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A Brief Reflection on the Side Effects of COVID-19 Vaccines

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Abstract

Less than two years after the COVID-19 epidemic, several vaccine candidates received emergency use permits in a wide range of countries. During public vaccination, diversity in the target groups, the presence of people with underlying diseases and vaccination of a large number of people in a short period of time will lead to an increase in the probability of complications due to vaccination compared to normal conditions. To date, no evidence of a cause-and-effect relationship between the administration of the COVID-19 vaccine and mortality has been reported in the literature. Also, the side effects of injectable vaccines have not been widely observed in recipients. However, some vaccine recipients have experienced complications such as gastrointestinal disorders, skin allergies, and even platelet clots. For example, only a few cases of anaphylaxis have been reported after receiving Pfizer-BioNTech and Moderna COVID-19 vaccines. Health authorities recognize that all of authorized COVID-19 vaccines can cause side effects. In general, the researchers believe that the benefits of the COVID-19 vaccination outweigh the side effects of these vaccines. In this review, we summarize the most important side effects known during the injection of 8 approved vaccines for COVID-19. The points presented will lead to providing effective knowledge about the risks that researchers are still investigating.

Keywords: COVID-19; Vaccines; Side Effects; Clinical Trials; Adverse Reactions

Introduction

According to the World Health Organization officials, most of the available vaccines in the field of COVID-19 are associated with side effects, and this is not uncommon. Most reported side effects are usually mild and short-lived [1]. Obtained results from clinical trials of vaccines around the world to immunize against COVID-19 are gradually being released. Therefore, all their side effects are not fully known [2]. Coronavirus (COVID-19) is a contagious disease caused by a new coronavirus (SARS-CoV-2). Globally, as of the publication of this review, a total of 259 COVID-19 vaccine programs have been developed [2]. The most important of these vaccines are: Oxford-Astrazenka, Moderna, Johnson & Johnson, Pfizer-Bivantek, Sputnik V, and Sinofarm vaccines, which have been licensed to enter the pharmaceutical market [1,2]. Vaccines are one of the best interventions developed to eradicate COVID-19, which could save millions of lives each year (Table 1). In addition, the best option in this regard is to use an effective and safe vaccine without severe side effects.

Name	Manufacturer	Type of vaccine	Approximate efficiency (%)
mRNA-1273	Moderna	mRNA	94.5
Ad26.COV2.S	Janssen (Johnson & Johnson)	Viral vector	66
AZD1222 (Vaxzevria)	Oxford-AstraZeneca	Viral vector	81.3
Sputnik V	Gamaleya	Viral vector	91.6
Covaxin	Bharat Biotech	Inactivated	80.6
BBIBP-CorV	Sinopharm (Beijing)	Inactivated	79.34
CoronaVac	Sinovac	Inactivated	50.38
BNT162b2	Pfizer–BioNTech	mRNA-based COVID-19 vaccine	66-91

Table 1: Some of the most important vaccines authorized for COVID-19 disease [3].

Side effects usually occur within the first few days of receiving the vaccine. These effects may be coincidental, and there is currently not enough conclusive evidence to link these effects to specific vaccines. However, regulatory agencies are taking precautionary measures to investigate these safety concerns. As of April 2021, a published recored by the US Centers for Disease Control and Prevention lists more than a thousand cases of inflammation of the muscle and outer wall of the heart. These side effects occur after receiving Pfizer-BioNTech or Moderna vaccines [4]. In another case, the U.S. Food and Drug Administration has limited the authorized use of the Johnson & Johnson vaccine because of the increased risk of platelet clotting in some patients after receiving the vaccine [5]. Of course, after some time this restriction was removed. The results showed that severe allergic reactions have rarely been seen in people with injection of COVID-19 vaccines [6]. A severe allergic reaction is called anaphylaxis and can cause low blood pressure, nausea and difficulty breathing, which has been observed in several cases of vaccine recipients [1].

While rare adverse events might not be recognized until after wide population use, based on both the current experience with COVID-19 vaccines and previous experience with other vaccines, most adverse events occur days to a few weeks of vaccination and will be identified in clinical trials. There will also be longer term follow up of those who participated in the clinical trials of each vaccine, which is standard practice in clinical trials, as well as population wide observational safety studies. Safety data from these longer-term clinical trials and population studies are being carefully reviewed by regulators as part of post approval monitoring of safety [6]. These effects may be accidental, and there is currently insufficient evidence to link these effects to specific vaccines. This review states the latest published results on the side effects of the most important COVID-19 vaccines used worldwide.

Vaccine Development for COVID-19

The COVID-19 vaccine, like any other vaccine, can cause mild side effects such as fever, pain, or redness at the injection site. Most of the reactions to the injection of COVID-19 vaccines are mild and disappear within a few days. No serious or long-term side effects have been reported in recipients of the COVID-19 vaccine [2,5]. Vaccination is specifically recommended for people with certain medical conditions that have been identified as increasing the risk of severe COVID-19, including obesity, cardiovascular, and respiratory disease [6]. The table 1 gives an overview of the 10 authorized vaccines, categorized by type, based on how they function. It also shows their efficacy. Each of the following vaccines has received use authorization in at least one country.

Sinopharm

Sinofarm has developed two vaccines produced by the Institute of Biological Products in Beijing and Wuhan, respectively. Published data for this vaccine show that it did not have any serious side effects. Data from a small phase 1/2 trial that involved about 600 volunteers appeared in a performed study by Xia, et al. [7]. They reported that the vaccine was safe and well-tolerated by trial participants. The most commonly side effects in these clinical trials were fever and pain at the injection site [7]. In this line, the WHO reviewed safety results from three clinical trials, which included data for 16,671 participants who received the Sinopharm vaccine. Based on these results, the most common side effects were headaches, fatigue, and injection site reactions relate to men aged 18–59 years [8,9].

A cross-sectional survey study was conducted by Saeed, et al. [8] for collection of data on the side effects of the Sinopharm vaccine. These experiments were performed on persons in two age groups (more and less than 49 years, (n= 1080)). Some people in this study had underlying diseases. In some

people who were vaccinated, some visible side effects after the first dose of the vaccine included pain, fatigue, and headache at the injection site. However, arm pain after vaccination, fatigue, lack of energy and enthusiasm, headache and discomfort were the most common complications after receiving the second dose in both groups. In both doses of the injected vaccine, side effects were more common in females compared with males Saeed BQ, et al. [10] (Table 2).

Side effect	The first dose (Total %)	The second dose (Total %)	after 1 st dose Sinopharm COVID-19 vaccination among 2 group of participants	Male (320)	Female (760)
Normal pain at the vaccination site	42.02.00	32.6	Normal Pain at the vaccination site	144	312
Severe pain at the vaccination site	2.6	8.15	Sever pain at the vaccination site	0	28
Tenderness	5.1	10	Tenderness	8	48
Redness	0.7	1.5	Redness	0	8
Induration and pruritus at the vaccination site	1.1	1.1	Induration and pruritus at the vaccination site	0	12
Fever			Fever	4	8
Headache	1.1	3	Headache	24	80
Fatigue	9.6	10	Fatigue	12	120
Nausea	12.2	16.3	Nausea	0	16
Diarrhea	1.5	1.1	Diarrhea	0	8
Cough	0.74	0.7	Cough	0	12
Allergy	1.1	0.7	Allergy	4	8
Muscle pain	1.1	0	Muscle pain	8	60
Abdominal pain	6.3	5.9	Abdominal pain	0	20
Back pain	1.85	1.5	Back pain	0	44
Lethargy	4.07	3	Lethargy	4	96
Others	9.2	13.7	None	144	132
None	0.7	0.7			
	24.4	14			

Table 2: Some of the negative effects of Sinopharm vaccine among 2 groups of participants (≤49 years old versus > 49 years old (n=1080)) [10].

Sinofarm COVID-19 vaccine without proper warming may cause pain at the injection site [11]. In a study, Abu-Hammad, et al. [12] investigated the side effects of Sinopharm COVID-19 vaccine among physicians, dentists, and nurses distributed in Jordan after the first or the second injection. Approximately 18% and 31% of participants reported no side effects after the first and second dose injection, respectively. More clinical trials are needed to include larger sample size and longer follow-up period to monitor possible serious and long-term side effects of the vaccine [12].

Between May 1 and May 22, (2021), adverse events registered by Iranian patients with multiple sclerosis after the first dose of Sinopharm vaccination was reported by Sahraian, et al. [13]. Basic characteristics of the vaccine side effects are summarized in Table 3.

Holt, et al. [9] investigated the effects of a standard vaccination schedule with the $HB0_2$ vaccine on antibody responses and clinical sequalae in haemodialysis patients. Although, intramuscular injection was performed along with standard dialysis anticoagulation, the results showed very few side effects. After vaccination, a small number of patients experienced side effects and no bleeding problems were observed. Six days after receiving the vaccine, one patient showed a moderately severe maculopapular rash [9].

According to the results, in order to further protect dialysis patients as a vulnerable group against COVID- 19 infection, they need a regular vaccination program with Sinofarm vaccine.

Side effect	Number (%)
Fever	99 (17%)
Fatigue	146(25)
Malaise	146(25)
Generalized body pain	106(18)
Shivering	13(2)
Nausea	23(4)
Diarrhea	18(3)
Abdominal pain	1(0.2)
Cough	16(3)
Dyspnea	10(2)
Headache	55(9)
Injection site reaction	43(7)
At least one gastrointestinal complain	33(6)
At least one respiratory complaint	24(4)

Table 3: The most common side effects after the first dose of the Sinopharm vaccination in patients with multiple sclerosis (13).

Sinovac

Published data to support adverse reactions to the Sinovac COVID-19 vaccine are lacking. On February 1, 2021, a preliminary analysis of the human phase 1 and 2 trials of Sinovac was published, showing the pain at the injection site in most people after taking the second dose of the vaccine. However, the results varied from 13% to 21% based on the duration of doses received. Adverse reactions were similar to many other vaccines, such as Sinofarm. The side effects were of minor or moderate intensity (i.e., without an effect on the ability to do daily tasks) [14].

Zhang, et al. [15] evaluated the side effects of Sinovac vaccine in healthy adults with a phase 1/2 clinical trial. According to the obtained results, the most common side effect reported was injection-site pain after 28 days of injection of the second dose (13–21%, depending on the dosing schedule). The occurrence of fever after vaccination was relatively low. Other side effects included fatigue, diarrhea, and muscle pain. Most of these side effects were mild and lasted only for 2 days [15].

In an independent descriptive study conducted by Serap, et al. [16], the side effects of Sinovac vaccine was investigated on health staff (n=355) in Turkey. The most common local side effect experienced after the vaccination was pain (54.6%), while the most common systemic effects were weakness (39.2%) and pain in your head or face (34.1%). Pain, among local side effects, was significantly higher among male healthcare who worked more than 40 hours a week [16] (Table 4).

Side effects	Total (%)
Fatigue	39.2
Headache	34.1
Arthritis	25.1
Sore Throat	10.4
Nausea	9.9
Fever	8.2
Vertigo	8.2
Nasal Flow	7.9
Appetite Changes	6.5
Diarrhea	5.9
Itchiness	5.9
Abdominal Pain	5.6
Cough	4.2
Changes in Mucosa	4.2
Changes in Taste Sensation	4.2

Table 4: The side effects after Sinovac COVID-19 vaccination [17].

Pfizer-BioNT

In a study conducted by Cameli, et al. [17], a 60-year-old patient developed pernio-like lesions in both hands two weeks after receiving the second dose of the Pfizer-BioNTech vaccine. Subsequently, mild to moderate local and systemic symptoms such as pain at the injection site, muscle weakness, and headache occurred after the first and second dose of the vaccine and disappeared after 48 hours. Erythematous-violaceous patches and swelling on the fingers accompanied by itching and burning sensation were the most common side effects with receiving this vaccine (Figure 1). These skin complications were also observed in the lower extremities [17].

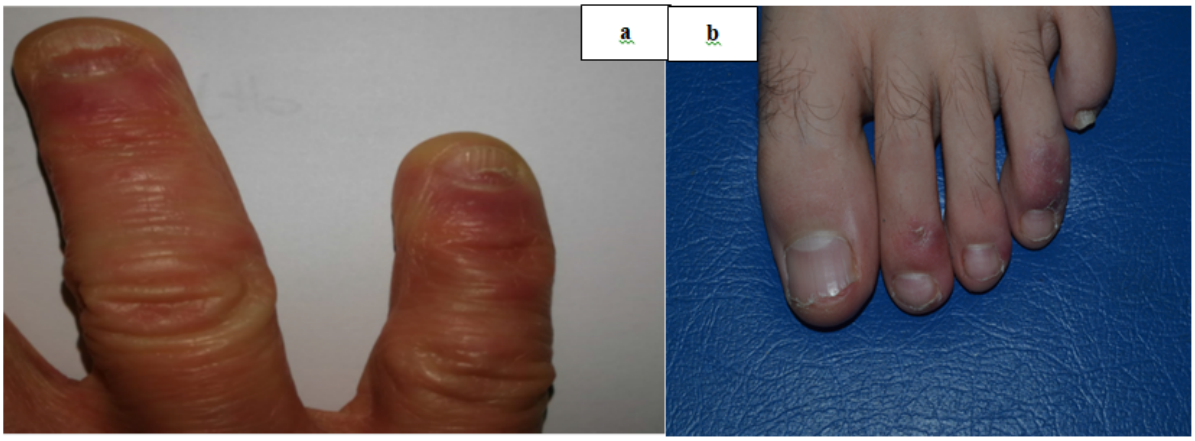

Figure 1: a) Pernio-like lesions were occurred after receiving the second dose of Pfizer-BioNTech vaccine.
b) chilblain-like lesions of toes were also appeared on the toe of a 14-year-old teenager. The figure is taken from reference Cameli, et al. [17] with permission from the Wiley Online Library.

During the first phase of European epidemic of COVID-19, a contemporary outbreak of chilblain-like lesions similar to this complication has been reported by Piccolo, et al. (Figure 1b) [18]. Therefore, a correlation between COVID-19 infection side effects and this cutaneous eruption has been hypothesized. In these clinical trials, the pernio-like manifestations occurred 14 days after the administration of the second dose of the Pfizer-BioNTech vaccine. The patient has never had symptoms related to chilblain-like eruptions before; therefore, it cannot be excluded that these manifestations were dependent on receiving the vaccine. Therefore, in this context, the relationship between the symptoms that appear on the skin and the side effects of receiving the vaccine cannot be ignored. So far, only a few of the available mRNA COVID-19 vaccines have shown pernio-like skin lesions, 5 of which were related to the Pfizer-BioNTech vaccine [18]. Identifying and having a database of such clinical findings is important for dermatologists to provide appropriate diagnosis and treatment management during COVID- 19 epidemic. In vaccinating specific groups, pre-vaccination counseling can be important. For example, in patients with allergies, a history of reaction at the injection site or urticaria may cause them to benefit from instructions and management of antihistamines and topical medications.

Covaxin

Covaxin is an inactivated virus-based COVID-19 vaccine developed by Bharat Biotech in collaboration with the Indian Council of Medical Research - National Institute of Virology.

In a review paper, Darbar, et al. [19] reported that Bharat Biotech listed the risks/side effects of the Covaxin (Table 5). Pregnant women and nursing mothers should not get this vaccine [19]. Recent studies show that COVID-19 antibodies can be passed from a pregnant mother to her baby, and early vaccination may protect the fetus through placenta [19-21]. However, it is not yet clear whether the number of antibodies that are passed on to the baby is enough to prevent COVID-19 in infants. Further research is needed to confirm this claim.

Number	Side effects
1	Injection site pain
2	Injection site swelling
3	Injection site redness
4	Injection site itching
5	Stiffness in the upper arm
6	Weakness in the injection arm
7	Body ache
8	Headache
9	Fever
10	Malaise
11	Dizziness and weakness
12	Rashes
13	Nausea
14	Vomiting
15	Allergic reactions
16	Swelling of face and throat
17	A fast heartbeat

Table 5: The side effects of Covaxin [19,20].

In a clinical study performed by Arora, et al. [22], an elderly male patient (about 60 years old) with type II diabetes and hypertension was hospitalized with fluid-filled lesions on

the thigh within 5 days of receiving the Covaxin vaccine. Other serious allergic reactions have been rarely reported. Histological studies, skin biopsy from the vesicle showed intraepidermal spongiotic vesicle containing acantholytic cells with large vesicular nuclei neutrophils and dyskeratotic cells. Occasional multinucleate cell with ground-glass chromatin and molded nuclei could be seen within the blister [22] (Figure 2).

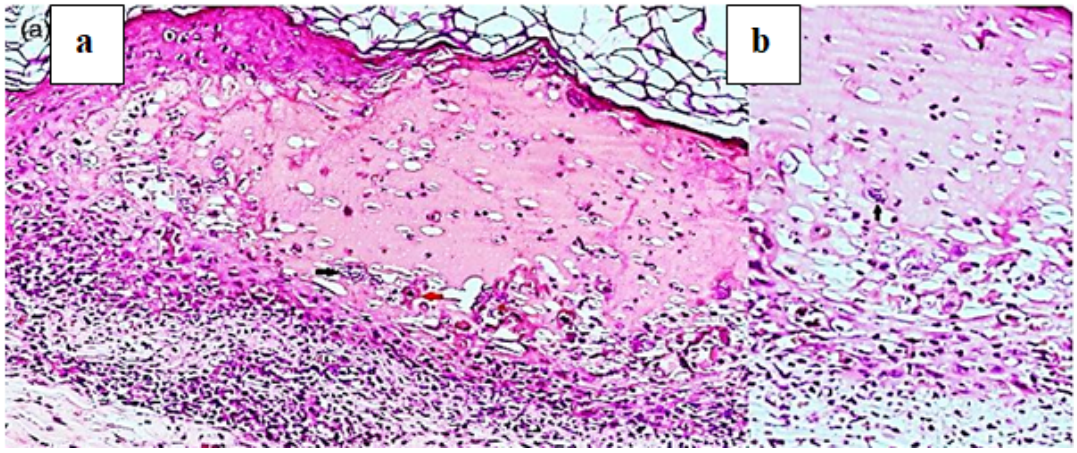

Figure 2: a) epidermal spongiotic blister with numerous epidermal and dermal eosinophils with large vesicular nuclei (black arrow), neutrophils, and dyskeratotic cells (red arrow).
b) Occasional multinucleate cell with ground-glass chromatin and molded nuclei within the blister (H&E ×200 and H&E ×400, respectively)**.** The image is taken from reference of Logunov DY, et al. [23] with copyright permission from the John Wiley & Sons library.

Sputnik V

In phase (3) of the clinical trials, the Sputnik V vaccine has shown excellent safety and efficacy against COVID-19 infection. In February 2021, In an observational study in Iran, Babama Ahmadi, et al. [24] presented independent evidence of adverse events and immunogenicity after sputnik V administration to health care workers (n= 13435). The most common side effect were mild to moderate with a pain in the injection site, exhaustion, body pain, headache, fever, chilling, and somnolence being the most common Pagotto V, et al. [25] (Table 6). These side effects were significantly higher in women and young people.

Side effect	the first dose (N=2194) (%)	second dose (N=1042) (%)	Total (N=3236)	Female (N=1982)	Male (N=1252)
Pain	58.2	54.1	56.9	62.6	48
Swelling	6.3	8.5	7		
Redness	5.7	6.5	6		
Fever	36.5	23.8	32.4	34.1	29.7
Chilling	33.1	22.7	29.8	33.8	23.5
Headache	38.1	30.8	35.7	38.8	30.9
Dizzying	14.5	12.4	13.8		
Body pain	48.6	38	45.2	48.3	40.4
Fatigue	54.2	44	50.9	54.6	45.1
Weakness	46.5	38.1	43.9	48	37.4
Nausea	9.2	6.5	8.3		
Vomiting	1.4	1.2	1.3		
Diarrhea	5.2	4.8	5		

Constipation	0.03	0.2	0.1		
Joint pain	32.2	26.5	30.3	32.7	26.6
Vasovagal syncope	0.7	0.6	0.6		
Anaphylaxis shock	0.2	0	0.1		
Rash	2.1	2.5	2.3		
Depression	6.5	5.2	6.1		
Drowsiness	21.4	17.9	20.3	21.9	17.7

Table 6: The side effects of the Sputnik V [24].

Logunov, et al. [23] conducted a randomized, double-blind, placebo-controlled study in phase 3 over 4 trials at 25 health centers in Russia. With the approval of the results by the Independent Data Monitoring Committee, no serious side effects associated with this vaccination were considered. Symptoms were usually seen in other programs within 24 hours of vaccination and resolved in less than three days. No deaths were reported with the Sputnik V vaccine [23]. All participants showed that the vaccine elicited a COVID-19 neutralizing antibody reaction with a low rate of adverse reactions.

Pagotto V, et al. [25] reported side effects of vaccination in healthcare workers (with median age 35 yrs, female 67%) who had been inoculated with the first component of the Sputnik V vaccine. A total of 469 local reactions were reported, 58% of the participants reported new or worsened muscle pain, fever referred by 40% of the participants, headache referred by 33%, diarrhea referred by 5%, had redness and swelling referred by 11% [25]. According to these results, the side effects of the vaccine after receiving the second dose were significantly reduced compared to the first dose. The difference between the results obtained from each dose of injectable vaccines in different groups may be explained by the nature and immunogenicity of these vaccines. Examining the results related to the side effects of Sputnik V, we found that these adverse events were more common in women than men and in younger participants than older people [26]. More clinical trials are needed to estimate the rare side effects of Sputnik V vaccines. In this line, cellular immunogenicity and long term surveillance studies in order to evaluation of the antibody titer are required for ensuring of protection persistence by the Sputnik V or probably needing booster dose of the vaccine.

Oxford/AstraZeneca

The vaccine is stable at refrigerator temperatures and has a good safety profile, with side effects including injection-site pain, headache, and nausea, all generally resolving within a few days. In very rare cases (about 1 in 100,000 people) the vaccine was associated with an increased risk of blood clots [27].

In a clinical trial performed by Alhazmi, et al. [28], they evaluated the side effects of Oxford/AstraZeneca on 515 participants with a median age of 26 years ranging from 18 to 70 years, of whom 57% were female (n = 294) (30). These data are also summarized in (Table 7).

Side effect	Total (n=255)	First dose (N=345 280) (28)	
		Systemic side-effects	
Fatigue	236	Any	116 473 (33·7%)
Pain or redness at the site of injection	217	Headache	78 734 (22.8%)
Fever	181	Fatigue	72 924 (21.1%)
Chills	96	Chills and shiver	50 761 (14.7%)
Headache	159	Diarrhoea	7546 (2.2%)
Nausea or vomiting	71	Fever	28 268 (8.2%)
Most vaccine recipients showed side effects on the first day (85%). The duration of complications was one day (75%).		Arthralgia	39 648 (11.5%)

	Myalgia	24 274 (7.0%)	
	Nausea	19 509 (5.7%)	
	Local side-effects		
		104 282 (58.7%)	
	Any	33 939 (19.1%)	
	Pain	9769 (5.5%)	
	Swelling	87 609 (49.3%)	
	Tenderness	6934 (3.9%)	
	Itch	1994 (1.1%)	
	Swollen armpit glands	7431 (4.2%)	
	Redness	14 033 (7.9%)	
	Warmth	4269 (2.4%)	
	Bruising		
	Allergic reactions		
	Rash	1432 (0.4%)	
	Skin burning	5940 (1.7%)	
	Red welts on face and lips	846 (0.2%)	

Table 7: The reported common side effects by receiving Oxford-AstraZeneca vaccine [26,28].

The results of this study showed that localized tenderness and pain around the injection site over a one-day period were the most common side effects. Fatigue and headache after vaccination were more common in younger participants (mean 26 years) than in older persons.

In a comprehensive review, Hekmat S, et al. [29] evaluated the possible risk of thrombotic events occurrence in women who take estrogen supplements after injection of AstraZeneca/ Oxford COVID-19 vaccine [29]. They found that menopausal women undergoing infertility treatment with estrogen supplements may experience symptoms of thrombosis and thrombocytopenia after receiving the Oxford-AstraZeneca vaccine. Therefore, women should first stop estrogen use before receiving the Oxford-AstraZeneca. To further reduce the risk of developing blood clots among women who are in the luteal phase, they should plan to receive this vaccine during the follicular phase of the menstrual cycle. The prevalence of vaccine-induced immune thrombotic thrombocytopenia is unclear; although it seems to be very rare [30]. Clots caused by the vaccine appeared in the brain and abdomen of people with low platelet counts. Current knowledge suggests that as part of the resultant immune response against antibodies, vaccine's protein components play a potential role in platelet activation [31]. However, the exact mechanism is not clear. Platelets are small components of blood clots that are constantly circulating in the bloodstream to be available if a wound needs to be healed. However, as soon as platelets are activated, they initiate a chain reaction of immune responses, releasing another protein known as PL4, which attaches to more proteins than the vaccine.

Johnson & Johnson

In people who received the vaccine, no one showed a severe allergic reaction, and the side effects of the vaccine were similar to those of other vaccines. 9% of vaccine recipients had a fever. The vaccine does not appear to cause serious side effects [32].

In a clinical trials performed by Shay et al. [33], 338,765 people received the Johnson & Johnson vaccine at least once after general vaccination. During days 0–7 after vaccination, 76% of enrollees reported at least one systemic reaction, and 61% reported at least one injection site reaction [33] (Table 8). The most common reactions reported were fatigue, pain, and headache. Most of the reported symptoms were recorded on the first day after vaccination. The proportion of reports related to specific reactions decreased after a few days of vaccination. On the first day after vaccination, 28% of recipients stated that they were unable to perform their daily activities. 16% stated that they are unable to do work. Only 1.4 percent of registrants said they used medical services after one week of vaccination. Studies on long-term safety, stratified by sex and age, are needed.

Side effects	First dose (N=345 280)
All recipients (n=338,765)	(%)
Fatigue	59.1
Injection site pain	57.9
Headache	52.2
Myalgia	47.8
Fever	37.7
Chills	34.2
Joint pain	26.1
Nausea	18.7
Diarrhea	9.4
Swelling	9.3
Abdominal pain	7.4
Redness	7.4
Itching	7.1
Vomiting	2.1

Table 8: Johnson & Johnson Vaccine recipients who completed at least one survey and reported health impact on days 0-7 vaccine - United States, March 2-April 12, 2021 [33].

The safety profile of the Johnson & Johnson is similar to that obtained from clinical trials. A rare but serious side effect in women after receipt of the vaccine was a blood clot in the large arteries with low platelet counts, which was quickly identified by the US Vaccine Immune Monitoring System [33].

Moderna

In general, clinical trials of mRNA-1273 vaccines commonly referred to as "moderna vaccine," have reported mild to mild side effects such as mild fever, myalgia, chills, and lethargy [34].

Malayala et al. [34] evaluated the effect of the Moderna vaccination on a 60-year-old male patient with several underlying diseases. Two days prior to the admission, he received the first dose of Moderna vaccine. Diffuse popular rash on the forearms, shins, and chest wall associated with some thrombocytopenia was observed two days after her second dose of the Moderna COVID-19 vaccine. The rash was brown to red-colored, purpuric, and not blanch-able. The sudden onset of symptoms, their absence in similar periods, and a short delay after vaccination in the first phase may lead experts to conclude that the patient developed these symptoms after receiving the second dose. Upon further investigation, they found that the rash symptoms typically occur 48 hours after vaccination and in rare cases may appear after 10 days [34,35].

In a study conducted by Kong et al. [36], a 66-years-old obese male with several underlying diseases including hypertension, hyperlipidemia, and diabetes mellitus showed a severe skin reaction within 24h after receiving the second dose of Moderna vaccine [36]. He had painful purple spots on his abdomen, buttocks, posterior shoulder, and lower limbs, many of which looks like large blisters. His COVID-19 test was negative. Skin blisters appeared after receiving the Moderna vaccine. Fever and muscle aches improved after 24 hours. However, the painful blisters did not heal and he was hospitalized five days after the onset of symptoms (Figure 1a). Histopathological evaluations demonstrated the toxic epidermal necrolysis but with features of Stevens–Johnson Syndrome. However, it has previously been reported that the occurrence of these symptoms rarely occurs during vaccination [37]. Pathology is characterized by full-thickness epidermal necrosis and very sparse lymphocytic inflammatory infiltrate. During a biopsy, bullous drug eruption with features of Stevens-Johnson syndrome was diagnosed because the lack of mucous membrane involvement or targetoid lesions (Figure 1b).

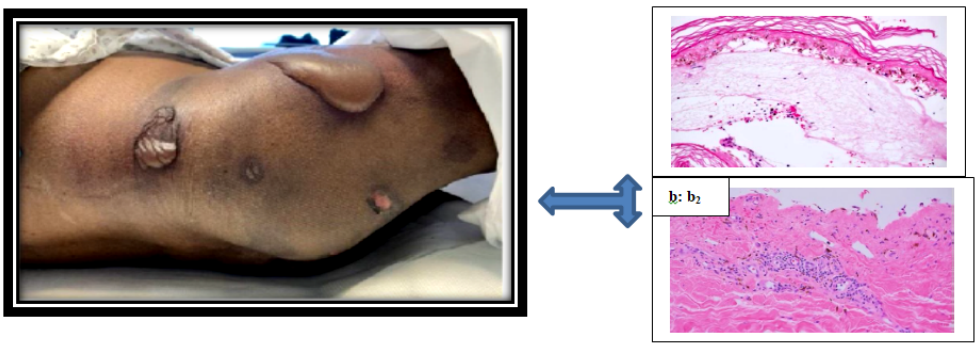

Figure 3: a) clinical image from purple blisters on the patient's buttocks with the injection of the Moderna vaccine. **b)** histopathology findings of delayed cutaneous reactions to the Moderna vaccine **b_1)** Full-thickness epidermal necrosis. **b_2)** red blood cells extravasation of sub-epidermal blister, melanophages, lymphocytic perivascular infiltrate with no evidence of inflammation of the blood vessels (H&E; ×100). The image is taken from references of Kong J, et al. [36] with permission from Elsevier.

Discussion

With the development of new drugs and vaccines, much of our information about side effects, especially rare ones, was obtained after the use of these drug combinations during clinical trials on a large scale of the treated population. Even a few cases in a clinical trial can foreshadow a phenomenon that may become a more common reaction in the larger population and should not be neglected, especially with estimates of 90% vaccinated population worldwide and demand continuing even during the pandemic. Note that the benefits of vaccination are much greater than its possible risks in the context of the COVID-19 pandemic. Respiratory and infectious disease specialists should work to encourage vaccination and dispel misconceptions [5]. We encourage physicians to document any adverse vaccine-related reactions and report them to the vaccine adverse event reporting to comprehensive system. This system will help health professionals and researchers to access the latest findings of side effects from the injection of COVID-19 vaccines. Most of the attention in this field should be paid to patients with special conditions.

Obesity, underlying diseases such as diabetes, sensitive groups such as pregnant women and children should be prioritized. As mentioned, side effects to the COVID-19 vaccine in clinical trials, although few at this early stage, may signal much more severe consequences to come as larger segments of the world's population become vaccinated. Questions may arise as patients hear of potential reactions, raising suspicion against vaccination or seeing side effects reactions in themselves or others. Public health professionals must be informed and prepared to address these situations as they arise, assisting patients through the vaccination process at this critical juncture for public health in our society. At the present, only a part of the side effects caused by vaccination were mentioned in some groups receiving the vaccine. For many of the serious adverse events reported after vaccination to date, these reviews are in progress. Therefore, vaccination-safe data might not be generalizable to the entire population of persons who have received the various COVID-19 vaccines.

Conclusion

The scholarly literatures related to any of the COVID-19 vaccines are not yet complete; however, the side effects results are almost the same in a few cases. The widespread distribution and prescription of COVID-19 vaccines allow us to examine more reliable results on their side effects, mechanism, and pharmacology. In one case, for example, it was found that most participants who were vaccinated with the Oxford-AstraZeneca vaccine had more systemic side effects, such as fatigue and fever, than those who received the Pfizer-BioNTech for a short time. Further clinical trials are needed on different population groups with different characteristics in terms of the presence of interfering factors such as underlying diseases (i.e. hepatitis, liver cirrhosis, thrombocytopenia) to evaluate the effectiveness of vaccines on controlling and preventing SARS-CoV-2 infection as well as their long-term side effects. Continuous monitoring to diagnose rare and common post-vaccination side effects is important in assessing the balance between the risks and benefits of each authorized COVID-19 vaccine. After reviewing the clinical data, we found that COVID-19 vaccines have very few side effects, and in the background of benefits over risks from the vaccine, this manuscript should not change the recommendations to get the vaccine. Monitoring for common and rare adverse events after receipt of all COVID-19 vaccines is continuing. However, we want to inform people about the possible relationship of these complications after receiving the vaccine, based on the published information from clinical findings, so that they can be sure about the safety of vaccines.

Conflict of Interest

The authors declare no competing interests.

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