COVID-19 Vaccines, What do we know so Far? A Narrative Review

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ABSTRACT: For more than a year, the world was paralyzed by the COVID-19 pandemic. It wasn’t until the last few months that hope to a return of a quasi-normal way of living was starting to materialize. The era of the COVID-19 vaccines begun, and with it all sorts of concerns and complaints about their safety and efficacy. Large numbers of people believed the conspiracy theories about the new vaccines thus becoming reluctant and sometimes refused to take the new vaccines. Others justified their concern with the lack of confidence and fears from side effects. For the time being, safety precautions must still be continued; wearing masks, social distancing and avoiding crowded places must be applied.

This review article summarizes the literature of these vaccines’ pathophysiology, mechanism of action, dosing and schedule, safety profile and lastly the documented side effects of each vaccine.

In conclusion, there is no certainty whether these vaccines will prevent infection and more importantly protect against forward transmission. It is sure that the immunity persists for several months, but the exact duration for every vaccine is yet to be determined. For the time being, safety precautions must still be continued; wearing masks, social distancing and avoiding crowded places must be applied.

KEYWORDS: AstraZeneca, COVID-19, Coronavac, Johnson&Johnson, Pfizer, Moderna, Sputnik

INTRODUCTION
After more than a year of declaring COVID-19 a pandemic by the World Health Organization, there is no current curative treatment for SARS-CoV-2 and the numbers of mortalities and morbidities continue to rise [1]. Moreover, safety measures such as hygiene, lockdown and social distancing have not been proven to be enough in limiting the spread of the virus, therefore a rapid plan was implemented, and in less than a year, several vaccines against SARS-CoV-2 have flooded the pharmaceutical market globally.

Governments and private firms have spent billions of dollars to develop vaccines within one year. Subsequently, several ones such as Pfizer-BioNTech, Moderna, and CoronaVac already approved by Food and Drug Association, and being distributed and hundreds of millions of people are inoculated so far [2]. As of February 2021, over two hundred million doses had been administered worldwide [2], and countries, such as Israel and the United Kingdom, are making remarkable progress in immunizing their citizens. However, the vast majority of the rest of the world have only vaccinated small proportions of their populations and others are yet to start [3]. When this is not due to lack of available vaccines in developing countries, it could be the result of popular lack of confidence and fears from side effects of the rapidly approved vaccines [3].

In fact, vaccines have globally been successful in limiting vaccine-preventable-diseases (VPD) and immunization, is the most effective strategy to inhibit spread of these diseases [4], and in hope that this strategy will end the current pandemic, researchers are still studying the available vaccines, their correct usage, their safety and efficacy.

In this review, we discuss and describe the different vaccines, their mechanism of action, the international committees and association’s recommendations about their use and safety in order to address readers’ questions and concerns, especially those reluctant to get vaccinated.
The currently available vaccines are believed to provide protection via neutralizing antibodies. Till this date, understanding the exact mechanisms by which antibodies confer this protection and induce such protective responses by the innate immune system is a key area of research [5]. The different available types are live attenuated vaccines that contain a weakened version of the living virus or bacteria, inactivated vaccines, toxoid vaccines, where toxins are weakened and injected into the body, subunit vaccines containing the essential antigen of the germs and conjugate vaccines that are effective against coated bacteria [5]. When it comes to COVID-19, new vaccination technologies have arisen, which differentiate them from one another.

The Chinese company Sinovac produced a coronavirus vaccine called CoronaVac. They used the Inactivated viruses’ technique that have been used for over a century against several diseases.

After being injected in the body, the inactivated viruses are engulfed by immune cells called antigen presenting cells. The latter degrade the inactivated virus and display some of its protein on the surface of the cell [6]. B cells and Helper T cells identify the spike proteins. The immune cells get activated and proliferate antibodies against the antigen [7].

The Pfizer–BioNTech and Moderna vaccines are manufactured using the messenger RNA (mRNA) technique and formulated as an RNA-lipid nanoparticle, nucleoside modified mRNA (modRNA). The mRNA or self-amplifying RNA (saRNA) are molecular templates that encode the antigen of interest, the spike protein [8,9]. After injection, the lipid nanoparticles (LPN) are absorbed by the cells while the mRNA is delivered into the cytosol where it is translated into the encrypted protein [8,9]. The spiked protein is displayed on the cell’s surface, where they can be identified by the immune system, activating a response. This response involves cytotoxic T cells which kill infected cells, in addition to B cells and helper T cells, which produce and support antibodies production respectively [8,9].

Instead of using mRNA, Vaxzervria, Sputnik V and Janssen vaccines, which are viral-vector based vaccines, use a double-stranded DNA [10,11,12]. The viral vector is a modified adenovirus that is stripped of any disease-causing genes to become a harmless virus [13]. Moreover, the researchers added the coronavirus spike protein gene to the viral vector which acts now as a delivery system, providing a mean to enter the cell and introduce the code of the targeted antigen. Once inside the cell, the modified virus enters to the nucleus, where the spike protein gene is copied into mRNA and then translated outside the nucleus to proteins. Consequently, the spike proteins migrate to the surface of the cells and trigger an immune response. B cells helper T cells as well as cytotoxic T cells are activated. To note, the adenovirus itself activate the immune system by turning on the cell’s alarm system. By initiating this alarm, these vaccines trigger the immune system to act more powerfully to the spike proteins [10,11,12].

DOsing, Schedule and Efficacy

Dosing and scheduling of the vaccines share some similarities. Pfizer-BioNTech is given intramuscularly for people 16 years and older, at 2 shots, given 3 weeks apart. Patient are fully vaccinated 2 weeks after the second shot [14]. Moderna also administered intramuscularly with 2 shots, given 4 weeks apart, and subjects get immunity also 2 weeks after the second dose, however it is recommended for people aged 18 years and older [14]. The Oxford-AstraZeneca vaccines, Vaxzervria, as found in most recent studies, shows top effectiveness when a person receives 2 doses, intramuscularly, 12 weeks apart [15]. Studies concerning Russian Sputnik V vaccine, show that in previously infected, the first dose elicits a strong humoral immune response that is even higher than that achieved after two doses in non-infected individuals [16]. Otherwise it should be administered in individuals of ≥ 18 years of age intramuscularly in two doses with interval of 21 days [17]. Moreover, studied concerning the Coronavac product encourage the use of 2 IM doses 14 days apart [18], and finally, after the resumption of J&J vaccines, the Center of Disease Control recommended the use of a single shot for adults 18 years or older [14].
Table: Vaccine Efficacy on Variants

<table>
<thead>
<tr>
<th></th>
<th>General Efficacy</th>
<th>B.1.1.7 variant</th>
<th>B.1.351 (South African variant)</th>
<th>P.1 (Brazilian variant)</th>
<th>B.1.427 and B.1.429 (California Variant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderna</td>
<td>94.1% effective in preventing infection and 100% against death</td>
<td>Protective [19]</td>
<td>Lesser protection [19]</td>
<td>Protective in mice [26]</td>
<td>No Studies</td>
</tr>
<tr>
<td>Sputnik V</td>
<td>91.6% in preventing infection and 100% against mortality</td>
<td>Markedly reduced efficacy [25]</td>
<td>Markedly reduced efficacy [25]</td>
<td>No studies</td>
<td>No Studies</td>
</tr>
<tr>
<td>Janssen</td>
<td>72% overall efficacy and 86% efficacy against severe disease</td>
<td>Protective [19]</td>
<td>64% overall efficacy and 82% efficacy against severe disease</td>
<td>Lesser protection [19]</td>
<td>No Studies</td>
</tr>
<tr>
<td>Vaxzevria</td>
<td>76% at preventing infection and 100% against severe disease</td>
<td>74.6% efficacy [19]</td>
<td>Not protective as per studies done so far</td>
<td>No studies</td>
<td>No Studies</td>
</tr>
</tbody>
</table>

Worldwide, people with and without scientific or medical backgrounds had concerns about vaccines’ safety and side effects. This prompted researchers and international committees in charge to constantly conduct trials, observational studies and issuing guidelines about the different vaccines adverse effects and safety profiles.

In a randomized, double-blind, placebo-controlled study published in the Lancet journal in November 2020, entitled “Safety and Immunogenicity Study of Inactivated Vaccine for Prophylaxis of SARS CoV-2 Infection (COVID-19)” it was found that two doses of CoronaVac given at different concentrations or with different dosing schedules were well tolerated in people aged 18 to 59 years [27]. Furthermore, majority of side effects were mild, the most common symptom was pain at injection-site, which was similarly reported in previous studies regarding CoronaVac Vaccine. Very few patients reported fever as compared to other attenuated viral based vaccines. CoronaVac in this study was well tolerated and reported humoral responses against SARS-CoV-2 [27].

Regarding the Pfizer-BioNTech vaccine, CDC stated that reactogenicity symptoms or side effects that happened within the first 7 days post vaccination were common but were mostly mild to moderate, based on several trials updated on April 16th, 2021. Also, concerning side effects such as fever, chills, lethargy and headaches, they were more common after the 2nd dose [28]. In a study
published on December 31st, 2020, Polack et al. observed in a multinational, placebo-controlled single blinded pivotal efficacy trial, that the safety profile of Pfizer-BioNTech vaccine was described as short-term, mild-to-moderate local pain at injection site, fatigue, and headaches. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups [29].

Moderna Vaccine, was not used to vaccine the population worldwide, however several studies and clinical trials were conducted to ensure its safety and efficacy. CDC states that, Moderna vaccine was 94.1% effective in preventing laboratory-confirmed COVID-19 infection, in people who received two doses of the product regardless of age, sex and ethnicity. Studies also showed that admission to hospital from COVID-19 infection was less in vaccinated group as compared to placebo group [30]. Modern groups reported that 9.7% of their participants felt fatigue and 4.5% complained of headaches [31]. In an early data analysis published in the New England Journal Medicine, in April 2021, researchers studied 35,600 pregnant women who reported their health status to the Centers for Disease Control and Prevention, and they found that Moderna vaccines, and also Pfizer-BioNTech do not cause any serious risks during pregnancy and moreover, are effective in pregnant women between 16 and 54 years old [32].

Furthermore, the European Medicines Agency, published in April 2021 updated the information regarding the safety profile of Vaxzervria, from AstraZeneca. They specified that the product has thrombocytopenia as a new common side effect affecting less than 1 in 10 persons; and also recognized thrombosis in combination with thrombocytopenia as a very rare side effect affecting less than 1 in 10,000 persons [33]. They assessed five reported cases of capillary leak syndrome, but a causality relationship could not be established and there are no recommendations to change or stop vaccine usage; it remains effective in preventing COVID-19 and the benefits continue to outweigh the risks [33]. In addition, the American Association for the Advancement in Science published in March 23rd 2021 an expert opinion article, stating that the vaccine has 79% efficacy in preventing symptomatic disease, but also, confirming positive results for antibodies that react to platelet factor 4 in at least 6 patients’ blood samples. This finding led them to conclude that the mechanism of the reported side effect resembles the autoimmune disorder heparin-induced thrombocytopenia (HIT) and named the process vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) [34].

Janssen usage, on the other hand, was stopped and in the United States, all already scheduled appointments were shifted to other available vaccines [35]. As of April 2021, CDC and Food and Drug Association have suggested a pause in its use because safety system received a small number of reports of severe type of blood clots; out of the 6.8 million vaccinated people, six cases were reported and are still being investigated. All six cases occurred in women 18 to 48 years old, and symptoms happened 6-13-daypost vaccination [36]. CDC advise people who have received the vaccine to seek medical help if they develop severe headache, new neurologic symptoms, severe abdominal pain, shortness of breath, leg swelling, tiny red spots on the skin (petechiae), or new or easy bruising, within the first 3 weeks [36]. There is still no scientific proof to say if the vaccine is related to these health issues. However, as of April 23rd the CDC and FDA have recommended its use to be resumed in the United States, but women 50 years old and younger should be aware of the rare risk of blood clots and thrombocytopenia [35].

A clinical trial done in Russia, published in Lancet, on 16427 participants, showed that the Sputnik vaccine is 91.6% effective against COVID-19 as of day 21 after first dose. The product induced vigorous humoral and cellular immune responses in all age groups (immune suppression of old age, in people above 60-year-old did not alter immunogenicity) [37]. The Federal Service for Surveillance in Healthcare, in Russia, reported that till date, no adverse side effects have been observed apart from classic post-vaccination reactions, mainly flu-like infections, skin irritations, headaches and fatigue [38] but data are still being collected for further deductions.

Table: different common and rare side effects [39]

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Fever</th>
<th>Chills</th>
<th>Pain and redness at injection site</th>
<th>Headache &amp; myalgias</th>
<th>Nausea</th>
<th>anaphylaxis</th>
<th>Thrombocytopenia and thrombosis</th>
<th>Cerebral Venous Sinus Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 per million</td>
<td>Rare, not significant</td>
<td>No data</td>
</tr>
<tr>
<td>Moderna</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>2.8 per million</td>
<td>Few Case Reports</td>
<td>No data</td>
</tr>
<tr>
<td>CoronaVac</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>2-5 per million</td>
<td>No data</td>
<td>No data</td>
</tr>
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It is also important to note, that for all approved and pending approval vaccines, not much absolute contraindications have been established yet; however, it is advisable to defer vaccination for 90 days for persons who have received monoclonal antibodies or convalescent plasma during a treatment of COVID-19 infection [40]. It is also advisable to postpone vaccination for patients exposed to an infected case until quarantine period is over [40]. The only absolute contraindication is severe allergic reaction to a previously administered dose of the same vaccine, or if person is known to have experienced anaphylaxis to any component of the vaccines, such as polyethylene glycol (PEG) for the Pfizer vaccine and polysorbate 80 for the Vaxzevria vaccine [41].

CONCLUSION
Historically, vaccines have been proven to be an efficacious mean to control many transmittable illnesses and have been proven priceless in many illnesses that lack effective treatment. The date when COVID-19 will disappear is still unknown, that is, if it will ever come. Nonetheless, it is expected that the rapidly mutating virus will become, similarly to the influenza family of viruses, a seasonal virus where annual vaccinations are required to keep the mortalities at bay. Meanwhile, A step in the right direction is to know how long the immunity will last from the currently available vaccines. What we are sure of, is that immunity lasts for several months but the full duration is not yet known [30]. Meanwhile, safety measures must be maintained, wearing masks, physical distancing, avoiding crowded spaces, hand, respiratory and cough hygiene must be applied.

ABBREVIATIONS
CDC Center of Disease Control
FDA Food and Drug Association
WHO World Health Organization
COVID-19 CoronaVirus Disease 19

DECLARATION AND CONFLICT OF INTEREST
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