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## Exploring Data and Literature Currently Available on the COVID-19 Vaccines

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## Exploring Data and Literature Currently Available on the COVID-19 Vaccines

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# Exploring Data and Literature Currently Available on the COVID-19 Vaccines

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## Abstract

The COVID-19 pandemic has been labeled one of the most lethal pandemics in human history. As a result, there has been a high level of urgency throughout the world to establish successful vaccinations to subdue the effects of the virus and return to a level of normalcy. This study aims to investigate the different COVID-19 vaccines available both in the United States and across the globe. Through exploration of how the vaccines were developed, how they elicit immunity, their efficacy, and their safety profiles, this review has the goal of increasing the amount of knowledge regarding the vaccines available to combat SARS-CoV-2, while also providing an epidemiological and biostatistical approach to interpreting acquired data available on the vaccines.

**Keywords:** COVID-19, Vaccine, Immunity, SARS-COV2, Efficacy

## 1. Introduction and background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus that was first identified in the city of Wuhan, China in December of 2019, has led to an outbreak of illness that has been declared a public health emergency by the World Health Organization (WHO), an agency of the United Nations responsible for international public health.<sup>1</sup> Widespread vaccination against SARS-CoV-2 has been considered to be the most propitious approach to curb the pandemic.<sup>2</sup> Therefore, unparalleled measures have been taken to manufacture and distribute a sufficient number of vaccines to immunize an adequate number of individuals to protect communities from the continued perils of morbidity and mortality from SARS-CoV-2. Historically, vaccine development has been known to take years to decades before a final product can become available for the general public. For example, the polio vaccine took 40 years to reach the public platform.<sup>3,4</sup> The development and approval of a vaccine requires advancements through a preclinical evaluation and three discrete clinical phases. The preclinical evaluation typically

consists of testing on animal models in order to assess for the level of antigen recognition, toxicology, and protective effects of the proposed vaccine. Phase I trials are designed to test vaccine safety and are centered around finding a balanced dose that the human body can tolerate without having serious side effects.<sup>5</sup> Phase II trials expand the safety profile and immune response assessment in a larger number of participants while also taking into consideration the effect of different variables such as age, gender, ethnicity, and the presence of other comorbid disease. Phase III trials are designed to determine efficacy through utilization of blinded randomized controlled trials.<sup>5</sup> These phases are conducted systematically and in a measurable stride. Therefore, before engaging resources in a subsequent phase, it is important to ensure that the data from previous phases is convincing enough to warrant further development.<sup>5</sup> However, during this public health emergency, vaccine development for SARS-CoV-2 has been expedited, and as a result, multiple vaccines have been made available worldwide in record time. Although several phases have progressed simultaneously, safety criteria have remained stringent. In the United States, the Food and Drug Administration (FDA) has approved the

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progression of phases based on data generated in the prior steps and has also allocated massive financial resources into vaccine development. Within months, several vaccine candidates have entered the clinical development pipeline.<sup>6</sup> There are three types of COVID-19 vaccines available: a genetic vaccine, a viral vector vaccine, and an inactivated/attenuated vaccine. The first two vaccines that have been made available in the USA have been created by Pfizer-BioNTech and Moderna, and are both genetic, or messenger RNA (mRNA) vaccines. As time progressed, vaccines using adenovirus vectors began to become available. The viral vector vaccines available include one developed by Janssen-Johnson & Johnson in the USA, and others developed by Astra-Zeneca, Sputnik-V, and CanSino outside the USA. Another type of vaccine developed are inactivated whole-virus SARS-CoV-2 vaccines made by Bharat Biotech and Sinovac, which are only available outside the United States.<sup>7</sup>

## 2. Review of literature

### 2.1. Materials and methods

A non-systematic search of the literature in the PubMed and MEDLINE database using the term “COVID-19 vaccine” was undertaken until May 12th, 2021. The database identified 7601 results out of which, 34 studies including randomized controlled trials (RCTs), non-RCTs, and quasi-RCTs were reviewed to assess the indications, administration, immunogenicity, efficacy, safety and side effects profile. The studies were selected with the thought in mind to have the most recent and up to date data that held statistical significance.

### 2.2. Mechanisms of action

After the SARS-CoV-2 genetic sequence was determined in January 2020, a lipid-nanoparticle (LNP) encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein was developed by two companies, Pfizer-BioNTech and Moderna. The mechanism of action of mRNA vaccines is through targeted delivery of mRNA, which is then translated using the host's cellular machinery to produce a folded, functional protein against which the adaptive immune system becomes targeted.<sup>8</sup> The use of mRNA as the primary component in order to stimulate immunity against the virus has been shown to have numerous advantages including a higher safety profile, increased efficacy, as well as low expenditure.<sup>8,9</sup> The Pfizer-BioNTech SARS-CoV-2 vaccine, referred to as BNT162b1, contains mRNA

that encodes a specific portion of the spike protein, the receptor-binding domain (RBD), which plays an important role in attaching to and infecting host cells. In order to establish higher degrees of immunogenicity, the vaccine also contains the addition of a T4 fibrinogen-derived foldon trimerization domain to the RBD antigen.<sup>10</sup> Furthermore, to help facilitate entry of the mRNA into cells and to prevent degradation by extracellular RNases the mRNA in this vaccine is coated in cationic lipid nanoparticles.<sup>8,11</sup> Moderna's SARS-CoV-2 vaccine, known as mRNA-1273, contains mRNA that encodes for the entire full length spike protein of SARS-CoV-2 instead of only the RBD, however, it is also composed of mRNA coated in lipid nanoparticles.<sup>11,12</sup> Ad26.COV2.S, a vaccine developed by Janssen-Johnson & Johnson, and AZD1222, a vaccine developed by Oxford-AstraZeneca, both use a viral vector as their primary component. Viral vector vaccines use a recombinant attenuated virus that is designed to encode a particular antigen sequence and is introduced into host cells via a process known as transduction. Thereby, there is endogenous production of the antigen of interest, which in turn stimulates the humoral and cellular immune systems. Viral vector vaccines have the ability to be either replicating or nonreplicating. Replicating vectors having the power to produce a more amplified and immunogenic response, but also risk having the capability of reverting to virulence. Instead, non-replicating viral vectors have the inability to produce virulence, however, increased dosing is needed to confer an efficient level of immunity.<sup>13,14</sup> The Ad26.COV2.S vaccine uses a human adenovirus type 26 vector that is nonreplicating and that encodes a version of the spike “S” protein of SARS-CoV-2, stabilized by two proline mutations. The vaccine created by Oxford-AstraZeneca, named AZD1222, is similar to Ad26.COV2.S in that it is a viral vector vaccine, however, it uses a strain of adenovirus that is only found in chimpanzees called ChAdOX1.<sup>14,15</sup> BBV152, a vaccine developed by Bharat Biotech and available outside the United States, is created differently from most available vaccines as it contains an entire virion inactivated SARS-CoV-2, which is produced in Vero cells.<sup>16</sup> Vero cells are derived from the kidney of an African green monkey, the grivet, and are commonly used in mammalian research pertaining to molecular and cellular biology. The growth and culture properties of Vero cells, particularly its continuous lineage, allow it to replicate through numerous cycles of division. Vero cells have been licensed in the United States for the production of both live and inactivated viral vaccines, including the inactivated poliovirus vaccine.<sup>17,18</sup>

### 2.3. Efficacy

In a large phase III trial of over 36,000 participants aged 16 years or older, an analysis of 170 confirmed COVID-19 cases (8 in the vaccine group versus 162 in the placebo group), demonstrated that the Pfizer-BioNTech COVID vaccine had 95 percent efficacy (95% CI 90.3–97.6) in preventing symptomatic COVID-19 on and even after seven days following the second dose with a median follow up of 2 months.<sup>19,20</sup> These results could be interpreted into saying that in a population of those who received two doses of the Pfizer-BioNTech COVID vaccine, 95% of the time, 90.3 to 97.6 of that population will not present with symptomatic disease. Additionally, nine out of the ten severe cases that occurred during the study were in the placebo group. In a multivariate analysis, which is historically based on an analysis of more than one variable, results showed that in adults  $\geq 65$  years with either established medical comorbidities or obesity, the vaccine demonstrated an efficacy of 91.7 percent (95% CI 44.2–99.8). The vaccine efficacy was 100% (95% CI 75.3–100) among 1983 participants aged 12–15 years without evidence of prior infection.<sup>21</sup> Hence, the vaccine is approved by the US FDA for the emergency use authorization (EUA) to include adolescents 12 through 15 years of age.<sup>22</sup> The trial findings corroborated the observational data from various countries.<sup>23–26</sup> In Israel, a study using national surveillance data from more than 6.5 million individuals, out of which 72 percent had received BNT162b2, reports estimated vaccine effectiveness seven days or more following the second dose was 92 percent for COVID-19 infection, 97 percent for symptomatic COVID-19, 97 percent for COVID-19-related hospitalization, and 97 percent for COVID-19-related death.<sup>23</sup>

The Moderna mRNA-1273 vaccine had a 94.1 percent vaccine efficacy (95% CI 89.3–96.8) in preventing symptomatic COVID-19 at or after 14 days following the second dose in a large placebo-controlled phase III clinical trial.<sup>27</sup> This trial had nearly 30,000 study participants aged 18 years and older, that ensued in 196 confirmed COVID-19 cases (11 in the vaccine group and 185 in the placebo group) with a median follow-up of two months after vaccination. The vaccine efficacy was 86.4 percent (95% CI 61.4–95.5) among adults  $\geq 65$  years of age. All thirty severe cases happened in the placebo group. Observational data evaluating vaccine effectiveness also supported the trial findings. The estimated vaccine effectiveness for preventing COVID-19 hospitalization was 94 percent, which was shown in a study of 489 individuals, 65 years, only one

individual with confirmed COVID-19 by SARS-CoV-2 testing (0.5 percent) was hospitalized that had received the recommended two doses of an mRNA vaccine, although confidence intervals were wide because of the small sample size.<sup>28</sup>

The Janssen-Johnson & Johnson (Ad26.COV2.S) vaccine in a phase III clinical trial, given as a single dose, had 66.9 percent efficacy (95% CI 59.0–73.4) in preventing COVID-19 infection at or after 14 days following vaccination.<sup>14</sup> This trial was done in 40,000 study participants aged 18 years and older with a median follow-up of two months after vaccination, with 464 confirmed moderate to critical COVID-19 cases (116 in the vaccine group and 348 in the placebo group). At 14- and 28-days post-vaccination, the vaccine efficacy against severe/critical disease was 78 and 85 percent respectively.<sup>14</sup>

The Oxford-AstraZeneca (AZD1222) vaccine, in a report from a multinational phase III randomized trial comprising over 11,000 patients showed, the vaccine had 70.4 percent efficacy (95% CI 54.8–80.6) in preventing symptomatic COVID-19 at or after 14 days following the second dose.<sup>29</sup> On analysis, there were 131 confirmed COVID-19 cases (30 in the vaccine group and 101 in the control group). All of the ten hospitalized COVID patients, including two severe COVID-19 patients were in the control group. In a subsequent analysis of this trial, vaccine efficacy for revealed that receipt of the second dose at 12 weeks or later was associated with higher vaccine efficacy than receipt at  $< 6$  weeks (81 versus 55 percent).<sup>30</sup> These findings contributed support to extending the time interval for the second dose to 12 weeks. In Scotland, a nationwide that included over 600,000 individuals who received at least one dose of vaccine was associated with an 88 percent reduction in hospitalization for COVID-19 in the fourth week after vaccination.<sup>24</sup> Covaxin, also known as BBV152, which was developed in India by Bharat Biotech, has not had published efficacy trial, however a press release stated that among 25,800 participants reported an efficacy rate of 81 percent against symptomatic COVID-19 after an interim analysis of 43 cases (36 with placebo and 7 with vaccine).<sup>31</sup> The rest of the trial results have not yet been made public.

The above trials use 95% confidence interval which are a range of values that you can be 95% confident contains the true mean of the population. The studies also use median numbers rather than mean to return the central tendency for skewed number distributions otherwise the value of the mean would be dominated by the outliers rather than the typical values.

#### 2.4. Safety and side effects

Local and systemic adverse effects with Pfizer-BioNTech COVID vaccine are relatively common, particularly after the second dose. Most of the adverse effects are of mild or moderate severity (ie, do not prevent daily activities) and are limited to the first two days after vaccination.<sup>19,32,33</sup> Among 1.6 million vaccine recipients in the United States, a local injection site reaction comprised of pain, redness and swelling was reported in approximately 65 percent after each dose. Other mild side effects including fatigue, headache, and myalgias were reported in 29 and 48, 25 and 40, and 17 and 37 percent after the first dose and the second, respectively.<sup>19</sup> These reactions were also commonly reported among adolescents aged 12–15 years and less frequently among recipients 65 years or older but are still relatively common. In about 5 events per one million doses, anaphylaxis following vaccination has been reported.<sup>34</sup> Bell's palsy has also been noted in the phase III trial (four in vaccine and zero in placebo recipients),<sup>19</sup> however, the rate did not exceed those found in the general population. No other major vaccine-associated adverse events were

identified.<sup>33</sup> Similarly, in the Moderna mRNA-1273 vaccine, local and systemic adverse effects are relatively common, particularly after the second dose. Most of the adverse effects are of mild or moderate severity (ie, do not prevent daily activities) and are limited to the first two days after vaccination.<sup>32,33,35</sup> In a survey amongst 2 million vaccine recipients in the United States, an injection site reaction that comprised of pain, redness and swelling was reported in approximately 74 and 82 percent after first and second dose respectively. Other mild side effects including fatigue, headache, and myalgias were reported in 33 and 60, 27 and 53, and 21 and 51 percent after the first dose and the second, respectively.<sup>19</sup> Among recipients aged 65 years or older, the local and systemic reactions occurred less frequently but were still relatively common. Anaphylaxis has been reported in about 2.8 events per one million doses.<sup>34,36</sup> Following the first 7,581,429 doses of mRNA-1273 administered in the United States, 21 cases of anaphylaxis were reported to the CDC, with 86 percent occurred among individuals with pre-existing allergies, and 90 percent occurred within 30 min. Bell's palsy has also been noted in the clinical trial (three in vaccine and zero

Table 1. Showing COVID- 19 Vaccine comparisons.

	Pfizer (BNT162b1)	Moderna (mRNA-1273)	Janssen-Johnson&Johnson (Ad26.COV2.S)	Oxford-AstraZeneca (AZD1222)	Bharat Biotech (BBV152)
Number of Doses	Two doses, 0.3 mL each, 21 days apart. <sup>19</sup>	Two doses, 0.5 mL each, 28 days apart. <sup>35</sup>	One dose, 0.5 mL <sup>14</sup>	Two doses 4–12 weeks apart. The World Health Organization (WHO) recommends that the two doses be given 8–12 weeks apart <sup>29</sup>	Two doses 29 days apart. <sup>31</sup>
Age considerations	Approved for ages 12 and up. <sup>19,22</sup>	Approved for ages 18 and up. <sup>35</sup>	Approved for ages 18 and up. <sup>14</sup>	Approved for ages 18 and up <sup>29</sup>	Approved for ages 18 and up <sup>31</sup>
Number of subjects tested	36,000 <sup>19,20</sup>	30,000 <sup>27</sup>	40,000 <sup>14</sup>	11,000 <sup>29</sup>	25,800 <sup>31</sup>
Vaccine type	mRNA <sup>19,20</sup>	mRNA <sup>26</sup>	Viral Vector <sup>14</sup>		Inactivated whole virion
Efficacy	95% effective in preventing symptomatic COVID-19 97% effective in preventing severe disease 97% effective in preventing death and hospitalization <sup>19,20</sup>	94.1% effective in preventing symptomatic COVID-19 100% effective in preventing severe disease 94% effective in preventing death and hospitalization <sup>27</sup>	66.9% effective in preventing symptomatic COVID-19 78 and 85% effective in preventing severe disease at 14- and 28-days post vaccination. <sup>14</sup>	70.4 percent efficacy in preventing symptomatic COVID-19 Associated with an 88% reduction in hospitalization in the 4th week after vaccination. <sup>29</sup>	81% efficacy rate in preventing symptomatic COVID-19 <sup>31</sup>
Side effects	Injection site pain, fatigue, fever headache, muscle pain, joint pain, anaphylactic reaction. <sup>19</sup>	Injection site pain, fatigue, fever, headache, muscle pain, joint pain, fever, anaphylactic reaction. <sup>32,33,35</sup>	Injection site reactions, headache, fatigue, myalgia, nausea, fever, thromboembolic events. <sup>37</sup>	Fever, headache and thromboembolic events. <sup>37</sup>	Injection site pain, fever, fatigue, malaise, headaches. <sup>31</sup>

in placebo recipients).<sup>34</sup> However, the rate did not exceed those found in the general population. No other major vaccine-associated adverse events were identified.<sup>33</sup>

In the Janssen-Johnson & Johnson (Ad26.COV2.S) vaccine, local and systemic adverse effects are also reported to be relatively common. Most effects are of mild or moderate severity (ie, do not prevent undertaking daily activities) and most commonly occur the first day after vaccination.<sup>35</sup> Among over 330,000 vaccine recipients in the United States, 76 percent reported at least one systemic reaction and 61 percent at least one injection site reaction in the first week. Fatigue, pain, and headache were the most common systemic reactions. Serious adverse event rates in the vaccine and placebo group were similar.<sup>29</sup> In vaccinated patients compared with placebo patients, there were more cases of thromboembolic events (11 versus 3) and seizures (4 versus 1), but these events were not significant to determine whether there is a causal association with vaccination.<sup>29,37</sup>

In the Oxford-AstraZeneca (AZD1222) vaccine, the earlier-phase trial data reveals mild to moderate side effects like fatigue, headache, and fever in up to 8 percent of recipients.<sup>38</sup> There were two reported cases of transverse myelitis. The vaccine has also been associated with an extremely small risk of thrombotic events associated with thrombocytopenia. No clear-cut data regarding vaccine adverse effects is yet available for Covaxin by Bharat Biotech.

Table 1 is depicting the comparisons between BNT162b1, mRNA-1273, Ad26.COV2.S, AZD1222 and BBV152 COVID-19 vaccines.

### 3. Conclusion

While the five vaccines mentioned may share their fair amount of similarities and differences, there is no uncertainty in stating that the data from this study shows that they all are efficacious in preventing COVID-19 and its complications. Although going against historical precedent in regard to how rapidly they were produced, COVID-19 vaccine development was nonetheless rooted in a strong understanding of vaccine technology and immunogenicity, with safety protocols still kept to a high level of importance. With the numbers of individuals who are vaccinated against COVID-19 climbing every single day, there is hope that a return to normalcy will arrive sooner rather than later.

### Author contributions

Conceptualization: PG, Data curation and methodology: PG, HA, SB, writing: PG, HA, SB, formal analysis: PG, HA, SB.

### Conflicts of interest

The authors have no conflicts of interest associated with the material presented in the paper.

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