

DEVELOPMENT PROCESS OF COVAXIN AND COVISHIED AND THEIR COMPARITIVE STUDIES

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1) AIMS AND OBJECTIVES OF WORK

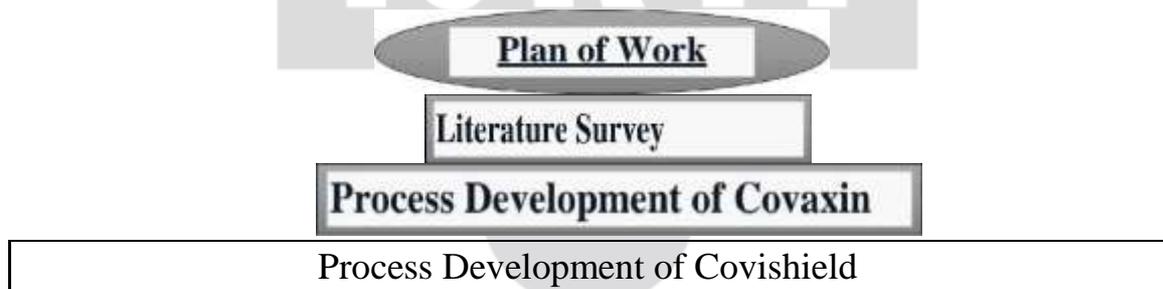
AIM: Development Process of COVAXIN and COVISHIELD and their comparative studies.

2) OBJECTIVE OF WORK

Covid-19 is a life threatening diseases. It spread all over the world. To prevent the transmission and prevent the spread of the virus in order to save lives vaccination has been shown to contribute to reducing deaths and severe illness from Covid-19. Vaccinating as many people as possible and reducing the spread of diseases is important. The main objectives of the projects are as follow :

- 1) To recognized the different types of vaccines which used in covid-19 treatments like
 - COVAXIN
 - COVISHEILD
- 2) To understand the Development process of Covaxin Indian"s first indegenious COVID vaccine successfully developed by Bharat Biotech collaboration with ICMR(Indian Council of Medical Research). It is giant leap for innovation and novel product development in India. The aim of vaccine is to provide it globally and highly purified.
- 3) To understand the Development process of Covishield. It produced by the Serum Institute of India and approved by Drug Controller General of India is one of vaccine approved by WHO. It is 70.4% effective against the novel coronavirus infection
- 4) To Discussed Comparative studies of development process of covishield and covaxin. Both drugs are used for Covid-19 treatments. The covishield developed by the University of Oxford and AstraZeneca. The covaxin developed by Bharat Biotech collaboration. The efficacy of covishield is 90% compared to efficacy of covaxin 60%to 70%.

3) PLAN OF WORK



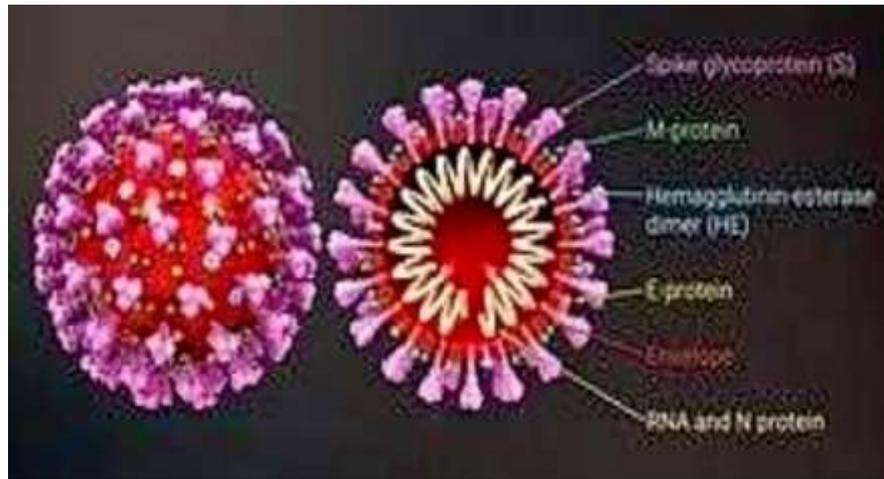
Comparative Study between Covaxin and Covishield

4) INTRODUCTION:

The Coronavirus (Covid-19) is a contagious disease caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2).The first known case was identified in Wuhan ,China in 31 December 2019 . The disease has since spread worldwide, leading to an on going pandemic. Novel coronavirus SARS-COV-2, designated as COVID-19 by the World Health Organization (WHO) on the February, is one of the highly pathogenic β - coronaviruses which infects human. The COVID-19 pandemic has become a significant

global health crisis. The virus has spread to more than countries worldwide and continues to infect more lives and cause more deaths. The second, and possibly the third wave, has begun, with hospitalizations and deaths rising continuously. The impact has galvanized research groups around the world that are working on novel diagnostics, vaccines, biotherapeutics, personal protective equipment, and epidemiological data analysis

STRUCTURE OF COVID-19:



• FIG 1: STRUCTURE OF COVID19

Coronavirus represents the large family of positive-sense ss RNA viruses belonging to the order Nidovirales. These usually cause diseases of the upper respiratory tract in birds and mammals, including humans. Seven coronaviruses have been identified as causing diseases in humans thus far. Coronaviruses are known to have a large genome, with sizes ranging from 26 to 30 kilobases. Corona, a Latin word for crown, depicts the spike-like protrusions on its surface.

ORIGIN OF SARS-COV-2:

The first COVID- case was reported in December in Wuhan, a city in Hubei province in China. The genomic sequences of SARS-CoV-2 isolated from many patients were shown to share a sequence identity higher than 99.9%, suggesting a very recent host shift from nature into humans. The phylogenetic tree constructed in research indicated that SARS-CoV-2 was closest to Ra TG (bat coronavirus), followed by GD Pangolin SARSr-COV-2, and then human SARS-COV-2e

SIGNS AND SYMPTOMS:

In people without prior ear, nose, and throat disorders, loss of taste combined with loss of smell is associated with COVID-19 of people who show symptoms, At least a third of the people who are infected with the virus do not develop noticeable symptoms at any point in time. These asymptomatic carriers tend not to get tested and can spread the disease.

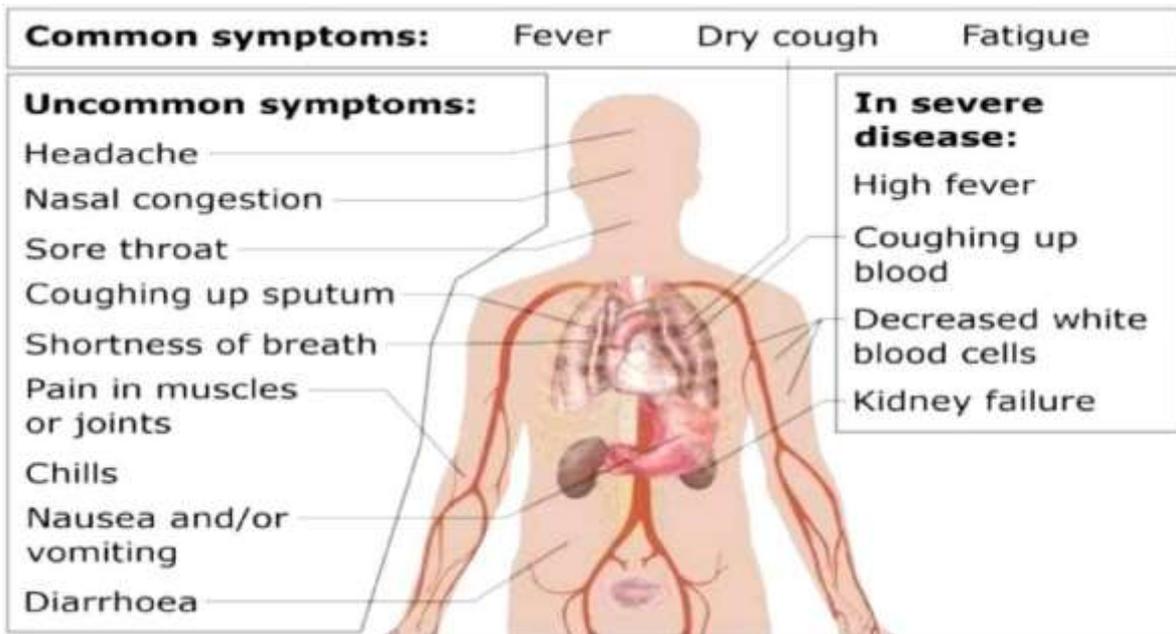


FIG 2: SIGN AND SYMPTOMS OF COVID-19

TRANSMISSION OF SARS-CoV-2:

SARS-CoV-2 is highly contagious and can be directly transmitted when an individual comes in contact with the respiratory droplets of an infected person or it can be indirectly transmitted by coming in contact with objects used or touched by an infected person.

The respiratory route of spread of COVID-19, encompassing larger droplets and aerosols. The disease is mainly transmitted via the respiratory route when people inhale droplets and particles that infected people release as they breathe, talk, cough, sneeze, or sing. Infected people are more likely to transmit COVID-19 the longer and closer they interact with others.

Infection can occur over longer distances, particularly indoors.



FIG 3: TRANSMISSION OF COVID19

VIROLOGY:

SARS-CoV-2 virion Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a novel severe acute respiratory syndrome coronavirus. It was first isolated from three people with pneumonia connected to the cluster of acute respiratory illness cases in Wuhan.

MECHANISM OF ENTRY AND REPLICATION OF

The virus enters the body through the nose, eyes, or mouth. The spike protein binds specifically to the ACE2 receptors present on the type pneumocytes in the alveoli in the lungs, just like the SARS-CoV-2. The type pneumocytes produce surfactants that reduce the collapsing pressure and also decrease the surface tension in alveoli.

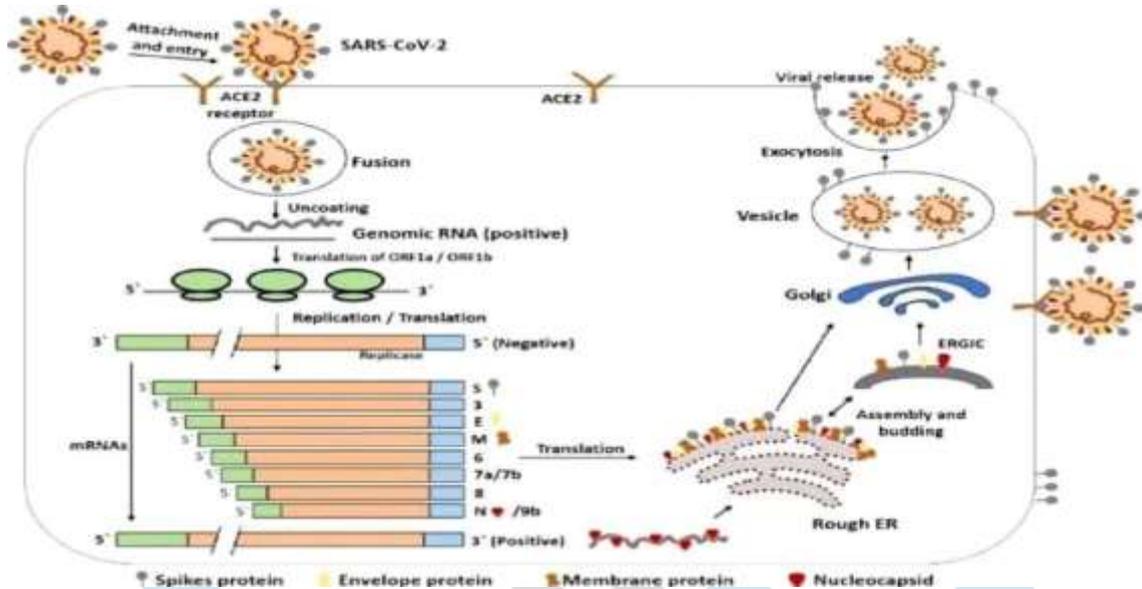


FIG 4: MECHANISM OF COVID-19

The binding of the ACE2 receptor allows the entry of the virus into the host cell due to host cell proteases that cleaves the spike protein of the virus. The virus enters the host cell either by direct cell entry by membrane fusion or by endocytosis. Unlike a typical flu virus that travels to the nucleus once inside the host cell, the SARS-CoV-2 releases its positive-sense RNA into the host cell cytoplasm.

This RNA is translated into polyproteins. These help in the replication and transcription of the viral RNA. The replication of positive-sense RNA using RNA-dependent RNA polymerase enzyme gives a negative-sense RNA. The negative-sense RNA is either replicated to give positive-sense RNAs (incorporated in the viral genome) or transcribed.

The transcribed mRNAs can be translated to produce viral proteins, like the spike, membrane, envelope, and nucleocapsid proteins. It is by exocytosis to infect other cells.

PATHOGENESIS:

COVID-19 pathogenesis COVID-19 can affect the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs). The lungs are the organs most affected by COVID- because the virus accesses host cells via the receptor for the enzyme angiotensin-converting enzyme (ACE), which is most abundant on the surface of type II alveolar cells of the lungs. The virus uses a special surface glycoprotein called "spike" (polymer) to connect to the ACE2 receptor and enter the host cell. Whether SARS-CoV-2 is able to invade the nervous system remains unknown however it is clear that many people with COVID- exhibit neurological or mental health issues.

IMMUNOPATHOLOGY:

Key components of the adaptive immune response to SARS-CoV-2. Clinical laboratory findings of elevated IL-2, IL-7, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma-induced protein (IP-), monocyte chemo attractant protein (MCP), macrophage inflammatory protein -alpha (MIP--

alpha), and tumor necrosis factor(TNF-u) Indicative of cytokine release syndrome (CRS) suggest an underlying immune pathology

DIAGNOSIS: COVID-19 can provisionally be diagnosed on the basis of symptoms and confirmed using reverse transcription polymerase chain reaction (RT-PCR) or other nucleic acid testing of infected secretions. Along with laboratory testing, chest CT scans may be helpful to diagnose COVID-19 in individuals with a high clinical suspicion of infection. Detection of a past infection is possible with serological tests, which detect antibodies produced by the body in response to the infection.

VIRAL TESTING:

Demonstration of a nasopharyngeal swab for COVID- testing *The standard methods of testing for presence of SARS-CoV-2 are nucleic acid tests, which detects the presence of Viral RNA fragments. As these tests detect RNA but not infectious virus, its "ability to determine duration of infectivity of patients is limited" The test is typically done on respiratory samples obtained by a nasopharyngeal swab; however, a nasal swab or sputum sample may also be used.

DIFFERENT TYPES OF VACCINES

2) **VACCINE :** It is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. Vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by a natural or "wild" pathogen), or therapeutic (to fight disease that has already occurred)

DIFFERENT TYPES OF COVID-19 VACCINES:

❖ **COVAXIN:**

COVAXIN, India's indigenous COVID-19 vaccine by Bharat Biotech is developed in collaboration with the Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV). The indigenous, inactivated vaccine is developed and manufactured in

Bharat Biotech's ,The vaccine is developed using Whole-Virion Inactivated Vero Cell derived platform technology. Inactivated vaccines do not replicate and are therefore unlikely to revert and cause pathological effects. They contain dead virus, incapable of infecting people but still able to instruct the immune system to mount a defensive reaction against an infection.

❖ **COVISHIELD•**

The Oxford-AstraZeneca vaccine is being manufactured locally by the Serum Institute of India, the world's largest vaccine manufacturer. It says it is producing more than 60 million doses a month. The vaccine is made from a weakened version of a common cold virus (known as an adenovirus) from chimpanzees. The Oxford-AstraZeneca vaccine is being manufactured locally by the Serum Institute of India. When the vaccine is injected into a patient, it prompts the immune system to start making antibodies and primes it to attack any coronavirus infection.

3) LITERATURE SURVEY:

1) Jeff Carven et al. (2021) COVID-19 as we know , it is dangerous virus spreads all over the world. To understand the origin, structure of covid, causes transmission of virus, virology, mechanism of replication and

how they enter into human cell. Also the pathogenesis, immunopathology, host factors, host cytokine, diagnosis, prevention, viral testing, and different types of vaccines. How vaccine are works into virus.

- 2) Pragya D Yadav et al. (2021) COVAXIN (BBV152) shows demonstration of Protective Efficacy and Immunogenicity in Non-Human Primates. A 2-dose vaccination regimen was administered in 20 rhesus macaques. The results showed protective efficacy, increase in SARS-CoV-2 specific IgG and neutralizing antibodies, reducing replication of the virus in the nasal cavity, throat and lung tissues of monkey. The vaccine candidate was found to generate robust immune responses.
- 3) Raches Ella, et al. (2021) safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double blind, randomized, multi center, phase 2 trials, and 3- month . The phase 2 trial on the immunogenicity and safety of BBV152, with the first dose administered on day 0 and the second dose on day 28.
- 4) Kamala Thiagarajan et al. (2021) COVAXIN -India's first Indigenous COVID-19 vaccine developed by Bharat Biotech collaboration with ICMR, using Whole Virion Inactivated Vero cell. Preclinical studies conducted in hamsters and non-human primates. The vaccine have DCGI approval for Phase I and Phase II India's first and largest phase 3 efficacy trial with 25,800 participants included in the trial.
- 5) To understand preclinical and clinical studies the vaccine shows the effective treatment against Covid-19 virus.
- 6) Jocelyn Solis Moreira et al. (2021) COVISHIELD -good safety profile. The medicine in India found the COVISHIELD (ChdOx1 nCoV-19) vaccine produced an immune response from severe acute respiratory syndrome. Study compares mRNA vaccine- elicited response to SARS-CoV-2 variants. the seropositivity rate at 98.2%. Side effects were reported two days after receiving a vaccine, then resolved soon.
- 7) Sohini Das and Ruchika Chitravanshi et al. (2021) COVAXIN AND COVISHIELD difference between -Covaxin is an inactivated viral vaccine. This vaccine is developed with Whole-virion inactivated vero cell derived technology. Covishield has been prepared using the viral vector platform which is a totally different platform. Second dose of covaxin and covishield are 4-6 weeks and 6-12 weeks respectively. The efficacy of covishield is 90% than covaxin is 70% after the phase 3 trials. The approval of covaxin granted approval for emergency restricted use and covishield has been allowed restricted use of emergency.
- 8) Abhay Pandey et al. (2020) Drug development process — The complexity in drug development has increased over the past 40 years, including preclinical testing, investigational new drug (IND), clinical testing before marketing approval from FDA .New drug application (NDAs) or biologicals license applications are comprehensively before approval. The drug performance is submitted to regulatory agencies for post marketing. The overall goal is more efficient and safer treatments.
- 9) Susan J. Bender and Susan R. Weiss et al. (2020) Pathogenesis, Prevention and Control of COVID-19 — It has spread rapidly across the globe. Scientists research is growing to develop a coronavirus vaccine and therapeutics for controlling the deadly covid-19. Health education knowledge is also important to control and reduce the coronavirus infection rate. Further research should be directed towards the study of SARS-CoV-2 on animals models for analyzing replication, transmission and pathogenesis in humans.

HOW COVID19 VACCINES ARE DEVELOPED RAPIDLY AS COMPARED TO TRADITIONAL VACCINES :

Vaccine development is a complex multidisciplinary activity, blending knowledge of host— pathogen Interactions with clinical science, population-level epidemiology, and the biomechanical requirements of production. The core is an insight into immune processes that influence the disease and protection and their

variation between individuals, risk groups, and populations. Traditional vaccine development has been a complex and time-consuming process that typically takes around 10—15 years.

Vaccine development usually begins with an exploratory stage focusing on basic research and computational modeling to find out potential natural or synthetic antigens as a vaccine candidate. After this, a pre-clinical study (18—30 months) starts with cell-culture followed

by animal studies to analyze the safety and immunogenic potential of the vaccine candidate. After appropriate in vivo results on safety, immunogenicity, and efficacy, human clinical trials initiated for safety and immunogenicity in small groups, and later in the large groups over 3 phases (Phase 1 or 1, 2 or 11 and 3 or 111)

The primary goal of Phase I trial (30 months) is to assess the safety and immunogenicity of the vaccine candidate. In Phase I trial, the vaccine is administered to less than a hundred healthy participants. If promising results are obtained in Phase 1, Phase 2 trial (32 months) is carried out in more than a hundred participants, divided into multiple groups by demographics. The goal of the phase 2 trial is to confirm the safety and immunogenicity of vaccine candidates. Also, the suitable dose required for Phase 3 is calculated. If encouraging results in Phase II trials are obtained, Phase 3 trial (— 30 months) is then carried out in thousands of participants to evaluate the efficacy. "Incidence of disease at the time of phase 3 trials Impacts the sample size" If there is a low incidence of disease in the community, large sample size will be required to satisfactorily decide the vaccine efficacy.

After completion of these trials, safety and the clinical efficacy are calculated, then the vaccine is reviewed for approval by regulatory bodies, such as Food and Drug Administration (FDA) of the United States of America (USA), or the European Medicines Agency in European Union (EU). Later, manufacturing and post-marketing surveillance are done after the vaccine is marketed for public use and monitored for general effectiveness within the population. Even after the vaccine is adopted for widespread use, events of adverse effects are recorded. The developer advances the vaccine development only if the data is promising, the risk of failure is relatively low and there is a market for the vaccine. The mumps was the only fastest developed and approved vaccine for use, taking about 5 years.

Even with this experience, it is clearly a big challenge to develop a vaccine against COVID19 in a span of 12—24 months. COVID-19 vaccine development has targeted to significantly reduce this 10—15-year timeline to 12—24 months. The initial process started as soon as the genome sequence of SARS-CoV-2 was available. The significant amount of time was saved by using the data from the preclinical development of vaccine candidates for SARS-CoV and MERS-CoV and omitting the initial step of the exploratory phase.

Some vaccine candidates used modified production processes from those of existing vaccine candidates while others used preclinical and toxicology data from related vaccines. Therefore, the first clinical trial of CVCS started in March 2020 (NCT04283461). Clinical trials were designed to reduce the time horizon by overlapping clinical trial phases. The initial phase I/II trials were followed by rapid advancement to phase III trials as soon as the interim analysis of the phase I/II data was completed.

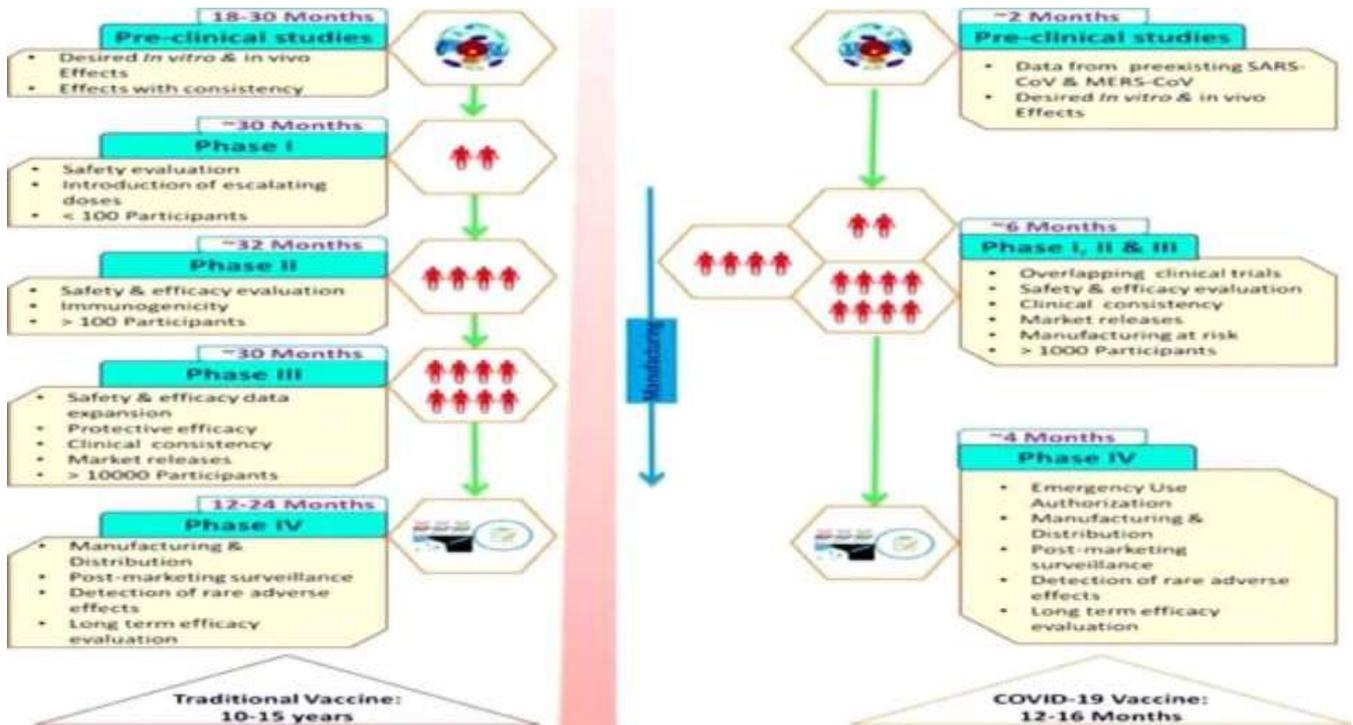
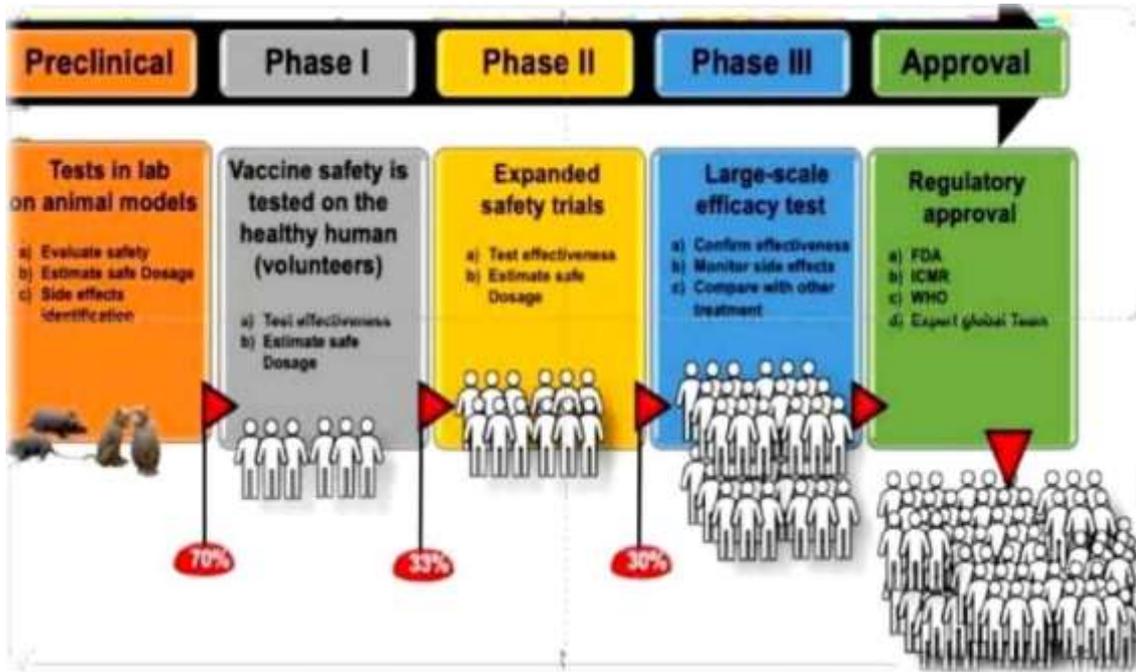


Fig. 5: Rapid development of COVID-19 vaccine as compared to traditional vaccine development. The US accelerated the development of five CVCs under the Operation Warp Speed to make them available by the end of 2020 for emergency use and have billions of doses ready by 2021. Manufacturers prepared themselves to rapidly produce billions of doses and few of them already started the commercial production of vaccines without any results from phase 3 trials.

7) ETHODS OF DEVELOPMENT PROCESS:

The development of a new therapeutic product is a long, complex and expensive process which typically takes 10 to 12 years from product to commercialization. It includes the process of drug discovery, preclinical research on microorganism and animals, FDA for an investigational new drug to initiate clinical trials on humans and may includes regulatory approval with anew drug application to market the dr'ug. Fives steps of development process are as follow:

- 1) Discovery and development
- 2) Preclinical studies
- 3) Clinical development
- 4) FDA approval
- 5) Post marketing surveillance



A) DEVELOPMENT PROCESS OF COVAXIN:

Bharat Biotech International Limited in partnership with the National Institute of Virology (NIV), a premier institute of ICMR has developed an indigenous whole virion inactivated SARS-CoV-2 virus vaccine (COVAXINTM). The non-clinical toxicity studies to assess the safety of the COVAXINTM were performed in compliance with the norms of Good Laboratory Practice (GLP).

As an inactivated vaccine, Covaxin uses a more traditional technology that is similar to the inactivated polio vaccine. Initially, a sample of SARS-CoV-2 was isolated by India's National Institute of Virology and used to grow large quantities of the virus using vivo cells. From then on, the viruses are soaked in beta-propiolactone, which deactivates them by binding to their genes, while leaving other viral particles intact. The resulting inactivated viruses are then mixed with an aluminium-based adjuvant. The vaccine is developed using Whole-Virion Inactivated Vero Cell derived platform technology. Inactivated vaccines do not replicate and are therefore unlikely to revert and cause pathological effects. They contain dead virus, Incapable of infecting people but still able to instruct the immune system to mount a defensive reaction against an infection.

PRECLINICAL STUDIES OF COVAXIN:

Two animal models Syrian hamster rhesus macaque were used to evaluate the immunogenicity and safety of the COVAXINTM vaccine and found to be safe and immunogenic in all the animal models.) by challenging vaccinated macaques with wild type virus. These studies demonstrate that a two-dose vaccination regimen induced significant immune response and provided effective protection in animals challenged with SARS-CoV2.

Method details

Inactivated SARS-COV-2 whole virion vaccine (BBV152) SARS-COV-2 strain (NIV- 2020770) isolated at ICMR-NIV, Pune was propagated in Vero CCL81 cells and harvested on observation of cytopathic effect in the cells. At BBL BPL (Ferak, Germany) was added to the virus harvest following filtration and stabilization of the harvest using a buffer. The mixture was kept at 2-8 °C with continuous stirring for 24 hrs and was further hydrolysed by incubating at 37 C for 2hrs. Column chromatography was used for further purification and the process intermediate was concentrated to prepare the whole virion vaccine.

Two different antigen concentrations (3 µg and 6 µg) and 2 adjuvants namely Algel I (Alum) and Algel 2 (TLR 7/8 (imidazole quinoline) agonist adsorbed alum) in combinations were used for the study. The vaccine formulations evaluated in the study were 6 µg antigen with Algel 1, 3 µg with Algel 2, and 6 µg with Algel 2.

Enzyme-linked Immunosorbent Assay

Ninety-six well microtitre plates were coated with 1:10 diluted inactivated SARS-CoV-2 antigen with carbonate buffer (pH 9.5) overnight at 4 °C. Subsequently, wells were blocked with liquid plate sealer (CANDOR Bioscience GmbH, Germany) for two hours at room temperature (25-30° C). The wells were washed 5 times with phosphate-buffered saline with

0.05% Tween 20 (PBS-T) and were incubated at 37°C for one hour with 100 µl of diluted hamster serum samples (1: 100). Negative control was added to each plate. After 5 washes with PBS-T, anti-hamster.

IgG antibodies 1:3000 (Thermo scientific, USA) were added and incubated for 1 hour at 37°C. Following 5 washes with PBS-T, of substrate, 3',3',5',5'-tetramethylbenzidine (TMB) was added to each well. The colour reactions were developed for 10 minutes and after termination, absorbance was measured at 450 nm. Serum IgG titres were determined by testing serial 10-fold dilutions of each sample, starting from 1 : 100 dilution. Titre values were determined as the highest dilution at which the optical density was more than 0.2 and positive/negative (P/N) ratio above 1.5.

Plaque Reduction Neutralization test

The four-fold serial dilution of hamster serum samples was mixed with an equal amount of virus suspension and incubated at 37°C for 1 hour. Further 0.1 ml of the mixture was inoculated in a 24-well tissue culture plate containing a confluent monolayer of Vero CCL 81 cells. The plate was incubated at 37 °C for 60 min and overlay medium (2% carboxymethyl cellulose with 2% FBS in 2X MEM) was added to the cell monolayer, which was further incubated at 37°C in 5% CO₂ incubator for 4-5 days and PRNT 50 titres were calculated as described earlier. Cytokine analysis

The serum cytokine levels (TNF-α, IFN-γ, IL-4, IL-6, IL-10 and IL-12) were assessed in hamsters post challenge at 3, 7, and 15 days. An ELISA based commercial assay (Immuntag, USA) was used for the hamster specific cytokine quantitation. For this, plates pre-coated with hamster specific cytokine antibody were used and a streptavidin based HRP system was used for detection and the absorbance was measured at 450 nm.

Nasal wash, throat swab and rectal swab samples were collected in 1 ml viral transport medium and weighed organ samples (lungs, nasal turbinate, trachea, spleen, kidney and intestine) were triturated in 1 ml sterile tissue culture media, using a tissue homogenizer (Eppendorf, Germany) and 200 µl of the homogenate/ swab specimens were used for further RNA extraction using Viral/Pathogen Nucleic Acid Isolation Kit as per the manufacturer's instructions. Real-time RT-PCR was performed for E and RdRp2 gene for SARS-CoV-2 as well as for detection of sgRNA of E gene using published primers.

Histopathology and immunohistochemistry

Lungs samples collected during necropsy were fixed in 10% neutral buffered formalin. The tissues were processed by routine histopathological techniques for hematoxylin and eosin staining. Duplicate sections were taken for immunohistochemical evaluation. An in-

house developed anti-SARS-CoV-2 mouse polyclonal serum was used as the primary antibody for detection. The tissue sections were rehydrated and antigen retrieval was performed using 0.3% hydrogen peroxide in methanol. The slides were incubated with 1: 500 dilution of primary antibody for an hour and an anti-mouse HRP antibody (Dako, USA) was used as a secondary antibody. For detection, 3, 3"-diaminobenzidine tetrahydrochloride substrate, and hydrogen peroxide were used.

Data analysis

For analysis of the data, Graphpad Prism version 8.4.3 software was used. The statistical significance was assessed using the Kruskal-Wallis test Dunn's multiple comparisons test. Two-tailed Mann-Whitney test was performed between the control and the vaccinated groups if the p-value for the Kruskal-Wallis test was found to be significant; p-values less than 0.05 were considered to be statistically significant. Results

Inactivated whole virion vaccine candidates induced specific IgG /neutralizing antibody and Th1 biased immune response: Anti-SARS-CoV—2 IgG antibody response was detected by 3 weeks in 8/9 hamsters of group IV with an average OD of 0.62, 8/9 hamsters in group III with an average OD of 0.42 and in 2/9 hamsters (average OD — 0.285) of group II. On day 48, IgG antibody response was found to be increasing in the vaccinated groups with an average OD of 132 in group IV (9/9 hamsters), 1.2 in group III (9/9 hamsters), 0.55 in group II (9/9 hamsters). All the animals in group I remained negative for IgG antibody during immunization period whereas post virus challenge, 2/3 hamsters showed IgG positivity by 7 DPI and 3/3 by 14 DPI (average OD = 0.29) in the group 1 . In the vaccinated groups, an increasing trend with an average OD of 0.84, 0.97 and 0.91 was observed on days 3, 7 and 15 DPI respectively No significant difference was observed in the IgG antibody response postinfection in group III and IV

IgG antibody response in vaccinated hamsters was further characterized to determine the IgG subclass profiles. On sub-typing IgG2 was detected in all the IgG antibody positive samples whereas it was negative for IgG1 during immunization and post-infection phase. All three formulations of vaccine candidates significantly induced IgG2 with an increasing trend postinfection indicating a Th1 biased immune response .

Neutralizing antibody (NAb) started appearing in the immunized groups at 3rd week of immunization and increased till 7th week with highest titre (mean = 28810) in group III. After virus infection the highest titre of NAb (mean — 85623) was seen in group III animals on 15 DPI. Group I did not show NAb response during immunization phase and after virus infection till 15 DPI.

EVALUATION IN RHESUS MACAQUE:

20 rhesus macaques who were divided into four groups. One group was given placebo, while three groups were immunised with three different vaccine candidates at zero and 14days. "All the macaques were exposed to viral challenge 14 days after the second dose," the company said. The results showed protective efficacy, increasing Sars-CoV-2 specific IgG and neutralising antibodies reducing the replication of the virus in the nasal cavity, throat and lung tissues of the monkeys.

Bharat Biotech also noted that no evidence of pneumonia was observed in the vaccinated groups unlike the placebo group. "Adverse events were not seen in animals immunized with a two-dose vaccination regimen," CLINICAL TRIALS :-

Phase I : In May 2020, Indian Council of Medical Research's, National Institute of Virology approved and provided the virus strains for developing a fully indigenous vaccine. In June 2020, the company received permission to conduct Phase I and Phase II human trials of a developmental COVID-19 vaccine codenamed BBV152, from the Drugs Controller General of India .

A total of 375 participants were enrolled in Phase I trial and generated excellent safety data without any reactogenicity. COVAXIN induced binding and neutralizing antibody responses and with the inclusion of the Algel-IMDG adjuvant, this is the first inactivated SARS-CoV-2 vaccine that has been reported to induce a Th1-biased response. Vaccine-induced neutralizing antibody titers were reported with two divergent SARS-CoV-2 strains.

Phase 1 trial overview (NCT04471519)				
Protocol Title	Phase 1, double blind, multi-centre study of safety, reactogenicity, tolerability, and immunogenicity in 375 healthy volunteers.			
Study Groups	Cohorts/ Vaccine Candidates	Age groups	Dosage (D0, D14)	Enrollment status
	BBV152A	= 18 to =55 years	0.5 mL of Whole Virion Inactivated SARS-CoV-2 Vaccine	(Fully enrolled) 100
	BBV152B			(Fully enrolled) 100
	BBV152C			(Fully enrolled) 100
	Placebo		0.5 mL placebo	(Fully enrolled) 75
Population	Participants of either gender of age between = 18 to =55 years.			
Study Endpoints	Safety (Mild AEs were noted within 2 hours after Dose 1. No immediate AEs were reported after Dose 2). Immunogenicity (e.g., neutralizing antibody titers are suggestive of protection)			
Study Duration	12-month follow up study after the last vaccine administration.			

TABLE 2: PHASE 1 TRIAL OVERVIEW

PHASE 2 : In between Sept 5 and 12, 2020, 921 participants were screened. In a double-blind multicenter, phase 2 clinical trial a total of 380 healthy adults and adolescents were to receive two vaccine formulations (n=190 each) with 3 pg and 6 pg with Algel-IMDG. The data showed that all the participants were safe and immunogenic in terms of generating Anti IgG titers (GMTs) to all epitopes (S1 protein, RBD, and N protein) which increased significantly after the administration of both the doses. COVAXIN™ led to tolerable safety outcomes and enhanced humoral and cell-mediated immune responses. The study showed that Phase II trials had a higher immune response and induced T-cell response due to the difference in dosing regime from Phase I. The doses in Phase II were given at 4 weeks interval as opposed to 2 weeks in Phase I. Neutralization response of the vaccine were found significantly higher in Phase II. Higher neutralising titres (2-fold) was observed in the phase 2 study than in the phase I study. Both vaccine groups elicited more

Th1-biased cytokines than Th2-biased cytokines.

Phase 2 trial overview (NCT04471519)				
Protocol Title	Phase 2, double-blind, multi-centre study of safety, reactogenicity, tolerability, and immunogenicity in 380 healthy volunteers.			
Study Groups	Cohorts/ Vaccine Candidates	Age groups	Dosage (Dose)	Enrollment status
	BBV152A	212 to 65 years	0.5 ml	(Fully enrolled) 190
	BBV152B		0.5 ml	(Fully enrolled) 190
Population	Participants of either gender of age between 212 to 65 years.			
Study Endpoints	No immediate AES occurred within 2 hrs after vaccination; there were no SAEs reported, Immunogenicity (e.g., neutralising antibody titers are suggestive of protection)			
Study Duration	6-month study after the last vaccine administration.			

■ TABLE 3 : PHASE 3 TRIAL OVERVIEW

PHASE 3:

In November 2020, Covaxin received the approval to conduct Phase III human trials after completion of Phase I and II. A randomised, double-blinded, placebo-controlled study among volunteers of age group 18 and above, it started on 25 November and involved around 26,000 volunteers from across 22 sites in India.

The primary endpoint of Phase 3 clinical trial is based on the first occurrence of PCR-confirmed symptomatic (mild, moderate, or severe) COVID-19 with onset at least 14 days after the second study vaccination in serologically negative (to SARS-CoV-2) adult participants at baseline.

The first interim analysis is based on 43 cases, of which 36 cases of COVID-19 were observed in the placebo group versus 7 cases observed in the BBV152 (COVAXIN®) group, resulting in a point estimate of vaccine efficacy of 80.6

Trials on minors

In May 2021, Drugs Controller General of India (DCGI) approved clinical trials in the age group of 2 to 18 years. The trials are conducted at AIIMS Delhi and Patna. As many as 54 children had registered at the AIIMS Patna.

USAGE AUTHORIZATION :

COVAXIN vaccine has been approved with permission number MF/BIO 21/000002, dated 03 Jan 2021, F. No: BIO/MN20/000103. This permission is given for restricted use in emergency situation

in public interest as an abundant precaution, in clinical trial mode, where COVAXIN™ vaccine will be administered to the adult vaccine recipients and they will be followed up for safety.

EMERGENCY USE AUTHORIZATION:-

Bharat Biotech has applied to the Drugs Controller General of India (DCGI), Government of India seeking an Emergency Use Authorization (EUA). It was the third firm after Serum Institute of India and Pfizer to apply for emergency use approval. On 2 January 2021, the Central Drugs Standard Control Organization (CDSCO) recommended permission for EUA, which was granted on 3 January. The emergency approval was given before Phase III trial data was published. This was criticized in some sections of the media.

OTHER NATIONS :

The vaccine was approved for Emergency Use in Iran and Zimbabwe.

- Mauritius received its first commercial supply of Covaxin on March 18, 2021.
- On 7 April Mexico gave emergency authorization for Covaxin On 19 April 2021,
- Philippines granted EUA to Covaxin Covaxin was granted EUA in Guatemala, Nicaragua, Guyana, Venezuela and Botswana

FDA REVIEW: Ocugen, Bharat Biotech's American partner for COVID-19 vaccine Covaxin, has submitted a "Master File" to the US Food and Drug Administration prior to seeking an emergency use authorization in that country. "The company is currently evaluating the clinical and regulatory path for CO VAXIN in the United States including obtaining Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA).

POST MARKET SURVEILLANCE :

ADVERSE EVENTS FOLLOWING IMMUNIZATION :

- a. Day 7 after dose I including symptoms related to Covid-19 and positive RT-PCR test (if any) b. Day28 after dose I including symptoms related to Covid-19 and positive RT-PCR test (if any) c. Day 7 after dose 2 including symptoms related to Covid-19 and positive RT PCR test (if any) d. Day28 after dose 2,including symptoms related to Covid-19 and positive RT-PCR test (if any)

Individuals who have a known severe allergy to any component of COVAXIN are NOT advised to be vaccinated. As COVAXIN contains 6yg of whole-virion inactivated SARS CoV-2 antigen (Strain: NIV-2020- 770), and the other inactive ingredients such as aluminium hydroxide gel 250 Mg, TLR 7 8 agonist (imidazoquinolinone) 15 pg, 2- phenoxyethanol 2.5 mg, and phosphate buffer saline up to 0.5 ml. Individuals with a history of severe allergic reactions NOT of severe allergic

reactions NOT related to vaccines or injectable medications such as environmental allergies, allergies to food, pet dander, venom, or latex - may still get vaccinated

Individuals with HIV infection or other immunocompromising conditions, or who take immunosuppressive medications or therapies might be at increased risk for severe COVID-19. Transplant recipients should be counselled that the vaccine's effectiveness and safety profile for them is not currently known.

CONTRAINDICATIONS:

1. Person with History of:

- Anaphylactic or Allergic Reaction to previous dose of COVID-19 vaccine.
- Immediate or delayed —onset anaphylaxis or allergic reaction to vaccines or injectable therapies, pharmaceutical products ,food-items etc.

2. Pregnancy & Lactation: Pregnant & Lactating women

3. Persons having active symptoms of SARS-CoV-2 infection.

4. SARS-CoV-2 patients who have been given anti-SARS-CoV-2 monoclonal antibodies or convalescent plasma.

A) DEVELOPMENT PROCESS OF COVISHIELD:

The Oxford—AstraZeneca COVID-19 vaccine, codenamed AZD1222, and sold under the brand names COVISHIELD and VAXZEVRIA among others, is a viral vector vaccine for prevention of COVID-19. Developed by Oxford University and AstraZeneca, using as a vector the modified chimpanzee adenovirus ChAdOx1. The efficacy of the vaccine is 76.0% at preventing symptomatic COVID-19 beginning at 22 days following the first dose and

81.3% after the second dose. Another analysis showed that, for symptomatic COVID-19 infection after the second dose, the vaccine is 66% effective against the Alpha variant. **DISCOVERY:-** 'Covishield' has been manufactured in Serum Institute of India, in Pune. According to sources, 95 per cent of the 1.1 crore doses of Covishield vaccine purchased by the government have been delivered and shipped to nearly 60 consignee points across India in two days. They explain how, "Typically, developing a vaccine takes decades — but we have several available for COVID-19 after just 12 months Here"s how we managed this for the Oxford vaccine."They also added how they had a head-start for the vaccine, even before Covid-19 was first detected in China. "We had already developed a delivery method or "platform" — for our vaccine and had been testing it for other diseases for almost ten years. Known as the ChAdOx1 viral vector technology, this platform was created by modifying a harmless adenovirus that causes the common cold in chimpanzees." They added that they chose ChAdOx1 as it can generate a strong immune response and is not a replicating virus, so it cannot cause an infection. It had already been used safely in thousands of subjects in clinical trials of vaccines for other diseases including Middle Eastern respiratory syndrome (MERS), which is caused by another type of coronavirus. Researchers in China had mapped the genetic sequence of the coronavirus, they were able to quickly produce the COVID-19 vaccine by combining

the ChAdOx1 vector with the genetic sequence of the SARS-CoV-2 spike protein. The preparation for Disease X ultimately allowed 't our research team to move straight into testing our vaccine in animals in early2020 .Speaking to the select media persons at the SII facility, Poonawalla said the real challenge lies in taking the vaccine to the "common man, to the vulnerable groups of people and to healthcare workers." He also said that once the SII get the requisite permission, the vaccine will be made available in the private market at the cost Rs 1,000. Responding to a query on the safety of the vaccine, he said all COVID-19 vaccines have passed all the safety parameters. "DCGI (Drugs Controller General of India) will not provide the license to a vaccine unless its efficacy and safety are not proved. All Indian vaccines are safe, effective, and it is advisable that people should take them.

PRECLINICAL STUDY FOR COVISHIELD: Direct clinical trials on humans for highly pathogenic viruses are not feasible and also not ethically permitted without prior preclinical studies. Therefore, animal studies play an essential role in characterizing the viral pathogenesis and evaluation of antiviral agents and vaccines for these viruses. The ideal animal models should be permissive to infection and must reproduce the clinical course and pathology observed in humans. In the search for vaccines and treatments for Covid-19 animals can play an essential role in both basic research and testing. Various animal species are currently being bred and used as suitable models for predicting what effects a vaccine or treatment for Coivd-19 may have on the human body.

➤ Vaccine type: Non-Replicating Viral Vector

➤ Administration method: Intramuscular injection

➤ Also known as: Oxford, AstraZeneca vaccme

➤ Vector: the modified chimpanzee

➤ Strain: B.1.617 strain

➤ Animal model used for Preclinal study: Rhesus macaque monkey (prevents SARSCov-2-pneumonia) and Mice (show good immunogenicity)

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The efficacy of AZD1222 vaccine was assessed in rhesus macaque monkeys

(2). Six animals per group were vaccinated intramuscularly with 2.5×10^{10} ChAdOx1-S (recombinant) virus particles each, using either a prime-only regimen (28 days before challenge) or a prime—boost regimen (56 and 28 days before challenge).

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As a control, six animals were vaccinated via the same route with the same dose of ChAdOx1-S (recombinant) green fluorescent protein (GFP) (one animal was vaccinated 56 and 28 days before challenge and five animals were vaccinated 28 days before challenge).

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No adverse events were observed after vaccination.

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Spike-specific antibodies were present as early as 14 days after vaccination and were significantly increased after the second vaccination (two-tailed signed-rank Wilcoxon test). Endpoint IgG titres of 400—6400 (prime) and 400—19 200 (prime—boost) were measured on the day of challenge.

- Virusspecific neutralizing antibodies were also significantly increased after the second vaccination (two-tailed signed-rank Wilcoxon test) and were detectable in all vaccinated animals before challenge (titres 5—40 (prime) and 10—160 (prime— boost)). No virus-specific neutralizing antibodies were detected in control animals.

- On the day of challenge, IgM antibodies were present in the serum of all six prime—boost animals and two of the six prime-only animals.

- ARS-CoV2 spike-specific T-cell responses were detected on the day of challenge by gamma interferon (IFN γ) ELISpot assay, after stimulation of peripheral blood mononuclear cells with a peptide library that spanned the full length of the spike protein. No statistically significant difference in the magnitude of the response was found between the prime—boost and primeonly group (Mann-Whitney U-test, P = 0.3723). Vaccination with ChAdOx1-S (recombinant) has been shown to induce neutralizing antibodies against the vaccine vector itself within 28 days of vaccination.

Nonetheless, a boost vaccination with ChAdOx1-S (recombinant) resulted in a significant increase in binding and neutralizing antibodies and an increase in the SARS-CoV-2 virus-neutralizing titre was not significantly correlated

- with the ChAdOx1-S (recombinant) virus neutralizing titre (two-tailed Pearson conelation, $r_2 = 0.6493$ P = 0.0529).

- After challenge, the animals were evaluated for the protection offered by the vaccine and the potential for vaccineassociated enhanced respiratory disease (VAERD) .

➤ Composition: One dose (0.5ml) contains 5×10^{10} ChAdOx1-S (recombinant) viral particles. The vaccine is produced in genetically modified human embryonic kidney

(HEK) 293 cells. In addition to ChAdOx1-S (recombinant), this product also contains the excipients I—histidine, L-histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate and water for injection. None of the excipients are of animal or human origin. The excipients are well established for pharmaceutical products.

➤ Lethal dose: Covishield, produced by the Serum Institute of India (SII), is expected to be available in vials containing I dose (0.5 ml), 2 doses (1.0 ml), 5 doses (2.5 ml), 10 doses (5.0 ml) or 20 doses (10 ml).

➤ Stability and Shelf-life: A shelf-life of 6 months is proposed. Chemical and physical in-use stability from the time of vial opening (first needle puncture) to administration is up to 48 hours in a refrigerator (2—8 °c). Within this period, the product may be kept and used at temperatures up to 30 °c for a single period of up to 6 hours, after which it must be discarded. It should not be returned to the refrigerator.

➤ Pharmacokinetics: Two biodistribution studies have been performed, which suggested that, after injection, the virus does not replicate or persist, and is not distributed in the body beyond the injection site in a way that would be clinically significant.

➤ Developmental and reproductive toxicity: Animal developmental and reproductive toxicity (DART) studies are ongoing. A dose-range study and a GLP embryofetal development study were completed. In top-line results from the latter study, no test item-related effects were seen for dams in-life, including at the injection site, for female reproduction, foetal or pup survival or pup physical development, and there were no abnormal gross pathology findings in pups before or after weaning or in dams in either phase. There were no test item-related foetal external, visceral or skeletal findings.

➤ Safety: Safety is particularly critical aspects of this scrutiny and a risk-versus-benefit evaluation is done in the context of a public health emergency. Full licensure is obtained when the manufacturer submits the complete data.

➤ Efficacy: Overall vaccine efficacy was found to be 70.42%

CLINICAL TRIALS

1 1077 Participants showed an acceptable safety profile, and homologous boosting increased antibody responses. COV 001 is a continuing single-blind phase 1/2 clinical trial in five sites in the UK, which began on April 23, 2020, and enrolled 1077 healthy volunteers aged 18—55 years, as previously described. Briefly, healthy adult participants were enrolled after screening to exclude those with pre-existing health conditions. Participants were randomly assigned 1:1 to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles (standard dose), measured using spectrophotometry, or meningococcal group. 1) This study was originally planned as a single-dose study and 88 participants in the phase I part of the study remain recipients of a single dose. However, the protocol was modified to a two-dose regime, following an amendment on July 30, 2020 (version 9.0; appendix 2 pp. 180—181), for the remaining phase 2 cohorts as a result of robust booster responses identified in the evaluation of the early immunogenicity cohorts, with the booster dose given at the earliest possible time.

PHASE II:

In prime boost regimen in 560 participants better tolerated in older adults than in younger adults and has similar Immunogenicity across all age groups after a boost dose. The LD/SD cohort (aged 18—55 years) was enrolled over 11 days between May 31 and June 10, 2020. The SD SD cohort (aged 18-55 years) was enrolled from June 9 to July 20, 2020.

Subsequently, enrolment of older age cohorts began (from Aug 8, 2020, for participants aged 56—69 years and from Aug 13, 2020, for participants aged 70 years), all of whom were assigned to two standard doses (SD SD cohort).

Each site implemented the protocol amendment before changing from low-dose administration to standard-dose administration, and therefore there was no overlap in enrolment of participants in these cohorts. The 18—55-year-old cohorts were originally planned as single-dose efficacy cohorts. However, the protocol was modified on July 20, 2020, to offer a second dose to the participants in

these cohorts as a result of robust booster responses identified in the evaluation of the early immunogenicity cohorts.

Boosting began on Aug 3, 2020, resulting in a longer gap between prime and booster vaccines in these cohorts than for those aged 55—69 years and those aged 70 years or older, as these participants were enrolled into two-dose groups from the start. Results for participants enrolled into immunogenicity subgroups have been previously published, including a small subset who received a low-dose boost.

PHASE 3 : In 11636 participants from UK and Brazil

- (COVISHIELD-300; Oxford/AZ chAdOx1 nCoV19Vaccine-100) Two standard doses (5x10¹⁰ to the power 10 viral particles), vaccine efficacy was 62.1%.
- Low dose to the power 10 viral particles) followed by a standard dose, efficacy was 90.096.
- Overall vaccine efficacy was 70.4%. **India Phase 2/3 Study**

- Number of participants: 1600
- Age group: 218 years
- Randomization: 3: 1 (COVISHIELD-900, Placebo-300)

Immunogenicity cohort: 400

- Interim analysis: COVISHIELD is safe and immunogenic

FDA REVIEW:

AstraZeneca announced its covid-19 vaccine is 76% effective at preventing symptomatic disease, based on its Phase 3 trial over 32000 participants mostly in the United States.

Vaccine has been approved for use in United Kingdom and several European Union countries.

It has not yet been approved in the U.S. because the Food and Drug Administration (FDA) asked the company to provide results from a large scale trial.

WHO: AstraZeneca's COVID-19 vaccine has been granted Emergency Use Listing (EUL) by the World Health Organization (WHO) for active immunization to prevent COVID-19 in individuals 18 years of age and older, including those over 65, a company statement said. The authorization of COVID-19 Vaccine AstraZeneca, manufactured by AstraZeneca, and COVISHIELD, manufactured by Serum Institute of India (SII), enables global access to the vaccine during the pandemic.

CDSCO :After adequate examination, CDSCO has decided to accept the recommendations of the Expert Committee and accordingly, vaccine of Serum is being approved for restricted use in

emergency situation and permission is being granted to M/S Cadila Healthcare for conduct of the Phase 3 clinical trial

MHRA : The UK government has accepted the recommendation from the Medicines and Healthcare Regulatory Agency (MHRA) to authorize Oxford University-AstraZeneca's Covid-19 vaccine, named Covishield, for emergency use. This has filled speculations that India, where it is being manufactured by Serum Institute of India, will also approve the Oxford vaccine soon. The vaccine developed by the Oxford University has shown 70 per cent efficacy, which can go up to 90 per cent under certain conditions.

FDA POST MARKET SAFETY MONITORING:-

The „One Million" Post-Authorization Study has been formed by the Drug Safety Research Unit (DSRU) in Southampton. The study aims to ensure vaccines are safe and working as they should be once they have made it to market. The consortium will invite one million members of the public who receive a Covid-19 vaccine to take part in the study. Participants will be contacted at set points after the vaccine to check on their health. The study is being designed so that any concerns regarding safety or efficacy can be acted upon quickly.

Vaccine makers need to demonstrate quality, safety and efficacy for their products before they can be used by members of the public. Since Covid-19 vaccines are being produced at a much faster pace than usual, it is necessary to conduct post-marketing observational studies to monitor the safety and effectiveness of these vaccines in case any action needs to be taken. Post-marketing studies also give developers a more detailed idea of how the products work and fill in any gaps in knowledge obtained from clinical trials before launch.

Professor Saad Shakir, of the DSRU, said: "It is well-known that a safe and effective vaccine is vital for protecting the public from Covid-19. The usual development process for a vaccine, including proving its safety and effectiveness, would normally take over a decade, but has been reduced to 12-18 months for Covid-19 vaccines.

The methods of the One Million Study benefit from the structure of the NHS and have been developed to allow near real-time reporting of safety and effectiveness signals, which will be crucial for monitoring newly licensed Covid-19 vaccines. This is a vital part of ensuring that any vaccine can be safely deployed around the world.

Side Effects/ Adverse Drug Reactions

Following effects have been reported with COVISHIELD™ vaccine.

-
- 1) 1. Very common (may affect more than 1 in 10 people) - tenderness, pain, warmth, or itching where the injection is given, generally feeling unwell, feeling tired (fatigue), chills or feeling feverish, headache, feeling sick (nausea), joint pain or muscle ache
 - 2) Common (may affect more than 1 in 10 people) - swelling or redness where the injection is given, fever, being sick (vomiting) or diarrhea, pain in legs or arms, flulike symptoms, such as high temperature sore throat, runny nose, cough and chills
 - 3) Uncommon (may affect up to 1 in 100 people) sleepiness or feeling dizzy, abdominal pain, enlarged lymph nodes, excessive sweating, itchy skin, rash or hives
 - 4) Not known (the frequency cannot be determined from the available data) -severe allergic reaction (anaphylaxis), severe swelling of the lips, mouth, throat (which may cause difficulty in swallowing or breathing)
 - 5) Rarest: Major blood clotting (venous and/or arterial thrombosis) in combination with low platelet count (thrombocytopenia) have been observed very rarely (with a frequency less than 1 in 100,000 vaccinated individuals).

COMPARATIVE STUDY OF COVAXIN AND COVISHIELD:

As we above discussed, the development process of COVISHIELD and COVAXIN. The COVISHIELD and COVAXIN are both the vaccine used in treatments of Covid-19. To understand the clearly difference between both vaccine. So we are doing comparative study of vaccines in tabular form.



■ TABLE 5: IMAGES OF COVAXIN AND COVISHIELD VACCINES

CONTENT	COVAXIN	COVISHEILD
DEVELOPED BY	HYDERBAD-BASED BHARAT BIOTECH IN COLLABORATION WITH ICMRAND PUNE BASED NATIONAL INSTITUTE OF VIROLOGY	UNIVERSITY OF OXFORD AND ASTRAZENECA, AND LOCALLY MANUFACTURED BY THE SERUM INSTITUTE OF INDIA
APPROVED BY	NOT APPROVED BY WHO	APPROVED BY WHO
ANOTHER NAME	BBV152	ChAdOx1
EFFECTIVE	EFFECTIVE AGAINST NEW MUTANAT	HIGHLY EFFECTIVE AGAINST NEW MUTANTS
IMMUNOGENECITY AND SAFETY	BOTH SHOW GOOD RESPONSE AND GOOD SATEYPROFILE	BOTH SHOW GOOD RESPONSE AND GOOD SATEYPROFILE

COMPOSITION OF VACCINE	L-HISTIDINE ETHANOL L- HISTIDINE HYDROCHLROIDE MONOHYDRATE MAGNESIUM CHLORIDE HEXAHYDARTE POLYSORBATE 80 SUCROSE SODIUM CHLORIDE DISODIUM EDETATE DIHYDRATE WATER FOR INJECTION	L-HISTIDINE L-HISTIDINE HYDROCHLORIDE MONOHYDRATE ALUMINUM HYDROXIDE GEL MAGNESIUM CHLORIDE POLYSORBATE-80 ETHANOL SODIUM CHLORIDE IMIDAZOQUINOLINONE 2-PHENOXYETHANOL PHOSPHATE BUFFER SALINE
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DIFFERENCE BETWEEN THE COVAXIN AND COVISHIELD:

COMPARATIVE STUDY OF COVAXIN AND COVISHIELD

VIRAL VECTOR VACCINE USE	USES AS ADENOVIRUS FOUND IN CHIMPANZEES	USES OF A DEAD VIRUS THAT DRAFT IMMUNE RESPONSE
VACCINE TYPE	INACTIVATED	NON REPLICATING VIRAL VECTOR
EFFICAY	WHEN THERE IS A GAP OF MORE THAN 28 DAYS BETWEEN THE DOSES	TO 70% BASED ON PHASE 3 OF CLINICALS TRIALS
STORAGE TEMPERATURE	2-8DEGREE CELCIUS	2-8 DEGREE CELCIUS
DOSES	NO OF DOSES IN EACH VIAL IS 20	NO OF DOSES IN EACH VIAL IS 10
COURSE	TWO DOSES(O-28 DAYS)	TWO DAYS (GAP OF 3 MONTHS)
SIDE EFFECTS	INJECTION SITE PAIN INJECTION SITE SWELLING INJECTION SITE REDNESS INJECTION SITE ITCHING STIFFNESS IN THE UPPER ARM WEAKNESS INJECTION ARM BODY ACHE HEADACHE FEVER MALAISE WEAKNESS RASHES NAUSEA	TENDERNESS PAIN REDNESS ITCHING FEELING TIRED CHILLS OR FEELING FEVERISH FEELING SICK JOINT PAIN OR MUSCLE ACHE A LUMP AT INJECTION SITE FEVER BEING SICK ENLARGED LYMPH NODE EXCESSIVE SWEATING DECREASES APPETIDE ABDOMINAL PAIN RUNNY NOSE SPRE THROAT

	• V OMITTING	
PHASE 1	375 VOLUNTEER	1077(UK STUDY) VOLUNTEER
PHASE 2	380 VOLUNTEER	560 (UK STUDY, 1600 (INDIAN STDUY)
PHASE 3	26000 VOLUNTER	11636 (UK STUDY AND BRAZIL STDUY
EEFICACY AFTER PHASE 3 TRIALS	AFTER PHASE 3 TRIALS WITH COVAXIN , IT WILL HAVE AN EFFECT 78100% OF	IF YOU USE THIS INJECTION , THE EFFECT IS 70-90%

COMPARATIVE STUDY OF COVAXIN AND COVISHIELD

AGES FOR VACCINE	THESE INJECTIONS ARE APPLIED ONLY TO PEOPLE ABOVE 18 YEARS OF AGE	IT CAN BE APPLIED TO PEOPLE OVER 12 YEAR OF AGE
PRECLINICAL TRIAL ON	RAT , MICE , RABBIT	MICE , RHESES MONKEY
ROUTES OF ADMINISTRATION	INTRAMUSCULAR	INTRAMUSCULAR
DOSE	0.5 ML EACH DOSE	0.5 ML EACH DOSE
SHELF LIFE	6 MONTHS	6 MONTHS
IF YOU ARE UNDER 18 AND SUFFERING FROM THIS PROBLEM , THEN DON'T TAKE VACCINE	1) IMMUNE COMPRESSED 2) PREGNANT 3) BREASTFEDDING 4) AON A MEDICINE THAT AFFECTS YOUR IMMUNE SYSTEM	1) PREGANT OR BREAST FEDDING 2) NOT SURE AND MAY PREFER TO CONSULT YOUR HEALTHCARE PROVIDER
ALLERGIC REACTION	DIFFICULTY BREATHING SWELLING OF FACE	SEVERE ALLERGIES REACTION AFTER A PREVIOUS DOSE OF THIS VACCINE

COMPARATIVE STUDY OF COVAXIN AND COVISHIELD

	THROAT, RAPID HEARBEAT RASHES THROUGHOUT BODY DIZZINESS	SEVERE REACTION INGREDIENT VACCINE MENTIONED CONDITION SUPERVISOR	ALLERGIES TO ANY OF THE MEDICAL AYS NO
CONTRAINDICATIO	HAVE ANY HISTORY OF ALLERGIES, FEVER, BLEEDING DISORDERS PREGANCY HAVE RECEIVED , ANOTHER COVID VACCINE	HAVE ANY HISTORY OF ALLERGIES , BREAST FEEDING PREGNANCY	
INDIAN AVAILBILITY	FIRST 'HALF 2021	ADAR: EXPECT FIRST BATCH IN 7-10 DAYS	
OTHER NATION APPROVED	IRAN ZIMBABWE MEXICO PHILIPPINESS EUA	AFGANISTHAN ARGENTIA BANGLADESH BHUTAN BRAZIL MALDIVES NEPAL SOUTH AFRICA SRI LANKA TONGA	
AFTER RECIVED 1 ST DOSE , POSITIVE TESTED	9.3 MILLION WHO RECEIVED THE FIRST DOSE OF COVAXIN , 4208 TESTED POSITIVE	OF THE 100.3 MILLION WHO RECIVED THE FIRST DOSE 17145 TESTED POSITIVE	
AFTER RECIVED 2 ^M) DOSE , POSTIVE TESTED	15 MILLION WHO RECEIVED THE SECOND DOSE OF COVAXIN , 5014 TEST POSITIVE	15 MILLION WHO RECEIVED THE SECOND DOSE OF COVAXIN , 5014 TEST POSITIVE	

RESULT AND CONCLUSION

RESULTS:

Coronavirus diseases(covid-19)is an infectious diseases caused by a newly discovered coronavirus To understand the covid-19 information and different type of vaccine We discussed in the article development process of COVAXIN . We also analysed the Development process of COVISHIELD. Both vaccine shown the good immune response and good safety profile .The efficacy of COVISHIELD is higher than COVAXIN. Also, we understand the discovery , development , preclinical , clinical studies , safety , post marketing surveillance.

 **CONCLUSION :** Covid-19 is life-threatening and contagious disease. We have a detailed analysis of Development process of COVISHEILD and COVAXIN. Vaccination has been shown to contribute to reducing deaths and transmission of Covid-19. COVAXIN is developed by Bharat biotech collaboration with ICMR. COVAXIN uses as inactive viral strain. COVAXIN received the approval to conduct human trails in phase III after completion of phase I and phase II. There 26,000 volunteers involved in phase III trails.

COVISHILED is locally manufactured by serum institute of India that a viral vector that uses an adenovirus found in chimpanzees. In serum institute phase 11/111 trails involved 1600 participants. The higher proportion of those inoculated with COVISHIELD produced antibodies compared to those who received COVAXIN , both slots shown a good immune response Both seropositivity rate and average rise in anti spike antibody was significant higher in

COVISHIELD. the study also show good safety profile for both vaccine. The efficacy of COVISHIELD goes helpful in understanding the difference between the compatibility of CCOVISHEILD and COVAXIN. Both the vaccine shown good immune response and safety profile.

References

1. Jeff Carveen, Gaurav Bhati, June 2021, COVID-19 Therapeutics tracker , Regulatory Focus, Page no-15-18.
- 2 Pragma D. Yadav,Raches Ella, Sanjay Kumar , Anita M. Shete, March 2021, Efficacy and Immunogenicity in Non-Human primates, Oxford University Press Public Health Emergency Collection, Page no 59-64.
- 3 Raches Ella -Pater Richmond , May 2021, Safety and Immunogenicity of Inactivated SARS-COV-19, The Lancet, vol -21, Page no 637-646.
- 4 Kamia Thiagarajan, April 2021, COVAXIN -India"s First indigenous COVID-19 vaccme, The BMJ , Page no - 337.
- 5 Jocelyn Solis Moreira ,Jennifer Giuglianotti , April 2021, COVIDSHIELD, Medical life Sciences, Page no 25-28.
- 6 Sohini Das and Ruchika Chitravanshi , June 2021, Difference between COVAXIN and COVISHIELD, Business Standards, Page no 9-11.
7. Abhay Pandey,june2020,Drug Discovery and Development Process, North East Biolab, Page no 34-42.

- 8 Susan R Weiss and Susan J. Bender, March 2021, Pathogenesis Prevention and Control Coronavirus, Elsevier Public Health Emergency Collection, Page no 12-16
9. Soleil Shah, Margaret Trexler Hessen, May 2021, COVID-19 vaccine challenges, Science Direct, Volume-125, Page no 553-567.
10. Emily Petter and Janice J. Eng., June 2021, Coronavirus research highlights, The BMC, Page no 65-74
11. Graham BS, Grapeal KW, 2020, Rapid COVID-19 vaccine development, Science Direct, Volume 368, Page no 945-946.
- 12 Serum Institute of India I Manufacturer of Vaccines & immuno-biologicals – GMP

