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Review Article

The Safety Profile of COVID-19 Vaccines: A Narrative Review

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Abstract

The ongoing COVID-19 pandemic inflicted a considerable burden on health systems and individuals worldwide. Thus, scientists intended to propose beneficial treatments and vaccines to fight against this virus. However, vaccination remained the only effective way to reduce death and hospitalization due to COVID-19 infection. To date, about five proposed COVID-19 vaccines have been approved as WHO emergency use listings (EUL). Yet, their safety profile needs the following actions to be revealed: (1) more follow-up registry systems and (2) global clinical trials in various countries in a period that they are experiencing a peak. By searching keywords 'COVID-19' and 'vaccination' in PubMed and Scopus databases, we aimed to summarize the current evidence in the literature regarding the safety profile (i.e., local and systemic adverse events) of ten COVID-19 vaccines: (1) Pfizer/BioNTech, (2) Moderna, (3) Sputnik V, (4) Bharat, (5) CanSino, (6) Sinovac, (7) AstraZeneca, (8) Johnson & Johnson, (9) Novavax, and (10) Sinopharm. Moreover, we demonstrated the data on the safety of heterologous schedules of these vaccines alongside further considerations in people with comorbidities and particular circumstances. Most of the COVID-19 vaccine adverse effects possess a mild-to-moderate, self-limiting nature. However, special circumstances such as severe hyper-sensitivity necessitate the use of an alternate COVID-19 vaccine. Vaccination is the only way to exit the global pandemic, and its benefits outweigh its adverse effects. Meanwhile, people should be aware of the signs of the probable rare, severe reactions to the vaccine.

Keywords: COVID-19; SARS-CoV-2; Vaccines; Safety; Side Effect

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Introduction

Coronavirus disease 2019 (COVID-19) first appeared in China in late December 2019 (1). Since then, the responsible virus, severe acute respiratory syndrome 2 (SARS-CoV-2), has spread viciously worldwide. Consequently, on March 11, 2020, the World Health Organization (WHO) characterized it as a global pandemic. (2). The COVID-19 pandemic and COVID-19 disease, mentally and physically, imposed a high burden on the involved communities and infected people. (3-5).

Up to now, several solutions such as wearing masks, quarantining, and social distancing have been introduced to control the spread of this virus; however, none of them could act as a permanent solution. (6). Moreover, in cases of confirmed infection, suggested therapeutic compounds and drugs remain supportive treatment options. (1). That necessitates the introduction of COVID-19 vaccines as the only way to achieve herd immunity in the world. (7).

As of July 28, 2021, 263 different COVID-19 vaccine candidates are being developed and assessed, according to the Milken Institute's COVID-19 treatment and vaccine tracker. The developers use platforms such as inactivated viruses, mRNA-based, protein subunits, and viral vectors to achieve their targets. (8). Among these vaccines, two mRNA-based vaccines (Pfizer/BioNTech and Moderna) were the first ones to get Food and Drug Administration (FDA) approval for emergency use in December 2020 (9). Less than a year has passed since the introduction of the SARS-CoV-2 genome to Emergency Use Authorization (EUA) status, and they were the fastest vaccines to be developed in history. So, raising concerns about their adverse effects is a natural phenomenon. (10). In addition to Pfizer/BioNTech and Moderna, many other COVID-19 vaccines have been introduced so far. However, the safety profile of the vaccines and the fear of their adverse effects remain the main reasons for vaccine hesitancy, e.g., the refusal of vaccines despite their availability. (11). Rumors such as the risk of infertility and the presence of DNA modifiers and microchips in these vaccines aggravate the situation. (12).

According to the Centers for Disease Control and Prevention (CDC), the most common adverse effects of COVID-19 vaccines include pain, redness, and swelling of the arm, along with fatigue, headache, muscle pain, chills, fever, and nausea as systemic adverse effects. Rarely people will develop severe adverse effects from these vaccines. (13).

The present study aims to highlight the evidence of adverse effects of 10 commonly administered COVID-19 vaccines across the world: Pfizer/BioNTech, Moderna, Sputnik V, Bharat, CanSino, Sinovac, AstraZeneca, Johnson & Johnson, Novavax, and Sinopharm. We have reviewed the results of clinical trials and case reports along with other original studies assessing the adverse effects of these vaccines in homologous and heterologous schedules. We have also mentioned the serious adverse effects of these vaccines, the ones that cause an inability to perform usual activities, hospitalizations, or potentially life-threatening ones. Finally, we will discuss further considerations of these vaccines in various at-risk populations, as well as the COVID-19 Delta variant, a newly-known devastating variant of this virus

Updates on the Safety profile of COVID-19 Vaccines

Herein, we provided updated data on the current literature regarding the administration of different vaccines worldwide. A brief introduction of these ten vaccines and their local and systemic adverse effects is provided in **Figure 1**. Meanwhile, the comparative data on type, doses, the incidence of adverse reactions, and related serious adverse effects are presented in **Table 1**.

Pfizer/BioNTech

Pfizer/BioNTech COVID-19 vaccine, also known as BNT162b1 and BNT162b2, is based on an mRNA vaccine platform with the technology of lipid nanoparticle nucleoside-modified mRNA vaccine, encoding the spike glycoprotein of SARS-CoV-2 (14-17). It was manufactured by Pfizer and BioNTech in the United States and Europe, respectively. According to the results of phase II/III clinical trials, the Pfizer/BioNTech vaccine was 95% effective in preventing COVID-19 (95% credible interval, 90.3% to 97.6%), recruiting 43548 participants. (15).

Phase I/II clinical trials of the current vaccine

were performed in the United States and Germany. (18). Pain, headache (3.8%), injection-site pain, and fatigue (2%) were common symptoms in vaccinated individuals in the two mentioned clinical trials (19). In addition, fever was reported in both groups but with a higher prevalence in the vaccinated group following the first dose of the vaccine. Moreover, they did not report any severe adverse reactions in this phase. However, in the phase II/III clinical trial of this novel vaccine, deaths from arteriosclerosis, cardiac arrest, and paroxysmal ventricular arrhythmia were reported as severe adverse events. Worth mentioning that the same events happened to the placebo group, which must be elucidated whether the vaccine causes such events. Death reports in the placebo group were due to hemorrhagic stroke and myocardial infarction. (15).

Recent real-world data has reported rare but severe adverse reactions shortly after the beginning of inoculations with the Pfizer/BioNTech vaccine. According to the United States Vaccine Adverse Event Reporting System (VAERS) (20), the Pfizer/BioNTech vaccine caused five anaphylactic reactions per million doses administered. Furthermore, according to 7,307 VAERS reports (20), the side effects were as follows: headache 1,550 (21.2%), fatigue 1,192 (16.3%), dizziness 1,113 (15.2%), nausea 1,014 (13.9%), chills 983 (13.5%), pyrexia 962 (13.2%), pain in extremity 610 (8.4%), and dyspnea 536 (7.3%). Based on an original study on the Pfizer/BioNTech, the rate of serious adverse effects was considerably low, and no significant differences were observed between the vaccinated and control groups (15). In a trial among adolescents vaccinated by the Pfizer/BioNTech COVID-19 vaccine, reports of reactogenicity were primarily mild to moderate local and systemic events. Regarding the adverse events among 12-to-15-year-old participants, the vaccinated group demonstrated a few higher rates of adverse effects (e.g., fever, injection-site pain, etc.) compared to the placebo group. This study reported no cases of anaphylaxis, hypersensitivity, or thromboses due to vaccination as serious adverse events. Moreover, according to VAERS, the incidence of anaphylaxis was 5.0 per million doses administered till January 18, 2021 (20). Also, VAERS published reports of myocarditis and pericarditis in men aged 30 years or younger who got vaccinated with mRNA COVID-19 vaccines (Pfizer/BioNTech, Moderna); nevertheless, the exact associations of these manifestations to the vaccine are not yet fully investigated (21). Consistent with the previous view, reports of a cohort study performed among health workers in the Czech Republic demonstrated the predominance of injection site pain (89.8%), fatigue (62.2%), and headache (45.6%) in the Pfizer/BioNTech safety profile (22).

Moderna

Moderna COVID-19 vaccine, also called mRNA-1273 vaccine, was co-manufactured by researchers at the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center and Moderna in Cambridge, Massachusetts. (23). This novel vaccine's phase III clinical trial results revealed that vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001), recruiting 30420 volunteers. (24).

According to the Phase I clinical trial of this novel vaccine, no serious adverse events were observed. Moreover, a diffuse maculopapular rash and paronychia were seen in a patient who was not vaccinated with the second dose. Of note, investigations did not reveal any significant association between the mentioned adverse effects and vaccine administration. (23). Furthermore, the most common adverse effects in the phase I clinical trial were headaches, fatigue, myalgia, chills, and injection-site pain. Local and systemic events were more common when the second dose of the vaccine was administered. Erythema, fever, mild myalgia, and fatigue were typical systemic reactions occurring on the vaccination day or one day after. 17 out of 71 unsolicited adverse events were investigated to have happened due to vaccine administration. Phase III clinical trial of the Moderna vaccine reported no significant difference in the occurrence of unsolicited severe adverse events and serious adverse events in both vaccinated and placebo groups. However, fatigue and headache are the most common vaccine-related adverse effects. (24).

Based on the VAERS reports results of adverse effects in 1737 individuals vaccinated with the Moderna COVID-19 vaccine are as follows: headache 430 (24.1%), pyrexia 333 (18.6%), chills 315 (17.6%), pain 290 (16.2%), dizziness 289

(16.2%), fatigue 287 (16.1%), nausea 281 (15.7%), injection-site pain 208 (11.6%), pain in extremity 189 (10.6%), and dyspnea 172 (9.6%). By January 2021, the Centers for Disease Control and Prevention (CDC) reported 108 cases of anaphylaxis due to the administration of the first dose of the vaccine. (25). Furthermore, by January 18, 2021, 21 confirmed cases (2.8 per million doses administered) of anaphylaxis due to the Moderna COVID-19 vaccine were reported. (20). According to VAERS reports, myocarditis and pericarditis attributable to mRNA COVID-19 vaccine administration were demonstrated as rare adverse effects, and it is not fully clear whether they are vaccine-related (21).

Sputnik V

In August 2020, Gam-COVID-Vac, known as Sputnik V, was first introduced and registered by the Russian Ministry of Health. Sputnik V is a two-dose adenovirus vaccine with two different types of adenovirus vectors manufactured by the Gamaleya National Centre of Epidemiology and Microbiology in Moscow. The above-mentioned recombinants are known as rAd26 and rAd5, which are utilized for the first and second doses of the Sputnik V vaccine, respectively.

Phase I/II clinical trial of the current vaccine in Russia demonstrated common adverse events such as hyperthermia, pain at the injection site, asthenia, headache, and muscle and joint pain. (26). Showing an efficacy of 91.6% (95% CI 85.6%–95.2%), reports from the Sputnik V phase III clinical trial claimed that although grade 1 adverse events were observed, they could not conclude a significant association between the vaccine and adverse events (27).

An interesting study using deep learning on the data of Telegram posts in the Russian language revealed the incidence of side effects as follows: pain (47%), fever (47%), fatigue (34%), and headache (25%) (28). A cohort study in Italy among 72 health workers reported that 11% had redness and swelling considering local reactions, and 54% complained of injection-site pain. Moreover, 40% reported fever, 5% had diarrhea, and 68% had new or worsened muscle pain regarding systemic responses. One of the participants was hospitalized due to severe adverse effects, and overall, 5% needed medical intervention. (29).

Bharat

The Bharat COVID-19 vaccine, also known as BBV152 and Covaxin, is an inactivated, whole-virion vaccine that was developed by Bharat Biotech and the Indian Council of Medical Research. (30). It was the first vaccine produced in India and got its emergency use approval from the Central Drugs Standard Control Organization of the Government of India (CDSCO) in January 2021 (31).

During its phase I and II clinical trials, adverse effects were reported. These are as follows: local ones included pain (5%) and itching (4%), while systemic ones included body aches (2%), fever (2%), headache (3%), nausea or vomiting (2%), and weakness (3%). No related profound adverse effect was reported. The second dose caused much fewer adverse effects. (32, 33).Lately, the results of phase III clinical trials have been published. Recruiting 25798 subjects, they reported an efficacy rate of 77.8% (95% CI: 65.2–86.4) along with adverse effects of this vaccine. The new adverse effect was chills (0.22% and 0.07% in the first and second doses). Moreover, one patient was diagnosed with thrombocytopenic purpura occurring 39 days after the second dose. (34). Additionally, another study reported adverse effects of this vaccine in 15 medical staff working in a tertiary health care center in New Delhi. Chest pain (in one subject), palpitation (in one subject), dizziness (in one subject), and vertigo (in two subjects) were the new rare mild adverse effects reported in this study. (35).However, the recent study by Desai et al. reported quite different results about this vaccine (36). In their test-negative, case-control study among employees of a tertiary care hospital in New Delhi, India, they retrospectively assessed people with symptoms suggestive of COVID-19. The adjusted effectiveness of Bharat against symptomatic COVID-19 was 50% (95% confidence interval 33–62; p-value<0.0001) after two doses administered at least 14 days before testing. (36). However, regarding the adverse effects, a systematic review by Ahmed et al. has reported that there have never been serious adverse events or deaths reported with this vaccine. (37).

CanSino

CanSino COVID-19 vaccine, also known as AD5-nCOV and Convidecia, is a viral vector

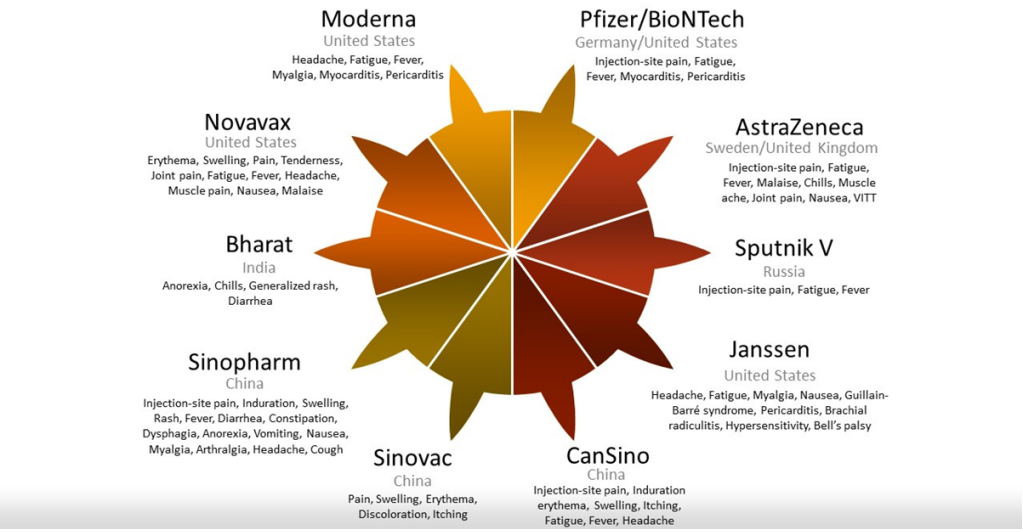

Figure 1. Graphical Abstract-Summary of COVID-19 vaccines and their most common reported local and systemic side effects

Table 1. The safety profile of COVID-19 vaccines according to published clinical trials

Vaccine	Type	Doses	Phase	Incidence rate of local adverse effects in vaccine group vs. placebo group	Incidence rate of systemic adverse effects in vaccine group vs. placebo group	Related serious adverse effects in that phase	Ref.
Pfizer/BioNTech	mRNA	2 doses-3 weeks apart	III	**Overall**=26.7% vs 12.2%		shoulder injury due to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg paresthesia	(145)
Moderna	mRNA	2 doses-4 weeks apart	III	**Overall**=84.2%, vs. 19.8% after the first dose and 88.6%, vs. 18.8% after the second dose	**Overall**=54.9%, vs. 42.2% after the first dose and 79.4%, vs. 36.5% after the second dose	Autonomic nervous system imbalance, dyspnea, severe nausea and vomiting, Rheumatoid arthritis, swelling face, and peripheral edema	(146)
Sputnik V	Viral vector	2 doses-3 weeks apart	III	**Overall**=5.4% vs 1.2%	**Overall**=n/a **Flu-like illness**=15.2% vs 8.8% **Asthenia**=2.4% vs 2.6% **Malaise**=0.5% vs 0.6% **Pyrexia**=0.5% vs 0.3% **Fever sensation**=0.4% vs 0.3% **Hypertension**=3.9% vs 2.9% **Headache**=2.9% vs 2.6% **Tonsillitis**=0.8% vs 0% **Cough**=1% vs 0.3% **Rhinorrhea**=0.7% vs 1.2% **Nasal congestion**=0.5% vs 0.6% **Contact dermatitis**=3.8% vs 0.9% **Diarrhea**=0.8% vs 0.3% **Nausea**=0.7% vs 0.9% **Dyspepsia**=0.5% vs 0% **Abdominal discomfort**=0.3% vs 0.3% **Elevated body temperature**=2.2% vs 0.9% **Muscle pain**=0.9% vs 0.9% **Joint pain**=0.4% vs 0.3%	none	(147)
Bharat	Inactivated virus	2 doses-4 weeks apart	III	**Overall**=3.35% vs 3.10% after the first dose and 2.16% vs 2.02% after the second dose **Pain**=3.04% vs 2.78% after the first dose and 1.81% vs 1.62% after the second dose **Redness**=0.26% vs 0.20% after the first dose and 0.16% vs 0.19% after the second dose **Induration**=0.25% vs 0.20% after the first dose and 0.14% vs 0.14% after the second dose **Swelling**=0.16% vs 0.25% after the first dose and 0.11% vs 0.12% after the second dose	**Overall**=2.57% vs 1.92% after the first dose and 1.79 vs 1.59% after the second dose **Pyrexia**=0.84% vs 0.63% after the first dose and 0.67% vs 0.61% after the second dose **Fatigue**=0.4% vs 0.32% after the first dose and 0.32% vs 0.16% after the second dose **Chills**=0.22% vs 0.17% after the first dose and 0.07% vs 0.12% after the second dose **Headache**=0.99% vs 0.86% after the first dose and 0.67% vs 0.54% after the second dose **Muscle pain**=0.38% vs 0.22% after the first dose and 0.29% vs 0.22% after the second dose **Joint pain**=0.13% vs 0.13% after the first dose and 0.09% vs 0.13% after the second dose **Nausea**=0.13% vs 0.09%after the first dose and 0.11% vs 0.08% after the second dose **Vomiting**=0.09% vs 0.06% after the first dose and 0.05% vs 0.06% after the second dose	thrombocytopenic purpura	(148)

Table 1 (continued).

CanSino	Viral vector	1 dose	II	**Overall**=n/a **Pain**=56% vs 9% **Induration**=2% vs 0% **Redness**=1% vs 2% **Swelling**=4% vs 0% **Itch**=2% vs 0%	**Overall**=n/a **Fever**=16% vs 10% **Headache**=28% vs 13% **Fatigue**=34% vs 17% **Vomiting**=1% vs 1% **Diarrhea**=8% vs 3% **Muscle pain**=18% vs 2% **Joint pain**=10% vs 3% **Oropharyngeal** Pain=5% vs 5% **Cough**=2% vs 2% **Hypersensitivity**=0% vs 2% **Dyspnea**=0% vs 0% **Impaired appetite**=5% vs 2% **Pruritus**=3% vs 5%	none	(149)
Sinovac	Inactivated virus	2 doses-2 weeks apart	III	**Overall**=61.5% vs 34.6% **Pain**=60.3% vs 32.5% **Swelling**=5.8% vs 2.1% **Pruritus**=4.2% vs 2.9% **Redness**=3.9% vs 1.4% **Induration**=3.8% vs 1.1%	**Overall**=48.4% vs 47.6% **Headache**=34.3% vs 34.8% **Fatigue**=16% vs 14.9% **Myalgia**=11.7% vs 10.5% **Nausea**=7.9% vs 8.4% **Diarrhea**=7.9% vs 8.1% **Joint pain**=5.7% vs 5.2% **Cough**=5.5% vs 5.2% **Chills**=5% vs 5.1% **Pruritus**=4.2% vs 3.6% **Impaired appetite**=3.5% vs 3.9% **Vomiting**=1% vs 1% **Hypersensitivity**=0.9% vs 0.9% **Rash**=0.8% vs 0.7% **Fever**=0.2% vs 0.1%	none	(46)
Novavax	Protein Subunit	2 doses-3 weeks apart	III	**Overall**=57.6% vs. 17.9% after the first dose and 79.6% vs. 16.4% after the second dose	**Overall**=45.7% vs. 36.3% after the first dose and 64.0% vs. 30.0% after the second dose	myocarditis	(150)
Sinopharm	Inactivated virus	2 doses-3 weeks apart	III	**Overall**=20.7% vs 29% **Pain**= 19.4% vs 27.9% **Induration**=0.6% vs 0.9% **Swelling**=0.8% vs 1.2% **Rash**=0.7% vs 0.6% **Redness**=0.9% vs 1.1% **Itch**=0.5% vs 0.4%	**Overall**=28.3% vs 27.8% **Fever**=2.1% vs 2.1% **Diarrhea**=3.6% vs 4% **Constipation**=0.8% vs 0.8% **Dysphagia**=0.4% vs 0.5% **Impaired appetite**=0.2% vs 0.2% **Vomiting**=0.6% vs 0.6% **Nausea**=1.2% vs 1% **Muscle pain**=5.5% vs 5.4% **Joint pain**=1.4% vs 1.3% **Headache**=13.1% vs 12.6% **Cough**=3.4% vs 3.6% **Dyspnea**=1.1% vs 1.2% **Pruritus**=1.5% vs 1.4% **Mucocutaneous abnormalities**=0.2% vs 0.3% **Acute allergic reaction**=0.3% vs 0.3% **Acute allergic reaction**=0.3% vs 0.3% **Fatigue**=10.9% vs 1.2%	possible demyelinating myelitis and severe emesis	(111)

n/a=not applicable, Ref=reference

*Note that there are published data on AstraZeneca phase I/II, II/III and combined phase I/II, II/III, and III studies. However, they lacked the needed quantitative data for the incidence rate column. High-grade fever, hemolytic anemia, and transverse myelitis were reported to be the related serious adverse reactions. This viral vector vaccine requires 2-dose regimen, 28 days apart [52, 54, 141, 142]. Regarding Johnson & Johnson, Guillain-Barre syndrome, pericarditis, brachial radiculitis, hypersensitivity, Bell's palsy, severe generalized weakness, fever, and headache were reported as serious adverse effects. This viral vector vaccine has 1-dose regimen [97]. The data on local and systemic reactions of these 2 vaccines **is** discussed **in** the text.

vaccine containing a replication-defective Adenovirus-5 that expresses the spike glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), developed by CanSino Biologics. (38). Along with the Moderna vaccine, it was one of the first vaccines to enter phase I clinical trials. (39). First, it got approval for Chinese military service use in June 2020 and then for public use in February 2021 by China's Central Military Commission and The National Medical Products Administration (NMPA), respectively. (40, 41).

In its phase I clinical trial, the most common local adverse effects were pain (54%), induration (4%), erythema (4%), swelling (7%), and itching (5%), while the systemic ones included fever (46%), headache (39%), and fatigue (44%). Two people (3%) experienced grade-III fever with an axillary temperature higher than 38.5°C (38). However, Phase II results revealed more systemic adverse effects, including vomiting (1%), diarrhea (8%), muscle and joint pain (18% and 10%), oropharyngeal pain (5%), cough (2%), nausea (5%), impaired appetite (5%), and mucosal abnormality (2%). No serious adverse effects were observed or reported. By means of this study, Zhu et al. determined the appropriate dosage to evaluate its efficacy in further studies. (42).

In a recent study, Halperin et al. reported the final interim safety analysis of a single dose of this vaccine. (43). Recruiting 36,727 participants from Argentina, Chile, Mexico, Pakistan, and Russia, systemic adverse effects included headache (44.2%), generalized muscle aches (41.2%), drowsiness (40·0%), and fever (12.5%). Meanwhile, the local side effects were as follows: redness (9.7%), swelling (7.1%), and injection site

pain (59.3%). Moreover, they observed 14 serious adverse events in participants who received CanSino, none of which were assessed as vaccine-related (43).

Sinovac

Sinovac COVID-19 vaccine, also known as CoronaVac, is an inactivated virus vaccine developed by Sinovac Biotech Ltd. in China. WHO approved this vaccine for emergency use in June 2021 (44). Multiple clinical trials tested this vaccine. Its phase I/II trial proved its appropriate safety profile. Accordingly, local adverse effects included pain, swelling, erythema, discoloration, and itching.

Fatigue (3.3%), diarrhea (5%), fever (3.3%), muscle pain (2.5%), nausea (1.7%), and impaired appetite (0.8%) were systemic adverse effects in the 24 participants. (45). In the phase III clinical trial carried out in Brazil, the efficacy against symptomatic COVID-19 was reported to be 50.7% (95%CI 36.0-62.0). Moreover, the adverse effects were consistent with the previous results, except that joint pain was observed in 2 people out of 6202 participants. No related serious adverse effect has been reported according to their study. (46).

In another study, a self-administered online survey was conducted to assess the adverse effects of this vaccine among 1526 subjects in China. Lymphadenopathy (2% of all the adverse reactions) and stuffy, runny nose (2.5% of all the adverse reactions) were reported as the new systemic adverse effects (47). Moreover, several case reports have been published regarding the adverse effects of this vaccine, such as type-1 Kounis Syndrome (co-existence of acute coronary syndromes and allergic reactions in people without risk factors for coronary artery diseases) (48), systemic drug-related intertriginous and flexural exanthema-like eruption (49), thyroiditis (50), reactive arthritis (51), petechial skin rash (52), and pityriasis rosea (53).

AstraZeneca

AstraZeneca COVID-19 vaccine, also known as ChAdOx1 or AZS1222M, is another viral vector vaccine developed by Oxford University and AstraZeneca Pharmaceutical Industry Company. The United Kingdom was the first country to approve this vaccine in December 2020 emergently, and since then, millions of people have been administered this vaccine. (54).

In phase I/II, there were reports of local adverse effects, along with headache, fatigue, muscle pain, chills, and fever, which were the most common adverse effects. The overall efficacy of this vaccine is 70.4% (95.8% CI: 54.8% to 80.6%), based on the results of four randomized controlled trials in Brazil, South Africa, and the United Kingdom. (55). Its adverse effects reported in phase II/III in HIV-positive people were as follows: pain at the injection site (49%), fatigue (47%), headache (47%), malaise (34%), chills (23%), muscle ache (36%), joint pain (9%), and nausea (8%), all of which could be prevented by prophylactic paracetamol administration. (56-58). Amongst more than 23000 subjects, high-grade fever, hemolytic anemia, and transverse myelitis were the probable serious adverse effects of this vaccine (59). However, as more people got vaccinated, reports of more serious adverse effects were published. Vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported multiple times as a serious adverse effect. (60). VITT manifestations could be portal vein thrombosis (61, 62), cerebral venous thrombosis (63-65), ischemic stroke (66, 67), deep vein and pulmonary artery thrombosis (68, 69), and cerebral arterial thromboembolism, alongside lab tests of high D-dimer, low platelet count, and low fibrinogen. Regarding the most prevalent manifestation, cerebral venous thrombosis (CVT), a multicenter cohort study documented post-vaccination CVT cases in people with and without VITT. In this study, Perry et al. demonstrated that people in the VITT group were significantly younger than those in the non-VITT group (median ages of 47 and 57, respectively). Moreover, the VITT group tended to have more thrombosed intracranial veins (median three compared with two, p-value=0.041). VITT was also associated with more death and dependency on others (47% compared with 16%) (70). The most probable underlying mechanism of VITT is similar to heparin-induced thrombocytopenia, as antibodies against PF4 (Platelet Factor 4) have been detected in patients. Yet, the exact vaccine particle responsible for VITT is unknown. It could be either an adenoviral particle or free viral DNA (71).

In terms of management, a complete evaluation of VITT-suspected patients should include a complete blood count (CBC), peripheral smear, fibrinogen, D-dimer, and coagulation tests, in addition to liver and renal function tests (72). In this situation, enzyme-linked immunosorbent assay (ELISA)--based PF4 methods can act as a suitable confirmatory test (73). Concerning their treatment, anticoagulation therapy alongside a high dose of intravenous immunoglobulin (IVIG) is administered. This treatment option has shown reduced antibody-induced platelet activation and improved clinical status in patients of VITT (74). In terms of management, a complete evaluation of VITT-suspected patients should include a complete blood count (CBC), peripheral smear, fibrinogen, D-dimer, and coagulation tests, in addition to liver and renal function tests (72). In this situation, enzyme-linked immunosorbent assay (ELISA)--based PF4 methods can act as a suitable confirmatory test (73). Concerning their treatment, anticoagulation therapy alongside a high dose of intravenous immunoglobulin (IVIG) is administered. This treatment option has shown reduced antibody-induced platelet activation and improved clinical status in patients of VITT (74).

VITT and reports of VITT-induced deaths were the reasons for this vaccine's suspension in Europe (first in Denmark, followed by other countries) (75). However, WHO defended this suspension (76). Moreover, leading to more vaccine refusal in the United States, the United States government decided to send six million doses abroad. (77). However, in evidence-based speaking, one should consider the cost-benefit status. The incidence rate of VITT is of great importance. Up to May 12, there were 309 reported cases of VITT in the United Kingdom, suggesting an overall incidence rate of 12.3 per million doses. Note that the incidence rate of cerebral venous thrombosis (CVT) due to COVID-19 itself is 42.8 per million cases, significantly higher than the vaccine. (78). That is why Europe and the United Kingdom later concluded that the benefits of the AstraZeneca vaccine outweigh its adverse effects and complications. Yet, for better medical confidence, the United Kingdom suggested an alternative vaccine for people under 40 (79, 80). Also, the European Medicines Agency (EMA) stated that VITT is a rare adverse effect, and vaccinated people presenting with shortness of breath, chest pain, swelling in the legs, persistent abdominal pain, neurological symptoms, and unusual small blood spots under the skin should seek medical care as soon as possible. (81).

Some studies have investigated the overall adverse effects on large scales apart from official clinical trials: serious adverse effects were absent or rare. However, it caused more mild-to-moderate adverse effects compared to the Pfizer/BioNTech vaccine. (82-84). Lymphadenopathy (85-87), Guillain-Barre syndrome (88, 89), myelitis (90, 91), status epilepticus (92), and mucosal and cutaneous reactions (93, 94) Other extremely rare adverse effects were reported in various case reports.

Conventionally, pregnant women, people with significant comorbidities, and the elderly are excluded from clinical trials. However, in one of the clinical trials of AstraZeneca, the vaccine was well-tolerated in people older than 70, with lower rates of mild-to-moderate adverse effects. The incidence rate of local and systemic adverse effects in people younger than 70 was 82%, while subjects aged 70 and older had incidence rates of 61% and 65%, respectively. (95). In terms of pregnant women, there is not enough data to set a fixed recommendation. WHO recommends COVID-19 vaccination for women at higher risk of virus exposure, such as health workers (96). In the setting of autoimmune rheumatic diseases, the Canadian Rheumatology Association recommends vaccination and mentions that there is very low certainty regarding the safety of the AstraZeneca vaccine. (97). Another study investigated the safety profile of this vaccine in 33 patients with multiple sclerosis. All the adverse effects were mild to moderate and well-tolerated, and no new ones were reported. (98).

Johnson & Johnson (Janssen)

Johnson & Johnson COVID-19 vaccine, also known as Ad26.CoV2.S or Janssen vaccine is a viral-based vaccine, first developed by Janssen Vaccines in the Netherlands. This vaccine was approved by the Food and Drug Administration (FDA) in February 2021 and EMA in March 2021 (99).

Johnson & Johnson's vaccine safety profile has been shown in multiple clinical trials. During

its phase I/II trial, subjects experienced different adverse effects, including fatigue, headache, muscle pain, nausea, and pyrexia as systemic adverse effects, along with erythema, pain, and swelling as the local ones, and no serious adverse effects were observed (100). Johnson & Johnson also reached a phase III trial in September 2020 in different countries (Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the United States). This vaccine's efficacy was 66.7% (55.6–75.2), and the profile of adverse effects was similar to the previous studies: the most common local adverse effect was pain at injection (48.6%), while the most common systemic ones were headache (38.9%), fatigue (38.2%), myalgia (33.2%), and nausea (14.2%). However, among 21895 subjects, seven related adverse effects were reported: Guillain-Barre syndrome, pericarditis, brachial radiculitis, hypersensitivity, Bell's palsy, severe generalized weakness, fever, and headache (101). In another study reviewing adverse effects of the Johnson & Johnson vaccine in 13725 subjects in the United States, 97% of reported adverse effects were consistent with the mild-to-moderate adverse effects previously reported in phase I/II and III trials. However, three new cases of VITT were reported. That would make a total of 17 cases in the United States by April 21 (102). That was why the Johnson & Johnson vaccine was suspended in the United States in April 2021 (102). The probable underlying mechanism of VITT is similar to AstraZeneca's (71). Since the benefits of this vaccine outweigh its infrequent risks of VITT, the FDA and EMA agreed that the suspension should halt, and the vaccination in the United States started again, warning women younger than 50, as it tended to happen more in this subgroup (103, 104). Another rare adverse effect is severe cutaneous adverse reactions that can be managed well (99).

Novavax

Developed by the Coalition for Epidemic Preparedness Innovations (CEPI) and Novavax in the United States, the Novavax vaccine, also known as NVX-CoV2373, is a protein-subunit vaccine made of SARS-CoV-2 spike glycoproteins along with a Matrix-M1, a Saponin-based adjuvant (105). During its phase I/II clinical trial, no serious adverse effect was observed. Local adverse effects included erythema, swelling, pain, and tenderness, while the systemic ones were joint pain, fatigue, fever, headache, muscle pain, nausea, and malaise (105). In its phase IIa-b clinical trial, the results were consistent with the previous study, and no related serious adverse effects were found (106). A recent phase III clinical trial study reported its efficacy as 89.7% (95% CI, 80.2 to 94.6) while demonstrating its adverse effects: headache (24.5%), muscle pain (21.4%), and fatigue (19.4%) as the most common ones in people. Moreover, a person developed a serious related adverse effect (myocarditis), which resolved after two days of hospitalization (107).

Another large study conducted in the United States and Mexico aimed to assess the efficacy and safety of this vaccine in adults (108). In their phase 3, randomized, placebo-controlled trial, 19,714 received the vaccine and 9868 placeboes. During their three-month follow-up, ten moderate and four severe COVID-19 cases occurred, all in placebo recipients, yielding vaccine efficacy against the moderate-to-severe COVID-19 infection of 100% (95% confidence interval, 87.0-100). There were no new local or systemic adverse effects compared to the previous studies. During their follow-up, they reported no episodes of the Guillain–Barré syndrome, myocarditis, pericarditis, or VITT (108).

Sinopharm

Sinopharm vaccine, also known as BBIBP-CorV or BIBP, is an inactivated virus vaccine developed by the Sinopharm Beijing Institute of Biological Products. (109). In May 2021, this vaccine got WHO approval for emergency use (110). During its phase I/II clinical trial, the safety and efficacy of this vaccine were assessed. The local adverse effects included pain, itching, swelling, and erythema, while the systemic ones were fever, fatigue, nausea, vomiting, headache, diarrhea, and joint pain. Moreover, no serious adverse effect was reported. (109). In its phase III clinical trial, 13465 subjects received the vaccine. Phase III clinical trial results showed 78.1% efficacy (95% CI, 64.8%-86.3%) and vaccine receivers experienced pain at the injection site (19.4%), induration (0.6%), swelling (0.8%), rash (0.7%), redness (0.9%), itching (0.5%) as the local adverse effects and fever (2.1%), diarrhea (3.6%), constipation

(0.8%), dysphagia (0.4%), anorexia (0.2%), vomiting (0.6%), nausea (1.2%), myalgia (5.5%), arthralgia (1.4%), headache (13.1%), cough (3.4%), dyspnea (1.1%), pruritus (1.5%), skin and mucosal abnormalities (0.2%), acute allergic reactions (0.3%), and fatigue (11.2%) as the systemic adverse effects. Two possibly related adverse effects were reported: a case of demyelinating myelitis and a case of severe emesis, resulting in emergency visits (111). Moreover, three studies assessed the adverse effects of this vaccine along with AstraZeneca and Pfizer/BioNTech vaccines in Jordan and Iraq. Adverse effects were as follows: pain and arm numbness as local adverse effects, and fever, fatigue, muscle pain, bone pain, joint pain, headache, diarrhea, dyspnea, dizziness, cough, nausea, vomiting, chills, ear symptoms, loss of smell and taste senses, abdominal pain, bruises on the body, bleeding gums, nosebleed, sweating, runny, stuffy nose, irregular heartbeat, and abnormal blood pressure. In contrast to official clinical trials, it is not known which one of these adverse effects was related to the vaccine. Moreover, in all three studies, Sinopharm was reported to have the best toleration as it had the highest percentage of people without any adverse effects. (1, 112, 113). Only two people, both female and older than 50, presented with thrombocytopenia in these studies. None have developed blood clots and life-threatening situations (1).

Integrated studies assessing adverse effects of different vaccines

Several studies have conducted cross-sectional assessments of the adverse effects of COVID-19 vaccines in different populations. For example, two studies have assessed and compared the adverse effects of AstraZeneca (60.1% and 43.8% in Iraq and Jordan, respectively), Pfizer/BioNTech (29.2% and 34.5%), and Sinopharm (10.7% and 21.8%) vaccines, recruiting 1012 general inhabitants and 409 health workers. Both reported that people receiving Pfizer/BioNTech experience more local adverse effects, while people receiving AstraZeneca experience more systemic ones (112, 113). In terms of the Sinopharm vaccine, this vaccine was associated with having no adverse effects (113). However, fatigue was the most commonly reported symptom in the two previously mentioned studies (112, 113). Moreover, young patients (18-49 years), females, and people with a history of COVID-19 infection or comorbidities such as diabetes and hypertension were more susceptible to developing adverse effects (112).

Another study assessed the adverse effects of AstraZeneca (31%), Pfizer/BioNTech (27.34%), Sinopharm (38.2%), and other vaccines such as Sputnik V, Moderna, Bharat, and Johnson & Johnson in 2213 Jordanian general inhabitants (1). Similarly, they reported fatigue and pain at the injection site as the most prevalent adverse effects. They also noted that the majority of adverse effects (61%) happen 5-12 hours after vaccination and last for 1-3 days afterward (56%). AstraZeneca vaccination had the highest overall rates of adverse effects and the most severe ones. Moreover, some specific adverse effects were significantly correlated with the vaccine type: Pfizer/BioNTech had the highest rate of pain at the injection site, AstraZeneca had the highest rates of chills and sleepiness, and Sinopharm had the highest rates of sore throat, dry throat, and runny nose (1).

Another study assessed the adverse effects of AstraZeneca (95%), Bharat (3.3%), and other vaccines such as Pfizer/BioNTech and Sinopharm in 5396 Indian health workers. Fatigue, myalgia, and fever were the most reported adverse effects. Moreover, statistical analysis showed that the chances of developing adverse effects decreased with advancing age (114). This result is consistent with those reported by the FDA: people of ≥55 years are less likely to develop post-vaccination symptoms (112). They also reported that people with a history of COVID-19 infection had the same adverse effect profile as those without it (114). It was inconsistent with the results of another study conducted in the United Kingdom (115). They analyzed symptoms of AstraZeneca (55.03%) and Pfizer/BioNTech (44.96%) vaccination of 627,383 people via COVID-19 Symptom Study application and reported that people with prior COVID-19 infection develop more adverse effects. They also stated that the overall incidence rates of adverse effects were lower than the published results of phase III clinical trials (115). In a similar study in the United States, adverse effects of Moderna (54%) and Pfizer/BioNTech (46%) vaccines were assessed in 3,643,918 people. Incidence rates of both local and systemic adverse

effects were lower in Pfizer/BioNTech-receiving individuals. In both vaccine groups, people developed more adverse effects after the second dose compared to the first one (116).

A systematic review and meta-analysis conducted by Chen et al. aggregated data from 14 randomized clinical trials and found that the total adverse effects incidence rate of inactivated-virus vaccines (Risk ratio (RR): 1.34 [95% confidence interval (CI) 1.11–1.61, P<0.001]) is less than the ones with viral vectors (RR: 1.65 [95% confidence interval (CI) 1.31–2.07, P<0.001]) and mRNA (RR: 2.01 [95% CI 1.78–2.26, P<0.001]) (6). Similarly, Pormohammad et al. analyzed the data of 25 randomized clinical trials and demonstrated the following results in their systematic review and meta-analysis: The mRNA-based vaccines develop the most adverse effects, such as injection site pain (Odds ratio (OR): 83.06 [95% confidence interval (CI) 37.05–186.1]), fever (OR: 36.90, [95% CI 12.34–105.21]), redness (OR: 24.40 [95% CI 18.73–31.77]), swelling (OR: 18.79 [95% CI 4.87–72.40]), induration (OR: 17.5 [95% CI 1.96–155.58]), pruritus (OR: 17.5 [95% CI 1.98–155.58]), chills (OR: 13.11 [95% CI 7.19–23.89]), myalgia (OR: 10.71 [95% CI 6.51–17.60]), vomiting (OR: 8.71 [95% CI 4.38–17.34]), fatigue (OR: 6.16 [95% CI 5.86–6.48]), and headache (OR= 5.13 [95% CI 2.32–11.31]) (117). In contrast, incidence rates of diarrhea and arthralgia were higher in viral vector-based vaccines (OR: 4.59 [95% CI 3.58–5.89] and OR: 10.61 [95% CI 7.60–14.83], respectively) (117).

Heterologous Vaccination

Most COVID-19 vaccines require two doses: the primary and the booster injection, with a specific time interval between them. However, since vaccination with AstraZeneca and Johnson & Johnson halted in some countries, the authorities suggested the idea of heterologous vaccination as the solution (118). Heterologous vaccination (different prime and boost vaccines) is not a new idea; it has been administered in illnesses such as HIV, malaria, Ebola, and influenza so far (119). The COVID-19 pandemic could be helpful as vaccine supplies might fluctuate in different countries (118).

For instance, a study assessed people's immune responses boosted with the Pfizer/BioNTech vaccine following initial AstraZeneca inoculation. Anti-spike immunoglobulin G (IgG) and spike-specific CD4+ and CD8+ T cells in people with AstraZeneca/Pfizer/BioNTech schedule were higher than in people receiving homologous AstraZeneca schedule (an 11.5-fold increase compared to a 2.9-fold increase) (120). Moreover, Liu et al. conducted a non-inferiority trial comparing homologous and heterologous AstraZeneca and Pfizer/BioNTech schedules.

They compared AstraZeneca/Pfizer/BioNTech with AstraZeneca/AstraZeneca and Pfizer/BioNTech/AstraZeneca with Pfizer/BioNTech/Pfizer/BioNTech schedules. Measuring serum anti-spike IgG levels, Liu et al. concluded that the AstraZeneca/Pfizer/BioNTech schedule was non-inferior to the homologous AstraZeneca one (12906 ELU/ml vs. 1392 ELU/ml). Still, the results of the other two groups were not the same (7133 ELU/ml in the heterologous group vs. 14080 ELU/ml in the homologous group). Regarding adverse effects, the systemic reactogenicity of the booster vaccine in heterologous schedule recipients was significantly higher than in people receiving the homologous one. The most common systemic adverse effects and the difference between their incidence rates are as follows: Chills (Pfizer/BioNTech/AstraZeneca-Pfizer/BioNTech/Pfizer/BioNTech=23% and AstraZeneca/ Pfizer/BioNTech-AstraZeneca/AstraZeneca=26%), fatigue (13% and 27%), fever (2% and 6%), headache (22% and 32%), joint pain (8%, 24%), and muscle ache (11% and 40%) (121, 122). Moreover, no related serious adverse effect was observed in any of these groups. These results were also consistent with reports from a prospective cohort conducted by Hillus et al. regarding systemic and local adverse effects (123).

Delta and Omicron variants; the current emergence

Similar to the previous SARS-CoV-2 variants, the B.1.617.2 (delta) variant has spread worldwide and become an emergence. Firstly, it was detected in India in December 2020 (124). But now, the delta variant is responsible for most of the confirmed COVID-19 cases because of its high transmissibility rates. (124). Accordingly, the effectiveness of the Pfizer/BioNTech and ChAdOx1 nCoV-19 vaccines against this contagious variant

was investigated. A test-negative case-control design was utilized in the era of the spreading of delta variant in the United Kingdom, and the study results exhibited significantly lower effectiveness after one shot of these two vaccines in people with delta variants (30.7%; 95% CI, 25.2%-35.7%), similarly for the two vaccines. The administration of two shots of the Pfizer/BioNTech vaccine resulted in 93.7% (95% CI, 91.6%-95.3%) and 88.0% (95% CI, 85.3%-90.1%) effectiveness among participants with the alpha and delta variants, respectively.

The effectiveness of two doses of the ChAdOx1 nCoV-19 vaccine was reported among people with the alpha and delta variant: 74.5% (95% CI, 68.4%-79.4%) and 67.0% (95% CI, 61.3%-71.8%), respectively (125). A test-negative case-control real-world study of 74 test-positive cases and 292 test-negative controls in Guangzhou, China, assessed the efficacy of inactivated COVID-19 vaccines in the era of the delta variant outbreak. They reported that two-dose vaccination yielded an efficacy of 59.0% (95% Cl: 16.0%-81.6%) (126). Recently, a study reported the effectiveness of Moderna and Pfizer/BioNTech vaccines in nursing home residents in the United States from March 1, 2021, to August 1, 2021. During the delta period, the estimated effectiveness was 53.1% (95% CI: 49.1%-56.7%). Effectiveness estimates were similar for Pfizer/BioNTech and Moderna vaccines (127). Regarding the Sputnik V vaccine, a statistically significant 2.5-fold reduction in the vaccine's neutralizing activity was observed (128).

The emergence of another variant, Omicron (B.1.1.529), highlighted this virus's dynamic evolution during the pandemic. First, it appeared in South Africa in November 2021 and began to spread all over the world (129). When compared with the Delta variant, Omicron was reported to have a higher affinity for human angiotensin-converting enzyme 2 (ACE2) due to a significant number of mutations in the SARS-CoV-2 receptor-binding domain (RBD), indicating a higher potential for transmission (130). However, the symptoms of the Omicron variant remained milder than Delta, characterized by higher rates of sore throats but lower rates of loss of smell and hospital admission than the Delta variant (131).

Similar to the Delta variant breakthrough, various studies aimed to assess the efficacy of available vaccines against the Omicron variant. For example, Andrews et al. evaluated immunization with two doses of Pfizer/BioNTech, AstraZeneca, or Moderna vaccines and after a booster dose of Pfizer/BioNTech, AstraZeneca, or Moderna by a test-negative case-control design (132). They found that vaccine effectiveness against the symptomatic COVID-19 disease was higher for the Delta variant than for Omicron for all combinations of primary course and booster vaccines. They also highlighted the effect of a booster dose of vaccine: Pfizer/BioNTech booster resulted in increased effectiveness of 62.4% and 67.2% at 2-4 weeks after the injection in people primarily vaccinated with two doses of AstraZeneca and Pfizer/BioNTech, respectively (132).

In a systematic review and meta-regression, Higdon et al. aggregated data on the duration of effectiveness of vaccination against COVID-19 caused by the omicron variant (133). They reported that although vaccine effectiveness against severe COVID-19 disease was lower for Omicron than for pre-omicron variants one month after primary vaccine series completion, the mean reduction in vaccine effectiveness from 1 month to 6 months after the primary vaccines was insignificant (1.0 percentage point (95% confidence interval 3.9-6.6)) during Omicron compared to 10.0 percentage points (95% confidence interval 6.1-15.4) before Omicron's emergence (133).

Special Considerations

This section elaborates on the specific points that healthcare providers should address regarding the safety of administering various vaccines in four main at-risk populations.

Older adults

Common vaccine-related adverse events (e.g., chills, headache, injection site pain, fatigue, and myalgias) mostly occur in individuals 55 years of age or older (23). Administrations of the second dose of the vaccine are more likely to cause local and systemic adverse events. For instance, short-lasting (5-7 days) mild erythema and myalgia were reported after the second dose. However, three people aged between 57 and 70 reported fever and fatigue as systemic adverse events after the second dose (15, 23, 24).

In addition, hypoglycemia in an individual

aged 50 – 70 years old was investigated as not being vaccine-related (23). Collectively, older people typically show mild to moderate adverse effects, which are mainly short-lasting, self-limiting, and less occurring (134).

Pregnant and breastfeeding women

The CDC claims that pregnant and recently pregnant women are at higher risk of severe illness and severe complications from COVID-19 infection. Remarkably, the CDC emphasizes that you can get vaccinated even if you are pregnant. To date, limited data are available assessing the safety profile of administration of the COVID-19 vaccines in pregnant people; however, many experiments are ongoing to reveal more aspects of them. Various clinical trials are being conducted in line with the gathering data of women getting pregnant after the vaccination. Experimental studies in subjects vaccinated with Moderna, Pfizer/BioNTech, or J&J/Janssen COVID-19 vaccine reported no serious adverse effects, and also, their babies were also safe (135, 136). The CDC and FDA developed COVID-19 vaccine monitoring systems for pregnant people to precisely follow-up vaccinated pregnant women and their babies (137). Considering breastfeeding, people are suggested to get vaccinated as their milk consists of antibodies, which provide immunity for their babies (136). Given all these considerations from the CDC, more studies are needed.

People with inflammatory bowel diseases

Similar to people with psoriasis and inflammatory arthritis, people with inflammatory bowel diseases (IBD) tend to administer anti-tumor necrosis factor drugs such as infliximab. In a study, Kennedy et al. assessed post-vaccination anti-SARS-CoV-2 antibody responses in IBD patients receiving infliximab and reported that this drug lowers antibody titers compared to similar people receiving vedolizumab (3.4% vs. 6%, p-value<0.0001) (138). Moreover, administration of thiopurine or methotrexate was reported to further blunt the immune responses against SARS-CoV-2 (138). Accordingly, a retrospective cohort study conducted by Khan et al. assessed the effectiveness of Covid-19 vaccines (Pfizer/BioNTech and Moderna) in people with IBD administrating different drugs (mesalamine, thiopurines, anti-tumor necrosis factor biologic agents, vedolizumab, ustekinumab, tofacitinib, methotrexate, and corticosteroid). They concluded that complete COVID-19 vaccination leads to 80.4% effectiveness in these people (139). Another noteworthy fact regarding people with IBD (ulcerative colitis) is that they are more likely to be hospitalized due to Covid-19 infection compared to people without it, with 28% higher adjusted odds rates (140). That is why CDC still recommends people with IBD get vaccinated as soon as possible (141).

People with cirrhosis

Similar to IBD patients consuming immune modulators, people with cirrhosis tend to have impaired immune functions. This immune dysfunction is responsible for 30% of mortality in these people (142). A retrospective cohort study conducted by John et al. assessed vaccinated people with cirrhosis (by Pfizer/BioNTech or Moderna) and compared them to people at similar risks of Covid-19 infection. The results showed that Covid-19 infection rates were similar during the first 28 days of follow-up after one dose of either vaccine. However, these vaccinated cirrhosis patients had a 64.8% reduction in Covid-19 infection rates afterward.

Moreover, cirrhosis patients had a 78.6% reduction in Covid-19 infection rates the week after the second dose. Vaccines also caused a 100% reduction in hospitalization or death due to Covid-19 (143). Accordingly, the American Association for the Study of Liver Diseases (AASLD) recommends prioritizing cirrhosis and liver cancer patients for Covid-19 vaccination (144).

Conclusion

Despite the negative consequences of each vaccine, the positive outcomes are guaranteed. Vaccination is recommended for all people, since it prevents mortality and serious sequelae due to COVID-19 infection in almost all cases: Pfizer/BioNTech, Moderna, Sinovac, AstraZeneca, Johnson & Johnson, Novavax, and Sinopharm all provide 100% protection against COVID-19-induced mortality, whilst Sputnik V and Bharat provide 99.9% protection. Therefore, controlling the spread of COVID-19 would not be possible unless worldwide vaccination rates were accelerated. In addition, authorities must consider

worldwide awareness as a tactic that might assist motivate individuals to get vaccinated.

Conflict of interest

The authors have no conflicts of interest.

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