smoking, pre-vaccination medication to prevent symptoms, and history of confirmed COVID-19 infection (**Table 6**). At dose 2, mRNA-1273 (Moderna) tripled the possibilities of feeling worse compared to the first dose (95% CI 1.82, 5.43; $p < 0.0001$). In contrast, ChAdOx1 (AstraZeneca) (adjusted OR 0.34, 95% CI 0.26, 0.42; $p < 0.0001$) and Gam-COVID-Vac (Gamaleya's Sputnik V) (adjusted OR 0.59, 95% CI 0.37, 0.94; $p = 0.025$) reduced them.

DISCUSSION

In the present study, we analyzed and explored associated factors to adverse reactions after COVID-19 vaccination from different laboratories and schemes (2 single-dose and 5 double-dose vaccines) in the Mexican population characterized by being in their 30s, being a woman, and with high schooling.

Prevalence of at least one side effect after the first dose varied between vaccines. CoronaVac (Sinovac Life Sciences)

TABLE 3 | Extension of side effects by the number of doses.

	First or single dose vaccination (n = 4,024)		Second dose vaccination (n = 2,050)	
	n	% (95% Confidence interval)	*n*	% (95% Confidence interval)
Extension				
No symptoms	975	24.2 (22.9, 25.6)	778	38.0 (35.9, 40.1)
Local symptoms	443	11.0 (10.1, 12.0)	274	13.4 (12.0, 14.9)
Systemic symptoms	370	9.2 (8.3, 10.1)	203	9.9 (8.7, 11.3)
Both, local and systemic symptoms	2,236	55.6 (54.0, 57.1)	795	38.8 (36.7, 40.9)
Type of local side effect[a]				
Arm /injection site pain	2,650	65.9 (64.4, 67.3)	1,061	51.8 (49.6, 53.9)
Injection site swelling	334	8.3 (7.5, 9.2)	103	5.0 (4.2, 6.1)
Injection site itching	210	5.2 (4.6, 5.9)	54	2.6 (2.0, 3.4)
Injection site redness	168	4.2 (3.6, 4.8)	50	2.4 (1.9, 3.2)
Type of systemic side effect[a]				
Headache	1,537	38.2 (36.7, 39.7)	541	26.4 (24.5, 28.3)
Muscle pain	1,293	32.1 (30.7, 33.6)	370	18.0 (16.4, 19.8)
Lack of energy	1,115	27.7 (26.3, 29.1)	312	15.2 (13.7, 16.8)
Fatigue or tiredness	1,107	27.5 (26.2, 28.9)	477	23.3 (21.5, 25.1)
Fever	926	23.0 (21.7, 24.3)	236	11.5 (10.2, 13.0)
Desire to sleep	912	22.7 (21.4, 24.0)	300	14.6 (13.2, 16.2)
Chills	817	20.3 (19.1, 21.6)	214	10.4 (9.2, 11.8)
Malaise	760	18.9 (17.7, 20.1)	259	12.6 (11.3, 14.1)
Bone or joint pain	713	17.7 (16.6, 18.9)	222	10.8 (9.6, 12.2)
Nausea	274	6.8 (6.1, 7.6)	69	3.4 (2.7, 4.2)
Dizziness and giddiness	265	6.6 (5.9, 7.4)	76	3.7 (3.0, 4.6)
Hot flashes	255	6.3 (5.6, 7.1)	60	2.9 (2.3, 3.7)
Eye movement pain	253	6.3 (5.6, 7.1)	55	2.7 (2.1, 3.5)
Sweating	236	5.9 (5.2, 6.6)	55	2.7 (2.1, 3.5)
Stuffy nose	197	4.9 (4.3, 5.6)	61	3 (2.3, 3.8)
Sore throat	191	4.7 (4.1, 5.4)	72	3.5 (2.8, 4.4)
Diarrhea	177	4.4 (3.8, 5.1)	71	3.5 (2.8, 4.3)
Chest pain	174	4.3 (3.7, 5.0)	45	2.2 (1.6, 2.9)
A faster or lower heartbeat	166	4.1 (3.6, 4.8)	41	2.0 (1.5, 2.7)
Irritated eyes	130	3.2 (2.7, 3.8)	31	1.5 (1.1, 2.1)
Running nose	124	3.1 (2.6, 3.7)	54	2.6 (2, 3.4)
Difficulty breathing (dyspnea)	107	2.7 (2.2, 3.2)	25	1.2 (0.8, 1.8)
Abdominal pain	96	2.4 (2.0, 2.9)	25	1.2 (0.8, 1.8)
Lymph nodes tenderness	91	2.3 (1.8, 2.8)	38	1.9 (1.4, 2.5)
Cough	90	2.2 (1.8, 2.7)	34	1.7 (1.2, 2.3)
Rise in blood pressure	87	2.2 (1.8, 2.7)	15	0.7 (0.4, 1.2)
Vomiting	57	1.4 (1.1, 1.8)	20	1.0 (0.6, 1.5)
Skin rash, hives, irritable skin	50	1.2 (0.9, 1.6)	11	0.5 (0.3, 1.0)
Loss of blood pressure	44	1.1 (0.8, 1.5)	7	0.3 (0.2, 0.7)
Other	92	2.3 (1.9, 2.8)	23	1.1 (0.7, 1.7)

Study on self-reported side effects of Coronavirus Disease-19 (COVID-19) vaccines in the Mexican population, August to September 2021.

[a]*Ordered from highest to lowest frequency after first dose.*

registered the lowest frequency (55%), which was higher than phases 2 and 3 clinical trials reports with values between 19 and 33% (31, 32). The next vaccine with less adverse effects was mRNA-1273 (Moderna) (69%), lower than 84% documented in a phase 3 clinical trial (33). Three vaccines showed prevalence around 70%, BNT162b2 (Pfizer-BioNTech; 73%), Ad5-nCoV (CanSinoBIO; 75%), and Ad26.CoV2.S (Johnson & Johnson/Janssen; 71%). The BNT162b2 (Pfizer-BioNTech) statistics of side effects are contrasting. An ongoing multinational placebo-controlled clinical trial reported 27% (34), but surveys with self-reported symptoms showed figures between 80 and 92% (21, 22, 35). Ad5-nCoV (CanSinoBIO) and Ad26.CoV2.S (Johnson & Johnson/Janssen) frequencies were close to the ones reported in phase 2 clinical trials. Zhu et al. (36) found 72–74% with Ad5-nCoV (CanSinoBIO) and Sadoff et al. (37) identified 62–63% with low Ad26.CoV2.S (Johnson & Johnson/Janssen) dose and 78–82% with high dose. The vaccines with the highest frequency of side effects were ChAdOx1 (AstraZeneca) and Gam-COVID-Vac (Gamaleya's Sputnik V) (85 and 80%, respectively). Both were within the range of self-report surveys. The former has shown prevalence ranging from 51 to 96% (21, 27, 35, 38, 39) and the second one, prevalence ranging from 71 to 82% (40, 41).

First vs. Second Doses

We found a stronger reaction to the first than the second dose. ChAdOx1 (AstraZeneca) presented the highest difference with +40%, Gam-COVID-Vac (Gamaleya's Sputnik V) with +22%, and CoronaVac (Sinovac Life Sciences) with +10%. The stronger reaction to ChAdOx1 (AstraZeneca) first dose was in line with other reports (14, 42). Jarynowski et al. (20) also showed a higher average of adverse effects with the first than the second dose Gam-COVID-Vac (Gamaleya's Sputnik V) (2.2 ± 1.8 vs. 1.9 ± 1.7). They attributed such a result to the vaccine vector used in dose 2, which is different from dose 1. BNT162b2 (Pfizer-BioNTech) registered an overall difference of +6 indicating higher side effects with dose 1, unlike other studies that had reported more effects with the second dose (15, 18, 19). The discrepancy may be due to differences in age, sex, comorbidities, and history of COVID-19 infection. In addition, to geographic region and immune response variations. A systematic review and meta-analysis conducted by Choe et al. (43) showed that the geographic region was an important source of variation in the immune response to pneumococcal conjugate vaccines. Further research is needed to identify the reasons for an observed result contrary to what was expected. mRNA-1273 (Moderna) was the only vaccine with higher side effects at dose 2, which was in accordance with what the Centers for Disease Control and Prevention (CDC) reports. That is mRNA-1273 (Moderna) tends to present higher symptomatology the second time (16).

Extension of Side Effects

Unlike other studies, this one distinguished the frequency of local and systemic symptoms in a single or combined presentation. At dose 1, very few had local or systemic symptoms in solitary instead they experienced both, which was considered of

TABLE 4 | The severity of side effects by the number of dose and type of vaccine.

	Type of vaccine							
	Pfizer[a]	AstraZeneca[b]	Moderna[c]	SinoVac[d]	Sputnik V[e]	Cansino[f]	J & J[g]	Chi-square *p*-value
Dose 1								
Suspended daily activities/missed work	164 (14.2%)	498 (49.2%)	5 (13.9%)	39 (23.8%)	63 (39.1%)	168 (37.7%)	16 (23.2%)	0.0001
Sought medical attention	42 (3.6%)	67 (6.6%)	1 (2.8%)	8 (4.9%)	5 (3.1%)	37 (8.3%)	(1) 1.4%	0.001
Took medicine	598 (51.7%)	804 (79.4%)	27 (75%)	69 (42.1%)	105 (65.2%)	252 (56.4%)	52 (75.4%)	0.0001
Severity index								
None	935 (59.2%)	312 (26.2%)	24 (46.2%)	212 (70.9%)	75 (37.1%)	289 (48.3%)	43 (44.3%)	
Mild	462 (29.3%)	369 (30.9%)	22 (42.3%)	46 (15.4%)	60 (29.7%)	128 (21.4%)	37 (38.1%)	
Moderate or severe	182 (11.5%)	512 (42.9%)	6 (11.5%)	41 (13.7%)	67 (33.2%)	181 (30.3%)	17 (17.5%)	0.0001
Dose 2								
Felt better	434 (31.5%)	190 (56.2%)	5 (10%)	41 (23.2%)	31 (43.7%)	–	–	
Felt the same	561 (40.7%)	107 (31.7%)	18 (36%)	105 (59.3%)	25 (35.2%)	–	–	
Felt worse	383 (27.8%)	41 (12.1%)	27 (54%)	31 (17.5%)	15 (21.1%)	–	–	0.0001

Study on self-reported side effects of Coronavirus Disease-19 (COVID-19) vaccines in the Mexican population, August to September 2021.
[a]*BNT162b2 (Pfizer-BioNTech).*
[b]*ChAdOx1 (AstraZeneca).*
[c]*mRNA-1273 (Moderna).*
[d]*CoronaVac (Sinovac Life Sciences).*
[e]*Gam-COVID-Vac (Gamaleya's Sputnik V).*
[f]*Ad5-nCoV (CanSinoBIO).*
[g]*Ad26.CoV2.S (Johnson & Johnson/Janssen).*

greater extension. ChAdOx1 (AstraZeneca) and Gam-COVID-Vac (Gamaleya's Sputnik V) were associated to greater extension while CoronaVac (Sinovac Life Sciences) to lesser extension, independent of sex, age, and other potential confounders. At dose 2, the absence of symptoms equaled the category of a combination of local and systemic symptoms and mRNA-1273 (Moderna) was the only vaccine associated with the greater extension. Regarding local symptoms, we identified important differences with the literature. For example, BNT162b2 (Pfizer-BioNTech) and ChAdOx1 (AstraZeneca) each registered 50% of participants with pain at the injection site in dose 1, which was less than that reported before between 68 and 81.2% (18, 21). At dose 2, the rates were 34.5 and 18%, respectively. Moreover, lower than in other studies >70% (18, 44). The rates of fatigue and muscle pain secondary to CoronaVac (Sinovac Life Sciences) in dose 1 were lower than those identified by Djanas et al. (45) (13% vs. 35.8% and 39.6%, respectively). Moreover, in dose 2, BNT162b2 (Pfizer-BioNTech) registered half the frequency reported elsewhere (18, 44). These differences remind the importance of estimating the prevalence of adverse effects in different populations. On the other hand, ChAdOx1 (AstraZeneca) registered higher systemic side effects than BNT162b2 (Pfizer-BioNTech) in dose 1, which was not surprising as this has been pointed out by other authors (18, 21).

The Severity of Side Effects

The severity of side effects varied by the type of vaccine and the number of doses. Four vaccines increased the possibilities of greater severity at the first dose, ChAdOx1 (AstraZeneca), Ad5-nCoV (CanSinoBIO), Gam-COVID-Vac (Gamaleya's Sputnik V), and Ad26.CoV2.S (Johnson & Johnson/Janssen), as compared to BNT162b2 (Pfizer-BioNTech), independent of sex, age, and other potential confounders. There were more respondents suspending activities/missing work and taking medicine for relieving symptoms with ChAdOx1 (AstraZeneca). Kim et al. (18) also reported ChAdOx1 (AstraZeneca) with a higher impact on work productivity (work performance was impaired, took vacation or holiday, missed work). We found more participants seeking medical attention with Ad5-nCoV (CanSinoBIO) followed by ChAdOx1 (AstraZeneca). Kim et al. (18) also identified the latter vaccine with a higher frequency of subsequent need for going to a doctor, an emergency room, or being hospitalized.

Associated Factors

Age, sex, and allergies were associated with greater extension and severity of side effects regardless of the type of vaccine and number of doses. Age <50 years presented the greatest risk, which doubled the chances of having local combined with systemic symptoms. Studies from different regions and different vaccines have documented respondents under 50 years with a higher risk of side effects (18, 20, 22, 27). It has been attributed to a decline in the function of the immune system with age. Women have a higher risk of adverse effects too (18–22). The disparity has been explained by differences in the immune response between men and women (46, 47). We also identified a history of allergies associated to greater extension and severity of side effects. Jahan et al. (27) found 45.1% of their participants had a history of allergic reactions to various allergens, which were associated with sneezing, coughing, itching, swelling, runny nose, and shortness of breath following the first

TABLE 5 | Multivariate ordinal regression analyses of factors associated to an extension of side effects in Mexican population, August to September 2021.

	Extension					
	Absent	**Local**	**Systemic**	**Local and systemic**	**Adjusted odds ratios[a] (95% CI)**	**Wald Chi-square *p*-value**
First dose						
Type of vaccine						
Pfizer[1]	43.4%	71.1%	20.0%	34.4%	1.00	
AstraZeneca[2]	18.6%	8.6%	36.5%	37.6%	2.53 (2.16, 2.96)	0.00001
Cansino[3]	15.5%	7.4%	26.5%	14.2%	1.18 (0.99, 1.42)	0.072
SinoVac[4]	13.8%	8.6%	7.6%	4.4%	0.52 (0.41, 0.66)	0.00001
Sputnik V[5]	4.2%	1.4%	4.9%	6.1%	2.41 (1.76, 3.29)	0.00001
J & J[6]	2.9%	0.2%	4.3%	2.3%	1.27 (0.85, 1.91)	0.246
Moderna[7]	1.6%	2.7%	0.3%	1.0%	0.82 (0.49, 1.38)	0.465
Female sex	73.5%	78.6%	77.8%	82.9%	1.45 (1.25, 1.68)	0.00001
Age < 50 years	70.8%	77.9%	78.6%	88.1%	2.29 (1.95, 2.69)	0.00001
Comorbidity (any)	19.7%	21.0%	16.5%	19.3%	1.19 (1.01, 1.41)	0.033
Allergies	23.0%	27.8%	27.6%	35.5%	1.58 (1.37, 1.81)	0.00001
Smoking	13.8%	12.4%	11.1%	13.2%	1.04 (0.87, 1.26)	0.645
Second dose						
Type of vaccine						
Pfizer[1]	58.5%	76.6%	68.2%	75.4%	1.00	
AstraZeneca[2]	24.1%	11.7%	20.4%	10.3%	0.46 (0.36, 0.58)	0.0001
SinoVac[4]	12.6%	8.8%	6.5%	5.6%	0.47 (0.35, 0.63)	0.0001
Sputnik V[5]	3.9%	1.5%	2.0%	4.3%	1.29 (0.80, 2.08)	0.294
Moderna[7]	0.8%	1.5%	3.0%	4.4%	2.88 (1.59, 5.21)	0.0001
Female sex	76.9%	79.9%	79.8%	83.4%	1.27 (1.03, 1.57)	0.025
Age < 50 years	57.7%	73.7%	63.1%	79.6%	2.03 (1.68, 2.45)	0.0001
Comorbidity (any)	25.2%	27.0%	26.1%	22.1%	1.04 (0.85, 1.26)	0.349
Allergies	26.0%	29.9%	35.0%	33.1%	1.2 (1.00, 1.44)	0.728
Smoking	14.1%	11.3%	10.3%	14.5%	1.13 (0.88, 1.44)	0.046

[a]*Adjusted by the preventive use of medication to prevent symptoms before vaccination and history of confirmed COVID-19 infection.*
[1]*BNT162b2 (Pfizer-BioNTech).*
[2]*ChAdOx1 (AstraZeneca).*
[3]*mRNA-1273 (Moderna).*
[4]*CoronaVac (Sinovac Life Sciences).*
[5]*Gam-COVID-Vac (Gamaleya's Sputnik V).*
[6]*Ad5-nCoV (CanSinoBIO).*
[7]*Ad26.CoV2.S (Johnson & Johnson/Janssen).*

application of ChAdOx1 (AstraZeneca). It appeared that the relative incidence of allergic reactions following administration of BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines had been higher for recipients with a prior history of allergies and/or anaphylaxis, respectively (48).

Limitations

Differences in the use of certain vaccines were consistent with the vaccination program in the country, which in turn was a function of vaccines availability. The distribution by age, sex, and schooling was not as heterogeneous as would have been desired; and there was a bias toward young age, female sex, and higher schooling. Some reasons may help to explain it. In Mexico, there are more women than men (51 vs. 49%) and people between 15 and 49 years make up more than half of the population according to the 2020 population census (49). Women tend to participate more in health surveys. The higher presence of young adults reflects their greater familiarity and use of social media compared to older adults. Other authors have also reported more women and young respondents (18–21); and a higher frequency of university or post-university participants in online surveys (19, 27). The combination of higher education and a job with the Ad5-nCoV (CanSinoBIO) can be explained by the fact that this vaccine was applied mainly to schoolteachers and university professors. Additionally, diabetes and hypertension were half the frequency reported in the 2021 National Health and Nutrition Survey (50), probably secondary to the low presence of older adults. These were the ones with the least participation, which agrees with the percentage distribution of population 60 and over that according to the census ranks second least in the country, after that of 50–59 years (12 and 10%, respectively) (49). Future research requires the inclusion of a greater number of men, older adults, and less educated individuals. The study relied on self-report and symptoms were not verified. Some respondents may

TABLE 6 | Multivariate ordinal regression analyses of factors associated to the severity of side effects in Mexican population, August to September 2021.

	Severity					
	Absent	**Mild**	**Moderate**	**Severe**	**Adjusted odds ratios[a] (95% CI)**	**Wald Chi-square *p*-value**
First dose						
Type of vaccine						
Pfizer[1]	49.5%	41.1%	16.6%	26.1%	1.00	
AstraZeneca[2]	16.5%	32.8%	52.7%	41.6%	4.32 (3.73, 5.0)	0.0001
Cansino[3]	15.3%	11.4%	17.0%	23.0%	1.96 (1.63, 2.36)	0.0001
SinoVac[4]	11.2%	4.1%	3.9%	5.0%	0.71 (0.54, 0.93)	0.013
Sputnik V[5]	4.0%	5.3%	7.3%	3.1%	3.00 (2.28, 3.94)	0.0001
J & J[6]	2.3%	3.3%	1.9%	0.6%	1.68 (1.15, 2.46)	0.008
Moderna[7]	1.3%	2.0%	0.6%	0.6%	1.43 (0.86, 2.38)	0.163
Female sex	75.4%	83.3%	83.3%	85.7%	1.52 (1.30, 1.78)	0.0001
Age < 50 years	77.2%	83.9%	88.9%	85.7%	1.58 (1.30, 1.87)	0.0001
Comorbidity (any)	18.8%	19.9%	18.9%	23.6%	1.22 (1.05, 1.43)	0.011
Allergies	25.7%	33.6%	37.3%	39.1%	1.49 (1.31, 1.70)	0.0001
Smoking	12.5%	13.5%	13.6%	13.7%	1.11 (0.93, 1.33)	0.233

[a]*Adjusted by the preventive use of medication to prevent symptoms before vaccination and history of confirmed COVID-19 infection.*
[1]*BNT162b2 (Pfizer-BioNTech).*
[2]*ChAdOx1 (AstraZeneca).*
[3]*mRNA-1273 (Moderna).*
[4]*CoronaVac (Sinovac Life Sciences).*
[5]*Gam-COVID-Vac (Gamaleya's Sputnik V).*
[6]*Ad5-nCoV (CanSinoBIO).*
[7]*Ad26.CoV2.S (Johnson & Johnson/Janssen).*

have incorrectly blamed the vaccine for the experienced side effect. Moreover, those who experienced side effects might have been more interested in participating than those who did not; and rates might be overestimated. Results might have been affected by memory bias. The use of mobile devices for reporting side effects in real-time might produce more accurate rates. Finally, the study focused on the short-term side effects; more research is needed for long-term effects.

CONCLUSIONS

Prevalence and degree of adverse reactions differed by the number of doses and type of vaccine. At dose 1, ChAdOx1 (AstraZeneca) was the vaccine with the highest rate of at least one side effect followed by Gam-COVID-Vac (Gamaleya's Sputnik V). Both were associated with greater extension and severity of side effects. ChAdOx1 (AstraZeneca) was the vaccine in which more participants were required to suspend everyday duties or had to miss work. Young age (<50 years), female sex, comorbidity, and history of allergies were associated with greater extension and severity of side effects after the first vaccination, regardless of the type of vaccine and potential confounders. At dose 2, mRNA-1273 (Moderna) was the vaccine with the highest rate of side effects and the only vaccine associated with greater extension and severity of symptoms. Female sex and age under 50 increased the odds of greater extension after the second vaccination. Therefore, after receiving the COVID-19 vaccination, recipients should be advised about potential vaccine symptoms according to the number of doses, the type of vaccine, sex, age, and history of allergies. An informed public will know what to expect, what to do, when and where to seek additional guidance if necessary. Furthermore, measures for preventing or eliminating the unwanted effect might be planned. Continuous studies are necessary to acknowledge more about the post-vaccine symptoms in different populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Committee of Health Research No. 1909, Mexican Social Security Institute. The patients/participants provided their written informed consent to participate in this study.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Mexican Social Security Institute (protocol 2021-1909-106, August 9, 2021).

AUTHOR CONTRIBUTIONS

MC and AS conceptualized the study and contributed to methodology, software, and writing—original draft preparation. BT and AS validated the data. MC, BT, and AS contributed to formal analysis. MC investigated the study. MC, AS, and JG contributed to data curation. MB, GN, JG, and BT contributed to writing, reviewing, and editing. AS and MB contributed to supervision. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

The authors thank to Universidad de Monterrey for the APC funding.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.834744/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 05 April 2022
doi: 10.3389/fmed.2022.826327

Characteristics and Comparison of Adverse Events of Coronavirus Disease 2019 Vaccines Reported to the United States Vaccine Adverse Event Reporting System Between 14 December 2020 and 8 October 2021

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OPEN ACCESS

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Specialty section:
This article was submitted to Infectious Diseases – Surveillance, Prevention and Treatment, a section of the journal Frontiers in Medicine

Received: *30 November 2021*
Accepted: *04 March 2022*
Published: *05 April 2022*

Citation:
Zou C, Xue X and Qian J (2022) Characteristics and Comparison of Adverse Events of Coronavirus Disease 2019 Vaccines Reported to the United States Vaccine Adverse Event Reporting System Between 14 December 2020 and 8 October 2021. Front. Med. 9:826327. doi: 10.3389/fmed.2022.826327

Background: This study assessed and compared the frequency and type of adverse events (AEs) of the Pfizer-BioNTech, Moderna, and Janssen coronavirus disease 2019 (COVID-19) vaccines reported in the Vaccine Adverse Event Reporting System (VAERS).

Methods: A retrospective analysis examined VAERS reports between 14 December 2020 and 8 October 2021 and focused on AE reports related to COVID-19 vaccines and AE outcomes [e.g., emergency room (ER) visits after being vaccinated, hospitalization, prolongation of existing hospitalization, life-threatening events, disability, birth defect, and death]. Reporting odds ratios (RORs) and Breslow-Day statistics were used to compare AE reporting between COVID-19 and non-COVID vaccines and between individual COVID-19 vaccines.

Results: A total of 604,157 AEs of COVID-19 vaccines were reported, including 43.51% for the Pfizer-BioNTech vaccine, 47.13% for the Moderna vaccine, and 9.12% for the Janssen COVID-19 vaccine. About 12.56% of patients visited ER after being vaccinated, 5.96% reported hospitalization, and 1.52% reported life-threatening events. Among the number of death cases (n = 7,674; mean age = 73), 2,025 patients (26.39%) had hypertension and 1,237 (16.12%) patients had cancer. RORs between COVID-19 vaccines and non-COVID vaccines identified increased ROR in ER visits, hospitalization, and life-threatening events. The results of the Breslow-Day statistics indicated heterogeneities between the disproportionality of reports across the four serious AE outcomes (i.e., ER visits, hospitalization, life-threatening events, and disability) between individual COVID-19 vaccines.

Conclusion: Most current VAERS reports showed that the most commonly reported AEs of COVID-19 vaccines were mild. Cases with a mortality outcome tended to occur in older adults with underneath conditions. Close ongoing surveillance in the

safety of COVID-19 vaccines is critical and will inform the use of individual COVID-19 vaccines. Given the known limitations associated with the passive spontaneous reporting system, such as VAERS, our findings need to be further assessed and verified through longitudinal, large healthcare data systems.

Keywords: COVID-19 vaccine, VAERS, adverse event reporting, vaccine safety, surveillance

INTRODUCTION

As of 29 October 2021, three vaccines are authorized for use in the United States (US) against SARS-CoV-2, the virus causing coronavirus disease 2019 (COVID-19) (**Supplementary Table 1**). The US Food and Drug Administration (FDA) issued the Emergency Use Authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine on 11 December 2020 (1), for the Moderna COVID-19 vaccine on 18 December 2020 (2), and for the Janssen (Johnson and Johnson) COVID-19 vaccine on 27 February 2021 (3). The Pfizer-BioNTech and the Moderna COVID-19 vaccines are administered as 2-dose series [the Centers for Disease Control and Prevention (CDC) recommended some groups of people to get a booster shot after 6 months of the second dose] (1–3), while the Janssen COVID-19 vaccine requires only one dose (CDC recommended some groups of people to get a booster shot after 2 months of the first dose) (3). The Advisory Committee on Immunization Practices (ACIP) recommended the use of the Pfizer-BioNTech COVID-19 vaccine to prevent COVID-19 in individuals aged 5 and above (1, 3, 4), whereas the Moderna and Janssen COVID-19 vaccines were recommended among individuals aged 18 and above (2, 3, 5). As of 29 October 2021, a total of 419,020,753 doses of the COVID-19 vaccine had been administered in the United States, and 191,997,869 people were fully vaccinated (6).

Vaccines are one of the most affordable and widely used public health interventions (7, 8), and vaccination has been recommended as a critical protective behavior for COVID-19 (9–15). The most recent Kaiser Family Foundation (KFF) COVID-19 Vaccine Monitor showed that about 62% of United States adults had received at least one dose of a vaccine, but 13% of participants indicated that they definitely would not get a COVID vaccine (16). Vaccine hesitancy for COVID-19 has been reported due to concerns about safety, potential adverse events (AEs), and effectiveness of current vaccines (15, 17–20). To detect possible safety problems from the COVID-19 vaccines, the safety monitoring systems for these vaccines, which is "the most intense and comprehensive in United States history," have been developed (21). It is run by the CDC, FDA, and other federal partners; this broad, continued, and extensive safety surveillance system uses several existing data sources and "additional layers" [such as V-safe, a smartphone-based "after vaccine health checker (22)"] for ongoing safety monitoring, including the Vaccine Adverse Event Reporting System (VAERS) (21, 23). VAERS is a passive surveillance system and relies on unsolicited AE reports from individuals (24). In contrast, active surveillance entails proactively collecting and rapidly analyzing reports pertaining to millions of records in large healthcare datasets (25). The US FDA is conducting active surveillance using the Sentinel Biologics Effectiveness and Safety (BEST) System and the Centers for Medicare and Medicaid Services (CMS) System, collaborating with other federal and non-federal partners (26). Although active surveillance systems usually generate higher quality data (i.e., high levels of completeness, validity, and timeline) compared with passive surveillance systems, passive surveillance systems, including VAERS, have provided timely evidence in supporting regulatory decision-making regarding COVID-19 vaccination in the United States (27–29). This study assessed the AE reporting of the three available COVID-19 vaccines in VAERS since the first administration on 14 December 2020 and compared the AE reporting among individual COVID-19 vaccines as of 8 October 8 2021.

MATERIALS AND METHODS

Data Source

Vaccine Adverse Event Reporting System, co-managed by the CDC and FDA, is a nationwide early warning system aimed to detect potential safety issues for all vaccines approved in the United States (30). It is a spontaneous reporting system, and vaccine manufacturers, healthcare professionals, patients, and customers can submit an AE report to VAERS, regardless of the seriousness of the AEs or how likely the vaccine has caused the AEs (30–32). VAERS is not intended to determine whether a vaccination caused a health problem, but to detect unexpected and unusual AEs and address possible reporting clusters (33). This study was approved by the Auburn University Institutional Review Board (IRB).

Coronavirus Disease 2019 Vaccine Adverse Event Reports

All reports of the three approved COVID-19 vaccines (i.e., Pfizer-BioNTech, Moderna, and Janssen) between 14 December 2020 and 8 October 2021 were identified through the public VAERS dataset (variable "VAX_TYPE"). In addition, the patient's age, sex, types of AE (variable "VAERS SYMPTOM"), and seven AE outcomes, namely, emergency room (ER) visit, hospitalization, prolongation of existing hospitalization, life-threatening events, disability, birth defect, and death, were extracted. For each death case reported from the AE reports for the three COVID-19 vaccines, we also assessed the patient's reported medical history and current conditions (variables "HISTORY" and "CUR_ILL," respectively).

Statistical Analyses

Descriptive analyses of frequencies and proportions of AE reports by patient's age, sex, type of COVID-19 vaccine administered, and AE outcomes were conducted. We also summarized the top 10 types of reported AEs from COVID-19 vaccines by frequency, overall and by individual vaccines. To compare the safety and AE reporting of COVID-19 vaccines with all other vaccines, we calculated the reporting odds ratio (ROR) and 95% confidence intervals (95% CIs) for each assessed AE outcome during the same period between 14 December 2020 and 8 October 2021 for all three COVID-19 vaccines combined together and for each individual COVID-19 vaccine. Given the surge of AE reporting for COVID-19 vaccines into VAERS after the initial administration, a sensitivity analysis was conducted by calculating RORs for COVID-19 vaccines compared to all other vaccines during a wider time window between 1 January 2020 and 8 October 2021. The Breslow-Day statistics was conducted to assess the homogeneity of RORs of assessed AE outcomes between individual COVID-19 vaccines (34). A p-value < 0.05 from the Breslow–Day test indicated a significant difference in RORs for a specific event between two individual COVID-19 vaccines. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC), and $p < 0.05$ was set as statistical significance.

TABLE 1 | Summary of COVID-19 vaccines adverse event (AE) reports to VAERS, 14 December 2020 to 8 October 2021.

VAERS AE reports	*N* (%)
Number of AE reports of COVID-19 vaccines	604,157
Pfizer-BioNTech COVID-19 vaccine	262,883 (43.51)
Moderna COVID-19 vaccine	284,765 (47.13)
Janssen COVID-19 vaccine	55,111 (19.73)
Reports with missing manufacturer	1,308 (0.22)
Mean age (range), years	49.43 (0.08–119)
0–18	26,454 (4.38)
19–44	200,776 (33.23)
45–64	186,073 (30.80)
65–84	119,189 (19.73)
85 +	12,776 (2.11)
Missing	58,889 (9.75)
Female sex	412,610 (68.30)
AE outcomes	
ER visits after being vaccinated	75,911 (12.56)
Hospitalization	36,030 (5.96)
Life-threatening events	9,193 (1.52)
Disability	8,890 (1.47)
Death	7,674 (1.27)
Birth defect	343 (0.06)
Prolongation of existing hospitalization	305 (0.05)

RESULTS

Between 14 December 2020 and 8 October 2021, a total of 661,614 AE reports were submitted to VAERS. Among these reports, 604,157 (91.32%) reports were of COVID-19 vaccines. Among all COVID-19 vaccine-related reports, there were 262,883 (43.51%) reports pertaining to the Pfizer-BioNTech COVID-19 vaccine, 284,765 (47.13%) reports pertaining to the Moderna COVID-19 vaccination, 55,111 (9.12%) reports pertaining to the Janssen COVID-19 vaccine, and 1,308 (0.22%) reports with the missing manufacturer (**Table 1**). Among the reports of AEs due to COVID-19 vaccines, 412,610 (68.30%) were women, and the mean age was 49.43 years (in the range of 0.08–119 years). There were 75,911 (12.56%) patients who visited the ER after being vaccinated and 36,030 (5.96%) patients reported hospitalization with an average length of 3.11 days (in the range of 1–22 days). In addition, 9,193 (1.52%) individuals reported to be experiencing life-threatening events, 8,890 (1.47%) individuals reported disability, 7,674 (1.27%) individuals were reported as dead, 343 (0.06%) individuals reported birth defect, and 305 (0.05%) individuals had prolongation of existing hospitalization after being vaccinated (**Table 1**).

The top ten AE reports for all COVID-19 vaccines and individual COVID-19 vaccines by frequency are listed in **Table 2**. Headache, fatigue, chills, pyrexia, and pain were among the top five commonly reported AEs for all three COVID-19 vaccines, overall and individually.

It was reported that 7,674 individuals died after they were administered the COVID-19 vaccines with a mean age of 72.75 (range: 0.42–106), accounting for 1.27% of all AE reports of COVID-19 vaccines (**Table 3**). Among these death cases, 3,500 (45.61%) received the Pfizer-BioNTech COVID-19 vaccine, 3,329 (43.38%) received the Moderna COVID-19 vaccine, 814 (10.61%) received the Janssen COVID-19 vaccine, and 31 (0.40%) deaths with unidentified vaccine manufacturer. A total of 2,025 (26.39%) death cases indicated previous diagnoses of hypertension, and 1,237 (16.12%) death cases had cancer. Other common comorbidities included diabetes mellitus (DM) (10.65%), heart disease (9.47%), chronic obstructive pulmonary disease (COPD) (5.75%), transient ischemic attack (TIA) (5.72%), and heart failure (5.20%).

During 14 December 2020 and 8 October 2021 (**Table 4** and **Supplementary Figure 1**), RORs of all seven serious AE outcomes between COVID-19 vaccines and non-COVID vaccines indicated a potentially higher ROR in ER visits (ROR = 1.08, 95% CI = 1.08–1.09), hospitalization, (ROR = 1.21, 95% CI = 1.14–1.28), prolongation of existing hospitalization (ROR = 1.41, 95% CI = 1.01–1.96), and life-threatening events (ROR = 1.20, 95% CI = 1.07–1.35). The increased ROR in ER visits, hospitalization, and life-threatening events for COVID-19 vaccines was consistent with results from sensitivity analysis, but not for prolongation of existing hospitalization (ROR = 0.56, 95% CI = 0.42–0.75 in sensitivity analysis) and death (ROR = 1.87, 95% CI = 1.69–2.07 in sensitivity analysis, **Table 4** and **Supplementary Figure 2**).

For the comparison between the Pfizer COVID-19 vaccine and all other vaccines, RORs for six serious AE outcomes (i.e., ER visits, hospitalization, life-threatening events, disability, birth defect, and death) indicated a higher ROR in these serious

TABLE 2 | Top 10 adverse events of COVID-19 vaccines reported to VAERS by frequency, 14 December 2020 to 8 October 2021.

Top 10 adverse events of all three COVID-19 vaccines	***N* (%)**
Headache	100,458 (16.63)
Fatigue	85,313 (14.12)
Chills	80,334 (13.30)
Pyrexia	74,047 (12.26)
Pain	64,924 (10.75)
Dizziness	61,925 (10.25)
Nausea	52,483 (8.69)
Pain in extremity	50,179 (8.31)
Arthralgia	36,192 (5.99)
Injection site pain	32,400 (5.36)
Top 10 adverse events of Pfizer-BioNTech COVID-19 vaccine *N* (%)	
Headache	41,122 (15.64)
Fatigue	35,407 (13.47)
Dizziness	29,812 (11.34)
Chills	29,620 (11.27)
Pyrexia	27,463 (10.45)
Pain	26,223 (9.98)
Nausea	22,474 (8.55)
Pain in extremity	19,040 (7.24)
Arthralgia	15,775 (6.00)
Dyspnea	14,637 (5.57)
Top 10 adverse events of Moderna COVID-19 vaccine *N* (%)	
Headache	46,037 (16.17)
Fatigue	40,479 (14.21)
Chills	40,030 (14.06)
Pyrexia	36,636 (12.87)
Pain	30,353 (10.66)
Pain in extremity	26,241 (9.21)
Dizziness	24,603 (8.64)
Nausea	23,682 (8.32)
Injection site erythema	20,207 (7.10)
Injection site pain	19,911 (6.99)
Top 10 adverse events of Janssen COVID-19 vaccine *N* (%)	
Headache	13,048 (23.68)
Chills	10,479 (19.01)
Pyrexia	9,735 (17.66)
Fatigue	9,251 (16.79)
Pain	8,177 (14.84)
Dizziness	7,396 (13.42)
Nausea	6,210 (11.27)
Pain in extremity	4,801 (8.71)
Arthralgia	3,268 (5.93)
Myalgia	3,190 (5.79)

TABLE 3 | Summary of death cases of COVID-19 vaccines reported to VAERS, 14 December 2020 to 8 October 2021.

Mean age (range), years	72.75 (0.42–106)
	Number (%)
Number of death reports of COVID-19 vaccines	7,674
Number of death reports of Pfizer-BioNTech COVID-19 vaccine	3,500 (45.61)
Number of death reports of Moderna COVID-19 vaccine	3,329 (43.38)
Number of death reports of Janssen COVID-19 vaccine	814 (10.61)
Number of death reports with missing manufacturer	31 (0.40)
Medical history and current conditions for all death cases	
Hypertension	2,025 (26.39)
Cancer	1,237 (16.12)
DM (Diabetes Mellitus)	817 (10.65)
Heart disease	727 (9.47)
COPD (Chronic Obstructive Pulmonary Disease)	441 (5.75)
TIA (Transient Ischemic Attack)	439 (5.72)
Heart failure	399 (5.20)
Hyperlipidemia	348 (4.53)
Dementia	316 (4.12)
Atrial fibrillation	315 (4.10)
Coronary artery	296 (3.86)
CHF (Congestive Heart Failure)	287 (3.74)
Atherosclerosis	272 (3.54)
Thyroid disease	269 (3.51)
CKD (Chronic Kidney Disease)	265 (3.45)
Obesity	199 (2.59)
Kidney disease	197 (2.57)
GERD (Gastroesophageal reflux disease)	195 (2.54)
Depression	179 (2.33)
Alzheimer's disease	137 (1.79)
Dysphagia	107 (1.39)
Pulmonary*	87 (1.13)
PVD (Peripheral Vascular Disease)	48 (0.63)
COVID-19	42 (0.55)
Hypercholesterolemia	37 (0.48)
ASCVD (Atherosclerotic cardiovascular disease)	33 (0.43)
Schizophrenia	27 (0.35)
AAA (Abdominal aortic aneurysm)	23 (0.30)
Hypokalemia	11 (0.14)

**Identified based on reported terms of "pneumonia" or "pulmonary" from variables "HISTORY" and "CUR_ILL".*

events for the Pfizer COVID-19 vaccine during 14 December 2020 and 8 October 2021. These RORs remained statistically significant in a sensitivity analysis. For the Moderna COVID-19 vaccine vs. all other vaccines, RORs for all seven assessed serious AE outcomes indicated a lower ROR (indicating no reporting risk) for the Moderna COVID-19 vaccine during 14 December 2020 and 8 October 2021, as well as in the sensitivity analysis. For the Janssen COVID-19 vaccine vs. all other vaccines, RORs for the five assessed serious AE outcomes (i.e., ER visits, hospitalization, prolongation of existing hospitalization, life-threatening events, and death) indicated a higher ROR in these serious events for the Janssen COVID-19 vaccine in both main and sensitivity analyses (**Table 4** and **Supplementary Figures 1**, **2**).

The results of the Breslow-Day statistics to compare RORs of seven serious AE outcomes for individual COVID-19 vaccines with all other vaccines are shown in **Table 5**. We found that the signals of disproportionate reporting for the four serious AE outcomes (i.e., ER visits, hospitalization, life-threatening events, and disability) with each individual COVID-19 vaccine were all different from another individual COVID-19 vaccine ($p < 0.05$).

TABLE 4 | Main and sensitivity analyses of RORs for COVID-19 vaccines, overall and by individual COVID-19 vaccine.

Main analysis: December 14, 2020–October 8, 2021				Sensitivity analysis: January 1, 2020–October 8, 2021			
Compare all three COVID-19 vaccines to other non-COVID vaccines				**Compare all three COVID-19 vaccines to other non-COVID vaccines**			
AE Outcomes	**ROR**	**95% CI**		**AE Outcomes**	**ROR**	**95% CI**	
ER visits*	1.08	1.08	1.09	ER visits*	1.08	1.08	1.08
Hospitalization*	1.21	1.14	1.28	Hospitalization*	1.43	1.37	1.49
Prolongation of existing hospitalization*	1.41	1.01	1.96	Prolongation of existing hospitalization*	0.56	0.42	0.75
Life-threatening events*	1.20	1.07	1.35	Life-threatening events*	1.73	1.59	1.89
Disability*	0.43	0.40	0.47	Disability*	0.53	0.50	0.56
Birth defect*	0.60	0.39	0.92	Birth defect	0.87	0.62	1.21
Death	1.11	0.98	1.25	Death*	1.87	1.69	2.07
Compare Pfizer-BioNTech COVID-19 vaccine to all other vaccines				**Compare Pfizer-BioNTech COVID-19 vaccine to all other vaccines**			
ER visits*	1.51	1.49	1.54	ER visits*	1.56	1.54	1.58
Hospitalization*	1.35	1.32	1.37	Hospitalization*	1.38	1.35	1.41
Prolongation of existing hospitalization	1.02	0.82	1.26	Prolongation of existing hospitalization	1.00	0.81	1.23
Life-threatening events*	1.09	1.05	1.14	Life-threatening events*	1.31	1.25	1.36
Disability*	1.25	1.20	1.30	Disability*	1.18	1.13	1.22
Birth defect*	1.35	1.10	1.65	Birth defect*	1.36	1.11	1.66
Death*	1.09	1.05	1.14	Death*	1.17	1.12	1.22
Compare Moderna COVID-19 vaccine to all other vaccines				**Compare Moderna COVID-19 vaccine to all other vaccines**			
ER visits*	0.66	0.65	0.67	ER visits*	0.69	0.68	0.70
Hospitalization*	0.70	0.69	0.72	Hospitalization*	0.74	0.72	0.75
Prolongation of existing hospitalization*	0.71	0.57	0.89	Prolongation of existing hospitalization*	0.71	0.57	0.88
Life-threatening events*	0.71	0.68	0.74	Life-threatening events*	0.76	0.73	0.79
Disability*	0.64	0.61	0.66	Disability*	0.62	0.59	0.65
Birth defect*	0.66	0.53	0.81	Birth defect*	0.68	0.55	0.84
Death*	0.87	0.83	0.91	Death*	0.93	0.89	0.97
Compare Janssen COVID-19 vaccine to all other vaccines				**Compare Janssen COVID-19 vaccine to all other vaccines**			
ER visits*	1.18	1.15	1.21	ER visits*	1.22	1.19	1.25
Hospitalization*	1.23	1.19	1.27	Hospitalization*	1.25	1.21	1.30
Prolongation of existing hospitalization*	1.43	1.03	1.99	Prolongation of existing hospitalization*	1.41	1.01	1.96
Life-threatening events*	1.40	1.32	1.50	Life-threatening events*	1.45	1.37	1.55
Disability*	1.09	1.01	1.16	Disability	1.05	0.98	1.13
Birth defect	0.93	0.64	1.35	Birth defect	0.94	0.65	1.36
Death*	1.19	1.10	1.28	Death*	1.24	1.15	1.33

ROR, reporting odds ratio; CI, confidence interval; AE, adverse event.
**Statistically significant based on 95% CIs.*

DISCUSSION

This study described the most up-to-date frequencies and types of AE reporting for the three approved COVID-19 vaccines (i.e., Pfizer-BioNTech, Moderna, and Janssen) and compared AE reporting rates among individual vaccines using the VAERS database between 14 December 2020 and 8 October 2021. Overall, the majority (over 68%) of AE reports about COVID-19 vaccines came from female patients. The reported AE outcomes involved large proportions of ER visits and hospitalizations after vaccination. However, most commonly reported AEs of COVID-19 vaccines were mild, and cases with a mortality outcome mainly occurred among older adults with underneath chronic conditions, such as hypertension, cancer, and DM.

Our findings are consistent with recently published review studies. A rapid review evaluated the safety profile of COVID-19 vaccines and reported that among the most common local reactions, pain at the injection site was the most common, while fatigue and headache were the most common systemic reactions. A very low frequency of serious AEs was reported (<0.1%) (35). Hernández and colleagues also reported that the most common AEs reported after the administration of three COVID-19 vaccines administered in Europe (i.e., Pfizer, Moderna, and Astra-Zeneca) included the injection site reactions (e.g., sore arm and erythema) and non-specific systemic effects

TABLE 5 | Breslow-day tests for paired comparisons between individual COVID-19 vaccines.

COVID-19 vaccine comparisons	Main analysis: December 14, 2020–October 8, 2021		Sensitivity analysis: January 1, 2020–October 8, 2021	
	Outcomes	***P*-value**	**Outcomes**	***P*-value**
Pfizer-BioNTech vs. Moderna	ER visits*	<0.0001	ER visits*	<0.0001
	Hospitalization*	<0.0001	Hospitalization*	<0.0001
	Prolongation of existing hospitalization*	0.0245	Prolongation of existing hospitalization*	0.0276
	Life-threatening events*	<0.0001	Life-threatening events*	<0.0001
	Disability*	<0.0001	Disability*	<0.0001
	Birth defect*	<0.0001	Birth defect*	<0.0001
	Death*	<0.0001	Death*	<0.0001
Pfizer-BioNTech vs. Janssen				
	ER visits*	< 0.0001	ER visits*	<0.0001
	Hospitalization*	<0.0001	Hospitalization*	<0.0001
	Prolongation of existing hospitalization	0.09	Prolongation of existing hospitalization	0.08
	Life-threatening events*	0.0045	Life-threatening events*	0.0012
	Disability*	<0.0001	Disability*	<0.0001
	Birth defect	0.08	Birth defect	0.09
	Death	0.06	Death	0.17
Janssen vs. Moderna				
	ER visits*	<0.0001	ER visits*	<0.0001
	Hospitalization*	<0.0001	Hospitalization*	<0.0001
	Prolongation of existing hospitalization*	0.0005	Prolongation of existing hospitalization*	0.0006
	Life-threatening events*	<0.0001	Life-threatening events*	<0.0001
	Disability*	<0.0001	Disability*	<0.0001
	Birth defect	0.11	Birth defect	0.14
	Death*	<0.0001	Death*	<0.0001

**Statistically significant based on 95% CIs.*

(e.g., myalgia, chills, fatigue, headache, and fever). Most of these AEs occurred soon after vaccination and resolved quickly (36). Our findings using VAERS, a passive surveillance system, are also consistent with some prospective, active surveillance studies. For example, in a large-scale SARS-CoV-2 surveillance program in Madurai, India, the authors found that increased risk of COVID-19 infection (3.6%) and death among positive cases (2.4%) were associated with older age, male sex, and comorbidities, such as cancer, DM, other endocrine disorders, hypertension, other chronic circulatory disorders, respiratory disorders, and chronic kidney disease (37).

In addition, largely consistent results from our main and sensitivity ROR analyses indicated minor or maybe ignorable reporting bias during the study period of 14 December 2020 and 8 October 2021. Over 90% of AE reports in VAERS during this time period were related to COVID-19 vaccines, and our analysis included more than 600,000 AE events across the country. Many studies have shown that routine immunization services faced severe challenges and the number of immunizations fell in the year 2020, especially for children (38–40), which may explain the small proportion of AE events related to non-COVID vaccination in VAERS during our study period. Assessing a longer time span of VAERS reports might reduce potential reporting bias (41). However, the COVID-19 vaccines have undergone the most intensive safety monitoring in United States history (21, 23). Compared to all previous vaccines, the prioritization of vaccines was unique (42–44), and healthcare providers are required to report serious AEs to VAERS after COVID-19 vaccination under EUA (45). These factors may have led to increased reporting of COVID-19 vaccines and the completeness of AE reports in VAERS. Nevertheless, the large amount of AE reports for COVID-19 vaccines in VAERS provides a great opportunity for practitioners, policymakers, and researchers to timely monitor the safety of COVID-19 vaccines.

Our findings provided up-to-date AE reporting evidence for the three currently marketed COVID-19 vaccines. Results from the Breslow-Day statistics demonstrated differences in ROR of four serious AE outcomes (i.e., ER visits, hospitalization, life-threatening events, and disability) between individual COVID-19 vaccines. Specifically, different from the Pfizer-BioNTech and Janssen COVID-19 vaccines, the Moderna COVID-19 vaccine showed no increased reporting risks for these AEs compared to all other vaccines. Although the nature of the spontaneous reporting VAERS data can only support AE signal detection instead of demonstrating the causal association between vaccine administration and reported AE outcomes (24, 32), US CDC and FDA have updated some new guidelines based on the growing number of COVID-19 vaccine administrated and AE reports. For example, according to the CDC's Morbidity and Mortality Weekly Report (MMWR), reports of syncope were approximately 164 times more common after the Janssen COVID-19 vaccination (8.2 per 100,000) than after influenza vaccination (0.05 per 100,000) (46). On 23 April 2021,

CDC and FDA ended the pause on the use of the Janssen COVID-19 vaccine but suggested that women younger than 50 years should be aware of the rare risk of blood clots with low platelets (47). On 16 December 2021, the CDC's ACIP held an emergency meeting to review the updated data on thrombosis with thrombocytopenia syndrome and an updated benefit-risk assessment. The ACIP made a recommendation for preferential use of mRNA COVID-19 vaccines (e.g., Pfizer-BioNTech and Moderna) over the Janssen COVID-19 vaccine, including both primary and booster doses administered to prevent COVID-19, for all persons aged ≥18 years (27). In addition, FDA approved the Pfizer-BioNTech COVID-19 vaccine for the prevention of COVID-19 disease in individuals aged 16 and above on 23 August 2021, (48) and further authorized it for children aged 5–11 years under a EUA on 29 October 2021 (1). Therefore, in time, continuous surveillance in existing, new, and serious safety problems of COVID-19 vaccines is critical.

It is critical to monitor the safety of authorized COVID-19 vaccines through both passive and active safety surveillance systems, which can detect and refine safety findings in a relatively rapid manner. Active surveillance systems provide the most accurate and timely information. For example, Australia's AusVaxSafety system has been used to evaluate the safety profile of live-attenuated herpes zoster vaccine among older (70–79 years of age) Australian adults in the first two program years at 246 sentinel surveillance immunization sites, and the authors found that the rates of medical attendance were low (0.3%) with no safety signals identified (49). Our results highlight the importance of constant vigilance in order to quickly evaluate the safety of COVID-19 vaccines, given that we found higher ROR in ER visits and hospitalization for COVID-19 vaccines compared to other vaccines that have been routinely used for years. A pharmacovigilance analysis using the World Health Organization (WHO) international database (VigiBase) compared AE reporting with mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) and influenza vaccines from 1 January 2020 to 17 January 2021 (50). The VigiBase study did not identify significant safety concerns regarding mRNA vaccination in real-world settings. The authors reported an overall lower risk of serious AEs following mRNA vaccines compared to influenza vaccines, and 103 (0.5%) deaths out of 18,755 COVID-19 vaccine-related AEs [compared to 104 (0.4%) deaths out of 27,895 influenza vaccine-related AEs] (50). Another study analyzed data from two passive surveillance systems, VAERS and European EudraVigilance, to compare the reporting rates of anaphylaxis, a severe, potentially life-threatening allergic reaction, between COVID-19 vaccines and other vaccines (51). The authors found that COVID-19 vaccines ranked fifth in reported anaphylaxis rates, behind rabies, tick-borne encephalitis, measles-mumps-rubella-varicella, and human papillomavirus vaccines (70.77, 20, 19.8, and 13.65 cases per 1,000,000 vaccine doses, respectively). Our analysis using VAERS included a larger number (more than 600,000) of AE reports related to COVID-19 vaccines compared to the VigiBase analysis. Our findings provide critical evidence to bring potential safety signals to the attention of public health professionals and policymakers.

Similar to most research using VAERS, our study also has some unavoidable limitations. First, VAERS is a passive spontaneous reporting system with substantial incomplete, inaccurate, and missing information, which could lead to under- or over-reporting, reporting biases, inconsistency in the quality of reports, and lack of denominator data and unbiased comparison groups (24, 30–33). For example, some mass vaccination sites reported more information than others (46). Second, the AE reporting date might not be the actual vaccination date and the duration of vaccination exposure varied in each AE report. In addition, we could not calculate the time between death and vaccination date due to a considerable amount of missing data on the date of vaccination or date of death in VAERS. Finally, the nature of VAERS data does not infer causality. VAERS accepts all reports without judging whether the event was caused by the vaccine (24, 30, 32, 33, 52). Our findings only identified signals or potential risks of AEs for signal generation and surveillance purposes. Future research using active surveillance systems including longitudinal, large healthcare data systems to verify safety signals identified through passive surveillance is warranted.

In conclusion, our findings provided up-to-date AE reporting evidence for the three United States marketed COVID-19 vaccines during the first 10 months of utilization. The most commonly reported AEs of COVID-19 vaccines were mild. Cases with a mortality outcome mainly occurred among older adults with underneath chronic conditions. We found differences in reporting of serious AE outcomes between individual COVID-19 vaccines. The preliminary evidence generated from this study needs to be verified through active surveillance systems in order to inform the selection of individual COVID-19 vaccines and guide current and upcoming COVID-19 vaccination in the United States and around the world.

DATA AVAILABILITY STATEMENT

Publicly available VAERS datasets were analyzed in this study. The data can be found here: https://vaers.hhs.gov/data/datasets.html?

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Auburn University Institutional Review Boards. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CZ: conceptualization, methodology, software, validation, formal analysis, data curation, writing (original draft), and visualization. XX: conceptualization, methodology, software, validation, formal analysis, data curation, writing (review and editing), and visualization. JQ: conceptualization, methodology, data curation, writing (original draft), and supervision. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to acknowledge Mr. Bang Cong Truong, Auburn University, for his feedback on analytical approaches.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.826327/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Public Health

SYSTEMATIC REVIEW
published: 14 April 2022
doi: 10.3389/fpubh.2022.829176

Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Adolescents, Children, and Infants: A Systematic Review and Meta-Analysis

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Background: As the epidemic progresses, universal vaccination against COVID-19 has been the trend, but there are still some doubts about the efficacy and safety of COVID-19 vaccines in adolescents, children, and even infants.

Purpose: To evaluate the safety, immunogenicity, and efficacy of COVID-19 vaccines in the population aged 0–17 years.

Method: A comprehensive search for relevant randomized controlled trials (RCTs) was conducted in PubMed, Embase, and the Cochrane Library from inception to November 9, 2021. All data were pooled by RevMan 5.3 statistical software, with risk ratio (RR) and its 95% confidence interval as the effect measure. This study protocol was registered on PROSPERO (CRD42021290205).

Results: There was a total of six randomized controlled trials included in this systematic review and meta-analysis, enrolling participants in the age range of 3–17 years, and containing three types of COVID-19 vaccines. Compared with mRNA vaccines and adenovirus vector vaccines, inactivated vaccines have a more satisfactory safety profile, both after initial (RR 1.40, 95% CI 1.04–1.90, $P = 0.03$) and booster (RR 1.84, 95% CI 1.20–2.81, $P = 0.005$) vaccination. The risk of adverse reactions was significantly increased after the first and second doses, but there was no significant difference between the first two doses (RR 1.00, 95%CI 0.99–1.02, $P = 0.60$). Nevertheless, the two-dose regimen is obviously superior to the single-dose schedule for immunogenicity and efficacy. After booster vaccination, both neutralizing antibodies (RR 144.80, 95%CI 44.97–466.24, $P < 0.00001$) and RBD-binding antibodies (RR 101.50, 95%CI 6.44–1,600.76, $P = 0.001$) reach optimal levels, but the cellular immune response seemed not to be further enhanced. In addition, compared with younger children, older children and adolescents were at significantly increased risk of adverse reactions after vaccination, with either mRNA or inactivated vaccines, accompanied by a stronger immune response.

OPEN ACCESS

Edited by:
Janja Marc,
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Reviewed by:
Dana Dolanová,
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Specialty section:
This article was submitted to Infectious Diseases – Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: *05 December 2021*
Accepted: *24 March 2022*
Published: *14 April 2022*

Citation:
Du Y, Chen L and Shi Y (2022) Safety, Immunogenicity, and Efficacy of COVID-19 Vaccines in Adolescents, Children, and Infants: A Systematic Review and Meta-Analysis. Front. Public Health 10:829176. doi: 10.3389/fpubh.2022.829176

Conclusion: The available evidence suggests that the safety, immunogenicity and efficacy of COVID-19 vaccines are acceptable in people aged 3–17 years. However, there is an urgent need for additional multicenter, large-sample studies, especially in younger children under 3 years of age and even in infants, with long-term follow-up data.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021290205, identifier: CRD42021290205.

Keywords: COVID-19 vaccine, adolescents, child, infant, randomized controlled trial, meta-analysis

INTRODUCTION

It is the epidemic of coronavirus disease 2019 (COVID-19) that has placed a heavy burden on people worldwide, both physically and mentally (1, 2). In order to control the epidemic, various types of COVID-19 vaccines have sprung up around the world, but the vast majority have only been approved for adults (3). However, with the prevalence of the Omicron variant, a highly divergent variant of syndrome coronavirus 2 (SARS-CoV-2), immune protection for adolescents, children and even infants seems to be imminent. Following the approval of CoronaVac for children aged 3–17 years, the BNT162b2-mRNA vaccine was urgently approved for children aged 5 years and older on November 2, 2021 (4). The sequential authorization of two different vaccines announces that the focus of vaccination is gradually shifting to younger children, as the fight against the epidemic progresses, which not only helps protect children's health and interrupt community epidemics but also promotes educational equity and economic recovery (5).

Compared with adults, teenagers and children infected with SARS-CoV-2 generally present with milder symptoms (6, 7). Therefore, the benefits of COVID-19 vaccines may not be as pronounced in this group as in adults (8). However, the possibility of critical illnesses, such as multisystemic inflammatory syndrome in children (MIS-C) (9), cannot be ruled out in this population, especially in those with underlying disease (10). Moreover, if left unchecked, this population has the potential to become a transit reservoir for SARS-CoV-2, leading to widespread community epidemics (11–13). Furthermore, vaccination helps promote regular back-to-school education (14), which not only prevents online instructions from becoming a barrier to education for poor students, but also removes the worry of working parents (5). In addition, maintaining good social activities also contributes to good psychological growth and sound character building in young children (15).

Advancing the childhood vaccination process should begin by eliminating parent's vaccination hesitancy. However, it is parental doubts about the safety, efficacy, and necessity of vaccinations that are holding back the process (16–19). After all, although a large number of vaccines have been shown to be safe and effective in adults, including the elderly (20–27), there is still a gap in research data for people under the age of 18. Considering the limited available clinical evidence and the urgency of advancing the vaccination process, we plan to conduct a meta-analysis based on existing randomized controlled trials (RCTs), to comprehensively evaluate the safety, immunogenicity, and efficacy of various COVID-19 vaccines in adolescents, children, and even infants.

METHODS

The systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (28), with a study protocol registered in the International Prospective Register of Systematic Evaluations database (CRD42021290205).

Search Strategy

We conducted a comprehensive search in Pubmed, Embase, and Cochrane Library databases from inception to November 9, 2021, using "COVID-19 Vaccines," "SARS-CoV-2," "COVID-19," "Adolescent," "Child," "Infant" and "Randomized controlled trial" as medical subject headings (MeSH) terms. The search details can be found in the **Supplementary Material**. The search in the clinical trials registers (Clinical Trials.gov, an ongoing NIH trial registry) was also performed to find potentially available studies. The electronic database search was additionally supplemented by a manual search of the reference lists of relevant systematic reviews and key articles.

Study Selection

Only randomized controlled trials were eligible, with no restrictions on language or publication status; cohort studies, case-control studies, single-arm studies, cross-sectional studies, case reports, reviews, comments, and letters were all excluded. These RCTs were conducted in healthy humans aged 0–17 years, with various types of COVID-19 vaccines as interventions, and placebo, adjuvant, or other vaccines as controls. The following statistical information should be provided as outcome indicators: (1) the incidence of adverse events after vaccination, including total adverse reactions, local adverse reactions, systemic adverse reactions, and any specific adverse reactions, (2) humoral immune responses, including the seroconversion after vaccination, (3) cellular immune responses, such as IFN-γ enzyme-linked immunospot, (4) incidence of confirmed COVID-19 post-vaccination. After removing duplicate records, two review authors (YD and LC) independently assessed the titles and abstracts of all records, and then conducted a full-text

review with predetermined criteria. Disagreements were resolved by consulting a third author (YS).

Data Extraction

Specific bibliographic software EndNote X9 was used to manage the literature. Using a pre-developed data extraction form in Microsoft Excel, two authors independently extracted the following data: name of the first author, date of publication, study protocol, baseline characteristics of participants, sample size, intervention details, and outcome indicators. The seroconversion was defined as at least a fourfold increase in geometric mean titres (GMT) from baseline after vaccination. A secondary case definition of COVID-19 was also adopted, according to which patients were diagnosed with COVID-19 as long as they were positive for SARS-CoV-2 by RT-PCR and accompanied by one or more associated symptoms. In order to avoid missing data as much as possible, we carefully read the original text and supplementary materials of the included studies. If the original article grouped vaccinees according to age, dose of vaccination, etc., we would combine the data for each subgroup. If the original article did not provide the data in the form we expected, the required data would be calculated manually based on the information provided. When the required dichotomous variables were provided in the form of totals and percentages, we would obtain the available data by calculating the product. When the original text did not provide the information we needed, we attempted to obtain the corresponding information from the supplementary material. Considering the limited time, we did not contact the corresponding author to obtain the original data. In case of any disagreement, consensus would be reached through discussion or consultation with a third authors (YS).

Risk of Bias Assessment and Evidence Quality Assessment

To evaluate the methodological quality of the studies, two reviewer (YD and LC) independently assessed the risk of each study according to the Cochrane collaboration tool for assessing the risk of bias (Rob) (29). In order to appraise the quality and certainty of the evidence, these two authors (YD and LC) also assessed the reliability of the primary results by Gradepro 3.6 software, according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) standard. Any differences in the assessment process would be resolved by consulting the third reviewer (YS). Considering that the currently available literature may be limited, we would pool all studies regardless of quality.

Data Synthesis and Analysis

We used RevMan 5.3 statistical software to pool dichotomous outcomes, with the risk ratio (RR) and its 95% confidence interval (CI) as the effect measures. RR $>$ 1 implies a higher risk in the observation group, and $P < 0.05$ indicates that this difference is statistically significant. The I^2 statistic was used to estimate the level of heterogeneity, and significant heterogeneity was considered when the I^2 value was $>$50% (30). Following the recommendations of the Cochrane Handbook (29) and taking into account the different characteristics of the included studies (31), all data would be pooled by using random-effects models, regardless of the heterogeneity. However, if there were $<$5 studies available, the random-effects model would no longer be applicable. In this case, the fixed-effects model would be chosen to pool the data. To trace the source of heterogeneity, we performed sensitivity analyses by excluding pooled studies one by one. Furthermore, subgroup analyses were conducted according to the number of vaccinations, type of vaccines, age of the recipients, and specific adverse reactions. When appropriate, direct comparisons were also conducted between prime and boost vaccinations, as well as among different ages. In addition, if ten or more RCT studies were eventually included, the funnel plot analysis of the primary outcome was planned to assess publication bias (32).

RESULTS

Characteristics of the Included Studies

In this meta-analysis, a total of 1,166 citations were retrieved, and after removing duplicates, we screened 805 records based on title and abstract, of which 766 were determined to be irrelevan. The remaining 40 articles were evaluated in full text and 34 of them were excluded for various reasons. Finally, a total of 6 studies were included (33–38), of which 1 trial was identified by manual search. No relevant trials providing available outcome indicators were found on ClinicalTrials.gov. The flow chart for identifying and selecting the studies was presented in **Figure 1**. These six RCTs included three types of COVID-19 vaccines, with mRNA vaccines being the most studied (60%) (33–35), followed by inactivated vaccines (40%) (35, 36) and adenoviral vector vaccines (20%) (38), all with saline or aluminum hydroxide adjuvants as controls. A total of 9,962 participants were enrolled, ranging in age from 3 to 17 years old. All participants received a two-dose injection, except for the vaccinees in one RCT (37), who received a three-dose regimen. In the two RCTs studying inactivated vaccines (36, 37), investigators grouped subjects according to age and the dose of vaccine administered. The characteristics of the included studies were summarized in **Table 1**. Overall, the risk of bias in these studies was low, with the main risk factors being incomplete outcome data and other biases, as shown in detail in **Figures 2**, **3**.

Safety of COVID-19 Vaccines

A total of six RCTs (33–38) evaluated possible adverse reactions after the first and second doses. Only four RCTs (33, 36–38) provided data on total adverse reactions, while all six RCTs reported the occurrence of specific adverse reactions after vaccination. Walter et al. did not provide the exact number of participants in the placebo group in the safety analysis. By reading the original article (35), we only know that there were 748 or 749 children in the placebo group after the first dose, and 740 or 741 children in the placebo group after the second dose. Nevertheless, after data analysis, it was found that the effect of small changes in

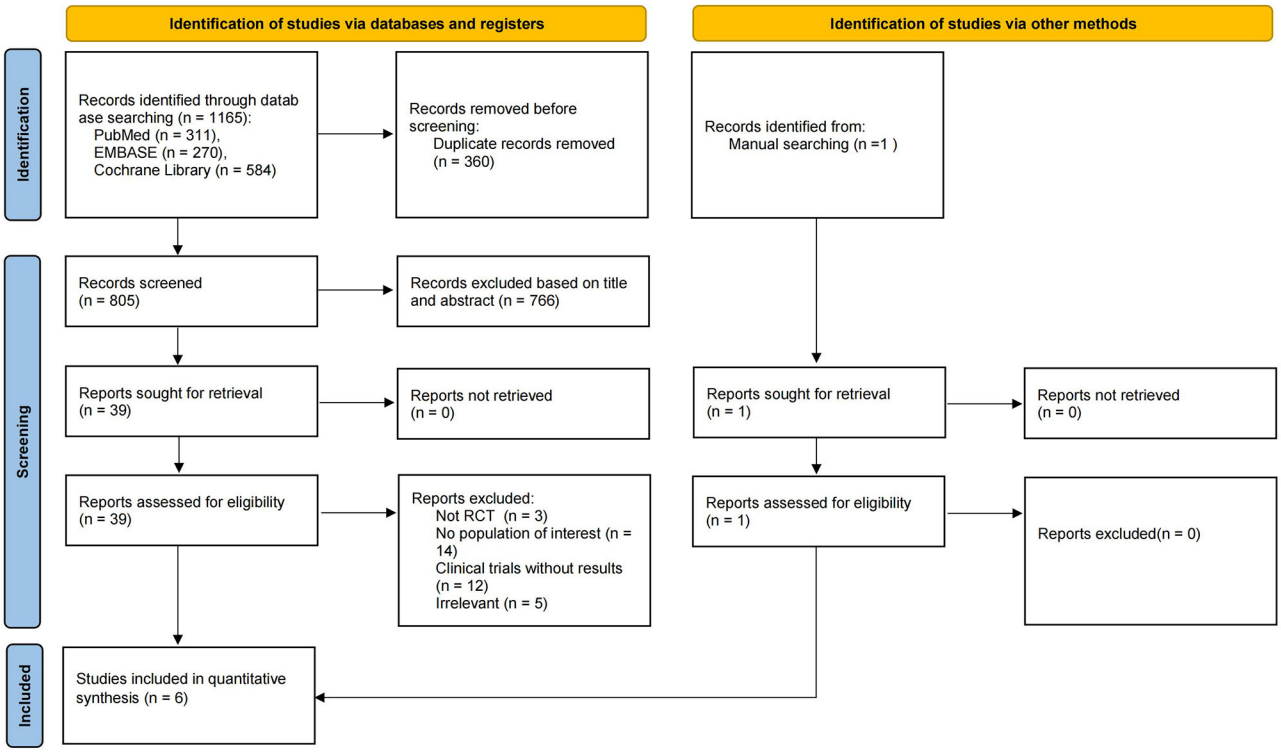

FIGURE 1 | Flow chart of study identification and selection.

this data on the results was largely negligible. Therefore, we still included this RCT.

The data showed that the risk of unsolicited (RR 1.21, 95%CI 1.07–1.36, $P = 0.002$; **Supplementary Figure 1**, **Table 2**) adverse reactions was significantly higher in the vaccine group than in the control group, within 28 or 30 days after the whole vaccination procedure. However, for severe (RR 2.35, 95%CI 0.78–7.03, $P = 0.13$), and even life-threatening (RR 1.00, 95%CI 0.06–15.94, $P = 1.00$) unsolicited adverse reactions, there was no significant difference between the two groups. No case reports of death, multisystem inflammatory syndrome in children (MIS-C), myocarditis, or pericarditis disease were found in any individual RCT.

Adverse Reactions to Different Inoculation Doses

Subgroup analyses of adverse reactions after different number of inoculations were performed. The data showed that the risk of adverse events was statistically higher in the vaccine group than in the control group after the first (RR 1.49, 95%CI 1.43–1.55, $P < 0.00001$; **Supplementary Figure 2**, **Table 3**) and second doses (RR 1.76, 95%CI 1.67–1.85, $P < 0.00001$; **Supplementary Figure 2**, **Table 3**), but no significant differences were found between the first and second dose groups (RR 1.00, 95%CI 0.99–1.02, $P = 0.60$; **Supplementary Figure 3**, **Table 4**). Only one RCT (37) assessed possible local (RR 1.86, 95%CI 0.55–6.30, $P = 0.32$; **Supplementary Figure 2**, **Table 3**) and systemic (RR 2.30, 95%CI 0.69–7.64, $P = 0.17$; **Supplementary Figure 2**, **Table 3**) adverse reactions after the third dose, and showed no significant difference between the two groups.

Adverse Reactions to Different COVID-19 Vaccines

Considering the relatively high statistical heterogeneity in the above analysis (I^2 from 8 to 70%), we further performed subgroup analyses according to different vaccine types. The data showed a significantly increased risk of total, local, and systemic adverse reactions after vaccination both in the mRNA vaccine group and in the adenovirus vector vaccine group, however, in the inactivated vaccine group, only the risk of local reactions after initial vaccination was significantly higher than in the control group (RR 6.34, 95%CI 1.54–26.10, $P = 0.01$; **Supplementary Figure 4**, **Table 5**).

Detailed analyses were conducted for specific adverse events after vaccination. In the mRNA vaccine group, the risk of adverse reactions such as pain, swelling, and fever were significantly higher, both after initial vaccination and booster vaccination (**Supplementary Figure 5**, **Supplementary Table 1**). In the inactivated vaccine group, only the risk of local pain was significantly higher, and the risk of all other known adverse reactions was not significantly different compared with the control group (**Supplementary Figure 6**, **Supplementary Table 1**). For the adenovirus vector vaccine, there was no significant difference in the risk of adverse reactions compared with placebo, except for a significantly

TABLE 1 | The characteristics of the included studies.

References	Clinical trials registration	Phase	Age range	Type of vaccine	Dose of administration	Number of scheduled doses (time of inoculations)	Control	Number of observation group	Number of control group
Ali et al. (33)	NCT04649151	Phase 2/3	12–17	mRNA-1273 vaccine (mRNA vaccine)	100 μg/dose	Prime and boost inoculation (0, 28 days)	Saline	2,486	1,240
Frenck et al. (34)	NCT04368728	Phase 3	12–15	BNT162b2 Covid-19 Vaccine (mRNA vaccine)	30 μg/dose	Prime and boost inoculation (0, 21 days)	Saline	1,131	1,129
Walter et al. (35)	NCT04816643	Phase 2/3	5–11	BNT162b2 Covid-19 Vaccine (mRNA vaccine)	10 μg/dose	Prime and boost inoculation (0, 21 days)	Saline	1,518	750
Han et al. (36)	NCT04551547	Phase 1/2	3–17 (3–5; 6–11; 12–17)	CoronaVac (Inactivated vaccine)	1.5 or 3 μg/dose	Prime and boost inoculation (0, 28 days)	Alum	436	114
Xia et al., (37)	ChiCTR2000032459	Phase 1/2	3–17 (3–5; 6–12; 13–17)	BBIBP-COV (Inactivated vaccine)	2 ug, 4 ug or 8 μg/dose	Three doses (0, 28, and 56 days)	Saline and aluminum hydroxide adjuvant	756	252
Zhu et al. (38)	NCT04566770	Phase 2	6–17	Ad5-vectored COVID-19 vaccine (Adenovirus vaccine)	0.3 ml/dose	Prime and boost inoculation (0, 56 days)	Placebo containing the same excipients as the vaccine, without viral particles	100	50

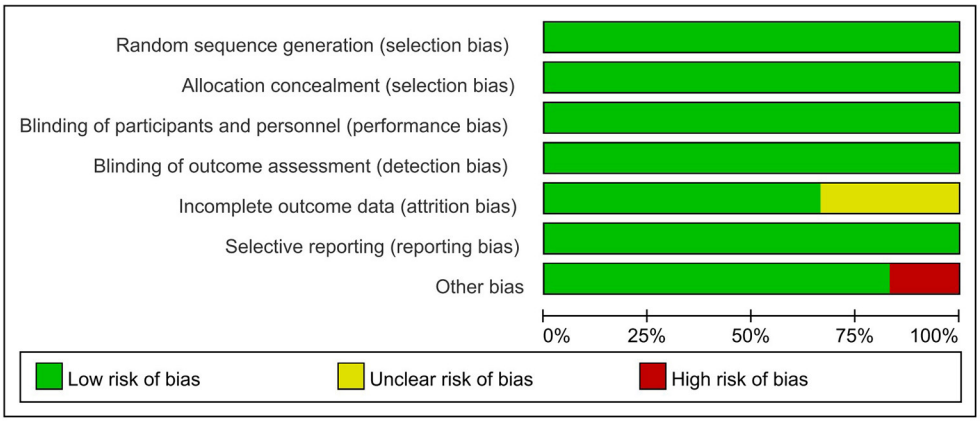

FIGURE 2 | Risk of bias graph for included RCTs.

higher risk of local pain (RR 5.67, 95%CI 1.83–17.55, $P = 0.003$; **Supplementary Figure 7**, **Supplementary Table 1**) and fever after (RR 7.00, 95%CI 1.74–28.21, $P = 0.006$; **Supplementary Figure 7**, **Supplementary Table 1**) the first dose. After pooling all available data on specific reactions, the risk was significantly higher in all vaccine groups than in the control group, but relatively lower in the inactivated vaccine group, both after initial vaccination (RR 1.40, 95% CI 1.04–1.90, $p = 0.03$) and after booster vaccination (RR 1.84, 95% CI 1.20–2.81, $p = 0.005$) (**Supplementary Table 1**).

Adverse Reactions in Different Age Groups

When subgroup analysis was performed according to different vaccine types, the data showed that heterogeneity remained generally high in the mRNA vaccine group, but lower heterogeneity could be found in most subgroups after removing the RCT study by Walter et al. (35). Considering that the RCT by Walter et al. targeted younger children aged 5–11 years, whereas the other two RCTs studying mRNA vaccines (33, 34) were conducted in children and adolescents aged 12 years and older, we decided to perform further subgroup analyses for specific adverse reactions depending on the different ages of mRNA vaccine recipients (**Supplementary Figure 8**, **Supplementary Table 2**). For older children aged 12–17 years, the risk of all adverse reactions after vaccination was significantly higher, except for systemic reactions such as vomiting and diarrhea. As for younger children aged 5–11 years, the risk of headache (RR 0.45, 95%CI 0.26–0.80, $P = 0.007$) and fatigue (RR 0.54, 95%CI 0.34–0.88, $P = 0.01$) after the first dose as well as the risk of diarrhea (RR 0.10, 95%CI 0.03–0.36, $P = 0.0003$) after booster vaccination were even significantly lower; but for other adverse reactions, there was no statistical difference between the two groups.

Overall, the risk of various adverse reactions after mRNA vaccination appears to be higher in older children aged 12–17 years than in younger children aged 5–11 years. Considering that both Frenck et al. (34) and Walter et al. (35) chose the mRNA-1273 vaccine as the intervention, we decided to directly compare the occurrence of various adverse reactions following mRNA-1273 vaccination in older and younger children (**Supplementary Figure 9**, **Table 6**). The data showed a significantly higher risk of various adverse reactions in participants aged 12–15 years, both after the initial (RR 1.40, 95%CI 1.21–1.62, $P < 0.00001$) and the booster (RR 2.04, 95%CI 1.75–2.38, $P < 0.00001$) vaccination, suggesting that the mRNA-1273 vaccine may have a greater safety profile in young children aged 5–11 years.

Two RCTs on inactivated vaccines (CoronaVac (36), BBIBP-COV (37)) both reported total adverse reactions in children of different ages within 28 days after the whole vaccination procedure, so subgroup analysis was performed according to the age of the participants (**Supplementary Figure 10**, **Table 7**). The data showed that the risk of adverse reactions was higher in all inactivated vaccine subgroups than in all control groups, especially in the 6-11/12 age group (RR 2.41, 95%CI 1.37–4.23, $P = 0.002$); however, the difference was not statistically significant in the 3–5 age group (RR 1.15, 95%CI 0.81–1.64, $P = 0.43$). Notably, participants in one RCT study (36) received a total of 2 doses of vaccine, whereas participants in the other RCT study (37) received a total of 3 doses of vaccine. However, it was not possible to specifically analyze the safety of inactivated vaccines after a single dose, because Han et al. (36) did not provide information on adverse reactions within 28 days after a single dose. In addition, there were minor differences in the grouping methods of the two RCTs, with one (36) grouping vaccinees into age groups of 3–5, 6–11, and 12–17 years, while the other (37) grouping participants into age groups of 3–5, 6–12, and 13–17 years. Overall, the risk of adverse reactions following inactivated vaccination was more noteworthy in older children than in younger children, which is generally consistent with the results of subgroup analyses of mRNA vaccines.

Since only one RCT (38) chose the adenovirus vector vaccine as an intervention, and no data were available for different age

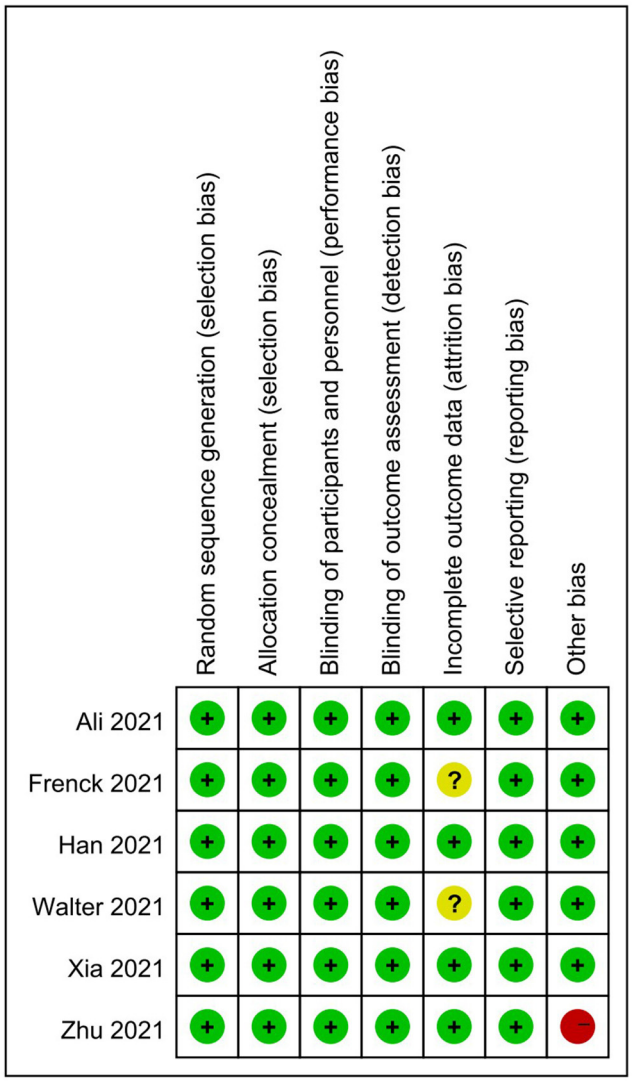

FIGURE 3 | Risk of bias summary for included RCTs.

groups, further subgroup analysis could not be performed for the adenovirus vector vaccine.

Adverse Reactions in Different Doses of Vaccines

Two RCTs (36, 37) provided information on recipients aged 3–17 years after receiving different doses of inactivated vaccine, but subgroup analyses failed to be performed on this basis because the vaccine doses differed in the two RCTs. However, data from both RCTs suggested acceptable safety and tolerability profiles for various doses of inactivated vaccines.

Immunogenicity

Humoral Immune Responses

Three RCTs (36–38) provided data on seroconversion, and the data showed that the seroconversion after inoculation was significant, especially after the second dose (RR 144.80, 95%CI 44.97–466.24, $P < 0.00001$; **Supplementary Figure 11**, **Table 8**). Notably, although participants reported by Xia et al. (37) received a total of three doses of adenoviral vector vaccine, their serological response rate had reached 100% at day 56 (28 days after the second dose).

In addition, given that Han et al. (36) and Xia et al. (37) both provided seroconversions for each age group at 28 days post-vaccination, a subgroup analysis was performed accordingly. The data showed a significant humoral immune response to SARS-CoV-2 after inactivated vaccination in all age groups, but the response appears to be relatively low in children aged 3–5 years (RR 110.57, 95%CI 15.87–770.57, $P < 0.00001$; **Supplementary Figure 11**, **Table 8**). Moreover, Han et al. (36) and Xia et al. (37) also provided data for different doses, which may suggest dose-dependent immunogenicity. Han et al. (36) indicated that the neutralizing antibody titer induced by the 3.0 μg dose group was obviously higher than that of the 1.5 μg dose group after boost vaccination ($P < 0.05$). Similarly, it was reported by Xia et al. (37) that the 4 and 8 μg dose groups elicited significantly higher antibody responses compared with the 2 μg dose group ($P < 0.05$).

Three other RCTs (33–35) with mRNA vaccine as the intervention compared immune responses 1 month after booster vaccination in vaccinees and young adults (16 or 18 years of age and older), and assessed non-inferiority by calculating the geometric mean ratio (GMR) with its 95% confidence interval. Ali et al. (33) reported the GMT of 1401.7 (95% CI: 1276.3, 1539.4) in adolescents aged 12–17 years, with a neutralizing antibody GMR of 1.08 (95% CI: 0.94 to 1.24) relative to young adults aged 18 to 25 years, meeting the non-inferiority criterion (i.e., lower limit of the two-sided 95% confidence interval $>$ 0.67). As reported by Frenck et al. (34) and Walter et al. (35), the GMRs of neutralizing antibodies in adolescents aged 12 to 15 years and children aged 5–11 years to young adults aged 16 to 25 years were respectively 1.76 (95% CI: 1.47–2.10), and 1.04 (95% CI: 0.93–1.18), which met the criteria of non-inferiority as well. In particular, the immune response to BNT162b2 Covid-19 vaccine might be greater in adolescents aged 12 to 15 years than in young adults aged 16 to 25 years, because the lower limit of the two-sided 95% confidence interval for the GMR is >1.

There were also two RCT studies (33, 38) evaluating the receptor binding domain (RBD)-binding ELISA antibody. The results of Ali et al. (33) showed a GMR of 1.09 (95% CI: 0.94–1.26) for RBD-binding ELISA antibodies in adolescents aged 12–17 years relative to young adults aged 16–25 years, while in the trial of Zhu et al. (38), the seroconversion rate of RBD-binding antibodies in the vaccine group reached 98%(RR 99.48, 95%CI 6.31–1,569.12, $P = 0.001$) and 100%(RR 101.50, 95%CI 6.44–1,600.76, $P = 0.001$) at day 28 after initial and booster vaccination, respectively (**Supplementary Figure 11**, **Table 8**).

Cellular Immune Responses

There was only one RCT (38) evaluating the potential of vaccines to induce specific cellular responses. It was reported that significant specific T-cell responses, particularly Th 1 cell responses, were induced after initial adenoviral vector

TABLE 2 | Overall adverse reactions and unsolicited adverse reactions within 28 or 30 days after whole vaccination procedure in inactivated vaccine group vs. control group.

	No. of studies	RR (95% CI)	I2	*P*-value
Overall adverse reactions within 28 or 30 days after whole vaccination procedure	2	1.59 [1.26, 2.01]	77	<0.05*
Unsolicited adverse reactions within 28 or 30 days after whole vaccination procedure				
Overall	4	1.21 [1.07, 1.36]	14	<0.05*
Related to study vaccination	3	1.96 [1.59, 2.41]	20	<0.05*
Severe	3	2.35 [0.78, 7.03]	0	>0.05
Life-threatening	3	1.00 [0.06, 15.94]	Not applicable	>0.05
Serious	3	1.63 [0.45, 5.88]	0	>0.05
Medically-attended	1	0.96 [0.74, 1.25]	Not applicable	>0.05
Leading to discontinuation	3	2.99 [0.36, 24.93]	0	>0.05

*$P < 0.05$.

TABLE 3 | Total adverse reactions in vaccination group vs. control group.

		No. of studies	RR (95% CI)	I2	*P*-value
After dose 1	Total adverse reactions	3	1.49 [1.43, 1.55]	70	<0.05*
	Local adverse reactions	3	2.60 [2.42, 2.80]	47	<0.05*
	Systemic adverse reactions	3	1.26 [1.19, 1.33]	68	<0.05*
After dose 2	Total adverse reactions	3	1.76 [1.67, 1.85]	60	<0.05*
	Local adverse reactions	3	2.89 [2.67, 3.14]	8	<0.05*
	Systemic adverse reactions	3	1.88 [1.77, 2.01]	29	<0.05*
After dose 3	Total adverse reactions	0	/	/	/
	Local adverse reactions	1	1.86 [0.55, 6.30]	Not applicable	>0.05
	Systemic adverse reactions	1	2.30 [0.69, 7.64]	Not applicable	>0.05

*$P < 0.05$.

vaccination, but the intensity of immunity appeared to diminish after booster vaccination.

Efficacy

Three RCTs (33–35) with mRNA vaccine as an intervention assessed vaccine efficacy, which was at 100.0% (95% CI: 28.9%-NE%), 100% (95% CI: 75.3%–100%), and 90.7% (95% CI: 67.4%–98.3%), respectively. Both types of mRNA vaccines provided satisfactory prevention against COVID-19, especially the BNT162b2 Covid-19 vaccine for adolescents aged 12 years and older (RR 0.03, 95%CI 0.00–0.44; **Supplementary Figure 12**, **Table 9**) (34). Other RCT studies (36–38) with inactivated vaccine or adenovirus vector vaccine as interventions did not evaluate the vaccine efficacy.

Sensitivity Analysis and Publication Bias

Through detailed subgroup analysis, we have tried to minimize the effect of heterogeneity on our results. However, when performing sensitivity analyses, we still found that the heterogeneity of pooled effects for certain outcomes may change substantially after removing individual RCT. Although the changes barely affect our conclusions, it still suggests that the results are not robust enough and need to be viewed with caution. As suggested by the Cochrane Handbook (29), it is well known that assessing publication bias with funnel plots is not reliable when fewer than 10 studies were included (32). It was only a total of 6 RCTs that were included in this meta-analysis, and there were essentially only 3 or fewer papers available for specific outcome indicators. Therefore, given the limited number of available literature, we did not assess the publication bias.

Grading of Evidence Quality

As shown in the **Supplementary Tables 3–6**, we assessed the quality of the primary outcomes. Overall, the quality of evidence for most outcomes was moderate and high, with inconsistency as the main downgrading factor.

DISCUSSION

The risk of various adverse reactions, mainly including local pain, swelling and fever, was increased to varying degrees after different types of vaccination, but they were generally mild and not fatal. There was insufficient evidence to attribute the reported severe adverse events exclusively to vaccination. It was inactivated vaccines that had a higher safety profile compared with mRNA vaccines and adenoviral vector vaccines, and data

TABLE 4 | Total and specific reactions in vaccination group after dose 1 vs. after dose 2.

	No. of studies	RR (95% CI)	I2	*P*-value
Overall				
Total adverse reactions	3	1.00 [0.99, 1.02]	90	>0.05
Local adverse reactions	3	1.02 [1.00, 1.04]	82	<0.05*
Systemic adverse reactions	3	0.83 [0.81, 0.86]	96	<0.05*
Overall	6	0.73 [0.71, 0.74]	97	>0.05
Local pain	6	1.02 [1.00, 1.04]	73	$P = 0.05$
Erythema/ Redness	5	0.70 [0.62, 0.79]	0	<0.05*
Induration	1	2.00 [0.18, 21.71]	Not applicable	>0.05
Pruritus/ Itch	3	1.15 [0.39, 3.41]	0	>0.05
Swelling	6	0.79 [0.70, 0.89]	0	<0.05*
Axillary Swelling	1	1.11 [1.00, 1.23]	Not applicable	$P = 0.05$
Fever	6	0.44 [0.37, 0.53]	95	<0.05*
Cough	3	1.76 [0.99, 3.12]	0	$P = 0.05$
Oropharyngeal pain	1	3.00 [0.32, 28.35]	Not applicable	>0.05
Headache	6	0.65 [0.62, 0.69]	65	<0.05*
Fatigue	6	0.72 [0.69, 0.76]	39	<0.05*
Myalgia	6	0.59 [0.55, 0.64]	39	<0.05*
Arthralgia	4	0.52 [0.47, 0.58]	0	<0.05*
Nausea/ vomiting	1	0.47 [0.42, 0.54]	Not applicable	<0.05*
Nausea	3	1.24 [0.49, 3.11]	0	>0.05
Vomiting	5	1.26 [0.58, 2.78]	0	>0.05
Diarrhea	4	1.45 [0.72, 2.94]	0	>0.05
Anorexia	2	1.81 [0.68, 4.83]	32	>0.05
Chills	3	0.44 [0.40, 0.48]	41	<0.05*
Pruritus (systemic adverse reaction)	1	3.00 [0.12, 72.77]	Not applicable	>0.05
Acute allergic reaction/ Hypersensitivity	1	0.33 [0.01, 8.13]	Not applicable	>0.05
Abnormal skin and mucosa	1	2.92 [0.31, 28.00]	Not applicable	>0.05
Dysphagia	1	0.33 [0.01, 8.09]	Not applicable	>0.05

*$P < 0.05$.

are available to support the safety and tolerability of inactivated vaccines at different doses. Besides, the risk of adverse reactions occurring after the first two doses was significantly increased, but no significant differences were found between the prime and boost vaccination groups. Relatively speaking, the third dose of vaccine might be safer for vaccinees. Moreover, there were subtle differences in the risk of adverse reactions among different age groups. For older vaccine recipients, adverse reactions caused by mRNA vaccine and inactivated vaccine warrant further attention.

In addition, good immunogenicity could be observed for all vaccine types and, in particular, dose-level-dependent immunogenicity was found in the inactivated vaccine group. The immunogenicity of vaccines varies slightly among age groups. Older children over 12 years of age would develop a stronger immune response after vaccination, especially after BNT162b2 Covid-19 vaccine. This difference may be related to the fact that immune function is not yet well developed in young children. Furthermore, although there was no significant difference in the risk of adverse reactions between single-dose and double-dose vaccines, the double-dose regimen was significantly superior to the single-dose schedule in terms of humoral immunogenicity and prophylactic efficacy. However, data from Zhu et al. (38) showed no further enhancement in the intensity of T-cell immune response after booster vaccination. This result should be viewed with caution due to the limited data on the cellular immune response. What's more, both types of mRNA vaccines have shown satisfactory efficacy in preventing COVID-19, especially the BNT162b2 Covid-19 vaccine applied in adolescents aged 12 years and older.

In general, in this meta-analysis based on RCTs, the safety, immunogenicity, and efficacy of the COVID-19 vaccines were confirmed to some extent in children and teenagers aged 3 to 17 years, but analyses in younger children under 3 years of age and even in infants were lacking. For different vaccine types, inactivated vaccines had better safety profiles significantly; for different injection regimens, double-dose vaccination induced a stronger humoral immune response and produced better prophylactic effects; for different age groups of vaccinees, the vaccine has better immunogenicity in older children, accompanied by a higher risk of adverse reactions; for different doses of inactivated vaccine, there were no significant differences in adverse reactions among different dose groups,

TABLE 5 | Adverse reactions among vaccination group vs. control group.

		No. of studies	RR (95% CI)	I2	*P*-value
Total adverse reactions					
After dose 1	Overall	3	1.49 [1.43, 1.55]	70	<0.05*
	mRNA vaccine	1	1.47 [1.41, 1.54]	Not applicable	<0.05*
	Inactivated vaccine	1	1.27 [0.76, 2.13]	Not applicable	>0.05
	Vectored vaccine	1	3.44 [1.78, 6.65]	Not applicable	<0.05*
After dose 2	Overall	3	1.76 [1.67, 1.85]	60	<0.05*
	mRNA vaccine	1	1.74 [1.66, 1.83]	Not applicable	<0.05*
	Inactivated vaccine	1	1.83 [0.90, 3.72]	Not applicable	>0.05
	Vectored vaccine	1	8.25 [2.06, 33.00]	Not applicable	<0.05*
After dose 3	Overall	0	/	/	/
	mRNA vaccine	0	/	/	/
	Inactivated vaccine	0	/	/	/
	Vectored vaccine	0	/	/	/
Local adverse reactions					
After dose 1	Overall	3	2.60 [2.42, 2.80]	47	<0.05*
	mRNA vaccine	1	2.56 [2.38, 2.76]	Not applicable	<0.05*
	Inactivated vaccine	1	6.34 [1.54, 26.10]	Not applicable	<0.05*
	Vectored vaccine	1	6.00 [1.94, 18.53]	Not applicable	<0.05*
After dose 2	Overall	3	2.89 [2.67, 3.14]	8	<0.05*
	mRNA vaccine	1	2.86 [2.64, 3.10]	Not applicable	<0.05*
	Inactivated vaccine	1	4.29 [1.03, 17.96]	Not applicable	P=0.05
	Vectored vaccine	1	19.69 [1.21, 319.62]	Not applicable	<0.05*
After dose 3	Overall	1	1.86 [0.55, 6.30]	Not applicable	>0.05
	mRNA vaccine	0	/	/	/
	Inactivated vaccine	1	1.86 [0.55, 6.30]	Not applicable	>0.05
	Vectored vaccine	0	/	/	/
Systemic adverse reactions					
After dose 1	Overall	3	1.26 [1.19, 1.33]	68	<0.05*
	mRNA vaccine	1	1.23 [1.17, 1.31]	Not applicable	<0.05*
	Inactivated vaccine	1	1.32 [0.87, 2.00]	Not applicable	>0.05
	Vectored vaccine	1	3.70 [1.55, 8.83]	Not applicable	<0.05*
After dose 2	Overall	3	1.88 [1.77, 2.01]	29	<0.05*
	mRNA vaccine	1	1.87 [1.76, 1.99]	Not applicable	<0.05*
	Inactivated vaccine	1	1.61 [0.76, 3.40]	Not applicable	>0.05
	Vectored vaccine	1	6.00 [1.48, 24.38]	Not applicable	<0.05*
After dose 3	Overall	1	2.30 [0.69, 7.64]	Not applicable	>0.05
	mRNA vaccine	0	/	/	/
	Inactivated vaccine	1	2.30 [0.69, 7.64]	Not applicable	>0.05
	Vectored vaccine	0	/	/	/

*$P < 0.05$.

but the humoral immune response was more pronounced in the high dose group. If possible, individualized vaccination programs can be considered. Countries can administer the most appropriate COVID-19 vaccine to children and adolescents of different ages in a variety of health conditions, depending on local circumstances.

In addition to six included RCTs, a comprehensive search identified three relevant trials (20, 39, 40) that included adolescents, all of which confirmed good safety and immunogenicity of the vaccine in this age group but were not included in the review because no information was specifically provided for specific age group. Notably, Thomas et al. (40) followed the subjects for 6 months and confirmed that the immune efficacy of the BNT162b2 Covid-19 vaccine, although gradually decreasing over time, could still be maintained at a good level.

To our knowledge, this is the first meta-analysis specifically targeting COVID-19 vaccine recipients under the age of 18 years, which has comprehensively assessed the safety, immunogenicity, and efficacy of COVID-19 vaccines in the population. Previously,

TABLE 6 | Specific adverse reactions in mRNA vaccine recipients aged ≥12 years vs. <12 years.

		No. of studies	RR (95% CI)	I2	*P*-value
After dose 1	Overall	2	1.40 [1.21, 1.62]	71	<0.05*
	Local pain	2	2.09 [1.56, 2.81]	93	<0.05*
	Erythema or Redness	2	1.77 [0.77, 4.03]	45	>0.05
	Swelling	2	2.72 [0.95, 7.74]	26	>0.05
	Fever	2	5.12 [1.25, 21.01]	36	<0.05*
	Headache	2	1.04 [0.75, 1.43]	92	>0.05
	Fatigue	2	1.00 [0.75, 1.34]	90	>0.05
	Myalgia	2	1.34 [0.78, 2.29]	67	>0.05
	Arthralgia	2	0.87 [0.41, 1.85]	69	>0.05
	Vomiting	2	1.85 [0.38, 9.07]	0	>0.05
	Diarrhea	2	0.97 [0.44, 2.12]	0	>0.05
	Chills	2	1.87 [1.05, 3.36]	82	<0.05*
After dose 2	Overall	2	2.04 [1.75, 2.38]	77	<0.05*
	Local pain	2	2.21 [1.62, 3.02]	93	<0.05*
	Erythema or Redness	2	2.28 [0.95, 5.48]	0	>0.05
	Swelling	2	2.97 [1.03, 8.57]	0	<0.05*
	Fever	2	10.52 [2.68, 41.29]	32	<0.05*
	Headache	2	1.69 [1.20, 2.38]	92	<0.05*
	Fatigue	2	1.60 [1.16, 2.22]	92	<0.05*
	Myalgia	2	2.30 [1.31, 4.01]	84	<0.05*
	Arthralgia	2	1.86 [0.88, 3.92]	74	>0.05
	Vomiting	2	1.85 [0.38, 9.05]	0	>0.05
	Diarrhea	2	0.53 [0.25, 1.13]	89	>0.05
	Chills	2	3.93 [2.11, 7.33]	80	<0.05*

*$P < 0.05$.

TABLE 7 | Overall adverse reactions within 28 days after whole vaccination procedure in inactivated vaccine group of different ages vs. control group.

	No. of studies	RR (95% CI)	I2	*P*-value
Overall adverse reactions within 28 days after whole vaccination procedure	2	1.60 [1.27, 2.01]	57	<0.05*
3–5 years old	2	1.15 [0.81, 1.64]	28	>0.05
6–11/12 years old	2	2.41 [1.37, 4.23]	83	<0.05*
12/13–17 years old	2	1.71 [1.19, 2.46]	0	<0.05*

*$P < 0.05$.

Liu et al. published a systematic review (41) evaluating COVID-19 vaccination in children and adolescents, but that review included only two RCTs and did not perform a quantitative analysis. Moreover, those included in this review are all recently published, high-quality randomized controlled trials, that can provide the strongest evidence to date. In addition, to reduce the effect of heterogeneity, we performed a rigorous subgroup analysis to figure more precise and detailed results. However, there are some limitations as well. First of all, we only included a limited number of RCTs, including only three types of COVID-19 vaccines (the mRNA vaccine, inactivated vaccine, and adenovirus vector vaccine), and lacked data on younger children under 3 years of age or even infants, as well as long-term follow-up data. Besides, the RCT (38) with adenoviral vector vaccine as an intervention was a small-sample study, so the data provided may be overridden by other large-sample studies. Although this possibility has been substantially reduced by detailed subgroup analysis, the small sample size may still limit the statistical validity of this trial. Furthermore, for the cellular immune response after vaccination, only one RCT (38) provided relevant data. In addition, although methodological heterogeneity and clinical heterogeneity were well controlled, statistical heterogeneity could not be ignored. Despite the implementation of careful subgroup analyses, high statistical heterogeneity could still be found in some subgroups, which may be related to potential factors such as geographic region, population ethnicity, and vaccine dose.

TABLE 8 | Seroconversion rate in vaccine group vs. control group.

	No. of studies	RR (95% CI)	I2	*P*-value
Pseudovirus neutralizing antibody				
28 days after Dose 1	3	77.99 [28.40, 214.14]	82	<0.05*
28 days after Dose 2	3	144.80 [44.97, 466.24]	73	<0.05*
Neutralizing antibody 28 days after Dose 2	2	118.74 [38.67, 364.63]	0	<0.05*
3-5 years old	2	110.57 [15.87, 770.57]	0	<0.05*
6–11/12 years old	2	124.37 [17.79, 869.21]	0	<0.05*
12/ 13–17 years old	2	121.28 [17.36, 847.06]	0	<0.05*
RBD–binding enzyme-linked immunosorbent assay antibody				
28 days after Dose 1	1	99.48 [6.31, 1569.12]	Not applicable	<0.05*
56 days after Dose 1 (Before Dose 2)	1	98.47 [6.24, 1553.30]	Not applicable	<0.05*
28 days after Dose 2	1	101.50 [6.44, 1600.76]	Not applicable	<0.05*

*$P < 0.05$.

TABLE 9 | COVID-19 diagnosed after vaccination in vaccine group vs. control group.

	No. of studies	RR (95% CI)	I2	*P*-value
Covid-19 after the vaccination	3	0.10 [0.05, 0.21]	0	<0.05*
After dose 1 to before dose 2	1	0.25 [0.07, 0.88]	Not applicable	<0.05*
Within 7 days after the second dose	1	0.09 [0.01, 1.64]	Not applicable	>0.05
7 days after second dose	2	0.06 [0.02, 0.20]	0	<0.05*
14 days after second dose	1	0.07 [0.01, 0.56]	Not applicable	<0.05*
Covid-19 after dose 2	3	0.06 [0.02, 0.18]	0	<0.05*
mRNA-1273 vaccine	1	0.07 [0.01, 0.56]	Not applicable	<0.05*
BNT162b2 Covid-19 Vaccine	2	0.06 [0.02, 0.20]	0	<0.05*

*$P < 0.05$.

Regarding vaccination of people under 18 years of age, the following issues remain to be urgently addressed.

To begin with, there is an urgent need to fill the gaps in long-term follow-up data, to assess the duration of immune response after vaccination, and whether vaccines cause long-term adverse outcomes, such as myocarditis. Although the available data (42) suggested that the incidence and long-term risk of myocarditis caused by the virus itself appeared to be more threatening than that of vaccine-associated myocarditis, which might be self-limiting, we still need stronger evidence to dispel this concern. Besides, recent data (43) indicates that inactivated vaccination may cause pathophysiological changes in vaccine recipients similar to those in infected individuals, suggesting that careful consideration is needed when vaccinating children, even with inactivated vaccines that appear to be safer, especially for children with underlying disease. What's more, given that MIS-C may be an immune disease associated with SARS-CoV-2 infection, we cannot exclude the possibility that this complication is instead induced after COVID-19 vaccination (11). Relevant studies are urgently needed to elucidate the mechanism underlying this rare but severe disease (44).

Moreover, assessment of children under 3 years of age and even infants is urgently needed on the agenda. As reported (45), Pfizer may respectively release the results of vaccination trials for children aged 2 to 5 years by the end of 2021, and for children aged 6 months to 2 years in the first quarter of 2022, which, if positive, will greatly facilitate the vaccination process for younger children. Besides, immune protection for this specific group of newborns could be considered starting with pregnant women. Recent studies (46–48) have shown that antibodies can be detected in the placenta or breast milk after vaccination of pregnant or lactating women without a significant increase in adverse fetal or neonatal outcomes, which may suggest an alternative route of immune protection for the fetus or newborn. Higher-level randomized controlled trials are needed to validate this idea in order to ensure maternal and infant safety.

Furthermore, considering the overall benefits to society, we have to assess whether the benefits of vaccinating children outweigh the burden on overall local epidemic control (49). In a situation where vaccines are in short supply, it seems more ethical to give priority to immunocompromised populations such as the elderly (50). Local tailoring may be the solution to this dilemma. However, it was the emergence of the Omicron variant that has reminded us the only a comprehensive vaccination program, including for low-risk populations, will allow us to achieve victory against the epidemic.

In addition, given the urgency of advancing childhood vaccination, there is a need for a comprehensive assessment of

the factors influencing vaccination, particularly those affecting parental intentions. Surveys around the world (16, 17, 51) have shown that distrust in the safety and efficacy of vaccines is an important reason why parents are reluctant to have their children vaccinated, and that most parents are willing to vaccinate their children when the vaccine is safe and reliable. Therefore, high-quality studies assessing the safety and efficacy of the COVID-19 vaccine in younger children appear to be essential to eliminate childhood vaccine hesitancy. Moreover, parental fear of COVID-19 is an important influencing factor in the decision to vaccinate children (51, 52), stemming not only from the health risks children may face, but also from the risk of family transmission due to children's infection, which may have a negative impact on the family's economic income as well as social activities. Therefore, in order to enhance parents' perception of COVID-19, local governments should proactively provide a platform for scientific communication and share valid data in a timely manner. Furthermore, race, religious affiliation, trust in government agencies, willingness to get vaccinated for themselves, education level, annual income, work environment, mother tongue, and age may all be important factors influencing parent's willingness (18, 51). As the epidemic progressed, surveys from various countries spurted out, but most were single-center surveys. Surveys may be contradictory from country to country (18, 19), and parental attitudes may change as the epidemic evolves. Therefore, in addition to continuing to advance research on vaccines, a systematic review that brings together various influencing factors is highly desirable (41) and will help us assess the influencing factors that affect parental willingness in different contexts, thus guiding us to take various effective measures to advance the childhood vaccination process for various populations in different regions.

CONCLUSIONS

In conclusion, our meta-analysis pooled the available randomized controlled trials and confirmed the favorable safety, immunogenicity, and efficacy of COVID-19 vaccines (mRNA-1273 vaccine, BNT162b2 Covid-19 Vaccine, CoronaVac, BBIBP-COV, and Ad5-vectored COVID-19 vaccine) in adolescents and children aged 3–17 years. Nevertheless, there is still a large gap in trials to confirm the safety and efficacy of different COVID-19 vaccines in people under 18 years of age, especially in younger children under 3 years old and even infants. There is an urgent need to conduct multicenter, large-sample clinical studies of COVID-19 vaccine in younger children with a wider range of vaccine types and longer follow-up periods, to promote global universalization and standardization of childhood vaccination. Given the rapidly changing epidemiological situation and the advancing vaccine research process, this meta-analysis should be updated in time when more data are available.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YD and YS conceived and designed the study, performed the data analysis, and prepared the figures and the tables. YD and LC conducted the database search and extracted the data. YD wrote the manuscript. LC and YS revised it critically for important intellectual content. YS is the guarantor. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.829176/full#supplementary-material

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ORIGINAL RESEARCH
published: 16 May 2022
doi: 10.3389/fpubh.2022.896343

Side Effects of COVID-19 Inactivated Virus vs. Adenoviral Vector Vaccines: Experience of Algerian Healthcare Workers

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Edited by:
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Chulalongkorn University, Thailand
Zeinab A. Kasemy,
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Specialty section:
This article was submitted to Infectious Diseases – Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: *15 March 2022*
Accepted: *22 April 2022*
Published: *16 May 2022*

Citation:
Lounis M, Rais MA, Bencherit D, Aouissi HA, Oudjedi A, Klugarová J, Pokorná A, Klugar M and Riad A (2022) Side Effects of COVID-19 Inactivated Virus vs. Adenoviral Vector Vaccines: Experience of Algerian Healthcare Workers. Front. Public Health 10:896343. doi: 10.3389/fpubh.2022.896343

Healthcare workers were prioritized in vaccination campaigns globally because they are exposed to the highest risk of contamination by SARS-CoV-2. This study evaluated the self-reported post-vaccination side effects of inactivated (BBIBP-CorV and CoronaVac) and adenoviral vector-based (AZD1222, Gam-COVID-Vac and Ad26.COV2.S) vaccines among Algerian healthcare workers using a validated questionnaire. The final analysis included 721 healthcare workers, with a predominance of females (59.1%) and younger individuals 20–30 years old (39.4%). Less than half (49.1%) of the respondents reported at least one local side effect, while 53.8% reported at least one systemic side effect. These side effects were more prevalent among viral vector vaccinees than inactivated virus vaccinees. The most common local side effects were injection site pain (39%) and arm pain (25.4%), while fatigue (34.4%), fever (28.4%), headache (24.8%) and myalgia (22.7%) were the most prevalent systemic side effects. The side effects appeared earlier among inactivated virus vaccines recipients and generally lasted for 2 to 3 days for the two vaccinated groups. The risk factors associated with a higher prevalence of side effects included female gender, allergic individuals, individuals with regular medication, those who contracted the COVID-19 disease and those who received two doses for both inactivated and viral-based vaccines groups. Despite the higher prevalence of post-vaccination side effects among adenoviral vector vaccines recipients, both vaccines groups were equally effective in preventing symptomatic infections, and no life-threatening side effects were reported in either vaccine group.

Keywords: adenoviral-based vaccine, COVID-19, health workers, inactivated virus vaccine, side effects

INTRODUCTION

As of March 2022, four hundred and forty-one million cases and nearly six million fatalities were recorded globally due to the coronavirus disease (COVID-19) pandemic (1). After the second anniversary of its emergence, the disease continues its rapid spread despite the drastic preventive measures applied in all countries worldwide. In the absence of vaccines or efficient medications against this disease during the first wave, countries had no alternatives other than non-pharmacological preventive measures like lockdowns, travel restrictions, physical distancing, quarantine, and using face masks to limit the disease propagation according to their capacities (2). These measures have helped to limit the propagation of the disease; however, they seem to be insufficient to control the disease entirely, and the COVID-19 resurged in multiple waves when countries started their deconfinement (3, 4).

Hence, researchers were racing against the clock to find the best strategy to fight this disease and return to normal life. In this way, herd immunity or population immunity through vaccination or immunity developed after a previous infection was one of the proposed strategies (5). Given the impossibility to achieve herd immunity through natural infection, the best approach to achieve herd immunity recommended by the World Health Organization (WHO) is to protect people by vaccination (6, 7). These exceptional circumstances have pushed researchers and laboratories to develop and produce different types of vaccines in a short period of about 1 year (8). In December 2020, the World Health Organization (WHO) had approved six vaccines types, and the mass vaccination campaign started since then (9).

Currently, 35 COVID-19 vaccines are approved by at least one country, and ten vaccines are approved by the WHO (9). However, myths, speculations, misinformation and conspiracy theories surrounding COVID-19 vaccines and their side effects have highly influenced vaccine uptake. These factors have caused delays due to unwillingness in people to get vaccinated, leading to vaccine hesitancy (10–14). Multiples studies have reported that this hesitancy is mainly related to vaccines' safety and effectiveness; however, all approved vaccines had high efficacy levels (10–17). Nevertheless, like any other pharmacological agents, these vaccines could induce some side effects that could include flu-like symptoms (e.g. headache, fatigue and myalgia) and injection site reactions and are mostly non-serious and of short duration (18–28).

Algeria started its mass vaccination campaign on December 31, 2020. The vaccines had been administered first to healthcare workers and individuals with comorbidities (29–31). Currently, the approved vaccines in the country include inactivated virus vaccines, i.e., BBIBP-CorV and CoronaVac, and adenoviral vector-based vaccines, i.e., Gam-COVID-Vac, AZD1222 and Ad26.COV2.S (30–32). On February 20, 2022, more than 7.46 million persons received at least one dose of COVID-19, representing about 16.7% of the total population (33).

The current work was conducted to determine the most common side effects reported by healthcare workers in Algeria after COVID-19 vaccination and to evaluate eventual risk factors associated with post-vaccination side effects. To the best of our knowledge, no such studies about COVID-19 vaccine side effects were conducted in Algeria.

MATERIALS AND METHODS

Design

The present study had been designed as an analytical cross-sectional survey-based study that utilized a self-administered questionnaire (SAQ) to collect data from the target population about their post-vaccination side effects. The study was designed and reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for cross-sectional studies (34).

Setting

This study was carried out between October 25 and November 25, 2021 after 6,328,806 (14.4%) of the Algerian population received at least one dose and 4,751,933 (10.8%) were fully vaccinated in order to ensure that a substantial proportion of the Algerian healthcare workers were already vaccinated. The study utilized a SAQ that was designed and administered digitally using Google Forms (Google LLC, Menlo Park, CA, USA, 2021)(35). A uniform resource locator (URL) and a quick response (QR) code were used to disseminate the SAQ and collect data from the target population.

Participants

The target population of this study were Algerian healthcare workers who received either one or two doses of COVID-19 vaccines that were approved for mass inoculation in Algeria. The participants who received inactivated virus and adenoviral vector vaccines were included, while the participants who received protein sub-unit mRNA-based vaccines were excluded from the subsequent analyses.

A non-random technique through convenience sampling was used as the potential participants were recruited using social media platforms (Facebook and WhatsApp groups) targeting especially those of medical interests.

Epi-Info ^{TM} version 7.2.4 (CDC. Atlanta, GA, USA, 2020) had been used to calculate the sample size using the following assumptions of an expected outcome frequency of 50%, an acceptable margin error of 4%, a confidence level (CI) of 95%, and a postulated proportion of responses resulted from careless/insufficient effort (C/IE) of 10%(36). The required sample size for this study was 660 responses.

Participation in this study was on voluntary basis and it was not incentivised by financial rewards or any other means of compensation. The participants' identity was kept anonymous in order to control Hawthorne's effect and information bias.

Instrument

The SAQ used in this study was adopted from previous studies and its items had been reviewed by a panel of experts to assess content validity. Consequently, test re-test reliability of the items was estimated to be acceptable with a mean Cohen's kappa

coefficient of 0.89 ± 0.13 and reported in detail previously (23–28, 37). The SAQ comprised 25 multiple choice items that were stratified into three categories; (i) demographic characteristics including sex, age group, and profession, (ii) anamnestic characteristics including chronic illnesses, medications, allergies, previous COVID-19 infection, and COVID-19 vaccine type and number of doses, and (iii) post-vaccination side effects, their onset and duration, and post-vaccination medical care and medications.

Ethics

The study protocol had been reviewed and approved by the Scientific Committee of the Faculty of Natural and Life Sciences/University of Djelfa on 20/10/2021 with the reference number 117/10/2021. The Declaration of Helsinki for research involving human subjects had guided the conception and execution of the entire study (38). All participants provided their informed consent digitally before filling the questionnaire. The responses of the participants who did not complete the questionnaire were not saved; and the participants were able to leave the study any time without justification. Given the fact that no identifying personal data was collected, retrospective identification of the participants was not possible.

Analyses

The Statistical Package for the Social Sciences (SPSS) version 28.0 (SPSS Inc. Chicago, IL, USA, 2021) was used to analyse the collected data (39). Initially, descriptive statistics used frequencies (*n*) and percentages (*%*) to summarize nominal and ordinal data. Then, inferential statistics through chi-squared test (χ^2) and Fisher's-exact test had been used to evaluate the association between independent and dependent variables. Eventually, multivariable logistic regression was used to evaluate the suggested risk factors of post-vaccination side effects following inactivated virus vaccines and adenoviral vector vaccines. All analytical tests were performed with a confidence level (*CI*) of 95% and a significance level (*Sig.*) of ≤ 0.05.

TABLE 1 | Demographic and anamnestic characteristics of Algerian healthcare workers receiving COVID-19 vaccines ($n = 721$).

Variable	Outcome	Frequency (*n*)	Percentage (%)
Sex	Female	426	59.1%
	Male	295	40.9%
Age group	20–30 years-old	284	39.4%
	31–40 years-old	229	31.8%
	41–50 years-old	126	17.5%
	51–60 years-old	66	9.2%
	> 60 years-old	16	2.2%
Tobacco smoking	Smoker	86	11.9%
	Non-smoker	635	88.1%
Chronic illnesses	Autoimmune disorders	5	0.7%
	Cardiovascular disease	9	1.2%
	Chronic hypertension	59	8.2%
	COPD	33	4.6%
	Diabetes mellitus	39	5.4%
	Gastrointestinal disease	3	0.4%
	Thyroid disorders	16	2.2%
	Others	43	6%
	Total	168	23.3%
Allergy	Yes	218	30.2%
	No	503	69.8%
Medications	Anti-asthma	38	5.3%
	Anticoagulants	4	0.6%
	Antidepressants	13	1.8%
	Anti-diabetes	35	4.9%
	Antihistamines	112	15.5%
	Antihypertensive	55	7.6%
	Anti-reflux	36	5%
	Cholesterol-lowering	10	1.4%
	Contraceptives	20	2.8%
	Thyroid hormone	34	4.7%
	Total	276	38.3%

RESULTS

Demographic Characteristics

A total of 724 responses were received during the study period (October 25–November 25, 2021), of which three responses were excluded because the respondents received mRNA-based vaccines (two received BNT162b2 and one received mRNA-1273).

Out of the 721 included participants, 450 received BBIBP-CorV or CoronaVac (inactivated virus group, $n = 450$), while 156 received Gam-COVID-Vac, 98 received AZD1222, and 17 received Ad26.COV2.S (adenoviral vector group, $n = 271$).

The most commonly represented age group was the 20–30 years-old (39.4%), followed by the 31–40 years-old (31.8%) and the 41–50 years-old (17.5%) **Table 1**.

More than half (54.4%) of the sample were married, while 45.1% were single and 0.4% were either divorced or widow. Physicians (35.5%) were the most participating profession, followed by dentists (20.4%), nurses (9.3%), paramedics (9.3%), and pharmacists (7.4%). Most participants worked for public (state-funded) healthcare providers (77.3%). The most contributing department was Algiers (25.2%), followed by Blida (5.7%), Tebessa (4.8%), Oran (4.7%), Sétif (4%), Annaba (3.9%), and Constantine (3.6%) **Supplementary Table 1**.

Anamnestic Characteristics

A total of 11.9% of the participants reported smoking tobacco regularly with no significant (*Sig.* = 0.526) difference between inactivated virus (11.3%) and adenoviral vector (12.9%) groups. Chronic hypertension was the most commonly reported chronic illness (8.2%), followed by diabetes mellitus (5.4%), and chronic obstructive pulmonary disease (4.6%). Overall, 23.3% of the participants reported suffering from at least one chronic illness, and 30.2% reported having allergy to at least one allergen with no significant differences between inactivated virus and adenoviral vector groups.

TABLE 2 | COVID-19-related anamnesis of Algerian healthcare workers receiving COVID-19 vaccines ($n = 721$).

Variable	Outcome	Inactivated virus vaccine ($n = 450$)	Adenoviral vector vaccine ($n = 271$)	Total ($n = 721$)	*Sig.*
Infection	Yes	216 (48%)	125 (45.6%)	341 (47.1%)	0.534
	No	234 (52%)	149 (54.4%)	383 (52.9%)	
Onset	Before vaccination	197 (91.2%)	112 (89.6%)	309 (90.6%)	0.625
	After second dose	19 (8.8%)	13 (10.4%)	32 (9.4%)	
Vaccination timing	Less than a week ago	13 (2.9%)	12 (4.4%)	25 (3.5%)	0.274
	From a week to a month ago	64 (14.2%)	43 (15.9%)	107 (14.8%)	0.547
	From a month to 3 months ago	187 (41.6%)	56 (20.7%)	243 (33.7%)	**< 0.001**
	More than 3 months ago	186 (41.3%)	160 (59%)	346 (48%)	**< 0.001**
Number of doses	One dose ‡	90 (20%)	63 (24.8%)	153 (21.7%)	0.138
	Two doses	360 (80%)	191 (75.2%)	551 (78.3%)	

Chi-squared test (χ^2) had been used with a significance level (Sig.) ≤ 0.05; ‡, Participants who received Ad26.COV2.S were excluded.
Bold values refer to the statisitically signifcant values which are below 0.05.

The most commonly administered medications were antihistamines (15.5%), followed by antihypertensive drugs (7.6%), anti-asthma (5.3%), anti-reflux (5%), anti-diabetes drugs (4.9%), and thyroid supplements (4.7%). Overall, 38.3% of the participants reported receiving at least one medication regularly, with no significant difference (*Sig.* = 0.907) between inactivated virus (38.4%) and adenoviral vector (38%) group **Table 1**.

When asked about their COVID-19-related anamnesis, less than half of the participants (47.1%) reported being infected previously with no significant (*Sig.* = 0.534) difference between inactivated virus (48%) and adenoviral vector (45.6%) groups. Most of the infections occurred before vaccination (90.6%), while 9.4% after the second dose without a significant difference between the two vaccine platforms (*Sig.* = 0.625).

Less than half of the participants (48%) were inoculated against SARS-CoV-2 more than three months before the survey, while 33.7% were inoculated 1 to 3 months before the survey. Most of the participants (78.3%) received two doses, with no significant (*Sig.* = 0.138) difference between inactivated virus (80%) and adenoviral vector (75.22%) groups **Table 2**.

Local Side Effects

Less than half of the participants (49.1%) reported at least one local side effect (related to the injection site), with the adenoviral vector vaccines (61.3%) being more significantly (*Sig.* < 0.001) associated with local side effects than inactivated virus vaccine (41.8%). Injection site pain was the most common local side effect (39%), followed by arm pain (25.4%), and injection site swelling (2.5%) and itching (2.5%). Prevalence of all the solicited local side effects was significantly higher among the adenoviral vector group **Figure 1**.

Regarding their onset, most local side effects emerged 12 h (77.4%) with a significant (*Sig.* = 0.021) difference between inactivated virus (82.3%) and adenoviral vector (72%) vaccines. Local side effects needed a significantly shorter interval (earlier onset) among the inactivated virus group than the adenoviral virus group. Regarding their duration, most local side effects lasted for only 24 h (38.7%) or 24–72 h (46.7%), without significant differences between the inactivated virus and the adenoviral vector vaccines **Table 3**.

Systemic Side Effects

More than half of the participants (53.8%) reported at least one systemic side effect (not related to the injection site), with the adenoviral vector vaccines (68.3%) being more significantly (*Sig.* < 0.001) associated with systemic side effects than inactivated virus vaccine (45.1%). Fatigue was the most common systemic side effect (34.4%), followed by fever (28.4%), headache (24.8%), myalgia (22.7%), chills (12.9%), and arthralgia (11.9%). Prevalence of most solicited systemic side effects was significantly higher among the adenoviral vector group except for dizziness, diarrhea, dyspnoea, skin rash, and abdominal pain where the difference was not statistically significant despite being more frequent among the adenoviral vector group **Figure 2**.

Regarding their onset, most systemic side effects emerged within two weeks (81.5%), with a significant (*Sig.* < 0.001) difference between inactivated virus (73.6%) and adenoviral vector (89.7%) vaccines. Systemic side effects tended to require a shorter interval (earlier onset) to emerge among the inactivated virus group than the adenoviral virus group. Regarding their duration, most systemic side effects lasted for only 2 days (59.1%) or up to a week (28.5%), without significant differences between the inactivated virus and the adenoviral vector vaccines. Among all the participants, six reported seeking medical care after vaccination due to their side effects, five (1.1%) from the inactivated virus and one (0.4%) from the adenoviral vector group (*Sig.* = 0.418) **Table 4**.

When asked about how they managed their post-vaccination side effects, 38.1% of the participants reported taking medications to manage their side effects. The adenoviral vector group (52%) was significantly (*Sig.* < 0.001) more associated with post-vaccination medications than the inactivated virus (29.8%) group. The most used medication was Paracetamol (36.9%) and to a lesser extent Aspirin (2.1%). **(Table 5)**.

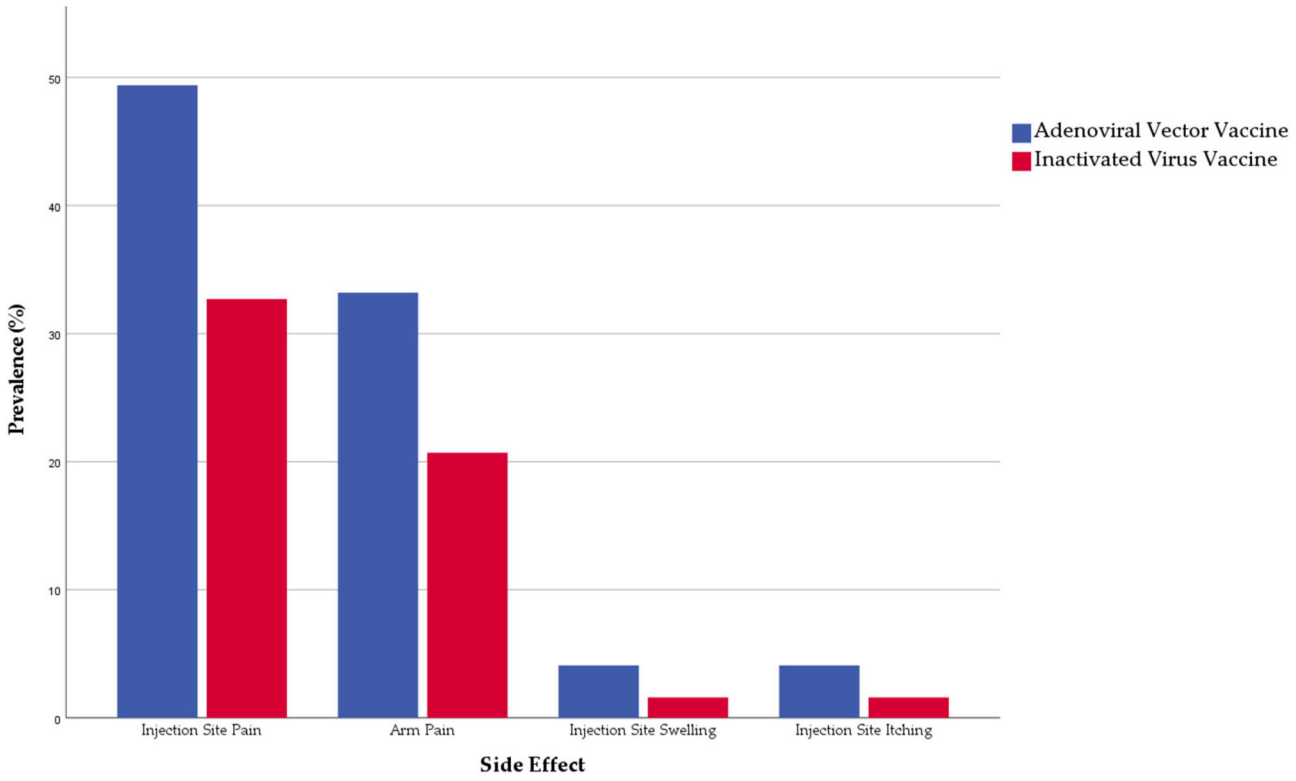

FIGURE 1 | Prevalence of local side effects reported by Algerian healthcare workers ($n = 721$).

TABLE 3 | Local side effects reported by Algerian healthcare workers receiving COVID-19 vaccines ($n = 721$).

Variable	Outcome	Inactivated virus vaccine ($n = 450$)	Adenoviral vector vaccine ($n = 271$)	Total ($n = 721$)	*Sig.*
Local Side effects	Injection site pain	147 (32.7%)	134 (49.4%)	281 (39%)	**< 0.001**
	Arm pain	93 (20.7%)	90 (33.2%)	183 (25.4%)	**< 0.001**
	Injection site swelling	7 (1.6%)	11 (4.1%)	18 (2.5%)	**0.037**
	Injection site itching	7 (1.6%)	11 (4.1%)	18 (2.5%)	**0.037**
	Total	188 (41.8%)	166 (61.3%)	354 (49.1%)	**< 0.001**
Onset	≤ 12 h	153 (82.3%)	118 (72%)	271 (77.4%)	**0.021**
	> 12 h	33 (17.7%)	46 (28%)	79 (22.6%)	
Duration	24 h	77 (41.2%)	58 (35.8%)	135 (38.7%)	0.304
	From 24 to 72 h	82 (43.9%)	81 (50%)	163 (46.7%)	0.251
	From 3 days to a week	20 (10.7%)	16 (9.9%)	36 (10.3%)	0.802
	More than a week	8 (4.3%)	7 (4.3%)	15 (4.3%)	0.984

Chi-squared test (χ^2) had been used with a significance level (Sig.) ≤ 0.05.
Bold values refer to the statisitically signifcant values which are below 0.05.

Risk Factors of Post-vaccination Side Effects

Females had significantly higher levels of overall side effects (71.6 vs. 55.3%), local side effects (58.5 vs. 35.6%), and systemic side effects (59.4 vs. 45.8%) than males, respectively. The local side effects were the most common among the age group of 31–40 years-old (56.8%), followed by the age group of 41–50 years-old (52.4%); on the other hand, the systemic side effects were the most common the age group of over 60 years-old (75%), followed by the age group of 51–60 years-old (66.7%).

Prevalence of local (51.3 vs. 32.6%) and systemic (55.1 vs. 44.2%) side effects was higher among non-smokers than smokers; while allergic participants had significantly higher prevalence of local (63.3 vs. 42.9%) and systemic (67 vs. 48.1%) side effects than their counterparts, respectively. The participants who reported suffering from at least one chronic illness had a significantly higher prevalence of local (57.7 vs. 46.5%) and systemic (61.3

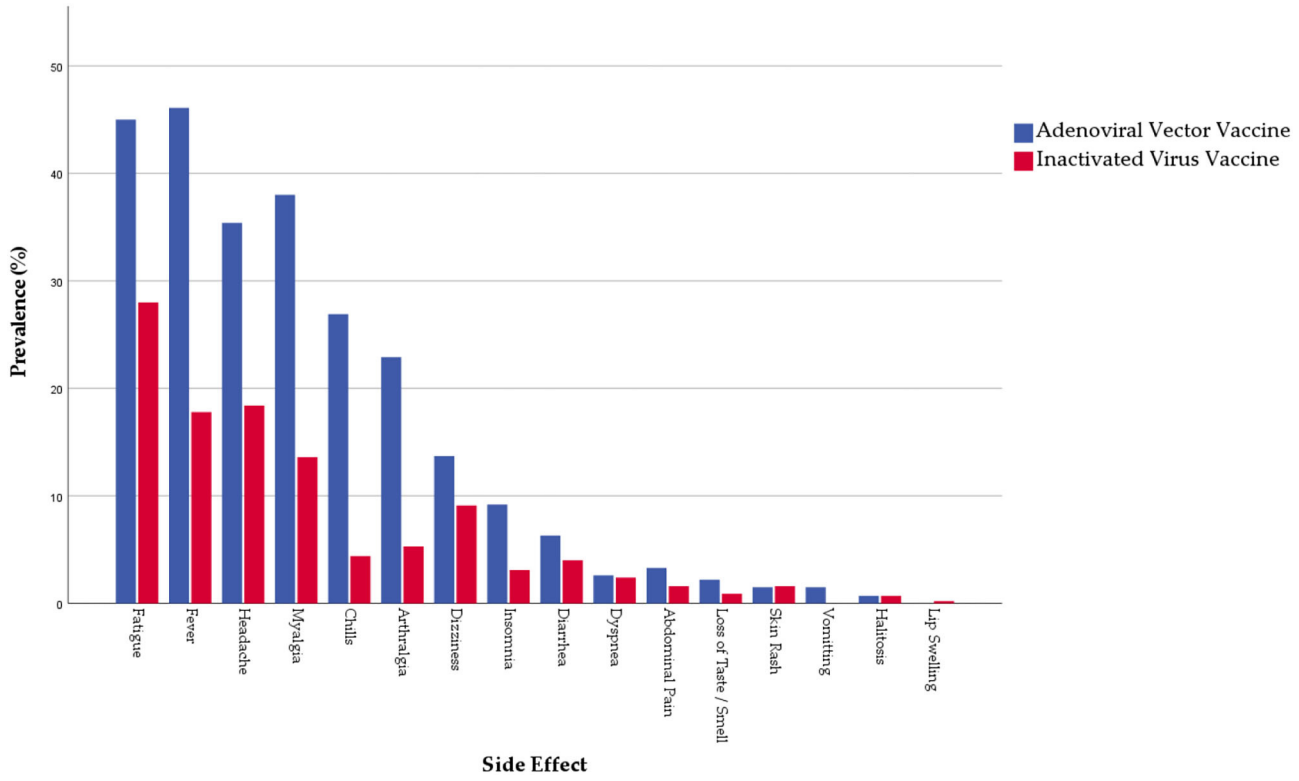

FIGURE 2 | Prevalence of systemic side effects reported by Algerian healthcare workers ($n = 721$).

vs. 51.5%) side effects than their counterparts, respectively. Similarly, the participants who reported taking medications regularly had a significantly higher prevalence of local (59.4% vs. 42.7%) and systemic (62 vs. 48.8%) side effects than their counterparts, respectively.

Previous COVID-19 infection was significantly associated with a higher prevalence of local (53.5 vs. 44.1%) and systemic (59.5 vs. 47.3%) side effects. Similarly, receiving two doses was significantly associated with a higher prevalence of local (52.1 vs. 39.4%) and systemic (56.4 vs. 45.3%) side effects compared with receiving one dose, respectively **Table 6**.

The participants who suffered from allergy (80.3 vs. 58.3%) and chronic obstructive pulmonary disease (87.9 vs. 63.8%) had significantly higher prevalence of post-vaccination side effects compared with their counterparts who did not report these diseases. Similarly, the participants who reported taking anti-asthmatic (81.6 vs. 64%), antihistaminic (76.8% *vs.* 62.7%), anti-reflux (83.3 vs. 63.9%), and thyroid hormone (82.4 vs. 64%) had significantly higher prevalence of post-vaccination side effects compared with their counterparts who did not report using these medications regularly.

Regression Analysis

Multivariate logistic regression was performed to analyse the demographic and anamnestic risk factors of post-vaccination side effects. For the inactivated virus vaccine, being a female (adjusted odds ratio "AOR": 2.500; confidence interval "CI" 95%: 1.579–3.959), suffering from allergy (AOR: 3.487; CI 95%: 2.061–5.901) and being infected previously with COVID-19 (AOR: 2.373; CI 95%: 1.555–3.621) had significantly higher odds of experiencing post-vaccination side effects in general. Compared to the youngest age group (20–30 years-old), all age groups had higher odds for experiencing side effects. Smoking and being disease-free were associated with lower odds but without statistical significance **Table 7**.

For the adenoviral vector vaccines, being a female (AOR: 2.503; CI 95%: 1.216–5.512) had significantly higher odds of experiencing post-vaccination side effects in general. Compared to the youngest age group (20–30 years-old), all other age groups had higher odds for experiencing side effects. Smoking and being disease-free were associated with lower odds but without statistical significance **Table 8**.

DISCUSSION

In the present work, an online survey-based study was carried out to evaluate the post-vaccination side effects among healthcare workers who received COVID-19 vaccines and their related risk factors in Algeria. The reported side effects were compared between inactivated (BBIBP-CorV and CoronaVac) and adenoviral vector-based (AZD1222, Gam-COVID-Vac and Ad26.COV2.S) vaccines approved in Algeria. In fact, healthcare

TABLE 4 | Systemic side effects reported by Algerian healthcare workers receiving COVID-19 vaccines (n = 721).

Variable	Outcome	Inactivated virus vaccine (*n* = 450)	Adenoviral vector vaccine (*n* = 271)	Total (*n* = 721)	*Sig.*
Systemic Side effects	Fever	80 (17.8%)	125 (46.1%)	205 (28.4%)	**< 0.001**
	Headache	83 (18.4%)	96 (35.4%)	179 (24.8%)	**< 0.001**
	Dizziness	41 (9.1%)	37 (13.7%)	78 (10.8%)	0.057
	Chills	20 (4.4%)	73 (26.9%)	93 (12.9%)	**< 0.001**
	Fatigue	126 (28%)	122 (45%)	248 (34.4%)	**< 0.001**
	Myalgia	61 (13.6%)	103 (38%)	164 (22.7%)	**< 0.001**
	Arthralgia	24 (5.3%)	62 (22.9%)	86 (11.9%)	**< 0.001**
	Diarrhea	18 (4%)	17 (6.3%)	35 (4.9%)	0.169
	Vomiting	0 (0%)	4 (1.5%)	4 (0.6%)	**0.020 ***
	Insomnia	14 (3.1%)	25 (9.2%)	39 (5.4%)	**< 0.001**
	Dyspnea	11 (2.4%)	7 (2.6%)	18 (2.5%)	0.908
	Skin rash	7 (1.6%)	4 (1.5%)	11 (1.5%)	1.000 *
	Loss of taste/smell	4 (0.9%)	6 (2.2%)	10 (1.4%)	0.189 *
	Halitosis	3 (0.7%)	2 (0.7%)	5 (0.7%)	1.000 *
	Lip swelling	1 (0.2%)	0 (0%)	1 (0.1%)	1.000 *
	Abdominal pain	7 (1.6%)	9 (3.3%)	16 (2.2%)	0.119
	Total	203 (45.1%)	185 (68.3%)	388 (53.8%)	**< 0.001**
Onset	Immediately	28 (14.5%)	16 (8.6%)	44 (11.6%)	**< 0.001**
	Within 2 week	142 (73.6%)	166 (89.7%)	308 (81.5%)	**< 0.001**
	After 2 weeks	23 (11.9%)	3 (1.6%)	26 (6.9%)	**< 0.001**
Duration	2 days	106 (55.5%)	112 (62.9%)	218 (59.1%)	0.147
	From 2 days to a week	54 (28.3%)	51 (28.7%)	105 (28.5%)	0.936
	From a week to 2 weeks	12 (6.3%)	7 (3.9%)	19 (5.1%)	0.307
	From 2 weeks to 4 weeks	8 (4.2%)	3 (1.7%)	11 (3%)	0.158
	More than 4 weeks	11 (5.8%)	5 (2.8%)	16 (4.3%)	0.164
Medical care	Yes	5 (1.1%)	1 (0.4%)	6 (0.8%)	0.418 *
	No	445 (98.9%)	270 (99.6%)	715 (99.2%)	

Chi-squared test (χ^2) and Fisher's-exact test; (*) had been used with a significance level (Sig.) ≤ 0.05.
Bold values refer to the statisitically signifcant values which are below 0.05.

TABLE 5 | Post-vaccination medications received by Algerian healthcare workers (*n* = 721).

Variable	Inactivated virus vaccine (*n* = 450)	Adenoviral vector vaccine (*n* = 271)	Total (*n* = 721)	*Sig.*
Paracetamol	129 (28.7%)	137 (50.6%)	266 (36.9%)	**< 0.001**
Aspirin	6 (1.3%)	9 (3.3%)	15 (2.1%)	0.070
Total	134 (29.8%)	141 (52%)	275 (38.1%)	**< 0.001**

Chi-squared test (χ^2) had been used with a significance level (Sig.) ≤ 0.05.
Bold values refer to the statisitically signifcant values which are below 0.05.

workers were among the prioritized groups for COVID-19 vaccine in Algeria. Also, their professional background guaranteed a better and more detailed description of the post-vaccination side effects. For these reasons, multiple studies were conducted to determine vaccines side effects among this population subset in different countries, e.g., Czech Republic, Germany, Jordan, Saudi Arabia, Slovakia, Turkey, and United Arab Emirates (19–28).

Overall, 49.1, and 53.8% of the surveyed healthcare workers in our study reported at least one local or systemic side effect, respectively. The local and systemic side effects were significantly more frequent among the adenoviral vector vaccines group (61.3, and 68.3%) than the inactivated virus vaccinated group (41.8, and 45.1%). This finding is consistent with the results of multiple previous studies that reported that the Chinese inactivated vaccines, i.e., BBIBP-CorV and CoronaVac induced fewer side effects than either adenoviral vector-based mRNA-based vaccines (18, 19, 40–42). Moreover, the reported side effects were generally mild in patients who received inactivated vaccines (19, 22, 41–44). The side effects duration was longer in BBIBP-CorV than

TABLE 6 | Risk factors of post-vaccination side effects reported by Algerian healthcare workers ($n = 721$).

Variable	Outcome	Local SE	*Sig.*	Systemic SE	*Sig.*	Total SE	*Sig.*
Sex	Female	249 (58.5%)	**< 0.001**	253 (59.4%)	**< 0.001**	305 (71.6%)	**< 0.001**
	Male	105 (35.6%)		135 (45.8%)		163 (55.3%)	
Age	20–30 years-old	121 (42.6%)	**0.005**	112 (39.4%)	**< 0.001**	151 (53.2%)	**< 0.001**
group	31–40 years-old	130 (56.8%)	**0.005**	145 (63.3%)	**< 0.001**	169 (73.8%)	**< 0.001**
	41–50 years-old	66 (52.4%)	0.417	75 (59.5%)	0.157	87 (69%)	0.284
	51–60 years-old	29 (43.9%)	0.379	44 (66.7%)	**0.028**	48 (72.7%)	0.163
	> 60 years-old	8 (50%)	0.942	12 (75%)	0.086	13 (81.3%)	0.166
Tobacco	Smoker	28 (32.6%)	**0.001**	38 (44.2%)	0.056	47 (54.7%)	**0.034**
smoking	Non-smoker	326 (51.3%)		350 (55.1%)		421 (66.3%)	
Allergy	Yes	138 (63.3%)	**< 0.001**	146 (67%)	**< 0.001**	175 (80.3%)	**< 0.001**
	No	216 (42.9%)		242 (48.1%)		293 (58.3%)	
Chronic	Yes	97 (57.7%)	**0.011**	103 (61.3%)	**0.026**	120 (71.4%)	**0.043**
illnesses	No	257 (46.5%)		285 (51.5%)		348 (62.9%)	
Medications	Yes	164 (59.4%)	**< 0.001**	171 (62%)	**< 0.001**	204 (73.9%)	**< 0.001**
	No	190 (42.7%)		217 (48.8%)		264 (59.3%)	
Infection	Yes	205 (53.5%)	**0.011**	228 (59.5%)	**0.001**	270 (70.5%)	**< 0.001**
	No	149 (44.1%)		160 (47.3%)		198 (58.6%)	
Number of doses	One dose	67 (39.4%)	**0.004**	77 (45.3%)	**0.011**	92 (54.1%)	**< 0.001**
	Two doses	287 (52.1%)		311 (56.4%)		376 (68.2%)	

Chi-squared test (χ^2) had been used with a significance level (Sig.) ≤ 0.05.
Bold values in all tables refer to the statisitically signifcant values which are below 0.05.

TABLE 7 | Logistic regression of risk factors for inactivated virus vaccine side effects reported by Algerian healthcare workers ($n = 450$).

Predictor	B (SE)	Wald	AOR	CI 95%	*Sig.*
Sex: female (vs. male)	0.916 (0.234)	15.288	2.500	1.579–3.959	**< 0.001**
Age group: 31–40 yo (vs. 20–30 yo)	0.601 (0.255)	5.552	1.823	1.106–3.004	**0.018**
Age group: 41–50 yo (vs. 20–30 yo)	0.231 (0.312)	0.551	1.260	0.684–2.323	0.458
Age group: 51–60 yo (vs. 20–30 yo)	– 0.028 (0.430)	0.004	0.972	0.418–2.261	0.948
Age group: > 60 yo (vs. 20–30 yo)	0.636 (0.930)	0.468	1.890	0.305–11.692	0.494
Tobacco: smoker (vs. non-smoker)	– 0.067 (0.356)	0.036	0.935	0.466–1.877	0.850
Allergy: yes (vs. no)	1.249 (0.268)	21.666	3.487	2.061–5.901	**< 0.001**
Non-communicable disease: yes (vs. no)	0.125 (0.309)	0.163	1.133	0.618–2.078	0.686
Medications: yes (vs. no)	– 0.158 (0.280)	0.316	0.854	0.493–1.480	0.574
Previous infection: yes (vs. no)	0.864 (0.216)	16.067	2.373	1.555–3.621	**< 0.001**
Number of doses: two (vs. one)	0.312 (0.260)	1.431	1.366	0.820–2.275	0.232

Bold values refer to the statisitically signifcant values which are below 0.05.

in the mRNA-based vaccines (43). The local and systemic side effects were more prevalent after the second dose than the first dose for both inactivated and adenoviral vector vaccines, thus, confirming what was previously reported in different studies (45, 46). Contrarily, Omeish et al. 2021 in Jordan and Jeon et al. 2021 in Korea found that side effects were more frequent and more severe after the first dose (18, 47).

The most common local side effects in this study was injection site pain (39%), followed by arm pain (25.4%), and injection site swelling (2.5%) and itching (2.5%). However, these side effects emerged generally with low frequencies than previously reported, especially with the adenoviral vector vaccines, i.e., AZD1222 where injection site pain was reported with a prevalence higher than 58% (24, 27, 47–49). Similarly, a large-scale multinational study covering more than 10,000 vaccinees in the Arab countries reported that more than 58% of the participants suffered from injection site pain and swelling (50).

In our study, the local side effects generally appeared earlier among the inactivated virus group than the adenoviral vector group, and they generally resolved within the first day (38.7%) or between the first and third day (46.7%) post-vaccination in the two groups. This finding is in consistence with what Solomon et al. 2021 reported, where most of the AZD1222 recipients developed injection site pain within the first 12 h

TABLE 8 | Logistic regression of risk factors for adenoviral vector vaccine side effects reported by Algerian healthcare workers ($n = 271$).

Predictor	B (SE)	Wald	AOR	CI 95%	*Sig.*
Sex: female (vs. male)	0.917 (0.368)	6.200	2.503	1.216–5.512	**0.013**
Age group: 31–40 yo (vs. 20–30 yo)	1.576 (0.409)	14.839	4.837	2.169–10.785	**< 0.001**
Age group: 41–50 yo (vs. 20–30 yo)	1.140 (0.495)	5.300	3.127	1.185–8.254	**0.021**
Age group: 51–60 yo (vs. 20–30 yo)	2.086 (0.825)	6.393	8.054	1.598–40.580	**0.011**
Age group: > 60 yo (vs. 20–30 yo)	1.582 (1.204)	1.727	4.863	0.460–51.443	0.189
Tobacco: smoker (vs. non-smoker)	0.199 (0.501)	0.158	1.220	0.457–3.258	0.691
Allergy: yes (vs. no)	0.122 (0.438)	0.078	1.130	0.479–2.665	0.780
Non-communicable disease: yes (vs. no)	– 0.473 (0.555)	0.727	0.623	0.210–1.849	0.394
Medications: yes (vs. no)	0.606 (0.461)	1.728	1.834	0.743–4.528	0.189
Previous infection: yes (vs. no)	0.508 (0.354)	2.058	1.662	0.830–3.327	0.151
Number of Doses: two (vs. one)	0.642 (0.358)	3.213	1.901	0.942–3.836	0.073

Bold values refer to the statisitically signifcant values which are below 0.05.

post-vaccination and disappeared between the first and the third day (49).

Regarding systemic side effects, the most commonly reported ones were fatigue (34.4%), fever (28.4%), headache (24.8%) and myalgia (22.7%). These symptoms with chills and dizziness are the most common reported side effects for all available vaccines and are generally reported with higher frequency than in our study, especially for adenoviral vector vaccines. (19, 21, 24). For instance, fatigue, fever and headache were reported by 90%, 66% and 62% of vaccinated individuals in Saudi Arabia following AZD1222 (21). In the same Saudi study, it was also reported that 75% of the systemic adverse effects lasted for 1 day (21). In our study, the systemic side effects generally emerged in the first day and lasted mostly for 2 days.

Additionally, 38.1% of our participants took post-vaccination medications, mainly Paracetamol, to manage these side effects and 1.1% reported being hospitalized, thus, confirming the mildness of these side effects. In Iraq, 57.2% of the vaccinated healthcare workers took Paracetamol, especially among those vaccinated with BNT162b2 and AZD1222, and 8.7% of them sought medical care (42).

The second objective of this study was to determine the risk factors related to the emergence of post-vaccination side effects. Our results showed that sex, age, tobacco, allergy, chronic diseases, regular medications and previous infection with COVID-19 were associated with the frequency of these side effects.

Being a female increased significantly the risk of developing side effects for both inactivated virus vaccines (OR = 2.641; CI 95% = 1.780–3.919) and adenoviral vector vaccines (OR = 2.002; CI 95% = 1.113–3.601). The same observation was also reported not only for COVID-19 vaccines but also for other bacterial and viral vaccines in which females were more likely to develop side effects signs than males (19, 28, 51–53). These results are unsurprising because of the hormonal and genetic differences between males and females, leading to different immunological reactions (54). Di Resta et al. 2021 reported that the antibody titer in BNT162b2 recipients was higher in female healthcare workers, which was associated with high side effects frequency (55).

Regarding age, our results showed that the young healthcare workers (20–30 years-old) had developed less frequent local and systemic side effects than the older ones for the two vaccine groups. Moreover, the most exposed to these side effects was the category of 30–50 years old. Our results are generally in line with multiple previous studies despite some differences in age categorization. Menni et al. 2021 reported a high frequency of post-vaccination side effects following mRNA-based and adenoviral vector-based vaccines the people under 55 years old (56). Similarly, other studies found the same observation for a younger individual of <49 years (Czech Republic), (23) <45 years (Jordan), (20) <39 years (Germany), (57) <38 years (Iran), (51) and <32 years (Turkey) (28) for both inactivated virus and adenoviral vector vaccines. In addition, Klugar et al. 2021 reported that the post-vaccination side effects were more reported in younger healthcare workers who received mRNA-based vaccines, i.e., BNT162b2 and adenoviral vector vaccine, i.e. AZD1222 (24).

Our participants with chronic diseases did not develop more side effects than those without chronic diseases for the two vaccinated groups. Contrarily, allergic individuals and those taking medications regularly developed significantly more side effects than their counterparts. This result supports the observation reported by Alhazmi et al. 2021 in Saudi Arabia, while other studies found that persons with chronic conditions and regular medication are more likely to develop side effects (21, 23, 24, 27, 28). For the association between regular medications and side effects, it is imperative to deal with this finding cautiously since the reported medications are various and include antihistaminic agents, anti-diabetics, antihypertensive drugs, contraceptives, and thyroid hormones and little is known about their interaction with the different COVID-19 vaccines. In the previous studies that found a lower prevalence of side effects among people with chronic diseases, this finding was attributed to their weak immune system, which leads to a weaker immune response (46).

The history of infection with COVID-19 increased significantly the risk of developing side effects even in both vaccine groups. The same results were found in multiple previous studies for different COVID-19 vaccines, including the mRNA-based ones (23, 24, 27, 28, 50, 57). Moreover, the antibody titer after COVD-19 vaccination was higher among individuals with a past history of SARS-CoV-2 infection than those who had not been in contact with this pathogen (44). On the contrary, two Saudi Arabia studies failed to find any association between the history of COVID-19 infection and post-vaccination side effects prevalence and severity (21, 46). Nevertheless, Zare et al. 2021 found a significant association between previous infection and post-vaccination side effects prevalence in the group of Gam-COVID-Vac but not in the group of AZD1222 (58). This finding should be however interpreted cautiously since the period between the COVID-19 recovery and the date of vaccination is unknown.

Limitations

At last, this study has several limitations related to the sample selection and the survey method. The survey was conducted using convenient and snowball sampling based on an online questionnaire that could marginalize individuals without access to the internet and overrepresent younger individuals who tend to spend more time with social media. Given the increase in familywise error rate across the reported statistical analyses, lack of control can be considered one of the limitations of this study findings. Another limitation is the lower number of healthcare workers who received vector-based vaccines; this could be explained by the fact that the inactivated vaccines are the most used and the most preferred vaccines by the Algerian population, as described in previous studies.

Strengths

To the best of the authors' knowledge, this study provides the first evidence about self-reported COVID-19 vaccines side effects among the Algerian population. It also provides a cross-vaccine comparison for the inactivated virus versus adenoviral vector vaccines.

CONCLUSION

In conclusion, this is the first study that concerns COVID-19 vaccines among healthcare workers in Algeria. Results showed that local and systemic are generally more prevalent with adenoviral vector vaccines than inactivated virus vaccines. Injection site pain (39%) and arm pain (25.4%) were the most common local side effects, while fatigue (34.4%), fever (28.4%), headache (24.8%) and myalgia (22.7%) were the most reported systemic side effects. Females, allergic individuals, and those with a history of COVID-19 infection had a significantly higher risk of developing post-vaccination side effects for either inactivated virus or adenoviral vector vaccines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Natural and Life Sciences, University of Djelfa on 20 October 2021 with reference number 117/10/2021. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML: conceptualization, validation, and project administration. ML and AR: methodology and writing—original draft preparation. AR: formal analysis and supervision. ML, MR, DB, HA, and AO: investigation. JK and MK: writing—review and editing. AP and MK: funding acquisition. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Masaryk University grants no. MUNI/IGA/1104/2021 and MUNI/A/1402/2021. The INTER-EXCELLENCE grant number LTC20031 supported the work of AR, JK, AP, and MK — Toward an International Network for Evidence-based Research in Clinical Health Research in the Czech Republic.

ACKNOWLEDGMENTS

This work is dedicated to the six million who have fallen victim to COVID-19 and their families worldwide. The authors would like to thank all the participating healthcare workers.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.896343/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Public Health

ORIGINAL RESEARCH
published: 17 May 2022
doi: 10.3389/fpubh.2022.878081

Allergic Reactions After the Administration of COVID-19 Vaccines

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Specialty section:
This article was submitted to Family Medicine and Primary Care, a section of the journal Frontiers in Public Health

Received: 17 February 2022
Accepted: 26 April 2022
Published: 17 May 2022

Citation:
Bian S, Li L, Wang Z, Cui L, Xu Y, Guan K and Zhao B (2022) Allergic Reactions After the Administration of COVID-19 Vaccines. Front. Public Health 10:878081. doi: 10.3389/fpubh.2022.878081

Background: Data on allergic reactions after the administration of coronavirus disease (COVID-19) vaccines are limited. Our aim is to analyze reports of allergic reactions after COVID-19 vaccine administration.

Methods: The Vaccine Adverse Event Reporting System database was searched for reported allergic reactions after the administration of any of the COVID-19 vaccines from December 2020 to June 2021. After data mapping, the demographic and clinical characteristics of the reported cases were analyzed. Potential factors associated with anaphylaxis were evaluated using multivariable logistic regression models.

Results: In total, 14,611 cases were reported. Most cases of allergic reactions comprised women (84.6%) and occurred after the first dose of the vaccine (63.6%). Patients who experienced anaphylaxis were younger (mean age 45.11 ± 5.6 vs. 47.01 ± 6.3 years, $P < 0.001$) and had a higher prevalence of a history of allergies, allergic rhinitis, asthma, and anaphylaxis than those who did not ($P < 0.05$). A history of allergies (odds ratio (OR) 1.632, 95% confidence interval (CI) 1.467–1.816, $P < 0.001$), asthma (OR 1.908, 95%CI 1.677–2.172, $P < 0.001$), and anaphylaxis (OR 7.164, 95%CI 3.504–14.646, $P < 0.001$) were potential risk factors for anaphylaxis. Among the 8,232 patients with reported outcomes, 16 died.

Conclusions: Female predominance in allergic reaction cases after the receipt of COVID-19 vaccines was observed. Previous histories of allergies, asthma, or anaphylaxis were risk factors for anaphylaxis post-vaccination. People with these risk factors should be monitored more strictly after COVID-19 vaccination.

Keywords: allergic reaction, anaphylaxis, COVID-19 vaccine, Vaccine Adverse Event Reporting System (VAERS), vaccination

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still pandemic globally and the number of patients with coronavirus disease (COVID-19) is increasing. As of October 2021, the number of accumulated confirmed cases is approximately 235 million, with 4.8 million deaths. To date, the disease remains endemic, and the number of confirmed cases continues to increase. The development of COVID-19 vaccines has brought new hope to combat the virus. The newly updated (October 1 2021) COVID-19 vaccine tracker and landscape of the World Health Organization showed that the number of COVID-19 vaccine candidates in both clinical and pre-clinical development was 317 (1). Several COVID-19 vaccines have been approved by the United States Food and Drug Administration (FDA) for emergency use since December 2020.

The Pfizer-BioNTech (BNT162b2) vaccines against COVID-19 are mRNA-based vaccines with lipid nanoparticle-encapsulated, and encode the prefusion-stabilized full-length spike protein of SARS-CoV-2. The Moderna (mRNA-1273) vaccines are also mRNA-based vaccines. The Janssen Ad26.COV2.S vaccine comprises a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector, and encodes a stabilized full-length spike protein of SARS-CoV-2. Randomized controlled trials of these vaccines showed a low rate (0.4–0.6%) of severe side effects (2–4).

Adverse events, including allergic reactions, have been reported after administration of the first dose of a COVID-19 vaccine (5–7). However, studies on allergic reactions after large-scale administration of COVID-19 vaccines are limited. In this study, we aimed to summarize reports of allergic reactions after COVID-19 vaccine administration according to the Vaccine Adverse Event Reporting System (VAERS) database.

METHODS

Data Source and Data Mining

Data for this study were based on the VAERS database. The VAERS database is operated by the FDA and Centers for Disease Control and Prevention (CDC). It was set up in 1990, used as a vaccine safety surveillance system of the United States (internet address: https://vaers.hhs.gov). Adverse events after administration of vaccines are collected and reported to the VAERS as an early warning. These adverse events are reported by vaccine recipients, healthcare workers, and vaccine manufacturers. If the adverse events of vaccines are regarded as contraindications to further doses, vaccine manufacturers and healthcare workers are required to report the adverse events by law. With this way, the opportunity of ignoring vital and relating adverse events is reduced. All adverse events possibly related to vaccines are collected in VAERS database. However, these adverse events are not determined of clinical significance or whether are caused by the vaccine. Even though, VAERS is still of vital significance as a hypothesis-generating system with the original target of detecting adverse events possibly associated with vaccines (8, 9).

TABLE 1 | Demographic characteristics and vaccine information of cases with hypersensitivity reactions after COVID-19 vaccine reported to VAERS database.

Characteristics	Reports, n (%)
Reporting date	
December 2020	568 (3.9)
January 2021	3,454 (23.6)
February 2021	2,427 (16.6)
March 2021	3,108 (21.3)
April 2021	3,526 (24.1)
May 2021	1,020 (7.0)
June 2021	508 (3.5)
Gender of reported cases	
Male	2,230/14,440 (15.4)
Female	12,210/14,440 (84.6)
Unknown or missing	171/14,611 (1.2)
Age groups (years)	
<18	210/14,143 (1.5)
18–44	6,706/14,143 (47.4)
45–64	4,847/14,143 (34.3)
≥65	2,380/14,143 (16.8)
Unknown or missing	468/14,611 (3.2)
Vaccine producer	
Janssen	987 (6.8)
Moderna	7,525 (51.5)
Pfizer-Biontech	6,070 (41.5)
Unknown	29 (0.2)
Dosage	
First dose	9,296 (63.6)
Second dose	3,412 (23.4)
Unknown or missing	1,903 (13.0)
Onset interval (days)	
0 day	6,117 (41.9)
1 day	2,192 (15.0)
2 days	1,061 (7.3)
3–7 days	2,567 (17.6)
>7 days	2,048 (14.0)
Unknown or missing	626 (4.3)

Onset interval: the interval between the day when the vaccine administrated and the day when symptom occurred.

Several files are included in the VAERS data: VAERSDATA.CSV (contains reports and patient information), VAERSVAX.CSV (contains vaccine information), and VAERSSYMPTOMS.CSV (contains adverse event information). The file of VAERSDATA.CSV includes demographic information; past medical history; and a history of allergies (allergies to medications, food, or other products). The file of VAERSVAX.CSV includes manufacturers and providers of the vaccine. The file of VAERSSYMPTOMS.CSV includes the date when vaccines received, date when symptoms occurred, symptom description, and outcome of the reported cases. Adverse events descriptions were coded using an internationally standardized, clinically validated terminology, the preferred

TABLE 2 | Comparison of reported cases with anaphylaxis and nonanaphylaxis allergic reactions.

Characteristics	Anaphylaxis (n = 3225, 22.1%)	Nonanaphylaxis allergic reactions (n = 11386, 77.9%)	P-value
Age-year (mean±SD)	45.11 ± 5.6	47.01 ± 6.3	<0.001*
Female-n (%)	2,727/3,152 (86.5)	9,483/11,288 (84.0)	0.001*
Previous history			
Allergies†	1,770 (54.9)	5,856 (51.4)	0.001*
Allergic rhinitis	25 (0.8)	48 (0.4)	0.012*
Hay fever	4 (0.1)	12 (0.1)	1.000
Asthma	456 (14.1)	910 (8.0)	<0.001*
Anaphylaxis	31 (1.0)	13 (0.1)	<0.001*
Eczema	20 (0.6)	79 (0.7)	0.653
Chronic urticaria	4 (0.1)	9 (0.1)	0.673

*SD, standard deviation; *p < 0.05; †, Allergies to medications, food, or other products.*

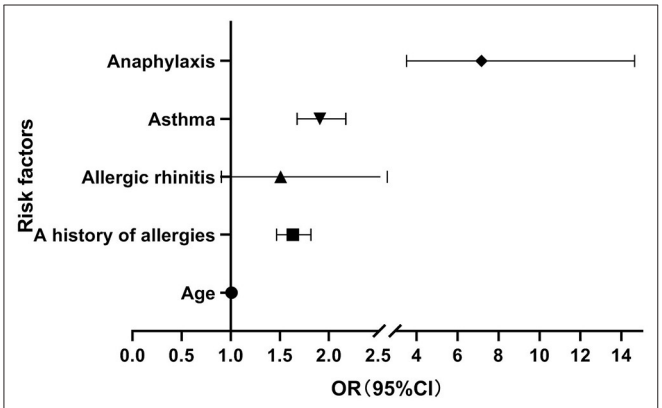

FIGURE 1 | Risk factors for anaphylaxis.

terms (PTs) of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Reports on COVID-19 vaccines in the VAERS database were included until 11 June 2021. The data were retrieved from the 2021 Zip File of VAERS Data Sets and were downloaded on 18 June 2021.

The study was approval by the Institutional Review Board of Peking Union Medical College Hospital (S-K1810).

Allergic Reactions Mapping

MedDRA Version 22.1 was used for allergic reaction mapping. The following terms were considered allergic reactions when COVID-19 vaccines were administered and these cases were included: "urticaria," "angioedema," "anaphylaxis," "anaphylactic shock," and "anaphylactic reaction." Reports were identified using the above PTs. Reports including the following PTs that possibly were consistent with the Brighton Criteria case definition for anaphylaxis were also identified: "acute urticaria," "acute angioedema," "pharyngeal swelling," "throat tightness," "dysphonia," "respiratory distress," "hypoxia," "cough," "wheezing," "dyspnea," "vomiting," "diarrhea," "hypotension," "loss of consciousness," "mental status changes," "syncope," "incontinence," "altered state of consciousness."

Anaphylaxis was defined based on the World Allergy Organization (WAO) anaphylaxis guidance (10). The available description of symptoms was reviewed to identify if the symptoms were accorded with the Brighton Collaboration case definition for anaphylaxis (11) or under the diagnosis of anaphylaxis by a physician.

Grading of systemic acute allergic reactions was based on WAO guidance (10).

Ratio of allergic reactions of different types of vaccines was compared.

This study was followed by the GATHER guidelines (12).

Data Statistical Analysis

Descriptive analysis was used to describe the clinical and demographic characteristics of patients with acute allergic reactions after COVID-19 vaccine immunization in the VAERS database. Data of normal distribution are expressed as mean±standard deviation (SD), and data of non-normal distribution are expressed as median and interquartile range (IQR). Continuous and categorical variables were compared using the independent samples t-test and Pearson $\chi 2$ test or Fisher's exact probability test, respectively. Non-parametric tests were used for non-normally distributed data. Potential factors associated with anaphylaxis were evaluated using multivariable logistic regression models. $P < 0.05$, with 95% confidence intervals (CI), indicated statistical significance. Statistical analysis was conducted using SPSS 22.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Characteristics of Cases With Allergic Reactions

A total of 14,611 cases were reported, with the highest in April 2021(3,526, 24.1%). Most cases of allergic reactions were of women (84.6%), comprised the 18–44-year age group (47.4%), had allergic reactions after the first dose of COVID-19 vaccination (63.6%), and occurred on the day of vaccine administration (41.9%) (**Table 1**).

Comparison of Cases With Anaphylaxis and Non-anaphylaxis Allergic Reactions

Among the 14,611 reported cases, 3,225 (22.1%) were of anaphylaxis. Most were skin allergic reactions (77.9%), with no other organs involved. Patients with anaphylaxis were younger (45.11 ± 5.6 vs. 47.01 ± 6.3 years, $P < 0.001$); more likely to be women (86.5 vs. 84.0%, $P = 0.001$); and more likely to have a history of allergies, allergic rhinitis, asthma, or anaphylaxis (P<0.05) than those without anaphylaxis (**Table 2**).

TABLE 3 | Grading of systemic allergic reactions according to the WAO systemic allergic reaction grading system.

	Reports (*n*)
Grade 1–2	10,141
Grade 3–4	2,315
Pharyngeal swelling	392
Throat tightness	528
Dysphonia	126
Respiratory distress	36
Hypoxia	13
Cough	299
Wheezing	222
Dyspnoea	1,138
Vomiting	344
Diarrhea	273
Grade 5	230
Hypotension	66
Loss of consciousness	85
Mental status changes	4
Syncope	91
Incontinence	2
Altered state of consciousness	5
NA	680

NA, Not available as no specific description of symptoms.

Among cases with anaphylaxis reported, 256 cases (7.9%), 1,323 cases (41.0%), and 1,636 cases (50.7%) received Janssen Ad26.COV2.S, mRNA-1273, and BNT162b2 vaccine, respectively. Among cases with non-anaphylaxis, 731cases (6.4%), 6,202 cases (54.5%), and 4,434 cases (38.9%) received Janssen Ad26.COV2.S, mRNA-1273, and BNT162b2vaccine, respectively. The differences were all significant ($p < 0.001$).

Risk Factors for Anaphylaxis

Age and a history of allergies, allergic rhinitis, asthma, and anaphylaxis were included in the logistic regression analysis. A history of allergies (OR 1.632, 95%CI 1.467–1.816, $P < 0.001$), asthma (OR 1.908, 95%CI 1.677–2.172, $P < 0.001$), and anaphylaxis (OR 7.164, 95%CI 3.504–14.646, $P<0.001$) were potential risk factors for anaphylaxis after vaccination. Allergic rhinitis was not a risk factor (OR 1.508, 95%CI 0.904–2.515, $P = 0.115$). A history of anaphylaxis had the largest OR (**Figure 1**).

Grading of Reported Systemic Allergic Reactions

Among the cases with allergic reactions, 10,141 (69.4%) had grade 1 allergic reactions with only generalized urticaria, 2,315 (15.8%) had grades 3–4 allergic reactions with respiratory and/or digestive tract involvement, and 230 (1.6%) had grade 5 allergic reactions with anaphylactic shock. There was no available description of symptoms for the 680 cases only reported as anaphylaxis (**Table 3**).

Outcome of Patients With Hypersensitivity Reactions

Among the 8,232 patients with reported outcomes, 16 died, 404 had life-threatening reactions, 3,185 visited an emergency room, 442 were hospitalized, and 52 were disabled. The median number of hospitalized days was 2.0 (IQR 1.0–3.0) days. At the time of reporting to VAERS, 39.8% of the patients had recovered and 39.0% had not recovered (**Table 4**). Among the 16 patients who died, 11 (68.8%) had grade 5 allergic reactions (**Supplemental Table 1**), and the other five were unavailable to undergo grading.

DISCUSSION

We conducted a study on allergic reactions after COVID-19 vaccination as a complement to clinical trials. In this study, we summarized the characteristics of cases with allergic reactions, risk factors for anaphylaxis, and prognosis of patients with allergic reactions.

Immunologically mediated allergic reactions can cause various manifestations ranging from skin disorders to life-threatening systemic reactions. The allergic reactions caused by vaccines can be the following pathophysiologic mechanisms. They can be caused by activation of mast cells via interaction with immunoglobin E (IgE) antibodies. Activation of the complement system can lead to Non-IgE-mediated mast cell degranulation. Direct activation of the Mas-related G protein-coupled receptor X2 can also cause allergic reactions. Type IV hypersensitivity is cell-mediated and generally cause delayed reactions (13, 14).

In this study, 84.6% of the patients with allergic reactions were women. An early study reported of 21 patients who were diagnosed of anaphylaxis after administration of Pfizer-BioNTech COVID-19 vaccine. It also indicated a female predominance (7). Studies that summarized allergic reactions after the administration of other vaccines also reported a female predominance (13). It is also possible that a greater proportion of allergic reactions in females partly because a greater proportion of vaccines was administered to females than to males. However, whether the sex difference in the development of post-vaccination hypersensitivity reactions was due to the function of sex hormones or other elements remains unknown.

More than half of the reactions occurred after the first vaccination dose, highlighting the importance of monitoring people who receive the first dose of the COVID-19 vaccine. Another study about the adverse effects following immunization also showed that 79.68% of adverse effects occurred after the first dose (9). However, in a recent study of the safety of mRNA vaccines showed over half participants reported local and systemic reactogenicity more frequently after dose two than after dose one (15). Maybe longer observations are needed to confirm this.

Although differences were found among different vaccines of allergic reactions reported, this only represent the difference of reports to the VAERS. As the total number of people received different vaccines was unknown in this database, we couldn't know the ratio of allergic reactions among different vaccines.

TABLE 4 | Outcome of cases with hypersensitivity reactions.

	Total N	Recovered-*N* (%)	Not recovered-*N* (%)	Unknown-*N* (%)
Total	8,232	3,099 (37.6)	3,305 (40.1)	1,828 (22.2)
Clinic visit	4,133	1,351 (32.7)	2,067 (50.0)	715 (17.3)
ER visit	3,185	1,384 (43.5)	881 (27.7)	920 (28.9)
Death	16	0	16 (100.0)	0
Life-threatening	404	199 (49.3)	135 (33.4)	70 (17.3)
Hospitalized	442	158 (35.7)	169 (38.2)	115 (26.0)
Disabled	52	7 (13.5)	37 (71.2)	8 (15.4)

ER, emergency room, N: number.

Past histories of allergies; allergic rhinitis; asthma; and anaphylaxis were more common in patients with anaphylaxis than in those without anaphylaxis. Further logistic regression showed that a history of allergies; asthma; and anaphylaxis were risk factors for anaphylaxis post-COVID-19 vaccination. Other studies have also reported a high proportion of patients with a history of allergies in cases of anaphylaxis. According to a previous study of 21 cases of anaphylaxis after the administration of Pfizer-BioNTech mRNA vaccine, 17 had a past history of hypersensitivity reactions and seven had a past history of anaphylaxis (16). In a subsequent report of 10 cases of anaphylaxis after receiving the first dose of the Moderna mRNA vaccine until 10 January 2021, nine had a past history of hypersensitivity reactions and five had a past history of anaphylaxis (6). According to the American Academy of Allergy Asthma and Immunology (AAAAI) (6), approximately 30% of the general population has some kind of hypersensitivity or past histories of hypersensitivity reactions. Thus, we can see that cases with allergic reactions had a relatively higher ratio of a history of allergies than the general population. Individuals with a past history of allergies should be observed more strictly.

Of all patients, 16 (0.1%) died, of whom 68.8% had grade 5 allergic reactions with anaphylactic shock. In a previous report, 20 (95%) patients had hospital discharge or had recovery at the time of reporting adverse events to VAERS. There were no reports of deaths due to anaphylaxis after COVID-19 vaccination (16). We deduce that the vaccine was relatively safe, and only rare cases resulted in death. Healthcare workers should pay more attention to cases of anaphylactic shock with a higher risk of death.

For most conventional vaccines such as influenza vaccine, hepatitis B vaccine, the rate of anaphylaxis after receipt of the vaccine was lower than 1 per million doses (17–20). According to the Centers for Disease Control and Prevention (CDC) (https://covid.cdc.gov/covid-data-tracker/#vaccination-trends_vacctrends-total-cum), the cumulative count of total doses administered and reported to the CDC was 340,837,941 until 11 June 2021. Based on the data of reports from VAERS, the estimated rate of anaphylaxis cases was nine per million doses, and the estimated rate of allergic reactions was 42.9 per million doses. Other reports of surveillance data show the rate of anaphylaxis for the Pfizer-BioNTech vaccine is approximate one per 200,000 doses, and the rate of anaphylaxis for the Moderna vaccine is 1 per 360,000 doses. A recent report of surveillance data shows the rate of anaphylaxis for both the mRNA vaccines is approximately at 5.5 per million doses (15). And the relative risk between COVID-19 and influenza vaccines was observed for allergic reactions by another study (21). The published results of phase 1/2 clinical trial of the inactivated SARS-CoV-2 vaccine in China showed that the most common symptom was injection-site pain (13 to 21% in different dose groups). Only one case of acute hypersensitivity manifesting as urticaria was reported (1/144) in this clinical trial (22). It is not surprising that anaphylaxis has not been reported in the clinical trials as the very low incidence and the exclusion of individuals with a past history of allergic reactions. In general, the COVID-19 vaccines are safe and the risk of hypersensitivity is perhaps a little greater compared to those of traditional vaccines (23).

A cross-sectional study about side effects of Pfizer-BioNTech COVID-19 vaccine among healthcare workers showed the prevalence of urticarial was 22.2% (24). Another study of adverse events of COVID-19 vaccines in 247 healthcare workers and medical students showed the most common systemic adverse events were fatigue, headache and muscle pain, no anaphylaxis was observed (25).

COVID-19 vaccines and other vaccines, as with other medicines, have the potency to induce hypersensitivity reactions. An active component and other attached elements of the vaccines may act as antigens. However, allergic reactions are infrequently due to the components of vaccines. Egg protein, gelatin, and other additives are the known common vaccine antigens that could induce allergic reactions after receipt of vaccines. In the majority of individuals with potential hypersensitivity to the antigens of vaccines, a lot of these antigens exist in very low levels that are commonly inadequate to cause hypersensitivity reactions. However, if there is a remarkably large amount of IgE antibody in some individuals, they can in theory respond to very low levels of these antigens and undergo serious allergic reactions, even anaphylaxis (13).

Two new lipid nanoparticles are included in the Pfizer-BioNTech vaccine; one is "pegylated" (Polyethylene glycol, molecular weight 2000 Da, PEG2000). The pegylated lipid (PEG2000) was also contained in the Moderna vaccine. Polyethylene glycol (PEG) is widely used in medicinal, cosmetic, and household products. PEGs are produced through the polymerization of ethyleneoxide, leading to PEG polymers with different molecular weight and chain length (26). Some cases of immediate-type hypersensitivity to PEGs have been reported (26, 27). PEG allergy is uncommon, and allergic reactions to PEG reported in previous published papers are owing to PEGs with high molecular weight. PEGs with low molecular weight are widely used in a lot of household products. Allergic reactions are unusually caused by these low molecular weight PEGs (26). In a previous study of patients with a past history of anaphylaxis caused by PEGs, they were performed for IgE antibodies to PEG and some

had positive results (28). However, the mechanism of PEG allergy still remains indefinite. In the international consensus of recommended evaluation and management COVID-19 vaccines that recently published, for patients with a past history of a serious hypersensitivity reaction, including anaphylaxis, to a COVID-19 vaccine or its excipients, the evidence suggests against *in vitro* test or routine skin test with COVID-19 vaccines or its excipients performed by the clinician for the purpose of vaccine withholding, except for researches. The reason is that the sensitivity and specificity of the *in vitro* or skin tests in predicting serious hypersensitivity reactions such as anaphylactic reactions to COVID-19 vaccines is unclear (29). Future studies are needed to further identify the mechanism of allergy to COVID-19 vaccines and to develop efficient testing methods.

As patients may consult allergists to get additional information prior to vaccination, a suggested approach provided a framework and guidance for practicing allergists. Physicians of allergy should plan for the main population health challenges: making sure that people with high risk of allergic reactions are suitably notified and given enough support to receive the COVID-19 vaccines (30).

There are some limitations to this study. First, we can only retrospectively obtain information from the symptoms reported, and the quality and completeness of information submitted by VAERS reporters vary widely, making the assessment of causality challenging. Second, reporting biases may exist in the VAERS, and over-reporting or under-reporting may exist. Third, the accurate incidence rates of allergic reactions cannot be calculated as the total number of vaccines administered, and the number administered for each vaccine is not mentioned on the VAERS database.

In conclusion, we conducted a large sample study of allergic reactions after COVID-19 vaccination based on the VAERS database. We found a female predominance in the allergic reaction cases. A history of allergies; asthma; and anaphylaxis were risk factors for anaphylaxis post-COVID-19 vaccination. People with these risk factors should be monitored more strictly after COVID-19 vaccination.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Peking Union Medical College Hospital. Written informed consent for participation was not provided by the participants' legal guardians/next of kin because this study was based on the Vaccine Adverse Event Reporting System (VAERS) database which publicly available and no potentially identifiable human image or data in the database.

AUTHOR CONTRIBUTIONS

KG and BZ conceived the work and edited the manuscript. SB did statistical analysis of the data and wrote the manuscript. LL, ZW, LC, and YX edited the manuscript. BZ conducted data mining in the VAERS database. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded by the National Natural Science Foundation of China (Funding Number: 82070033).

ACKNOWLEDGMENTS

We give our thanks to Editage (www.editage.cn) for polishing English language.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.878081/full#supplementary-material

Supplemental Table 1 | Features of the 11 death cases with grade 5 anaphylaxis.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
published: 27 May 2022
doi: 10.3389/fpubh.2022.907652

Generalized Edema and Pseudothrombocytopenia After ChAdOx1 nCoV-19 COVID-19 Vaccination: A Case Report

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Reports of side effects of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are increasing worldwide. Capillary leak syndrome and vaccine-induced immune thrombotic thrombocytopenia are very rare but life-threatening adverse events that should be identified early and treated. However, isolated thrombocytopenia can indicate pseudothrombocytopenia. In certain people, ethylenediaminetetraacetic acid (EDTA) induces an *in vitro* platelet aggregation, resulting in misleading underestimation of platelet counts. It is essential to recognize pseudothrombocytopenia to prevent diagnostic errors, overtreatment, anxiety, and unnecessary invasive procedures. We present a case who developed generalized edema and persistent pseudothrombocytopenia after the first dose of the ChAdOx1 nCoV-19 vaccine (AstraZeneca).

Keywords: generalized edema, pseudothrombocytopenia, spurious thrombocytopenia, COVID-19 vaccine safety, vaccine-induced pseudothrombocytopenia

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Infectious Diseases–Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: *07 April 2022*
Accepted: *06 May 2022*
Published: *27 May 2022*

Citation:
Bokel J, Mendes-de-Almeida DP, Martins-Gonçalves R, Palhinha L, Vizzoni AG, Correa DF, Brandão LGP, Bozza PT and Grinsztejn B (2022) Generalized Edema and Pseudothrombocytopenia After ChAdOx1 nCoV-19 COVID-19 Vaccination: A Case Report. Front. Public Health 10:907652. doi: 10.3389/fpubh.2022.907652

INTRODUCTION

Side effects of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been increasingly reported worldwide. Systemic capillary leak syndrome (SCLS), a cause of edema after vaccination, is an extremely rare condition caused by fluid leak from small blood vessels mainly in individuals with a previous history of this syndrome.[1] Causes of thrombocytopenia following vaccination can have a broad clinical spectrum, ranging from asymptomatic laboratory findings to catastrophic events. Adenovirus vectoral vaccines were associated with vaccine-induced immune thrombotic thrombocytopenia (VITT), a rare but life-threatening adverse event that occurs 5–30 days after vaccination, most commonly after the first dose (1). It is clinically manifested by thrombosis in atypical sites, such as cerebral venous sinus or splanchnic vessels, thrombocytopenia, strikingly high D-dimer levels, and positive anti-PF4 ELISA

[1] Available online at: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#annex-2-glossary

antibodies (2). Once VITT diagnosis is suspected, prompt treatment with immunoglobulin, non-heparin anticoagulation, and in some instances, corticosteroids, plasma exchange, and fibrinogen replacement should be administered (2). However, isolated thrombocytopenia after vaccination can indicate more frequent conditions, such as immune thrombocytopenic purpura (ITP) (3) or pseudothrombocytopenia. Recently, a case was reported of transient pseudothrombocytopenia (VIP) after Ad26.COV2.S vaccination (4).

Platelet counts are usually determined by automated hematologic analyzers using ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood specimens in routine clinical care. In rare cases, EDTA induces time- and temperature-dependent *in vitro* platelet aggregation, resulting in platelet count underestimation known as pseudothrombocytopenia or spurious thrombocytopenia. Although it occurs most often in EDTA–anticoagulated blood, other anticoagulants have also been implicated (5). Mainly due to the presence of EDTA-dependent antiplatelet antibodies, it is a relatively common laboratory finding in thrombocytopenia investigation and can lead to diagnostic errors, overtreatment, anxiety, unnecessary invasive testing, or surgery (splenectomy). It does not encompass platelet number or function abnormalities and can be readily missed if not considered in the differential diagnosis.

Herein we present a clinical case of generalized edema and persistent pseudothrombocytopenia after the first dose of the ChAdOx1 nCoV-19 vaccine (AstraZeneca), with immunophenotypical platelet characterization.

CASE DESCRIPTION

A 46-years-old white female, smoker with pulmonary emphysema, sought medical consultation in mid-February 2021 after presenting progressive face and lower limbs edema (**Figure 1A**). She had received the first ChAdOx1 nCoV-19 vaccine dose 12 days before symptoms started, on January 29. She was admitted for investigation in a general hospital named Hospital Duque de Caxias, in Rio de Janeiro. During hospitalization, despite generalized edema, the patient had normal blood pressure (100 × 80 mmHg), no evidence of hemoconcentration (hemoglobin 13.9 g/dL, hematocrit 37.4%), normal liver (total protein 7.5 g/dL, albumin 4.5 g/dL, AST 19 U/L, ALT 18 U/L) and renal functions (creatinine 1.10 mg/dL, urea 33 mg/dL) and her urine sample showed no abnormalities. Arterial and venous doppler of the lower limbs ruled out thrombosis. There was no evidence of rheumatologic disorder (negative antinuclear factor), and her serologies were negative for dengue (IgM), syphilis, HIV, hepatitis C, and hepatitis B infections. She presented an isolated low platelet count (36×10^9/L- reference $150–450 \times 10^9$/L) in the automated analyzer, and subsequent counts confirmed this finding. As there was no evidence of bleeding or other life-threatening disorder she was discharged and oriented to continue investigation as an outpatient from the hospital. For comparison, the patient had normal platelet levels documented on a blood count done 1 month before the vaccination in December 2020 and had no blood count done in January 2021. Despite the absence of hemorrhagic symptoms, the assistant physician from the general hospital suspected vaccine-induced ITP and prescribed a course of corticosteroids in March 2021. After 1 month of prednisone 20 mg once a day, she persisted with low platelet count (45×10^9/L platelets), had no significant symptoms, and therapy was discontinued. The edema had progressive spontaneous resolution throughout the investigation, with complete remission after 4 months. In May 2021, she was diagnosed with acute COVID-19 infection and had only mild symptoms, with no need for hospitalization. In July 2021 the patient had no symptoms, maintained the low platelet count and was referenced to Fundação Oswaldo Cruz (Fiocruz/RJ) institute for further investigation. Five months after symptoms onset, she had a consultation with a Fiocruz's hematologist. Blood count using citrate anticoagulant showed normal platelet count, and peripheral blood smear of the EDTA sample showed platelet aggregates (**Figure 1B**). One month later, the blood counts on EDTA and citrate confirmed these findings (**Figure 1C**), and pseudothrombocytopenia was diagnosed. She received the BNT162b2 vaccine (Pfizer–BioNTech) as a second dose in October 2021 (9 months after the first one) and reported no symptoms. In November 2021, blood samples from the patient and two age- and sex-matched healthy donors were collected into Acid-Citrate-Dextrose (ACD) and EDTA; platelet activation, hyperreactivity, and aggregation with leukocytes were evaluated through flow cytometry. Both ACD and EDTA samples showed no changes in platelet activation, as demonstrated by CD62p and CD63 surface expression (**Figures 2A,B**, respectively). Furthermore, no alterations were observed regarding platelet aggregation with neutrophils (**Figure 2C**) or monocytes (**Figure 2D**). However, isolated platelets from the patient's EDTA sample, but not ACD, presented hyperreactivity compared to healthy donors, as shown by CD62p and CD63 mean fluorescence intensity (MFI) in platelets stimulated with thrombin (**Figures 2E,F**). Of note, after centrifugation, the platelets pellet from the patient's EDTA blood sample, but not from healthy donors, was much more challenging to resuspend than the ACD sample, as expected due to increased platelet aggregation with EDTA. Platelet concentrations after resuspension were the same in patients' EDTA and ACD samples (10^9/mL, data not shown) and in healthy donor samples. The decreased platelet counts in the patient's EDTA samples obtained by automated counting may not account for the enhanced platelet aggregation, thus leading to underestimating platelet counts mistakenly indicating thrombocytopenia. Although it is standard practice to analyze the blood smear and repeat the platelet count using another anticoagulant it was not done in her initial care resulting in a diagnostic failure. Pseudothrombocytopenia was diagnosed only when she was referred to a hematologist specialist, 5 months later. The patient maintained pseudothrombocytopenia when EDTA was used with no clinical findings until February 2022.

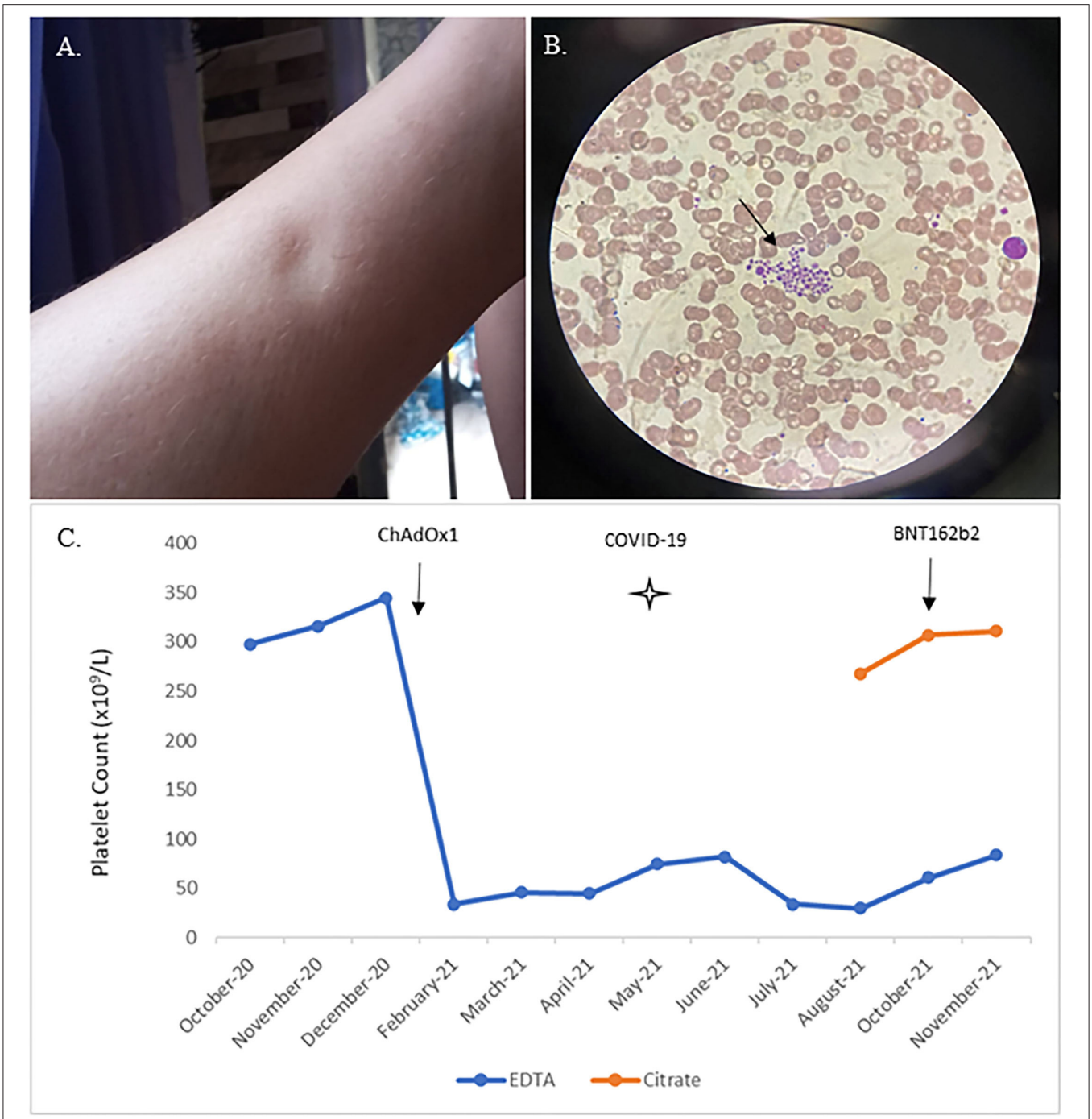

FIGURE 1 | Skin edema, platelet aggregates on the EDTA blood smear, and platelet count evolution in EDTA and citrate anticoagulated blood. Lower limb skin edema in patient 12 days after ChAdOx1 nCoV-19 vaccination, with spontaneous resolution after four months **(A)**; Peripheral blood smear from the EDTA-anticoagulated patient's blood showing platelet aggregates (arrow) **(B)**; Platelet counts in EDTA anticoagulation are shown in blue; platelet counts in citrate anticoagulation are shown in orange starting in August 2021. COVID-19 infection is indicated by a star, ChAdOx1 nCoV-19 and BNT162b2 vaccinations are shown by black arrow s **(C)**.

DISCUSSION

The pathophysiology of pseudothrombocytopenia is not clearly defined, but it is suggested that an immune-mediated mechanism accounts for platelet clumping. In the presence of EDTA *in vitro*, cryptic epitopes of the glycoprotein IIb/IIIa complex on the platelet membrane suffer a conformational change and are exposed to acquired or naturally occurring autoantibodies leading to the formation of immune complexes and platelet agglutination. This phenomenon often occurs at low temperatures and has no other laboratory or clinical thrombocytopenia manifestations. Pseudothrombocytopenia

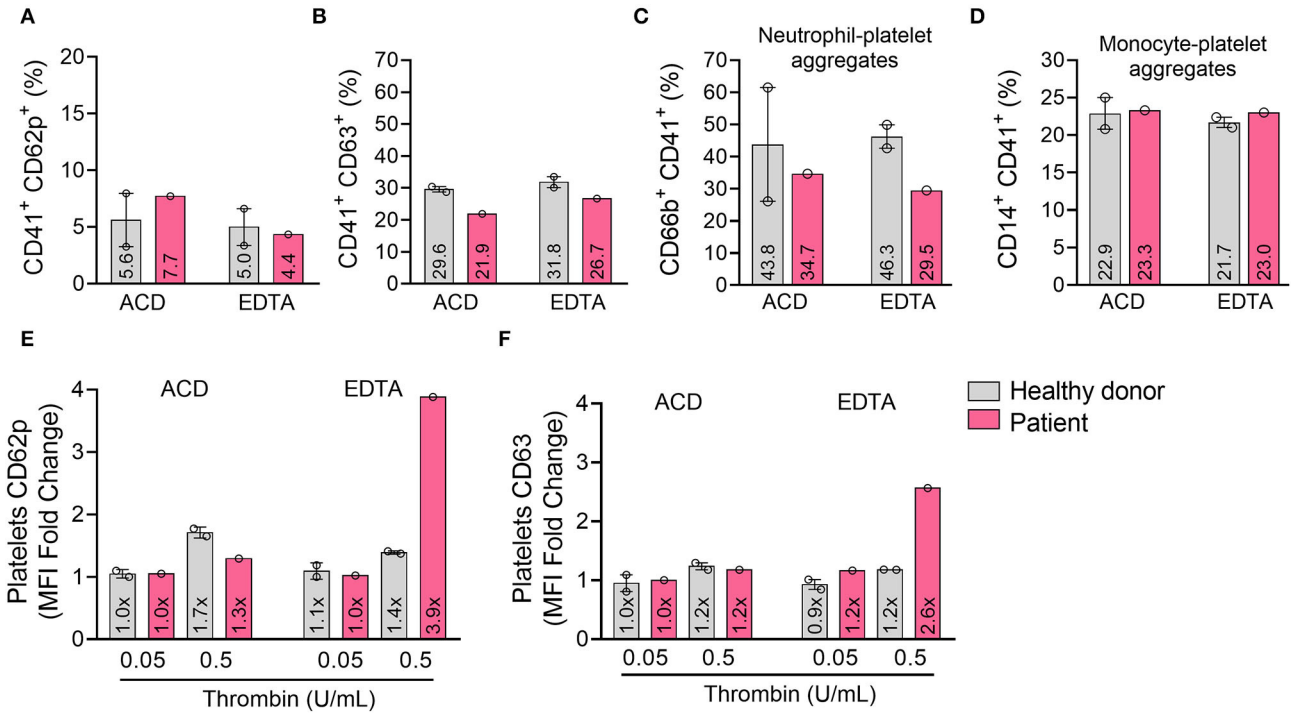

FIGURE 2 | EDTA induced platelets hyperreactivity but did not increase basal activity or heterotypic aggregation with leukocytes. Platelets were isolated from the patient and healthy donors' fresh blood collected with ACD or EDTA and analyzed by flow cytometry for surface expression of CD62p **(A)** and CD63 **(B)**. Platelet-leukocyte aggregates were assessed by the percentage of $CD41^+$ platelets among neutrophils ($CD66b^+$) **(C)**, total monocytes ($CD14^+$) **(D)**, Platelet reactivity was analyzed by the mean fluorescence intensity (MFI) of CD62p **(E)** and CD63 **(F)** after stimulation with thrombin at 0.05 and 0.5 U/mL. Bars represent the mean ± SEM, and each dot represents one individual. ACD: acid-citrate-dextrose.

could also be related to increased platelet–leukocyte aggregation, characterized by platelet rosetting mainly around monocytes and neutrophils and monocytes, less frequently observed around lymphocytes (6). However, platelet–leukocyte aggregation was ruled out in the blood smear and the flow cytometry analysis of our patient. Alternatively, proteins from alpha granules or thrombospondin expressed on the platelet membrane may cause adhesion to neutrophils and trigger a more generalized agglutination cascade, forming large aggregates. This mechanism is rare and specific for EDTA anticoagulant (6).

EDTA-pseudothrombocytopenia incidence is ∼0.07–0.2% in hospitalized patients, increasing to 15.3% in patients investigated for isolated thrombocytopenia (6). Risk factors for pseudothrombocytopenia include hospitalization, males over 50 years old, malignant neoplasms, chronic liver disease, infection, pregnancy, autoimmune diseases, and thrombotic and cardiovascular diseases, heparin-induced thrombocytopenia, surgical settings, post-stem cell transplantation, treatment with valproic acid, insulin, antibiotics, low-molecular-weight heparin, chemotherapeutic agents such as sunitinib, and lately COVID-19 (6–8). EDTA-pseudothrombocytopenia has also been observed in healthy persons (5).

Pseudothrombocytopenia can typically be identified by collecting information about the patient's history of previous abnormalities on complete blood count or signs and symptoms of platelet disorder; reviewing the peripheral blood smear in the EDTA sample; confirming the finding using a different anticoagulant than EDTA for blood collection, or maintaining the sample at around 37°C before testing (9). Rapid analysis of EDTA blood specimens is advocated to lower the chances of error due to time-dependent falls in platelet counts (6). Because of initial diagnostic failure, our patient experienced iatrogenic immunosuppressive treatment and an immunization delay. As no other cause for the pseudothrombocytopenia was identified, and the EDTA platelet levels became low after ChAdOx1 nCoV-19 vaccine exposure, we hypothesized that this effect was related to the vaccine.

EDTA used as a stabilizer in the ChAdOx1 nCoV-19 vaccine also increases vascular permeability (10) and can cause SCLS. Classical criteria for diagnosing SCLS are diffuse edema, hypoalbuminemia, hemoconcentration, and arterial hypotension. Clinically it can vary from mild symptoms, like edema, to more severe presentations as hypotension and hypovolemic shock (11). The European Medicines Agency safety committee determined that the product information should add SCLS as a vaccine side effect on June 11th 2021 and released a warning to raise awareness among healthcare professionals and patients (12). Despite

the edema, our patient did not fulfill the formal criteria for SCLS.

In conclusion, we strongly recommend excluding pseudothrombocytopenia, particularly before further investigation of thrombocytopenia and before starting treatment. We illustrated the first VIP case following a first dose of the COVID-19 ChAdOx1 nCoV-19 vaccine associated with generalized edema. We also presented the longstanding of this diagnosis and the immunophenotypical platelet findings that corroborate the *in vitro* phenomenon. It is essential to perform a comprehensive evaluation of thrombocytopenia following vaccination. Our patient was submitted to an extensive laboratory analysis, missed workdays to attend medical consultations, was put on medical license throughout the diagnostic procedures, had her COVID-19 immunization delayed and was unnecessary medicated with a course of corticosteroids. This falsely low automated platelet count is not associated with a clinical bleeding tendency and does not have any therapeutic consequences, but when misdiagnosed, it can be harmful to the patient.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Review Board of the Evandro Chagas National Institute of Infectious Diseases (#54561321.0.0000.5262). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JB, DPMA, PTB, and BG designed the study. JB and DFC attended the patient. DPMA and AGV analyzed the clinical data. RM-G and LGPB performed the platelet assay. JB, DPMA, RM-G, and LP wrote the manuscript. LGPB, BG, and PTB revised the manuscript and supervised the study. All authors have seen and approved the manuscript and its submission.

FUNDING

This paper publication was supported by the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ).

ACKNOWLEDGMENTS

We thank the patient for their informed consent, Wagner Rangoni for sample preparation, and Dr. Valdiléa Veloso for technical support.

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ORIGINAL RESEARCH
published: 01 June 2022
doi: 10.3389/fpubh.2022.883113

No Differences in Wound Healing and Scar Formation Were Observed in Patients With Different COVID-19 Vaccination Intervals

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OPEN ACCESS

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Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: *24 February 2022*
Accepted: *29 April 2022*
Published: *01 June 2022*

Citation:
Dong C, Yu Z, Quan X, Wei S, Wang J and Ma X (2022) No Differences in Wound Healing and Scar Formation Were Observed in Patients With Different COVID-19 Vaccination Intervals. Front. Public Health 10:883113. doi: 10.3389/fpubh.2022.883113

Background: Safety concerns are one of the most common reasons for COVID-19 vaccination refusal. In the field of plastic and reconstructive surgery, whether COVID-19 vaccination influences wound healing and scar formation is worthy of special attention.

Methods: In this study, patients with adult trauma with subcutaneous sutures placed by a single plastic surgeon in a single center were included. The vaccination interval was defined as the interval between the last dose of the COVID-19 vaccine and when surgical sutures were introduced. The patients were categorized by vaccination interval into three groups of <1, 1–3, and ≥ 3 months. Wound healing and scar formation were rated according to the Wound Assessment Inventory (WAI) and Patient and Observer Scar Assessment Scale (POSAS) in the groups at 7 days and after a 3-month follow-up.

Results: All total and individual scores of WAI and POSAS were not significantly different among the groups.

Conclusion: No differences in wound healing and scar formation were observed in patients with different COVID-19 vaccination intervals. Thus, it is not necessary to postpone COVID-19 vaccination, as the vaccine does not affect wound healing and scar formation in patients undergoing surgery. This study aimed to eliminate concerns and hesitancy in receiving the COVID-19 vaccine.

Keywords: vaccine hesitancy, COVID-19, wound healing, scar formation, vaccination, COVID-19 vaccine, plastic surgery

INTRODUCTION

Vaccines designed to elicit protective immune responses remain key for containing the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). However, global surveys have revealed that ∼30% of participants were hesitant about COVID-19 vaccination (2, 3). Doctors also lack adequate evidence to address vaccine hesitancy, and many doctors are vaccine-hesitant themselves (4, 5). Hesitancy is primarily driven by vaccine safety concerns (6). Although the overall safety of COVID-19 vaccines has been demonstrated by placebo-controlled trials (7), few studies on whether a specific physiological state or pathological process is changed after the COVID-19 vaccination have been published (8–10).

Research on wound healing and scar formation is highly valued by plastic surgeons (11, 12). In our daily clinical practice, concerns about vaccine safety are manifested in the thought that

vaccination may be detrimental to wound healing and result in scar formation after surgery, which is a common concern of patients we have treated during the pandemic. Until now, no evidence-based study has been published regarding how soon patients can undergo plastic and aesthetic surgery after receiving the COVID-19 vaccine and whether the COVID-19 vaccine affects wound healing and scar formation. Therefore, in this study, differences in wound healing and scar formation were investigated in patients with trauma with subcutaneous sutures after different COVID-19 vaccination intervals.

MATERIALS AND METHODS

Study Design

This study was performed in accordance with the ethical standards of our institution and the 1964 Declaration of Helsinki. This was a retrospective study performed on a consecutive cohort from June 2021 to October 2021 in a single center. Inclusion criteria included patients who (1) were 18–60 years of age, (2) were diagnosed with simple and open skin injuries, who received a full course of COVID-19 vaccination, and (3) underwent subcutaneous suture placement by a single plastic surgeon (CD). Exclusion criteria included patients who (1) were vaccinated after suture placement or (2) were lost to follow-up. The vaccination interval was defined as an interval between the last dose of the COVID-19 vaccine and the surgical suture placement. Patients were categorized by vaccination interval into three groups: (1) <1, (2) ≥ 1 and <3, and (3) ≥ 3 months according to the appearance of vaccine side effects and changes in neutralizing antibodies. Most cutaneous reactions after COVID-19 vaccination lasted no more than 30 days (13). At the 3–6-month interval, the level of neutralizing antibodies against COVID-19 plateaued and gradually decreased (14, 15). Surgical wound healing of the patients was assessed according to the Wound Assessment Inventory (WAI) at 7 days. The WAI has good validity and was designed to visually judge the apparent degree of soft tissue healing in post-surgical incision wounds according to three criteria: edema, erythema, and exudates (16). Scar formation was evaluated according to the Patient and Observer Scar Assessment Scale (POSAS) after a 3-month follow-up. POSAS is a reliable and feasible tool for scar assessment that includes both a patient and an observer scar assessment scale (17). Moreover, vaccination time, doses, and type of COVID-19 vaccine were recorded preoperatively and at the 3-month follow-up. The main outcomes were the scale scores of wound healing and scar formation. Other outcomes were complications during the 3-month follow-up, such as surgical site infection and wound dehiscence, among others.

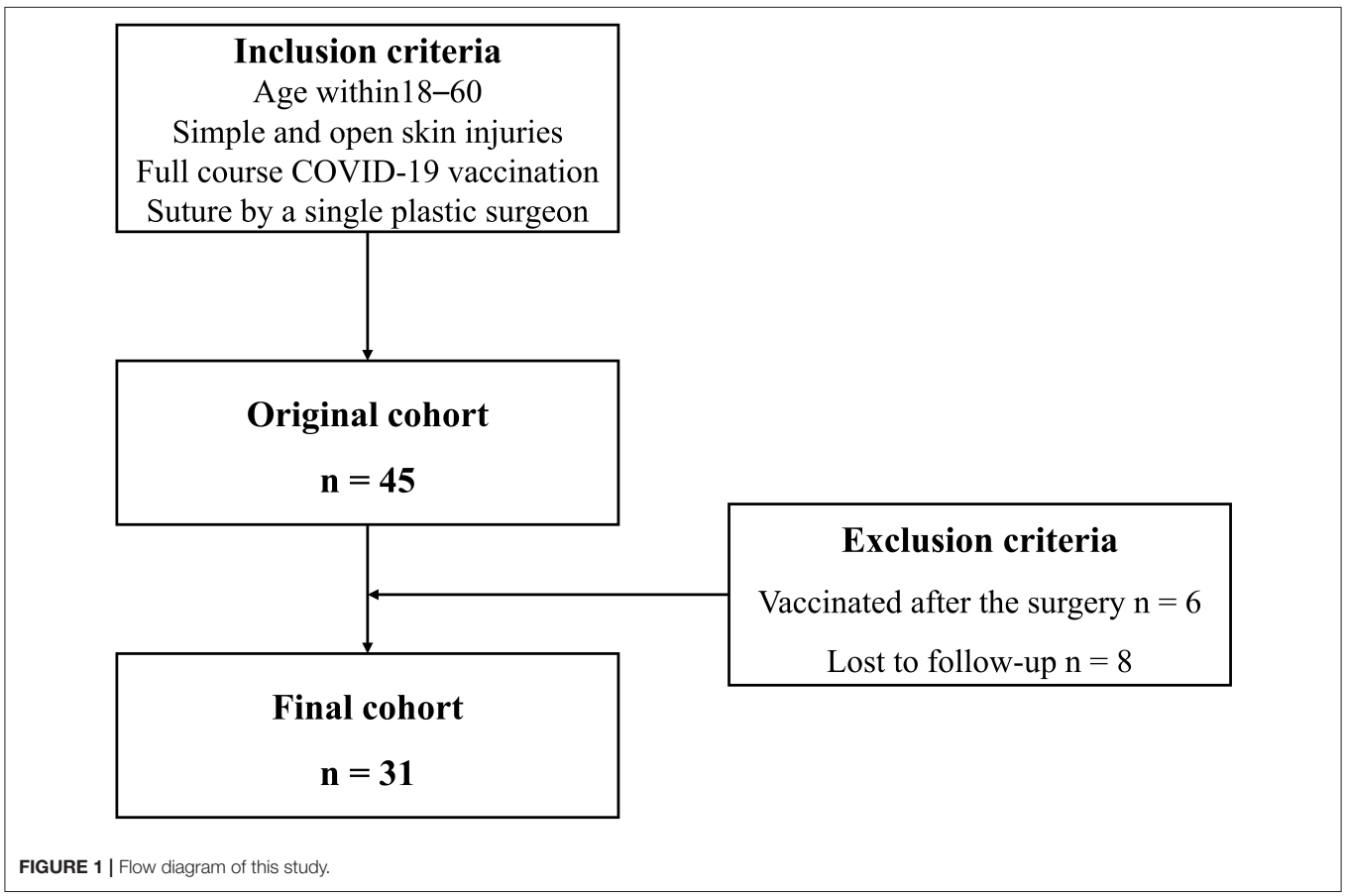

FIGURE 1 | Flow diagram of this study.

Bias Control

Selection Bias

- The cohort was consecutive during the COVID-19 pandemic.
- One surgeon performed the surgeries, which avoided the bias of different surgical techniques.
- The vaccination interval in the study was almost random because the wound sutures were unplanned surgeries, which reduced patients' and surgeons' subjective selection bias.

Information Bias

- All ratings were given independently by two plastic surgeons (XQ and SW) and were analyzed by a third person (JW).
- Clinical images were obtained after patient consent after verification by a senior author (ZY, not publicly available).

Confounding Bias

- All patients were diagnosed with simple and open skin injuries, which eliminated interference with the results by other comorbidities.
- Subgroup analyses were conducted to evaluate the effects of different COVID-19 vaccine types.

Statistical Analysis

The sample size was estimated using the following formula (18):

$$n = 2\left(\sigma \frac{z_{1-\alpha/(2\tau)+z_{1-\beta}}}{\mu_A - \mu_B}\right)$$

According to the previous publication and clinical observations, the average scores on the POSAS patient scale in groups of <1, ≥1 and <3, and ≥3 months were estimated to be 30, 28, and 20,

TABLE 1 | Patient characteristics.

Items	Group, media (IQR) or *n* (%)			Total	*p*
	<1 month (*n* = 8)	1–3 months (*n* = 12)	≥3 months (*n* = 11)		
Age, year	24 (11)	25 (11)	31(11)	26 (11)	0.261*
Gender					
Male	5 (62.5)	9 (75.0)	6 (54.5)	20 (64.5)	0.576#
Female	3 (37.5)	3 (25.0)	5 (45.5)	11 (35.5)	
Wound causes					
Fallen	5 (62.5)	4 (33.3)	8 (72.7)	17 (54.8)	0.526#
Cut	1 (12.5)	4 (33.3)	1 (9.1)	6 (19.4)	
Smashed	2 (25.0)	3 (25.0)	1 (9.1)	6 (19.4)	
Bitten	–	1 (8.3)	1 (9.1)	2 (6.5)	
Wound sites					
Head & face	7 (87.5)	10 (83.3)	10 (90.9)	27 (87.1)	0.545#
Trunk	1 (12.5)	–	–	1 (3.2)	
sLimbs	–	2 (16.7)	1 (9.1)	3 (9.7)	
Wound type					
Lacerations	8 (100.0)	8 (66.7)	10 (90.9)	26 (83.9)	0.201#
Avulsions	–	3 (25.0)	–	3 (9.7)	
Defects	–	1 (8.3)	1 (9.1)	2 (6.5)	
Wound length, cm	4 (2)	4 (2)	3 (1)	4 (2)	0.851*
Interval from injury to surgery, hr	12 (9)	14 (10)	16 (23)	14 (11)	0.369*
Surgical interval, min	35 (28)	53 (23)	45 (20)	45 (25)	0.122*
Topical silicone application					
No	3 (37.5)	5 (41.7)	4 (36.4)	12 (38.7)	1.000#
Yes	5 (62.5)	7 (58.3)	7 (63.3)	19 (61.3)	
Laser therapy					
No	8 (100.0)	12 (100.0)	10 (90.9)	30 (96.8)	0.613#
Yes	–	–	1 (9.1)	1 (3.2)	
Vaccine type					
Inactivated	5 (62.5)	12 (100.0)	6 (54.5)	23 (74.2)	0.027#
Adenovirus type 5 vector	2 (25.0)	–	4 (36.4)	6 (19.4)	
Others	1 (12.5)	–	1 (9.1)	1 (6.4)	

**Fisher's exact test; #Krusal-Wallis test; IQR, interquartile range.*

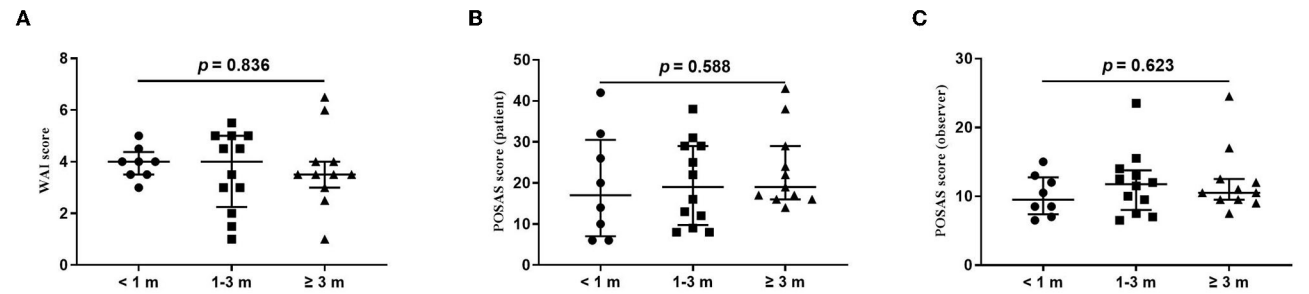

FIGURE 2 | Comparison of total score of wound assessment inventory (WAI) and patient and observer scar assessment scale (POSAS) between patients undergoing the surgical suture with different vaccination intervals. **(A)** WAI at 7 d follow-up; **(B)** POSAS patient scale at three-month follow-up; **(C)**. POSAS observer scale at three-month follow-up; vaccination interval was defined as an interval between the time of the last dose of COVID-19 vaccination and the time of surgical sutures. The numbers of patients in groups of <1 month, 1–3 months, and ≥3 months were 8, 11, and 12, respectively.

respectively (19). Also, the standard deviation (SD) of each group was 5. $\tau = 2$, $\alpha = 0.05$, and $\beta = 0.2$. Thus, 8 patients in each group and a total of 24 patients were needed at least. To account for 25% of dropouts, at least 30 patients were needed to recruit for this study. The distribution of data in this study was shown as median (interquartile range). Differences in continuous data and ranked data were evaluated by the Kruskal–Wallis test, and categorical data were evaluated by Fisher's exact test. Values of $p < 0.05$ were considered statistically significant. Analyses were conducted using SPSS Version 25 (IBM, Chicago, IL, USA) and GraphPad Prism Version 7.00 (GraphPad Prism Inc., San Diego, CA, USA).

RESULTS

Study Cohort

A total of thirty-one patients were included in the final cohort. The process of study inclusion is illustrated in the flow diagram in **Figure 1**. Details of patients' characteristics were shown in **Table 1**. None of the patient characteristics was statistically different among the three groups [<1 month ($n = 8$), 1–3 months ($n = 12$), and ≥3 months ($n = 11$)] in age, wound causes, wound sites, wound type, wound length, topical silicone application, and laser therapy. However, in vaccine type, the proportions of inactivated vaccine in the three groups were 62.5, 100, and 54.5%, respectively ($p = .027$).

Primary and Secondary Outcomes

The wound healing and scar formation assessments by the WAI and POSAS are illustrated in **Figure 2**. The results of each item for the WAI and POSAS scales are illustrated in **Figures 3–5**. All total and individual scores of the WAI and POSAS scales showed no statistically significant difference among the groups. No complications were observed in any patients.

Subgroup Analysis of Different Vaccine Types

In patients who received inactivated vaccine, no statistically significant difference was observed both in wound healing and scar formation among the three groups of <1, 1–3, and ≥3 months (WAI: $p = 0.553$; POSAS patient scale: $p = 0.399$; POSAS observer scale: $p = 0.976$). In patients who received adenovirus type 5 vector vaccine, no statistical difference was observed in wound healing or scar formation between the <1-month group and the ≥3-month group (WAI: $p = 1.000$; POSAS patient scale: $p = 1.000$; POSAS observer scale: $p = 0.533$).

DISCUSSION

The World Health Organization (WHO) has stated that "vaccine hesitancy" is one of 10 current global health threats (20). Safety concerns are one of the most common reasons for COVID-19 vaccine refusal (21). In the field of plastic and reconstructive surgery, whether COVID-19 vaccination influences wound healing and scar formation is worthy of special attention.

Dermatologic side effects and cutaneous reactions, such as local injection site reactions, morbilliform rash, pernio, pityriasis rosea, and erythema multiforme, due to the COVID-19 vaccine are very common (22). Moreover, cutaneous small-vessel vasculitis after COVID-19 vaccination has also been reported, which may aggravate these existing cutaneous injuries (23, 24). However, after comparing different vaccination intervals, no difference was found in wound healing. This is likely due to a short period, during which cutaneous reactions caused by COVID-19 vaccination occur. McMahon et al. found that local injection site reactions occurred after a median of 1 day and that delayed large local reactions occurred after a median of 7 days after vaccination (13). Wrafter et al. recommended that patients with burn injuries should be vaccinated against SARS-CoV-2 once they recovered from the acute phase of injury (25). Therefore, it is not necessary to postpone COVID-19 vaccination, as the vaccine does not affect wound healing.

Several studies have reported that Bacillus Calmette-Guérin (BCG) local scars are reactivated as a result of the COVID-19 vaccination (26–28). The interaction between angiotensin-converting enzyme 2 (ACE2) receptors and spike proteins of SARS-CoV-2 in the dermis favors a pro-inflammatory, loco-regional TH1 cascade, which promotes a $CD8^+$T cell-mediated

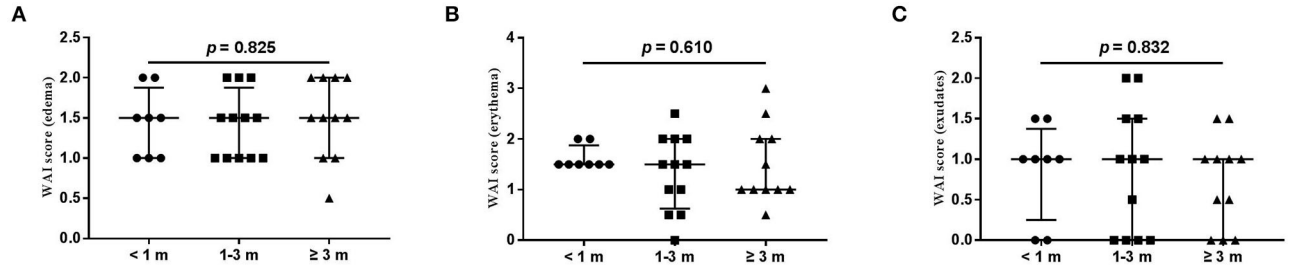

FIGURE 3 | Each item of WAI. **(A)** edema; **(B)** erythema; **(C)** exudates. Numbers of patients in groups of <1 month, 1–3 months, and ≥3 months were 8, 11, and 12, respectively.

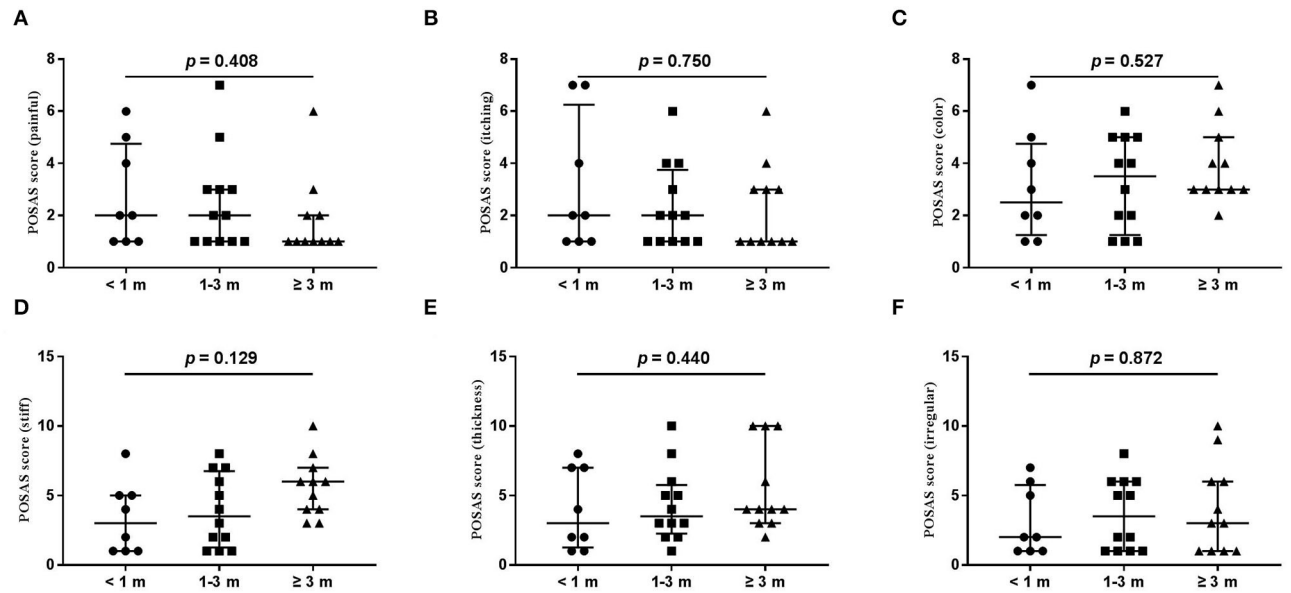

FIGURE 4 | Each item of the POSAS patient scale. **(A)** painful; **(B)** itching; **(C)** color; **(D)** stiff; **(E)** thickness; **(F)** irregular. The numbers of patients in groups of <1 month, 1–3 months, and ≥3 months were 8, 11, and 12, respectively.

reaction to incipient granulomas (29). However, no difference in scar formation among different vaccination interval groups was observed in this study. One possible reason is that the patients with scar formation are only isolated cases. Another possible reason is that the reactivation of BCG scars is attributed to vaccine-induced immune activation under T cell bystander stimulation, whereas scars caused by trauma do not exhibit a similar phenomenon (28). Besides, some viruses, such as human T-cell lymphotropic virus type 1 (HTLV-1) and human papillomavirus (HPV), can result in healing dysregulation and infective dermatitis (1, 30). Meanwhile, the COVID-19 vaccine is a type of virus vaccine. The public may be concerned that COVID-19 vaccination will cause side effects similar to viral infections mentioned above to affect wound healing and even lead to hypertrophic scar formation. However, no change in wound healing is observed in our study, possibly attributing to the fact that inactivated vaccines are the main vaccine type used in the Chinese mainland, and the immune mechanism of inactivated vaccines is the stimulation of non-pathogenic viral proteins to the immune system; this may minimize the influence of virus to the participants or patients.

Given the measures of radical debridement, necrotic tissue removal, and fine suturing, primary healing of the wounds was achieved for all patients in this study. Thus, any differences in complication rates were not compared among the groups.

This study has some limitations. First, the follow-up to determine scar formation ended at 3 months because of the widespread prevalence of booster doses on the Chinese mainland. If patients were vaccinated both pre- and post-operatively, the researchers would not have known exactly which dose affected the patients. However, this article does provide preliminary clues in the comparison of the effects of different COVID-19 vaccination intervals on early-stage wound healing and scar formation. Second, the sample size

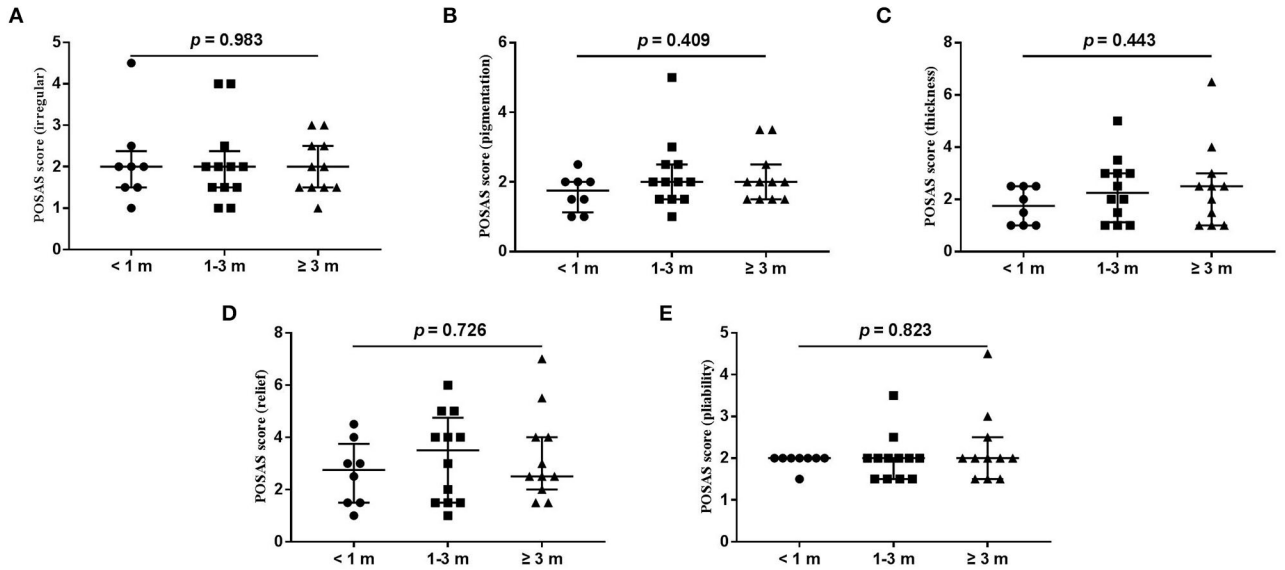

FIGURE 5 | Each item of POSAS observer scale. **(A)** vascularization; **(B)** pigmentation; **(C)** thickness; **(D)** relief; **(E)** pliability. Numbers of patients in groups of <1 month, 1–3 months, and ≥3 months were 8, 11, and 12, respectively.

is relatively small. However, all surgeries were performed by the same plastic surgeon, which enhanced comparability among the groups. Third, because the patients in this study came from a single center and were treated by a single surgeon, the conclusions may not be applicable to patients in other centers and treated by other surgeons. Fourth, this is a descriptive study, some basic conditions of patients, such as wound type, have considerable heterogeneity.

CONCLUSIONS

No differences in wound healing and scar formation were observed in patients with different COVID-19 vaccination intervals. Therefore, it is unnecessary to postpone COVID-19 vaccination in patients undergoing surgery if they are concerned that the vaccine affects wound healing and scar formation. This study is beneficial for eliminating concerns and hesitancy regarding COVID-19 vaccines.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Fourth Military Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CD: conducting the surgeries, designing the study, acquiring data, and writing the manuscript. ZY: concept of the study, designing the study, acquiring data, and writing the manuscript. XQ and SW: evaluating the scales and editing the manuscript. JW: analyzing data and editing the manuscript. XM: concept of the study, designing experiments, and writing and editing the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The first author, CD thank his wife, Qian He, and their son, Kecheng Dong, for their whole-hearted support.

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ORIGINAL RESEARCH
published: 07 June 2022
doi: 10.3389/fmed.2022.899517

Side Effects and Perceptions of COVID-19 Vaccination in Saudi Arabia: A Cross-Sectional Study

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OPEN ACCESS

Edited by:
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Reviewed by:
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Benha University, Egypt
Ahmad Sofi-Mahmudi,
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Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Medicine

Received: 18 March 2022
Accepted: 28 April 2022
Published: 07 June 2022

Citation:
Al-Hanawi MK, Keetile M, Kadasah NA, Alshareef N, Qattan AMN and Alsharqi O (2022) Side Effects and Perceptions of COVID-19 Vaccination in Saudi Arabia: A Cross-Sectional Study. Front. Med. 9:899517. doi: 10.3389/fmed.2022.899517

Background: Vaccination against any disease is critical in improving and maintaining public health. However, the overall effectiveness of a vaccine largely depends on the willingness of a population to receive it. The main aim of this study was to assess the side effects and perceptions about COVID-19 vaccines among adults following vaccination in Saudi Arabia.

Methods: An online cross-sectional survey was conducted from July 13 to July 20, 2021, among adults aged 18 years and older who had taken one or both doses of COVID-19 vaccines in Saudi Arabia. The survey included questions on socio-demographics, health behavior, vaccine type, knowledge about sources of information about COVID-19 vaccines, and perceptions and beliefs following vaccination. Bivariate and multivariable regression analyses were the major data analytic tools employed in the study.

Results: The most common vaccine side effects reported were tiredness/fatigue (52.6%), swelling (38%), fever (31.3%), headache (29.1%), and muscle pain (22.2%). In multivariable analyses, the odds of experiencing severe side effects were significantly higher among males [adjusted odds ratio (aOR) = 2.76, 95% confidence interval (CI) = 1.71–4.45, $p < 0.01$], those aged 40–49 years (aOR = 3.10, 95% CI = 1.10–8.72, $p < 0.1$), and Saudi nationals (aOR = 3.64, 95% CI = 1.58–8.38, $p < 0.05$) compared to their counterparts. The odds of believing that COVID-19 vaccines are safe in the long-term were significantly higher among men (aOR = 1.76, 95% CI = 1.16–2.65, $p < 0.01$) and among individuals who had received two doses (aOR = 1.62, 95% CI = 1.09–2.40, $p < 0.05$), and the odds of advising others to get vaccinated for COVID-19 were also significantly higher among respondents who had received two doses (aOR = 2.81, 95% CI = 1.60–4.93, $p < 0.01$) compared to their counterparts.

Conclusion: This study identified the most common COVID-19 vaccine side effects in Saudi Arabia, therefore making them predictable. This information will help reduce vaccine hesitancy as booster doses become available.

Keywords: COVID-19, perceptions, Saudi Arabia, side effects, vaccination

INTRODUCTION

The advent COVID-19 pandemic brought about enduring consequences to the health, economy and people's social lives across the globe (1). The pandemic has caused an enormous burden of illness worldwide, and several vaccines have been introduced to reduce morbidity and mortality. Moreover, the latest estimates indicate that over 20 million years of life have been lost to COVID-19 so far, and millions of new cases of COVID-19 are still being recorded every week despite the introduction of vaccines in many countries across the world (2).

Vaccination against any disease is very critical in improving and maintaining public health. Vaccines help to control the transmission of infectious diseases; however, the overall effectiveness of a vaccine largely depends on the willingness of the population to receive it (3–5). A global survey on the potential acceptance of COVID-19 vaccines showed varying acceptance rates among countries, ranging from almost 90% in China to <55% in Russia (6). In Australia (7), a study indicated that 80% of respondents generally held positive views toward COVID-19 vaccination while in Chile, a study on COVID-19 vaccine perception showed that about 91% of the sampled population were willing to be vaccinated (8). On the other hand, a study conducted in the Kingdom of Saudi Arabia (KSA) showed that only 48% of the Saudi population were willing to receive the COVID-19 vaccine (9).

Moreover, studies conducted to assess the acceptance, perceptions and attitudes of people toward COVID-19 vaccines have shown mixed results on the perceptions of people about COVID-19 vaccines and the factors influencing uptake of vaccines. Several factors have been observed to influence the uptake of vaccination, including perceptions about vaccine effectiveness and side effects, attitudes toward vaccination, perceived susceptibility to an illness, social influence and trust of the healthcare system, and knowledge and information about the vaccine (9–13). As a result, the availability of COVID-19 vaccines alone does not guarantee that people will readily receive vaccination.

Most countries across the world started the rollout of COVID-19 vaccination toward the last quarter of 2020. Consequently, it became important to examine people's willingness to get the COVID-19 vaccines. However, knowledge about people's willingness to get the COVID-19 vaccine was very limited even in developed countries. Perceptions and attitudes concerning the benefits and risks of vaccination are often premised on the claimed safety and efficacy of vaccines. Several rumors have been spread about COVID-19 vaccines since their development. These rumors have linked COVID-19 vaccines to various adverse effects such as infertility, reports of blood clots, several cases of death, immune thrombocytopenia, internal bleeding, low platelet counts, and cerebral venous thrombosis. These side effects have quite significantly affected vaccination campaigns in many countries (14–17).

As of February 26, 2022, there have been 742,541 confirmed cases of COVID-19 with 8,991 reported deaths in the KSA according to the World Health Organization (18). Several COVID-19 protocols and prevention measures such as social distancing, wearing masks, and using hand sanitizers have been put in place by the KSA public health authorities (19). However, vaccinating the population is one of the most effective ways to prevent the spread of COVID-19 and reduce its complications (20). Studies in several countries, including China, the United States, Italy, and Saudi Arabia, examined the willingness of people to accept the vaccine and the associated beliefs and barriers, showing that certain negative perceptions, beliefs, and attitudes are inhibiting some segments of the population from being vaccinated for COVID-19 (20–23).

Moreover, there is paucity of evidence about the side effects of COVID-19 vaccination and people's perceptions about COVID-19 vaccination in Saudi Arabia. Understanding side effects of COVID-19 vaccination and people's perception about COVID-19 vaccines will help to come up with effective interventions. The main aim of this study was to assess the side effects and perceptions about COVID-19 vaccines among Saudi Arabia's adult population following vaccination. Providing empirical evidence on the perceptions about COVID-19 vaccines and their side effects will be valuable in predicting the trends about future vaccine uptake and consequently developing strategies to improve acceptability (and uptake following vaccine availability).

MATERIALS AND METHODS

Study Design

Data used for this study were derived from an online cross-sectional survey conducted between July 13 and July 20, 2021. The survey was self-administered using an online survey tool (SurveyMonkey Inc., San Mateo, CA, USA). Social media platforms such as Twitter and WhatsApp were used to send respondents invitations to participate in the study. The study was entirely conducted and reported according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (24).

Participants

The study conducted among individuals aged 18 years and older who had received one or both doses of the COVID-19 vaccines. All study participants had to be living in the KSA at the time of the survey. Participants were recruited for the survey using a simplified snowball sampling technique in which participants were asked to send on the invitations to their contacts. The online platform was used to minimize physical contact with study participants in line with COVID-19 protocols. Moreover, the online approach gave us the opportunity to gather information from as many respondents as possible.

Based on the latest KSA census, the population of Saudi Arabia was estimated to be 35,013,414 (25). From this population, a sample size calculator (26) was used to calculate the required sample for the study. A representative target sample of 1,037 participants, using a ±4% margin of error, confidence level of 99%, and 50% response distribution, was derived. A total of 1,094 participants successfully completed the questionnaire across the 13 regions of the KSA. Participants who lived outside Saudi Arabia at the time of completing the survey and those with missing data on variables of interest for the current study

were excluded. Hence, the final sample included for analysis was 1,058 participants.

Instrument

The self-reported questionnaire used for this study was adopted from previous studies and frameworks used to assess side effects of vaccines following vaccination (17, 27, 28). The questionnaire was assessed and validated by a panel of experts in medicine and infectious diseases that carefully reviewed the items of the questionnaire and provided feedback, which was used to further improve the questionnaire. The Cronbach alpha coefficient for the questionnaire was 0.75, indicating good internal validity (29).

There were four main sections of the questionnaire: (i) sociodemographic questions; (ii) health behavior, type of vaccination received, and knowledge and sources of information about COVID-19 vaccines; (iii) perceptions and beliefs following vaccination; and (iv) reactions after vaccination. The survey questionnaire was written in English and then translated to Arabic. The Arabic version was used to administrate the survey.

Measurement of Variables

Dependent Variables

There were two major outcomes used for analysis: side effects and perceptions of COVID-19 vaccines. For side effects, the question used was: "following vaccination have you noticed any symptoms?" The response categories were: No symptoms at all (0); Yes, mild symptoms (1); Yes, moderate symptoms (2); and Yes, severe symptoms (3). These same categories were used for the multinomial logistic regression analysis. For perceptions about COVID-19 vaccinations, the following questions were used: "Do you think COVID-19 vaccines are safe in the long term?" "Are you monitoring your vital signs more frequently after vaccination?" and "Do you advise others to get vaccinated for COVID-19?" All of these questions were based on binary responses (yes = 1 and no = 0), and this same coding was maintained for binary logistic regression analysis.

Independent Variables

Sociodemographic characteristics of individuals were used as independent variables. These variables included: gender, age, educational level, employment status, and nationality. Health-related variables used were smoker, suffering from a chronic illness, number of vaccine doses received, infected with COVID-19 before vaccination, and feeling anxious about the COVID-19 vaccine before receiving it. Other variables used for descriptive analysis included preferred vaccine brand, source of information on vaccines, type of COVID-19 vaccines received, and side effects experienced. A description of the independent variables and their measurements are presented in **Table 1**.

TABLE 1 | Independent variable specifications.

Variables	Measurement
Sociodemographic	
Gender	Whether the respondent is male or female; 0 for female, 1 for male
Age	Age of respondent; 18–29 (reference category), 30–39, 40–49, 50–59, ≥60 years.
Marital status	The marital status of the respondent; 0 for unmarried (single, widowed, or divorced), 1 for married.
Educational level	Educational level of the respondents; high school or below (reference category), university degree, post-graduate degree.
Employment status	Government sector employee (reference category), private sector employee, student, retired, unemployed.
Nationality	Whether the respondent is Saudi or non-Saudi; 0 for non-Saudi, 1 for Saudi.
Health-related variables	
Smoker	Whether the respondent is smoker; 0 for no, 1 for yes.
Chronic illness	Whether the respondent suffering from a chronic illness (diabetes mellitus, obesity, hypertension, chronic respiratory diseases, cardiovascular diseases, joint inflammation, autoimmune diseases, thyroid disorders, cancers, osteoporosis, and other chronic diseases), categorized as a binary variable; 0 for no, 1 for yes.
Number of vaccine doses received	0 for one dose, 1 for two doses.
Infected with COVID-19 before vaccination	Whether the respondent infected with COVID-19 before vaccination; 0 for no, 1 for yes.
Anxiety	Whether the respondent feeling anxious about the COVID-19 vaccine before receiving it; 0 for no, 1 for yes.
Other variables	
Preferred vaccine brand	No preference, AstraZeneca/Oxford, Pfizer/BioNTech, others including Moderna and Johnson and Johnson.
Source of information on vaccines	Government-owned media platforms, scientific and medical platforms, social media platforms, friends and relatives, no information.
Type of COVID-19 vaccines received	AstraZeneca/Oxford or Pfizer/BioNTech.
Side effects experienced	Whether the respondent noticed any symptoms after vaccination. These including: tiredness/fatigue, swelling, fever, headache, muscle pains, joint pains, sleepiness, dizziness, decreased sleep, nausea, chills, heart beats, cold, dry throat, haziness, dyspnea, body sweats, abdominal pain, irritation, chest pains, diarrhea, runny nose, bruises, blood pressure, vomiting, swollen feet, bleeding gums, and nose bleeding.

Data Analysis

Data analysis for this study were conducted through descriptive statistics such as the frequency distribution using Statistical Package for the Social Sciences (SPSS) software, version 27.0. Descriptive statistics was used to assess the prevalence of side effects and perceptions about COVID-19 vaccines following vaccination. This was followed by a Pearson chi-square test ($\chi 2$) and multicollinearity test using the variance inflation factor. The multicollinearity test was performed to check for

TABLE 2 | Classification of participants involved in the study based on their demographic and health data.

Variable	*N*	%
Gender		
Female	540	51.0
Male	518	49.0
Age (years)		
18–29	143	13.5
30–39	363	34.3
40–49	294	27.8
50–59	154	14.6
≥60	104	9.8
Marital status		
Unmarried	262	24.8
Married	796	75.2
Educational level		
High school or below	229	21.6
University degree	460	43.5
Postgraduate degree	369	34.9
Employment status		
Government sector employee	541	51.1
Private sector employee	161	15.2
Student	70	6.6
Retired	110	10.4
Unemployed	176	16.7
Nationality		
Non-Saudi	72	6.8
Saudi	986	93.2
Smoker		
No	798	75.4
Yes	260	24.6
Chronic illness		
No	705	66.6
Yes	353	33.4
Number of doses received		
One	538	50.9
Two	520	49.1
Infected with COVID-19 before vaccination		
No	906	85.6
Yes	152	14.4
Anxiety		
No	503	47.5
Yes	555	52.5
Total	1,058	100

possible collinearity between the explanatory variables used in this study. Bivariate and multivariable logistic regression analyses were performed, followed by testing model fitness (Hosmer-Lemeshow, $p = 0.3530$). The multivariable logistic regression (for both binary and multinomial) results are presented as the adjusted odd ratio (aOR) and 95% confidence interval (CI). Given the sampling used for the survey and the complex nature of the data, we used the "complex samples" module in SPSS for these analyses.

RESULTS

Sample Description

Table 2 shows the classification of participants involved in the study based on their demographic and health data. A slightly higher proportion of participants were females (51.0%), aged 30–39 years (34.3%), married (75.2%), university degree holders (43.5%), of Saudi nationality (93.2%), and government employees (51.1%). The percentage of individuals who reported being smokers was 24.6%, and 33.4% reported suffering from chronic conditions. Approximately half of the participants (49.2%) had taken two doses, 52.5% of participants reported that they were anxious about COVID-19 vaccines, and 14.4% indicated that they were infected with COVID-19 before vaccination.

Pre-vaccination

Preferred Vaccine

Figure 1 shows the frequencies of vaccines preferred by study participants. A high proportion of study participants preferred receiving the Pfizer-BioNTech vaccine (74.5%), followed by AstraZeneca/Oxford (13.5%), and other vaccines such as Johnson & Johnson and Moderna (1%). The remaining proportion constituted participants who did not have any vaccine preference (11%).

Source of Information About COVID-19 Vaccination

Figure 2 indicates that slightly more than half (51.0%) of the participants obtained information about COVID-19 vaccines from government-owned media platforms, while 43.3% of the participants obtained information from other various sources such as social media platforms, friends and relatives, scientific and medical platforms.

Type and Doses of COVID-19 Vaccine Taken by Participants

Table 3 shows the classification of participants based on the type of COVID-19 vaccine they received. Slightly over half (50.9%) of the respondents reported that they had received a single dose. From this proportion, over two thirds (66.9%) had received AstraZeneca/Oxford while over two-fifths (45.8%) had received Pfizer/BioNTech. Among those who had received two doses, a higher proportion had received Pfizer-BioNTech (54.2%) than AstraZeneca/Oxford (33.1%).

Post-vaccination

Side Effects of COVID-19 Vaccination

Figure 3 shows the distribution of side effects from COVID-19 vaccines in the sampled population. More than half of the participants (52.6%) reported that they experienced tiredness/fatigue after vaccination with COVID-19 vaccines. Other side effects experienced included swelling (38%), fever (31.3%), headache (29.1%), and muscle pain (22.2%).

Severity of Side Effects After Vaccination

Figure 4 shows the severity of side effects after vaccination. A high proportion of participants indicated that they experienced mild symptoms (42.7%). The remaining proportion constituted

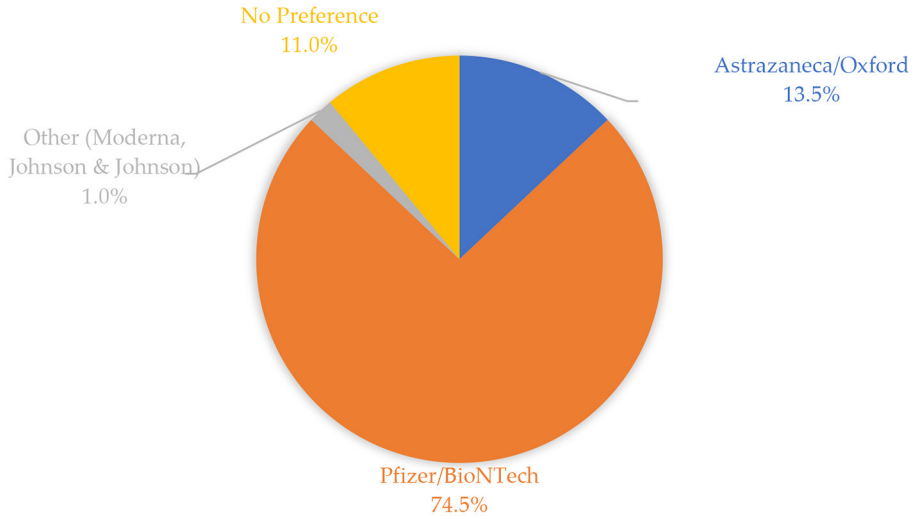

FIGURE 1 | Frequencies of vaccines preferred by study participants.

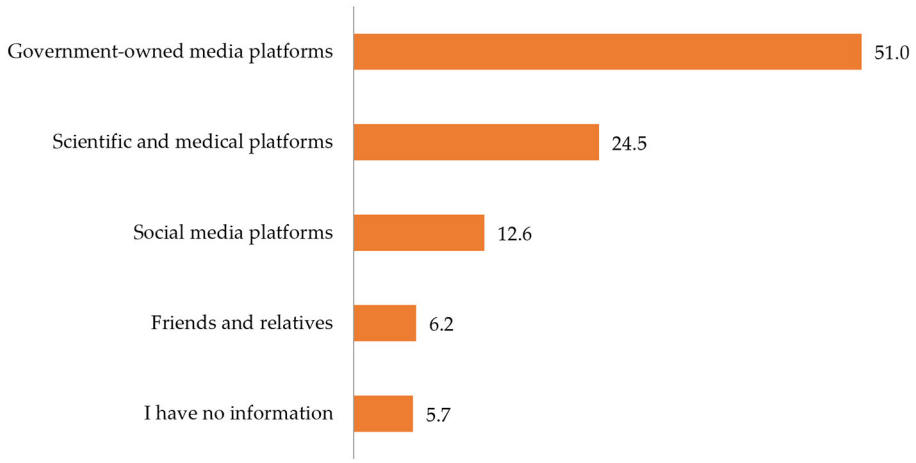

FIGURE 2 | Source of information about COVID-19 vaccination.

TABLE 3 | Classification of participants based on types of COVID-19 vaccine received.

Vaccine	One dose *n* (%)	Two doses *n* (%)	Total n (%)
AstraZeneca/Oxford	170 (66.9)	84 (33.1)	254 (24.0)
Pfizer-BioNTech	368 (45.8)	436 (54.2)	804 (76.0)
Total	538 (50.9)	520 (49.1)	1,058 (100)

those who experienced no symptoms at all (24.4%), moderate (23.2%), and severe (9.7%) symptoms.

Table 4 shows the results of the severity of side effects by the socio-demographic and health characteristics of participants, which were compared using the $\chi 2$ statistic. The severity of side effects is associated with gender ($\chi 2 = 32.75$, $p < 0.01$). A slightly higher percentage among females than males reported mild (44.3 vs. 41.1%), moderate (25.7 vs. 20.5%), and severe (12.4 vs. 6.9%) symptoms. The severity of side effects was also associated with smoking status ($\chi 2 = 17.63$, $p < 0.01$); a higher proportion of smokers experienced moderate symptoms compared to non-smokers (43.1 vs. 42.6%), while higher proportions of non-smokers experienced mild (25.2 vs. 16.9%) and severe (10.5 vs. 7.3%) symptoms than smokers.

Moreover, moderate (42.9 vs. 42.5%), mild (24.9 vs. 21.3%), and severe (11.2 vs. 8.2%) side effects were also observed to be higher among individuals who reported that they felt anxious about the COVID-19 vaccine compared to those who were not anxious ($\chi 2 = 9.18$, $p = 0.03$). However, there was no statistically significant association observed between the severity of side effects

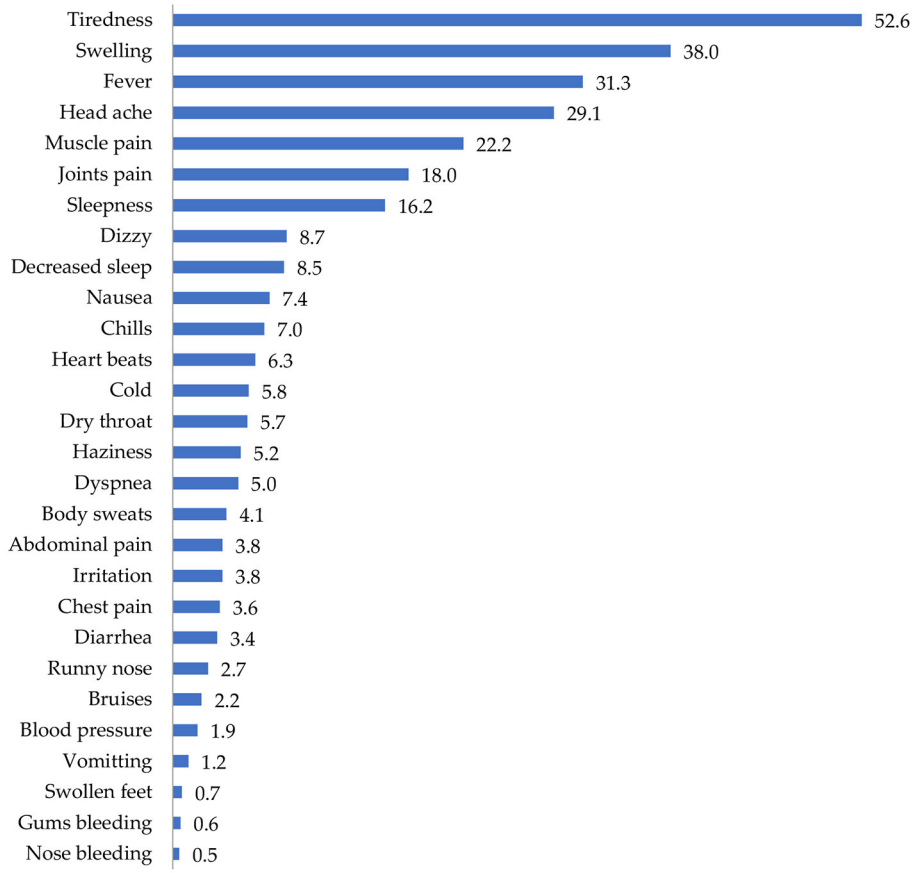

FIGURE 3 | Side effects of COVID-19 vaccination in the sampled population.

and age, marital status, educational level, employment status, number of doses, whether one had a chronic condition, and whether they were infected with COVID-19 before vaccination.

Logistic Regression Analyses for the Severity of Side Effects

Table 5 shows the results of logistic regression analyses for the severity of side effects. The odds of experiencing severe side effects were significantly higher among males (aOR = 2.76, 95% CI = 1.71–4.45, $p < 0.01$) than females. For age, the odds of experiencing mild side effects were significantly higher among people aged 30–39 years (aOR = 3.52, 95% CI = 1.61–7.68), 40–49 years (aOR = 2.44, 95% CI = 1.31–4.57, $p < 0.05$), 50–59 years (aOR = 2.63, 95% CI = 1.41–4.92, $p < 0.05$), and 60 years and above (aOR = 1.94, 95% CI = 1.08–3.48, $p < 0.1$) compared to individuals aged 18–29 years. Saudi nationals had significantly higher odds of reporting mild (aOR = 2.44, 95% CI = 1.23–4.86, $p < 0.05$), moderate (aOR = 2.65, 95% CI = 1.27–2.71, $p < 0.05$), and severe (aOR = 3.64, 95% CI = 1.58–8.38, $p < 0.05$) side effects compared to non-Saudis.

Considering employment status, the odds of reporting mild side effects were significantly higher among students (aOR = 1.70, 95% CI = 1.01–2.86, $p < 0.1$) and unemployed individuals (aOR = 2.03, 95% CI = 1.23–4.86, $p < 0.1$) compared to government employees, whereas the odds of

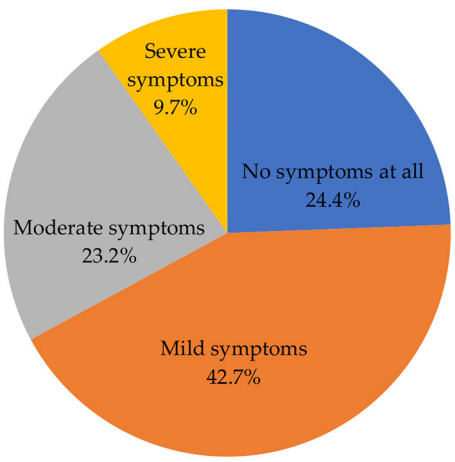

FIGURE 4 | Severity of side effects after vaccination.

TABLE 4 | Participants' experience and severity of side effects by sociodemographic and health characteristics.

Variable	Severity of side effects					
	No side effects *n* (%)	Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)	χ^2	*P*-value
Gender						
Female	95 (17.6)	239 (44.3)	139 (25.7)	67 (12.4)	32.75	< 0.01
Male	163 (31.5)	213 (41.1)	106 (20.5)	36 (6.9)		
Age (years)						
18–29	30 (21.0)	69 (48.3)	29 (20.3)	15 (10.5)	17.98	0.12
30–39	88 (24.2)	150 (41.3)	85 (23.4)	40 (11.0)		
40–49	64 (21.8)	128 (43.5)	73 (24.8)	29 (9.9)		
50–59	36 (23.4)	64 (41.6)	41 (26.6)	13 (8.4)		
≥60	40 (38.4)	41 (39.4)	17 (16.3)	6 (5.8)		
Marital status						
Unmarried	60 (22.9)	120 (45.8)	55 (21.0)	27 (10.3)	1.91	0.59
Married	198 (24.9)	332 (41.7)	190 (23.9)	76 (9.5)		
Educational level						
High school or below	63 (27.5)	95 (41.5)	49 (21.4)	22 (9.6)	3.96	0.68
University degree	105 (22.8)	192 (41.7)	113 (24.6)	50 (10.9)		
Postgraduate degree	90 (24.4)	165 (44.7)	83 (22.5)	31 (8.4)		
Employment status						
Government sector employee	131 (24.2)	229 (42.3)	129 (23.8)	52 (9.6)	12.99	0.37
Private sector employee	37 (23.0)	74 (46.0)	35 (21.7)	15 (9.3)		
Student	13 (18.6)	31 (44.3)	18 (25.7)	8 (11.4)		
Retired	37 (33.6)	49 (44.5)	18 (16.4)	6 (5.5)		
Unemployed	40 (22.7)	69 (39.2)	45 (25.6)	22 (12.5)		
Nationality						
Non-Saudi	8 (11.1)	33 (45.8)	20 (27.8)	11 (15.3)	8.91	0.03
Saudi	250 (25.4)	419 (42.5)	225 (22.8)	92 (9.3)		
Smoker						
No	173 (21.7)	340 (42.6)	201 (25.2)	84 (10.5)	17.63	< 0.01
Yes	85 (32.7)	112 (43.1)	44 (16.9)	19 (7.3)		
Chronic illness						
No	177 (25.1)	304 (43.1)	161 (22.8)	63 (8.9)	2.01	0.571
Yes	81 (22.9)	148 (41.9)	84 (23.8)	40 (11.3)		
Number of doses received						
One	131 (24.3)	217 (40.3)	131 (24.3)	59 (11.0)	3.84	0.28
Two	127 (24.4)	235 (45.2)	114 (21.9)	44 (8.5)		
Infected with COVID-19 before vaccination						
No	220 (24.3)	396 (43.7)	204 (22.5)	86 (9.5)	2.96	0.40
Yes	38 (25.0)	56 (36.8)	41 (27.0)	17 (11.2)		
Anxiety						
No	141 (28.0)	214 (42.5)	107 (21.3)	41 (8.2)	9.18	0.03
Yes	117 (21.1)	238 (42.9)	138 (24.9)	62 (11.2)		
Total	258 (24.4)	452 (42.7)	245 (23.2)	103 (9.7)		

reporting moderate side effects were significantly higher among retired individuals (aOR = 2.64, 95% CI = 1.11–6.27, $p < 0.1$) compared to government employees. Conversely, individuals who were smokers (aOR = 1.86, 95% CI = 1.27–2.71, $p < 0.01$) had higher odds of reporting moderate side effects compared to those who did not smoke. The odds of reporting moderate (aOR = 0.68, 95% CI = 0.47–0.98, $p < 0.1$) and severe (aOR = 0.48, 95% CI = 0.30–0.75, $p < 0.05$) side effects were significantly lower among individuals who indicated that they suffer from chronic illnesses compared to their counterparts. Individuals who had received two doses (aOR = 0.72, 95% CI = 0.53–0.98, $p < 0.1$) also had lower odds of reporting mild side effects compared to those who had received one dose.

TABLE 5 | Logistic regression analysis results for the severity of side effects.

	Severity of side effects†		
Variable	**Mild aOR (95% CI)**	**Moderate aOR (95% CI)**	**Severe aOR (95% CI)**
Gender			
Female (ref)			
Male	1.93 (1.40–2.66)***	1.97 (1.37–2.84)***	2.76 (1.71–4.45)***
Age (years)			
18–29 (ref)			
30–39	3.52 (1.61–7.68)***	1.90 (0.74–4.84)	2.99 (0.86–10.3)
40–49	2.44 (1.31–4.57)**	2.19 (1.05–4.59)*	3.10 (1.10–8.72)*
50–59	2.63 (1.41–4.92)**	2.34 (1.12–4.88)*	2.61 (0.93–7.36)
≥60	1.94 (1.08–3.48)*	2.19 (1.09–4.38)*	1.83 (0.67–4.97)
Marital status			
Unmarried (ref)			
Married	0.90 (0.62–1.32)	0.76 (0.49–1.18)	0.80 (0.46–1.39)
Educational level			
High school or below (ref)			
University degree	0.81 (0.55–1.20)	0.83 (0.53–1.30)	1.03 (0.56–1.87)
Postgraduate degree	0.95 (0.69–1.30)	1.20 (0.83–1.73)	1.42 (0.87–2.31)
Employment status			
Government sector employee (ref)			
Private sector employee	1.58 (0.99–2.51)	1.44 (0.86–2.40)	1.64 (0.87–3.09)
Student	1.70 (1.01–2.85)*	1.35 (0.75–2.43)	1.39 (0.67–2.89)
Retired	1.66 (0.78–3.55)	2.64 (1.11–6.27)*	2.21 (0.76–6.37)
Unemployed	2.03 (1.23–4.86)*	1.04 (0.48–2.25)	1.10 (0.37–3.22)
Nationality			
Non-Saudi (ref)			
Saudi	2.44 (1.23–4.86)**	2.65 (1.27–2.71)**	3.64 (1.58–8.38)**
Smoker			
No (ref)			
Yes	1.34 (0.98–1.82)	1.86 (1.27–2.71)***	1.64 (0.98–2.73)
Chronic illness			
No (ref)			
Yes	0.76 (0.56–1.05)	0.68 (0.47–0.98)*	0.48 (0.30–0.75)**
Number of doses received			
One (ref)			
Two	0.72 (0.53–0.98)*	0.83 (0.58–1.18)	0.87 (0.55–1.36)
Infected with COVID-19 before vaccination			
No (ref)			
Yes	1.08 (0.72–1.61)	0.83 (0.54–1.29)	0.87 (0.49–1.53)
Anxiety			
No (ref)			
Yes	0.83 (0.63–1.09)	0.76 (0.55–1.05)	0.71 (0.47–1.08)

$^{***}p < 0.01$, $^{**}p < 0.05$, $^{*}p < 0.1$; aOR, adjusted odd ratios, CI, confidence interval.
†No side effects is the reference category in the multinomial logistic regression model.

Perceptions About COVID-19 Vaccines

Participants' Perceptions About COVID-19 Vaccines by Sociodemographic and Health Characteristics: Bivariate Association Analysis

Table 6 shows the bivariate association between participants' perceptions about COVID-19 vaccines by demographic and health characteristics. A significantly high proportion among males (66.8%), high school or below participants (62.0%), retired individuals (67.3%), smokers (62.7%), those who had received two doses (64.2%), and those who reported that they did not feel anxious about the COVID-19 vaccine before receiving it believed that COVID 19 vaccines are safe in the long-term. However, only a significantly higher percentage among married (51.5%) respondents compared to unmarried (45.4%)

TABLE 6 | Participants' perceptions about COVID-19 vaccines after vaccination by demographic and health characteristics.

Variable	Believing that COVID-19 vaccines are safe in the long-term *n* (%)	Monitoring signs became more frequent after vaccination *n* (%)	Advise others to get vaccinated for COVID-19 *n* (%)
Gender			
Female	254 (47.0)	257 (47.6)	431 (79.8)
Male	346 (66.8)***	272 (52.5)	459 (88.6)***
Age (years)			
18–29	76 (53.1)	70 (49.0)	117 (81.8)
30–39	200 (55.1)	169 (46.6)	298 (82.1)
40–49	165 (56.1)	153 (52.0)	248 (84.4)
50–59	89 (57.8)	78 (50.6)	134 (87.0)
≥60	70 (67.3)	59 (56.7)	93 (89.4)
Marital status			
Unmarried	143 (54.6)	119 (45.4)*	213 (81.3)
Married	457 (57.4)	410 (51.5)	677 (85.1)
Educational level			
High school or below	142 (62.0)*	121 (52.8)	197 (86.0)
University degree	244 (53.0)	236 (51.3)	379 (82.4)
Postgraduate degree	214 (58.0)	172 (46.6)	314 (85.1)
Employment status			
Government sector employee	313 (57.9)***	264 (48.8)	458 (84.7)***
Private sector employee	88 (54.7)	78 (48.4)	136 (84.5)
Student	46 (65.7)	36 (51.4)	60 (85.7)
Retired	74 (67.3)	65 (59.1)	103 (93.6)
Unemployed	79 (44.9)	86 (48.9)	133 (75.6)
Nationality			
Non-Saudi	37 (51.4)	36 (50.0)	64 (88.9)
Saudi	563 (57.1)	493 (50.0)	826 (83.8)
Smoker			
No	437 (54.8)	401 (50.3)	658 (82.5)
Yes	163 (62.7)**	128 (49.2)	232 (89.2)
Chronic illness			
No	398 (56.5)	343 (48.7)	591 (83.8)
Yes	202 (57.2)	186 (52.7)	299 (84.7)
Number of doses received			
One	266 (49.4)***	261 (48.5)	412 (76.6)***
Two	334 (64.2)	268 (51.5)	478 (91.9)
Infected with COVID-19 before vaccination			
No	510 (56.3)	461 (50.9)	770 (85.0)
Yes	90 (59.2)	68 (44.7)	120 (78.9)*
Anxiety			
No	380 (75.5)	257 (51.1)	476 (94.6)
Yes	220 (39.6)***	272 (49.0)	414 (74.6)***

$^{***}p < 0.01$, $^{**}p < 0.05$, $^{*}p < 0.1$.

respondents reported that monitoring signs became more frequent after vaccination.

A significantly higher proportion of males (88.6%) than females (79.8%) reported that they would advise others to get vaccinated for COVID-19. Similarly, a significantly higher proportion among students (85%), individuals who had taken two doses (91.9%), those not infected with COVID-19 before vaccination (85%), and those who indicated that they did not feel anxious about the COVID-19 vaccine before receiving it (94.6%) reported that they would advise others to get vaccinated for COVID-19 compared to their counterparts.

Logistic Regression of Participant's Perceptions About COVID-19 Vaccines After Vaccination

Table 7 shows the results of the logistic regression analyses for participants' perceptions about COVID-19 vaccines after vaccination. After adjusting for covariates, the odds of believing

that COVID-19 vaccines are safe in the long-term were significantly higher among males (aOR = 1.76, 95% CI = 1.116–2.65, $p < 0.01$) than females. Similarly, the odds of believing that COVID-19 vaccines are safe in the long-term were significantly higher among individuals who had received two doses (aOR = 1.62, 95% CI = 1.09–2.40, $p < 0.05$) compared to those who had received only one dose. Moreover, individuals who were feeling anxious about the COVID-19 vaccine before receiving it (aOR = 0.24, 95% CI = 0.17–0.35, $p < 0.01$) had lower odds of believing that COVID-19 vaccines are safe in the long-term.

Conversely, there was no statistically significant association between the perception that monitoring signs became more frequent after vaccination and participants' sociodemographic and health characteristics. The odds of advising others to get vaccinated for COVID-19 were significantly higher among respondents who had received two doses (aOR = 2.81, 95% CI = 1.60–4.93, $p < 0.01$) compared to their counterparts. By contrast, individuals who indicated that they were feeling anxious about the COVID-19 vaccine before receiving had significantly lower odds of advising others to get vaccinated for COVID-19 compared to those who did not feel anxious about the COVID-19 vaccine before receiving it.

DISCUSSION

The aim of this study was to assess the side effects and perceptions about COVID-19 vaccines among Saudi Arabia's adult population following vaccination. The findings indicate that a high proportion of participants preferred the Pfizer-BioNTech vaccine compared to AstraZeneca/Oxford and other vaccine types offered. As a result, most participants in this study were vaccinated with Pfizer-BioNTech (76.0%) and AstraZeneca/Oxford (24.0%). The preference for Pfizer-BioNTech and AstraZeneca/Oxford vaccines among study participants likely had more to do with vaccine availability, at the time of the study, than personal choice. Approximately half (50.9%) of the participants had taken the first dose at the time of completing the survey, with the remaining proportion constituting those who had received two doses (49.1%).

About than half of the participants indicated that they obtained information about COVID-19 vaccines from government-owned media platforms, with the remaining half obtaining relevant information from various sources such as social media platforms, friends and relatives, and scientific and medical platforms. To avoid misinformation about the pandemic and to ensure that people access accurate information, the Ministry of Health (MOH) of the KSA acted as a main and official source responsible for communicating COVID-19 information to the public (30). The dissemination of information has been implemented through engaging the community, using traditional channels such as television and text messages, as well as technology and digital health platforms. Moreover, the MOH developed high-quality media materials to be distributed and government-coordinated press conferences providing updates have been held on a daily basis during this pandemic. Furthermore, government leaders such as ministers and other prominent public figures have shared videos recommending that the public follow precautionary measures (30).

In this study, slightly more than two-fifths (42.7%) of the participants indicated that they experienced mild symptoms, with more than one-fifth (23.2%) and approximately one-tenth (9.7%) of the participants reporting that they experienced moderate and severe symptoms, respectively. Consistent with other studies in other countries, mild to moderate symptoms were the most common side effects reported following COVID-19 vaccination in our study (31, 32). Severe side effects were reported in almost one-tenth of the participants, which is similar to previous studies indicating that severe side effects are experienced by less than one-tenth of the vaccinated population (33, 34).

The most common types of side effects experienced by the study participants included tiredness/fatigue, swelling, fever, headache, muscle pains, joint pains, sleepiness, dizziness, decreased sleep, nausea, chills, heart beats, cold, dry throat, haziness, dyspnea, body sweats, abdominal pain, irritation, chest pains, diarrhea, runny nose, blood pressure, vomiting, swollen feet, bleeding gums, and nose bleeding. Similar findings have been observed in countries where Pfizer-BioNTech and AstraZeneca/Oxford vaccines have been used. For instance, injection fatigue and headache were the most common side effects reported in a several similar studies (35–37).

After adjusting for covariates, the odds of experiencing severe side effects were found to be significantly higher among males than among females. This is in contrast with the findings of the majority of previous studies showing that women have higher odds of reporting COVID-19 vaccine side effects compared to men, especially headache and fatigue (38). It has been argued that women are more likely to report their symptoms than men (39–41). Our findings thus provide important insights about the gendered dimensions of vaccination in the KSA. Therefore, there is a need to further investigate why men experienced and reported COVID-19 vaccination side effects more often than women in Saudi Arabia.

We also found that smokers were more likely to report having experienced moderate side effects compared to non-smokers. Previous investigations have also shown that smokers are more likely to experience some side effects (42). Since smoking is a health hazard, this can provide a plausible explanation for this finding. In particular, smoking is a common risk factor for most respiratory infections and has been noted to increases the severity of respiratory diseases. As a result, smokers are more likely to develop side effects after COVID-19 vaccination compared to non-smokers due to the weakened immune system (43).

With respect to age, the odds of experiencing severe side effects were significantly higher among people aged 30 years and above compared to those aged 18–29 years. This finding is consistent with results from several studies about COVID-19 vaccine side effect (38). The plausible explanation is that vaccine reactogenicity has been linked to raising of inflammatory cytokines, which shows that the vaccine reactogenicity declines with age, although it is not considered a reliable sign of a desirable immune response (44).

TABLE 7 | Logistic regression analyses for participants' perceptions about COVID-19 vaccines after vaccination broken down by sociodemographic and health characteristics.

Variable	Believing that COVID-19 vaccines are safe in the long-term aOR (95% CI)	Monitoring signs became more frequent after vaccination aOR (95% CI)	Advise others to get vaccinated for COVID-19 aOR (95% CI)
Gender			
Female (ref)			
Male	1.76 (1.16–2.65)***	1.19 (0.81–1.74)	1.22 (0.70–2.12)
Age (years)			
18–29 (ref)			
30–39	1.32 (0.62–2.79)	0.92 (0.46–1.81)	0.87 (0.34–2.22)
40–49	1.40 (0.50–2.98)	1.09 (0.53–2.23)	0.92 (0.34–2.50)
50–59	1.22 (0.50–2.98)	0.90 (0.38–2.03)	0.79 (0.25–2.50)
≥60	1.20 (0.40–3.53)	1.01 (0.38–2.69)	0.44 (0.10–1.88)
Marital status			
Unmarried (ref)			
Married	0.96 (0.59–1.57)	1.28(0.81-2.01)	1.24(0.67-2.30)
Educational level			
High school or below (ref)			
University degree	0.74 (0.46–1.20)	0.96 (0.61–1.48)	0.75 (0.39–1.45)
Postgraduate degree	0.89 (0.52–1.51)	0.77 (0.47–1.24)	0.91 (0.44–1.89)
Employment status			
Government sector employee (ref)			
Private sector employee	0.98 (0.56–1.70)	0.9 (0.59–1.61)	0.99 (0.47–2.07)
Student	2.37 (0.87–6.42)	1.23 (0.51–2.98)	1.45 (0.39–5.30)
Retired	1.00 (0.44–2.29)	1.30 (0.58–1.70)	2.07 (0.52–8.18)
Unemployed	1.08 (0.60–1.92)	1.00 (0.58–1.70)	0.85 (0.42–1.73)
Nationality			
Non-Saudi (ref)			
Saudi	1.16 (0.56–2.41)	0.95 (0.49–1.83)	0.49 (0.17–1.44)
Smoker			
No (ref)			
Yes	1.03 (0.67–1.61)	0.60 (0.60–1.34)	1.37 (0.72–2.61)
Chronic illness			
No (ref)			
Yes	1.01 (0.67–1.52)	1.12 (0.77–1.63)	1.02 (0.59–1.74)
Number of doses received			
One (ref)			
Two	1.62 (1.09–2.40)**	1.01 (0.70–1.46)	2.81 (1.60–4.93)***
Infected with COVID-19 before vaccination			
No (ref)			
Yes	1.21 (0.72–2.05)	0.77 (0.48–1.25)	0.79 (0.42–1.49)
Anxiety			
No (ref)			
Yes	0.24 (0.17–0.35)***	0.97 (0.69–1.36)	0.19 (0.10–0.35)***

$^{***}p < 0.01$, $^{**}p < 0.05$, $^{*}p < 0.1$; aOR, adjusted odds ratio; CI, confidence interval.

The study also found that individuals who reported that they were suffering from chronic illnesses were less likely to report moderate and mild side effects compared to those who did not report any chronic illness. There was no statistically significant association between reporting suffering from chronic illnesses and experiencing severe side effects after vaccination. There is little information from studies about COVID-19 vaccines to explain this observation. Although chronic diseases generally weaken the immune system and are more likely to create complications from COVID-19, which may lead to long-term illness, hospitalization, and even death, recent clinical trials show that COVID-19 vaccines are safe and effective among people with underlying medical conditions (28).

With respect to perceptions about COVID-19 vaccines after vaccination, after adjusting for covariates, the odds of believing that COVID-19 vaccines are safe in the long-term

were significantly higher among men than among women. Similarly, the odds of believing that COVID-19 vaccines are safe in the long-term were significantly higher among individuals who had received two doses compared to those who had received only one dose. Although there is a dearth of evidence to ascertain this observation, this finding is quite indicative, and suggests that the experience or perception of safety and reduced risk of exposure to COVID-19 in the future, along with confidence in the vaccine may have collectively influenced the view of men and people who had received two doses that COVID-19 vaccines are safe in the long-term. As would be expected, individuals who were feeling anxious about the COVID-19 vaccine before receiving it had lower odds of believing that COVID-19 vaccines are safe in the long-term.

Quite conversely, there was no statistically significant association between the perception that monitoring signs became more frequent after vaccination and participants' sociodemographic and health characteristics. The odds of advising others to get vaccinated for COVID-19 were significantly higher among respondents who had received two doses compared to their counterparts. This finding agrees with other previous studies showing that being fully vaccinated is vital, given that infections are often mild or asymptomatic after receiving two doses of the vaccine (45–47). Being fully vaccinated was noted in preventing infection with SARS-CoV-2 variants by at least 50% (48), and this is expected to motivate those who are fully vaccinated to recommend the vaccine to others.

There are some limitations of this study. This was an online cross-sectional study, which also used the snowball sampling technique for recruitment that might have impacted the generalizability and affected the representativeness of the sample. As a result, our findings may not be representative of the opinions of people who live in areas where there is limited internet connectivity. However, an online cross-sectional survey was the only viable study design to be employed at the time of the survey due to social distance requirements. Another main limitation of this study was the use of a non-standardized questionnaire to collect the data.

Nevertheless, our findings will have several implications. First, our study can provide vital insights on people's perceptions and attitudes after receiving COVID-19 vaccines. This will in turn help in the design of effective behavior change communication campaigns by the healthcare system to dispel negative vaccination perceptions. Second, although there have been several studies on COVID-19 vaccine hesitancy published to date, there is a paucity of studies on the side effects of the vaccines experienced by the Saudi population. Therefore, our results will enlighten healthcare professionals and policymakers to address the perceptions and concerns regarding vaccinations and their side effects. The findings of this study are not only important at this current point in the COVID-19 pandemic and vaccine rollout but can further be used as a reference for policy effort in facing possible future epidemics. In particular, the information derived from this study can be used to educate the public regarding the importance of vaccination, side effects notwithstanding.

CONCLUSIONS

This study provides evidence about the side effects and perceptions of COVID-19 vaccines among adults in Saudi Arabia. Common side effects reported by participants were tiredness/fatigue, swelling, fever, headache, muscle pains, joint pains, dizziness, decreased sleep, nausea, chills, heart beats, cold, dry throat, haziness, dyspnea, body sweats, abdominal pain, irritation, chest pains, diarrhea, and runny nose. These symptoms were linked to the two vaccine types predominately used in Saudi Arabia: Pfizer-BioNTech and AstraZeneca/Oxford. The odds of reporting severe side effects after vaccination were significantly higher among men, people aged 40–49 years, and Saudi nationals compared to their respective counterparts. Regarding the perceptions about COVID-19 vaccines, the odds of believing that COVID-19 vaccines are safe in the long-term were significantly higher among men and among individuals who had received two doses, and the odds of advising others to get vaccinated for COVID-19 were also significantly higher among respondents who had received two doses compared to their counterparts.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to privacy and confidentiality agreements as well as other restrictions but are available from the corresponding author on reasonable request.

ETHICS STATEMENT

All procedures performed in this study involving human participants complied with the institutional and/or national research committee ethical standards and the 1964 Helsinki Declaration and subsequent amendments or equivalent ethical standards. The study was designed and conducted according to the ethical principles established by King Abdulaziz University. Ethical approval was obtained from the Biomedical Ethics Research Committee, Faculty of Medicine, King Abdulaziz University (Ref-380-21). The patients/participants provided online informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MKA and MK: conceptualization, data curation, formal analysis, software, validation, and writing—original draft preparation. MKA: methodology, project administration, supervision, and funding acquisition. MKA, MK, NK, NA, AQ, and OA: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

FUNDING

This research was funded by the Institutional Fund Projects under grant number IFPRC-207-121-2020. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

The authors gratefully acknowledge technical and financial support from the Ministry of Education and King Abdulaziz University, Jeddah, Saudi Arabia.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
published: 17 June 2022
doi: 10.3389/fmed.2022.876017

Changes in the Blood Viscosity in Patients With SARS-CoV-2 Infection

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Specialty section:
This article was submitted to Infectious Diseases – Surveillance, Prevention and Treatment, a section of the journal Frontiers in Medicine

Received: *14 February 2022*
Accepted: *31 May 2022*
Published: *17 June 2022*

Citation:
Al-kuraishy HM, Al-Gareeb AI, Al-Hamash SM, Cavalu S, El-Bouseary MM, Sonbol FI and Batiha GE-S (2022) Changes in the Blood Viscosity in Patients With SARS-CoV-2 Infection. Front. Med. 9:876017. doi: 10.3389/fmed.2022.876017

Coronavirus disease 2019 (COVID-19) is caused by a novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2-induced hyperinflammation together with alteration of plasma proteins, erythrocyte deformability, and platelet activation, may affect blood viscosity. Thus, this review aimed to study the link between SARS-CoV-2 infection and alteration of blood viscosity in COVID-19 patients. In order to review findings related to hyperviscosity in COVID-19, we suggested a protocol for narrative review of related published COVID-19 articles. Hyperviscosity syndrome is developed in different hematological disorders including multiple myeloma, sickle cell anemia, Waldenstorm macroglobulinemia, polycythemia, and leukemia. In COVID-19, SARS-CoV-2 may affect erythrocyte morphology *via* binding of membrane cluster of differentiation 147 (CD147) receptors, and B and 3 proteins on the erythrocyte membrane. Variations in erythrocyte fragility and deformability with endothelial dysfunction and oxidative stress in SARS-CoV-2 infection may cause hyperviscosity syndrome in COVID-19. Of interest, hyperviscosity syndrome in COVID-19 may cause poor tissue perfusion, peripheral vascular resistance, and thrombosis. Most of the COVID-19 patients with a blood viscosity more than 3.5 cp may develop coagulation disorders. Of interest, hyperviscosity syndrome is more commonly developed in vaccine recipients who had formerly received the COVID-19 vaccine due to higher underlying immunoglobulin concentrations, and only infrequently in those who have not received the COVID-19 vaccine. Taken together, these observations are untimely too early to give a final connotation between COVID-19 vaccination and the risk for development of hyperviscosity syndrome, consequently prospective and retrospective studies are necessary in this regard.

Keywords: COVID-19, hyperviscosity syndrome, COVID-19 vaccination, SARS-CoV-2, immunoinflammatory disorders

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a current pandemic disease that began in Wuhan, China in late December 2019. COVID-19 is caused by novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which produced a worldwide crisis with high morbidity and mortality (1). It has been shown that COVID-19 led to more than 500 million affected cases with more than 6 million confirmed deaths till late May 2022. Different variants of SARS-CoV-2 strains emerged in the early months of 2020, and the last variant was Omicron SARS-CoV-2, which was mild with moderate transmission and low mortality (2). Up to date, a new variant strain of SARS-CoV-2 named the BA2 subtype has spread in specific regions of China. Besides, a new mutant variant of Omicron SARS-CoV-2 BA1 and BA2 has been observed and detected in the United Kingdom, with about 637 confirmed cases. This new strain has been renamed as the XE variant of SARS-CoV-2, which is now with outstanding spread in China (3). Thus, we are challenged by the emergence of new strains that could be highly virulent and may cause the propagation of new waves.

Most COVID-19 patients are asymptomatic or present with mild flu-like illnesses in about 85% of the cases. However, 15% of COVID-19 patients may present with moderate symptoms, including headache, fever, sweating, arthralgia, myalgia, dry cough, and fatigue (4). However, 5% of COVID-19 patients may develop severe and critical presentations due to the development of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (5). COVID-19 patients with ALI/ARDS require ICU admission and mechanical ventilation for respiratory support (6, 7). Moreover, COVID-19 may cause extra-pulmonary manifestations, including neurological complications (8), acute kidney injury (9), testicular injury (10), heart failure (11), new-onset diabetes mellitus (12), and thromboembolic disorders (13).

Of note, SARS-CoV-2 exploits diverse receptor types to reach the affected cells. The angiotensin converting enzyme 2 (ACE2) is an innovator one correlated in the pathogenesis of SARS-CoV-2 infection (14). This interface triggers down-regulation of ACE2, which is essential for alteration of pro-inflammatory/vasoconstrictor angiotensin II (AngII) to vasodilator/anti-inflammatory Ang1-7 (15). Notably, SARS-CoV-2 infection in severe cases may exaggerate human immune responses, leading to hyperinflammation, hypercytokinemia, and cytokine storm (16). Furthermore, SARS-CoV-2-induced hyperinflammation together with alteration of plasma proteins, erythrocyte deformability, and platelet activation may affect blood viscosity (17).

Thus, this narrative review aimed to study the link between SARS-CoV-2 infection and alteration of blood viscosity in COVID-19 patients.

METHOD AND SEARCH STRATEGY

In order to review findings related to hyperviscosity in COVID-19, the search was conducted from late December 2019 to early January 2022 by using search engines including MEDLINE, Scopus, Web of Science, PubMed, China National Knowledge Infrastructure, Embase, Wanfang Data, and China Biology Medicine by using the following keywords and terms; COVID-19 or SARS-CoV-2 or 2019-nCov and Hyperviscosity or Erythrocyte deformability or Thrombosis. There were no limitations for language and article types.

BLOOD VISCOSITY AND HYPERVISCOSITY SYNDROME

Blood viscosity is a measure of blood flow resistance and can also be recognized as the stickiness and thickness of blood (18). The main determinants of blood viscosity are erythrocyte deformability, hematocrit, erythrocyte aggregation, and plasma viscosity, which depend on plasma macromolecules and water content. Hematocrit represents the main determinant of blood viscosity; an increase in hematocrit can elevate it by 4% (19). When the hematocrit rises to 60–70% as in polycythemia, the blood viscosity become higher than water by 10 times with consequent increment resistance to the blood flow. As well, increasing body temperature may induce dehydration with an increase in blood viscosity (20). An increase in blood viscosity leads to the development of hyperviscosity syndrome. Of note, hyperviscosity syndrome is developed in different hematological disorders, including multiple myeloma, sickle cell anemia, Waldenstorm macroglobulinemia, polycythemia, and leukemia (21, 22). Normal BV is usually between 1.4 and 1.8 centipoise (cp), and symptoms of hyperviscosity syndrome develop when blood viscosity exceeds 4.0 cp (23). Patients with hyperviscosity syndrome are presented with diving symptoms due to impairment of blood flow, including headache, confusion, visual disturbances, vertigo, and thrombotic events with or without mucosal hemorrhage (21, 22). Sloop and colleagues found that inflammation and hypergammaglobulinemia together with the fostering of erythrocyte aggregation in sepsis could be the potential mechanisms of increasing blood viscosity in different infectious diseases (24). Hyperviscosity syndrome in severe infections provokes thromboembolic disorders with reduction of tissue perfusion resulting in multi-organ injury (MOI) and fatal outcomes (24).

IMMUNOLOGICAL DISORDERS AND HYPERVISCOSITY SYNDROME

Blood viscosity is highly sensitive to acute-phase reactants and inflammatory reactions. Thus, acute and chronic inflammatory disorders are linked with elevations of blood viscosity and the development of hyperviscosity syndrome (25). It has been reported that the development of hyperviscosity syndrome was linked with an increase in inflammatory biomarkers like erythrocyte sedimentation rate and C-reactive protein (CRP) (25). Therefore, hyperviscosity syndrome may progress in various immunoinflammatory disorders like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) due to formation of intermediate immunocomplex and hyperparaproteinemia

respectively (26, 27). Hyperviscosity syndrome in RA patients is correlated with levels of rheumatoid factor, fibrinogen, and inflammatory levels (26). However, hyperviscosity syndrome in RA patients treated with immunosuppressive agents and plasmapheresis is rare (28). Further, hyperviscosity syndrome could be the presenting symptoms in patients with SLE due to the development of monoclonal gammopathy and an unusual increase of immunoglobulin type G4 (29). Moreover, there is an interacted relationship between hyperviscosity syndrome and inflammation due to the increase of acute phase reactant fibrinogen, whose level is correlated with increasing blood viscosity (30). Notably, fibrinogen-related proteins are augmented during the immune response to numerous inflammatory stimuli (31). Fibrinogen and related proteins play a perilous role in neutralizing invading pathogens (31). Sequentially, exaggerated immune responses and exaggerated levels of fibrinogen-related proteins are connected with the development of hyperviscosity syndrome (32).

In addition, abnormal immune response in some viral infections may trigger activation of macrophage cluster of differentiation 169 (CD169), which is involved in immune response and activation of bone marrow for production of erythrocytes (33). Over-activation of CD169 macrophages may be linked with the propagation of polycythemia (33). Besides, CD169 macrophages control immunological responses during viral infections by recruiting monocytes and producing pro-inflammatory cytokines and chemokines (34). In this state, immunological response to various stimuli may increase blood viscosity with the development of hyperviscosity syndrome. These verdicts indicate that abnormal immuno-inflammatory disorders are associated with the progression of hyperviscosity syndrome.

VIRAL INFECTIONS AND HYPERVISCOSITY SYNDROME

It has been reported that hyperviscosity syndrome may develop in different viral infections. For example, impaired humoral and cellular immunity may increase immunoglobulin (IgG) levels in patients with human immunodeficiency virus type 1 (HIV-1) infections with subsequent development of hyperviscosity syndrome (35). Increased blood viscosity and the development of hyperviscosity syndrome in HIV-1 infected patients may be related to B cell hyperactivation, increased IgG production, changes in T cell-mediated B cell regulation, chronic exposure to HIV-1 antigens, increased production of interleukin 6 (IL-6), and direct activation of B cells by HIV-1 (36). Likewise, production of myeloma associated IgG1 paraprotein against HIV-1 p24 antigen in HIV-1 patients (37).

Moreover, indicators of blood viscosity are augmented in patients with hepatitis B virus (HBV) infection (38). A prospective study revealed that patients with HBV infection had greater RBCs aggregation index, hematocrit, and blood viscosity as compared with control groups (38). As well, soluble fibrinogen like protein 2 (sFGL2) is elevated in patients with HBV infection (39). Into the bargain, hyperviscosity syndrome has been reported to be linked with respiratory viral infections like influenza pneumonia (40). In their study, Bogomolov et al. observed that influenza pneumonia and other severe acute respiratory viral infections can cause hyperviscosity syndrome through induction of hypercoagulation, alteration of fibrinolytic activity, intravascular homeostasis, and failure of microcirculation (40). High blood viscosity in influenza pneumonia and respiratory viral infections may provoke progression of thrombosis due to an increase in vascular resistance, which hampers peripheral tissue perfusion (24). Piñol-Ripoll and coworkers found that chronic bronchitis predisposes to the development of hyperviscosity syndrome and an increased risk of ischemic stroke (41). Thus, these observations point out that acute respiratory viral infections as well as other viral infections may increase the risk of development of vascular complications through induction and progression of viral infections.

COVID-19 AND HYPERVISCOSITY SYNDROME

SARS-CoV-2 infection has been shown to reduce erythrocyte deformability and increase erythrocyte aggregation in COVID-19 patients in low-shear flow and stasis, which, combined with an increase in fibrinogen level, may increase blood viscosity and lead to the development of hyperviscosity syndrome (42). Increasing blood viscosity and hyperviscosity syndrome progression in COVID-19 may be linked to a variety of mechanisms, including endothelial dysfunction, exaggerated immune response, hypoxia, and coagulation disorders (17). Likewise, platelet hyper-reactivity, high ferritin, and P-selectin activity together with changes in erythrocyte function in COVID-19 might participate in the development of hyperviscosity syndrome (43). In severe SARS-CoV-2 infections, fever and dehydration due to anorexia, vomiting, and diarrhea may increase blood viscosity in COVID-19 patients (44).

Concerning the clinical perspective regarding the potential role of SARS-CoV-2 infection in the propagation of hyperviscosity syndrome, SARS-CoV-2 infection is linked with microcirculation failure in hospitalized COVID-19 patients (42). Of note, microcirculatory failure in COVID-19 patients leads to noteworthy alterations in the erythrocytes deformability and aggregation, resulting in stasis and augmentation of blood viscosity (45). Besides, coagulation disorders, endothelial dysfunction, and cytokine storm all contribute to microcirculation dysfunction in septic COVID-19 patients (46). The Renoux et al. study, which included seven hospitalized COVID-19 patients, seven non-COVID-19 septic patients, and seven healthy controls, found that erythrocyte deformability was lower in both COVID-19 patients and non-COVID-19 septic patients compared to controls (42). In addition, erythrocyte aggregation was higher in COVID-19 patients as compared to non-COVID-19 patients without noteworthy variations in fibrinogen levels and blood viscosity (42). This small sample size study may not give a tangible clue regarding normal blood viscosity in COVID-19. However, a

retrospective study including 41 COVID-19 patients reported that assessed blood viscosity was superior in COVID-19 patients compared with healthy control subjects (17).

Hyperviscosity Syndrome and Inflammatory Signaling Pathways in COVID-19

Exaggerated immune response and the release of pro-inflammatory cytokines, primarily IL-6, have been linked to the development of cytokine storm and MOI (47). In COVID-19, IL-6 is thought to be an important activator of fibrinogen synthesis (48). In addition, deregulation of the renin-angiotensin system (RAS) with an increase in circulating AngII levels in COVID-19 may prompt expression and synthesis of fibrinogen (49). In turn, high fibrinogen levels activate erythrocyte membrane integrinαvβ3 receptors, which induce erythrocyte aggregation and the development of hyperviscosity syndrome (48). Of interest, CD169 macrophages, which are involved in the maturation of erythrocytes, are activated in SARS-CoV-2 infection, resulting in polycythemia and the development of hyperviscosity syndrome (50). It has been observed that CD169 monocytes are expressed in 93.7% of COVID-19 patients and are regarded as having diagnostic benefits (50). Consequently, SARS-CoV-2-induced expression of CD169 by macrophages/monocytes may promote the development of polycythemia and hyperviscosity syndrome in COVID-19.

Significantly, increased blood viscosity in COVID-19 patients stimulates the release of arginine vasopressin (51), which causes the release of pro-inflammatory cytokines *via* activation of the nuclear factor kappa B (NF-κB) and nod-like receptor pyrin 3 (NLRP3) inflammasomes, both of which contribute to increased blood viscosity (51). Of note, both of NF-κB and NLRP3 inflammasome persuade asymmetry of erythrocyte membrane with decrease of erythrocyte deformability in normal and sickle erythrocytes (52, 53). Besides, NF-κB and NLRP3 inflammasome are extremely triggered in COVID-19 (54), and might a latent causes for lessening of erythrocyte deformability in COVID-19.

Moreover, p38 mitogen activated protein kinase (p38MAPK), mechanistic target of rapamycin (mTOR) and high mobility group box protein 1 (HMGP1) are also activated in COVID-19, leading to the release of pro-inflammatory cytokines (55–57). In turn, increased pro-inflammatory cytokines promote elevation of blood viscosity by inducing expression of fibrinogen with a reduction of erythrocyte deformability (58). Likewise, COVID-19 is usually associated with psychological stress and sympathetic outflow (59). In relevant, psychological stress increases circulating AngII as well, AngII promotes psychological stress through augmentation of sympathetic activation (60). Similarly, AngII receptor blockers attenuate stress pressor in young adults (60). Therefore, COVID-19-induced psychological stress may augment the dysregulated RAS by increasing AngII with the consequent development of hyperviscosity syndrome. As well, high circulating AngII in COVID-19 promotes the release of pro-inflammatory cytokines with the induction of erythrocyte aggregation and an increase in blood viscosity (61).

These observations suggest that activated inflammatory signaling pathways and the release of pro-inflammatory cytokines might be the latent causes for the development of hyperviscosity syndrome in COVID-19.

Hyperviscosity Syndrome and Erythrocyte Deformability in COVID-19

In COVID-19, SARS-CoV-2 may affect erythrocyte morphology *via* binding of membrane cluster of differentiation 147 (CD147) receptors and Band3 protein on the erythrocyte membrane (62, 63). These changes reduce the functional capacity of erythrocytes for oxygen transport and result in the development of tissue hypoxia (63). It has been shown that erythrocyte distribution width and other indices were brutally affected in SARS-CoV-2 infection and were associated with COVID-19 severity (64). Besides, severe hypoxia and acidosis encourage changes in the erythrocyte morphology (65). These explanations propose that direct SARS-CoV-2-induced erythrocyte dysmorphology and connected metabolic acidosis with hypoxia may induce the development of hyperviscosity syndrome in COVID-19.

Moreover, lipoproteins can disturb blood viscosity as low density lipoprotein (LDL) is clearly correlated while high density lipoprotein (HDL) is negatively correlated with blood viscosity (66). Indeed, HDL is required for erythrocyte morphology and deformability; thus, a decrease in HDL may shorten erythrocyte life by increasing osmotic fragility and decreasing erythrocyte deformability (67). In COVID-19, there is a notable variation in lipoprotein serum levels, and low HDL levels are linked with COVID-19 severity (68, 69). Thus, the decrease of HDL in SARS-CoV-2 infection may increase blood viscosity with the development of hyperviscosity syndrome in COVID-19.

Notably, COVID-19-induced oxidative stress may prompt an increase in blood viscosity (70). High oxidative stress in COVID-19 can trigger atypical hemorheological alterations with a decrease in erythrocyte deformability (71). In severe SARS-CoV-2 infections, oxidative stress may lead to endothelial dysfunction and thrombotic complications (72). Hence, variations in erythrocyte fragility and deformability with endothelial dysfunction and oxidative stress in SARS-CoV-2 infection may cause hyperviscosity syndrome in COVID-19.

Remarkably, erythrocyte morphology and functions are also affected in SARS-CoV-2 infection with the progression of erythrocrine dysfunction (73). In this state, the development of abnormal erythrocytes may contribute to the development of endothelial dysfunction and vascular injury by aggregate oxidative stress (74). Of interest, erythrocytes from COVID-19 patients promote expression of endothelial arginase with the generation of reactive oxygen species (ROS), reduction of endothelial NO and development of endothelial dysfunction (74). Thus, SARS-CoV-2 infection-induced oxidative stress might in part be mediated by the development of abnormal erythrocytes in COVID-19.

Hyperviscosity Syndrome and Thrombosis in COVID-19

Conspicuously, severe COVID-19 is linked with the development of thromboembolic events due to direct SARS-CoV-2 cytopathic effects and related platelet activation, coagulation activation, endothelial dysfunction, and inhibition of the fibrinolytic

pathway (75). Also, down-regulation of ACE2 with deregulation of RAS together with exaggerated release of pro-inflammatory cytokines may induce endothelial dysfunction through reduction of prostacyclin and nitric oxide (NO) (76). Thrombotic events may increase the risk of the development of hyperviscosity syndrome (77). These observations suggest a mutual interaction between HVS and thrombotic events in COVID-19.

Additionally, hypoalbuminemia is linked with an increase in blood viscosity and the development of hyperviscosity syndrome (78). Of note, serum albumin is negatively correlated with D-dimer and CRP, and hypoalbuminemia is linked with the development of coagulopathy in COVID-19 patients through a decrease in the anticoagulant and antiplatelet effects of albumin (79). A study of 113 COVID-19 patients by Bi et al. found that a high fibrinogen/albumin ratio was associated with an increased risk of thrombotic events, disease severity, and poor clinical outcomes (80). Thus, the blood viscosity is increased and reaches up to 4.2 cp. Consequently, hyperfibrinogenemia and hypoalbuminemia may increase blood viscosity and contribute to the progression of hyperviscosity syndrome and thrombotic complications in COVID-19 (80).

Strangely, most of the COVID-19 patients with higher blood viscosities of more than 3.5 cp may develop coagulation disorders (81). In this condition, there is a close relationship between hyperviscosity syndrome and thrombotic events in COVID-19. It has been shown that critical COVID-19 patients were associated with thrombotic complications and blood viscosity greater than 3.5 cp (the normal range is 1.4–1.8 cp) was correlated with thrombotic complications (81). In addition, Truong et al. reported that symptoms of hyperviscosity syndrome were more obvious in COVID-19 patients with a blood viscosity of more than 4.2 cp (82). These findings suggest that higher blood viscosity is connected with more severe hyperviscosity syndrome in COVID-19.

These verdicts propose that severe SARS-CoV-2 infection in COVID-19 patients can increase blood viscosity by modulating fibrinogen, albumin, lipoproteins, and erythrocyte deformability and aggregations (**Figure 1**).

Complications of Hyperviscosity Syndrome in COVID-19

Of interest, hyperviscosity syndrome in COVID-19 may cause poor tissue perfusion, peripheral vascular resistance, and thrombosis (24). In particular, low-shear areas are vulnerable to thrombosis due to a decrease in the dispersion of clotting factors and a reduction in the shear-induced release of antithrombotic molecules like NO and prostacyclin (24).

Indeed, hyperviscosity syndrome may lead to extra-pulmonary complications, including acute kidney injury, skeletal muscle ischemia, glucose intolerance, and myocardial necrosis (83). In addition, hyperviscosity syndrome leads

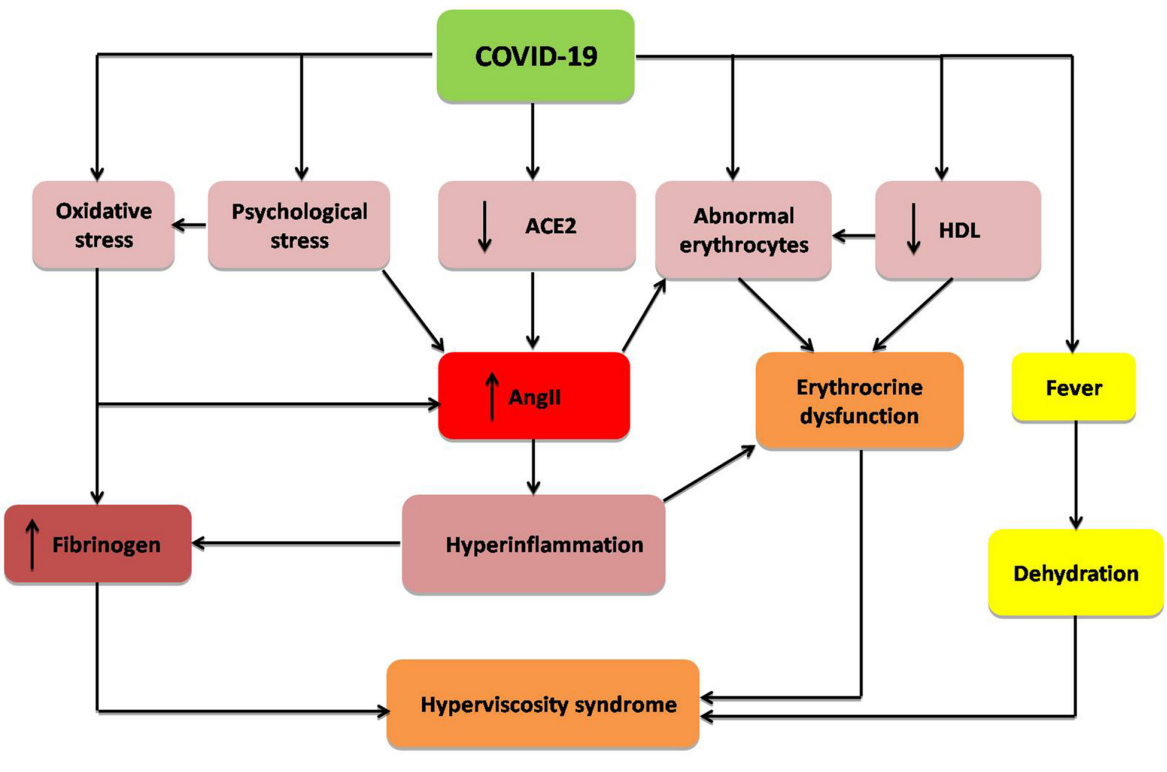

FIGURE 1 | Mechanism of hyperviscosity syndrome in COVID-19: COVID-19 through down-regulation of angiotensin converting enzyme 2 (ACE2), psychological stress, hyperinflammation, oxidative stress, abnormal morphology of erythrocytes, and reduction of high density lipoprotein (HDL). These changes increase fibrinogen level and angiotensin II (AngII), with induction of erythrocrine dysfunction and subsequent development of hyperviscosity syndrome.

to ventilation-perfusion mismatch and the development of pulmonary hypoperfusion. These pathological changes lead to silent hypoxemia and exaggerated pulmonary vascular resistance (84). Furthermore, COVID-19-induced hyperviscosity syndrome has been associated with numerous cardiovascular and neurological complications like stroke and myocardial infarction (85, 86). In particular, hyperviscosity syndrome increases the risk of the development of myocardial infarction in COVID-19 patients (87). As well, immunothrombosis and endothelial dysfunction, which are induced by SARS-CoV-2 infection, could be potential causes of hyperviscosity syndrome in COVID-19 (82). These vicissitudes escalate the risk of the development of myocardial infarction in surviving COVID-19 patients due to the progression of coronary microangiopathy (88).

Indeed, hyperviscosity syndrome is connected with the progression of post-COVID-19 syndrome (long COVID-19), which is characterized by dyspnea, fatigue, cognitive dysfunction, and headache following recovery from COVID-19 (89). It has been shown that long COVID-19 is linked with cardio-pulmonary fibrosis and immunosuppression due to upregulation of transforming growth factor beta (90). Protracted inflammatory changes and high blood viscosity in patients with long COVID-19 can decrease tissue perfusion with induction of abnormal cellular metabolism (91). In this state, COVID-19-induced abnormal erythrocrine function may promote tissue hypoxia and subnormal cell metabolism, which may prolong symptoms of long COVID-19 (74). Herein, hyperviscosity syndrome with or without erythrocrine dysfunction in COVID-19 contributes to the decrease in tissue oxygenation and the development of cardio-metabolic complications in long COVID-19 (**Figure 2**).

COVID-19 VACCINATION AND HYPERVISCOSITY SYNDROME

The management of COVID-19 heavily relies on the presence of safe and effective vaccines. There are various types of vaccines against SARS-CoV-2. One type is mRNA vaccines encoding the S protein antigen of the virus, like the Pfizer-BioNTech COVID-19 Vaccine (92). Another type of COVID-19 vaccine is the vector-based vaccine that delivers the code for the spike antigen of SARS-CoV-2. Examples of vector-based vaccines include the Oxford–AstraZeneca vaccine, Convidecia vaccine, Sputnik-V vaccine, and Johnson vaccine (93). Also, there are inactivated vaccines, such as the Sinopharm vaccine (93). Another potential COVID-19 vaccine is the NVX-CoV2373 vaccine, which contains a recombinant nanoparticle spike protein (94). The COVID-19 vaccine was developed in the early part of April 2020 to control the spread of the SARS-CoV-2 infection (95). It is of note that the FDA approved the first COVID-19 vaccine on August 23, 2021, which is an mRNA vaccine that has been known as the Pfizer-BioNTech COVID-19 Vaccine. This vaccine was approved for those who are 16 years of age or older (95). Subsequent to the COVID-19 vaccination, some reports disclosed that the blood viscosity was augmented due to induction of immune response and an increase in anti-SARS-CoV-2 immunoglobulins (96). It has been shown that hyperviscosity syndrome may develop following COVID-19 vaccination, causing immunoinflammatory changes (96). Hyperviscosity syndrome is associated with the concentration of immunoglobulins; nevertheless the lowest normal immunoglobulins concentrations are below 545 mg/dl whereas the lowest blood viscosity is 1.5 cp (97). The blood viscosity will be 2.6 cp when the immunoglobulin concentrations reach up to 6160 mg/dl (94). Of note, symptoms of HVS develop when BV exceeds 4.0 cp (97).

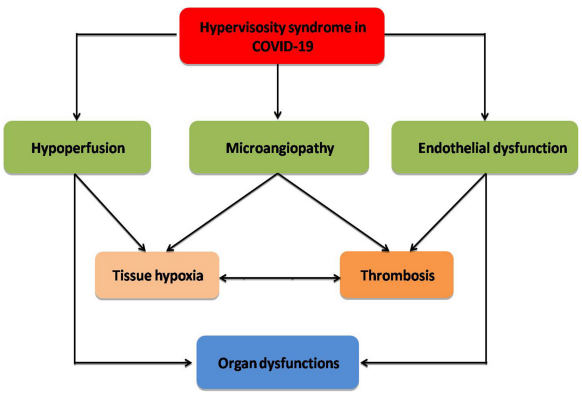

FIGURE 2 | Complications of hyperviscosity syndrome in COVID-19: Hyperviscosity syndrome provokes the development of endothelial dysfunction, microangiopathy, and hypoperfusion with the development of thrombosis and tissue hypoxia, which eventually cause organ dysfunction.

Normally, in healthy COVID-19 vaccine recipients, the blood viscosity is increased by 2.4 cp (98). However, COVID-19 vaccine-induced hyperviscosity syndrome is more common in patients with metabolic syndrome due to metabolic disorders which increase blood viscosity (99). Of interest, hyperbilirubemia in chronic liver diseases may induce the development of hyperviscosity syndrome following COVID-19 vaccination (99). Interestingly, hyperbilirubinemia provokes the development of hyperviscosity syndrome by an unknown mechanism (99). Therefore, patients with metabolic disorders are regarded as high-risk factors for the development of hyperviscosity syndrome after COVID-19 vaccination. Hence, monitoring of blood viscosity in COVID-19 vaccine recipients is compulsory to avoid post-vaccine complications (100, 101).

It has been reported that patients with metabolic syndrome had higher blood viscosity and were more susceptible to the propagation of hyperviscosity syndrome (102). In particular, metabolic syndrome is associated with underlying systemic inflammation and oxidative stress, which increases the blood viscosity by reducing erythrocyte deformability (103). Consequently, patients with metabolic syndrome are at a superior risk for the development of hyperviscosity syndrome following COVID-19 vaccination. Herein, COVID-19 vaccinations may increase the risk for development of hyperviscosity syndrome in patients with metabolic syndrome (104). It has been demonstrated that the blood viscosity was elevated by 2.7 times in healthy subjects compared to 2.99 times in patients with metabolic syndrome after COVID-19 vaccinations (104). This elevation in the blood viscosity did not reach the state of

hyperviscosity syndrome, which might be due to the validity of the method in the assessment of blood viscosity (105).

Remarkably, oxidative stress can persuade a reduction in erythrocyte deformability with a successful increase in blood viscosity (106). High oxidative stress and fibrinogen together with prolonged low-grade inflammation in obesity are related to the development of hyperviscosity syndrome (107, 108). Thus, obese patients are at great risk for the development of hyperviscosity syndrome following COVID-19 vaccination. Likewise, the immune response in obese patients to the COVID-19 vaccine is weak due to the decreased reactivity of lymphocytes (109). Hence, interruption of the immune response may reduce the concentration of immunoglobulins after COVID-19 vaccination (110). As well, the immune response in obese patients was low after the influenza vaccine (110).

Astonishingly, hyperviscosity syndrome is more commonly developed in vaccine recipients who have formerly received the COVID-19 vaccine due to higher underlying immunoglobulin concentrations and only infrequently in those who have not received the COVID-19 vaccine (96). Therefore, screening of subjects for previous COVID-19 vaccination is vital before introducing COVID-19 vaccination to avert the development of hyperviscosity syndrome and related complications. Besides, use of contraceptives may increase the risk of development of hyperviscosity syndrome following COVID-19 vaccination (111). Hence, we suggest taking the risk into consideration for patients taking contraceptives at the time of COVID-19 vaccination.

Taken together, these findings are too preliminary to draw any conclusions about the relationship between COVID-19 vaccination and the risk of developing hyperviscosity syndrome; therefore, further research, both prospective and retrospective, is required.

The present review had numerous limitations, including the scarcity of prospective studies which appraised the blood viscosity of COVID-19. As well, most of the studies were hypothetical in their explanation of hyperviscosity syndrome in COVID-19 and COVID-19 vaccination. However, regardless of these limitations, the present critical review reveals that hyperviscosity syndrome is an imperative mechanistic pathway in the progression of COVID-19 complications and associated vaccines.

CONCLUSION

The present review showed that COVID-19 and linked vaccines are associated with the development of hyperviscosity syndrome, particularly in patients with previous COVID-19 and metabolic disorders. The potential mechanism of hyperviscosity syndrome in COVID-19 and COVID-19 vaccines is augmentation in the levels of fibrinogen and immunoglobulins. As well, dehydration, oxidative stress, and inflammatory reactions could be additional contributing factors in the development of hyperviscosity syndrome in COVID-19. Though, this review did not determine the ultimate causal relationship between COVID-19 and COVID-19 vaccines with the development of hyperviscosity syndrome. Therefore, experimental, *in vitro*, and clinical studies are necessary in this regard.

AUTHOR CONTRIBUTIONS

HA-k and AA-G performed data collection and analysis. HA-k, AA-G, SC, SA-H, ME-B, FS, and GE-SB wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors contributed to the study conception and design and read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 11 July 2022
doi: 10.3389/fpubh.2022.952781

Oral Adverse Events Following COVID-19 Vaccination: Analysis of VAERS Reports

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OPEN ACCESS

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Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: 25 May 2022
Accepted: 22 June 2022
Published: 11 July 2022

Citation:
Riad A, Põld A, Kateeb E and Attia S (2022) Oral Adverse Events Following COVID-19 Vaccination: Analysis of VAERS Reports. Front. Public Health 10:952781. doi: 10.3389/fpubh.2022.952781

Background: Oral adverse events (AEs) following COVID-19 vaccination have been sporadically reported during the previous months, warranting further investigation for their prevalence and suspected relationship with vaccine-elicited immune response.

Methods: A retrospective analysis using the Vaccine Adverse Event Reporting System (VAERS) data was conducted to evaluate AEs within the oral cavity (mucosa, tongue, lips, palate, dentition, salivary glands) and AEs involving taste and other sensations. Oral AEs reported after receiving COVID-19 vaccination (test group) and seasonal influenza vaccination (control group) were extracted and cross-tabulated to assess their relative prevalence.

Results: Among the 128 solicited (suspected) oral AEs, oral paresthesia (0.872%) was most reported after receiving COVID-19 vaccines, followed by the swelling of lips (0.844%), ageusia (0.722%), oral hypoesthesia (0.648%), swollen tongue (0.628%), and dysgeusia (0.617%). The reported prevalence of oral AEs was higher in the COVID-19 vaccine group than in the seasonal influenza group. The distribution pattern of the most reported oral AEs was similar for both COVID-19 and seasonal influenza vaccines. Female sex, older age (>39 years old), primer doses, and mRNA-based COVID-19 vaccines exhibited a higher reported prevalence of oral AEs.

Conclusion: Within the limitations of this study, COVID-19 vaccines were found to be associated with rare oral AEs that are predominantly similar to those emerging following seasonal influenza vaccines. The most commonly reported oral AEs were oral paraesthesia (mouth-tingling), lip swelling, and ageusia, representing various pathophysiologic pathways that remain unclear. Taste-related AEs should be acknowledged in the context of the COVID-19 pandemic and the public should be adequately informed about a potential taste dysfunction after receiving the COVID-19 vaccination. Dentists and dental teams need to be aware of the prevalence, severity, and prognosis of oral AEs to inform their patients and increase public confidence in vaccines.

Keywords: anaphylaxis, COVID-19 vaccines, drug-related side effects and adverse reactions, oral manifestations, pharmacovigilance oral adverse events following COVID-19 vaccination 2

INTRODUCTION

A wide array of clinical manifestations associated with coronavirus disease (COVID-19) have been reported within the oral cavity, including taste dysfunction, oral mucosal lesions, and salivary gland disorders (1). Therefore, dentists and dental team members encountered additional challenges in providing their services amid the pandemic while attempting to protect their patients and colleagues from cross-infection (2).

Fortunately, a strong global collaboration between pharmaceutical companies enabled the rapidly developing vaccines against this novel respiratory disease leading to certain vaccines receiving emergency authorization by the end of the first year of the pandemic. As vaccines offer the best solution to control this pandemic by establishing herd immunity, it is essential to achieve substantial vaccine uptake levels across the global community (3). To ensure a high vaccine uptake and prevent vaccine hesitancy, it is necessary to manage with its key triggers including the fear of potential post-vaccination side effects (3).

Individual reports were published sporadically during the previous months about oral adverse events (AEs) that emerged after receiving various COVID-19 vaccines, thus, warranting further investigation by epidemiologic researchers and careful attention by dental practitioners (4). The overarching aim of this study was to evaluate the oral AEs reported within the United States (US) population following COVID-19 vaccination, their prevalence and demographic risk factors, and compare them against oral AEs of seasonal influenza.

MATERIALS AND METHODS

Design

A retrospective analysis for the Vaccine Adverse Event Reporting System (VAERS), an open-access database co-managed by the US Food and Drug Administration (FDA) and the Centers for Diseases Control and Prevention (CDC), was conducted in April 2022 (5). VAERS reports had been accessed through the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) tool, which provides summarized frequencies of reported symptoms based on the Medical Dictionary for Regulatory Activities (MedDRA) scheme (5, 6).

Population

All VAERS reports of the individuals who received COVID-19 vaccination from January 1st to December 31st, 2021, were accessed through the WONDER tool and used as a "test group." To select an appropriate "control group," VAERS reports of all vaccines administered during 2021 were thoroughly examined. The decision to use seasonal influenza vaccines as a "control group" was made based on the following reasons: (a) seasonal influenza and COVID-19 vaccines are recommended/administered to all age groups and sexes in all US states and territories indiscriminately, (b) the frequency of seasonal influenza vaccine-related AEs reported during 2021 came second after the frequency of COVID-19 vaccine-related AEs, (c) both vaccines are primarily administered through intramuscular injection, and (d) both vaccines target respiratory infections that can spread similarly and synergistically in the community leading to similar clinical complications (7).

Variables

MedDRA uses a logical classification hierarchy consisting of five levels starting from the "System Organ Class" level e.g., (gastrointestinal disorders) until the "Preferred Term" and the "Lowest Level Term" e.g., (aphthous stomatitis) and (aphthous ulcer), respectively (6). Oral AEs are scattered across various levels of the MedDRA hierarchy; therefore, we developed an anatomo-physiological scheme to extract all potential AEs related to oral cavity structures and functions. Our *de novo* scheme divided the oral cavity into six regions, including oral mucosa (e.g., oral herpes), tongue (e.g., swollen tongue), lips (e.g., lip swelling), palate (e.g., palatal oedema), salivary glands (e.g., dry mouth), and dentition (e.g., hyperaesthesia teeth), and two functions, including taste (e.g., dysgeusia) and other sensory disorders (e.g., oral paraesthesia) (**Figure 1**).

An exhaustive list of potential oral AEs ($n = 310$) was extracted based on our proposed scheme, and two oral surgery specialists reviewed it for further validation and filtration (**Supplementary Table S1**). A total of 182 preferred terms / lowest level terms (PT/LLT) had been excluded from the original list due to de-duplication ($n = 43$), being of congenital or developmental nature e.g., ankyloglossia congenital ($n = 16$), behavioral and traumatic injuries e.g., tooth fracture ($n = 20$), clinical dental procedures e.g., x-ray dental ($n = 42$), chronic conditions e.g., salivary gland cancer ($n = 52$) and irrelevant to oral cavity e.g., oral contraception ($n = 9$). A final list of 128 potential oral AEs was used in the downstream analyses.

Analyses

The primary outcome was the proportion of oral AEs within all VAERS reports of the same vaccine group, e.g., [(number of ageusia reports related to COVID-19 vaccines)/(total reports related to COVID-19 vaccines)] * 100. The secondary outcome was the prevalence of reported AEs per 100,000 administered vaccine doses. Given the median age of the US population which is 38.5 years old, the age of 39 years was used as a cut-off point for the age-specific analysis of oral AEs prevalence (8). Chi-squared test (χ^2) and Fisher's exact test were used to compare percentages and rates of oral AEs between COVID-19 vs. seasonal influenza vaccines, females vs. males, and $\leq$39 years old vs. >39 years old. Crosstabulation tests also compared oral AEs across various COVID-19 vaccine brands and doses. Moreover, taste-related AEs were compared between the pre-COVID-19 pandemic period (January 2010–December 2019) *vs.* the pandemic period (January 2020–December 2021). All analytical tests were performed using GraphPad Prism version 9.3.1 (GraphPad Software Inc. San Diego, CA, USA, 2021) and following the assumptions of confidence interval (CI) 95% and significance level (Sig.) ≤ 0.05.

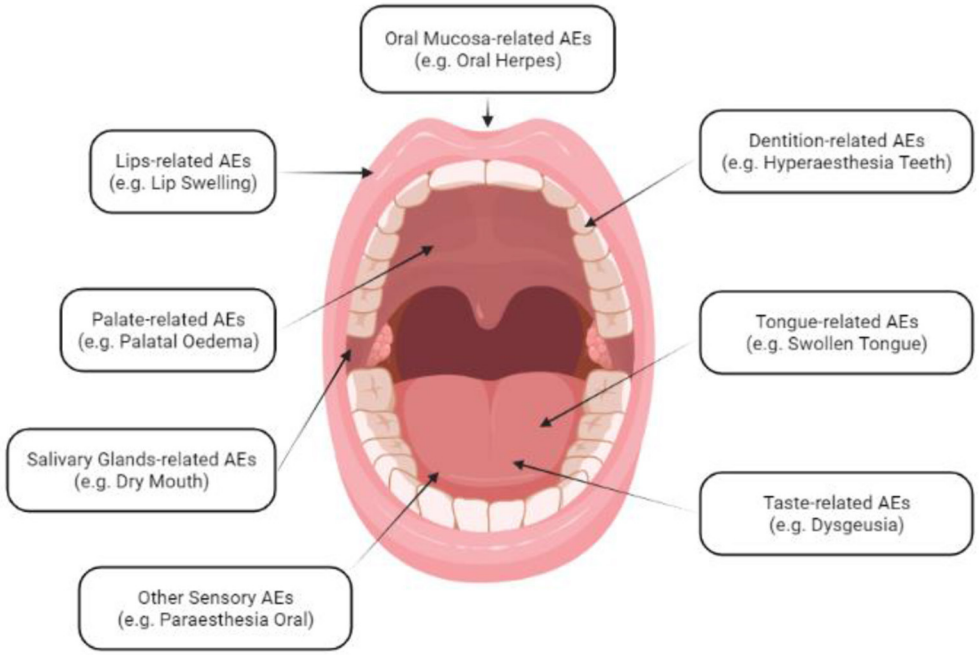

FIGURE 1 | Anatomo-physiological Scheme of Oral Adverse Events Following Immunization (AEFI); created in BioRender.com.

TABLE 1 | Demographic characteristics of COVID-19 and seasonal influenza vaccines recipients in the United States, January–December 2021 (CDC; VAERS-WONDER).

Variable	Outcome	COVID-19 vaccine (n = 507 M)	Seasonal influenza vaccine (n = 173.3 M)	*Sig.*
Received reports[†]	*N* (rate)	690,853 (136.3 per 100,000 doses)	6,970 (4.0 per 100,000 doses)	**<0.001**
[†]Sex	Female	466,323 (67.5%)	4,587 (65.8%)	**0.003**
	Male	211,597 (30.6%)	2,189 (31.4%)	0.162
	Unknown	12,933 (1.9%)	194 (2.8%)	**<0.001**
[†]Age group	<6 years	1,000 (0.1%)	439 (6.3%)	**<0.001**
	6–17 years	33,817 (4.9%)	734 (10.5%)	**<0.001**
	18–29 years	76,243 (11.0%)	625 (9.0%)	**<0.001**
	30–39 years	103,093 (14.9%)	789 (11.3%)	**<0.001**
	40–49 years	104,505 (15.1%)	655 (9.4%)	**<0.001**
	50–59 years	111,229 (16.1%)	877 (12.6%)	**<0.001**
	60–64 years	55,859 (8.1%)	596 (8.6%)	0.158
	65–79 years	133,504 (19.3%)	1,620 (23.2%)	**<0.001**
	80+ years	36,135 (5.2%)	370 (5.3%)	0.766
	Unknown	35,468 (5.1%)	265 (3.8%)	**<0.001**

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.
Bold values represents significant values.
[†]*Total number of received reports.*

RESULTS

Demographic Characteristics

In total, 690,853 and 6,970 reports were received for COVID-19 and seasonal influenza vaccines, respectively, from individuals who were vaccinated in 2021, thus, constituting the denominator of the primary outcome in each vaccine group. Most reports in both COVID-19 (67.5%) and seasonal influenza (65.8%) groups were from females. The 65–79 years old was the most reporting age group in both COVID-19 (19.3%) and seasonal influenza (23.2%) groups, while the least reporting age group for COVID-19 vaccines was <6 years old, and for seasonal influenza vaccine was ≥80 years old (**Table 1**).

It is worth noting that the overall rate of reported AEs is significantly (*Sig.* < 0.001) higher in the COVID-19 group (136.3 reports per 100,000 administered doses) than in the seasonal influenza group (4 reports per 100,000 administered doses).

Overall Prevalence of Oral AEs

In the domain of oral mucosa-related AEs, oral herpes was the most commonly reported AE in both COVID-19 and seasonal influenza vaccine groups (0.189 vs. 0.086%; *Sig.* = 0.050), followed by stomatitis and aphthous ulcer (0.168 vs. 0.158%; *Sig.* = 0.829), mouth swelling (0.131 vs. 0.115%; *Sig.* = 0.868), oral discomfort (0.108 vs. 0.072%; *Sig.* = 0.463), oral pain (0.103 vs. 0.086%; *Sig.* = 0.851), oral pruritus (0.065 vs. 0.014%; *Sig.* = 0.147), and oral mucosal blistering (0.057 vs. 0.043%; *Sig.* = 1.000). Despite the lack of statistically significant differences between vaccine groups in terms of the primary outcome (proportion of oral AEs to all reported AEs in VAERS), differences between vaccine groups in terms of the secondary outcome (proportion of oral AEs to all administered vaccine doses) were all statistically significant (*Sig.* < 0.001; **Table 2**).

Swollen tongue (0.628% *vs*. 0.072%; *Sig.* = 0.007) was the most common tongue-related AE in both COVID-19 and seasonal influenza groups, followed by tongue discomfort (0.083 vs. 0%), tongue disorder (0.075 vs. 0.057%; *Sig.* = 0.598), and tongue pruritus (0.070 vs. 0.057%; *Sig.* = 0.694). Lip swelling (0.737 vs. 0.588%; *Sig.* = 0.148) and lip pruritus (0.050 vs. 0.029%; *Sig.* = 0.424) were the most common lip-related AEs in both vaccine groups. Dry mouth (0.301 vs. 0.043%; *Sig.* < 0.001) was the most common salivary glands-related AE, while toothache (0.142 vs. 0.043%; *Sig.* = 0.023) was the most common dentition-related AE in both vaccine groups (**Supplementary Figure S2**).

Ageusia (0.722 vs. 0.143%; *Sig.* < 0.001) was the most common taste-related AE in both vaccine groups, followed by dysgeusia (0.617 vs. 0.244%; *Sig.* < 0.001) and taste disorder (0.317 vs. 0.115%; *Sig.* < 0.001). Oral paraesthesia (0.872 vs. 0.473%; *Sig.* < 0.001) and oral hypoaesthesia (0.648 vs. 0.430%; *Sig.* < 0.001) were the most frequently reported sensory AEs in both vaccine groups (**Figure 2**).

Sex- and Age-Specific Prevalence

In the COVID-19 group, analysis of the top twenty oral AEs sex-specific prevalence revealed that females had a significantly (*Sig.* < 0.001) higher prevalence than males in all solicited AEs except for ageusia. The prevalence of ageusia was similar among females (0.683%) and males (0.708%), *Sig.* = 0.238. Likewise, females reported more oral AEs than males in the seasonal influenza group except for oral herpes, toothache, and tongue discomfort which were almost equally prevalent across sexes (**Figure 3**).

Interestingly, in the COVID-19 group, the older age group (>39 years old) had significantly (*Sig.* < 0.001) higher prevalence of oral AEs compared to the younger age group (≤39 years old) except for lip swelling, tongue pruritus, and oral pruritus. Similarly, the older age group reported oral AEs more frequently than the younger age group following seasonal influenza vaccination, except for dysgeusia, oral herpes and tongue pruritus (**Table 3**).

Dose- and Vaccine Brand-Related Prevalence

The first dose of COVID-19 vaccination was significantly (*Sig.* < 0.001) associated with more oral AEs than the second dose, except for ageusia, stomatitis and aphthous ulcer, oral herpes, and toothache where the second dose was associated more frequent oral AEs. On comparing the primer doses (first dose and second dose) with the booster doses (third dose), the primer doses were significantly associated with a higher prevalence of all solicited AEs compared to the booster doses (*Sig.* < 0.001; **Figure 4**).

Pfizer-BioNTech COVID-19 vaccine (BNT162b2) was associated with more frequently reported oral AEs than Moderna COVID-19 vaccine (mRNA-1273), except for oral herpes and oral pain. Overall, mRNA-based vaccines (BNT162b2 and mRNA-1273) had a significantly higher prevalence of oral paraesthesia (0.838 vs. 0.582%; *Sig.* < 0.001), lip swelling (0.706 vs. 0.525%; *Sig.* < 0.001), swollen tongue (0.599 vs. 0.447%; *Sig.* < 0.001), mouth swelling (0.127 vs. 0.090%; *Sig.* = 0.021), oral discomfort (0.106 vs. 0.058%; *Sig.* = 0.001), tongue disorder (0.072 vs. 0.038%; *Sig.* = 0.004), tongue pruritus (0.068 vs. 0.038%; *Sig.* = 0.011), and oral pruritus (0.063 vs. 0.040%; *Sig.* = 0.040; **Tables 4**, **5**).

Longitudinal Analysis of Taste-Related AEs

On comparing the overall percentage of taste-related AEs before (January 2010–December 2019) and during (January 2020–December 2021) the COVID-19 pandemic, ageusia was significantly more commonly reported during the pandemic (0.622 vs. 0.035%; *Sig.* < 0.001) than before the pandemic interval. Likewise, dysgeusia (0.581 vs. 0.182%; *Sig.* < 0.001), taste disorder (0.279 vs. 0.006%; *Sig.* < 0.001), and hypogeusia (0.019 vs. 0.006%; *Sig.* < 0.001) were significantly more common during the pandemic interval (**Table 6**).

DISCUSSION

The present analysis aimed to synthesize population-based evidence about oral adverse events (AEs) after COVID-19 vaccination utilizing a national surveillance database. Comparison between COVID-19 and seasonal influenza vaccines revealed a remarkable similarity in the distribution of the most reported oral AEs. Among the top twenty oral AEs, oral paresthesia was most reported after COVID-19 and seasonal influenza vaccination (14 and 16%, respectively), followed by lip swelling (12 and 20%), ageusia (12 and 5%), oral hypoesthesia (11 and 14%), swollen tongue (10 and 7%), dysgeusia (10 and 8%), taste disorder (5 and 4%), dry mouth (5 and 1%), and oral herpes (3 and 3%). Cohen et al. found that constitutional AEs such as headache, fatigue, and pyrexia had a significantly higher prevalence following COVID-19 than seasonal influenza and hepatitis B vaccines in the VAERS database (9). Likewise, a recent comprehensive analysis of the US and European Union surveillance systems indicated that the largest absolute risks following COVID-19 vaccines were constitutional, dermatological, neurological and gastrointestinal AEs (10). Given the nature of passive surveillance systems, including VAERS, which are inclined toward under-reporting than over-reporting, the higher prevalence of oral AEs following COVID-19 vaccines as compared with seasonal influenza vaccines can be attributed to reporting bias that might be triggered by public anxiety due to the novelty of COVID-19 vaccines (10, 11).

TABLE 2 | Oral adverse events reported after receiving COVID-19 and seasonal influenza vaccines in the United States, January–December 2021 (CDC; VAERS-WONDER).

Preferred term	COVID-19 vaccine		Seasonal influenza vaccine		*Sig.*		
	% of Total AE (n = 690,853)	Rate per 100,000 doses	% of total AE (n = 6,970)	Rate per 100,000 doses	% of total AE	Rate per 100K D	Group
Dental discomfort (10054217)	57 (0.008%)	0.011	1 (0.014%)	0.001	0.441	**0.006**	Dentition-Related AE[a]
Dental paraesthesia (10078276)	22 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	
Hyperaesthesia teeth (10082426)	159 (0.023%)	0.031	0 (0%)	N/A	N/A	N/A	
Hypoesthesia teeth (10051780)	15 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Toothache (10044055)	981 (0.142%)	0.193	3 (0.043%)	0.002	**0.023**	**<0.001**	
Ageusia (10001480)	4,985 (0.722%)	0.983	10 (0.143%)	0.006	**<0.001**	**<0.001**	Taste-Related AE
Dysgeusia (10013911)	4,263 (0.617%)	0.841	17 (0.244%)	0.010	**<0.001**	**<0.001**	
Hypogeusia (10020989)	141 (0.020%)	0.028	1 (0.014%)	0.001	1.000	**<0.001**	
Taste disorder (10082490)	2,193 (0.317%)	0.433	8 (0.115%)	0.005	**0.001**	**<0.001**	
Salivary duct stenosis (10039388)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	Salivary glands and saliva-related AE[b]
Salivary gland pain (10039421)	19 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	
Salivary gland enlargement (10039408)	41 (0.006%)	0.008	0 (0%)	N/A	N/A	N/A	
Salivary gland calculus (10039394)	3 (<0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Salivary gland mass (10057002)	8 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Salivary gland disorder (10061935)	11 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Salivary hypersecretion (10039424)	259 (0.037%)	0.051	1 (0.014%)	0.001	0.529	**<0.001**	
Dry mouth (10013781)	2,080 (0.301%)	0.410	3 (0.043%)	0.002	**<0.001**	**<0.001**	
Aptyalism (10003068)	32 (0.005%)	0.006	0 (0%)	N/A	N/A	N/A	
Saliva discolouration (10049069)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Saliva altered (10039379)	16 (0.002%)	0.003	1 (0.014%)	0.001	0.157	0.625	
Sialoadenitis (10040628)	31 (0.004%)	0.006	0 (0%)	N/A	N/A	N/A	
Non-infective sialoadenitis (10075243)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Atrophic glossitis (10069085)	3 (<0.001%)	0.001	0 (0%)	N/A	N/A	N/A	Tongue-Related AE[c]
Hypertrophy of tongue papillae (10020893)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Glossitis (10018386)	148 (0.021%)	0.029	0 (0%)	N/A	N/A	N/A	
Glossodynia (10018388)	564 (0.082%)	0.111	5 (0.072%)	0.003	0.773	**<0.001**	
Macroglossia (10025391)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Plicated tongue (10035630)	9 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Swollen tongue (10042727)	4,340 (0.628%)	0.856	26 (0.373%)	0.015	**0.007**	**<0.001**	
Tongue oedema (10043967)	31 (0.004%)	0.006	0 (0%)	N/A	N/A	N/A	
Tongue blistering (10043942)	155 (0.022%)	0.031	3 (0.043%)	0.002	0.255	**<0.001**	
Tongue ulceration (10043991)	126 (0.018%)	0.025	0 (0%)	N/A	N/A	N/A	
Tongue coated (10043945)	39 (0.006%)	0.008	0 (0%)	N/A	N/A	N/A	
Tongue discolouration (10043949)	188 (0.027%)	0.037	1 (0.014%)	0.001	0.516	**<0.001**	
Trichoglossia (10080276)	7 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Tongue pigmentation (10069164)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Tongue erythema (10079075)	138 (0.020%)	0.027	1 (0.014%)	0.001	0.740	**<0.001**	
Strawberry tongue (10051495)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Tongue eruption (10052002)	66 (0.010%)	0.013	0 (0%)	N/A	N/A	N/A	
Tongue movement disturbance (10043963)	49 (0.007%)	0.010	0 (0%)	N/A	N/A	N/A	
Stiff tongue (10081491)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Tongue paralysis (10043972)	24 (0.003%)	0.005	0 (0%)	N/A	N/A	N/A	
Tongue discomfort (10077855)	573 (0.083%)	0.113	0 (0%)	N/A	N/A	N/A	
Tongue disorder (10043951)	516 (0.075%)	0.102	4 (0.057%)	0.002	0.598	**<0.001**	
Tongue exfoliation (10064488)	12 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Tongue induration (10084548)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	

(Continued)

TABLE 2 | Continued

Preferred term	COVID-19 vaccine		Seasonal influenza vaccine		*Sig.*		
	% of Total AE (*n* = 690,853)	Rate per 100,000 doses	% of total AE (*n* = 6,970)	Rate per 100,000 doses	% of total AE	Rate per 100K D	Group
Tongue dry (10049713)	75 (0.011%)	0.015	0 (0%)	N/A	N/A	N/A	
Tongue pruritus (10070072)	483 (0.070%)	0.095	4 (0.057%)	0.002	0.694	**<0.001**	
Tongue rough (10043977)	12 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Tongue spasm (10043981)	14 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Tongue fungal infection (10075845)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Tongue thrust (10082545)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Angular cheilitis (10002509)	14 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	Lip-Related AE[d]
Cheilitis (10008417)	303 (0.044%)	0.060	2 (0.029%)	0.001	0.547	**<0.001**	
Chapped lips (10049047)	210 (0.030%)	0.041	1 (0.014%)	0.001	0.443	**<0.001**	
Lip blister (10049307)	283 (0.041%)	0.056	4 (0.057%)	0.002	0.501	**<0.001**	
Lip discolouration (10024549)	102 (0.015%)	0.020	2 (0.029%)	0.001	0.343	**<0.001**	
Lip disorder (10048470)	125 (0.018%)	0.025	2 (0.029%)	0.001	0.514	**<0.001**	
Lip dry (10024552)	189 (0.027%)	0.037	3 (0.043%)	0.002	0.432	**<0.001**	
Lip erythema (10080124)	145 (0.021%)	0.029	1 (0.014%)	0.001	0.703	**<0.001**	
Lip exfoliation (10064482)	63 (0.009%)	0.012	2 (0.029%)	0.001	0.092	**0.003**	
Lip oedema (10024558)	60 (0.009%)	0.012	1 (0.014%)	0.001	0.615	**0.003**	
Lip pain (10024561)	266 (0.039%)	0.052	5 (0.072%)	0.003	0.161	**<0.001**	
Lip pruritus (10070721)	347 (0.050%)	0.068	2 (0.029%)	0.001	0.424	**<0.001**	
Lip scab (10082767)	7 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Lip swelling (10024570)	5,092 (0.737%)	1.000	41 (0.588%)	0.024	0.148	**<0.001**	
Lip ulceration (10024572)	24 (0.003%)	0.005	1 (0.014%)	0.001	0.131	0.219	
Palatal disorder (10052453)	18 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	Palate-Related AE[e]
Palatal oedema (10056998)	13 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Palatal swelling (10074403)	74 (0.011%)	0.015	2 (0.029%)	0.001	0.176	**0.001**	
Palatal ulcer (10077519)	5 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Anesthesia oral (10082548)	20 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	Other sensory AE
Paraesthesia oral (10057372)	6,024 (0.872%)	1.188	33 (0.473%)	0.019	**<0.001**	**<0.001**	
Hypoaesthesia oral (10057371)	4,477 (0.648%)	0.883	30 (0.430%)	0.017	**0.024**	**<0.001**	
Burn oral cavity (10075532)	9 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Burning mouth syndrome (10068065)	31 (0.004%)	0.006	0 (0%)	N/A	N/A	N/A	
Oral dysaesthesia (10050820)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Aphthous ulcer (10002959)	340 (0.049%)	0.067	0 (0%)	N/A	N/A	N/A	Oral mucosa-related AE[f]
Circumoral oedema (10052250)	8 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Circumoral swelling (10081703)	44 (0.006%)	0.009	0 (0%)	N/A	N/A	N/A	
Coating in mouth (10075366)	21 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	
Leukoplakia oral (10024396)	5 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Mouth swelling (10075203)	908 (0.131%)	0.179	8 (0.115%)	0.005	0.868	**<0.001**	
Oedema mouth (10030110)	9 (0.001%)	0.002	1 (0.014%)	0.001	0.096	1.000	
Oral blood blister (10076590)	46 (0.007%)	0.009	1 (0.014%)	0.001	0.376	**0.022**	
Oral candidiasis (10030963)	108 (0.016%)	0.021	0 (0%)	N/A	N/A	N/A	
Oral discomfort (10030973)	747 (0.108%)	0.147	5 (0.072%)	0.003	0.463	**<0.001**	
Oral disorder (10067621)	191 (0.028%)	0.038	2 (0.029%)	0.001	0.720	**<0.001**	
Oral fungal infection (10061324)	14 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Oral herpes (10067152)	1,309 (0.189%)	0.258	6 (0.086%)	0.003	**0.050**	**<0.001**	
Oral lichen planus (10030983)	39 (0.006%)	0.008	1 (0.014%)	0.001	0.331	**0.039**	
Oral lichenoid reaction (10083833)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oral mucosa erosion (10064594)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oral Mucosal Blistering (10030995)	394 (0.057%)	0.078	3 (0.043%)	0.002	1.000	**<0.001**	

(Continued)

TABLE 2 | Continued

Preferred term	COVID-19 vaccine		Seasonal influenza vaccine		*Sig.*		
	% of Total AE (n = 690,853)	Rate per 100,000 doses	% of total AE (n = 6,970)	Rate per 100,000 doses	% of total AE	Rate per 100K D	Group
Oral mucosal discolouration (10030996)	6 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Oral mucosal eruption (10030997)	175 (0.025%)	0.035	4 (0.057%)	0.002	0.106	**<0.001**	
Oral mucosal erythema (10067418)	78 (0.011%)	0.015	0 (0%)	N/A	N/A	N/A	
Oral mucosal exfoliation (10064487)	32 (0.005%)	0.006	0 (0%)	N/A	N/A	N/A	
Oral mucosal roughening (10084009)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Oral pain (10031009)	715 (0.103%)	0.141	6 (0.086%)	0.003	0.851	**<0.001**	
Oral pigmentation (10077552)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oral pruritus (10052894)	452 (0.065%)	0.089	1 (0.014%)	0.001	0.147	**<0.001**	
Oral purpura (10083533)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Oral pustule (10056674)	12 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Oral viral infection (10065234)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oropharyngeal blistering (10067950)	46 (0.007%)	0.009	0 (0%)	N/A	N/A	N/A	
Oropharyngeal plaque (10067721)	6 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Perioral dermatitis (10034541)	8 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Stomatitis (10042128)	824 (0.119%)	0.163	11 (0.158%)	0.006	0.379	**<0.001**	

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.

[a] *The preferred term Sensitivity of Teeth (10040012) was not reported in any vaccine groups.*

[b] *The preferred terms Salivary Duct Obstruction (10039386), Salivary Duct Inflammation (10056681) and Salivary Gland Induration (10071363) were not reported in any vaccine groups.*

[c] *The preferred terms Acquired Macroglossia (10058835), Ankyloglossia Acquired (10049243), Atrophy of Tongue Papillae (10003712), and Tongue Black Hairy (10043941) were not reported in any vaccine groups.*

[d] *The preferred term Lip Erosion (10051992) was not reported in any vaccine groups.*

[e] *The preferred term Palatal Palsy (10072012) was not reported in any vaccine groups.*

[f] *The preferred terms Aphthous Stomatitis (10002958), Buccal Mucosal Roughening (10048479), Mouth Plaque (10028032), Mouth Ulceration (10028034), Oral Soft Tissue Disorder (10061326), Oral Mucosal Hypertrophy (10062956), Oral Mucosal Petechiae (10030998), Oral Mucosal Scab (10082769), and Oral Papule (10031010) were not reported in any vaccine groups.*

Bold values represents significant values.

Taste disorders, including complete (ageusia) and partial (hypogeusia) loss of taste and disturbed taste (dysgeusia) had been among the most reported oral AEs following COVID-19 vaccination per our analysis. Taste dysfunction was depicted as one of the characteristic symptoms of COVID-19 infection due to its high prevalence, estimated to be 39.2% (CI 95%: 35.34–43.12%) according to latest meta-analyses (12–14). Therefore, public health authorities had broadly used taste dysfunction in case finding protocols and triage recommendations (15). Lechien et al. reported a series of six cases with new-onset taste disorders following COVID-19 vaccination with repeated negative PCR results for SARS-CoV-2. Thus ruling out the possibility of COVID-19 infection as the etiology of taste disorders in this particular case series; however it does not rule it out in the VAERS reports (16). On reviewing random VAERS reports manually, we found out that breakthrough infection was commonly reported in association with taste disorders. One of the hypotheses we suggest for the remarkably higher prevalence of ageusia (0.722 vs. 0.143%; *Sig.* < 0.001), dysgeusia (0.617 vs. 0.244%; *Sig.* < 0.001), and taste disorder (0.317 vs. 0.115%; *Sig.* < 0.001) among COVID-19 vaccinees is the increased public awareness of taste dysfunction as one of the characteristic symptoms of COVID-19 infection (17, 18). Our hypothesis can be supported by the overall reporting prevalence of taste disorders during the COVID-19 pandemic period compared to the pre-pandemic years.

Xerostomia, or dry mouth, was among the common oral AEs following COVID-19 vaccination with female and older age predominance and without a preference for a particular vaccine brand. Active surveillance through the cross-sectional studies of self-reported COVID-19 vaccines side effects revealed varying prevalence of xerostomia that ranged between 0.4 and 2.7% (19–21). It remains unclear whether the humoral immune response triggered by COVID-19 vaccination and manifested in salivary secretions has any link with salivary gland-AEs, including xerostomia (22, 23).

Anaphylactic symptoms e.g., lip swelling (MedDRA ID: 10024570), swollen tongue (10042727) and tongue pruritus (10070072) were more common among COVID-19 vaccinees and females as compared to seasonal influenza vaccinees and males. Interestingly, Maltezou et al. concluded that anaphylactic reactions rates are the lowest after COVID-19 vaccines (10.67 cases per one million doses) as compared with rabies, tick-borne encephalitis, measles-mumps-rubella-varicella, and human papillomavirus vaccines (70.77, 20, 19.8, and 13.65 cases per one million doses, respectively) (24). Earlier VAERS-based analyses indicated that anaphylactic rates were higher following BNT162b2 than mRNA-1273 vaccine, which is consistent with our findings (25, 26). Female predominance for post-vaccination allergic reactions was attributed to polyethene glycol

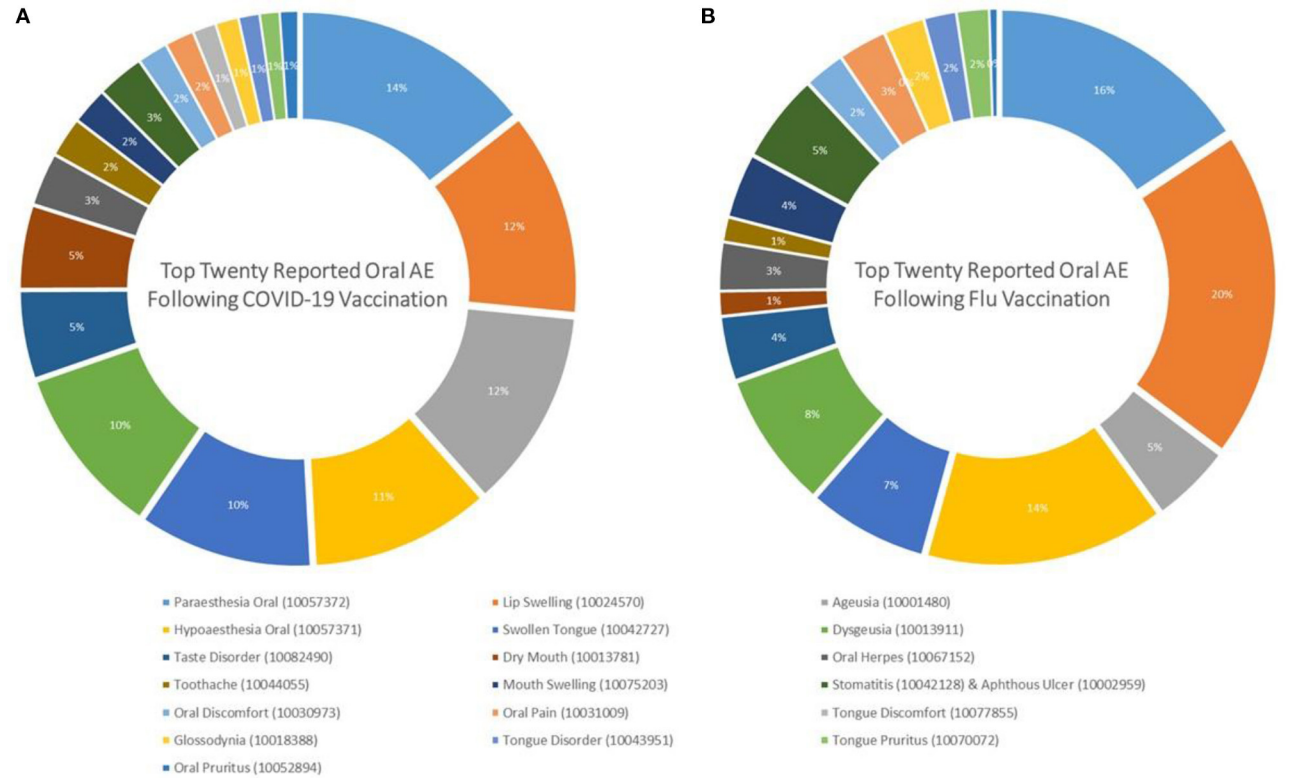

FIGURE 2 | Top twenty oral adverse events reported after **(A)** COVID-19 and **(B)** Seasonal Influenza Vaccination in the United States, January–December 2021 (CDC; VAERS-WONDER).

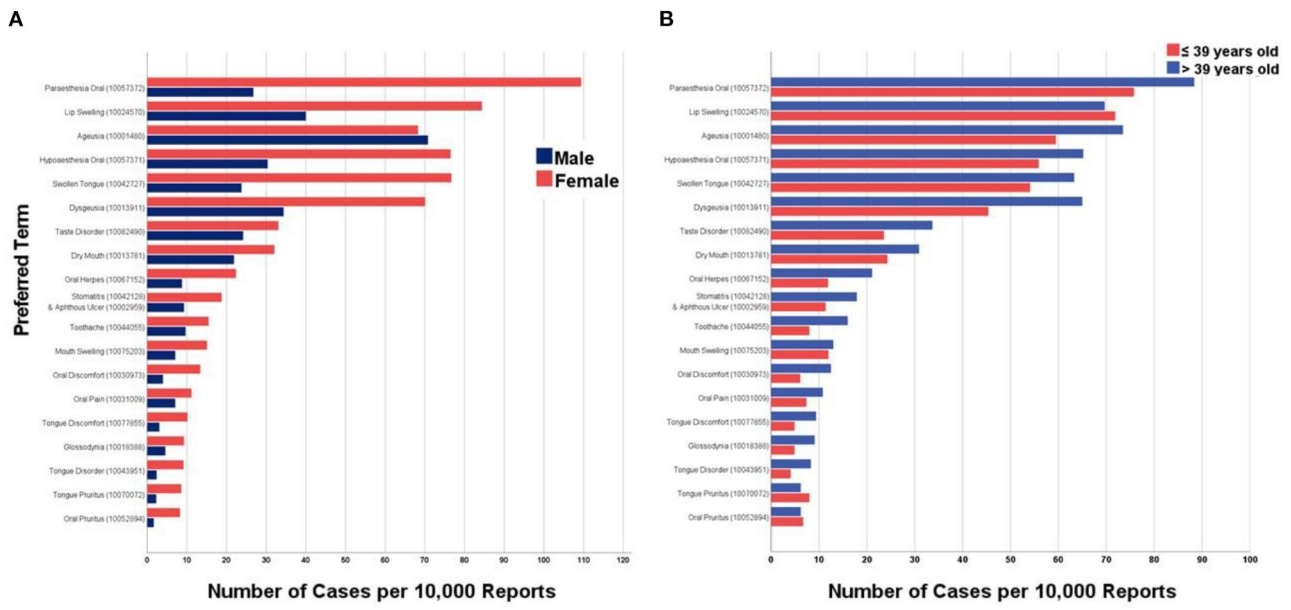

FIGURE 3 | Top twenty oral adverse events reported after COVID-19 vaccination in the United States stratified by **(A)** Sex and **(B)** Age Group, January–December 2021 (CDC; VAERS-WONDER).

TABLE 3 | Top twenty oral adverse events reported after COVID-19 and seasonal influenza vaccines in the United States stratified by sex and age group, January–December 2021 (CDC; VAERS-WONDER).

#	Preferred term	COVID-19			Seasonal flu		
		Female (n = 489,571)	Male (n = 226,792)	*Sig.*	Female (n = 4,629)	Male (n = 2,210)	*Sig.*
1	Paraesthesia oral (10057372)	5,355 (1.094%)	608 (0.268%)	**<0.001**	26 (0.562%)	7 (0.317%)	0.195
2	Lip swelling (10024570)	4,132 (0.844%)	907 (0.400%)	**<0.001**	35 (0.756%)	6 (0.271%)	**0.018**
3	Ageusia (10001480)	3,342 (0.683%)	1,605 (0.708%)	0.238	8 (0.173%)	2 (0.090%)	0.516
4	Hypoaesthesia oral (10057371)	3,743 (0.765%)	689 (0.304%)	**<0.001**	25 (0.540%)	5 (0.226%)	0.078
5	Swollen tongue (10042727)	3,749 (0.767%)	540 (0.238%)	**<0.001**	23 (0.497%)	3 (0.136%)	**0.021**
6	Dysgeusia (10013911)	3,431 (0.701%)	781 (0.344%)	**<0.001**	16 (0.346%)	1 (0.045%)	**0.018**
7	Taste disorder (10082490)	1,619 (0.331%)	549 (0.242%)	**<0.001**	6 (0.130%)	2 (0.090%)	1.000
8	Dry mouth (10013781)	1,573 (0.321%)	497 (0.219%)	**<0.001**	3 (0.065%)	0 (0%)	N/A
9	Oral herpes (10067152)	1,097 (0.224%)	200 (0.088%)	**<0.001**	4 (0.086%)	2 (0.090%)	1.000
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	919 (0.188%)	211 (0.093%)	**<0.001**	8 (0.173%)	3 (0.136%)	1.000
12	Toothache (10044055)	758 (0.155%)	219 (0.097%)	**<0.001**	1 (0.022%)	2 (0.090%)	0.246
13	Mouth swelling (10075203)	738 (0.151%)	162 (0.071%)	**<0.001**	6 (0.130%)	2 (0.090%)	1.000
14	Oral discomfort (10030973)	654 (0.134%)	91 (0.040%)	**<0.001**	5 (0.108%)	0 (0%)	N/A
15	Oral pain (10031009)	547 (0.112%)	161 (0.071%)	**<0.001**	6 (0.130%)	0 (0%)	N/A
16	Tongue discomfort (10077855)	500 (0.102%)	71 (0.031%)	**<0.001**	0 (0%)	0 (0%)	N/A
17	Glossodynia (10018388)	457 (0.093%)	104 (0.046%)	**<0.001**	5 (0.108%)	0 (0%)	N/A
18	Tongue disorder (10043951)	448 (0.092%)	55 (0.024%)	**<0.001**	3 (0.065%)	1 (0.045%)	1.000
19	Tongue pruritus (10070072)	422 (0.086%)	53 (0.023%)	**<0.001**	4 (0.086%)	0 (0%)	N/A
20	Oral pruritus (10052894)	406 (0.083%)	39 (0.017%)	**<0.001**	1 (0.022%)	0 (0%)	N/A
#	**Preferred Term**	**COVID-19**			**Seasonal flu**		
		≤39 years old (n = 223,053)	>39 years old (n = 471,468)	*Sig.*	≤39 years old (n = 2,606)	>39 years old (n = 4,099)	*Sig.*
1	Paraesthesia oral (10057372)	1,691 (0.758%)	4,168 (0.884%)	**<0.001**	10 (0.384%)	23 (0.561%)	0.373
2	Lip swelling (10024570)	1,604 (0.719%)	3,288 (0.697%)	0.312	13 (0.499%)	27 (0.659%)	0.516
3	Ageusia (10001480)	1,327 (0.595%)	3,467 (0.735%)	**<0.001**	1 (0.038%)	10 (0.244%)	0.060
4	Hypoaesthesia oral (10057371)	1,246 (0.559%)	3,075 (0.652%)	**<0.001**	8 (0.307%)	23 (0.561%)	0.144
5	Swollen tongue (10042727)	1,206 (0.541%)	2,984 (0.633%)	**<0.001**	6 (0.230%)	18 (0.439%)	0.209
6	Dysgeusia (10013911)	1,013 (0.454%)	3,063 (0.650%)	**<0.001**	8 (0.307%)	9 (0.220%)	0.619
7	Taste disorder (10082490)	526 (0.236%)	1,589 (0.337%)	**<0.001**	2 (0.077%)	6 (0.146%)	0.496
8	Dry mouth (10013781)	542 (0.243%)	1,458 (0.309%)	**<0.001**	1 (0.038%)	2 (0.049%)	1.000
9	Oral herpes (10067152)	265 (0.119%)	996 (0.211%)	**<0.001**	3 (0.115%)	3 (0.073%)	0.683
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	255 (0.114%)	845 (0.179%)	**<0.001**	2 (0.077%)	9 (0.220%)	0.220
12	Toothache (10044055)	178 (0.080%)	755 (0.160%)	**<0.001**	2 (0.077%)	1 (0.024%)	0.564
13	Mouth swelling (10075203)	268 (0.120%)	614 (0.130%)	0.271	2 (0.077%)	5 (0.122%)	0.713
14	Oral discomfort (10030973)	137 (0.061%)	587 (0.125%)	**<0.001**	1 (0.038%)	4 (0.098%)	0.655
15	Oral pain (10031009)	165 (0.074%)	510 (0.108%)	**<0.001**	0 (0%)	6 (0.146%)	N/A
16	Tongue discomfort (10077855)	109 (0.049%)	443 (0.094%)	**<0.001**	0 (0%)	0 (0%)	N/A
17	Glossodynia (10018388)	110 (0.049%)	428 (0.091%)	**<0.001**	0 (%)	2 (0.049%)	N/A
18	Tongue disorder (10043951)	91 (0.041%)	392 (0.083%)	**<0.001**	0 (0%)	4 (0.098%)	N/A
19	Tongue pruritus (10070072)	179 (0.080%)	292 (0.062%)	**0.006**	2 (0.077%)	2 (0.049%)	0.645
20	Oral pruritus (10052894)	149 (0.067%)	293 (0.062%)	0.473	0 (0%)	1 (0.024%)	N/A

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.
Bold values represents significant values.

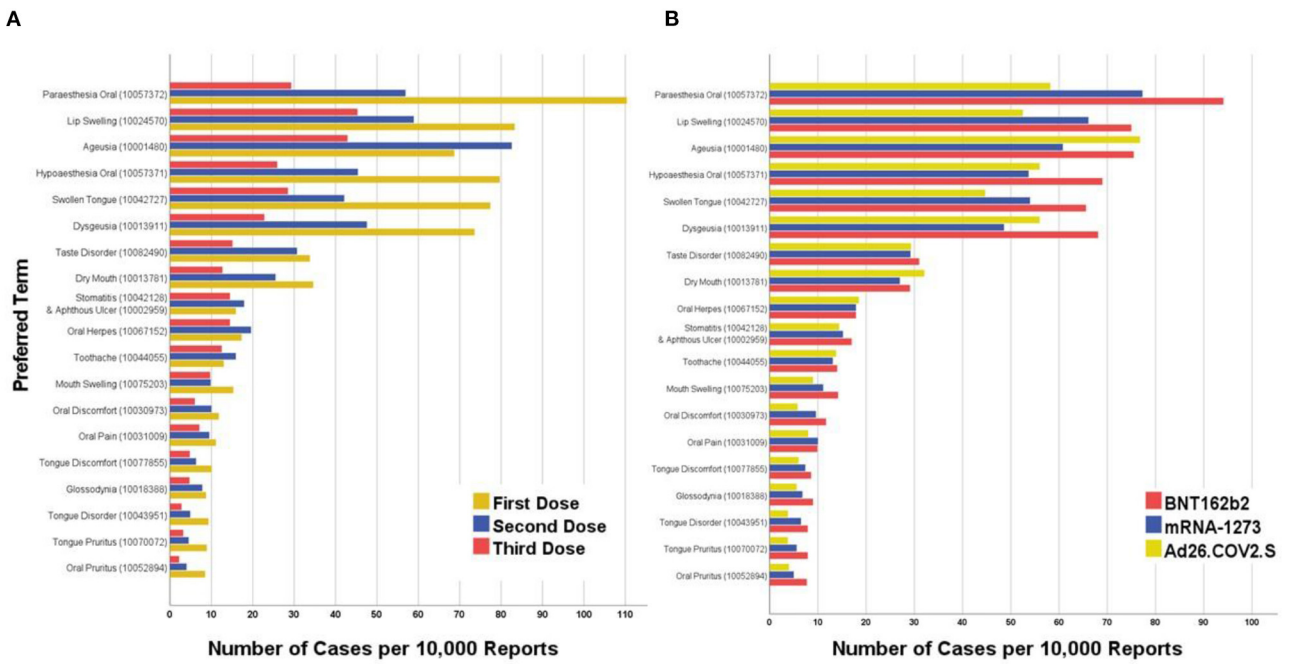

FIGURE 4 | Top twenty oral adverse events reported after COVID-19 vaccination in the United States stratified by **(A)** Dose and **(B)** Vaccine Brand, January–December 2021 (CDC; VAERS-WONDER).

TABLE 4 | Top twenty oral adverse events reported after COVID-19 vaccines in the United States stratified by dose, January–December 2021 (CDC; VAERS-WONDER).

Order	Preferred term	First dose (n = 350,247)	Second dose (n = 227,377)	Third dose (n = 53,620)	*Sig.*	
					1st vs. 2nd	(1st & 2nd) vs. 3rd
1	Paraesthesia oral (10057372)	3,868 (1.104%)	1,294 (0.569%)	157 (0.293%)	**<0.001**	**<0.001**
2	Lip swelling (10024570)	2,918 (0.833%)	1,339 (0.589%)	243 (0.453%)	**<0.001**	**<0.001**
3	Ageusia (10001480)	2,406 (0.687%)	1,877 (0.826%)	230 (0.429%)	**<0.001**	**<0.001**
4	Hypoaesthesia oral (10057371)	2,793 (0.797%)	1,033 (0.454%)	139 (0.259%)	**<0.001**	**<0.001**
5	Swollen tongue (10042727)	2,710 (0.774%)	958 (0.421%)	153 (0.285%)	**<0.001**	**<0.001**
6	Dysgeusia (10013911)	2,577 (0.736%)	1,082 (0.476%)	122 (0.228%)	**<0.001**	**<0.001**
7	Taste disorder (10082490)	1,183 (0.338%)	697 (0.307%)	81 (0.151%)	**0.042**	**<0.001**
8	Dry mouth (10013781)	1,212 (0.346%)	580 (0.255%)	68 (0.127%)	**<0.001**	**<0.001**
9	Oral herpes (10067152)	606 (0.173%)	445 (0.196%)	78 (0.145%)	**0.050**	0.061
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	557 (0.159%)	406 (0.179%)	78 (0.145%)	0.080	0.266
12	Toothache (10044055)	455 (0.130%)	361 (0.159%)	67 (0.125%)	**0.005**	0.365
13	Mouth swelling (10075203)	536 (0.153%)	222 (0.098%)	52 (0.097%)	**<0.001**	**0.032**
14	Oral discomfort (10030973)	413 (0.118%)	227 (0.100%)	32 (0.060%)	**0.047**	**<0.001**
15	Oral pain (10031009)	389 (0.111%)	217 (0.095%)	38 (0.071%)	0.074	**0.016**
16	Tongue discomfort (10077855)	355 (0.101%)	144 (0.063%)	26 (0.048%)	**<0.001**	**0.003**
17	Glossodynia (10018388)	304 (0.087%)	178 (0.078%)	25 (0.047%)	0.284	**0.003**
18	Tongue disorder (10043951)	324 (0.093%)	112 (0.049%)	15 (0.028%)	**<0.001**	**<0.001**
19	Tongue pruritus (10070072)	313 (0.089%)	103 (0.045%)	17 (0.032%)	**<0.001**	**<0.001**
20	Oral pruritus (10052894)	299 (0.085%)	91 (0.040%)	12 (0.022%)	**<0.001**	**<0.001**

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.
Bold values represents significant values.

TABLE 5 | Top twenty oral adverse events reported after COVID-19 vaccines in the United States stratified by vaccine type, January–December 2021 (CDC; VAERS-WONDER).

Order	Preferred term	BNT162b2 (n = 341,389)	mRNA-1273 (n = 337,518)	Ad26.COV2.S (n = 50,138)	*Sig.*	
					Pfizer vs. Moderna	mRNA vs. Vector
1	Paraesthesia oral (10057372)	3,212 (0.941%)	2,475 (0.773%)	292 (0.582%)	**<0.001**	**<0.001**
2	Lip swelling (10024570)	2,562 (0.750%)	2,232 (0.661%)	263 (0.525%)	**<0.001**	**<0.001**
3	Ageusia (10001480)	2,578 (0.755%)	2,053 (0.608%)	385 (0.768%)	**<0.001**	**0.027**
4	Hypoaesthesia oral (10057371)	2,354 (0.690%)	1,812 (0.537%)	281 (0.560%)	**<0.001**	0.145
5	Swollen tongue (10042727)	2,241 (0.656%)	1,823 (0.540%)	224 (0.447%)	**<0.001**	**<0.001**
6	Dysgeusia (10013911)	2,324 (0.681%)	1,639 (0.486%)	281 (0.560%)	**<0.001**	0.523
7	Taste disorder (10082490)	1,057 (0.310%)	986 (0.292%)	147 (0.293%)	0.191	0.800
8	Dry mouth (10013781)	992 (0.291%)	912 (0.270%)	161 (0.321%)	0.113	0.098
9	Oral herpes (10067152)	611 (0.179%)	603 (0.179%)	93 (0.185%)	0.977	0.702
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	580 (0.170%)	512 (0.152%)	72 (0.144%)	0.065	0.385
12	Toothache (10044055)	477 (0.140%)	442 (0.131%)	69 (0.138%)	0.338	0.900
13	Mouth swelling (10075203)	485 (0.142%)	375 (0.111%)	45 (0.090%)	**<0.001**	**0.021**
14	Oral discomfort (10030973)	399 (0.117%)	324 (0.096%)	29 (0.058%)	**0.009**	**0.001**
15	Oral pain (10031009)	338 (0.099%)	336 (0.100%)	40 (0.080%)	0.969	0.208
16	Tongue discomfort (10077855)	295 (0.086%)	249 (0.074%)	30 (0.060%)	0.072	0.137
17	Glossodynia (10018388)	306 (0.090%)	229 (0.068%)	28 (0.056%)	**0.002**	0.080
18	Tongue disorder (10043951)	270 (0.079%)	219 (0.065%)	19 (0.038%)	**0.030**	**0.004**
19	Tongue pruritus (10070072)	271 (0.079%)	188 (0.056%)	19 (0.038%)	**<0.001**	**0.011**
20	Oral pruritus (10052894)	262 (0.077%)	169 (0.050%)	20 (0.040%)	**<0.001**	**0.040**

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.
Bold values represents significant values.

TABLE 6 | Taste-related adverse events reported after all vaccines in the United States, January 2010–December 2021 (CDC; VAERS-WONDER).

Preferred term	Before COVID-19 pandemic; January 2010–December 2019 (n = 311,941)	During COVID-19 Pandemic; January 2020–December 2021 (n = 786,047)	*Sig.*
Ageusia (10001480)	109 (0.035%)	4,893 (0.622%)	**<0.001**
Dysgeusia (10013911)	567 (0.182%)	4,566 (0.581%)	**<0.001**
Taste disorder (10082490)	20 (0.006%)	2,193 (0.279%)	**<0.001**
Hypogeusia (10020989)	18 (0.006%)	146 (0.019%)	**<0.001**

Fisher's exact test had been used with a significance level (Sig.) < 0.05.
Bold values represents significant values.

hypersensitivity which was found to be higher among females than males (27, 28).

Other allergic AEs such as oral paraesthesia and oral hypoaesthesia were commonly reported among COVID-19 vaccinees and females. In the product assessment report of the mRNA-1273 vaccine published by the European Medicines Agency (EMA), oral paraesthesia was mentioned among the rare AEs (29). Likewise, mouth-tingling was enlisted as a rare allergic AE by regulators and professional societies in other countries (30).

Sporadic case reports/series for oral mucosa-related AEs following COVID-19 vaccination had been published during the previous months, calling for further investigation about the potential link between those AEs and the vaccine-elicited immune response (4). Oral lichen planus (OLP) was diagnosed in recently vaccinated individuals who received mRNA-(BNT162b2) and viral vector-based vaccines (Ad26.COV2.S) and whose medical anamneses and serological investigations ruled out suspected infections and allergens (31–33). Therefore, Hertel et al. performed a retrospective analysis for COVID-19 vaccinated *vs*. non-vaccinated cohorts of normal and overweight individuals and figured out that OLP incidence was higher in the vaccinated group (0.067 vs. 0.027%; *Sig.* < 0.001) (34). Contrarily, our current analysis found that OLP prevalence was lower among COVID-19 than among seasonal influenza vaccinees (0.006 vs. 0.014%; *Sig.* = 0.331). A recent meta-analysis of OLP point prevalence exhibited remarkably higher levels (0.89% for general populations and 0.98% for clinical patients) than reported after vaccination (35).

Oral herpes zoster (OHZ) is one of the suggested mucosa-related AEs empirically diagnosed in vaccinees with an irrelevant underlying anamnesis who received BNT162b2 (36). However,

the pathophysiologic pathway remained unclear for how COVID-19 vaccines can trigger OHZ reactivation and the investigators warned the clinical and scientific communities from misdiagnosing OHZ as oral herpes (37). Prevalence of oral herpes (MedDRA ID: 10067152) that may include both herpes simplex and herpes zoster infections was significantly higher in the COVID-19 (0.189 vs. 0.086%; *Sig.* = 0.050) than seasonal influenza group. Within the COVID-19 group, prevalence of oral herpes was significantly higher among females (0.224 vs. 0.088%; *Sig.* < 0.001) and older age group (0.211 vs. 0.119%; *Sig.* < 0.001), and it was not significantly different between primer *vs*. booster doses (0.182 vs. 0.145%; *Sig.* = 0.061) or among vaccine brands. Female sex and older age predominance correspond with the current US demographics of oral herpes infection (38).

Aphthous stomatitis was suspected to be linked with recent COVID-19 vaccination in a few reported cases where patients presented with non-specific oral ulcers (39, 40). Unlike oral herpes, the prevalence of aphthous stomatitis was not significantly higher among COVID-19 vaccinees (0.168 vs. 0.158%; *Sig.* = 0.829); even though it resembled oral herpes in female and older age predominance and lack of preference for a particular dose or vaccine brand.

Limitations

Several limitations should be taken into consideration while reading our analysis. Firstly, it is based on a passive surveillance database which is usually biased toward the less common moderate-to-severe AEs rather than the common mild AEs. Secondly, passive surveillance systems do not provide accurate epidemiologic estimates such as prevalence or incidence of the reported AEs; instead, they are used as an early alerting tool. Thirdly, most oral conditions, including neurological and mucosal AEs do not have background estimates that would have enabled us to perform the conventional observed-to-expected (O:E) analysis; therefore, we had to compare COVID-19 rates with another preemptively similar vaccine, i.e., seasonal influenza. Fourthly, the reported AEs were not systematically classified according to their exact onset, i.e., the interval between injection and AE emergence, by the VAERS database. Therefore, it is imperative that future research on oral AEs should record their onset to help determine the required resources for their management.

Strengths

Heretofore, this analysis is the first to provide population-based evidence for COVID-19 AEs that might affect oral cavity structures and functions. It also suggests a *de novo* methodology that can be used for evaluating oral AEs of other vaccines e.g., H1N1, human papillomavirus and herpes zoster vaccines.

Implications

By reading the findings of our analysis, dentists and dental team members can become more knowledgeable about the prevalence, severity, and prognosis of oral AEs that might arise after vaccination. Dentists are seen as trustworthy information sources by their patients and their knowledge and attitudes toward vaccine effectiveness and safety play a crucial role in enhancing the public uptake of vaccines. Moreover, oral health specialists should be actively engaged in the pharmacovigilance process as pragmatic point-of-care diagnostic schemes are urgently needed to improve the reporting quality of oral AEs—the Brighton Collaboration scheme for anaphylaxis diagnosis can be taken as an example. Finally, the general public should be reassured that the present analysis found that most COVID-19 oral AEs greatly resemble those of seasonal influenza vaccines and may not require particular attention except for those emerging immediately after the shot as they can be anaphylactic reactions.

CONCLUSION

Within the limitations of this study, COVID-19 vaccines were found to be associated with rare oral AEs that were predominantly similar to those emerging following seasonal influenza vaccines. The most reported oral AEs were oral paresthesia (mouth-tingling), lip swelling, and ageusia, representing various pathophysiologic pathways that remain unclear. Taste-related AEs should be acknowledged in the context of the COVID-19 pandemic and the public should be adequately informed about a potential taste dysfunction after receiving the COVID-19 vaccination. Dentists and dental teams need to be aware of the prevalence, severity, and prognosis of oral AEs to inform their patients and increase public confidence in vaccines.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://wonder.cdc.gov/vaers.html.

AUTHOR CONTRIBUTIONS

AR: conceptualization, methodology, formal analysis, and project administration. AR and SA: validation. AR, AP, and EK: writing—original draft preparation. SA: writing—review and editing and funding acquisition. All authors have read and agreed to the published version of the manuscript.

FUNDING

The work of AR was supported by Masaryk University Grant Nos. MUNI/IGA/1104/2021 and MUNI/A/1402/2021.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.952781/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 19 July 2022
DOI 10.3389/fpubh.2022.937794

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

RECEIVED 06 May 2022
ACCEPTED 27 June 2022
PUBLISHED 19 July 2022

CITATION
Yesuf EA, Riad A, Sofi-Mahmudi A, Sudhakar M, Mekonnen A, Endalkachew S, Mama F, Muhidin S, Ayele B, Yahya M, Usman A, Abafita J and Klugar M (2022) Self-reported side effects of the Oxford AstraZeneca COVID-19 vaccine among healthcare workers in Ethiopia, Africa: A cross-sectional study. *Front. Public Health* 10:937794. doi: 10.3389/fpubh.2022.937794

Self-reported side effects of the Oxford AstraZeneca COVID-19 vaccine among healthcare workers in Ethiopia, Africa: A cross-sectional study

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Introduction: Ethiopia is the second most populous country in Africa. Ethiopia received most of its COVID-19 vaccines through donations. The Oxford AstraZeneca vaccine is the first to be donated to Ethiopia by the COVAX facility. Healthcare workers were the priority population that received the Oxford AstraZeneca COVID-19 vaccine. However, there was no nationwide study on the safety of the vaccine in Ethiopia. This study aimed to measure the prevalence and predictors of self-reported side effects of the Oxford AstraZeneca vaccine.

Materials and methods: The study employed a cross-sectional design. A sample of healthcare workers who took Oxford AstraZeneca COVID-19 vaccine was drawn from four regions of Ethiopia; namely, Amhara, Oromia, Somali, and Southwest. Data were collected on sociodemographic characteristics, medical anamnesis, COVID-19 related anamnesis, and COVID-19 vaccine anamnesis *via* telephone interview. Descriptive and inferential analyses were done. The software, IBM SPSS Statistics v21.0, was used for analyses of data.

Results: Out of 384 people, 346 responded (response rate: 90.1%). Female accounted for 34.1% of the respondents. The mean age of the respondents was 31.0 years (Standard Deviation (SD) = 7.4).

10.3389/fpubh.2022.937794

Nurses accounted for 43.7% of the respondents. The prevalence of at least one local- and systemic-side effect was 50.6 and 44.5%, respectively. The most frequent local- and systemic- side effect were injection site pain and headache, respectively. Both types of side effects mostly subsided in the first 3 days. A third of healthcare workers with side effects took at least one medication. Paracetamol followed by diclofenac sodium were taken by healthcare workers to overcome side effects. There was no independent predictor of local side effect. After controlling for age and chronic diseases, the odds of healthcare workers with COVID-19 like symptoms to experience systemic side effects was 1.38 (Confidence Interval (CI): 1.04–1.82) times more than that of healthcare workers without COVID-19 like symptoms.

Conclusions: The prevalence of local- and systemic-side effects of the Oxford AstraZeneca COVID-19 vaccine was modest. As the symptoms were mostly common in the first 3 days, it is preferable to monitor healthcare workers at least in the first 3 days following the administration of the vaccine.

KEYWORDS

Healthcare workers, COVID-19 vaccine, side effects, Oxford AstraZeneca, Ethiopia, Africa

Introduction

Coronavirus disease 19 (COVID-19) started as a local outbreak in Wuhan, China and subsequently spread all over the world becoming a pandemic. It resulted in millions of deaths across the world (1).

Several COVID-19 control strategies were devised. The strategies are broadly classified as non-pharmacological interventions, vaccines, and treatment. Social distancing is one of the most effective interventions (2). For Low- and Middle-Income Countries (LMICs), generalized lockdown, zonal lockdown, and rolling lockdown are recommended depending on the epidemiologic, economic, and health system capabilities (3).

While some drug treatments for COVID-19 have been suggested (4), vaccines which were introduced in the second year of the pandemic seem to be the most effective treatments against the disease to date (4). There are five types of vaccines, such as live attenuated, inactivated, protein-based, nucleic acid, and viral vector (5). Few of the COVID-19 vaccines approved through the Emergency Use Authorization (EUA) include Pfizer/BioN-Tech, Moderna, Oxford Astra-Zeneca, Sputnik V, Covaxin, and Sinovac. United States of America, United Kingdom, Russia, India, and China are the major countries which have granted authorization for the vaccines (5).

Before authorization by relevant authorities, vaccines undergo rigorous studies in phase I and phase II clinical trials to determine their efficacy and safety. One particular safety concern is vaccine-related immunopathology that occurs in vaccinated people during a natural infection (6). Once COVID-19 vaccines are found to be efficacious and safe during clinical trials, then they will be deployed. However, the safety of vaccines after deployment should be studied. Several tools can be used to study the safety of COVID-19 vaccines. A few of the tools are active surveillance and passive surveillance (7).

In countries, such as Ethiopia passive surveillance using administrative data is not feasible because of resource limitations. In order to overcome this limitation, active surveillance using cross-sectional studies is helpful.

Ethiopia received most of its vaccines through donations. Two million two hundred thousand million doses of Oxford Astra Zeneca COVID-19 vaccine were the first batch (27) and were received from the COVAX facility –which is an international partnership aimed at supplying vaccines to lower income countries. Subsequently China donated 1.8 million doses of the Sinopharm COVID-19 vaccine with the aim of improving vaccine accessibility (8). Finally, the United States donated nearly two million doses of the Pfizer COVID-19 vaccine to Ethiopia (9). Despite all these efforts, the percentage of the population which received COVID-19 vaccines is still very low.

Priority was given to healthcare providers to receive vaccine shots followed by elderly and people with co-morbidities. When the vaccines were rolled-out in Ethiopia on March 13, 2021 with Oxford AstraZeneca COVID-19 vaccine, most healthcare workers received the Oxford AstraZeneca COVID-19 vaccine because it was the first vaccine shipped to Ethiopia in large quantities.

According to some studies, in Ethiopia, half of healthcare workers (10) and a third of the general population are willing to accept COVID-19 vaccines (11).

In Low- and Middle-Income Countries (LMIC) compared with high income a higher mean acceptance rate of 80% was reported for COVID-19 vaccines (12). For example, vaccine acceptance among university students in a high income country, such as the Czech Republic was 73.3% (13). Similar rates of hesitancy were observed among healthcare workers in Arab countries (14). Perceived vaccine safety helps to increase vaccine acceptance. Vaccine hesitancy was negatively associated with willingness to accept COVID-19 vaccines (10) including booster doses (13).

It is important to study the safety of vaccines to improve acceptance and increase inoculation percentages. Studies reported the prevalence of adverse effects in Ethiopia. One study undertaken in South Ethiopia found a 44% prevalence of local pain and a 40% prevalence of fever. However, this study focused on one region (15). Another study from Ethiopia reported 65% prevalence of injection site pain and 50% prevalence of headache (16). Nevertheless, this study did not report the determinants of the side effects. Therefore, there is a need for a national study on the prevalence and determinants of side effects of the Oxford AstraZeneca COVID-19 vaccine.

The study was aimed at measuring the prevalence of self-reported side effects of the Oxford AstraZeneca COVID-19 vaccine among health care workers in Ethiopia.

Materials and Methods

Oxford AstraZeneca COVID-19 vaccine

The Oxford AstraZeneca vaccine was developed by the University of Oxford. It has SARS CoV-2 surface protein (nCoV-19) in a vector from chimpanzee adenovirus (ChAdOx1) (17). It's route of administration is intramuscular.

Design

A cross-sectional study design was conducted and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (18). Data were collected from the target population between July and August 2021.

Setting

This study was set up in Ethiopia. Ethiopia has 11 administrative regions and two city states. Four administrative regions were randomly selected for the study; namely Amhara, Oromia, Somali, and Southwest. See Supplementary Material 1 for sampling frame.

Population

The population of interest was healthcare workers.

Study size

Using a single proportion population formula, local or systemic side effect of Oxford AstraZeneca COVID-19 vaccine as an outcome measure, assuming that 50% of healthcare workers experience at least one side effect, 95% confidence level, and type I error of 5%, the sample size was 384.

The inclusion criterion was all healthcare workers who took at least one dose of the Oxford AstraZeneca COVID-19 vaccine because it was the main vaccine administered to healthcare workers during the first phase of the vaccination campaign in Ethiopia.

Sampling

The sample size was distributed across the four regions. One healthcare institution was selected from each region because of the assumption that the type of healthcare institution will not influence the side effects and that the characteristics of healthcare workers among the healthcare institutions within a region were similar. Then, a list of vaccinated individuals from that healthcare institution was obtained. Finally, a random sample was taken from each list using MS Excel 2010 random number generator in Windows 10 operating system.

Instrument

Data collection tool had been developed according to COVID-19 Vaccine Safety Tracking (CoVaST) methodology; and it had general demographic characteristics, medical anamnesis, COVID-19 Related anamnesis, and vaccine related anamnesis (19). The tool was pre-tested among 10 healthcare workers who took the Oxford AstraZeneca COVID-19 vaccine and were not part of the sample. Then, the tool was revised, for example by removing repeated question and re-writing a few questions for clarity. Please see Supplementary Material 2 for the tool. Data were collected by telephone interview.

Variables measured in this study were mentioned below:

- Predictor: Body Mass Index (BMI) (underweight, normal, overweight, and obese), presence of at least one chronic disease (yes vs. no), at least one medication currently taken by the patient (yes vs. no), diagnosis with COVID-19 (yes vs. no), and presence of COVID-19 like symptoms (yes vs. no). The source was the healthcare worker who responded to the study.

- Confounders: age (≤30 vs. >30), and sex (female vs. male) according to the healthcare worker
- Outcomes: the development of at least one local side effect (yes vs. no), and the development of at least one systemic side effect (yes vs. no).

Ethics

The study was approved by the Institutional Review Board of Jimma University (IHRPG/320/21). Respondents provided informed verbal consent. Personal identifiers were not used to protect the confidentiality of the respondents. This study is important to improve clinical practice during vaccine delivery. Moreover, it is useful to improve national policy toward COVID-19 vaccines. These benefits were explained to the respondents.

Analyses

Descriptive and inferential statistics were used. Test for confounders was done using X^2 test and t-test depending on the type of variables. Moreover, X^2 test was done to check correlation between predictors. Statistical significance was declared at p-value < 0.05. Finally, logistic regression was applied to measure the predictors of the outcome variables.

Results

A total of 346 participated in the study with a response rate of 90.1%. All the 346 respondents took the first dose of the Oxford AstraZeneca COVID-19 vaccine.

General characteristics of the respondents

One hundred and eighteen out of 346 (34.1%) respondents were female. The age of the respondents ranged from 20 to 62 with a mean of 31.0 and a standard deviation of 7.4.

Regarding the body mass index of the respondents, the majority of the respondents ($n = 185$ out of 282, 65.1%) had normal BMI. Only 2.1% of the respondents were obese. The mean BMI was 23.6 (SD = 3.0).

The most frequent profession of the respondents was nurse, 152 (43.70%). The least frequent were dentists (1), physiotherapists (1), and health educators (1).

The most frequent number of responses, 149 out of 346 (43.1%) were from the Oromia region. The rest were from three other regions. See Figure 1. General characteristics of the respondents were described in Table 1.

Medical anamnesis

Thirty six out of 346 respondents (10.4%) reported at least one chronic disease. asthma (8), allergy (7), hypertensive heart disease (7), and type II diabetes mellitus (5) were frequently reported by the respondents. Fifty two out of 346 (15.0%) of the respondents reported that they are taking at least one medication at the time of the study. contraceptive (27), anti-asthma (8), anti-hypertension (6), and antidiabetic (6) drugs were frequently taken. see table 2.

All of the respondents, 346 out of 346 (100.00%) reported to not smoke cigarettes.

Forty-three out of 346 (12.4%) of the respondents reported to drink alcohol. Forty-one respondents reported drinking beer and two reported wine. The number of glasses of 0.5 liter beer consumed per week per individual ranged from one to 98 (mean = 6.4, SD = 15.1).

Five out of 118 (4.2%) females and 18 out of 118 (15.3%) females were pregnant and breastfeeding at the time of vaccination, respectively.

More female (28.0%) compared to male (7.0%) reported to take at least one medication (p-value<0.0001). See Table 3 for a description of medical anamnesis by sex.

The prevalence of chronic diseases was more among respondents older than 30 years of age (16.4%) compared with respondents who were at least 30 years of age (p-value = 0.004). See Table 4.

COVID-19 related anamnesis

Thirteen out of 346 (3.8%) respondents have been diagnosed with COVID-19. 11 out of 13 (84.62%) of these were diagnosed before vaccination and the rest two were diagnosed after vaccination. Moreover, nine out of 13 (69.20%) had at least one mild symptom and the rest four (30.8%) had at least one moderate symptom. Five out of nine (55.6%) respondents had fever. Cough and headache each accounted for four out of nine (44.4%) respondents. Difficulty breathing, fatigue, and new loss of smell were each reported by three out of nine (33.3%) respondents. muscle ache, sore throat, and runny nose were each experienced by two out of nine (22.2%) respondents.

Sixty-one out of 346 (17.6%) respondents reported at least one COVID-19 like symptom even though they had never been diagnosed with COVID-19. Fever, cough, headache, fatigue, and muscle ache were the commonest symptoms. see Table 5.

respondents' experience of COVID-19 symptoms without being diagnosed with COVID-19 ranged from 2 days to 30 days. the mean duration of symptoms in days was 6.4 (SD = 5.1)

Fifty-three out of 348 (15.20%) respondents were tested for antibodies of COVID-19. Twenty-two out of 53 (41.51%) were positive.

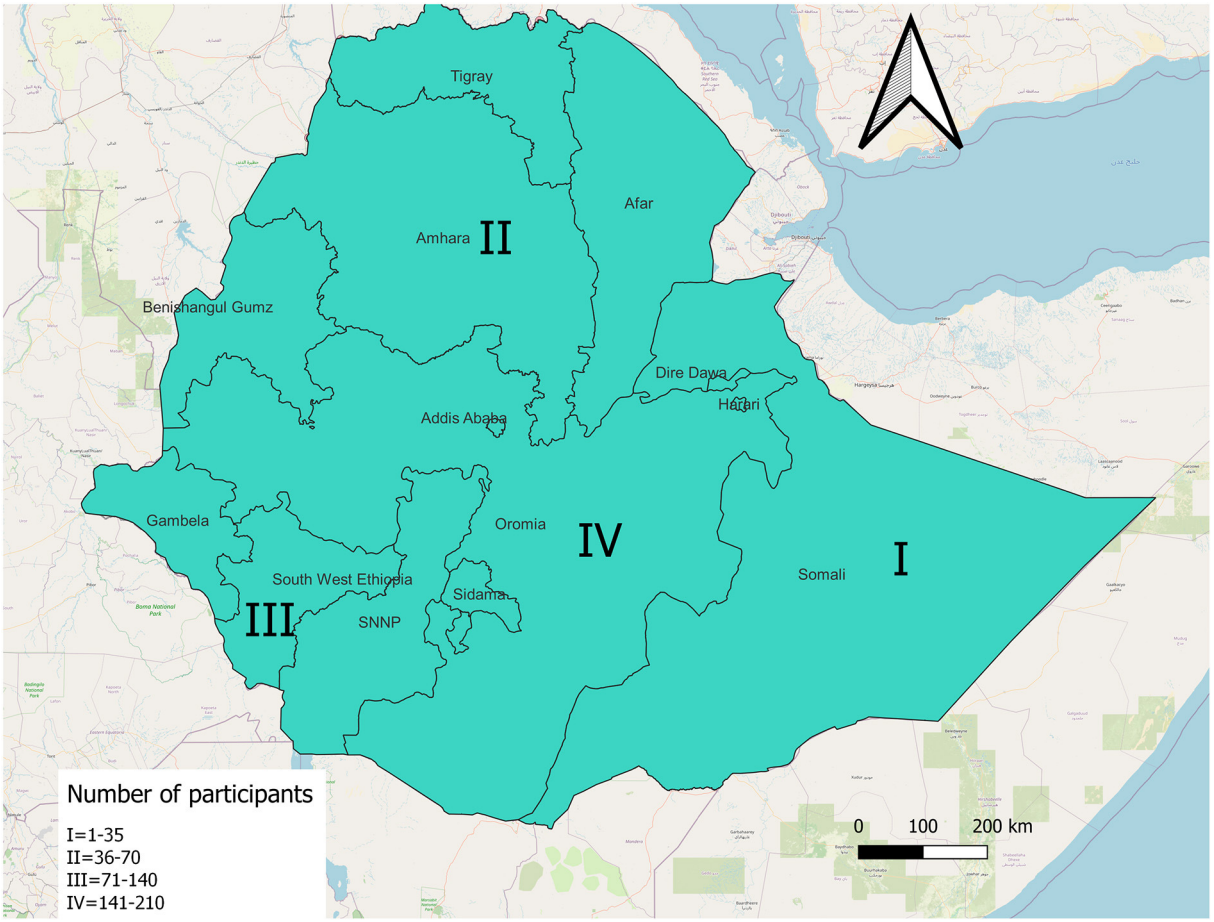

FIGURE 1
Study setting of self-reported side effects of COVID-19 vaccines, Ethiopia, 2021.

There was no statistically significant relationship between COVID-19 anamnesis, and sex (Table 6) and age (Table 7).

Vaccine-related anamnesis

Three hundred forty-six out of 346 (100.0%) took the first dose of the Oxford AstraZeneca COVID-19 vaccine, 137 out of 346 (39.6%) took the second dose of the vaccine after 2 month.

One hundred and seventy five out of 346 (50.6%) respondents experienced at least one local side effect within 4 weeks of taking the vaccine. The most frequent local side effect was injection site pain experienced by 173 out of 346 (50.0%) respondents. see Table 8.

Local side effects were observed after the first dose only among the solid majority of the respondents with local side effects, 156 out of 175 (89.1%), after the second dose among three out of 175 (1.7%), and after both doses in 16 out of 175 (9.1%).

The duration of the local side effects were more frequent during the first, second, and third day after vaccination waning after day three. See Table 9.

One-hundred and fifty four out of 346 (44.5%) experienced at least one systemic side effect within 4 weeks of taking the COVID-19 vaccine. Headache, fever, and fatigue were frequent systemic side effects. see Table 10.

The systemic side effects emerged mostly after the first dose only, 136 out of 154 (88.3%), after the second dose only, 10 out of 154 (6.5%), and after both doses, eight out of 154 (5.2%).

The one day and 2 days duration of systemic side effects were frequent. See Table 11.

Fifty three out of 154 (34.4%) took at least one medication to relieve the side effect. Paracetamol, 30 out of 50 (60.0%) and diclofenac sodium, 11 out of 50 (22.0%) were the most frequently taken medications to relieve the side effects. One

10.3389/fpubh.2022.937794

TABLE 1 Distribution of characteristics on demography, profession, and region of respondents of self-reported side effects of COVID-19 vaccines, Ethiopia, 2021.

Variable	Category	Frequency	Percentage
Sex ($n = 346$)	Female	118	34.1
	Male	228	65.9
Age ($n = 346$)	≤30	230	66.5
	>30	116	33.5
Body mass index ($n = 284$)	Underweight	10	3.5
	Normal body weight	185	65.1
	Overweight	83	29.2
	Obese	6	2.1
Profession ($n = 346$)	Nurse	152	43.9
	Physician	124	35.8
	Health officer	15	4.3
	Laboratory technologist/technician	11	3.2
	Anesthetist	8	2.3
	Pharmacist	8	2.3
	Midwife	8	2.3
	Radiographer	6	1.7
	Other*	14	4.0
Region ($n = 346$)	Amhara	45	13.0
	Oromia	149	43.1
	Somali	32	9.2
	Southwest	120	34.7

*Other, environmental health (3), biomedical (3), public health (3), health informatics (2), dentist (1), physiotherapist (1), health education (1).

healthcare worker with chills was administered with ceftriaxone. see Table 12 on the medications taken by the respondents to relieve side effects.

Forty two out of 51 (82.4%) took the medications after the vaccination. the remaining nine (17.6%) took the medications before the vaccination.

Predictors of Side Effects

Correlation test

Chronic disease and taking medication were not independent. 24 out of 34 (70.6%) with chronic disease took medication while only 25 out of 312 (8.0%) without chronic disease took medication. This was statistically significant using an x^2 test (p-value <0.0001).

TABLE 2 Chronic diseases and medications taken by the respondents of COVID-19 vaccine side effects, Ethiopia, 2021.

Chronic disease ($n = 346$)	Frequency	Percentage
Asthma	8	2.3
Allergy	7	2.0
Hypertensive heart disease	7	2.0
Type II diabetes mellitus	5	1.4
Renal disease	3	0.9
Other*	6	1.7
Medication ($n = 346$)		
Contraceptive	27	7.8
Anti-asthma	8	2.3
Antihypertensive	6	1.7
Antidiabetic	6	1.7
Antireflux	2	0.6
HAART**	2	0.6
Antibiotic	1	0.3

*Other, HIV/ AIDS (2), Deep Venous Thrombosis (1), cardiac disease (1), hepatologic disease (1), neurologic disease (1).
**HAART, Highly Active AntiRetroviral Therapy.

TABLE 3 Medical anamnesis by sex of the respondents of COVID-19 vaccine side effects, Ethiopia, 2021.

Variable	Number	Sex Frequency (percent) Female	Male	Sig.*
Had chronic disease	346	13 (11.2)	21 (9.2)	0.593
Took medication	346	33 (28.0)	16 (7.0)	**<0.0001**
Mean alcohol consumption	41	2.0	8.1	0.258

*Significance values are two-sided and were based on x^2 test for chronic disease and medication, and two-sample t-test for mean 0.5 liter beer consumed per week. Bold value of the Sig. column indicates statistical significance.

TABLE 4 Medical anamnesis by age of the respondents of COVID-19 vaccine side effects, Ethiopia, 2021.

Variable	Number	Age frequency (percent) ≤30	>30	Sig.*
Had chronic disease	346	15 (6.5)	19 (16.4)	**0.004**
Took medication	346	31 (13.5)	18 (15.5)	0.608
Mean alcohol consumption	41	8.2	5.2	0.541

*Significance values are two-sided and were based on x^2 test for chronic disease and medication, and two-sample t-test for mean 0.5 liter beer consumed per week. Bold value of the Sig. column indicates statistical significance.

TABLE 5 Distribution of COVID-19 like symptoms among the respondents who reported COVID-19 like symptoms of respondents of side effects of COVID-19 vaccine, Ethiopia, 2021.

Symptom ($n = 52$)	Frequency	Percent
Fever or chills	42	80.8
Cough	37	71.2
Headache	29	55.8
Fatigue	27	51.9
Muscle or body aches	24	46.2
New loss of taste or smell	12	23.1
Shortness of breath or difficulty breathing	7	13.5
Sore throat	6	11.5
Congestive or runny nose	3	5.8
Loss of appetite	2	3.8
Nausea or vomiting	1	1.9

TABLE 6 Relationship between COVID-19 anamnesis and sex among respondents of self-reported side effects of COVID-19 vaccines, Ethiopia, 2021.

Variable	Number	Sex frequency (percent) Female	Male	Sig.*
Diagnosis with COVID-19	346	4 (3.4)	9 (3.9)	0.796
Ever had symptoms of COVID-19	333	18 (15.8)	43 (19.6)	0.389

*Significance values are two-sided and were based on x^2 test.

TABLE 7 Relationship between COVID-19 anamnesis and age among respondents of self-reported side effects of COVID-19 vaccines, Ethiopia, 2021.

Variable	Number	Age frequency (percent) ≤30	>30	Sig.*
Diagnosis with COVID-19	346	8 (3.5)	5 (4.3)	0.701
Ever had symptoms of COVID-19	333	39 (17.5)	22 (20.0)	0.577

*Significance values are two-sided and were based on x^2 test.

Using independent sample *t*-test, the mean number of 0.5 liter beer consumed per week and chronic disease are not statistically significantly associated, *p*-value = 0.788.

TABLE 8 Local side effects of COVID-19 vaccine among healthcare workers in Ethiopia, 2021.

Local side effect ($n = 346$)	Frequency	Percent
Injection site pain	173	50.0
Injection site swelling	4	1.2
Injection site redness	4	1.2
Itching	2	0.6

TABLE 9 Duration of local side effects of COVID-19 vaccine among healthcare workers in Ethiopia, 2021.

Duration of local side effects ($n = 175$)	Frequency	Percent
1 day	59	33.7
2 day	54	30.9
3 days	42	24.0
5 days	13	7.4
1 week	5	2.9
2 weeks	1	0.6
4 weeks	1	0.6

TABLE 10 Systemic side effects of COVID-19 vaccines among healthcare workers in Ethiopia, 2021.

Systemic side effect ($n = 346$)	Frequency	Percent
Headache	87	25.1
Fatigue	68	19.7
Fever	68	19.7
Joint pain	55	15.9
Muscle pain	50	14.5
Chills	31	9.0
Nausea	7	2.0
Change of taste	3	0.9
Loss of appetite	3	0.9
other *	8	2.3

*Other, Oral ulcers, blisters, vesicles (1), Skin rash (1), blurring of vision (1), cough (1), diaphoresis (1), rhinorrhea (1), vertigo (1), vomiting (1).

Predictors of local side effect

There was no a statistically significant association between COVID-19 like symptoms and local side effects of the Oxford AstraZeneca COVID-19 vaccine after controlling for age and chronic diseases. See Table 13.

Predictors of systemic side effect

There was a statistically significant association between COVID-19 like symptoms and systemic side effects of the Oxford AstraZeneca COVID-19 vaccine after controlling for age and chronic diseases. See Table 14.

TABLE 11 Duration of systemic side effects of COVID-19 vaccines among healthcare workers in Ethiopia, 2021.

Duration of systemic side effects ($n = 154$)	Frequency	Percent
1 day	51	33.1
2 day	51	30.1
3 days	31	20.1
5 days	12	7.8
1 week	6	3.9
2 weeks	3	1.9

TABLE 12 Medications taken by healthcare workers to relieve the side effects of COVID-19 vaccines, Ethiopia.

Medication to relieve side effects ($n = 50$)	Frequency	Percent
Paracetamol	30	60.0
Diclofenac sodium	11	22.0
Ibuprofen	8	16.0
Ceftriaxone	1	2.0

TABLE 13 Binary logistic regression model, the association between COVID-19 like symptom and local side effect among healthcare workers in Ethiopia, 2021.

Variable	Response	Adjusted OR	Sig
COVID-19 like symptom*	Yes	0.8 (0.5, 1.3)	0.582
	No	1	
Age	≤30	1.1 (0.7, 1.7)	0.611
	>30	1	
Chronic disease	Yes	1.2 (0.6, 2.3)	0.606
	No		

*controlling for age and chronic disease.

TABLE 14 Binary logistic regression model, the association between COVID-19 like symptom and systemic side effect among healthcare workers in Ethiopia, 2021.

Variable	Response	Adjusted OR	Sig
COVID-19 like symptom*	Yes	1.38 (1.04, 1.82)	**0.025**
	No	1	
Age	≤30	0.86 (0.68, 1.09)	0.204
	>30	1	
Chronic disease	Yes	1.37 (0.93, 2.00)	0.108
	No	1	

*controlling for age and chronic disease. Bold value of the Sig. column indicates statistical significance.

Discussion

The results of our study showed that all the respondents have taken the Oxford AstraZeneca COVID-19 vaccine at least once. Nearly 40% took the second dose. Slightly above 50% of the respondents experienced local side effects of the Oxford AstraZeneca COVID-19 vaccine, the major local side effect being injection site pain experienced by 50% of all the respondents. It commonly occurs after the first dose and lasts mostly until the third day after vaccination.

Like the local side effects, systemic side effects were experienced by nearly 44.5% of the respondents. Headache, fatigue, fever, joint pain, muscle pain, and chills are the most common systemic side effects of the Oxford AstraZeneca COVID-19 vaccine. They are commonly observed after the first dose and they usually lasted for 1 to 3 days waning afterwards. Paracetamol, diclofenac sodium, and ibuprofen are commonly used after systemic side effects.

Studies elsewhere in Africa, such as Ghana reported higher rates of at least one side effect (81%) among healthcare workers (20). Nonetheless, the prevalenve of headache and fever among healthcare workers after receiving the Oxford AstraZeneca COVID-19 vaccine in Ethiopia is similar with Ghana. Contrary to Ethiopia, Egyptian healthcare workers reported a higher rate of fatigue, 20 vs. 57% and headache, 25 vs. 50% (21). The reasons for the differences in systemic side effects between healthcare workers in Ethiopia and Egypt are unclear.

The prevalence of headache, fever and muscle ache in this study is similar with a study from the Czech Republic and Slovakia (22, 23). However, injection site pain, fatigue and chills after vaccination are much lower in our study. This might be due to the type of vaccine (24). Pfizer–BioNTech COVID-19 vaccine was used in both the Czech Republic and Slovakia, in Ethiopia Oxford AstraZeneca vaccine was used. Duration of symptoms in our study is also similar with studies from the Czech Republic and Slovakia, the symptoms mostly lasting between the first and the third day after vaccination (22, 23).

A study from Jordan which mainly used vaccines Oxford AstraZeneca and Pfizer–BioNTech also reported a similar prevalence of headache, fever, and muscle pain (25). However, it reported more fatigue. Even though the mean age of the participants from the Czech Republic (42.6) and Slovakia (37.8) were older than in Ethiopia (31.0), the mean age from Jordan (35.0) is similar. Therefore, age might not explain the differences in the prevalence of fatigue.

Antihistamines were commonly used in the Czech Republic (23), but analgesics and non-steroidal anti-inflammatory drugs were commonly used in Ethiopia. Similarly, in Togo analgesics were commonly used (26).

There is no a statistically significant predictor of local side effects.

After controlling for confounders, such as age and chronic diseases, presence of COVID-19 like symptom is the only statistically significant predictor of systemic side effects of the Oxford AstraZeneca COVID-19 vaccine.

Policy and practice implications

Physicians might help by counseling the clients with the fact that even though local side effects are common, systemic side effects are less common and that they subside within a day, two, or three. Moreover, physicians and pharmacists can help in monitoring the doses of paracetamol and diclofenac sodium taken by people to relieve side effects so as to prevent toxicity.

Policy wise, the Ministry of Health should consider the presence of COVID-19 symptoms before giving vaccines. It may revise the guidelines to instruct vaccine providers that healthcare workers wait for their COVID-19 like symptoms to subside before taking the vaccines.

This study is strong in that we took sample of healthcare workers across four regions of Ethiopia.

We did not measure psychological factors reported as predictors of side effects by other study. This might limit the findings of the study. Moreover, the design is a cross-sectional study which limits the ability to establish temporality between the predictors and the outcome measure, and suffers from recall bias. Finally, non-response rate and design effect were not considered during sample size calculation. These also limit the findings of the study.

Conclusion

The prevalence of local- and systemic-side effects of the Oxford AstraZeneca vaccine was modest. As the symptoms were mostly common in the first 3 days, it is preferable to monitor healthcare workers at least in the first 3 days following the administration of the vaccine. Moreover, physicians and pharmacists should monitor the use of paracetamol and diclofenac sodium. Vaccination guidelines by the Ministry of Health should consider COVID-19 like symptoms before the provision of the COVID-19 vaccine to an individual.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Jimma University. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional requirements.

Author contributions

EY: conception, design, data collection, data analysis, first draft writing, and final draft writing. AR and MK: conception, design, data collection, and final draft review. AS-M, MS, AM, SE, FM, SM, BA, MY, AU, and JA: design, data collection, and final draft review. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to thank Jimma University for providing office space for the study. We also thank the respondents for taking tie to participate in the study. This work of AR was supported by Masaryk University grant MUNI/IGA/1104/2021. AR and MK were supported by the INTER-EXCELLENCE grant number LTC20031 – "Towards an International Network for Evidence-based Research in Clinical Health Research in the Czech Republic".

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.937794/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 16 September 2022
DOI 10.3389/fpubh.2022.881903

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Infectious Diseases – Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

RECEIVED 23 February 2022
ACCEPTED 24 August 2022
PUBLISHED 16 September 2022

CITATION
Wang L, Wang Y, Cheng X, Li X, Yang Y and Li J (2022) Acceptance of coronavirus disease 2019 (COVID-19) vaccines among healthcare workers: A meta-analysis.
Front. Public Health 10:881903.
doi: 10.3389/fpubh.2022.881903

Acceptance of coronavirus disease 2019 (COVID-19) vaccines among healthcare workers: A meta-analysis

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Background: The coronavirus disease 2019 (COVID-19) pandemic has posed increasing challenges to global health systems. Vaccination against COVID-19 can effectively prevent the public, particularly healthcare workers (HCWs), from being infected by this disease.

Objectives: We aim to understand the factors influencing HCWs' acceptance of COVID-19 vaccines.

Methods: We searched PubMed, Embase and Web of Science to collect literature published before May 15, 2022, about HCWs' acceptance of COVID-19 vaccines. The Newcastle–Ottawa quality assessment scale was used to assess the risk of bias and the quality of the included studies. We utilized Stata 14.0 software for this meta-analysis with a random-effects model, and odds ratios (ORs) with 95% confidence intervals (CIs) were reported. This meta-analysis was conducted in alignment with the preferred reporting items for systematic review and meta-analysis (PRISMA) guideline.

Results: Our meta-analysis included 71 articles with 93,508 HCWs involved. The research showed that the acceptance of vaccines had significantly increased among HCWs compared to non-HCWs (OR = 1.91, 95% CI: 1.16–3.12). A willingness to undergo COVID-19 vaccination was observed in 66% (95% CI: 0.61–0.67) of HCWs. Among the HCWs involved, doctors showed a generally increased intention to be vaccinated compared with nurses (OR = 2.22, 95% CI: 1.71–2.89). Additionally, males were found to hold more positive attitudes toward vaccination than females (OR = 1.81, 95% CI: 1.55–2.12). When the effectiveness of COVID-19 vaccines was improved, the vaccination acceptance of HCWs was greatly increased accordingly (OR = 5.03, 95% CI: 2.77–9.11). The HCWs who were willing to vaccinate against seasonal influenza showed an increased acceptance of COVID-19 vaccines (OR = 3.52, 95% CI: 2.34–5.28). Our study also showed that HCWs who were willing to be vaccinated against COVID-19 experienced a reduced rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (OR = 0.78, 95% CI: 0.66–0.92).

Conclusions: Our analysis revealed that the five factors of occupation, gender, vaccine effectiveness, seasonal influenza vaccines, and SARS-CoV-2 infection presumably affected the acceptance of COVID-19 vaccines among HCWs. It is essential to boost the confidence of HCWs in COVID-19 vaccines for the containment of the epidemic.

KEYWORDS

COVID-19, vaccines, meta-analysis, seasonal influenza, healthcare workers

Introduction

Rationale

On March 16, 2020, the first mRNA vaccine for coronavirus disease 2019 (COVID-19) developed by Moderna entered the clinical trial stage in the United States. Subsequently, various COVID-19 vaccines, including DNA-based vaccines, have been popularized throughout the world (1). Developing safe and effective vaccines to promote large-scale vaccination is probably the most effective way for humankind to fight against COVID-19 (2).

In 2022, millions of doses of COVID-19 vaccines are now administered each day globally (3). Surprisingly, numerous people showed distrust and concerns about COVID-19 vaccines (4). A large number of studies have shown that some healthcare workers (HCWs) remain skeptical about whether to receive COVID-19 vaccination (5). In one survey, approximately one-sixth of HCWs claimed that they would not choose to be vaccinated against COVID-19 even if mandated (6). The risk of the members of HCWs infected with COVID-19 was nearly three times that of the non-HCWs (7). In some countries, approximately 10% of HCWs are infected with SARS-CoV-2 (8). The acceptance of COVID-19 vaccines among non-HCWs can be easily affected by HCWs; in particular, HCWs with a negative attitude tend not to recommend vaccines to patients (9).

Objectives

We aim, through meta-analysis, to understand the factors influencing HCWs' acceptance of vaccination against COVID-19. Our study may provide insights for promoting future immunization programs worldwide.

Materials and methods

Eligibility criteria

Studies meeting the following criteria were included in the meta-analysis: (1) the content must include the acceptance of HCWs about COVID-19 vaccines, (2) the number of HCWs who are willing and unwilling (including refusal and hesitation) to vaccinate should be recorded separately, and (3) the sample sizes of both the experimental group and the control group were more than 10.

Information from abstracts, comments, reviews, posters and case reports was excluded.

Information sources

All the literature published before May 15, 2022, about the acceptance of HCWs toward COVID-19 vaccines was searched in PubMed, Embase, and Web of Science, regardless of the language of the literature, to collect the most useful information.

Search strategy

The method of "key words" + "free words" was adopted for retrieval. Search terms were limited to the titles and abstracts. Detailed strategies are listed in Supplementary File 1.

Study selection process

Literature collected from the database was imported into NoteExpress software for filtration. After deleting duplicated literature, we first read the titles and abstracts before we eliminated irrelevant pieces. Articles that did not meet the requirements were then further screened based on the abstracts or the full text. Articles that were fairly related were adopted for subsequent data selection.

Data selection process and items

Data extraction was completed independently by two authors. When those two authors disagreed on data selection, they would debate the problem before delivering it to a third author for the final conclusion.

The following data were recorded: the number of HCWs willing and unwilling to be vaccinated against COVID-19; the number of HCWs who had been vaccinated against seasonal influenza in 2019–2020 and who preferred to be vaccinated against the same disease in 2020–2021; the number of HCWs in favor of compulsory COVID-19 vaccination; the number of doctors and nurses willing to receive COVID-19 vaccines; the number of non-HCWs willing to be vaccinated with COVID-19; the number of HCWs willing to be vaccinated with different effective rates (bounded by 70%); the gender, age, and education level of HCWs; the number of HCWs afflicted with chronic diseases; the number of HCWs who contacted closely with COVID-19 patients; and the number of people vaccinated against influenza and the number of COVID-19 cases in the two groups of HCWs who were willing and unwilling to be vaccinated against COVID-19. If an article could extract several groups of data without intersection or the data record research results under different conditions, they were represented by "-A," "-B" or "-C."

Study risk of bias assessment

The quality and the risk of bias of the included studies were independently assessed using the Newcastle–Ottawa quality assessment scale. A low risk of bias and high quality were considered if the overall score was equal to or above seven. The assessment was completed by one author and reviewed by another.

Reporting bias assessment

Egger's test was used for quantitative analysis. A p-value < 0.05 indicates the presence of bias.

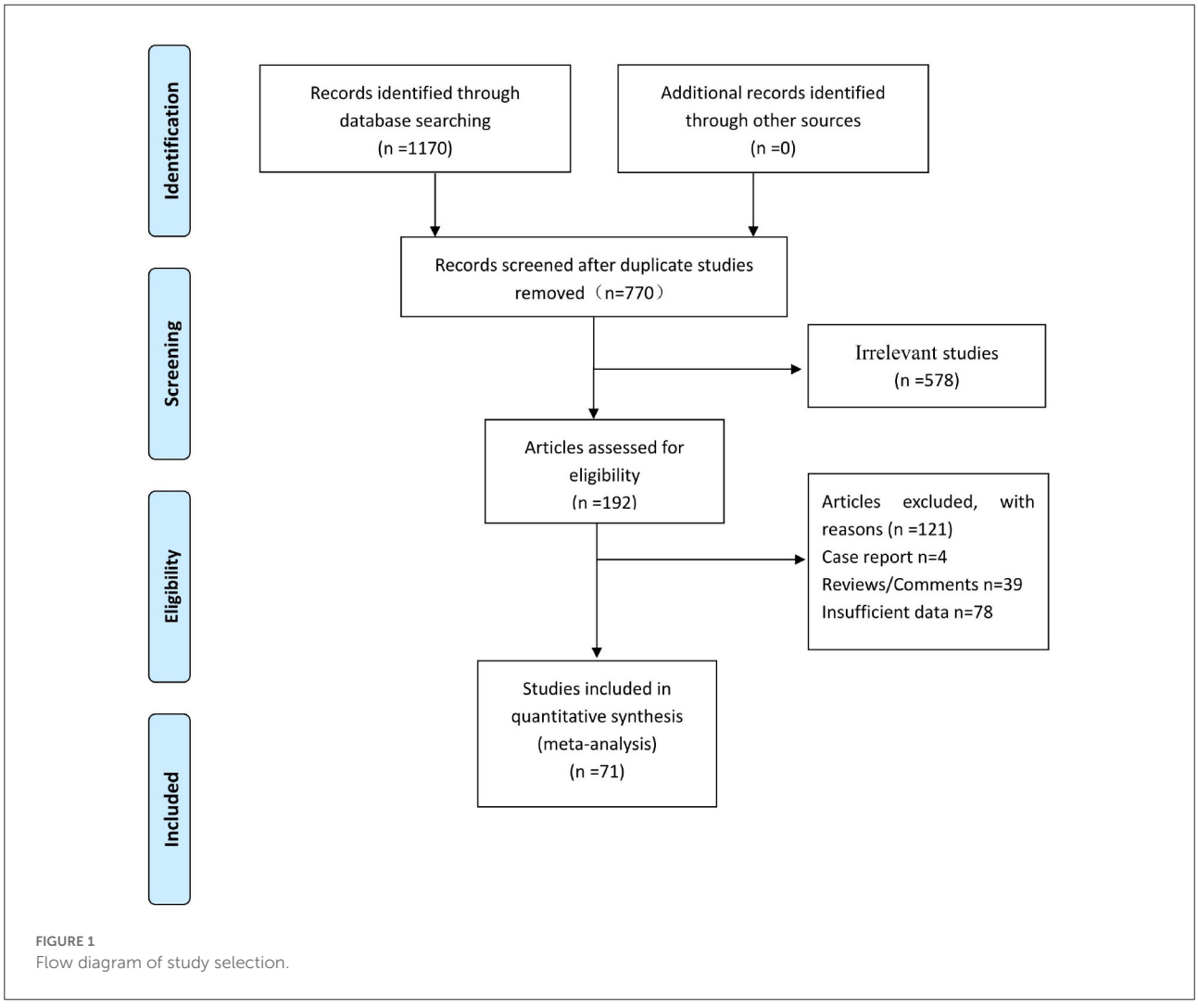

FIGURE 1
Flow diagram of study selection.

TABLE 1 The characteristics of HCWs and non-HCWs.

Reference	Rigion	Publication year	Study period	HCWs	The number of HCWs in favor of compulsory vaccination	Doctors	Nurses	Non-HCWs	Vaccine effectiveness (over 70%)	Willing to receive COVID-19 vaccines among HCWs	Willing to receive COVID-19 vaccines among doctors	Willing to receive COVID-19 vaccines among nurses	Willing to receive COVID-19 vaccines among non-HCWs	Vaccination against seasonal influenza in 2019–2020 among HCWs	Willing to receive seasonal influenza vaccines in 2020–2021 among HCWs
Mascarenhas et al. (6)	America	2021	NA	245	98	NA	NA	NA	NA	136	NA	NA	NA	148	178
Qattan et al. (10)	Saudi Arabia	2021	2020.12.8–2020.12.14	673	NA	NA	NA	NA	NA	340	NA	NA	NA	NA	NA
Papagiannis et al. (11)	Greece	2021	2020.12.15–2020.12.22	340	NA	NA	NA	NA	NA	267	NA	NA	NA	NA	251
Nzaji et al. (12)	Congo	2020	2020.3.20–2020.4.30	613	NA	NA	NA	NA	NA	170	NA	NA	NA	NA	NA
Harapan et al. (13)-A	Indonesia	2020	2020.3.25–2020.4.6	264	NA	NA	NA	1,095	Yes	252	NA	NA	1,016	NA	NA
Harapan et al. (13)-B	Indonesia	2020	2020.3.25–2020.4.6	264	NA	NA	NA	1,095	No	193	NA	NA	718	NA	NA
Singhania et al. (14)	India	2021	2021.1.20–2021.1.24	721	NA	615	56	NA	NA	572	496	32	NA	NA	NA
Kanyike et al. (15)	Uganda	2021	2021.3.15–2021.3.21	600	NA	NA	NA	NA	NA	224	NA	NA	NA	NA	NA
Chew et al. (16)	Asia-Pacific	2021	2020.12.12–2020.12.21	1,720	NA	892	404	NA	NA	1,655	859	389	NA	NA	NA
Papagiannis et al. (17)	Greece	2020	2020.2.10–2020.2.25	461	NA	140	215	NA	NA	200	85	73	NA	NA	NA
Shaw et al. (18)	America	2021	2020.11.23–2020.12.5	5,287	NA	NA	NA	NA	NA	3,032	NA	NA	NA	NA	NA
Szmyd et al. (19)	Poland	2021	2020.12.22–2021.1.8	387	NA	NA	NA	1,913	NA	321	NA	NA	1,039	NA	NA
Ledda et al. (20)	Italy	2021	2020.9.1–2020.12.20	787	NA	324	357	NA	NA	593	261	251	NA	NA	NA
Verger et al. (21)-A	France	2021	2020.10.1–2020.11.30	1,209	NA	NA	NA	NA	NA	910	NA	NA	NA	1,031	NA
Verger et al. (21)-B	Belgium	2021	2020.10.1–2020.11.30	414	NA	NA	NA	NA	NA	315	NA	NA	NA	347	NA
Verger et al. (21)-C	Canada	2021	2020.10.1–2020.11.30	1,055	NA	NA	NA	NA	NA	743	NA	NA	NA	636	NA
Gennaro et al. (22)	Italy	2021	2020.10.1–2021.11.1	1,723	NA	NA	NA	NA	NA	1,115	NA	NA	NA	810	1,364
Bauernfeind et al. (23)	Germany	2021	2020.12.12–2020.12.21	2,454	NA	423	629	NA	NA	1,469	350	335	NA	1,025	1,325
Abuown et al. (24)	England	2021	2020.12.1–2020.12.21	514	NA	NA	NA	NA	NA	304	NA	NA	NA	NA	NA
Fares et al. (25)	Egypt	2021	2020.12.1–2021.1.31	385	NA	205	89	NA	NA	80	49	10	NA	NA	NA
Manning et al. (26)	America	2021	2020.8.10–2020.9.14	1,212	NA	NA	NA	NA	NA	561	NA	NA	NA	NA	NA
Shekhar et al. (27)	America	2021	2020.10.7–2020.11.9	3,479	NA	NA	NA	NA	NA	1,247	NA	NA	NA	3,363	NA
Dzieciolowska et al. (28)	Canada	2021	2020.12.15–2020.12.28	2,761	NA	NA	NA	NA	NA	2,233	NA	NA	NA	NA	NA
Theodore et al. (29)	America	2020	2020.4.26–2020.7.22	121	NA	NA	NA	NA	NA	94	NA	NA	NA	NA	NA
Maraqa et al. (30)	Palestine	2021	2020.12.25–2021.1.6	1,159	NA	374	483	NA	NA	438	231	118	NA	NA	NA
Lucia et al. (31)	America	2020	NA	167	110	NA	NA	NA	NA	126	NA	NA	NA	NA	NA
Gadoth et al. (32)	America	2021	2020.9.24–2020.10.16	540	NA	201	207	NA	NA	447	187	147	NA	NA	NA
Maltezou et al. (33)	Greece	2021	2020.9.1–2020.10.31	1,571	1,299	480	607	NA	NA	803	343	261	NA	NA	NA
Janssens et al. (34)	Germany	2021	2020.12.1–2020.12.31	2,305	NA	NA	NA	NA	NA	1,471	NA	NA	NA	NA	NA
Ahmed et al. (35)	Saudi Arabia	2021	2020. 10.1–2020.10.31	236	NA	38	146	NA	NA	115	18	69	NA	NA	NA
Kwok et al. (36)	Hong Kong	2021	2020.3.15–2020.4.30	1,205	NA	NA	NA	NA	NA	759	NA	NA	NA	590	NA
Wang et al. (37)	Hong Kong	2020	2020.2.26–2020.3.31	806	NA	NA	NA	NA	NA	322	NA	NA	NA	383	360
Konopinska et al. (38)	Poland	2021	2021.1.1–2021.1.31	126	NA	NA	NA	NA	NA	90	NA	NA	NA	NA	NA
Elhadi et al. (39)-A	Libya	2021	2020.12.1–2020.12.18	3,967	NA	1,394	821	NA	Yes	3,174	1,138	643	NA	NA	NA
Elhadi et al. (39)-B	Libya	2021	2020.12.1–2020.12.18	3,967	NA	1,394	821	NA	No	1,552	494	314	NA	NA	NA

(Continued)

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TABLE 1 (Continued)

Reference	Rigion	Publication year	Study period	HCWs	The number of HCWs in favor of compulsory vaccination	Doctors	Nurses	Non-HCWs	Vaccine effectiveness (over 70%)	Willing to receive COVID-19 vaccines among HCWs	Willing to receive COVID-19 vaccines among doctors	Willing to receive COVID-19 vaccines among nurses	Willing to receive COVID-19 vaccines among non-HCWs	Vaccination against seasonal influenza in 2019–2020 among HCWs	Willing to receive seasonal influenza vaccines in 2020–2021 among HCWs
Szmyd et al. (40)	Poland	2021	2020.12.22–2020.12.25	687	NA	NA	NA	1,284	NA	632	NA	NA	763	NA	NA
Gonullu et al. (41)	Turkey	2021	2020.11.1–2020.11.15	506	303	NA	NA	NA	NA	420	NA	NA	NA	198	354
Socarras et al. (42)-A	Columbia	2021	2021.1.1–2021.1.31	1,066	NA	NA	NA	NA	Yes	821	NA	NA	NA	NA	NA
Socarras et al. (42)-B	Columbia	2021	2021.1.1–2021.1.31	1,066	NA	NA	NA	NA	No	967	NA	NA	NA	NA	NA
Kuter et al. (43)	America	2021	2020.11.13–2020.12.6	12,034	NA	NA	NA	NA	NA	7,284	NA	NA	NA	NA	NA
Yu et al. (44)	China	2021	2020.10.1–2020.11.30	2,264	NA	362	1,902	NA	NA	294	55	239	NA	NA	NA
Hoke et al. (45)	America	2021	2020.5.1–2020.5.31	350	NA	NA	NA	NA	NA	297	NA	NA	NA	NA	NA
Giuseppe et al. (46)	Italy	2021	2020.9.14–2020.11.30	779	NA	437	194	NA	NA	629	395	132	NA	NA	NA
Kaplan et al. (47)	Turkey	2021	2020.12.25–2020.12.31	1,574	NA	1,115	275	NA	NA	1,331	1,003	183	NA	NA	NA
Kose et al. (48)	Turkey	2020	2020.9.17–2020.9.20	1,138	NA	53	306	NA	NA	781	27	200	NA	312	NA
Saied et al. (49)	Egypt	2021	2021.1.1–2021.1.31	2,133	1,487	NA	NA	NA	NA	746	NA	NA	NA	112	51
Dror et al. (50)	Israel	2020	2020.3.19–2020.3.25	549	NA	338	211	1,112	NA	393	264	129	834	NA	NA
Unroe et al. (51)	America	2021	2020.11.14–2020.11.17	8,243	NA	NA	NA	NA	NA	5,705	NA	NA	NA	NA	NA
Kukreti et al. (52)	Taiwan	2021	2020.9.24–2020.12.31	500	NA	NA	NA	238	NA	117	NA	NA	73	NA	NA
Gakuba et al. (53)	France	2021	2021.2.1–2021.2.28	61	NA	NA	NA	NA	NA	34	NA	NA	NA	NA	NA
Wang et al. (54)	China	2021	2020.9.15–2020.9.20	3,634	NA	1,123	1,841	NA	NA	2,874	929	1,400	NA	NA	NA
Yurttas et al. (55)	Turkey	2021	2021.1.4–2021.1.13	320	113	NA	NA	732	NA	168	NA	NA	214	NA	NA
Noushad et al. (56)	Twelve countries	2022	2021.2–2021.4	2,962	NA	NA	NA	NA	NA	2,038	NA	NA	NA	NA	NA
Dkhar et al. (57)	India	2022	NA	511	NA	NA	NA	NA	NA	340	NA	NA	NA	NA	NA
Adeniyi et al. (58)	South Africa	2021	2020.11–2020.12	1,308	NA	176	591	NA	NA	1,179	158	527	NA	NA	NA
Ayele et al. (59)	Ethiopia	2021	2021.3.1–2021.3.30	422	NA	60	148	NA	NA	191	39	52	NA	NA	NA
Vignier et al. (60)	French Guiana	2021	2021.1.22–2021.3.26	579	NA	NA	NA	NA	NA	373	NA	NA	NA	183	140
Do et al. (61)	America	2021	2020.12.10–2020.12.20	1,076	NA	63	275	NA	NA	563	52	144	NA	NA	NA
Khan et al. (62)	Pakistan	2022	NA	248	NA	NA	NA	NA	NA	219	NA	NA	NA	NA	NA
Wiysonge et al. (63)	South Africa	2022	2021.3–2021.5	395	NA	49	191	NA	NA	233	44	97	NA	NA	NA
Koh et al. (64)	Singapore	2022	2021.5–2021.6	528	NA	NA	NA	NA	NA	501	NA	NA	NA	NA	487
Sharaf et al. (65)	Egypt	2022	2021.8–2021.10	171	NA	NA	NA	NA	NA	78	NA	NA	NA	NA	NA
Raja et al. (66)	Sudan	2022	2021.6.30–2021.7.11	217	NA	NA	NA	NA	NA	121	NA	NA	NA	NA	NA
Pal et al. (67)	America	2021	2021.2.1–2021.3.31	1,358	NA	NA	NA	NA	NA	1,251	NA	NA	NA	NA	NA
Saddik et al. (68)	United Arab Emirates	2021	2020.11.20–2021.1.3	517	NA	NA	NA	NA	NA	312	NA	NA	NA	NA	NA
Hara et al. (69)	Japan	2021	2021.1.19	1,030	NA	120	369	6,180	NA	477	65	168	3,003	NA	NA
Boche et al. (70)	Ethiopia	2022	2021.6.30–2021.7.30	319	NA	NA	NA	NA	NA	232	NA	NA	NA	NA	NA
Thomas et al. (71)	America	2022	2021.3.12–2021.4.22	505	NA	NA	NA	NA	NA	457	NA	NA	NA	NA	NA
Otiti-Sengeri et al. (72)	Uganda	2022	2021.6–2021.8	300	NA	NA	NA	NA	NA	293	NA	NA	NA	NA	NA

(Continued)

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TABLE 1 (Continued)

Reference	Region	Publication year	Study period	HCWs	The number of HCWs in favor of compulsory vaccination	Doctors	Nurses	Non-HCWs	Vaccine effectiveness (over 70%)	Willing to receive COVID-19 vaccines among HCWs	Willing to receive COVID-19 vaccines among doctors	Willing to receive COVID-19 vaccines among nurses	Willing to receive COVID-19 vaccines among non-HCWs	Vaccination against seasonal influenza in 2019–2020 among HCWs	Willing to receive seasonal influenza vaccines in 2020–2021 among HCWs
Rosental et al. (73)	Israel	2021	2020.8.27–2020.9.28	628	NA	321	307	NA	NA	517	283	234	NA	NA	NA
Kashif et al. (74)	Pakistan	2021	2020.12.19–2021.1.10	208	NA	NA	NA	196	NA	112	NA	NA	56	NA	NA
Kateeb et al. (75)	Palestine	2021	2021.2–2021.3	417	NA	NA	NA	NA	NA	241	NA	NA	NA	NA	NA
Xu et al. (76)	China	2021	2021.4.16–2021.4.18	1,051	NA	NA	NA	NA	NA	906	NA	NA	NA	NA	NA
Yilma et al. (77)	Ethiopia	2022	2021.2–2021.4	1,314	NA	NA	NA	NA	NA	982	NA	NA	NA	NA	NA
Li et al. (78)	China	2021	2021.1.20–2021.2.20	1,779	NA	300	1,317	NA	NA	1,670	290	1,232	NA	NA	NA
Yurttas et al. (55)	Turkey	2021	2021.1.4–2021.1.13	320	NA	NA	NA	763	NA	168	NA	NA	264	NA	NA

HCWs, Healthcare workers; NA, not applicable; -A, -B or –C, an article could extract several groups of data without intersection, or the data record research results under different conditions; COVID-19, coronavirus disease 2019.

Synthesis methods

The I^2 statistic was used to quantify the heterogeneity among studies. An I^2 value $< 50\%$ indicated mild heterogeneity, while an I^2 value $\geq 75\%$ suggested significant heterogeneity. Moderate heterogeneity was considered if $50\% \leq I^2 < 75\%$. We conducted subgroup analysis to explore the source of heterogeneity. A random-effects model was used to estimate the effect value. Stata 14.0 software was applied for all analyses. A p-value of z test <0.05 was considered to be statistically significant.

Effect measures and certainty assessment

In this study, the ratio and odds ratio (OR) were used for data analysis, and the confidence interval (CI) was 95%.

Results

Study selection

A total of 1,170 studies were searched in the database, of which 400 duplicated studies were deleted with NoteExpress software. According to the titles and abstracts, 578 articles irrelevant to this study were eliminated. Of the remaining 192 papers, 121 were excluded after further screening, including comments, reviews, case reports, and papers with insufficient data. Seventy-one articles were finalized for inclusion in our meta-analysis. The flow diagram of the study selection is shown in Figure 1.

Study characteristics

The HCWs in our study came from various occupations, including doctors, nurses, paramedics, medical teachers, and students. The whole sample we extracted from the literature included 75,345 HCWs and 13,513 non-HCWs, covering 40 countries and regions.

Risk of bias in studies

All the studies included in the Newcastle–Ottawa quality assessment scale indicated a fairly low risk of bias and high quality (Supplementary Table 1).

Results of individual studies

The results of individual studies are presented in structured tables. The information of HCWs and non-HCWs is listed in

TABLE 2 The characteristics of HCWs who are willing and unwilling to receive coronavirus disease 2019 vaccines.

Reference	Rigion	Publication year	Study period	HCWs		Age < 40		Age < 50		Male		Less than bachelor's degree		Close contact with COVID-19 patients		Chronic diseases		Married		Willing to receive seasonal influenza vaccines in 2020–2021		Vaccination against seasonal influenza in 2019–2020		SARS-CoV-2 infection	
				Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No
Mascarenhas et al. (6)	America	2021	NA	136	109	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	120	58	100	49	7	18
Qattan et al. (10)	Saudi Arabia	2021	2020.12.8–2020.12.14	340	333	227	225	306	287	228	177	NA	NA	183	144	70	61	234	236	NA	NA	NA	NA	NA	NA
Papagiannis et al. (11)	Greece	2021	2020.12.15–2020.12.22	267	73	NA	NA	NA	NA	142	31	NA	NA	NA	NA	NA	NA	NA	NA	205	43	NA	NA	NA	NA
Nzaji et al. (12)	Congo	2020	2020.3.20–2020.4.30	170	443	118	303	NA	NA	110	202	NA	NA	NA	NA	NA	NA	120	288	NA	NA	NA	NA	NA	NA
Singhania et al. (14)	India	2021	2021.1.20–2021.1.24	572	149	NA	NA	NA	NA	NA	NA	NA	NA	389	112	NA	NA	NA	NA	NA	NA	NA	NA	109	40
Kanyike et al. (15)	Uganda	2021	2021.3.15–2021.3.21	224	376	NA	NA	NA	NA	160	217	NA	NA	NA	NA	NA	NA	20	54	NA	NA	NA	NA	NA	NA
Chew et al. (16)	Asia-Pacific	2021	2020.12.12–2020.12.21	1,655	65	NA	NA	NA	NA	646	24	91	0	NA	NA	561	44	1,019	35	NA	NA	NA	NA	NA	NA
Papagiannis et al. (17)	Greece	2020	2020.2.10–2020.2.25	200	261	NA	NA	NA	NA	69	49	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Shaw et al. (18)	America	2021	2020.11.23–2020.12.5	3,032	2,255	NA	NA	NA	NA	992	376	NA	NA	1,670	1,423	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ledda et al. (20)	Italy	2021	2020.9.1–2020.12.20	593	194	259	70	423	164	312	56	NA	NA	NA	NA	230	37	NA	NA	NA	NA	NA	NA	NA	NA
Gennaro et al. (22)	Italy	2021	2020.10.1–2021.11.1	1,115	608	900	389	993	496	538	265	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	54	33
Bauernfeind et al. (23)	Germany	2021	2020.12.12–2020.12.21	1,469	985	NA	NA	NA	NA	595	188	823	762	777	823	NA	NA	NA	NA	1,004	321	787	238	NA	NA
Fares et al. (25)	Egypt	2021	2020.12.1–2021.1.31	80	305	NA	NA	NA	NA	28	44	3	11	47	111	NA	NA	NA	NA	NA	NA	NA	NA	32	113
Manning et al. (26)	America	2021	2020.8.10–2020.9.14	561	651	455	538	499	600	79	52	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Shekhar et al. (27)	America	2021	2020.10.7–2020.11.9	1,247	2,232	640	1,237	867	1,696	425	439	86	241	814	1,402	733	1306	NA	NA	NA	NA	1,237	2,126	31	59
Maraqa et al. (30)	Palestine	2021	2020.12.25–2021.1.6	438	721	NA	NA	382	619	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	90	172
Lucia et al. (31)	America	2020	NA	126	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	1
Maltezou et al. (33)	Greece	2021	2020.9.1–2020.10.31	803	768	334	311	556	539	365	185	NA	NA	456	376	586	374	NA	NA	NA	NA	NA	NA	NA	NA
Ahmed et al. (35)	Saudi Arabia	2021	2020. 10.1–2020.10.31	115	121	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	22	10	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al. (37)	Hong Kong	2020	2020.2.26–2020.3.31	322	484	189	236	267	376	67	39	NA	NA	190	247	83	97	NA	NA	NA	NA	202	181	NA	NA
Gonullu et al. (41)	Turkey	2021	2020.11.1–2020.11.15	420	86	NA	NA	NA	NA	184	25	NA	NA	352	72	75	14	NA	NA	316	38	180	18	57	14
Socarras et al. (42)-A	Columbia	2021	2021.1.1–2021.1.31	821	245	NA	NA	NA	NA	440	123	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Socarras et al. (42)-B	Columbia	2021	2021.1.1–2021.1.31	967	99	NA	NA	NA	NA	519	44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kuter et al. (43)	America	2021	2020.11.13–2020.12.6	7,284	4,750	3,835	2,296	NA	NA	2,064	461	618	893	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Giuseppe et al. (46)	Italy	2021	2020.9.14–2020.11.30	629	150	NA	NA	474	104	NA	NA	NA	NA	319	65	127	37	280	73	NA	NA	NA	NA	NA	NA
Kaplan et al. (47)	Turkey	2021	2020.12.25–2020.12.31	1,331	243	612	176	977	224	563	85	NA	NA	768	153	421	51	972	152	NA	NA	NA	NA	214	85
Kose et al. (48)	Turkey	2020	2020.9.17–2020.9.20	781	357	NA	NA	NA	NA	234	79	NA	NA	NA	NA	101	55	NA	NA	NA	NA	NA	NA	NA	NA
Saied et al. (49)	Egypt	2021	2021.1.1–2021.1.31	746	1,387	NA	NA	NA	NA	276	466	NA	NA	NA	NA	NA	NA	NA	NA	23	28	50	62	147	304
Gakuba et al. (53)	France	2021	2021.2.1–2021.2.28	34	27	NA	NA	NA	NA	6	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al. (54)	China	2021	2020.9.15–2020.9.20	2,874	760	NA	NA	2,499	703	689	131	422	63	526	136	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

(Continued)

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TABLE 2 (Continued)

Reference	Rigion	Publication year	Study period	HCWs		Age < 40		Age < 50		Male		Less than bachelor's degree		Close contact with COVID-19 patients		Chronic diseases		Married		Willing to receive seasonal influenza vaccines in 2020–2021		Vaccination against seasonal influenza in 2019–2020		SARS-CoV-2 infection	
				Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No	Willing	No
Noushad et al. (56)	Twelve countries	2022	2021.2–2021.4	2,038	924	NA	NA	1,903	890	853	332	NA	NA	NA	NA	263	116	NA	NA	NA	NA	NA	NA	334	197
Dkhar et al. (57)	India	2022	NA	340	171	NA	NA	NA	NA	132	64	NA	NA	139	84	NA	NA	206	104	NA	NA	NA	NA	73	36
Adeniyi et al. (58)	South Africa	2021	2020.11–2020.12	1,179	129	NA	NA	NA	NA	223	19	352	22	906	103	767	91	NA	NA	NA	NA	NA	NA	356	45
Ayele et al. (59)	Ethiopia	2021	2021.3.1–2021.3.30	191	231	146	202	NA	NA	NA	NA	NA	NA	NA	NA	53	39	112	140	NA	NA	NA	NA	15	24
Vignier et al. (60)	French Guiana	2021	2021.1.22–2021.3.26	373	206	NA	NA	220	165	150	36	NA	NA	NA	NA	NA	NA	NA	NA	127	13	164	19	72	38
Do et al. (61)	America	2021	2020.12.10–2020.12.20	563	513	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	38	64
Khan et al. (62)	Pakistan	2022	NA	219	29	NA	NA	NA	NA	147	12	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	102	9
Wiysonge et al. (63)	South Africa	2022	2021.3–2021.5	233	162	NA	NA	NA	NA	NA	NA	100	95	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Koh et al. (64)	Singapore	2022	2021.5–2021.6	501	27	NA	NA	NA	NA	64	1	NA	NA	406	18	NA	NA	NA	NA	462	25	NA	NA	NA	NA
Sharaf et al. (65)	Egypt	2022	2021.8–2021.10	78	93	59	73	73	89	19	7	NA	NA	59	71	9	12	NA	NA	NA	NA	NA	NA	39	46
Raja et al. (66)	Sudan	2022	2021.6.30–2021.7.11	121	96	NA	NA	NA	NA	57	43	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pal et al. (67)	America	2021	2021.2.1–2021.3.31	1,251	107	NA	NA	NA	NA	258	15	503	64	691	56	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Thomas et al. (71)	America	2022	2021.3.12–2021.4.22	457	48	126	18	NA	NA	70	5	NA	NA	336	33	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Xu et al. (76)	China	2021	2021.4.16–2021.4.18	906	145	NA	NA	NA	NA	95	16	69	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Li et al. (78)	China	2021	2021.1.20–2021.2.20	1,670	109	1,388	88	1,621	107	202	8	255	14	NA	NA	NA	NA	976	80	NA	NA	NA	NA	NA	NA

HCWs, Healthcare workers; NA, not applicable; -A or –B, an article could extract several groups of data without intersection, or the data record research results under different condition; COVID-19, coronavirus disease 2019.

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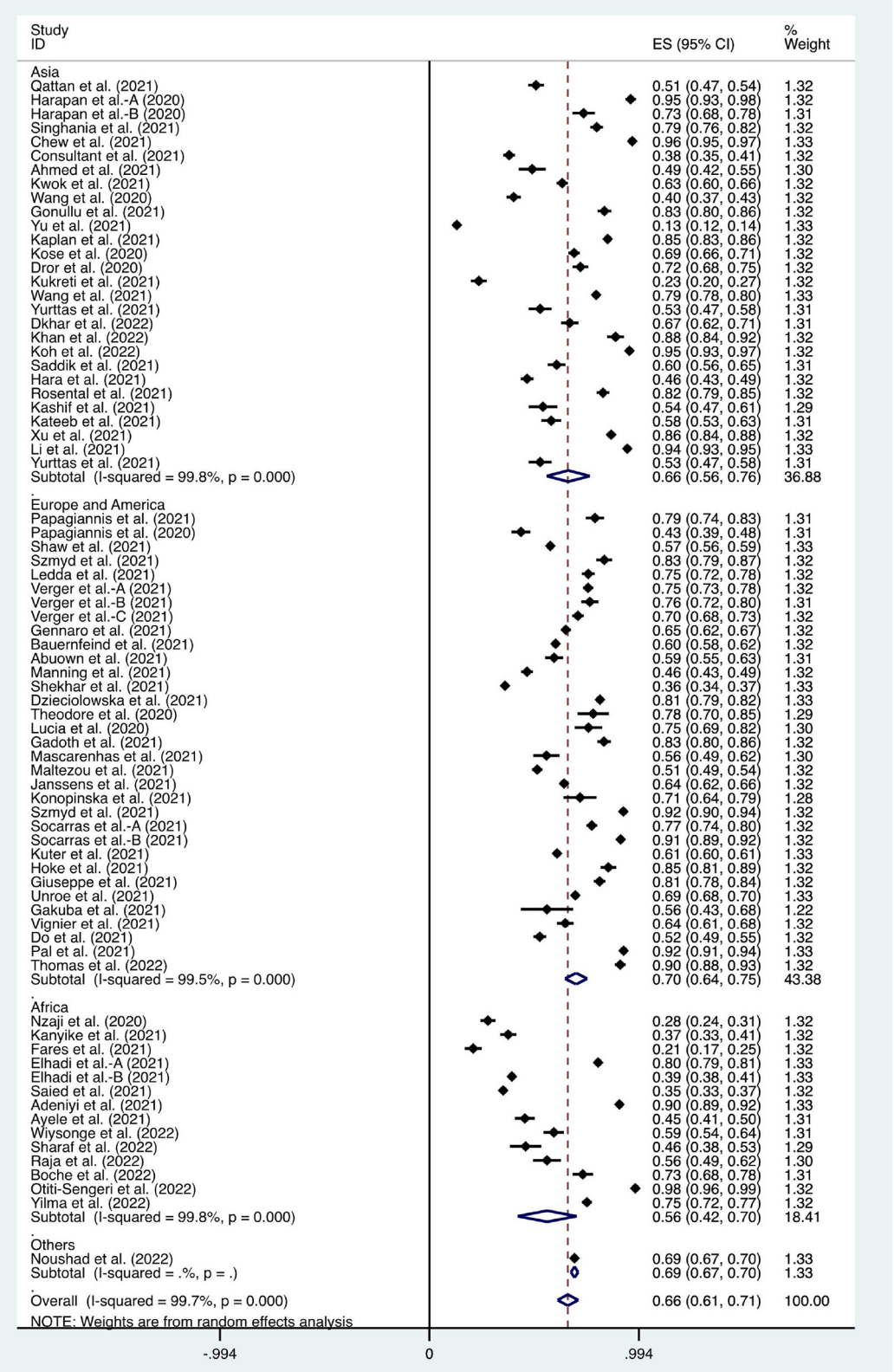

FIGURE 2
Forest plot of the acceptance of coronavirus disease 2019 vaccines by healthcare workers.

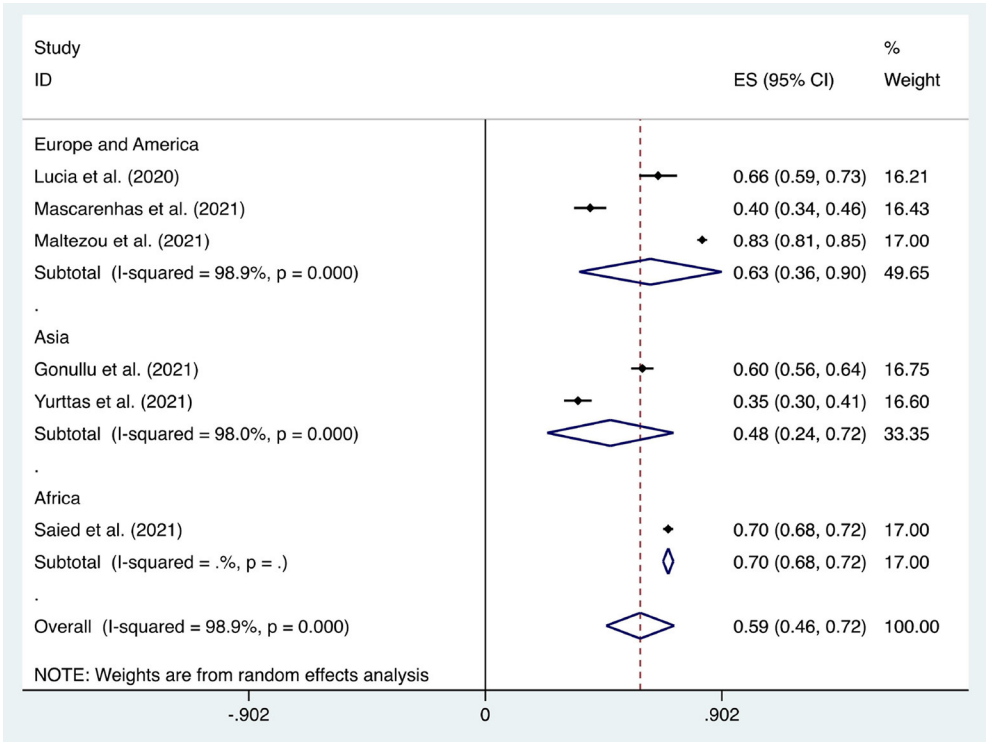

FIGURE 3
Forest plot of the acceptance of healthcare workers of compulsory vaccination.

Table 1. Among HCWS, information on people's willingness to receive COVID-19 vaccines is shown in Table 2.

Reporting biases

We used Egger's test for reporting bias analysis (Supplementary File 2). The study of the acceptance of HCWs with different education levels about COVID-19 vaccines showed a slight bias ($p = 0.049$), while other results carried no significant bias.

Certainty of evidence and results of syntheses

We considered the continent where the study was conducted as the basis of subgroup division and explored the source of heterogeneity through subgroup analysis (Figures 2–10). We found that the heterogeneity in some subgroups remained high.

Seventy-one articles were used to study the acceptance of HCWs about COVID-19 vaccines, which showed that a willingness to undergo COVID-19 vaccination was observed in 66% (95% CI: 0.61–0.67, $I^2 = 99.7\%$, Figure 2) of HCWs. A recent study showed that up to 98% of HCWs in Uganda were willing to be vaccinated against COVID-19 (72). However, through subgroup analysis, we found that only 56% (95% CI: 0.42–0.70, $I^2 = 99.8\%$, Figure 2) of HCWs in African countries were willing to receive COVID-19 vaccination, which was lower than that in Asian (ratio = 0.66, 95% CI: 0.56–0.76, $I^2 = 99.8\%$, Figure 2) and European & American countries (ratio = 0.70, 95% CI: 0.64–0.75, $I^2 = 99.5\%$, Figure 2).

Six articles were used to study the acceptance of HCWs about compulsory vaccination, showing that the proportion of HCWs who agreed with this was 59% (95% CI: 0.46–0.72, $I^2 = 98.9\%$,s Figure 3). We analyzed 24 articles to examine the variance in willingness to take the COVID-19 vaccine between doctors and nurses, and the results indicated that doctors showed a higher willingness to receive COVID-19 vaccination than nurses (OR = 2.22, 95% CI: 1.71–2.89, $I^2 = 91.9\%$, $p < 0.001$, Figure 4). Nine articles were studied to compare the willingness of HCWs and non-HCWs to receive COVID-19 vaccination, and it was found that the willingness of HCWs was greatly increased compared to that of non-HCWs (OR = 1.91, 95% CI: 1.16–3.12, $I^2 = 97.0\%$, $p = 0.01$, Figure 5). Additionally, by analyzing three other articles, we found that with an increased effectiveness of the vaccines in preventing COVID-19 (bounded by 70%), the willingness of HCWs to receive the vaccination also rose accordingly (OR = 5.03, 95% CI: 2.77–9.11, $I^2 = 93.6\%$, $p < 0.001$, Figure 6). The research revealed that male members of HCWs showed a higher

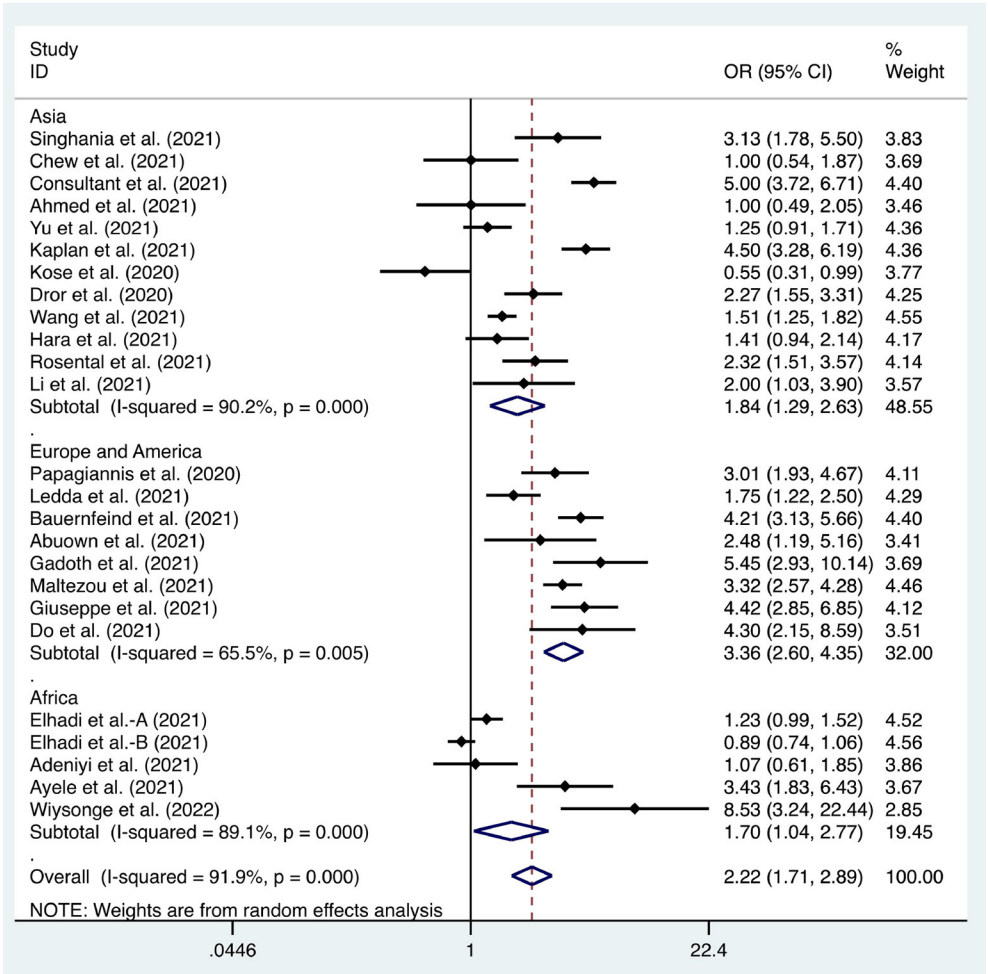

FIGURE 4
Forest plot of the difference in the willingness between doctors and nurses to receive coronavirus disease 2019 vaccines.

willingness to be vaccinated (OR = 1.81, 95% CI: 1.55–2.12, I^2 = 89.5%, $p < 0.001$, Figure 7). The HCWs with a higher acceptance of COVID-19 vaccines were more inclined to receive seasonal influenza vaccines in 2019–2020 (OR = 3.44, 95% CI: 2.45–4.82, I^2 = 81.3%, $p < 0.001$, Figure 8) and 2020–2021 (OR = 3.52, 95% CI: 2.34–5.28, I^2 = 77.9%, $p < 0.001$, Figure 9). Furthermore, the rate of SARS-CoV-2 infection among HCWs willing to be vaccinated was significantly lower than that among HCWs who showed hesitancy (OR = 0.78, 95% CI: 0.66–0.92, I^2 = 65.4%, $p < 0.001$, Figure 10).

Nine articles were used to study the differences between the willingness of HCWs to receive COVID-19 vaccination and the 2020–2021 seasonal influenza vaccines (OR = 1.71, 95% CI: 0.83–3.52, I^2 = 98.9%, $p = 0.145$, Supplementary Figure 1). Seven articles were used to study the impact of the COVID-19 epidemic on seasonal influenza vaccination (2019–2020 and 2020–2021) (OR = 1.43, 95% CI: 0.81–2.53, I^2 = 98.2%, p = 0.214, Supplementary Figure 2), and no significant difference was observed in either study.

Some studies have shown that elderly HCWs are more willing to be inoculated with COVID-19 vaccines (20, 28, 51). Nevertheless, a study from Zhejiang Province, China, showed that a large number of HCWs aged over 50 years experienced SARS in 2003, influenza A (H1N1) in 2009 and avian influenza A (H7N9) in 2013. With the exception of H1N1, the other two were well contained without introducing vaccination, so some people would inevitably assume that vaccination against COVID-19 was probably not necessary (54). Married HCWs were remarkably more willing to be vaccinated for the protection of their families (47). However, a study from Uganda came to the opposite conclusion. Their study revealed that single HCWs showed a higher acceptance of COVID-19 vaccines (15). To solve similar contradictions, we compared the characteristics of HCWs from two groups, one with HCWs who were willing to

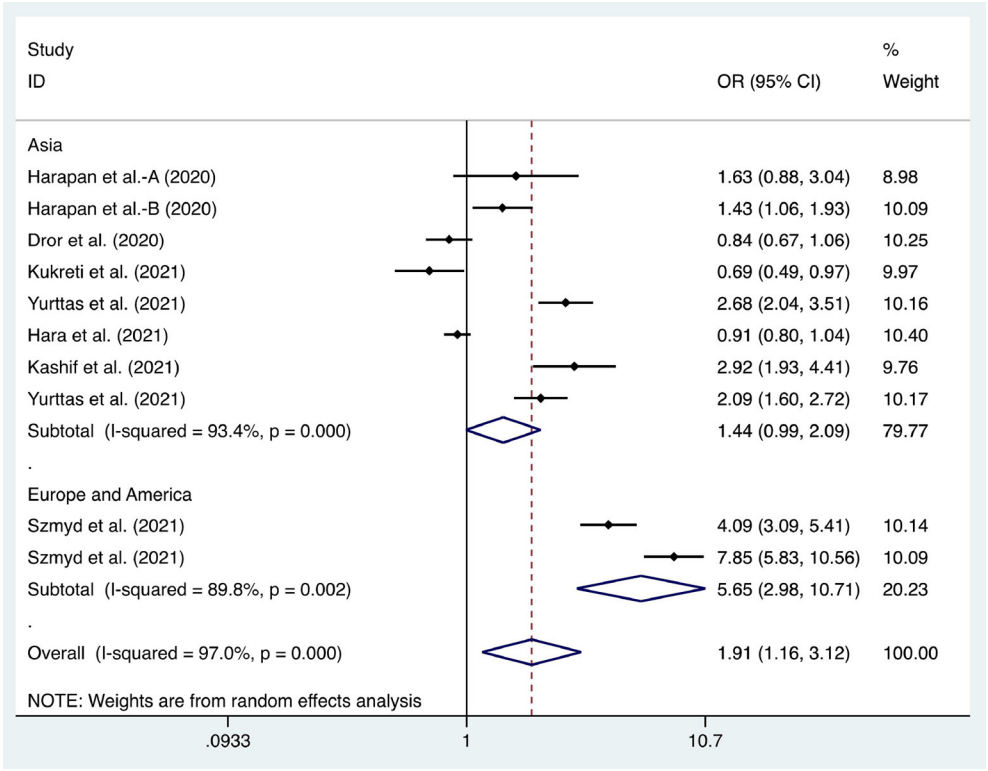

FIGURE 5
Forest plot of the willingness of healthcare workers (HCWs) and non-HCWs to receive coronavirus disease 2019 vaccines.

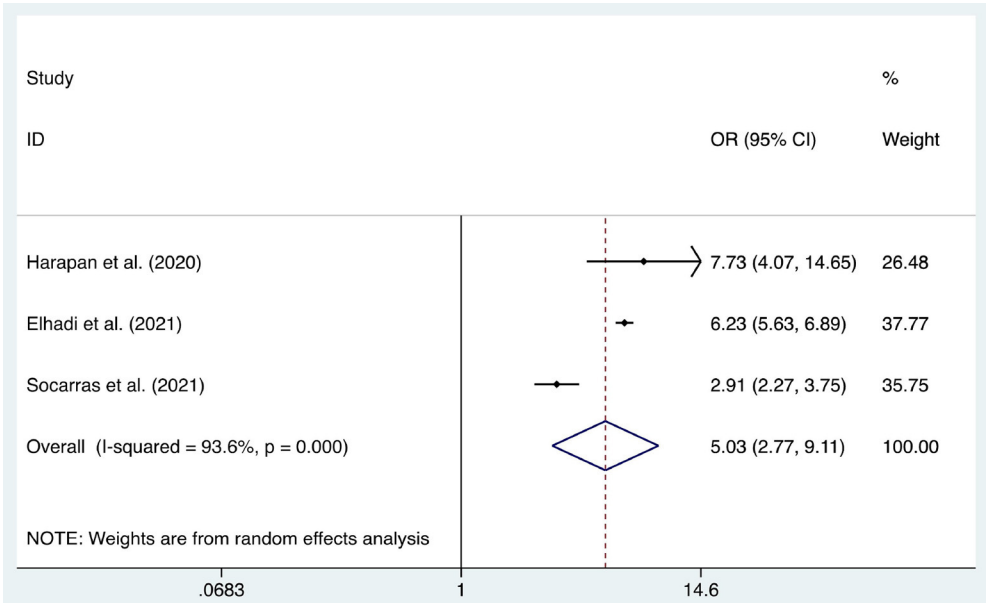

FIGURE 6
Forest plot of the acceptance of healthcare workers of coronavirus disease 2019 vaccines with different effectiveness (bounded by 70%).

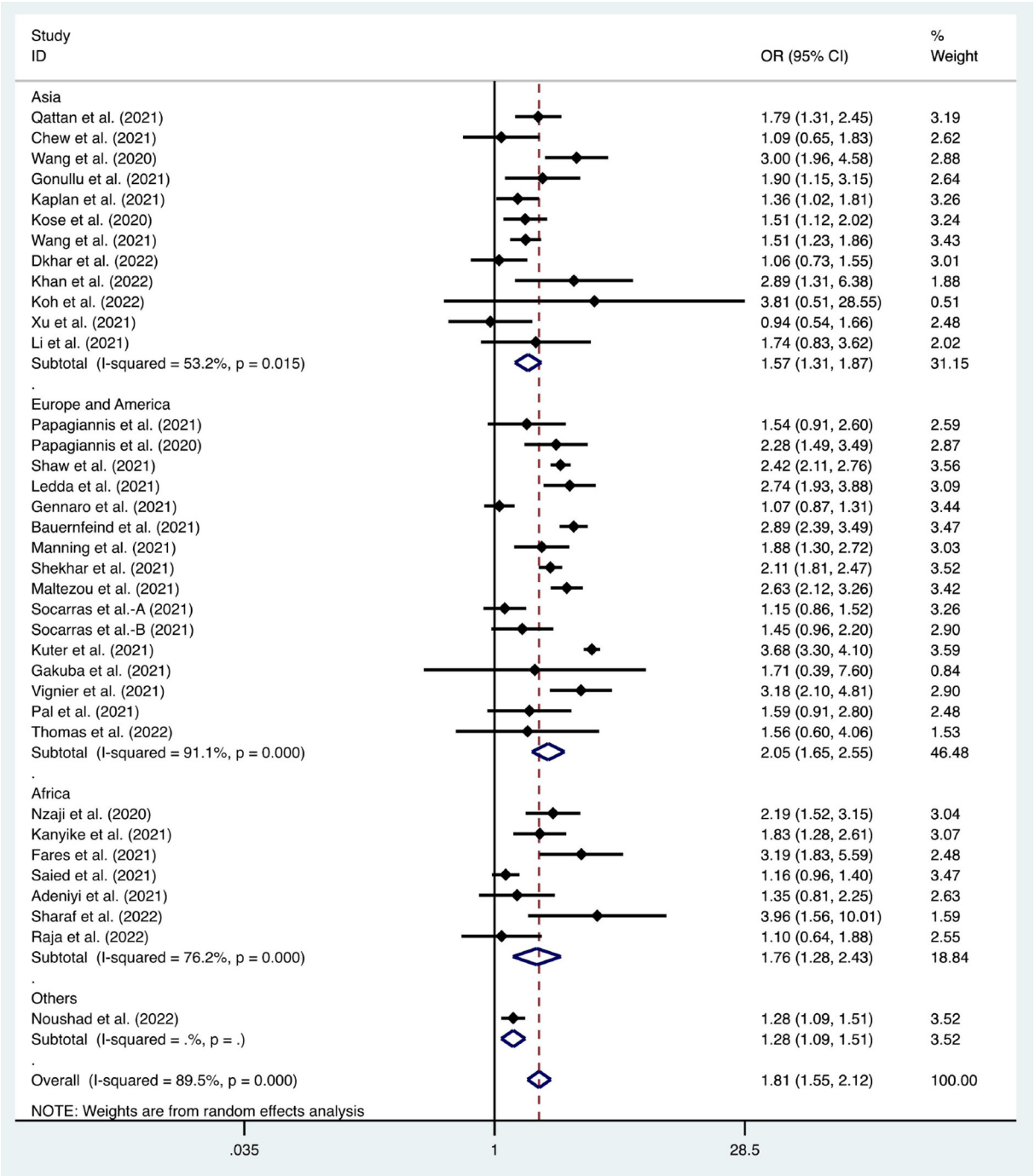

FIGURE 7
Forest plot of the effect of gender on the willingness of healthcare workers to receive coronavirus disease 2019 vaccines.

be inoculated with COVID-19 vaccines and another with those who were not. The results showed that age [(OR = 0.91, 95% CI: 0.75–1.12, I^2 = 89.3%, p = 0.145, Supplementary Figure 3) and (OR = 0.85, 95% CI: 0.63–1.14, I^2 = 90.1%, p = 0.288, Supplementary Figure 4)], education level (OR = 0.81, 95% CI: 0.54–1.22, I^2 = 94.2%, p = 0.315, Supplementary Figure 5), marriage status (OR = 0.96, 95% CI: 0.75–1.23, I^2 = 71.9%, p = 0.758, Supplementary Figure 6), close contact with COVID-19 patients (OR = 1.01, 95% CI: 0.77–1.32, I^2 = 94.1%, p = 0.959, Supplementary Figure 7), and chronic diseases (OR = 1.19, 95%

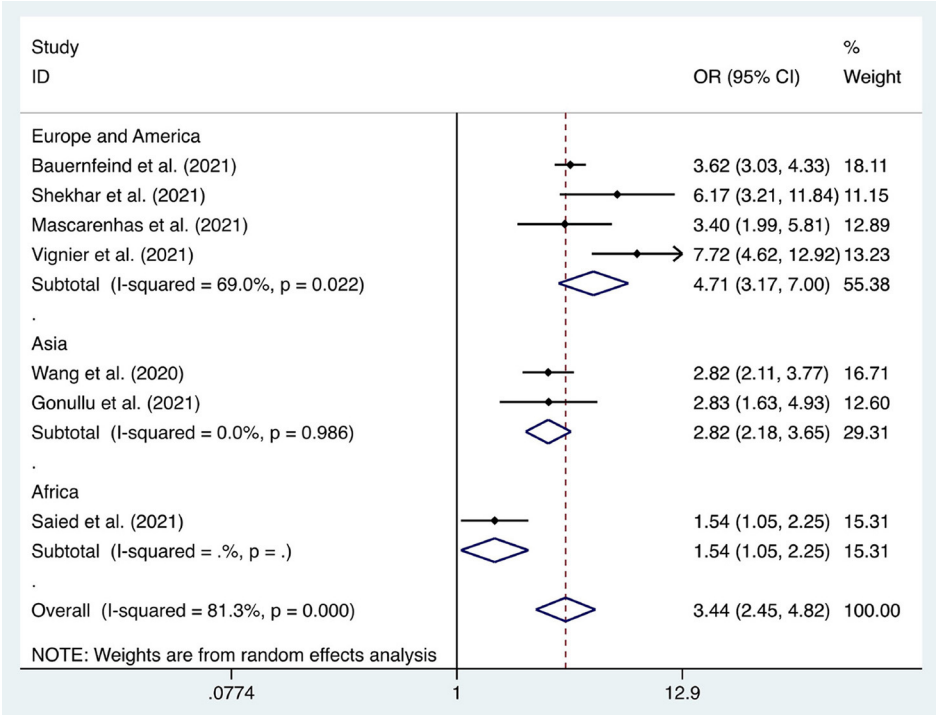

FIGURE 8
Forest plot of the acceptance of seasonal influenza vaccines by healthcare workers (2019–2020).

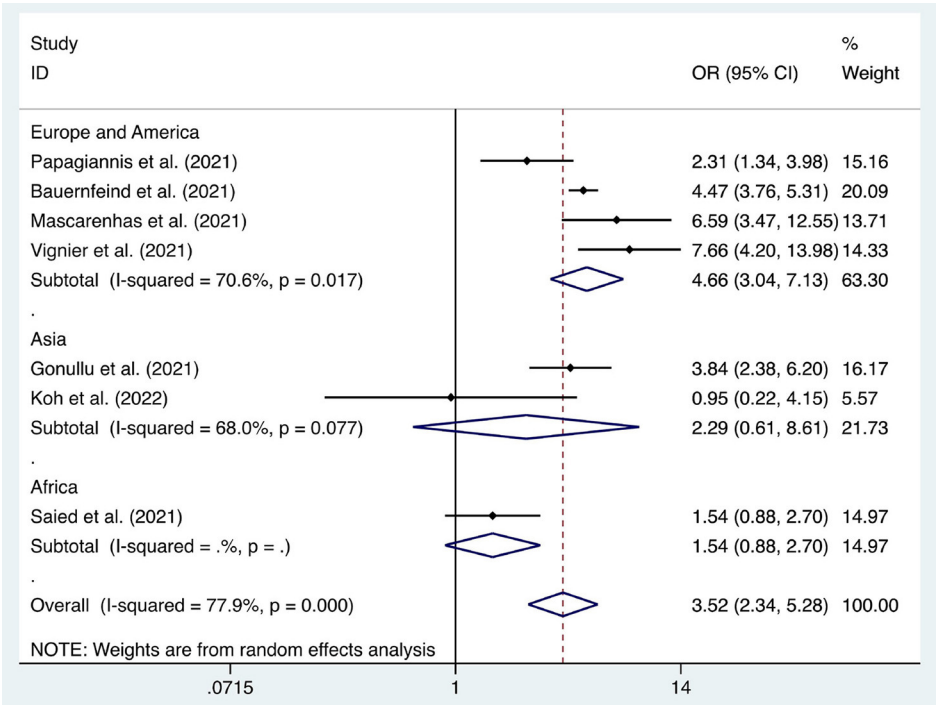

FIGURE 9
Forest plot of the acceptance of seasonal influenza vaccines by healthcare workers (2020–2021).

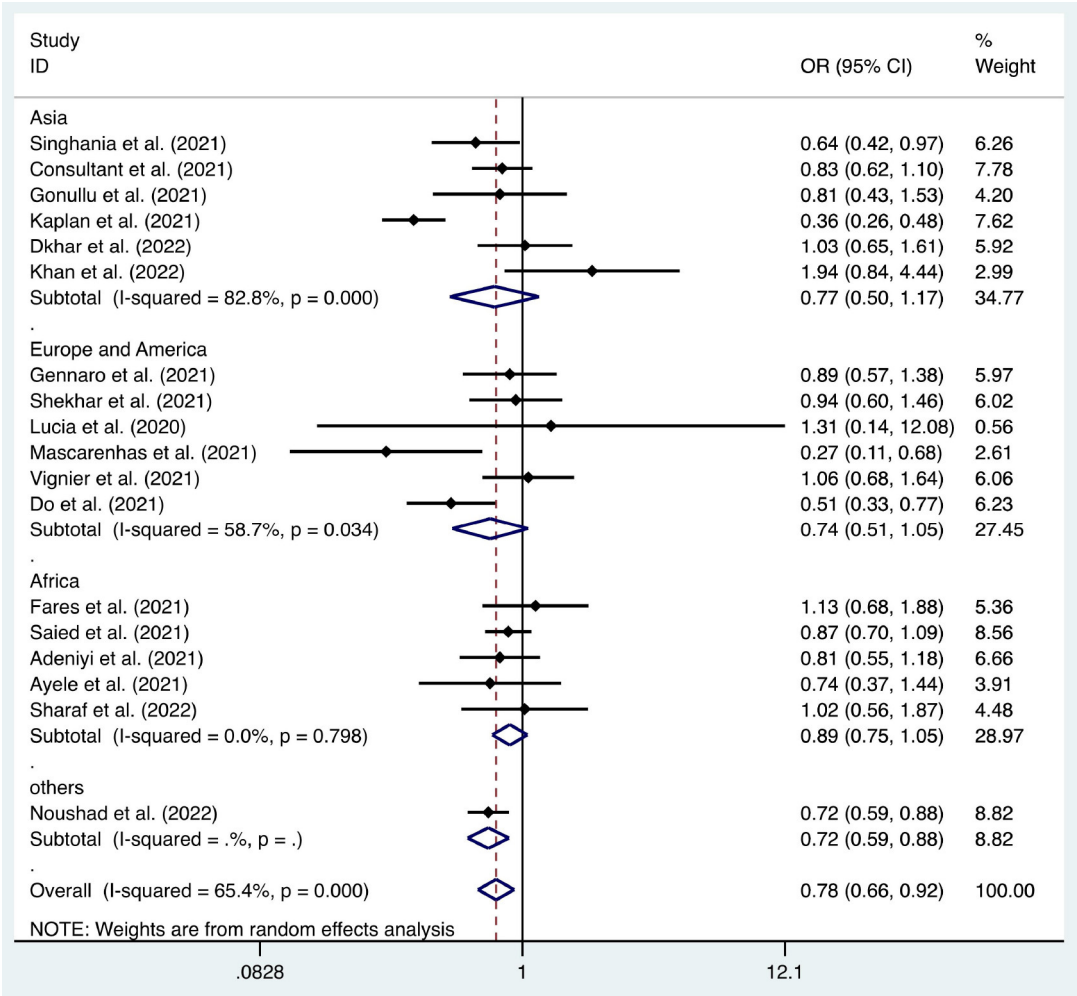

FIGURE 10
Forest plot of the relationship between healthcare workers' acceptance of the coronavirus disease 2019 vaccination and the infection rate of severe acute respiratory syndrome coronavirus 2.

CI: 0.90–1.59, $I^2 = 90.6\%$, $p = 0.222$, Supplementary Figure 8) did not significantly affect the acceptance of COVID-19 vaccines by HCWs. The factors associated with COVID-19 vaccine acceptance of HCWs are listed in Table 3.

Discussion

The vaccine is metaphorically known as the "seatbelt against the disease," which can effectively protect people against infectious diseases at the lowest cost (79). In improving public health, vaccination functions as one of the most important advances. It successfully promoted the elimination of smallpox worldwide and the control of numerous infectious diseases (e.g., rubella, diphtheria, polio) (80). It is estimated that approximately two to three million deaths can be avoided each year by vaccination (81). Despite this, public distrust of vaccines is widespread. The most typical example is the boycott of polio vaccination in northern Nigeria in 2003–2004 (82). Frontline HCWs are frequently and closely exposed to highly contagious patients with COVID-19, posing them at highly increased risk of infection and transmission. Therefore, they became the primary concern of authorities around the world when they formulated COVID-19 vaccination policies (19). Our research showed that approximately 66% of HCWs were willing to receive COVID-19 vaccines, which might vary among different regions. A report showed that only 21% of HCWs in Egypt held a positive attitude toward COVID-19 vaccines (25). A survey on the Asia Pacific region showed that the acceptance of COVID-19 vaccines by HCWs in six countries, including China and India, approached nearly 96% (16). Since a compulsory vaccination program can

TABLE 3 The factors associated with COVID-19 vaccine acceptance of HCWs.

Variables	Included studies	OR	95% CI	*P*-value	I^2
Occupation (doctors and nurses)	[14, 16, 17, 20, 23, 24, 30, 32, 33, 35, 39, 44, 46–48, 50, 54, 58, 59, 61, 63, 69, 73, 78]	2.22	1.71–2.89	<0.001	91.90%
Occupation (HCWs and non-HCWs)	[13, 19, 40, 50, 52, 55, 65, 74, 79]	1.91	1.16–3.12	0.01	97.00%
Vaccine effectiveness	[13, 39, 42]	5.03	2.77–9.11	<0.001	93.60%
Gender	[10–12, 15–18, 20, 22, 23, 25–27, 33, 37, 41–43, 47–49, 53, 54, 56, 57, 58, 60, 62, 64, 65–67, 71, 76, 78]	1.81	1.55–2.12	<0.001	89.50%
Seasonal influenza vaccines (2019–2020)	[6, 23, 27, 37, 41, 49, 60]	3.44	2.45–4.82	<0.001	81.30%
Seasonal influenza vaccines (2020–2021)	[6, 11, 23, 41, 49, 60, 64]	3.52	2.34–5.28	<0.001	77.90%
SARS-CoV-2 infection	[6, 14, 22, 25, 27, 30, 31, 41, 47, 49, 56, 57, 58, 59, 60, 61, 62, 65]	0.78	0.66–0.92	<0.001	65.40%
Age (bounded by 40)	[10, 12, 20, 22, 26, 27, 33, 37, 43, 47, 59, 65, 71, 78]	0.91	0.75–1.12	0.145	89.30%
Age (bounded by 50)	[10, 20, 22, 26, 27, 30, 33, 37, 46, 47, 54, 56, 60, 65, 78]	0.85	0.63–1.14	0.288	90.10%
Education level	[16, 23, 25, 27, 43, 54, 58, 63, 67, 76, 78]	0.81	0.54–1.22	0.315	94.20%
Marriage status	[10, 12, 15, 16, 46, 47, 57, 59, 78]	0.96	0.75–1.23	0.758	71.90%
Close contact with COVID-19 patients	[10, 14, 18, 23, 25, 27, 33, 37, 41, 46, 47, 54, 57, 58, 64, 65, 67, 71]	1.01	0.77–1.32	0.959	94.10%
Chronic diseases	[10, 16, 20, 27, 33, 35, 37, 41, 46, 47, 48, 56, 58, 59, 65]	1.19	0.90–1.59	0.222	90.60%

HCWs, Healthcare workers; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, odds ratio; CI, confidence interval.

effectively increase the overall vaccination coverage rate (83), we considered the views of HCWs on this measure, and the results showed that approximately 59% of HCWs agreed with it. We additionally studied the impact of the COVID-19 epidemic on vaccination against seasonal influenza and the association between the two. The prior experience gained from seasonal influenza vaccination provides a reference and guidance for COVID-19 vaccination. It was noticed that the COVID-19 epidemic did not significantly affect the seasonal influenza vaccination of HCWs; however, interestingly, HCWs who showed a stronger intention to vaccinate against COVID-19 were more likely to receive seasonal influenza vaccination. The experience of influenza vaccination has been known as one of the drivers of accepting COVID-19 vaccines (84). It was also discovered that when the effectiveness of the vaccines changed, the acceptance of the vaccines by HCWs varied accordingly. In our meta-analysis, HCWs demonstrated a higher acceptance of COVID-19 vaccines than non-HCWs. Even in HCWs, the acceptance of COVID-19 vaccines varied among individuals with different occupations. In particular, doctors showed significantly higher acceptance of COVID-19 vaccines than nurses.

It was comparatively found that males were more willing to be vaccinated against COVID-19 than females among HCWs. The higher willingness of males to receive COVID-19 vaccination could be attributed to social and cultural differences and males' risk-taking tendency (85). Some reports indicated that males were at a higher risk of experiencing COVID-19 complications, infections, and even deaths (86). Our study showed that HCWs willing to be vaccinated against COVID-19 experienced a lower risk of infection, probably owing to a high level of protection awareness among them.

The HCWs who remained skeptical about vaccination against COVID-19 were mainly concerned about the efficacy and safety of the vaccines due to the short duration of vaccine development (18, 22, 25, 33). The rapid spread of misleading information about COVID-19 vaccines on various media platforms has aggravated HCWs' doubts about them (10). Since the acceptance of HCWs directly affects the trust of non-HCWs in COVID-19 vaccines, it is necessary to boost their confidence.

Limitations

The data were collected from various countries and regions in the world. Due to the different severities of the outbreak, various prevention and control measures, and cultural and cognitive differences, the heterogeneity of our results was generally high.

People's intention to vaccinate against COVID-19 will change with the epidemic situation (37). Even in the same region, there will be certain variations in the statistical data at different periods.

Conclusions

Our research revealed that a considerable percentage of HCWs remained skeptical about COVID-19 vaccines. Five factors: occupation, gender, vaccine

effectiveness, seasonal influenza vaccines, and SARS-CoV-2 infection; significantly affected the willingness of HCWs to be vaccinated against COVID-19. Herein, it is essential to boost the confidence of HCWs in COVID-19 vaccines for the containment of the epidemic.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Project administration and data curation: JL. Writing-original draft preparation: LW and YW. Writing-review and editing: XC and XL. Software: YY. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.881903/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 21 September 2022
DOI 10.3389/fmed.2022.859682

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Medicine

RECEIVED 21 January 2022
ACCEPTED 09 August 2022
PUBLISHED 21 September 2022

CITATION
Wu G, Zhang M, Xie X, Zhu Y, Tang H, Zhu X, Liang Y, Chen T, Zhu K, Zhang D, Jiang S, Jiang Z and Ke S (2022) A survey on the safety of the SARS-CoV-2 vaccine among a population with stroke risk in China. *Front. Med.* 9:859682. doi: 10.3389/fmed.2022.859682

A survey on the safety of the SARS-CoV-2 vaccine among a population with stroke risk in China

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Background: The safety of the COVID-19 vaccine in patients at stroke risk is poorly understood.

Methods: A survey was conducted on risk factors related to stroke and adverse reactions to vaccines. The participants were divided into low-, medium-, and high-risk groups, according to the stroke risk scorecard recommended by the Stroke Prevention and Control Engineering Committee of the National Health and Family Planning Commission. Factors associated with adverse reactions were analyzed. Reasons for non-vaccination and the aggravation of underlying diseases after vaccination were investigated.

Results: 1747 participants participated (138 unvaccinated) and 36.8, 22.1, 41.1% of the vaccinated participants had low, medium, high risk of stroke, respectively. The incidence of adverse reactions after the first and second injection was 16.6, 13.7%, respectively. There was no difference in the incidence of adverse reactions among different risk groups. Sex, vaccine type, sleep quality, worry of adverse reactions, age, and education level were significantly related to adverse reactions to vaccination. The most popular reason for non-vaccination for medium- or high risk-participants was the aggravation of the existing disease. Only 0.3% of vaccinated participants reported slight changes in blood pressure, sugar levels, and lipid levels. No aggravation of stroke sequelae, atrial fibrillation, or transient ischemic attack was reported.

Conclusions: Vaccination against COVID-19 (inactive virus) is safe for people at risk of stroke when the existing disease condition is stable. It is suggested to strengthen vaccine knowledge and ensure good sleep before vaccination.

KEYWORDS

SARS-CoV-2 vaccine, safety, stroke risk, adverse reactions, sleep, vaccine knowledge

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a great impact on people's physical and mental health and social life. SARS-CoV-2 not only causes damage to the respiratory system, but also leads to nervous system-related damage, such as loss of sense of smell, memory loss and so on (1). The nerve injury caused by SARS-CoV-2 is related to vascular injury (2). SARS-CoV-2 enters the host cells through Angiotensin-converting enzyme 2 (ACE2) which is abundantly expressed in brain endothelial cells and pericytes, and thereafter causes functional impairment of endothelial cells and pericytes and cerebrovascular disorders (3–7).

In the current lack of specific drugs, vaccination is an effective way to control the COVID-19 pandemic (8). However, sporadic adverse events in the cardiovascular system (9, 10) were reported to occur after SARS-CoV-2 vaccination, such as immune thrombotic thrombocytopenia (11), idiopathic thrombocytopenic purpura, arterial thromboembolic events (such as ischemic stroke), hemorrhagic events (such as hemorrhagic stroke), and cerebral venous sinus thrombosis (12–15). These might increase the hesitation of people with cardiovascular disease or at risk of cardiovascular disease to be vaccinated against COVID-19.

An important goal of the global vaccination campaign is to persuade people to get vaccinated, which will be accelerated by instilling confidence in potential COVID-19 vaccines with safety data (16, 17). Stroke has become the leading cause of death and disability in China and many elderly have high risk of stroke (18), and it needs urgently to know the safety of SARS-CoV-2 vaccine among this population with stroke risk. The purpose of this study was to investigate the safety of the COVID-19 vaccine in people at risk of stroke and guide the implementation of vaccination worldwide.

Methods

Study design and population

We conducted the National Stroke Screening Survey on people over 40 years old in a rural village and a urban community in Linhai City, China, to obtain information about risk factors of cardiovascular and cerebrovascular diseases (19). The two areas were chosen according to the proportion to the local population size and geographical locations. Meanwhile, adverse reactions to the COVID-19 vaccine were investigated. The cluster sampling method was used and all residents aged ≥40 years in both two areas were surveyed. The survey was conducted face-to-face at the appointed time by trained investigators, and the participants were asked to answer the questions on the questionnaires. The investigators recorded the answers in the questionnaire, imported the data into MS Excel. The investigators had the same background of cerebrovascular disease. They had been trained on knowledge of COVID-19 vaccine and the standardized procedures, and passed the training examination. Professional quality control personnel supervised the conduction of the research. The survey was conducted between 3 June 2021 and 18 September 2021.

Questionnaires

The questionnaire was divided into two parts as follows: The investigation of risk factors related to stroke and adverse reactions to the vaccine. The survey of risk factors related to stroke was based on questionnaire of China National Stroke Screening and Prevention Project (20), which included basic demographic information (such as age, sex, education level, occupation, and marital status), lifestyle (e.g., smoking, drinking, exercise, and dietary habits), major medical history (heart disease, hypertension, diabetes, dyslipidemia, etc.), and family history. At the same time, physical examination, ECG examination, and laboratory examination of blood sugar and blood lipids were performed. Laboratory examination results were also imported into MS Excel and used to diagnose emerging diseases, such as heart disease, hypertension, diabetes, and dyslipidemia.

The eight risk factors for stroke included high blood pressure, dyslipidemia, diabetes, smoking, atrial fibrillation or valvular heart disease, obesity, lack of exercise, and family history of stroke. According to the stroke risk scorecard recommended by the Stroke Prevention and Control Engineering Committee of the National Health and Family Planning Commission (21), the population was divided into low-, medium-, and high-risk groups: people with three or more of the above factors or a history of stroke or transient ischemic attack (TIA) were considered to have a high stroke risk. People with one of the three factors (hypertension, diabetes, and atrial fibrillation) were considered to have a medium stroke risk. The rest were considered to have a low stroke risk.

The questionnaire on adverse reactions was based on the vaccine manual and revised according to the advice of preventive experts, which included the following: (1) the producer of the used SARS-CoV-2 vaccine. In Linhai city, the vaccines that had been marketed and used were inactivated vaccines produced by Beijing SINOVAC LIFE Sciences Co., Ltd., Beijing Institute of Biological Products Co., Ltd., Wuhan Institute of Biological Products Co., Ltd., adenoviral vector vaccine produced by CanSino Biologics Inc., and recombinant subunit vaccine produced by Anhui Zhifei Longcom Biopharmaceutical Co., Ltd.; (2) allergy history; (3) the number of doses, local and systemic adverse reactions after each dose; (4) knowledge of vaccine being used (What type of SARS-CoV-2 vaccine were you injected?); (5) attitude toward the SARS-CoV-2 vaccine ("Will you take the SARS-CoV-2 vaccine for your family proactively?" and "Are you worried about the adverse reactions of the SARS-CoV-2 vaccine?") (22); (6) whether

existing diseases were aggravated after vaccination. The reasons for the non-vaccination of the unvaccinated population were also investigated. The questionnaire was included in the Supplementary material.

Statistical analysis

Categorical variables were expressed as proportions (%) and continuous variables were expressed as the mean ± standard deviation when the data conformed to the normal distribution or median (quartile) when non-normal distribution was observed. Univariate analysis *via* the χ^2 test was used to assess the potential factors associated with adverse reactions. Multinomial logistic regression was used to identify the factors associated with adverse reactions. Tests were two-sided, with significance set at $P \leq 0.05$. Data analysis was performed using SPSS software (version 16.0, SPSS Inc.).

Results

Demographics and characteristics of the study population

A total of 1,747 (74%, 1,747/2,374) community or village residents over the age of 40 completed the survey. Reasons for non-participation included subjective refusal after knowing the content of the survey, or lack of time to participate in the survey. Of the participants surveyed, 138 were unvaccinated, and 1,609 were vaccinated. Among the vaccinated participants, the age is 59.1 ± 9.5, 1,124 were female (69.9%). Marital status, education level, and occupation are presented in Table 1. Five hundred and ninety-two (36.8%) had a low risk of stroke, 355 (22.1%) had a medium risk of stroke, and 662 (41.1%) had a high risk of stroke. The frequency distribution of stroke risk factors (such as TIA, previous stroke history, hypertension, diabetes) is shown in Table 1. One thousand three hundred and twenty-four participants received the inactive vaccines, 11 received the adenoviral vector vaccine, and 20 received the recombinant subunit vaccine. The rest did not know the vaccine type they received. 81.3% of the participants knew the vaccine being used. 7.8% of the participants worried about adverse reactions to the vaccine, but 98.6% of participants would receive the vaccine for their family and friends. 4.8% had an allergy history (Table 1).

TABLE 1 Baseline characteristics of the vaccinated participants ($n = 1,609$).

Variables	Category	*n* (%)
Sex	Male	485 (30.1)
	Female	1,124 (69.9)
Age (years)	40–49	267 (16.6)
	50–59	634 (39.4)
	60–69	461 (28.7)
	70–79	211 (13.1)
	80–90	36 (2.2)
Marital status	Married	1,535 (95.4)
	Others	74 (4.6)
Education level	Primary and below	793 (49.3)
	Junior school	547 (34.0)
	Senior school	211 (13.1)
	College and above	58 (3.6)
Occupation	Mental worker	94 (5.8)
	Business and service personnel	130 (8.1)
	Production personnel in agriculture, forestry, animal husbandry, fishery and water conservancy	750 (46.6)
	Production and transportation equipment operators	163 (10.1)
	Others	472 (29.3)
Risk level	Low risk	592 (36.8)
	Medium risk	355 (22.1)
	High risk	662 (41.1)
Previous TIA	No	1,602 (99.6)
	Yes	7 (0.4)
Previous Stroke	No	1,577 (98.0)
	Yes	32 (2.0)
Family history of stroke	No	1,396 (86.8)
	Yes	213 (13.2)
Aatrial fibrillation or valvular heart disease	No	1,600 (99.4)
	Yes	9 (0.6)
Hypertension	No	743 (46.2)
	Yes	866 (53.8)
Dyslipidemia	No	640 (39.8)
	Yes	969 (60.2)
Diabetes	No	1,352 (84.0)
	Yes	257 (16.0)
Smoking history	No	1,420 (88.3)
	Yes	189 (11.7)
Overweight or obesity	No	1,395 (86.7)
	Yes	214 (13.3)
Lack of exercise	No	673 (41.8)
	Yes	936 (58.2)

(Continued)

Adverse reactions in participants with different risk grades of stroke

We analyzed the incidence of adverse reactions in people with a low, moderate, and high risk of stroke after the first

TABLE 1 (Continued)

Variables	Category	*n* (%)
Type of vaccine	Inactivated vaccine	1,324 (82.3)
	Adenovirus vector vaccine	11 (0.7)
	Recombinant subunit vaccine	20 (1.2)
	Don't know	254 (15.8)
Knowledge of vaccine being used	No	254 (18.7)
	Yes	1,355 (81.3)
Worry about adverse reactions	No	1,481 (92.2)
	Yes	125 (7.8)
Take vaccine for the family proactively	No	22 (1.4)
	Yes	1,585 (98.6)
Allergic history	No	1,531 (95.2)
	Yes	78 (4.8)

and second injection. After the first injection, the incidence of adverse reactions was 18.2, 14.1, and 16.5% in people with low, medium, and high risk of stroke, respectively. The main types of adverse reactions were pain, fatigue at the injection site, and systemic muscle soreness, but there was no difference among the different grades of stroke risk (Table 2). After the second injection, the incidence of adverse reactions was 14.4, 13.7, and 13.3% in people with low, medium, and high risk of stroke, respectively. The main adverse reactions were pain, swelling or itching at the injection site, as well as fatigue, systemic muscle soreness, and rash. There was no difference among the different grades of risk after the second dose (Table 3). The non-solicited adverse reactions include abnormal menstruation, numbness of the limbs, insomnia and palpitations.

In addition, we investigated whether vaccination aggravated existing diseases, such as atrial fibrillation, hypertension, dyslipidemia, diabetes, stroke sequelae, and frequency of TIA attacks. The results showed that 3 people reported a slight increase in blood pressure, 1 reported a slight increase in blood lipid levels, and 3 reported a slight increase in blood sugar levels. In the vaccinated population, there was no increase in the frequency of TIA attacks and aggravation of stroke sequelae.

Analysis of factors associated with adverse reactions

To identify the factors associated with adverse reactions, univariate analysis using the χ^2 test was carried out for participants who were double vaccinated. The factors included sex, age, marital status, education level, occupation, type of vaccine, risk level, previous TIA, previous stroke, family history of stroke, atrial fibrillation or valvular heart disease, hypertension, dyslipidemia, diabetes, smoking history, overweight or obesity, lack of exercise, knowledge of inactivated vaccine being used, worry about adverse reactions, proactive vaccination for the family, and sleep quality before vaccination. The results indicated that sex, age, education level, knowledge of inactivated virus being used, worry about adverse reactions, and sleep quality before vaccination were significantly associated with adverse reactions (Table 4).

Then, a multinomial logistic regression model was developed to identify the factors associated with adverse effects. Variables that were significant at $P < 0.05$ as a result of the univariate analyses were included. As shown in Table 5, sex [female vs. male, Odds Ratio (OR) = 1.90, 95% confidence interval (CI): 1.33–2.72], knowledge of inactivated vaccine being used (no vs. yes, OR = 1.67, 95% CI: 1.15–2.42), sleep quality before vaccination (good vs. poor, OR = 0.34, 95% CI: 0.18–0.62; moderate vs. poor, OR = 0.29, 95% CI: 0.15–0.55), worry of adverse reactions (no vs. yes, OR = 0.50, 95% CI: 0.27–0.94) were significantly associated with adverse reactions after one vaccination. In addition, age (40–50 vs. ≥70, OR = 1.60, 95% CI: 0.88–2.92), worry of adverse reactions (no vs. yes, OR = 0.12, 95% CI: 0.06–0.24), and sleep quality before vaccination (Good vs. poor, OR = 0.33, 95% CI: 0.13–0.81; moderate vs. poor, OR = 0.18, 95% CI: 0.07–0.47), education level (primary and below vs. college and above, OR = 0.28, 95% CI: 0.1–0.81) were significantly associated with adverse reactions after both vaccinations.

Reasons for not being vaccinated and the effect of SARS-CoV-2 vaccine on existing diseases

In this survey, 138 people were not vaccinated, of whom 120 (87.0%) were at medium or high risk of stroke. We investigated the reasons for not being vaccinated. The results showed that worry about the aggravation of the existing disease was the main cause, with a total of 63 people accounting for 64.9%. Other causes were fear of adverse reactions to the vaccine (17.5%), vaccination taboos (6.2%), and concern about interactions with drugs (5.2%) (Figure 1).

Discussion

SARS-CoV-2 vaccine is still the effective way to control the pandemic (23). This is a survey study on the safety of the COVID-19 vaccine in a population with stroke risk factors, which guides COVID-19 vaccinations in this population.

We investigated and obtained information on stroke risk factors and adverse reactions of the vaccine in 1747 residents over 40 years old. The results showed that overall, the incidence of adverse reactions after the first injection was 16.6%, and that after the second injection was 13.7%. The main adverse

TABLE 2 Distribution of multiple types of adverse reactions after first vaccination.

Adverse reactions	Total ($n = 1,609$)			Low risk ($n = 592$)			Median risk ($n = 355$)			High risk ($n = 662$)			P*
	No. of subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	No. of subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	No. of Subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	No. of Subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	
Total adverse reactions	267	16.6	100.0	108	18.2	100.0	50	14.1	100.0	109	16.5	100.0	0.244
Injection site adverse reactions (pain, induration, redness, swelling or itch)	123	7.6	46.1	47	8.0	43.5	22	6.2	44.0	54	8.1	49.5	0.503
Pain	96	6.0	36.0	35	5.9	32.4	17	4.8	34.0	44	6.6	40.4	0.501
Induration	10	0.6	3.7	5	0.8	4.6	2	0.6	4.0	3	0.5	2.8	0.664
Redness	9	0.6	3.4	5	0.8	4.6	2	0.6	4.0	2	0.3	1.8	0.426
Swelling or itch	23	1.4	8.6	8	1.4	7.4	5	1.4	10.0	10	1.5	9.2	1.000
Systemic adverse reactions	166	10.3	62.2	68	11.5	63.0	30	8.5	60.0	68	10.3	62.4	0.328
Fatigue	51	3.2	19.1	21	3.5	19.4	10	2.8	20.0	20	3	18.3	0.798
Muscle pain	41	2.5	15.4	19	3.2	17.6	8	2.3	16.0	14	2.1	12.8	0.432
Headache	4	0.2	1.5	1	0.2	0.9	1	0.3	2.0	2	0.3	1.8	1.000
Dizziness	25	1.6	9.4	12	2	11.1	5	1.4	10.0	8	1.2	7.3	0.534
Fever	5	0.3	1.9	1	2	0.9	1	3	2.0	3	5	2.8	0.848
Vomiting	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Diarrhea	6	0.4	2.2	4	0.7	3.7	1	0.3	2.0	1	0.2	0.9	0.330
Appetite impaired	3	0.2	1.1	1	0.2	0.9	0	0	0.0	2	0.3	1.8	0.799
Nausea	4	0.2	1.5	4	0.7	3.7	0	0	0.0	0	0	0.0	0.054
Cough	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Throat pain	6	0.4	2.2	4	0.7	3.7	0	0	0.0	2	0.3	1.8	0.280
Allergic reaction	2	0.1	0.7	1	0.2	0.9	0	0	0.0	1	0.2	0.9	1.000
Urticaria	5	0.3	1.9	0	0	0.0	1	0.3	2.0	4	0.6	3.7	0.136
Rash	26	1.6	9.7	10	1.7	9.3	4	1.1	8.0	12	1.8	11.0	0.718
Stuffy	3	0.2	1.1	2	0.3	1.9	0	0	0.0	1	0.2	0.9	0.612
Runny nose	1	0.1	0.4	1	0.2	0.9	0	0	0.0	0	0	0.0	0.588
Lymphadenopathy	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Non-solicited adverse reactions	40	2.5	15.0	19	3.2	17.6	6	1.7	12.0	15	2.3	13.8	0.316

*P-value of the incidence of adverse reactions in three stroke risk grades.

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TABLE 3 Distribution of multiple types of adverse reactions after second vaccination.

Adverse reactions	Total ($n = 1,410$)			Low risk ($n = 523$)			Median risk ($n = 307$)			High risk ($n = 580$)			P*
	No. of subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	No. of subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	No. of subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	No. of subjects	Incidence of adverse reactions (%)	Proportion of adverse reactions (%)	
Total adverse reactions	193	13.7	100.0	74	14.1	100.0	42	13.7	100.0	77	13.3	100.0	0.910
Injection site adverse reactions (pain, induration, redness, swelling or itch)	74	5.2	38.3	28	5.4	37.8	15	4.9	35.7	31	5.3	40.3	0.964
Pain	57	4.0	29.5	22	4.2	29.7	12	3.9	28.6	23	4.0	29.9	0.969
Induration	5	0.4	2.6	1	0.2	1.4	1	0.3	2.4	3	0.5	3.9	0.847
Redness	4	0.3	2.1	3	0.6	4.1	0	0	0.0	1	0.2	1.3	0.357
Swelling or itch	21	1.5	10.9	10	1.9	13.5	4	1.3	9.5	7	1.2	9.1	0.610
Systemic adverse reactions	129	9.1	66.8	51	9.8	68.9	32	10.4	76.2	46	7.9	59.7	0.393
Fatigue	27	1.9	14.0	17	3.3	23.0	4	1.3	9.5	6	1	7.8	0.019
Muscle pain	30	2.1	15.5	13	2.5	17.6	8	2.6	19.0	9	1.6	11.7	0.453
Headache	2	0.1	1.0	0	0	0.0	0	0	0.0	2	0.3	2.6	0.354
Dizziness	9	0.6	4.7	2	0.4	2.7	4	1.3	9.5	3	0.5	3.9	0.318
Fever	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Vomiting	2	0.1	1.0	0	0	0.0	0	0	0.0	2	0.3	2.6	0.354
Diarrhea	2	0.1	1.0	0	0	0.0	0	0	0.0	2	0.3	2.6	0.354
Appetite impaired	1	0.1	0.5	0	0	0.0	0	0	0.0	1	0.2	1.3	1.000
Nausea	1	0.1	0.5	0	0	0.0	0	0	0.0	1	0.2	1.3	1.000
Cough	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Throat pain	3	0.2	1.6	2	0.4	2.7	0	0	0.0	1	0.2	1.3	0.612
Allergic reaction	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Urticaria	2	0.1	1.0	1	0.2	1.4	0	0	0.0	1	0.2	1.3	1.000
Rash	29	2.1	15.0	9	1.7	12.2	8	2.6	19.0	12	2.1	15.6	0.696
Stuffy	5	0.4	2.6	1	0.2	1.4	1	0.3	2.4	3	0.5	3.9	0.847
Runny nose	6	0.4	3.1	1	0.2	1.4	1	0.3	2.4	4	0.7	5.2	0.517
Lymphadenopathy	0	0.0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	/
Non-solicited adverse reactions	41	2.9	21.2	16	3.1	21.6	11	3.6	26.2	14	2.4	18.2	0.594

*P-value of the incidence of adverse reactions in three stroke risk grades.

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TABLE 4 Univariate analysis of factors associated with adverse reactions in completed two doses vaccinated group ($n = 1,410$).

Variables	Categories	*n*	Adverse reaction in one vaccination		Adverse reaction in both vaccination		*P*
			n	Frequency (%)	*n*	Frequency (%)	
Total		1,410	232	16.5	78	5.5	
Sex	Male	430	49	11.4	20	4.7	**0.001**
	Female	980	183	18.7	58	5.9	
Age (years)	40–49	230	39	17.0	2222	9.6	**0.001**
	50–59	541	88	16.3	38	7.0	
	60–69	414	76	18.4	8	1.9	
	70–90	225	29	12.9	10	4.4	
Marital status	Married	1,344	227	16.9	74	5.5	0.123
	Others	66	5	7.6	4	6.1	
Education level	Primary and below	710	115	16.2	26	3.7	**0.032**
	Junior school	473	82	17.3	34	7.2	
	Senior school	178	26	14.6	12	6.7	
	College and above	49	9	18.4	6	12.2	
Occupation	Mental worker	82	14	17.1	9	11.0	0.156
	Business and service personnel	114	14	12.3	8	7.0	
	Production personnel in agriculture, forestry, animal husbandry, fishery and water conservancy	673	104	15.5	29	4.3	
	Production and transportation equipment operators and relevant personnel	142	29	20.4	9	6.3	
	Others	399	71	17.8	23	5.8	
Type of vaccine	Inactivated vaccine	1,153	177	15.4	70	6.1	0.336
	Adenovirus vector vaccine	4	1	25.0	1	25.0	
	Recombinant subunit vaccine	19	2	10.5	1	5.3	
Risk level	Low risk	522	86	16.5	35	6.7	0.631
	Medium risk	308	52	16.9	13	4.2	
	High risk	580	94	16.2	30	5.2	
Previous TIA	No	1,404	231	16.5	78	5.6	1.000
	Yes	6	1	16.7	0	0.0	
Previous stroke	No	1,383	224	16.2	77	5.6	0.171
	Yes	27	8	29.6	1	3.7	
Family history of stroke	No	1,231	203	16.5	68	5.5	1.000
	Yes	179	29	16.2	10	5.6	
Atrial fibrillation or valvular heart disease	No	1,404	232	16.5	77	5.5	0.237
	Yes	6	0	0.0	1	16.7	
Hypertension	No	652	111	17.0	44	6.7	0.139
	Yes	758	121	16.0	34	4.5	
Dyslipidemia	No	553	95	17.2	35	6.3	0.461
	Yes	857	137	16.0	43	5.0	

(Continued)

TABLE 4 (Continued)

Variables	Categories	*n*	Adverse reaction in one vaccination		Adverse reaction in both vaccination		*P*
			n	Frequency (%)	*n*	Frequency (%)	
Diabetes	No	1,190	191	16.1	67	5.6	0.623
	Yes	220	41	18.6	11	5.0	
Smoking history	No	1,236	209	16.9	70	5.7	0.359
	Yes	174	23	13.2	8	4.6	
Overweight or obesity	No	1,222	190	15.5	67	5.5	0.057
	Yes	188	42	22.3	11	5.9	
Lack of exercise	No	590	94	15.9	31	5.3	0.830
	Yes	820	138	16.8	47	5.7	
Knowledge of inactivated vaccine being used	No	230	51	22.2	6	2.6	**0.007**
	Yes	1,176	180	15.3	72	6.1	
Worry about adverse reactions	No	1,332	216	16.2	59	4.4	**<0.001**
	Yes	76	16	21.1	19	25.0	
Take vaccine for the family proactively	No	16	3	18.8	1	6.3	1.000
	Yes	1,393	229	16.4	76	5.5	
Sleep quality before vaccination	Good	816	132	16.2	44	5.4	**<0.001**
	Moderate	511	74	14.5	23	4.5	
	Poor	58	19	32.8	8	13.8	

The bold values indicated statistically significant difference.

reactions were pain at the injection site, fatigue, systemic soreness, and rash. The relatively low incidence of adverse reactions might be related to the fact that most anticipants (98.0%) were vaccinated with the inactive virus and they showed a lower incidence of adverse reactions than other candidate vaccines (22, 24, 25). However, there was no difference in the incidence of adverse reactions among the different grades of risk after the first or second doses. Hypertension, diabetes mellitus, and cerebrovascular disease have been reported to predispose patients to a more severe outcome of COVID-19 (26). However, the adverse reactions of the COVID-19 vaccine (mainly inactivated vaccine) did not increase with an increase in stroke risk factors.

To identify the factors associated with adverse reactions, univariate analysis was performed first. It was discovered that sex, age, education level, knowledge of inactive virus being used, worry of adverse reactions, and sleep quality before vaccination were associated with adverse reactions for double vaccinated participants. Stroke risk rating and stroke risk factors, such as previous TIA, previous stroke, family history of stroke, atrial fibrillation or valvular heart disease, hypertension, dyslipidemia, diabetes, smoking history, overweight or obesity, and lack of exercise did not show an association with the adverse reaction after completing two doses of vaccination ($P > 0.05$).

However, it is notable that the frequency of adverse reactions upon one vaccination in people with previous stroke events or obesity was 29.6%, and the frequency of adverse reactions upon both vaccinations was the same as observed in people without previous stroke events. In this study, there were 27 participants with previous stroke events who completed two doses of vaccinations. The time between the last cerebrovascular event and the vaccination was 4(10) years, and the mRS was 0(0). Due to the small sample size, the long interval between stroke event and vaccination, and mild neurological impairment of previous stroke events, a more comprehensive investigation needs to be designed to study the relationship between past stroke events and vaccine adverse reactions.

After multinomial logistic regression analysis, it was found that female sex and little knowledge of the vaccine being used was linked to more adverse reactions and less worry of adverse reactions, good sleep before vaccination, and an education level of primary and below were linked to fewer adverse reactions. Therefore, before vaccination, we should strengthen the vaccine type knowledge, ensure a good sleep, and alleviate the worry of adverse reactions. In addition, the potential anxiety states of vaccine recipients might be a contributing factor of adverse reactions, as female, aged around 50 years, fear of adverse reactions, and poor sleep quality are indicative of anxiety states in people about to receive the vaccine. Some psychological interventions are necessary to reduce adverse reactions before vaccination.

The population is aging in the world and one in 11 people (9%) was over 65 in 2019 (27). It is necessary to pay special

TABLE 5 Multinominal logistic regression of factors associated with adverse reactions in completed two doses vaccinated group (n = 1,410).

Variables	Adverse reaction in one vaccination vs. No adverse reaction			Adverse reaction in both vaccination vs. No adverse reaction		
	OR			OR		
Sex (female vs. male)	1.90	1.33–2.72	**0.000**	1.2289	0.7–2.15	0.471
Knowledge of vaccine being used (no vs. yes)	1.67	1.15–2.42	**0.007**	0.61	0.25–1.48	0.274
Age (years)						
40–50 vs. ≥70	1.32	0.73–2.4	0.353	1.60	0.63–4.01	0.321
50–60 vs. ≥70	1.33	0.81–2.19	0.261	1.35	0.6–3.02	0.466
60–70 vs. ≥70	1.53	0.94–2.48	0.086	0.47	0.18–1.26	0.134
Education level						
Primary and below vs. College and above	0.65	0.28–1.51	0.319	0.28	0.1–0.81	**0.019**
Junior school vs. College and above	0.93	0.41–2.11	0.860	0.47	0.18–1.26	0.136
Senior school vs. College and above	0.71	0.29–1.74	0.458	0.39	0.13–1.17	0.092
Worry about adverse reactions (no vs. yes)	0.50	0.27–0.94	**0.032**	0.12	0.06–0.24	**0.000**
Sleep quality before vaccination						
Good vs. poor	0.34	0.18–0.62	**0.001**	0.33	0.13–0.81	**0.015**
Moderate vs. poor	0.29	0.15–0.55	**0.000**	0.18	0.07–0.47	**0.000**

The bold values indicated statistically significant difference.

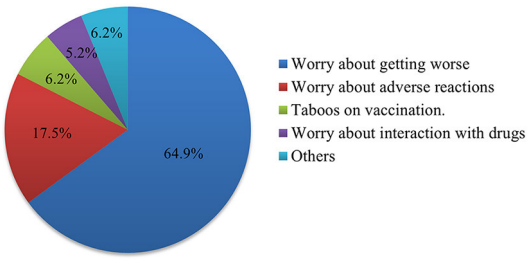

FIGURE 1
Pie chart showing the reasons why people at medium and high risk of stroke do not want to be vaccinated against COVID-19. The number of each part of the pie chart represents the count and percentage.

attention to the vaccination among the elderly population. Some elderly remain reluctant to be vaccinated against COVID-19 and factors influencing vaccination among them included the underlying chronic diseases and polypharmacy (28). Notably, the first cause of not being vaccinated in participants with medium- or high- risk of stroke was the possibility of aggravation of the existing disease. However, the number of people reporting changes in blood pressure, lipid levels, and sugar levels was 3(0.2%), 1(0.06%), 3(0.2%), respectively. For 1609 participants, aggravation of stroke sequelae or TIA attack was not reported. Therefore, the incidence rate of aggravation of the existing disease is very low, and there is no need to worry too much that the vaccine will aggravate the existing condition if the condition is stable.

Since obesity, diabetes, and hypertension and other risk factors of cerebrovascular or cardiovascular disease have been associated with severe outcome of COVID-19 infection, those with relatively higher-risk cardiovascular or stroke conditions should prioritize their receipt of the vaccine (29, 30).

This study has some limitations. First, it is not certain whether the reported adverse events are attributable to vaccination, and the incidence of adverse reactions may be overestimated. Second, the sample size of previous stroke events is small; therefore, it is impossible to determine the relationship between previous stroke type, infarction size, last onset time, mRS score, and vaccine adverse reactions, which requires further investigation. Third, as this is a survey study, bias cannot be avoided due to the presence of subjective factors, although we have taken many measures to reduce it.

Conclusions

For people at risk of stroke, vaccination against COVID-19 (inactive virus) is safe when the existing disease condition is stable and potentially reduces the risk of infection or critical illness. Age, sex, level of awareness of vaccine, worry of adverse reactions to the vaccine, and education level are related to adverse reactions after vaccination. It is suggested to strengthen vaccine knowledge and ensure good sleep before vaccination. This positive evidence for the safety of the vaccine (inactivated vaccine) may help to enhance the vaccination rate and provide guidelines for the

implementation of vaccination among people at stroke risk in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Taizhou Hospital of Zhejiang Province. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: GW, SK, and ZJ. Investigation: XX, SJ, YZ, HT, XZ, YL, TC, KZ, and DZ. Formal analysis and writing—original draft: GW and MZ. Writing—review and editing and resources: SK and ZJ. All authors reviewed the manuscript, contributed to the article, and approved the submitted version.

Funding

This study was in part supported by National Natural Science Foundations of China (No. 81903584) and Zhejiang Provincial Basic and Public Welfare Research Program (LGD20H310002 to GW).

Acknowledgments

We would like to thank all the participants for their cooperation and support.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.859682/full#supplementary-material

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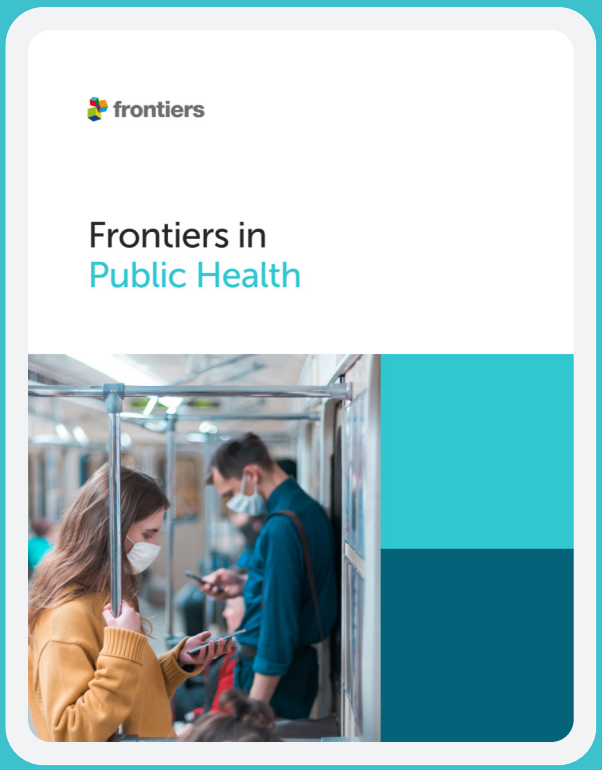

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