Review Article

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A comparative analysis on the safety and efficacy of Covaxin versus other vaccines against COVID-19: a review

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Abstract: Since the identification of the genomic sequence of SARS-CoV-2, an unprecedented effort is being made until this date for the development of a safe and effective vaccine by pharma companies and laboratories worldwide. To attain herd immunity and quite possibly recover from this pandemic, which has claimed the life of about 4.23 million people, an exceptional effort has been made by the scientific community for the development of a vaccine. Various vaccines have been developed based on different platforms and each of them seems to possess its own merits and demerits based on its safety, immunogenicity, the durability of immunity, dosing schedule, technological platform, and ease of manufacture and transport. Based on these parameters this review aims to critically assess the efficacy of Covaxin and compare it with other vaccines in the WHO EUL list and perform a comparative analysis of COVID-19 vaccines which are in phase 3 and phase 4 of clinical trials. This will help us determine where COVAXIN stands against other vaccines and vaccine candidates based on these parameters which will ultimately help us

determine the best vaccine that could potentially eradicate the COVID-19 pandemic.

Keywords: COVAXIN; herd immunity; SARS-CoV-2; vaccine; WHO EUL list.

1 Introduction

The coronavirus outbreak came into light on December 31, 2019, when China informed the World Health Organization (WHO) about a cluster of cases of pneumonia of an unknown cause in Wuhan city of Hubei province. Subsequently, the disease spread to more provinces of China, and the rest of the world and WHO declared it as a pandemic. The virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease is called coronavirus disease 2019 (COVID-19). The SARS-CoV-2 pandemic continues to spread throughout the world to this date [1].

After the identification of the SARS-CoV-2 virus and genome, the scientific community has made an exceptional effort to develop a safe and effective vaccine. According to WHO, 102 vaccines are in clinical development and 185 vaccines are in preclinical development. Seven of these vaccines are in Phase 4 clinical trials and are in phase 3 clinical trials, and vaccines are authorized to be used worldwide [1].

COVAXIN (code-named BBV152) is India's effort to make an indigenous COVID-19 vaccine. COVAXIN by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) – National Institute of Virology (NIV) [1].

COVAXIN is an inactivated virus-based COVID-19 vaccine and is developed using whole virion inactivated vero cell-derived platform technology that acts mainly targeting the viral spike protein. They contain a deadly virus that is incapable of infecting people but still able to instruct the immune system to trigger an immune response. Inactivated vaccines do not replicate and are therefore

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unlikely to revert and cause pathological effects. Additionally, COVAXIN also contains adjuvants toll-like receptor (TLR) 7/8 agonists and aluminum hydroxide which prompts a strong immune response [2].

With the increasing cases of COVID 19, there is a rapid rise of various virus variants. These variants had a mutation in the receptor-binding domain of S-protein, responsible for a high transmission rate among the individuals [3].

- The Alpha variant, also known as lineage B.1.1.7, is a subtype of the virus that causes COVID-19, SARS-CoV-2. The variant is 40-80% more transmissible than the wild-type SARS-CoV-2 (with most estimates occupying the middle to the higher end of this range). It was discovered in November 2020 from a sample obtained in September from the United Kingdom, and it swiftly spread by mid-December, about the same time when illnesses were on the rise. This rise is assumed to be caused by one or more mutations in the virus's spike protein. The variation is also remarkable for having a higher number of mutations [4].
- The Beta variant, also known as lineage B.1.351, was first detected from South Africa in October 2020 [5].
- The Gamma variant, also known as lineage P.1, was first detected in Brazil in November 2020 [6].
- The delta variant, also known as lineage B.1.617.2 was first detected in India in October 2020 [7].
- The Omicron variant, also known as lineage B.1.1.529 is one of the SARS-CoV-2 mutations that caused COVID-19. First detected in South Africa in November 2021. Studies are underway to understand the severity, transmissibility and effectiveness of vaccines on this variant [8].

The World Health Organization has not yet approved COVAXIN for emergency use listing and as a result, people vaccinated with COVAXIN are finding it difficult to be treated as vaccinated and be allowed to cross international borders. The WHO approval process of a vaccine consists of four steps: an acceptance of the manufacturer's expression of interest (EOI), a pre-submission meeting between WHO and the manufacturer, acceptance of the dossier for review by WHO, the decision on the status of assessment, and the final approval decision. For the case of COVAXIN by Bharat Biotech, the first step itself that is its EOI has not been accepted yet, and in its status report, WHO remarks that more information is required [9].

Emergency use listing by WHO is a procedure implemented during public health emergencies for assessing and listing new or unlicensed products. Only seven vaccines have been given EUL till now, including the Serum

Institute of India's Covishield. To grant a EUL the WHO will determine if Covaxin demonstrates a reasonable likelihood (of) quality, safety and effectiveness and if the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC (public health emergency of international concern) [10].

This study aims to critically assess the efficacy of Covaxin and compare it with other vaccines in the WHO EUL list and perform a comparative analysis of COVID-19 vaccines which are in phase 3 and phase 4 of clinical trials based on its attributes related to safety, immunogenicity, the durability of immunity, dosing schedule, technological platform, and ease of manufacture and transport. This analysis will help us determine how COVAXIN performs as compared to other vaccines and vaccine candidates based on its safety, immunogenicity, the durability of immunity, dosing schedule, technological platform, and ease of manufacture and transport. Furthermore, this study will help us determine the best vaccine that would be most practical and most effective for the ultimate goal of eradication of the COVID-19 pandemic.

2 What is Covaxin?

COVAXIN is an inactivated virus-based vaccine (Code name: BBV152). It mainly targets SARS-CoV-2 and is used intramuscularly (Route of administration). Covaxin was originated by "Bharat Biotech" and "Indian Council of Medical Research". After the final analysis of the phase III clinical trial, the efficacy of the vaccine was found to be 78%. In June 2020, the National Institute of Virology (ICMR's) received the permission of conducting Phase I and phase II clinical trials of this particular BBV152 vaccine from DCGI (Drug Controller General of India [11].

Phase II trial was found to have greater immune responses than that of Phase I clinical trial and also BBV152 had shown significantly greater neutralization responses in Phase II [12].

This vaccine is referred to as India's indigenousinactivated COVID-19 vaccine. Whole-virion inactivated vero cell is used to develop this particular vaccine. The inactivated vaccines mainly contain the dead virus and create a defensive action against infection. For decades these inactivated vaccines have been used against various viral diseases like encephalitis, influenza, polio, and rabies. Similarly, BBV152 has also been created by using the same technologies and methods. The immunepotentiators, the vaccine adjuvants, are added to BBV152 mainly to increase and boost its immunogenicity. This vaccine is stable at about 2-8 °C. It involves two

vaccination regimens. Covaxin received the approval of conducting Phase III human trials [13].

The overall efficacy rates as claimed by Bharat biotech include: For Asymptomatic cases: 63% Covaxin efficacy: For mild, moderate, and severe cases: 78% Covaxin efficacy; For Delta variant: 65% Covaxin efficacy; and regarding severe Covid-19 cases there is 93% Covaxin efficacy. The Alpha variant was identified in December 2020 and Covaxin was found to be effective in neutralizing this strain. The particular vaccine was found to have the neutralizing capacity regarding the Beta and Delta variant too which causes Covid-19 [14].

It is considered to be one of the important vaccines for everyone including children and has the potential to play a key role in saving lives. The vaccine destroys the ability of the particular coronavirus from its multiplication and increases the immune system to fight against the virus. It helps in preventing the spreading of SARS-CoV-2 [15].

The vaccine is not having such serious side effects but there may be pain and inflammation at the site of injection, pyrexia, body pain, pain in the abdomen, cold and cough, drowsiness, headaches, wooziness, and retching [16].

The clinical trials in the case of the age groups of about 2-18 years were conducted in AIIMS Delhi and Patna (Approved by the Drug Controller General of India). The vaccine can lower the risk of getting serious infections. The vaccine was accorded in the emergency list in Venezuela, Iran, the Philippines, Nepal, and many more [17].

The person who is more sensitive regarding the side effects can choose COVAXIN as a safer option as the side effects are mild in this case. This particular vaccine has the ability to prevent the risks of blood clotting like side effects that are rarely caused by some other vaccines and can be replaced in place of that. The vaccine cannot fully prevent the particular Covid infection but it can minimize the severity as well as mortality risks associated with Covid [16].

2.1 Mechanism of Covaxin

Covaxin (Codenamed as BBV152) is obtained from SARS-CoV-2 strain isolated at the NIV, Pune (Indian virology research institute) which is an inactivated vaccine. Inactivated vaccines are incapable of replication and hence do not cause pathological effects and do not revert. They contain dead viruses, incapable of infecting people but still instruct the immune system to mount a defensive action against infection. Inactivated vaccines have been used for diseases such as seasonal influenza,

polio, pertussis, rabies, and Japanese encephalitis. It is a well-established and time-tested platform in the world of vaccine technology. BBV152 is a whole-virion β-propionolactone inactivated SARS-COV2 vaccine (3 or 6 ug) formulated with a toll-like receptor 7/8 agonist molecule (IMDG) adsorbed to alum (Algel) [12].

Covaxin works by making antibodies against the SARS-CoV-2 coronavirus [12]. The antibodies attach to the spike proteins that are present on the surface of the virus. After producing a large number of coronaviruses, the researchers doused them with a chemical compound called beta propiolactone that disabled the coronaviruses by bonding to their genes. The inactivated coronaviruses could no longer replicate. But their proteins, including spike, remained intact. The researchers withdrew the inactivated viruses and mixed them with a tiny amount of an adjuvant, an aluminum-based compound that stimulates the immune system to boost its response to a vaccine. Once inside the body, some of the inactivated viruses are swallowed by a type of immune cell called an antigenpresenting cell. The antigen-presenting cell tears the virus apart and displays some of its fragments on the surface. The helper T cell may detect the fragment. If the fragment fits into one of its surface proteins, the T cell gets activated and can help recruit other immune cells to respond to the vaccine [18].

Another type of immune cell, called the B cell, also encounters the inactivated coronavirus. When a B cell locks on, it can pull part or all of the virus inside and present coronavirus fragments on its surface. A helper T cell activated against the coronavirus latches onto a similar fragment and the B cell gets activated as well. It proliferates and pours out antibodies that have the same shape as their surface proteins. After vaccination with Covaxin, the immune system responds to an infection of live coronaviruses. The B cells produce antibodies that stick to the invaders. Antibodies that target the spike protein can prevent the virus from entering the cells. Other types of antibodies may block the virus by another means (Figure 1) [19].

2.2 Efficacy of COVAXIN

Bharat biotech concludes the final analysis of Covaxin phase III clinical trial efficacy as 77.8% effective against symptomatic COVID19, 93.4% effective against severe symptomatic COVID-19 Efficacy against asymptomatic COVID19is 63.6%, Efficacy data demonstrates 65.2% protection against the SARS-CoV-2, B.1.617.2 Delta variant [20].

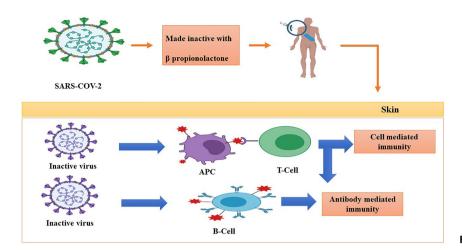


Figure 1: Mechanism of Covaxin.

3 COVAXIN versus other vaccines

3.1 COVISHIELD

- COVISHIELD was manufactured by cooperation and a technology transfer from AstraZeneca – The University of Oxford to SIIPL. COVISHIELD is a monovalent vaccine made of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2 [21]. Following administration, the S glycoprotein of SARS-CoV-2 has expressed locally stimulating neutralizing antibody and cellular immune responses [22].
- Covishield is highly immunogenic, with a seroconversion of binding antibodies >97% and of live virus-neutralizing antibodies >80% after a single standard dose (SD) or low dose (LD), and >99% of both antibodies after a second SD Seroconversion for both binding and neutralizing antibodies increased with increasing dose intervals between the first and second vaccine dose. Moreover, the efficacy of the vaccine increased if the dosing interval was kept between 4 and 12 weeks [23].
- Safety reports concluded as safe in adults and older adults with low serious adverse effects. Immunocompromised persons must be vaccinated after counselling. Very low data were available to assess vaccine safety in pregnancy. It is not recommended to people with a severe allergic reaction to any component of the vaccine and persons younger than 18 years [24]. However, the Global Advisory Committee on Vaccine Safety (GACVS) reviewed the latest evidence of rare adverse blood coagulation events called Thrombocytopenia syndrome (TTS). However, the available data appears to be very low [24].

On the other hand, Covaxin is recommended and safe for adults and older adults. The person below 18 years is barred from taking Covaxin. There are insufficient data available about safety profile in pregnant women. Individuals who are allergic to any component of Covaxin are not advised to take it. An immunocompromised person can take Covaxin if they have no contraindication to vaccination. Overall efficacy of Covieshield is 70.42% and Covaxin is 77.8% [25].

3.2 Ad26.COV2.S

- Ad26.COV2.S, manufactured by Janssen pharmaceuticals, is a viral vector vaccine that uses adenovirus as a delivery vehicle. The adenoviral genes are removed making it replication-incompetent due to deletions in the E1 gene. In addition to this genomic deletion, a part of the E3 gene region has been removed to create sufficient space in the viral genome for the insertion of foreign antigens [26]. The viral vector (Ad26.COV2.S) contains a transgene that encodes a modified full-length SARS-CoV-2 spike protein. Following administration, the spike protein is expressed and stimulates an adaptive humoral and cellular immune response [27].
- Immunogenicity of AD26.COV2.S gives cellular responses such that a single dose of Ad26.COV2.S elicited SARS-CoV-2 CD4 and CD8 T-cell responses by Day 15 (14 days post-dose 1) and up to Day 29 (28 days post-dose 1) in adult participants ≥18 to ≤55 years and ≥65 years of age. In all participants with a CD4 T-cell response, the response was skewed towards the Th1 phenotype [28].
- Safe in adults, older people and with people having a medical condition like hypertension, chronic lung

disease, cardiac disease, obesity, and diabetes. The vaccine can be offered to breastfeeding women. Very little data is available to access vaccine safety in pregnancy and vaccines can be given if only benefits outweigh the potential risk. Vaccines are not recommended to the person below 18 and individuals with a history of anaphylaxis and anyone with a body temperature above 38.5 °C. On the other hand, Covaxin is recommended and safe to adults and older adults. Person below 18 years are barred from taking Covaxin. There is insufficient data available about the safety profile of pregnant women. Individuals who are allergic to any component of Covaxin are not advised to take it. An immunocompromised person can take Covaxin if they have no contraindication to vaccination [29]. Overall efficacy of Ad26.COV2.S is 66.9% and Covaxin is 77.8% [30].

3.3 TOZINAMERAN/BNT162b2

- BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. It is a vaccine for preventing coronavirus disease 2019 (COVID-19) in individuals aged 16 years and older [31].
- Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) that is produced by using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 [32].
- Immunogenicity was measured with neutralization assay and S1-binding IgG assay. Immune responsiveness also seems to be age-dependent. The immunogenicity data generated in phase 1 and phase 2 studies suggest that the vaccine is capable of inducing a strong immune response, in both the neutralization assays as well as the S1-binding IgG assay [33].
- Safety studies were reviewed for solicited local/systemic reactions, unsolicited and serious adverse events. The reported local and systemic adverse reactions include injection site pain, fatigue, headache, myalgia, chills, arthralgia, and fever. The only unsolicited adverse event reported was lymphadenopathy [34].
- Safe in adults and older adults. A person with comorbidities and an immunocompromised person should take a vaccine after proper counselling. Vaccine effectiveness is expected to be similar in lactating women as in other adults. The WHO recommends the

use of the COVID-19 vaccine in pregnant women when the benefits of vaccination to the pregnant woman outweigh the potential risks. Children aged 12-15 years having comorbidities can take the vaccine. Individuals with age below 12 years are barred from vaccination [34]. Covaxin is recommended and safe for adults and older adults. The person below 18 years is barred from taking covaxin. There are insufficient data available about safety profile in pregnant women. Individuals who are allergic to any component of covaxin are not advised to take it. An immunocompromised person can take covaxin if they have no contraindication to vaccination. The overall efficacy of BNT162b2 is 95% and covaxin is 77.8% [35].

3.4 ChAdOx1-S [recombinant]/AZD1222

- The ChAdOx1 nCoV-19 vaccine (AZD1222) consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2, with a tissue plasminogen activator leader sequence. ChAdOx1 nCoV-19 expresses a codon-optimized coding sequence for the spike protein [36].
- The genetic material in the vaccine, once injected into a person, enables the synthesis of spike protein that triggers the immune response that protects against COVID-19. When a vaccinated person comes in contact with SARS-CoV-2, the immune system will recognize the virus and prevent it from infecting the body's cells [37].
- AZD1222 was highly immunogenic, with a seroconversion of binding antibodies >97% and of live virusneutralizing antibodies >80% after a single standard dose (SD) or low dose (LD), and >99% of both antibodies after a second SD Seroconversion for both binding and neutralizing antibodies increased with increasing dose intervals between the first and second vaccine dose [38].
- The vaccine is well tolerated with mild to moderate local and systemic adverse events including headache, nausea, myalgia, arthralgia, injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia, and chills [39]. Safety reports concluded as safe in adults and older adults with low serious adverse effects. Immunocompromised persons must be vaccinated after counselling. Very low data are available to assess vaccine safety in pregnancy. It is not recommended to people with a severe allergic reaction to any component of the

vaccine and persons younger than 18 years (WHO Newsroom, 2021). However, the Global Advisory Committee on Vaccine Safety (GACVS) reviewed the latest evidence of rare adverse blood coagulation events called Thrombocytopenia syndrome (TTS). However, the available data appears to be very low [39].

On the other hand, Covaxin is recommended and safe for adults and older adults. The person below 18 years is barred from taking Covaxin. There are insufficient data available about safety profile in pregnant women. Individuals who are allergic to any component of Covaxin are not advised to take it. An immunocompromised person can take Covaxin if they have no contradiction to vaccination. Overall efficacy of Covishield is 63.09% and Covaxin is 77.8%.

3.5 mRNA-1273

- This vaccine encodes a stabilized version of the SARS-CoV-2 full-length spike glycoprotein trimer, S-2P, which has been modified to include two proline substitutions at the top of the central helix in the S2 subunit. The mRNA is encapsulated in lipid nanoparticles at a concentration of 0.5 mg per ml and diluted with normal saline to achieve the final target vaccine concentrations [40].
- The vaccine is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 [41].
- Intracellular cytokine stimulation assay was used to evaluate T-cell responses elicited by the mRNA-1273 vaccine. The 25, 100, and 250 µg doses elicited CD4+ T-cell responses that upon stimulation by S-specific peptide pools were strongly biased toward the expression of Th1 cytokines, with minimal Th2 cytokine expression. CD8+ T-cell responses to S-2P were detected at low levels after the second injection in the 100-µg dose group [40]. This Th1-dominant profile adds to the body of nonclinical data suggesting that mRNA-1273 is unlikely to lead to enhanced disease following natural exposure to SARS-CoV-2 [42].
- The mRNA-1273 vaccine is safe in adults and older adults. A person with comorbidities is also safe to take the vaccine. An immunocompromised person should take a vaccine before proper counselling. The WHO recommends the use of the COVID-19 vaccine in pregnant women when the benefits of vaccination to

the pregnant woman outweigh the potential risks. An individual with allergic to any component of vaccine, person younger than 18 years should not be administered the vaccine [43]. Covaxin is recommended and safe for adults and older adults. The person below 18 years is barred from taking Covaxin. There are insufficient data available about safety profile in pregnant women. Individuals who are allergic to any component of Covaxin are not advised to take it. An immunocompromised person can take Covaxin if they have no contraindication to vaccination. Overall, the efficacy of mRNA-1273 is 94.1% and Covaxin is 77.8% [44].

3.6 SINOVAC (CoronaVac)

Sinovac or Coronavac developed by Sinovac Research and Development Co., Ltd is a vaccine with inactivated SARS-COV2 virus (Inactivated vaccine). It is an inactivated SARS-CoV-2 virus adsorbed on aluminum hydroxide and diluted in sodium chloride and phosphate-buffered saline [45]. The vaccine is recommended for persons with comorbidities that have been identified as increasing the risk of severe COVID-19, which includes obesity, cardiovascular disease, and respiratory disease [46]. CoronaVac was well-tolerated and safe and induced humoral responses in children and adolescents aged 3-17 years [47].

Safe in adults and older adults, and insufficient data for pregnant women. A person with comorbidities can take the Sinovac vaccine. Its effectiveness is similar in lactating women as in other adults. An immunocompromised person should be given a vaccine after proper counselling. An individual with anaphylaxis to any component of vaccines, children below 18, and those body temperatures over 38.5 °C is not recommended to take vaccine [48]. On the other hand, Covaxin is recommended and safe for adults and older adults. The person below 18 years is barred from taking Covaxin. There are insufficient data available about safety profile in pregnant women. Individuals who are allergic to any component of Covaxin are not advised to take it. An immunocompromised person can take Covaxin if they have no contraindication to vaccination. The overall efficacy of Sinovac is 50.4% [49] and Covaxin is 77.8%.

3.7 BIBP(Sinopharm) vaccine

SINOPHARM vaccines manufactured by China National Pharmaceutical CO., Ltd and Beijing Institute of Biological products are also referred to as BIBP-CorV or BIBP Covid-19 vaccine. The vaccine contains the inactivated form of virus (inactivated with β-propiolactone) It involves the purification of the SARS-CoV-2 which is absorbed by using aluminum hydroxide and thus produces no harm after the administration. It has completed the phase III clinical trials in Pakistan, Argentina, Egypt, Peru, and many more [50].

- It is considered to be the first vaccine containing a "Vaccine Vial Monitor" which is a kind of little sticker that changes colour if and only if the vaccine is exposed to heat [51]. Between the two doses of vaccination of Sinopharm, a period of 3-4 weeks has been suggested by the WHO [52]. The Sinopharm vaccine helps in producing antibodies against the SARS-CoV-2 coronavirus and supports the immune system [53]. The antibodies get attached to the spike proteins present on the surface of the virus. This helps in preventing the virus from entering the cell. In the case of healthy people, it is considered to be the safer and more immunogenic vaccine [50].
- It is a vaccine with a good safety profile and can be used in the case of pregnant women. The vaccine is also recommended to people who have suffered from Covid-19 earlier. It can be used in the case of people around 18 years of age and above but not below 18 years. The effectiveness of the vaccine is found to be similar between other adults as well as lactating women and discontinuing breastfeeding has not been recommended vet after the vaccination. Persons associated with a history of anaphylaxis should not take this vaccine and also the person suffering from fever should postpone the vaccination. The side effects of the vaccine are mild and nonserious. Safety monitoring is maintained in the case of the older patients regarding vaccination [52]. On the other hand, Covaxin is recommended and safe for adults and older adults. The person below 18 years is barred from taking Covaxin. There are insufficient data available about safety profile in pregnant women. Individuals who are allergic to any component of Covaxin are not advised to take it. An immunocompromised person can take Covaxin if they have no contraindication to vaccination.

Overall efficacy of Sinopharm (BIBP-CorV) is 78% [50] and Covaxin is 77.8% (Table 1).

4 Discussion

The COVID-19 pandemic continues to spread till this date and the emergence of multiple variants (Alpha, Beta,

Gamma, Delta) which is believed to spread more rapidly than other variants have led to even more cases of COVID-19 which is a cause of great concern [56, 57]. The scientific community continues to work for the development of a cure, but until a cure is developed vaccination is the only way to prevent and perhaps someday completely eradicate the COVID-19 pandemic [58, 59].

Different pharma companies and laboratories worldwide have made a tremendous effort to the development of a vaccine [60]. According to WHO, 102 vaccine candidates are in clinical development and 185 vaccine candidates are in preclinical development [61]. A massive vaccination strategy is required that is systematically planned to ensure maximum possible vaccination in the shortest period, with coverage to highly vulnerable groups like healthcare workers. To meet the tremendous global demand for the COVID-19 vaccine, many strategic alliances are being formed between pharmaceutical companies and institutions.

Vaccines that are based on an inactivated virus platform and some viral vector platforms that require storage at 2-8 °C are relatively easier for transport and distribution than nucleic acid that require storage at around -90 to -60 °C may face problems for distribution in rural areas [62]. Vaccines are administered through the intramuscular route [63]. Some vaccines are based on an inactivated virus platform when mixed with a tiny amount of an adjuvant, an aluminum-based compound that stimulates the immune system to boost its response to a vaccine as used by Bharat Biotech's Covaxin [64]. Newer vaccines are now boasting an efficacy rate of over 90% after administration of 2nd dose like BioNTech'sTozinameran has an efficacy of 94.7-95% after 2nd dose and Moderna Biotech's mRNA-1273 where the mRNA is encapsulated in lipid nanoparticles has yielded an efficacy of 94.1%. mRNA vaccines have shown a greater efficacy against alpha, beta, and delta variants (BioNTech'sTozinameranis effective against both alpha and beta variants with 95% effective against severe disease or death, it is 88% effective against symptomatic disease and 96% against hospitalization caused by delta variant) [64].

Covaxin is effective against the beta variant although with a three-fold reduction in neutralization. Covaxin came out to be 65% effective against delta variant [65]. Vaccine effectiveness against all variant-related COVID-19 illness was 71%, with 90% efficacy against Kappa and 65% efficacy against Delta [66]. In light of these findings, WHO advises using the BBV152 vaccine in accordance with the WHO Prioritization Roadmap, even if the nation contains presently recognised variants of concern (VOC). If new VOCs emerge that impact vaccination performance, the guidelines will be

Table 1: Comparison of different vaccines in terms of safety and efficacy [54, 55].

Vaccine	Manufacturer	Platform	Shot and route of administration	Storage	Efficacy	Gap between 1st and 2nd dose	Adverse drug reactions
COVAXIN	Bharat biotech	Whole-virion inactivated vero cell	2 I.M	2-8 °C	77.8%	4 weeks	Injection site pain, Swelling, Redness, Itching Headache Fever Malaise, body ache Nausea Vomit- ing Rashes
Covishield (ChAdOx1_nCoV19)	Serum Institute of India Pvt.Ltd	Recombinant ChAdOx1 adenoviral vector encoding the Spike protein antigen of the SARS-CoV-2	1–2 I.M	2-8 °C.	70.42%	12–16 weeks	Headache, nausea, myalgia, arthralgia, fatigue, malaise, fever- ishness, chills, fever, and local in- jection site reactions
Ad26.COV2.S	Janssen pharmaceutical	Recombinant, replication- incompetent adenovirus type 26 (Ad26) vectored vaccine encod- ing the (SARS-CoV-2) Spike (S) protein	1 M.:	Unopen vial- (-25 to -15 °C) or (2-8 °C UPTO 3 months) Open vial-(2- 8 °C.)for 6 h	%6.99	2-6 months	Headache, Nausea, Myalgia, Fatigue; injection site pain, Arthralgia, Cough, Pyrexia; injection site erythema; injection site swelling; chills, anaphylaxis.
Tozinameran/ BNT162b2	BioNTech Manufacturing GmbH	Nucleoside modified mRNA	2; IM	−90 to −60 °C	Before 2nd dose – 52.4% After 2nd dose – 94.7–95%	21 to 28-day	Pain at the injection site; Fatigue; Headache; Muscle pain; Chills; Joint pain; Fever Rare ADR- Bell's palsy;
ChAdOx1-S [recombinant]/AZD1222	SK Bioscience Co Limited (Republic of Korea)	ChAdOx1 nCov-19, a recombinant, replication-deficient simian adenovirus encoding SARS-CoV-2 (nCoV-19) spike protein with a tissue plasminogen activator (tPA) leader sequence	2; IM	2–8 °C	63.09%	8–12 weeks	Pain at the injection site; Fatigue; Chills; Fever; Headache; Joint pain; Muscle pain; Nausea; Vomiting; Diarrhoea Rare ADR- Dizziness; Abdominal pain; Lymph node enlargement; Thrombocytopenia
mRNA- 1273	Moderna Biotech	A novel, lipid nanoparticle (LNP)- encapsulated, mRNA-based vaccine against SARS-CoV-2	2; IM	–25 to –15 °C.	94.1%	28 days or 42 days	Anaphylaxis
SINOVAC Commercial name (CoronaVac)	Sinovac Research and Development Co., Ltd	Inactivated virus	A	2-8 °C	50.4% (symptomatic infection 100% (against severe Covid 19) 100% (against hospitalization starting 14 days after 2nd dose	2–4 weeks	Pain, swelling, pruritus, erythema, induration, burn at the injection site Headache, fatigue, nausea, diarrhoea, cough, chills, anorexia, vomiting, hypersensitivity, abdominal pain, oedema, drowsiness, dizziness, muscle spasms, eyelid oedema, hyposmia, ocular

Vaccine	Manufacturer	Platform	Shot and route Storage of administration	Storage	Efficacy	Gap between 1st and 2nd dose	Gap between Adverse drug reactions 1st and 2nd dose
SINOPHARM (BIBP-CorV)	China National Pharmaceutical Group Co., Ltd + Beijing Institute	InactivatedVirus	1–2; IM	2–8°C for 24 months	78%	3-4 weeks	congestion, hot flashes, hiccup, conjunctival congestion, constipation Cough, fever, sore throat Injection site reactions, headaches, fatigues, pain, fever, serious nausea, sleeping sickness.
	מו בומנים וביות לו מתכנים						

Table 1: (continued)

revised accordingly. There is currently no information available for Covaxin efficacy on omicron [67].

Further research is required to explore the quality, efficacy, and safety of these vaccines as a result of the exclusion of children, pregnant women, and other vulnerable groups from the clinical studies conducted till now. Moreover, the long-term safety of these vaccines and durability of immunity remains to be explored [68].

To combat the disease the only strategy until a cure is developed is to attain herd immunity among the populations which is necessary to prevent the spread of the disease. For achieving herd immunity, a proper vaccine is to be administered that is effective and safe not only symptomatically but could also prevent further infections, and can be produced and distributed in adequate quantities to meet the global demands. A massive vaccination strategy is to be developed ensuring that a maximum number of individuals can be vaccinated in the shortest period for the world to recover from this pandemic and someday return to normality [64].

5 Conclusion

The combined efforts of companies are producing an efficacious vaccine. For mass vaccination of people of a different country, we require a lot number of vaccine candidate which is safe as well effective. For that greater number of vaccines should be added to the EUL list of the WHO. Moreover, from the above comparison of our indigenous Bharat biotech vaccine "Covaxin" with other EUL list vaccines, we can say that Covaxin is equally safe and effective.

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References

- 1. Singh AK, Phatak S, Singh NK, Gupta A, Sharma A, Bhattacharjee K, et al. Antibody response after first-dose of ChAdOx1-nCOV (Covishield) and BBV-152 (Covaxin) amongst health care workers in India: preliminary results of crosssectional coronavirus vaccine-induced antibody titre (COVAT) study. Vaccine 2021;39:6492-509.
- 2. Vasilakos JP, Tomai MA. The use of Toll-like receptor 7/8 agonists as vaccine adjuvants. Expet Rev Vaccine 2013;12:809-19.
- 3. Malik IA, Ahmed S, Mir A, Shinde M, Bender O, Alshammari F. et al. The SARS-CoV-2 mutation versus vaccine effectiveness: new

- opportunities to new challenges. J Infect Public Health 2022;15: 228-40.
- 4. Peacock S. Here's what we know about the new variant of coronavirus. The Guardian; 2020. p. 22.
- 5. Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 2020:182:812-27.
- 6. Kumar S, Sharma V, Sarkar S, Ludhiadch A. Battle against the pandemic: emergence of SARS-CoV2 variants and global challenge. Trav Med Infect Dis 2021;44. https://doi.org/10.1016/ j.tmaid.2021.102173.
- 7. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 2021;596:276-80.
- 8. COVID C, Team R. SARS-CoV-2 B. 1.1. 529 (omicron) variant-United States, December 1-8, 2021. Morb Mortal Wkly Rep. 2021; 70:1731.
- 9. Mehrotra A, Gupta B. COVAXIN approval: need for recognition.
- 10. BIO S. Status of COVID-19 vaccines within WHO EUL/PQ evaluation process. Assessment 2021.
- 11. Ella R, Reddy S, Jogdand H, Sarangi V, Ganneru B, Prasad S, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis 2021;
- 12. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis 2021;21:637-46.
- 13. Ganneru B, Jogdand H, Daram VK, Das D, Molugu NR, Prasad SD, et al. Th1 skewed immune response of whole virion inactivated SARS CoV 2 vaccine and its safety evaluation. iScience 2021;24: 102298.
- 14. Sapkal GN, Yaday PD, Ella R, Deshpande GR, Sahay RR, Gupta N, et al. Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B. 1.1. 7 variant of SARS-CoV-2. J Trav Med 2021;28:taab051. https://doi.org/10.1093/jtm/
- 15. Singh Y, Fuloria NK, Fuloria S, Subramaniyan V, Almalki WH, Gupta G, et al. Disruption of the biological activity of proteaseactivated receptors2/4 in adults rather than children in SARS CoV-2 virus-mediated mortality in COVID-19 infection. Drug Dev Res 2021;82:1075-8.
- 16. Pattanaik SS. COVID-19 pandemic and India's regional diplomacy. South Asian Surv 2021;28:92-110.
- 17. Kumar VM, Pandi-Perumal SR, Trakht I, Thyagarajan SP. Strategy for COVID-19 vaccination in India: the country with the second highest population and number of cases. NPJ Vaccines 2021;6:
- 18. Crasto A. BBIBP-CorV, sinopharm COVID-19 vaccine. New drug approvals. Available from: https://newdrugapprovals.org/2021/ 03/23/bbibp-corv-sinopharm-covid-19-vaccine/ [Accessed 12
- 19. Pollard AJ, Bijker EM. A guide to vaccinology: from basic principles to new developments. Nat Rev Immunol 2020:1-8. https://doi.org/10.1038/s41577-020-00479-7.

- 20. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet 2021; 398:2173-84.
- 21. Singh Y, Fuloria NK, Fuloria S, Subramaniyan V, Meenakshi DU, Chakravarthi S, et al. N-terminal domain of SARS CoV-2 spike protein mutation associated reduction in effectivity of neutralizing antibody with vaccinated individuals. J Med Virol 2021;93:5726-8.
- 22. van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, et al. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature 2020;586:578-82.
- 23. World Health Organisation, "Recommendation for an emergency use listing of oncovisheild" Submitted by SIIPL; 2021. Available from https://extranet.who.int/pqweb/vaccines/covid-19-vaccine-chadox1-s-recombinant-covishield.
- 24. World Health Organisation. News Detail "Global Advisory Committee on Vaccine Safety (GACVS) review of latest evidence of rare adverse blood coagulation events with AstraZeneca COVID-19 Vaccine (Vaxzevria and Covishield)"; 2021. Available from https://www.who.int/news/item/16-04-2021-globaladvisory-committee-on-vaccine-safety-(gacvs)-review-of-latestevidence-of-rare-adverse-blood-coagulation-events-withastrazeneca-covid-19-vaccine-(vaxzevria-and-covishield).
- 25. Phase BB. Results of COVAXIN®: India's first COVID-19 vaccine demonstrates interim clinical efficacy of 81%. covaxinphase3-efficacy-results.pdf (bharatbiotech.com). [Accessed 30 Mar 2021].
- 26. World Health Organisation. Newsroom features stories detail "The Janssen Ad26.COV2.S COVID-19 vaccine: What you need to know". Available from: https://www.who.int/news-room/ feature-stories/detail/the-j-j-covid-19-vaccine-what-you-needto-know [Accessed 2 Sep 2021].
- 27. Bos R. Rutten L. van der Lubbe IE. Bakkers MI. Hardenberg G. Wegmann F, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. NPJ Vaccines 2020;5. https://doi.org/10.1038/s41541-020-00243-x.
- 28. Stephenson KE, Le Gars M, Sadoff J, De Groot AM, Heerwegh D, Truyers C, et al. Immunogenicity of the Ad26. COV2. S vaccine for COVID-19. JAMA 2021;325:1535-44.
- 29. Wang C, Rademaker M, Tate B, Baker C, Foley P. SARS-CoV-2 (COVID-19) vaccination in dermatology patients on immunomodulatory and biologic agents: recommendations from the Australasian Medical Dermatology Group. Australas J Dermatol 2021;62:151-6.
- 30. Günl F, Mecate-Zambrano A, Rehländer S, Hinse S, Ludwig S, Brunotte L. Shooting at a moving target-effectiveness and emerging challenges for SARS-CoV-2 vaccine development. Vaccines 2021;9:1052.
- 31. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020. https://doi.org/10.1056/ nejmoa2034577.
- 32. Kim J, Eygeris Y, Gupta M, Sahay G. Self-assembled mRNA vaccines. Adv Drug Deliv Rev 2021;170:83-112.

- 33. Klasse PJ, Nixon DF, Moore JP. Immunogenicity of clinically relevant SARS-CoV-2 vaccines in nonhuman primates and humans. Sci Adv 2021;7:eabe8065.
- 34. World Health Organization. Recommendation for an emergency use listing of Tozinamaren (COVID-19 mRNA Vaccine(NUCLEOSIDE MODIFIED)Submitted byBioNTech Manufacturing GmbH; 2021. Available from: https://extranet. who.int/pgweb/vaccines/who-recommendation-covid-19-mrnavaccine-nucleoside-modified-comirnaty.
- 35. Dar MA, Chauhan P, Kumar P, Chauhan R, Murti K, Charan J, et al. Safety, efficacy, and immunogenicity of COVAXIN: a review. J Appl Pharmaceut Sci 2021;11:018-25.
- 36. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020;396:467-78.
- 37. Conti P, Caraffa A, Gallenga CE, Kritas SK, Frydas I, Younes A, et al. The British variant of the new coronavirus-19 (Sars-Cov-2) should not create a vaccine problem. J Biol Regul Homeost Agents 2021;35:1-4.
- 38. Chakraborty S, Mallajosyula V, Tato CM, Tan GS, Wang TT. SARS-CoV-2 vaccines in advanced clinical trials: where do we stand. Adv Drug Deliv Rev 2021;172:314-38.
- 39. World Health Organization. Recommendation for an emergency use listing of AZD1222 submitted by AstraZeneca AB and manufactured by SK Bioscience Co Ltd.; 2021. Available from: https://extranet.who.int/pqweb/vaccines/covid-19-vaccinechadox1-s-recombinant.
- 40. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383: 2427-38.
- 41. Granados-Riveron JT, Aquino-Jarquin G. Engineering of the current nucleoside-modified mRNA-LNP vaccines against SARS-CoV-2. Biomed Pharmacother 2021:142:111953.
- 42. Galdiero M, Folliero V, Zannella C, De Filippis A, Mali A, Rinaldi L, et al. SARS-CoV-2 vaccine development: where are we? Eur Rev Med Pharmacol Sci 2021;25:2752-84.
- 43. World Health Organization. Recommendation for an emergency use listing of Covid-19 mRNA Vaccine (nucleoside modified) Submitted by Moderna Biotech (Spain); 2021. Available from https://extranet.who.int/pqweb/vaccines/covid-19-mrnavaccine-nucleoside-modified.
- 44. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-16.
- 45. Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:803-12.
- 46. Güzel EÇ, Çelikkol A, Erdal B, Sedef N. Immunogenicity after CoronaVac vaccination. Rev Assoc Méd Bras 2021;67:1403-8.
- 47. Han B, Song Y, Li C, Yang W, Ma Q, Jiang Z, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a

- double-blind, randomised, controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;21:1645-53.
- 48. World Health Organization. Background document on the inactivated vaccine Sinovac-CoronaVac against COVID-19: background document to the WHO interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac, 24 May 2021. World Health Organization; 2021.
- 49. Mallapaty S. China COVID vaccine reports mixed results—what does that mean for the pandemic? Nature 2021:15. https://doi. org/10.1038/d41586-021-00785-7.
- 50. Crasto A. BBIBP-CorV, Sinopharm COVID-19 Vaccine. New Drug Approvals. Available from: https://newdrugapprovals.org/2021/ 03/23/bbibp-corv-sinopharm-covid-19-vaccine/ [Accessed 12 Apr 2021].
- 51. Zipursky S, Djingarey MH, Lodjo JC, Olodo L, Tiendrebeogo S, Ronveaux O. Benefits of using vaccines out of the cold chain: delivering meningitis A vaccine in a controlled temperature chain during the mass immunization campaign in Benin. Vaccine 2014; 32:1431-5.
- 52. World Health Organisation. Newsroom features stories detail "The Sinopharm COVID-19 vaccine: What you need to know"; 2021. Available from: https://www.who.int/news-room/featurestories/detail/the-sinopharm-covid-19-vaccine-what-you-needto-know.
- 53. Awadasseid A, Wu Y, Tanaka Y, Zhang W. Current advances in the development of SARS-CoV-2 vaccines. Int J Biol Sci 2021;
- 54. Narayanan DK, Kayarohanam S, Fuloria S, Fuloria NK, Janakiraman AK, Djearamane S, et al. Covid-19 vaccine candidates under clinical evaluation - a review. Int J Pharm Res 2021;13:4588-98.
- 55. Fan YJ, Chan KH, Hung IF. Safety and efficacy of COVID-19 vaccines: a systematic review and meta-analysis of different vaccines at phase 3. Vaccines 2021;9:989.
- 56. Jones A, Strigul N. Is spread of COVID-19 a chaotic epidemic? Chaos, Solit Fractals 2021:142:110376.
- 57. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 2021;596:276-80.
- 58. Atala A, Henn A, Lundberg M, Ahsan T, Greenberg J, Krukin J, et al. Regen med therapeutic opportunities for fighting COVID-19. Stem Cells Transl Med 2021;10:5-13.
- 59. Roberts R. Prevention pays: COVID-19 tells us it's time for a Sovereign Health Fund for disease prevention. Aust J Rural Health 2021;29:488-91.
- 60. Ciotti M, Ciccozzi M, Pieri M, Bernardini S. The COVID-19 pandemic: viral variants and vaccine efficacy. Crit Rev Clin Lab Sci 2021:1-0. https://doi.org/10.1080/10408363.2021. 1979462.
- 61. Al-Jighefee HT, Najjar H, Ahmed MN, Qush A, Awwad S, Kamareddine L. COVID-19 vaccine platforms: challenges and safety contemplations. Vaccines 2021;9:1196.
- 62. Li Y, Tenchov R, Smoot J, Liu C, Watkins S, Zhou Q. A comprehensive review of the global efforts on COVID-19 vaccine development. ACS Cent Sci 2021;7:512-33.
- 63. Cook IF. Subcutaneous vaccine administration-an outmoded practice. Hum Vaccines Immunother 2021;17:1329-41.

- 64. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines 2021;6:1-7.
- 65. Choudhary OP, Choudhary P, Singh I. India's COVID-19 vaccination drive: key challenges and resolutions. Lancet Infect Dis 2021;21:1483-4.
- 66. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, et al. Efficacy, safety, and lot-to-lot immunogenicity of an
- inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet 2021; 398:2173-84.
- 67. Ettaboina SK, Nakkala K, Laddha KS. A mini review on SARS-COVID-19-2 omicron variant (B. 1.1. 529). SciMed J 2021;3:399-406.
- 68. Hazarika I. Therapeutic drug monitoring (TDM): an aspect of clinical pharmacology and pharmacy practice. Ther Drug Monit 2015;5:27-34.