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DOUBTS ABOUT COVID-19 VACCINE: A CRITICAL EVALUATION

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ABSTRACT

The emergence of COVID-19 put a lot of pressure on many the entire world and racing for solutions became highly competitive, resulting in getting trapped in acclaimed solutions for the disease. One area of common interest is the inability to get drug treatment for the disease but a preventive measure vaccine. In this respect high expectations that heralded the development of COVID-19 vaccines has been dragged into mud as a result of doubts about the efficacy and safety of the vaccine. To this end we take the task of thoroughly evaluating various types of vaccine that has been approved and considered safe for the human administration, by following after dose effects and reviewing various questions arising from the candidates that received the jab. In such cases associated health challenges if any were searched for and complained as per the refusal in some quarters. It was discovered that most of the doubts were as a result of the inability of the vaccine to prevent the spread of the diseases and the huge record failure and side effects associated with some vaccines. Poor information as per the side effects of the vaccine fuelling the doubts and hesitancy to that vaccine. Doubts in vaccine acceptability are high considering the number of reviews we undertake and more work need to be done to remove the doubts and assurance of improvement from the disease after the jabs are very sacrosanct.

Keywords: Vaccine, Covid-19, SARS-CoV-2

INTRODUCTION

Coronaviruses are a diverse group of viruses infecting many different animals, and they can cause mild to severe respiratory infections in humans. In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory illness, making emerging coronaviruses a new public health concern in the twenty-first century (Cui and Shi, 2019). At the end of 2019, a novel coronavirus designated as SARS-CoV-2 emerged in the city of Wuhan, China, and caused an outbreak of unusual viral pneumonia. Being highly transmissible, this novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has

spread fast all over the world (Wu *et al.,* 2020; Hui *et al*., 2020). It has overwhelmingly surpassed SARS and MERS in terms of both the number of infected people and the spatial range of epidemic areas. The outbreak of COVID-19 has posed an extraordinary threat to global public health (Deng and Peng, 2020; Han *et al*., 2020).

COVID-19 is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARSCoV-2 infection maybe asymptomatic may cause a wide spectrum of symptoms, such as mild symptoms of upper respiratory tract infection and life-threatening sepsis. As of November 2021, over two hundred and sixty-two million confirmed cases of COVID- 19 had been reported globally, with over five million associated deaths, which has led to huge psychological, sociological, and economic turmoil around the globe (WHO, 2021).

The World Health Organization (WHO) declared the novel human coronavirus disease (COVID-19) outbreak, which began in Wuhan, China on December 8, 2019, a Public Health Emergency of International Concern (PHEIC) on January 30, 2020 (WHO, 2020). COVID-19 had a devastating impact on almost all countries in the world. Because the new coronavirus was highly contagious and spreads quickly, it was not easy to find in mild cases and asymptomatic infections. In addition, it was easy to cause "hidden" transmission in communities and medical institutions. Even if the virus can be completely eliminated from the population, the transmission mechanism from the host to the person is still unclear due to the population's general susceptibility. Currently, there is a risk of recurrence or periodic epidemics, meaning that vaccines need to be administered as soon as possible.

At the peak of the pandemic, globally, 7.8 billion people were at risk of SARS-CoV-2 infection including the associated morbidity and mortality. People are today looking forward to developing an effective and safe COVID-19 vaccine to contain the ever-present risk of another COVID-19 pandemic and prevent another outbreak. An indication of the seriousness of the issue is seen where more than 200 COVID-19 vaccines were listed in the WHO as under development (Han *et al*., 2021).

Vaccines are one of the most reliable and cost-effective public health interventions ever implemented that are saving millions of lives each year (Hussein *et al*., 2015; Ehreth, 2003). They have been and are a key strategy for improving health outcomes and life expectancy by controlling and preventing infectious diseases, such as smallpox, polio, and plague (Harrison and Wu, 2020). Following the deciphering of the genome sequence of SARS-CoV-2 in early 2020 (Wu *et al*., 2020) and the declaration of the pandemic by WHO in March 2020 (Cucinotta and Vanelli, 2020), scientists and pharmaceutical companies started the race against time in efforts to develop vaccines (Coustasse *et al*., 2021; Zimmer *et al*., 2020). Given the elevated morbidity and mortality associated with COVID-19, the development of a safe and effective COVID-19 vaccine is a critical step to halt the pandemic. As of December 22, 2020, at least 85 vaccines were in preclinical development in animals and 63 in clinical development in humans, out of which 43 are in phase I, 21 in phase II, 18 in phase III, while 6 have been approved for early or limited use, 2 have been approved for full use, and one vaccine has been abandoned (Zimmer *et al*., 2020).

Coronavirus vaccines

Given the absence of a dedicated treatment for SARS-COVID-19, coronavirus vaccines

serve as a potential means of safeguarding individuals from infection and severe symptoms by stimulating the immune system to generate antibodies (Elgendy *et al*., 2021; Solomon *et al*., 2021; Andrzejczak-Grza˛dko *et al*., 2021; Mehboob *et al*., 2020). After vaccination, the antibodies produced adhere to the invader spike protein and prevent the virus from gaining entry into the cells (Noda *et al*., 2021). Four coronavirus vaccines are authorized for use all over the world: BNT162 (Pfizer BioNTech, New York, NY, USA), ChAdOx1 (AstraZeneca, Oxford, UK), mRNA1273 (Moderna, Cambridge, MA, USA), and Ad26.COV2-S (Johnson & Johnson, New Brunswick, NJ, USA).In addition, there are other vaccines, such as BBIBP-CorV (Sinopharm, Beijing, China), CoronaVac (Sinovac, Beijing, China), Sputnik V (Gamaleya, Moscow, Russian), and COVAXIN(Bharat Biotech, Hydrabad, India), which are authorized for use in many countries (Mehboob *et al*., 2020).

Worldwide, four vaccines have approved. They are: COVID - 19 messenger RNA (mRNA) vaccine BNT162b2 (Pfizer), mRNA - 1273 vaccine (Moderna), ChAdOx1n CoV - 19 vaccine/AZD1222 (AstraZeneca), and Sinovac that have low safety risk and higher efficacies of 95, 94.1, 70.4 and 78%, respectively were used in many countries (Zhao *et al*., 2021; He, 2021). The Oxford AstraZeneca, Johnson and Johnson, and Sputnik vaccines use engineered live viral vectors to demonstrate the coronavirus spike protein, while the vaccines developed by Pfizer and Moderna make use of recent technology, such as messenger RNA (Sharma *et al*., 2021; Dyer, 2020). The Oxford AstraZeneca, Johnson and Johnson, and Sputnik vaccines use engineered live viral vectors to demonstrate the coronavirus spike protein, while the vaccines developed by Pfizer and Moderna make use of recent technology, such as messenger RNA (Sharma *et al*., 2021; Dyer, 2020).

Mechanism of Action of Covid-19 Vaccines

The design of the COVID-19 vaccines must take into account both humoral and cellular immunity. In addition, COVID-19 is mainly spread through the respiratory tract and contact, so the role of mucosal immunity in preventing viral infections should be paid more attention. The virus contains four structural proteins (Han *et al*., 2021). They are Spike S protein, Envelope E protein, Membrane/matrix protein, and Nucleocapsid N protein. The S protein has two subsections, S1 and S2 (Han *et al*., 2021). The S protein binds to specific receptors, causing the virus to infect cells (Agnihothram *et al*., 2014; Li *et al*., 2005; Li *et al*., 2003). The neutralizing antibody against the S protein can block this process and prevent the virus from invading 8 S protein can also effectively stimulate T-cell immune response, so it is the most important target antigen for vaccine design. N and M proteins have also been shown to induce the body to produce an efficient cellular immune response (Wang, *et al*., 2005; Zhu *et al*., 2004; Kim *et al*.,2004).

SARS-CoV- 2 is unusual for a respiratory virus that binds to a receptor, angiotensin-converting enzyme 2 (ACE2). This enzyme, ACE2, can be expressed in virtually all organs, but especially in the lungs (Kuba *et al*., 2006), gut (Wang *et al*., 2020) and brain (Xia and Lazartigues, 2008). Therefore, unlike most respiratory viruses, SARS-CoV-2 has a wider biological distribution and may cause considerable damage outside the respiratory system. It adversely affects the genitourinary system, digestive system, circulatory system, and central nervous system. The universality of the distribution of ACE2 receptors leads to multiple changes

in symptoms, such as dyspnea, headache, diarrhea, venous thromboembolism and high blood pressure (Zhang *et al*., 2020). The S protein binds to ACE2 on cells to mediate infection. The S1 subunit contains the receptor-binding domain (RBD) and is responsible for initial attachment to the host cells through the ACE2 receptor, while the S2 subunit promotes viral fusion with cells to initiate infection (Astuti and Ysrafil, 2020) The S protein is a frequent vaccine target as it is expected that antibodies binding to the correct epitope on the S protein may be neutralizing and block intercellular viral spread (Astuti and Ysrafil, 2020).

Types of Vaccines and their Names

The vaccines currently under study can be roughly divided into the following categories. Different types of vaccines have their characteristics.

DNA Vaccines

DNA vaccines can enter cells like viral infections and use the host protein translation system to generate target antigens. As an endogenous immunogen, it can induce humoral and cellular immune responses at the same time. Given the advantages of nucleic acid vaccines, DNA vaccines do not require live viruses, so safety is improved. DNA vaccines insert genes encoding foreign antigens into plasmids containing eukaryotic expression elements and then directly introduce the plasmids into humans or animals, allowing them to express antigen proteins in host cells and induce immune responses to prevent diseases (Astuti and Ysrafil, 2020). The manufacturing process of plasmid DNA is relatively straightforward, and the double-strand DNA molecules are more stable than the virus and can be freeze-dried for long-term storage. DNA vaccine vaccination method limits its application. Since the vaccine is mainly distributed in the intercellular space after vaccination, only a very small amount can enter the cell to produce protein immunogen, so the immune effect is greatly reduced. The plasmid DNA vaccine's main prohibitory factor is the low transfection efficacy, which requires transfection modalities. For example, Inovio's COVID-19 vaccine candidate, INO-4800, uses a handheld electroporation device, Cellectra (INOVIO EXPANDS). The vaccine will be injected intradermal along with the electrodes. An electric pulse is then applied to open the cell membrane so that the plasmid can enter the cells. Using an established device may allow fast launch in clinical trials, but it also brings other obstacles to large-scale vaccination. Although nucleic acid vaccines can effectively induce systemic immune responses, their immunogenicity is weak, and mucosal immune responses are not easy to produce. Although a few animal DNA vaccines have been on the market, no human DNA vaccine has been approved for marketing so far. Combination with other vaccines will achieve better immune effects.

mRNA Vaccines

Compared with DNA vaccines that need to enter the nucleus, mRNA vaccines only need to enter the cytoplasm to achieve target antigens' expression, so they are theoretically safer. In recent years, mRNA vaccines have been developed rapidly. Although the mRNA vaccines for rabies virus and influenza virus have completed phase I clinical evaluation (Alberer *et al*., 2017; Feldman *et al*., 2019), the immune effect is not satisfactory, such as a relatively high proportion of headaches, fatigue, and side effects such as muscle pain. The immune protection generated by the vaccine declined rapidly within one year, and no cellular immune response was detected. Therefore, it is necessary to improve further the immune efficacy and long-term

protection of mRNA vaccines. So far, there is no mRNA vaccine on the market. However, the research of mRNA vaccines has been in the process of exploration and advancement. Many institutions have quickly initiated the research and development of COVID-19 mRNA vaccines. The mRNA vaccine developed by the National Institute of Allergy and Infectious Diseases (NIAID), United State of America and Moderna has taken the lead to initiate a phase I clinical trial. Moderna's vaccine, mRNA-1273, specifically encodes the S antigen's perfusion form, including a transmembrane anchor and an entire S1−S2 cleavage site (Jackson *et al*., 2020).

Non-replicating Viral Vector Vaccines

One of the most explored viral vector options is the Adenovirus (Ad), currently being used by both CanSino and Oxford/ AstraZeneca. Adenovirus is a common cold virus with a double-stranded DNA genome. CanSino is using Ad type 5 (Ad5) and named the vaccine, Ad5-nCoV (Zhu *et al*., 2020). Ad5-nCoV can encode for the full-length S protein of SARS-CoV- 2. This gene is derived from the Wuhan-Hu-1 sequence of SARS-CoV- 2 and is cloned into the E1- and E3-deleted Ad5 vector together with the tissue plasminogen activator signal peptide (Astuti and Ysrafil, 2020). The effectiveness of this vaccine is relatively high, but the disadvantage is that it may not be effective for people with recessive infectious viruses.

Inactivated Vaccines

Inactivated vaccines are the most classic form of vaccines. They are easy to prepare and can efficiently cause humoral immune responses. They are often the first choice for new infectious diseases. Inactivated vaccines are mainly obtained through three inactivation methods, such as formaldehyde, β-propiolactone, and ultraviolet. SARS and MERS inactivated vaccines can cause mice, hamsters, ferrets, and monkeys to produce high-titer neutralizing antibodies. The SARS-inactivated vaccine has completed phase I clinical trials, proving that it is safe in humans and can induce neutralizing antibodies' production (Deng *et al*., 2018). However, the T-cell immune response caused by inactivated vaccines is generally weak. Previous studies have shown that SARS-and MERS-inactivated vaccines cannot effectively stimulate the body to produce cellular immune responses (See *et al*., 2008; Xiong *et al*., 2004). Although high titers of serum neutralizing antibodies are produced, the protective effect is also not satisfactory. Some studies have found that the MERS-inactivated vaccine can cause pathological allergic reactions in mice's lungs (Agrawal *et al*., 2016). Currently, the inactivated SARS-CoV- 2 vaccine (Vero cells) is being used. In addition, vaccine production requires the operation of high concentrations of live viruses, which poses a certain biological safety risk.

Live Attenuated Vaccines

Live attenuated vaccine reduces virus virulence through point mutation or deletion of crucial virus protein but does not affect its immunogenicity and replication ability. This vaccine program has very good immunogenicity and can induce systemic immunity and mucosal immune response, and the immunity is lasting. Several live attenuated vaccines have been on the market, including yellow fever, smallpox, measles, polio, mumps, rubella, and chickenpox. The SARS live attenuated vaccine will recover its virulence after continuous passage in cells or mice, suggesting that the vaccine scheme has a greater biological safety risk (Jimenez *et al*., 2015). Without sufficient evidence to ensure that live attenuated vaccines will not regain strength, this strategy is not currently

recommended for COVID-19 vaccine development.

Subunit Vaccines

Subunit vaccines are composed of purified recombinant proteins and are considered to be the safest vaccines. There are currently several subunit vaccines on the market, including hepatitis B, hepatitis E, and human papillomavirus vaccines. SARS and MERS subunit vaccines can produce high-titer neutralizing antibodies in mice, and nasal or oral vaccination can also induce a mucosal immune response, thereby more effectively blocking the virus transmission through the respiratory tract. The data also prove the protective efficacy of mucosal vaccination better than intramuscular inoculation (Li *et al*., 2019; New *et al*., 2019; Wang *et al*., 2017; Ma *et al*., 2014). However, as a non-endogenous antigen, subunit vaccines cannot be presented through MHC-I and cannot effectively produce sensitized cytotoxic T cells (CTL). Considering the key role of cellular immunity in clearing coronavirus infections, the subunit vaccine of COVID-19 is best used in conjunction with other platform vaccines. It is recommended to include nasal and oral mucosal vaccination routes to activate mucosal immune responses.

Trained Immunity-based Vaccines

Trained immunity-based vaccines can activate the adaptive immune system and provide pathogen-specific protection (Sanchez-Ramons *et al*., 2008; Quintin *et al*., 2012). Currently, Bacille Calmette-Guerin (BCG), a vaccine against tuberculosis, can induce trained immunity against COVID-19 and is currently undergoing clinical evaluation, which will take time to prove (Texas, 2020). Even if the BCG vaccine is effective against COVID-19, it also faces unique challenges. That is, the production standards of the BCG vaccine will vary from country to country, and it is not clear whether certain quality standards are required to provide protection against COVID-19 (Angelidou *et al*., 2020).

Covid-19 vaccine acceptance and hesitancy

With the encouraging development of SARS-CoV-2 vaccine approvals, optimism is growing, offering hope for the eventual end of the pandemic through the achievement of herd immunity (Omer *et al*., 2020; Fine *et al*., 2011). The threshold for SARS-CoV-2 herd immunity is estimated to range between 50 and 67 % (Omer *et al*., 2020). One major obstacle facing the achievement of such a goal is believed to be vaccine hesitancy and skepticism across the global population (MacDonald, 2015; Schoch-Spana *et al*., 2020; Neumann-Bohme *et al*., 2020). Vaccine acceptability is determined by three factors: confidence, convenience, and complacency (Al-Mohaithef and Padhi, 2020). Confidence is defined as the trust in the safety and effectiveness of the vaccine, trust in the delivery system as the healthcare system, and the trust in the policymakers (French *et al*., 2020). Many people have doubts about vaccine safety, and this is going to be a major challenge to be resolved by health care providers, policymakers, community leaders, and governments to increase the widespread acceptance of the vaccines (MacDonald, 2015; Schoch-Spana *et al*., 2020; Coustasse *et al*., 2021). Furthermore, the concept of vaccination convenience encompasses factors such as the vaccine's physical availability, affordability, and accessibility (MacDonald, 2015).

Vaccine complacency is associated with a low realized risk of the vaccine-preventable disease and hence more negative attitudes towards the vaccines (French *et al*., 2020). Such skepticism was demonstrated in a poll that was conducted in the United States of America, where 50 % of the Americans said

they were willing to take the vaccine, 30 % were unsure, while 20 % did not intend to take the vaccine (Neergaard and Fingerhut, 2020). In another survey of adult Americans, 58 % intended to be vaccinated, 32 % were not sure, and 11% did not intend to be vaccinated (Fisher *et al*., 2020). However, one more study reported 67% of the Americans would accept a COVID-19 vaccine if it is recommended to them, although there were significant demographic differences in vaccine acceptance (Malik *et al*., 2020).

Vaccine hesitancy was defined by the WHO Strategic Advisory Group of Experts (SAGE) as delay in acceptance or refusal of vaccination despite availability of vaccination services (MacDonald, 2015). Factors such as religion, gender, political ideology, and trust in medical and scientific institutions have been shown to be associated with vaccine hesitancy, both in general and regarding COVID-19 vaccines specifically (Lin *et al*., 2021; DeFigueiredo *et al*., 2020; kerr *et al*., 2020). While these broader factors are important, research has also shown that specific beliefs about and attitudes towards COVID-19 vaccinations are also closely linked to vaccination intentions (Lin *et al*., 2021; Freeman *et al*., 2021). Whether these attitudes can be, and should be, changed by communication 'campaigns' is a matter of active debate worldwide.

Efficacy of Vaccine and their Side Effects

Vaccine efficacy is assessed by using the relative risk (RR) method, the relation of COVID-19 attacks rates with and without a COVID-19 vaccine which is stated as 1–RR. In a study, the effectiveness of the vaccine was assessed by using the cohort study design which compared the incidence in the general cohort of persons with the incidence of COVID-19 infection in the vaccinated persons who were antibody negative (Abu-Raddad *et al*., 2020). The effectiveness of different vaccines was estimated as 87.0 % is the efficacy of the B117 variant of the Pfizer vaccine and 72.1 % is the efficacy of the B1351 variant of the Pfizer vaccine (Abu-Raddad *et al*., 2020).

For effective vaccine development, clinical and preclinical trials are important to minimize the associated adverse effects (Sharma *et al*., 2020). However, worldwide collaboration among the different organizations such as the Gavi Alliance, Accelerating COVID - 19 Therapeutic Interventions and Vaccines, World Health Organization, Coalition for Epidemic Preparedness Innovations, as well as the Bill and Melinda Gates Foundation shows cooperation to the SARS - COVID - 19 pandemic and ensuring the acceptable funding for the vaccines' development (Sharma *et al*., 2020). The efficacy as well as the adverse effects of different types of COVID - 19 vaccines are discussed below:

Astra Zeneca Vaccine

The AstraZeneca is a monovalent vaccine comprised of a single recombinant, adenoviral vector (the icosahedral virions, nonencapsulated with a single linear molecule of DNA) encoding the S glycoprotein of Covid - 19 (WHO, 2021; Graham *et al*., 2020). Furthermore, the AstraZeneca vaccine also contains polysorbate 80, disodium edetate dihydrate, magnesium chloride hexahydrate, sucrose, L - histidine hydrochloride monohydrate, L-histidine, sodium chloride, ethanol, and water for injection. The efficacy of the AstraZeneca Vaccine was 63.09 % (95 % confidence interval (WHO, 2021).

The time of vaccine opening to administration requires 2-8°C temperature due to the small shelf-life of vaccines, which is 6 months (Ramsamy *et al*., 2020). The

vaccine developed by Astra Zeneca, a British - Swedish company, has been a source of considerable promise (Vogel and Kupferschmidt, 2021). The Oxford AstraZeneca vaccine is inexpensive and may be stored in a regular refrigerator. Because it is projected to be manufactured in large quantities, it could be significant in limiting the pandemic (Mallapaty and Callaway, 2021; Wise, 2021). For the time being, the Astra Zeneca vaccine is the only one that will be available in considerable quantities in many places, particularly on the African continent (Mallapaty and Callaway, 2021). The vaccine shows some adverse reaction, which is mild to moderate in some cases. Most adverse reactions were reported after the second dose such as injection site pain, headache, injection site tenderness, fatigue, malaise, myalgia, arthralgia, and nausea (Graham *et al*., 2020). The Oxford Astra Zeneca COVID - 19 vaccine has a low level of perceived safety, particularly among vaccine skeptics (Sonderskov *et al*., 2021). Some European governments banned the use of the AstraZeneca vaccination on March 15, 2021, as a precautionary measure following the deaths of a few hundred patients who developed blood clots because of deep vein thrombosis (Vallee *et al*., 2021). Tenderness, discomfort, warmth, redness, itching, inflammation, and blisters at the injection site are common Indian Astra Zeneca adverse effects (Ghiasi *et al*., 2021). Recent studies of thrombocytopenia-related cerebral venous sinus thrombosis, repeated thrombosis, and hemorrhage occurring within a short time after receiving the vaccination are alarming, and health officials are paying close attention. Multiple thrombosis, bleeding, and thrombocytopenia, all of which seem to be symptoms of disseminated intravascular coagulation (Ostergaard *et al*., 2021).

Sinopharm Vaccine

This SARS - CoV - 2 vaccine was established as a result of the collaboration of the Beijing Institute of Biological Products, Prevention China, National Biotech Group Company Limited, and the Chinese Center for Disease Control (Wang *et al*., 2020). This Sinopharm vaccine has been approved as a 2 - dose vaccine first given at 0 and 21 days for the prevention of Coronavirus disease. This vaccine is composed of aluminum hydroxide adjuvant in phosphate - buffered saline and inactivated antigens of Covid - 19 and the shelf - life of the vaccine is 24 months at 2-8°C (Belete, 2021). The 41301 participants were enrolled in the vaccine phase trial, from this 98 % were aged between 18 and 60 years, while 893 applicants were of 59 years of age, and 294 were registered in the COVID - 19 vaccine. Out of this, 85 % of applicants were male, 87 % of applicants were recognized as Asian and 13 % were Chinese (Belete, 2021). The vaccine efficacy demonstrated among participants was 80.7 % (Huang *et al*., 2021) while the adverse effects were seen during the clinical trials such as injection site pain, fever, pruritus, fatigue, headache, erythema, myalgia, cough, dyspnea, arthralgia, nausea, diarrhea, vomiting, and dysphagia (Belete, 2021). The Clinical Event Committee confirmed that 142 cases of SARS - CoV - 2 were reported after the second vaccination (Huang *et al*., 2021).

Sinovac/CoronaVac Vaccine

The inactivated Sinovac vaccines used against SARS - Covid - 19 were developed by some vaccine manufacturers (Sinovac, 2021). This vaccine is used as a 2 - dose vaccine for individuals aged 18 years and older (Sinovac, 2021). The Sinovac vaccine was approved by the national medical product administration (NMPA) on February 6th, 2021. It is used in different

countries in the time of emergency (Zhang *et al*., 2021). On April 21st 2021, more than 260 million doses were distributed to the public in China and more than 160 million individuals have been vaccinated through Sinovac (Sinovac, 2021). The Sinovac vaccine is composed of 3 μg of inactivated SARS - CoV - 2 virus, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium chloride, aluminum hydroxide, or water for injection (Zhang *et al*., 2021).

Sinovac, a Beijing - based pharmaceutical company, created the Corona vaccine. This vaccine is also based on an inactivated SARS - CoV - 2 strain (Baraniuk, 2021), with an efficacy of 56.5 %. According to the study conducted by the University of Chile, one dose was just 3 % effective (increasing to 27.7 % within 2 weeks after the second dose, and up to 56.5 % after 2 weeks (Dyer, 2021). Corona vacine, created by Beijing-based Sinovac, was found to be 50.4 % effective in late-stage trials in preventing severe and mild COVID-19. This is far less than the 90 % efficacy of several popular vaccines (Mallapaty and Callaway, 2021). The adverse reactions reported during the Sinovac trial were fatigue, fever, muscle pain, anorexia, muscle distention, acute allergic reaction, and diarrhoea (Halim *et al*., 2020).

Pfizer Vaccine

The Pfizer–BioNTech BNT162b2 is a messenger RNA vaccine that shows 95 % efficacy against SARS - COVID - 19. (Abu-Raddad *et al*., 2020; Polack *et al*., 2020). The Pfizer - vaccine is composed of ALC - 0315, potassium chloride, cholesterol, sodium chloride, disodium hydrogen phosphate dihydrate, potassium dihydrogen phosphate sucrose, and water for injection (Knight *et al*., 2020) The Pfizer vaccine was assessed using a cohort study design in which the effectiveness of the vaccine was measured by comparing the incidence in the general cohort of persons with the incidence of COVID-19 infection in the vaccinated persons who were antibody negative (Abu-Raddad *et al*., 2020; Jullian *et al*., 2014). The Pfizer vaccine effectiveness in the B117 variant was 89.5% and the B1351 variant was 75.0% at 14 days after the second dose (Abu-Raddad *et al*., 2020). In May, 2020, its Phase 2 trial was introduced on two varieties of the vaccine (Corum *et al*., 2020) and both varieties lead to the production of antibodies against SARS - COVID - 19 and T cells in response to COVID-19. One of the vaccines known as BNT162b2 produces some adverse effects like fatigue or fevers, and the next Phase 2/3 trials of the vaccine was commenced (Corum *et al*., 2020). On July 27, 2020, the companies revealed the second Phase 2/3 trial in which 30 000 volunteers participated in the United States and other countries like Brazil, Germany, and Argentina also participated (Corum *et al*., 2020).

Moderna vaccine

This vaccine is composed of such components as messenger ribonucleic acid, PEG, cholesterol, DSPC, tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate trihydrate, and sucrose (Fact sheet, 2019). The efficacy of the Moderna vaccine after one dose was 50.8 %; however, after the second dose it was 92.1 % effective (Moderna Vaccine, 2021). This messenger - RNA-based Moderna vaccine was approved by the FDA and was used for the emergency during the SARS-COVID-19 pandemic in 2020 (Kaur and Gupta, 2020). In efficacy trials of the Moderna vaccine, 15,185 participants were enrolled and they received one dose of the vaccine (Kaur and Gupta, 2020; Wei *et al*., 2021); 228 cases were reported showing the adverse side effects such as injection site rash and urticaria, which manifested for 48 h post

vaccination (Wei *et al*., 2021). Those who received one dose of the Moderna COVID - 19 showed adverse effects in participants 18 years of age or older, pain at the injection site, headache, myalgia, fever, arthralgia, chills, vomiting, and axillary swelling sometimes erythema at the injection site (Meo *et al*., 2021).

Gamaleya (Sputnik V)

Gamaleya vaccine is also known as Gam-COVID-Vac/Sputnik V vaccine. The Gamaleya vaccine was developed through heterologous recombinant adenovirus and using adenovirus 5 and adenovirus 26 as vectors for the appearance of Covid-19 spike protein (Jones *et al*., 2021). The Sputnik V Vaccine is a two-vector vaccine, that is, composed of sodium chloride, tris aminomethane, Sodium EDTA, ethanol, magnesium chloride hexahydrate, polysorbate 80, sucrose, and water for Injection (Turner *et al*., 2021). The Gam-COVID-Vac efficacy was 91.6 % in the short-term study of Phase 3 trials which were conducted in Russia in the middle of Sept 7 and Nov 24, 2020 (Ikegame *et al*., 2021.) The Sputnik vaccine was not commonly used in Russia but in other countries such as Chile, Hungary, and Argentina (Ikegame *et al*., 2021). Some side effects were reported such as headache, fatigue, flulike symptoms, and injection site reaction (Longunov *et al*., 2021). From June 18 to August 3rd, 2020, a total of 76 volunteers were registered for two studies, and two groups each with nine participants received adenovirus-26-S and adenovirus-5-S in the 1st phase, respectively, while 20 volunteers received adenovirus-26-S or adenovirus-5-S in the 2nd phase. The outcomes show that both formulated vaccines were well tolerated and safe with better efficacy (Longunov *et al*., 2020).

Side Effects of Covid-19 Vaccine as a Factor for Vaccine Hesitancy

Building immunity after vaccination may sometimes cause side effects. These potential post vaccine side effects are considered the main cause of vaccine hesitancy among the population (Alhazmi *et al*., 2021). Increasing public awareness of the vaccine efficacy and being honest in clarifying the side effects are important to improving vaccine acceptance (Alhazmi *et al*., 2021).

The associated side effects of vaccine varied according to the vaccine type, and post vaccination side effects are more prevalent after vaccination with RNA (mRNA) than with other vaccines (Hatmal *et al*., 2021). Most people develop immunity against coronavirus after vaccination, regardless of the absence or presence of side effects. A previous study showed that only one in four people suffered from mild and short-onset side effects after receiving coronavirus vaccines (Klugar *et al*., 2021). According to the World Health Organization, the most common side effects following coronavirus vaccines are fatigue, fever, headaches, pain at the injection site, nausea, and diarrhea (Amdrzejizak-Grzdko *et al*., 2021).

Post-vaccine First-dose Side Effects

BBIBP-CorV vaccine

Regarding the side effects after receiving the first dose of the BBIBP-CorV vaccine, the most common ones were pain, redness, or swelling at the site of vaccine injection (52.5 %); fatigue and lethargy (45 %); headache (15 %); joint pain, muscle pain, and runny nose (10 %); fever (7.5 %); sore throat (6 %); dizziness (5 %); and cough, allergies, rashes, decreased appetite, and inflammation of the nervous system, including numbness, tingling, and loss of sensation (2.5 %). However, 25 % of the participants who received the BBIBP-CorV vaccine did not report any side effects. There were gap

differences between BBIBP-CorV-vaccinated participants in answering the question on, "To what extent do you rate the severity of these side effects?"; 49 % answered that the side effects were mild, 18 % answered that they were moderate, and 8 % answered that they were severe. The majority of the BBIBP-CorV-vaccinated participants (67 %) answered that the side effects appeared after the first dose, on the first day after receiving the vaccine. In addition, 25 % of the BBIBP-CorV-vaccinated participants answered that the side effects that appeared after the first dose persisted for one day, 30 % answered that they persisted for two days, and 20 % answered that they persisted for more than two days. Regarding their post vaccine practices, 22.5 % answered that they took pain relievers after taking the first dose of the vaccine, but 77.5 % did not need to take any pain relievers.

ChAdOx1 Vaccine

The most common side effects were pain, redness, or swelling at the site of vaccine injection (90.5 %); muscle pain (71.5 %); fatigue and lethargy (57 %); joint pain (52 %); fever and headache (38 %); dizziness, abdominal pain, and convulsions and tremors (14 %); inflammation of the nervous system, including numbness, tingling, and loss of sensation (13.5 %); decreased appetite, nausea, and vomiting (9.5 %); cough, allergies, rashes, and runny nose (5 %); and sore throat (4.5 %). Only 5 % of the participants who received the ChAdOx1 vaccine did not feel any side effects, while 27 % of the ChAdOx1-vaccinated participants answered that the side effects were mild, 54 % answered that they were moderate, and 14 % answered that they were severe. The majority of the ChAdOx1-vaccinated participants (76 %) answered that the side effects appeared after the first dose during the first day after vaccination; 14 % of the ChAdOx1-vaccinated participants answered that the side effects that appeared after the first dose persisted for one day, 28.5 % answered that they persisted for two days, and 52.5 % answered that they persisted for more than two days. Regarding their post vaccine practices, 81 % answered that they took pain relievers after the first dose vaccination, but 19 % did not need to take any analgesic drug in the forms of pain relievers.

BNT162 Vaccine

The most common side effects reported with this vaccine were pain, redness, or swelling at the site of vaccine injection (88 %); fatigue and lethargy (50 %); muscle pain and joint pain (20 %); headache and runny nose (8 %); and fever, dizziness, cough, allergies, rashes, convulsions, and tremors (4 %). However, 8 % of the participants who received the BNT162 vaccine did not feel any side effects; 32 % of the BNT162-vaccinated participants answered that the side effects were mild, 50 % answered that they were moderate, and 10 % answered that they were severe. The majority of the BNT162-vaccinated participants (84 %) answered that the side effects appeared after the first dose on the first day after vaccination; 64 % of the BNT162-vaccinated participants answered that the side effects that appeared after the first dose persisted for one day, 16 % answered that they persisted for two days, and 12 % answered that they persisted for more than two days. Regarding their post vaccine practices, 28 % answered that they took pain relievers after the first dose of vaccination, but 72 % did not need to take any pain relievers.

Post-vaccine Second-dose Side Effects

BBIBP-CorV Vaccine

Most of the participants who received the BBIBP-CorV vaccine received the second

dose of the vaccine three weeks after the first dose, and answered that they were not infected with coronavirus between the first and second doses (or suffered from severe side effects of coronavirus for more than two days after receiving the first dose). Regarding the side effects after receiving the second dose of the BBIBP-CorV vaccine, the most common ones were fatigue and lethargy (37.5 %); pain, redness, or swelling at the site of vaccine injection (17.5 %); headache, muscle pain, and runny nose (7.5 %); sore throat, allergies, and rashes (5 %); and joint pain, convulsions, and tremors (2.5 %). On the other hand, 50 % of the participants who received a second dose of the BBIBP-CorV vaccine did not report any side effects. There were differences in answering the question, "To what extent do you rate the severity of the side effects after the second dose?" 32.5 % answered that the post vaccine side effects were mild, and 17.5 % answered that they were moderate. The majority of the participants (45 %) answered that the post vaccine side effects appeared after the second dose on the first day after receiving the vaccine; 22.5 % of the participants answered that the post vaccine side effects that appeared after the second dose persisted for one day, 15 % answered that they persisted for two days, and 12.5 % answered that they persisted for more than two days. Regarding their post vaccine practices, 17.5% answered that they took a pain reliever after taking the second dose of the vaccine, but 82.5 % did not need to take any pain relievers.

ChAdOx1 Vaccine

All of the participants who received the ChAdOx1 vaccine received the second dose of the vaccine three months after the first dose, and answered that they were not infected with coronavirus between the first and second doses. Regarding the side effects after receiving the second dose of the ChAdOx1 vaccine, the most common ones were pain, redness, or swelling at the site of vaccine injection (82 %); muscle pain (56 %); fatigue and lethargy (48 %); joint pain and fever (34 %); headache (23 %); decreased appetite (14 %); and dizziness, nausea, and vomiting (5 %). Only 14 % of the participants who received the ChAdOx1 vaccine did not feel any side effects; 41 % of the ChAdOx1-vaccinated participants answered that the side effects were mild, 40 % answered that they were moderate, and 5 % answered that they were severe. The majority of the ChAdOx1-vaccinated participants (80 %) answered that the side effects appeared after the second dose on the first day after vaccination; 43 % of the ChAdOx1-vaccinated participants answered that the side effects that appeared after the second dose persisted for one day, 27 % answered that they persisted for two days, and 16 % answered that they persisted for more than two days. Regarding their post vaccine practices, 55 % answered that they took pain relievers after the second dose of vaccination, but 45 % did not need to take any pain relievers.

BNT162 Vaccine

All of the participants who received the BNT162 vaccine received the second dose of the vaccine three weeks after the second dose, and answered that they were not infected with coronavirus between the first and second doses. Regarding the side effects after receiving the second dose of BNT162 vaccine, the most common ones were pain, redness, or swelling at the site of vaccine injection (92 %); fatigue and lethargy (52 %); fever (28 %); joint pain (24 %); muscle pain (20%); runny nose (8 %); and dizziness, cough, allergies, rashes, convulsions, and tremors (4 %). However, 8 % of the participants who received the second dose of BNT162 vaccine did not feel any side effects; after the second dose of BNT162, 26 % participants answered that the side effects were mild, 54 % answered

that they were moderate, and 12 % answered that they were severe. The majority of the BNT162-vaccinated participants (84 %) answered that the side effects appeared after the second dose on the first day after vaccination; 28 % of the BNT162-vaccinated participants answered that the side effects that appeared after the second dose persisted for one day, 24 % answered that they persisted for two days, and 40 % answered that they persisted for more than two days. Regarding their post vaccine practices, 44% answered that they took pain relievers after the second dose of vaccination, but 66 % did not need to take any pain relievers. As per the BNT162-vaccinated participants answered that the side effects that appeared after the second dose persisted for one day, 24 % answered that they persisted for two days, and 40 % answered that they persisted for more than two days. Regarding their post vaccine practices, 44 % answered that they took pain relievers after the second dose of vaccination, but 66 % did not need to take any pain relievers.

The immune system produces inflammatory mediators after vaccination, such as cytokines, which have inflammatory effects on body organs. Therefore, the post-coronavirus-vaccine side effects persist for days after taking the vaccine (Elgendy *et al*., 2021). Most post vaccine side effects start during the first 24 h following vaccination and persist for 1–2 days (Menni *et al*., 2021).

The clinical trials conducted on Pfizer BioNTech (BNT162) showed that 50 % of vaccinated people did not suffer from side effects, despite 90 % of them developing immunity against the virus (Menni *et al*., 2021). Most of the ChAdOx1-vaccinated participants used pain relievers, but most of the BBIBP-CorV- and BNT162-vaccinated participants did not use any pain relievers. This indicated that the severity of side effects after the ChAdOx1 first dose was greater than that which occurred after BBIBP-CorV and BNT162 first-dose vaccination. Most of the participants did not use any pain relievers after the second dose of BBIBP-CorV and ChAdOx1 vaccines, in contrast to most of the BNT162-vaccinated participants, who needed to use pain relievers. This indicated that the severity of side effects after BNT162 was greater than what occurred after BBIBP-CorV and ChAdOx1 second-dose vaccination. These side effects may have indicated that the body was building the desired immunity for protection (Abu-Hammad *et al*., 2021). It was obvious that post-BBIBP-CorV vaccine side effects after the first and second doses were commonly mild; therefore, a low percentage of participants needed to use pain relievers. Previous research has also found this (Elgendy *et al*., 2021; Khadka *et al*., 2020). After receiving the vaccine, the immune system produces sufficient amounts of antibodies to protect the body from coronavirus infection.

Many people take nonsteroidal anti-inflammatory drugs (NSAIDs) to control the post-coronavirus-vaccine side effects. Some studies reported fears of taking NSAIDs to control the postvaccine side effects. NSAIDs cause inhibition of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, as well as inflammatory mediators such as cytokines. COX enzymes are important for sufficient antibody production after vaccination. Thus, using NSAIDs decreases the production of antibodies after coronavirus vaccination or infection (Elgendy *et al*., 2021; Zawbaa *et al*., 2021). Studies show that after three weeks of the first dose of ChAdOx1 vaccination, the IgG anti-spike-protein antibodies test had positive results, but for the BBIBP-CorV vaccine, it had negative results.

The average of positive results of the quantitative anti-spike-protein antibodies test (IgG) after three weeks of first-dose ChAdOx1 vaccination was close to the average of the positive results of the quantitative anti-spike-protein antibodies test (IgG) after three weeks of second-dose BBIBP-CorV vaccination. This indicated a higher efficacy of ChAdOx1 over BBIBP-CorV, and that one dose of ChAdOx1 produced an immune response similar to that of two doses of BBIBP-CorV. Another study reported a significant 39 % drop in the rates of infection after 12 to 21 days of Astra Zeneca (ChAdOx1) first-dose vaccination (El-Shitany *et al*., 2021).

Based on the previous studies carried out Most of the side effects were mild to moderate, indicating that the body's building of immunity was compromised. The severity of side effects was greater after the first dose of the BBIBP-CorV and ChAdOx1 vaccines than after the second dose, but in contrast, the severity of side effects was greater after the second dose of the BNT162 vaccine than after the first dose. ChAdOx1 was more effective than BBIBP-CorV, and one dose of ChAdOx1 produced an immune response similar to that of two doses of BBIBP-CorV. Vaccinated people with past coronavirus infections developed better immunity than those who were only vaccinated.

The Challenge before COVID-19 Vaccine

While a vaccine will help protect individual patients and those around them, a large proportion of the population must be immunized and protected before transmission is substantially reduced. Especially for 2-dose regimens, this will take months. No vaccine will be 100 % effective and a vaccine that protects against developing clinical illness may not prevent transmission to others. In addition, the duration of naturally occurring immunity to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown and may wane with time (Huang *et al*., 2020). Therefore, the likely duration of protection by new COVID-19 vaccines is unknown. For these reasons, even after vaccines become available, SARSCoV-2 will be a continuing concern. Effective public health measures, such as social distancing, limiting the size of gatherings, and wearing face masks, will be needed for at least several more months, and potentially longer.

CONCLUSION

Many individuals are hesitant about receiving COVID-19 vaccines. Reasons include the novelty and rapid development of the vaccines, as well as the politicization of the pandemic and inconsistent messages from scientists and government leaders. Many people are still willing to take the vaccine for personal reasons such as job interviews, travelling documentations, for pass at various functions etc. and not really for the prevention of the virus. It is critical that clinicians stay well informed about emerging data so that they can help patients make sound decisions about the vaccines needed to help end the pandemic.

Conflict of interest

The authors report no conflict of interest concerning the work.

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