

A Reflection on the Types of COVID-19 Vaccines with Emphasis on the Side Effects of Vaccines; A Review

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Abstract

Vaccines save thousands of lives each year. Producing a safe and effective coronavirus vaccine is a huge step forward in global efforts to end the COVID-19 pandemic. COVID-19 vaccines are safe, and getting vaccinated will help protect people against developing severe COVID-19 disease and dying from it. Side effects usually occur within the first few days of getting a vaccine. Since the first mass vaccination program started in early December 2020, hundreds of millions of vaccine doses have been administered. Like any vaccine, COVID-19 vaccines can cause side effects, most of which are mild or moderate and go away within a few days on their own. As shown in the results of clinical trials, more serious or long-lasting side effects are possible. Vaccines are continually monitored to detect adverse effects. Reported side effects of COVID-19 vaccines have mostly been mild to moderate and have lasted no longer than a few days.

According to the Centers for Disease Control and Prevention (CDC) Trusted Source and the World Health Organization (WHO) Trusted Source, common side effects of a COVID-19 vaccine include fever, fatigue, headaches, body aches, chills, and nausea. A person might also experience side effects around the injection site, which is usually the upper arm. These might include swelling, pain, redness, and itchy rash, and other mild forms of irritation. The chances of any of these side effects following vaccination differ according to the specific COVID-19 vaccine. Pfizer-BioNTech, Moderna, and Sputnik V vaccines are more effective in the human population than other vaccines. Novavax vaccine has fewer side effects than Pfizer-BioNTech and Moderna.

Key Words: COVID-19, Vaccine, Side Effects, Pfizer-BioNTech, Moderna, Sputnik V, Novavax.

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1- INTRODUCTION

Since the onset of the COVID-19 disease outbreak in December 2019, more than 90 million people have been infected with the disease and of these numbers, two million people have lost their lives in different countries of the world. The world is now in the phase of fighting the pandemic, with COVID-19 various companies producing the vaccines they claim can end the epidemic, and some begun countries have widespread vaccination by purchasing these vaccines. Vaccines usually should pass several years of testing and research to reach the clinical stage or to inject patients, but the rapid outbreak of COVID-19 in the world and resulting economic and the social problems have put companies producing the vaccine into competition, with each one trying to reach the desired result sooner than the others (4-1).

In the meantime, the media has mentioned the two vaccines Pfizer and Moderna more than others, but reports from the World Health Organization express that there are currently 69 vaccines in the human testing stage worldwide that include 43 vaccines in phases 1 and 2 and 26 vaccines in phases 2 and 3 (5, 6). According to official statistics, before June 6, 2021, about 15.2 billion doses of vaccines have been injected worldwide (7). On the other hand, the process of developing a vaccine for diseases such as COVID-19 usually takes between three and seven years in normal conditions and without emergency in laboratory processes. This extensive time interval helps scientists develop a vaccine that they can ensure is safe for the general public without any side effects. But the same process also has different stages, which are mentioned below:

Phase 1 - Safety tests: In the first phase, scientists inject the vaccine into a small sample of people to test its safety and the correct dose to be injected, or its effect on humans.

Phase II - Extensive testing: At this stage, the vaccine is injected into hundreds of people to test its effects on different types of humans of different ages. At this stage, both the elderly and children are put on the test list.

Phase 3 - Efficacy test: At this stage, the number of the sample population is in the thousands and how they are affected by the vaccine is examined. It is only at this stage that it can be concluded whether the vaccine can be effective in people with the virus or not, and the efficacy rate of the vaccine is evaluated at this stage. At this stage, the side effects of the vaccine are also identified (8, 9).

Over time, in line with coronavirus mutations, more and more information is being published daily about the efficacy or dangers of the various vaccines that are being tested around the world. Many countries, because of political issues or showing their scientific capability to produce a vaccine, have begun to test these vaccines on different groups of people, and now the effects of the vaccine are appearing more than before and scientists are faced with a new challenge every day.

The first issue that points to the dangers of the Pfizer vaccine more than any other problem for different groups of people, including people over the age of 80 or people with a history of allergic diseases, is the side effects of this vaccine on humans. The news shows that the ten leading countries in providing vaccines to specific treatment groups are Israel, UAE, Bahrain, Canada, USA, UK, Denmark, China, Russia, and India. Statistics on the health level of people who have received the vaccine show that the available vaccines have different side effects, and these side effects and risks are becoming more apparent every day (4, 10-12). This study aimed to review the common side effects of coronavirus vaccines on the human population.

2- MATERIALS AND METHODS

2-1. Data sources

In this review study, a systemic search of electronic databases of Medline (via PubMed), SCOPUS, Web of Science, ProQuest, Cochrane Library, SID. Magiran, CIVILICA, and Google Scholar search engine was performed with no time limit up to May 2021, using the following keywords alone or in combination: "COVID-19", "Side effects", "Advantage", "Disadvantage", "Vaccines", and "Type". The search was performed independently and in duplicate by two reviewers and any disagreement between the reviews was resolved by the supervisor.

2-2. Study selection

Database search was done for suitable studies. Abstracts of the studies were screened for identification of eligible studies, full-text articles were obtained and assessed, and a final list of eligible studies was made. This process was done independently and in duplication by two reviewers and any disagreement was resolved by a third reviewer. References were organized and managed using EndNote software (version X8).

3- RESULTS

Vaccines save thousands of lives each year. Production of a safe and effective COVID-19 vaccine is a big forward step in scientists' global efforts to end the epidemic and return to normal life (2, 3).

3-1. The different types of vaccines

Until April 2021, 17 vaccines had received therapeutic use licenses for injection and general use from at least one country. These vaccines include two RNA vaccines (*Covid-19 Pfizer vaccine and Covid-19 Moderna vaccine*), eight inactivated virus vaccines (*Cronavac, Covaccine, Koviran* Barakat, Kovivak, Minhai-Kangtai, QazVac and WIBP-Corv, and BBIBPspherical), six viral vector vaccines (Sputnik V, Sputnik Light, Johnson & Johnson, Convidecia, and Oxford-AstraZeneca), and two peptide vaccines (EpiVacCorona and RBD-Dimer) (13-15).

Most of the platforms of vaccine candidates in clinical trials are focused on the coronavirus spike protein and its primary antigen of variants as the COVID-19 infection (14). Platforms being developed in 2020 involved nucleic acid technologies (nucleoside-modified messenger RNA and DNA), nonreplicating viral vectors. peptides, recombinant proteins, live attenuated viruses, and inactivated viruses (14, 16-18). Vaccination, like any other medical measure, can always be associated with effects, and accordingly, side the usefulness and side effects of the vaccine should be evaluated appropriately. Using vaccines for COVID-19 immunization is still in preliminary stages, and not all of their side effects are still fully understood. At the same time, research and clinical activities are carried out in this field.

3-2. Authorized and approved vaccines

All COVID-19 vaccines approved by WHO for emergency use have passed through randomized clinical trials to test their quality, safety, and efficacy. To be approved, vaccines are required to have an efficacy rate of 50% or above. After approval, they continue to be monitored for ongoing safety and effectiveness. Approximately 96 COVID-19 vaccines are at various stages of clinical development (19). A summary of the information on nine vaccines that have received a license from credible international organizations for use in emergencies is listed in **Table.1**.

Table-1: Vaccines	authorized for	emergency use	or approved	for full use.

Vaccines	Country	Type Doses Storage temperature		Storage temperature	Pre-marketing study, participants	Pre-marketing study, participants
Oxford– AstraZeneca COVID-19 vaccine	UK	Adenovirus vector (Ch AdOx1) (20)	2 doses 4–12 weeks, (21, 22)	2–8 °C, (21)	Phase III (30,000), (23)	Phase IV (10,000), (24)
Pfizer–BioNTech COVID-19 vaccine	Germany, USA	RNA (modRNA in lipi d nanoparticles), (25)	2 doses 3–4 weeks, (26)	-70±10 °C (ULT)	Phase III (43,998), (27)	Phase IV (10,000), (24)
Johnson & Johnson COVID-19 vaccine	USA, Netherlands	Adenovirus vector (rec ombinant Ad26), (28)	1 dose, (29)	2–8 °C, (28)	Phase III (40,000) (30, 31)	
BBIBP-CorV	China	Inactivated SARS-Co V-2 (vero cells), (32)	2 doses 3–4 weeks, (33)	2–8 °C, (34)	Phase III (48,000), (35)	
Moderna COVID- 19 vaccine	USA	RNA (modRNA in lipi d nanoparticles), (36)	2 doses 4 weeks, (37)	-20±5 °C, (38) (freezer)	Phase III (30,000), (39)	Phase IV (10,000), (24)
Sputnik V COVID- 19 vaccine	Russia	Adenovirus vector (rec ombinant Ad5 and Ad 26), (40)	2 doses 3 weeks, (41)	≤-18 °C[e] (freezer)	Phase III (40,000), (42)	
CoronaVac	China	Inactivated SARS-Co V-2 (vero cells), (43)	2 doses 2–4 weeks, (44)	2–8 °C, (45)	Phase III (33,620)	Phase IV (37,867), (46, 47)
Covaxin	India	Inactivated SARS-Co V-2 (vero cells) (48)	2 doses 4 weeks (49)	2–8 °C, (49)	Phase III (25,800), (50)	Phase IV (1,000), (51)
Sputnik Light	Russia	Adenovirus vector (rec ombinant Ad26), (52)	1 dose, (52)	2–8 °C, (53)	Phase III (7,000), (54)	
Convidecia	China	Adenovirus vector (rec ombinant Ad5), (55)	1 dose, (56)	2–8 °C, (56)	Phase III (40,000), (56)	
WIBP-CorV	China	Inactivated SARS-Co V-2 (vero cells)	2 doses 3 weeks, (57-59)	2–8 °C	Phase III (51,600), (60, 61)	
EpiVacCorona	Russia	Subunit (peptide) (62)	2 doses 3 weeks (62)	2–8 °C (63)	Phase III (40,150(planne d), 3,000 (started))(64)	
ZF2001	China	Subunit (recombinant)	3 doses 30 days (65, 66)	2–8 °C (67)	Phase III (29,000), (65)	
Abdala	CUBA	Subunit	3 doses 2 weeks (68)	2-8 °C (69)	Phase III (48,290) (70)	
CoviVac	Russia	Inactivated SARS-Co V-2 (vero cells) (71)	2 doses 2 weeks (72)	2-8 °C (72)	Phase III (32,000) (732)	
QazCovid-in	Kazakhstan	Inactivated SARS-Co V-2	2 doses 3 weeks (74)	2–8 °C (75)	Phase III (3,000), (76)	
Minhai COVID-19 vaccine	China	Inactivated SARS-Co V-2 (vero cell)	2 doses 4 weeks (77)	2–8 °C	Phase III (28,000) (77)	
COVIran Barakat	Iran	Inactivated SARS-Co V-2	2 doses 4 weeks (78)	2–8 °C	Phase III (30,500), (78)	
Chinese Academy of Medical Sciences COVID-19 vaccine	China	Inactivated SARS-Co V-2	2 doses 2 weeks (79)	2–8 °C	Phase III (34,020), (79, 80)	
Soberana 02	Cuba	Subunit (conjugate)	2 doses 4 weeks (81)	2–8 °C[248]	Phase III (44,010) (81, 82)	

3-3. Common side effects of COVID-19 vaccines

Like any vaccine, COVID-19 vaccines can cause side effects, most of which are mild or moderate and go away within a few days on their own. As shown in the results of clinical trials, more serious or longlasting side effects are possible. Vaccines are continually monitored to detect adverse events. Reported side effects of COVID-19 vaccines have mostly been mild to moderate and have lasted no longer than a few days; typical side effects include pain at the injection site, fever, fatigue, headache. muscle pain, chills. and diarrhea. The chances of any of these side effects occurring after vaccination differ according to the specific vaccine (10-12).

3-4. Less common side effects

Upon receiving the vaccine, a person should be requested to stay for 15-30 minutes at the vaccination site so health workers are available in case of any immediate reactions. Individuals should alert their local health providers if they experience any unexpected side effects or other health events following vaccination such as side effects lasting more than three days. Less common side effects reported for some COVID-19 vaccines include severe allergic reactions such as anaphylaxis; however, this reaction is extremely rare (10-12).

3-5. Long-term side effects

Side effects usually occur within the first few days of getting a vaccine. Since the first mass vaccination program started in early December 2020, hundreds of millions of vaccine doses have been administered. There have been concerns about COVID-19 vaccines themselves making people sick with COVID-19. But none of the approved vaccines contain the live virus that causes COVID-19, which means that COVID-19 vaccines cannot make people sick with COVID-19. After vaccination, it usually takes a few weeks for the body to build immunity against SARS-CoV-2, the virus that causes COVID-19. So it is possible that a person could be infected with SARS-CoV-2 just before or after vaccination and get sick with COVID-19. This is because the vaccine has not yet had enough time to provide protection. Experiencing side effects after getting vaccinated means the vaccine is working and the immune system is responding as it should. Vaccines are safe, and getting vaccinated will help protect people against COVID-19 (15).

3-6. Vaccine doses

For some COVID-19 vaccines, two doses are required. It is essential to get the second dose if the vaccine requires two doses. For vaccines that require two doses, the first dose introduces antigens proteins that stimulate the production of antibodies – to the immune system for the first time. Scientists call this priming the immune response. The second dose acts as a booster, ensuring the immune system develops a memory response to fight off the virus if it encounters it again. Because of the urgent need for a COVID-19 vaccine, initial clinical trials of vaccine candidates were performed with the shortest possible duration between doses. Therefore, an interval of 21–28 days (3–4 weeks) between doses is recommended by WHO. Depending on the vaccine, the interval may be extended for up to 42 days - or even up to 12 weeks for some vaccines – based on the current evidence. There are many COVID-19 vaccines being developed and produced by different manufacturers around the world. WHO recommends that a vaccine from the same manufacturer be used for both doses if you require two doses. This recommendation may be updated as further information becomes available (16).

3-7. Summary of Vaccines safety and possible side effects

1. Oxford-AstraZeneca vaccine

This vaccine is produced using an attenuated virus called adenovirus, which causes the common cold in chimpanzees. This vaccine contains the genetic material of the coronavirus spike protein. After vaccination, the body's cells begin to produce this type of protein and as a result, the immune system is stimulated to attack the *SARS-CoV-2* virus.

This vaccine has been made in collaboration with *AstraZeneca* (a Swedish-British multi-national company) and the University of Oxford. So far, this vaccine has been injected into 34 million people, of whom 222 people have developed blood clots and more than 30 of them have died.

This vaccine has little effect on the African-mutated coronavirus, but it can fight with British and Brazilian samples.

Vaccine dosage: two doses 28 days apart.

Efficacy of two doses: about 70%.

Storage: at a temperature of 2 °C to 8 °C for 6 months (83-85).

2. Sputnik V of Russia

The Gamalia Institute for Epidemiological and Microbiological Research in Russia has developed the Sputnik V vaccine. This vaccine is also made using the attenuated adenovirus.

This vaccine had been extensively tested before new mutations in the coronavirus, so it is not yet clear whether it will be able to fight against new mutated coronaviruses or not.

Dosage: two doses 21 days apart.

Efficacy of two doses: 91.6% (all ages).

Storage: at a temperature of 2 °C to 8 °C for 6 months and at -20 °C for 2 years (86, 87).

3. Sinovac Biotech

CoronaVac, also known as the *Sinovac* COVID-19 vaccine.

The Sinovac vaccine is made in China and has had 50.38% efficacy in clinical trials in Brazil. The review results of this vaccine have been different in various countries (for example, the efficacy of the vaccine in people who received both doses varied between 66%, 86%, 88%, and 90%).

Inactivated coronavirus (*SARS-CoV-2*) was used to produce this vaccine.

Dosage: two doses, 14 days apart.

Efficacy of two doses: 50.38% to 91.25% depending on clinical trials in different regions.

Storage: at a temperature of 2 °C to 8 °C (88-91).

4. Novavax

The *Novavax* vaccine was produced with the help of the American company *Novavax* and is based on proteins similar to the virus. According to clinical trials, this vaccine has up to 89.3% efficacy against the British mutated coronavirus as well as South African coronavirus.

This vaccine has been produced using recombinant nanoparticle technology. The proper storage temperature for the vaccine is $2 \degree C$ to $8 \degree C$.

Dosage: two doses, 21 days apart.

Efficacy of two doses: in different areas between 51, 86, and 96%.

Storage: at a temperature of 2 $^{\circ}$ C to 8 $^{\circ}$ C for six months, and -20 $^{\circ}$ C for two years (91-92).

5. Johnson & Johnson

The Johnson & Johnson multi-national super-company has produced a self-titled vaccine which, unlike most other vaccines that require two phases of injections to be effective, needs to be injected only once.

Clinical studies have shown that 28 days after the injection of Johnson & Johnson

vaccine, up to 66% of people become immune to the coronavirus from mild to severe, which increases to 100% after 49 days.

After this vaccine caused blood clots in six women between the ages of 18 and 48 six to 13 days after the vaccine injection, the vaccination was temporarily stopped. But in the subsequent studies, it was found that the complications were very rare, and of the approximately seven million people who received this vaccine, only six people developed such a complication. Therefore, the injection of this vaccine was resumed.

Dosage: one dose.

Efficacy: 64% to 72% (after 28 to 49 days).

Storage: at 2°C to 8 °C for 6 months and - 20 °C for 2 years (93-98).

6. Bharat Biotech vaccine (Covaxin)

Covaxin (codenamed as BBV152) is an inactivated-virus-based COVID-19 vaccine developed by Bharat Biotech in collaboration with the Indian Council of Medical Research.

This vaccine is manufactured by *Bharat Company* in India and has been shown in its clinical trials to have 100% efficacy against the severe coronavirus infection. This vaccine is made using inactivated coronavirus (SARS-CoV-2).

Dosage: two doses, 28 days apart.

In July 2021, Bharat Biotech reported the be 64% (95% CI, 29-82%) vaccine to asymptomatic effective against cases, 78% (65–86%) effective against symptomatic cases, 93% (57–100%) effective against severe COVID-19 infection. and 65% (33–83%) effective against the Delta variant (98, 99).

7. Pfizer-BioNTech vaccine

Pfizer-BioNTech vaccine, which is made in the United States based on mRNA coding, can protect against the coronavirus up to 95%. This vaccine can provide immunity against the British, South Africa, and Latin America corona and is highly effective.

Dosage: two doses, 21 days apart.

Efficacy: about 97.4%. It can provide 100% immunity against the possibility of hospitalization and death due to this disease.

A case-control study published in May 2021 reported that the effectiveness of the Pfizer-BioNTech vaccine against severe, critical, or fatal variants of SARS-CoV-2 is 97.4%.

Storage: at -70 °C in special freezers (100-105).

8. Moderna

This vaccine can provide up to 94.5% immunity against the coronavirus. This vaccine is also produced using mRNA encoding and remains stable at 2°C to 8 °C.

Dosage: two doses, 28 days apart.

Evidence of vaccine efficacy starts about two weeks after the first dose. High efficacy is achieved with full immunization two weeks after the second dose and was evaluated at 94.1%.

Efficacy: 94.1% immunity against infection with the disease and 100% in the prevention of hospitalization and death.

Storage: at 2° C to 8° C and normal refrigerator temperature for 30 days, at -20 °C for 6 months (106-110).

9. Sinopharm

BBIBP-CorV, also known as the Sinopharm COVID-19 vaccine or BIBP vaccine, is one of the two inactivated virus COVID-19 vaccines developed by Sinopharm's Beijing Institute of Biological Products (also written as Beijing Bio-Institute of Biological Products, hence the two

different acronyms BBIBP and BIBP for the same vaccine).

This vaccine was produced by a Chinese pharmaceutical company using an inactivated vaccine. The efficacy of this vaccine, which is used in the *United Arab Emirates*, is 86%.

Dosage: two doses, 3 to 4 weeks apart.

In May 2021, peer-reviewed results of Phase III trials in the United Arab Emirates and Bahrain showed BBIBP-CorV is 74% (61–82%) effective against asymptomatic and symptomatic infections, 78% (95% CI, 65–86%) effective against symptomatic cases only, and nearly 100% against severe cases (zero cases in the vaccinated group, two cases in the placebo group). In these trials, a total of 12,726 people received the vaccine and 12,737 people received the placebo.

Efficacy: 86% immunity against infection with coronavirus disease.

3-8. Which Corona vaccine has the least risk and side effects?

Some of the side effects of different corona vaccines types are listed in **Table.2**.

Table-2:	Efficacy	and	some	side	effects	of	different	types	of	corona	vaccines	by	country	of
manufact	ure.													

	Manufacturing Country	The main complications
Pfizer- BioNTech	Germany/USA	During clinical trials, the side effects deemed very common ^a are (in order of frequency): pain and swelling at the injection site, tiredness, headache, muscle aches, chills, joint pain, and fever. Fever is more common after the second dose (117).
Moderna	US	The most common adverse events were pain at the injection site, fatigue, headache, myalgia (muscle pain), and arthralgia (joint pain) (118).
AstraZeneca- Oxford	UK	 Headache (52.6%) Fatigue (53.1%) Muscle or joint pain (44% or 26.4%) Fever (33.6%) Chills (31.9%) Nausea (21.9%). The percentages are based on reports from four clinical trials with a total of 23,745 participants (119).
Sinovac Biotech	China	The most common side effect reported within 28 days of the second dose was injection-site pain (13–21%, depending on the dosing schedule). Injection site reactions are common with other COVID-19 vaccines, including the two inactivated COVID-19 vaccines by Sinopharm. Other side effects included fatigue, diarrhea, and muscle pain. Most of these side effects were mild and lasted only for 2 days (120).
Sputnik V	Russia	The most common side effects were: • Flu-Like Illness • Headache • Fatigue • Injection-site reactions (121).
Sinopharm	China	The most commonly reported side effects in this trial were fever and pain at the injection site (122). The WHO reviewed safety data from three clinical trials, which included data for 16,671 participants who received the Sinopharm vaccine. Most of these

		 data relate to men aged 18–59 years. Based on these data, the most common side effects were: Headaches Fatigue Injection site reactions (123).
Johnson and Jonson	USA	The most common side effects are pain at the injection site, headache, tiredness, muscle pain and nausea, affecting more than 1 in 10 people. Coughing, joint pain, fever, chills, redness, and swelling at the injection site occurred in less than 1 in 10 people (124).
Covaxin	India	 According to the Indian government's Ministry of Health and Family Welfare (MoHFW), the vaccine's main side effects include: Fever Headaches Irritability Pain, swelling, or both at the site of injection (125).
Novavax	US	Based on their data, the Novavax vaccine has a significantly lower rate of side effects compared to the Pfizer-BioNTech and Moderna vaccines.1 The symptoms commonly reported were similar to those already associated with COVID-19 vaccines like fatigue, headache, and muscle pain (126).

a. According to the British National Formulary and MedDRA conventions, side effects are "very common" when they occur in more than 1 in 10 instances; "common", 1 in 100 to 1 in 10; "uncommon", 1 in 1,000 to 1 in 100; "rare", 1 in 10,000 to 1 in 1,000; and "very rare" when they occur in less than 1 in 10,000 instances (127).

3-9. The horizon ahead of vaccines

Fortunately, vaccination seems to be effective against the coronavirus. The history of previous studies on other viruses of this family for vaccine production and large investments by various countries and international organizations helped control this pandemic by producing vaccines (128). It is estimated that by the end of 2021, between eight and 21 billion doses of vaccine will be produced worldwide. The horizon before rich and developed countries is to achieve collective safety with vaccination before the beginning of summer or at the latest until the beginning of autumn, and it is predicted that they will complete the vaccination by the end of 2021. It should be noted that countries that rely solely on the COVAX portfolio cannot expect more than 20% of their population to be vaccinated, so investing in the production and use of domestic vaccines in any country can be an important priority in fighting this pandemic.



5- CONCLUSION

Up to April 2021, 17 vaccines had received therapeutic use licenses for injection and general use in at least one country. These vaccines include two RNA vaccines (Covid-19 Pfizer vaccine and Covid-19 Moderna vaccine). eight inactivated virus vaccines (Cronavac, Covaccine, Koviran Barakat, Kovivak, Minhai-Kangtai, QazVac, WIBP-Corv, and BBIBP-spherical), six viral vector vaccines (Sputnik V, Sputnik Light, Johnson & Johnson, Convidecia, and Oxford-AstraZeneca), and two peptide vaccines of EpiVacCorona and RBD-Dimer. Pfizer-BioNTech, Moderna, and Sputnik V vaccines have more efficacy in the human population. On the other hand, the side effects of vaccines are almost the same and include injection site reactions, headache, swelling, fatigue, chills, and nausea. The Novavax vaccine seems to have fewer side effects than Pfizer-BioNTech and Moderna vaccines.

6- AUTHORS' CONTRIBUTIONS

Study conception or design: AE, MMF, FF, and MM; Data analyzing and draft manuscript preparation: HJ, ZT, BM, and MM, Critical revision of the paper: AE and FF, Supervision of the research: FF, and AE; Final approval of the version to be published: AE, MMF, HJ, ZT, BM, MM, and FF.

7- CONFLICT OF INTEREST: None.

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