



Recent updates on effectiveness of COVID-19 vaccines

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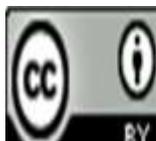


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Abstract

Coronavirus disease 2019 (COVID-19) has infected millions of people worldwide. Vaccines are urgently needed to mitigate COVID-19 pandemic and return to the pre-pandemic era. The aims of the current literature review were to discuss the administered vaccines and/or those under trials, and to summarize the effectiveness of the available COVID-19 vaccines. Scientists worldwide have made extensive efforts for vaccine development in record time. Several vaccine candidates have been developed; where many of them have passed stage III clinical trials and have recorded positive results. About 18 vaccines candidates are currently in phase III clinical trial. Almost all the developing vaccine candidates have T cell response and detectable numbers of neutralizing antibodies. The most common vaccine side effects include; fever, chills, fatigue, headache, muscle and joint pains. The post stage III successful vaccines have been administered to individuals worldwide.

Keywords: Coronavirus, COVID-19, Virus, Pandemic, Vaccine



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1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic that emerged late in December, 2019; is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infection had spread out in about 220 countries and several areas all over the world ([Ullah *et al.*, \(2021a\)](#)). According to the World Health Organization ([WHO. 2021a](#)); up to August 13, 2021, about 205,338,159 of confirmed cases, 4,333,094 deaths and 4,428,168,759 vaccine doses have been administered globally. In order to mitigate the current pandemic; vaccines are urgently needed to cure and bring an end to this worldwide disease ([Jeyanathan *et al.*, 2020](#); [Ullah *et al.*, 2021b](#)).

SARS-CoV-2 belongs to the Coronaviridae family, which contains many virulent strains such as; the severe acute respiratory virus (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), which have the capability to infect the humans and animals ([Borriello *et al.*, 2021](#); [Gull *et al.*, 2020](#)). A number of CoV antiviral vaccines had been developed for domestic animals against infectious bronchitis virus (IBV); porcine epidemic diarrhea virus, transmissible gastroenteritis virus (TGEV), feline CoV, bovine CoV (BCoV) and canine CoV ([Tizard, 2020](#)). These prior experiences of animal's vaccine development have provided vital hope for the development of human vaccines for COVID-19. In order to further control human morbidities and mortalities; an effective vaccine administration is urgently needed ([Docherty *et al.*, 2020](#)). The main purpose of vaccine development is to use it effectively for protection of humans from COVID-19 infection. An ideal COVID-19 vaccine must have the capability to reduce the infection rate and disease transmission, which could thus contribute to the control of viral infection ([Hodgson *et al.*, 2020](#)).

Several pharmaceutical companies have worked and are still working on the development of COVID-19 vaccine; where many vaccines are under trials, whereas several others have passed the last clinical trials and are being administered. The objectives of the

current study were to discuss the vaccines that are under clinical trials, and summarize the effectiveness of the available vaccines.

2. COVID-19 vaccines Phase III under trials

Scientists worldwide are exerting their efforts for the development of COVID-19 vaccine; where most of the scientists are using the S protein of SARS-CoV-2 as their target region ([Dhama *et al.*, 2020](#)). Currently, the other strategies under trials for developed COVID-19 vaccines include; mRNA vaccine, protein subunit vaccine, viral vectored vaccine and others ([Kaur and Gupta, 2020](#)). According to [WHO. \(2021b\)](#), as of July 30, 2021; there are 184 vaccine candidates under pre-clinical phases, 102 vaccines in clinical phases while 18 vaccines are in phase III clinical trials. Candidate vaccines and their clinical development are presented in Table (1).

3. Results of Phase III vaccines trials and their reported clinical implications

Covid-19 pandemic has mobilized the whole world for the synthesis of a safe and effective vaccine, which is the only solution to get rid of this pandemic and to bring life back to its normality ([Bhopal *et al.*, 2020](#)). The vaccines Phase III clinical trials were conducted in several countries including; Belgium ([Sadoff *et al.*, 2020](#)), Australia ([Keech *et al.*, 2020](#)), Germany ([Sahin *et al.*, 2020](#)), China ([Zhu *et al.*, 2020](#)), United Kingdom ([Folegatti *et al.*, 2020](#)), United states ([Mulligan *et al.*, 2020](#)), and Russia ([Logunov *et al.*, 2020](#)). Most of these studies were double blinded and only 8 of them were randomized controlled trials ([Bhopal *et al.*, 2020](#)). The different strategies used to generate these vaccine candidates involved: RNA vaccine ([Sahin *et al.*, 2020](#)), Viral vectored vaccine ([Folegatti *et al.*, 2020](#); [Logunov *et al.*, 2020](#); [Sadoff *et al.*, 2020](#)), protein based vaccine ([Keech *et al.*, 2020](#)), and Inactivated SARS-CoV-2 vaccine ([Xia *et al.*, 2020](#); [Zhang *et al.*, 2021](#)).

Table 1. Candidate vaccines under Phase III and their clinical developments; used through intramuscular route of administration

Vaccine candidate	Developer	Vaccine platform	Number of doses	Dosing schedule
SARS-CoV-2 vaccine (Inactivated)	Sinovac	Inactivated virus	2	Day 0 + 14
Inactivated SARS-CoV-2 vaccine (Vero cell)	Sinopharm	Inactivated virus	2	Day 0 + 21
ChAdOx1-S-(AZD1222) (Covishield)	AstraZeneca + University of Oxford	Viral vector (Non-replicating)	1-2	Day 0 + 28
Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	CanSino Biologics	Viral vector (Non-replicating)	1	Day 0
Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)	Gamaleya Research Institute	Viral vector (Non-replicating)	2	Day 0 + 21
SARS-CoV-2 rS/Matrix M1-adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M)	Novavax	Protein subunit	2	Day 0 + 21
mRNA -1273	Moderna	RNA based vaccine	2	Day 0 + 28
BNT162 (3 LNP-mRNAs)	BioNTech + Pfizer	RNA based vaccine	2	Day 0 + 28
Recombinant SARS-CoV-2 vaccine (CHO Cell)	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Protein subunit	2-3	Day 0 + 28/ Day 0 + 28 + 56
Ad26.COV2. S	Janssen Pharmaceutical	Viral vector (Non-replicating)	1-2	Day 0/ Day 0 + 56

All these vaccines were administered in the human body through intramuscular injection. Almost all of these vaccine candidates had T cell responses and detectable numbers of neutralizing antibodies ([Sahin *et al.*, 2020](#)). Some of the reported vaccines side effects include: fatigue, fever, feeling feverish or chills, headache, joint and muscle pain. These symptoms were common among most of the vaccine candidates, but the occurrence rate differed from one vaccine to another ([Bhopal *et al.*, 2020](#); [Sprent and King, 2021](#)). A recent study conducted by [Bhopal *et al.*, \(2020\)](#) reported that about 70 % of participants reported to suffer from fatigue after vaccination (48 % in control); 60 % muscle pain (25 % control), 18 % fever (< 1 % control), 68 % headache (38 % control) and 51 % feeling chills (8 % in control). In another study by [Folegatti *et al.*, \(2020\)](#), neutropenia was detected in 46 % of subgroup of 54 participants. The occurrence of these symptoms was temporary and were mostly reported either as mild or moderate. [Bhopal *et al.*, \(2020\)](#) documented that one participant injected with the Johnson & Johnson vaccine suffered from symptoms similar to COVID-19 infection and was hospitalized overnight.

4. COVID-19 vaccines ready to use

Scientists worldwide are hopeful to combat COVID-19 infections and there are reasons for this optimism. Currently as of July 30, 2021, there are 184 vaccine candidates that are under pre-clinical phase, 102 vaccines in clinical phase, and 18 vaccines are in phase III clinical trial ([WHO, 2021b](#)). Pfizer and BioNTech companies had published results of the phase III clinical trial of their candidate vaccine (BNT162b2). Their studies included 43,448 healthy participants with no prior COVID-19 infection at the time of vaccination. Half of participant (21,720) received the candidate vaccine (BNT162b2) while the other half (21,728) received placebo vaccine. Vaccination consisted of 2 doses with 21 days apart. After first dose of vaccination, 9 cases of COVID-19 were reported; where 1 case was reported in participants receiving the candidate vaccine, while 8 cases were reported on treatment with placebo ([Baden](#)

[et al., 2021](#)). After the second dose of vaccination, about 170 cases of COVID-19 were recorded; 8 cases were among participants that received the candidate vaccine, while 162 cases were reported in the control group. Therefore, 95 % efficacy was recorded for this vaccine. The reported side effects in < 2% of the vaccine participants included; headache, fever and fatigue. The symptoms were transient and fixed within two days; with no recorded death cases due to COVID-19. All the trial participants will be followed for two years to assess their long-term protection and safety. This candidate vaccine was approved for emergency use in several countries including; Canada, United Kingdom and Bahrain ([Bernal *et al.*, 2021](#)); the vaccine is now currently administered globally. Two Chinese companies named Sinopharm and Sinovac have tested their phase III clinical trial outside of China in more than 10 countries including; United Arab Emirates, Turkey, Peru, Bahrain, Egypt, Morocco and Argentina, which involves 60,000 participants. The director of the vaccine development program reported that about one million people have been given the vaccine outside of the trial; however, no side effects were noticed in them. Phase III clinical trial of the Sinovac vaccine conducted in Turkey showed 91 % efficacy rate, which included 7,371 participants. According to the data recorded from 1,322 participants, 752 volunteers were administered with Sinovac vaccine while 570 were injected with placebo. Placebo looks like the real medical treatment that is being studied except it does not contain an active medication. Among the placebo group; 26 suffered from COVID-19. The clinical trials continued until the number of effectiveness reached 40, later the scientists analysed those 40 effectiveness (Table 2), as reported by [Acharya *et al.*, \(2021\)](#). The developers of Sinopharm and Sinovac vaccines claimed also that their vaccines can be stored above freezing; making these vaccines easier to transport and store in the less-developing countries. The United Arab Emirates, China and Bahrain have approved the emergency use of these vaccines in their countries, as highlighted by [Mendell, \(2020\)](#); Sinopharm and Sinovac are currently effectively administered.

Table 2. Results of clinical trials of the candidate vaccines

Pharmaceutical Company	Total number of participants	Number of placebo administered participants	Number of vaccine administered participants	Efficacy of placebo on participants after 1/2 dose	Efficacy of vaccine on participants after 1/2 dose	References
Pfizer and BioNTech	43,448	21,728	21,720	8 cases / 162 cases	1 case / 8 cases	(Bernal <i>et al.</i>, 2021).
Sinovac	7,371	570	752	26 cases	3 cases	(Acharya <i>et al.</i>, 2021)
AstraZeneca	11,636	5,829	5,807	101 cases	30 cases	(Beusekom, 2021)
Moderna	30,000	15,000	15,000	185 cases	11 cases	(Herper and Garde, 2020).

Another pharmaceutical company named AstraZeneca together with the University of Oxford, United Kingdom, have developed adenovirus vectored vaccine ChAdOx1 nCoV-19; made of DNA encoding coronavirus protein. The product is cheap as the company has agreed to supply the vaccine for US\$ 2-3 per dose. This vaccine is easy to distribute and to store; as it does not need low temperature like the RNA vaccines, which need to be stored at temperature near -70°C until they are administered ([Knoll and Wonodi, 2021](#)). A clinical trial was conducted in Britain and Brazil that included 11,636 participants aged 18-55. Two doses of the vaccine were administered with 4-12 days apart. The achieved efficacy rate was 90 %; when the initial half dose and the full second dose were used, while it was 62 % effective when two full doses were administered ([Beusekom, 2021](#)). The investigators found difficulties to explain the reasons of the high efficacy of the initial lower dose; as this initial low dose trial also did not include participants over the age of 55. However, exclusion of aged population raised concerns about the higher efficacy rate of the lower dose ([Knoll and](#)

[Wonodi, 2021](#)). Another concern of the vaccine developers was fighting the asymptomatic infections. The Oxford-AstraZeneca team was the only one of the three leading vaccine developers that monitored the asymptomatic infections, by collecting samples from the studied participants to detect their asymptomatic infections. Data of their asymptomatic infections showed that the low-dose vaccine was about 60 % effective, however it was not clear whether the standard dose was also effective or not. The company submitted the results of its clinical trial to the regulators around the world, as reported by recent studies conducted by [Ledford, \(2020\)](#); [Knoll and Wonodi, \(2021\)](#).

Moderna pharmaceutical company released the outcome of its study on the 16th of November (2020) including 30,000 volunteers. Half of the participants were given placebo, while the second half was injected with the candidate vaccine at two doses with 14 days apart. About 196 cases of symptomatic COVID-19 were recorded in which 185 were in the placebo group; while 11 cases were in the tested vaccine group. Furthermore, 30 cases of severe COVID-19 with a

single mortality case were recorded in the group treated with placebo; however, no severe cases were observed in the treated vaccine group. The efficacy rate of the company candidate vaccine preventing COVID-19 was 94.5 %. The most observed side effects in the vaccine treated group include; fatigue, headache, bone and muscle pain, and redness at the site of injection. These reactions were serious in participants who received the second dose of the candidate vaccine ([Herper and Garde, 2020](#)).

In case of both Moderna and Pfizer vaccines, it was not confirmed how long the immunity will last. Both companies had used messenger RNA (mRNA) platform for synthesis of their vaccines. This mRNA was designed to encode for a protein that is present on

the surface of SARS-CoV-2. When this mRNA enters our bodies; the immune system recognizes it as a foreign particle, and then later in the life on exposure to this virus; the immune system starts producing antibodies against this foreign particle ([Herper and Garde, 2020](#)). It is expected that both Pfizer and BioNTech companies will manufacture up to 1.3 billion doses in 2021 for the worldwide use ([Chagla, 2021](#); [Herper and Garde, 2020](#)). Results demonstrated in Fig. (1) show the COVID-19 cases recorded in the control and the vaccines treated groups of the different pharmaceutical companies such as; Pfizer/BioNTech, Sinovac, AstraZeneca and Moderna. Meanwhile, the Sinopharm company did not share data of its clinical results.

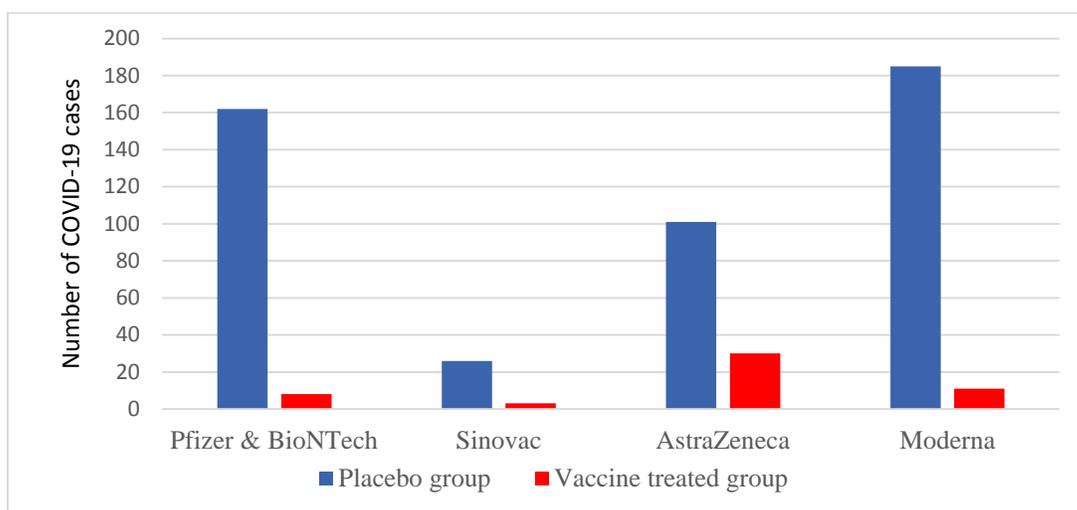


Fig. 1. The recorded COVID-19 cases in placebo and vaccine treated groups of the different pharmaceutical companies including; Pfizer & BioNTech, Sinovac, AstraZeneca and Moderna

5. COVID-19 vaccines effectiveness

The effectiveness of COVID-19 vaccine is very complex; because an effective vaccine not only protects from severe disease, but its effectiveness must be observed in older adults (age > 60 years) and in vulnerable individuals ([Hodgson *et al.*, 2020](#)). Currently there are multiple candidate vaccines that are ready for emergency use authorization from the

world regulators. The focus has now been directed towards allocation; distribution and verification of these new vaccines ([Weintraub *et al.*, 2021](#)).

6. Vaccines delivery, distribution and administration

Previous studies conducted by [Fanciullino *et al.*, \(2021\)](#); [Shin *et al.*, \(2020\)](#) reported that the efficacy of COVID-19 vaccine depends on willingness of the

public for administration of this vaccine and on how fast the vaccine is delivered and distributed worldwide. As several vaccines require continuous refrigeration, the need for a continuous cold chain makes it difficult for distribution of the vaccine to the developing and underdeveloped countries.

According to WHO, 2.8 million vaccines were lost in 5 countries due to absence of cold chain facility ([Shin *et al.*, 2020](#)). The vaccines developed by Pfizer/BioNTech and Moderna companies need continuous refrigeration at very low temperature i.e., Pfizer's vaccine must be kept at $-70\text{ }^{\circ}\text{C}$, while Moderna's vaccine at $-20\text{ }^{\circ}\text{C}$. These vaccines are based on RNA platform, which makes distribution of the vaccine to the developing countries acts as a hinder due to lack of such facility. Pfizer has developed its shipping containers that can keep the temperature of $-70\text{ }^{\circ}\text{C}$ for 10 days. For longer periods of cold storage; the airport freezer and warehouses can be used but will cost up to US\$10,000 ([Holm and Poland, 2021](#)).

In case of AstraZeneca vaccine, after the results of phase III clinical trial; the need for cold chain had been dissipated because this vaccine was based on adenoviral platform that uses the weakened form of the virus, and need to be kept at temperature of a home refrigerator ($2\text{-}8\text{ }^{\circ}\text{C}$); thus making it easier to distribute. However, questions were raised on the transparency of AstraZeneca's data because the most effective results were from the dosing error ([Rastegar *et al.*, 2020](#)). Similar to AstraZeneca; Sinovac and Sinopharm developed vaccines that can be delivered at a temperature around $2\text{-}8\text{ }^{\circ}\text{C}$, because their vaccines were based on inactivated form of COVID-19; thus filling the gap left by Pfizer and Moderna ([Mcgregor, 2020](#)).

7. Side-effects of COVID-19 vaccines on treated patients

After the emergency authorization; some COVID-19 vaccines have raised hope for ending this pandemic; however, along with this hope there have been some concerns over their potential side effects.

7.1. Pfizer and BioNTech vaccine

Pfizer and BioNTech COVID-19 vaccines are based on mRNA technology. The overall result of the trial was safe, which involved almost 40,000 individuals. Some mild side-effects of these vaccines were recorded including; pain at the site of injection, swollen lymph nodes, headache, muscle pain and fatigue. These side-effects were transient and intense for the young people.

In addition, there were some severe but temporary side effects such as facial paralysis (Bell's palsy), which was also observed in 18,000 volunteers; however it is not confirmatory that this side effect was due to injection with the vaccine; as Bell's palsy occurs normally with the same frequency in the general population. Furthermore, 8 cases of appendicitis also occurred in the participants receiving this vaccine, which was double the number of those receiving placebo ([Menni *et al.*, 2021](#)). There was one recorded case from USA and two from Britain who suffered from anaphylactic shock (redness of skin and shortness of breath), which may be attributed to an allergic reaction to any component of the vaccine that was not known ([Freund, 2021](#))

7.2. Moderna vaccine

The Moderna vaccine is like Pfizer vaccine in principle; as both companies use mRNA platform for synthesis of their vaccines. The vaccine was well tolerated by the participants during the clinical trials. The common side effects observed were; pain, fatigue, redness at the site of injection, swelling, tiredness throughout the body and headache. These side effects were mild to moderate; however, a small group of people had severe side effects ([CDC, 2021](#)). Few patients suffered from facial paralysis and allergic reactions, which were not permanent.

[Freund, \(2021\)](#) revealed that this reaction might not be due to the candidate vaccine but may be attributed to the lipid nanoparticles that carries this mRNA to body, which later on become degraded.

7.3. Oxford University and AstraZeneca vaccine

AstraZeneca's vaccine trial was halted in September, (2020) for a small period due to an incident; where one person soon after vaccination suffered from inflammation of the spinal cord. Later, independent panel of experts confirmed that the inflammation was not due to vaccination ([Leng *et al.*, 2021](#); [Freund, 2021](#)). The most observed common side effects of AstraZeneca COVID-19 vaccine include; pain, muscle pain, joint pain, redness, itching, swelling at the site of injection, warmth, fever, fatigue, chills, nausea and headache. These side effects were recorded in 1 out of 10 people, and were mild or moderate in nature, which become dissipated after few days of vaccination ([Singh, 2021](#)). The vaccine reactions were milder in older people than in young ones ([Freund, 2021](#)).

7.4. Sinopharm vaccine

A recent study conducted by [Foley, \(2020\)](#) highlighted that Sinopharm vaccine company is the only pharmaceutical company that did not share its data with the general public, and submitted its data

directly to the China's drug regulatory authority. There is no information about the study size, participant demographics or side effects. The only shared data available is that the company used an inactivated form of the virus for vaccine synthesis, and used two doses of immunization. All the vaccine participants produced high titer of antibodies, the positive conversion rate was 99.52 % and the efficacy of the clinical trial results was 79.34 %. These recorded results fulfill the relevant technical standards of China and WHO.

7.5. Sinovac vaccine

Sinovac vaccine also used inactivated form of the virus just like the Sinopharm vaccine, where no adverse effects were observed. The participants were monitored regularly for 28 days after the second dose and the side effects were recorded daily. The most observed common side effects were; headache, muscle pain, tiredness and fever ([Yurttas *et al.*, 2021](#)). According to results of phase III clinical trial of the pharmaceutical companies; the highest efficacy rate was observed for Pfizer/BioNTech (95 %) and the lowest for Sinopharm (79.9 %), as shown in Fig. (2).

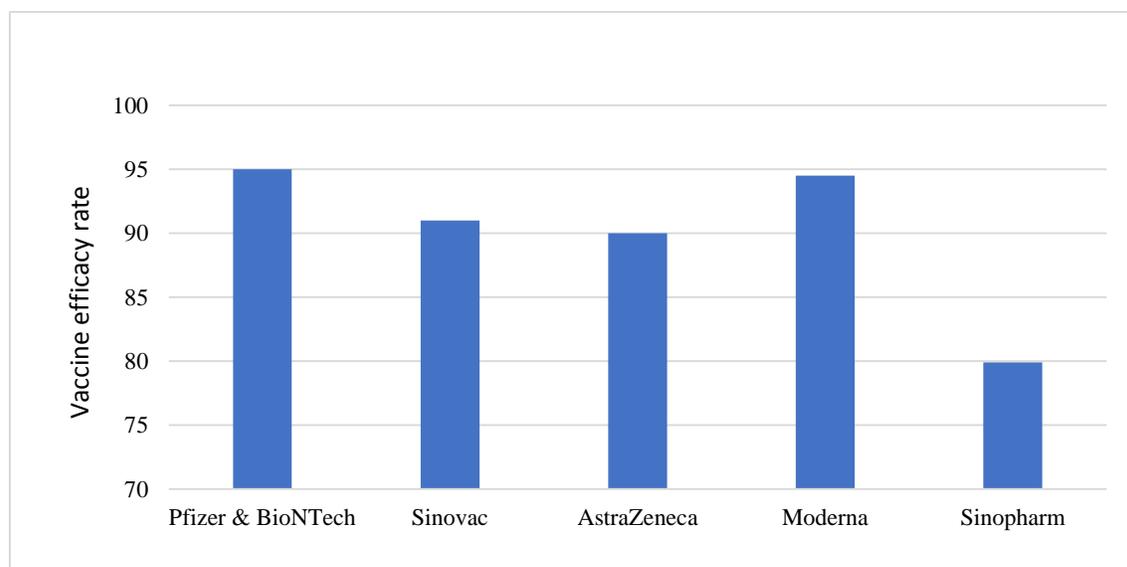


Fig. 2. Efficacy rates of the candidate vaccines produced by the different pharmaceutical companies including; Pfizer & BioNTech, Sinovac, AstraZeneca, Moderna and Sinopharm

These companies studied their candidate vaccines in participants aged between 18-60 years. The most common side-effects of the vaccines were headache, fever, chills, joint and muscle pain, redness at the site of injection and others; however, these side effects were transient. These side effects of vaccines were observed in adult population (18-60 years); excluding minors with the age lower than 12 years. The Food and drug administration (FDA) has ruled out these serious events and declared that they were not related to the vaccine use. However, these events cannot be completely ignored. In general, the efficacy of a medicine/vaccine is measured by weighing the benefits against the risks ([Zhu *et al.*, 2020](#)).

Conclusion

Scientists throughout the world have exerted their full efforts for the development of COVID-19 vaccine. Currently, many vaccines are successfully administered globally. Almost all the vaccine candidates had T cell responses and detectable numbers of neutralizing antibodies. Some of the common vaccine side effects include; fatigue, fever, chills, headache, muscle and joint pain. The occurrence of these symptoms was temporary and were mostly reported either as mild or moderate. The older participants showed milder forms of these symptoms compared to the young ones.

Conflict of interest

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

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Ethical approval

The study was approved by the Ethical Committee of Allied Hospital, Faisalabad, Pakistan.

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