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Covid 19 Vaccines

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ABSTRACT

Pandemic COVID-19 is an infectious disease caused by a newly discovered coronavirus SARS-COV-2 leads to mild to moderate respiratory illness and recover without entailing particular treatment. And serious infection may also occur in older people and those having medical problems such as diabetes, cardiovascular disease, chronic respiratory disease and cancer. Vaccines have a significant tool in combating the coronavirus disease (COVID-19) pandemic condition. A highly efficacious vaccine against severe coronavirus disease caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2); such as mRNA vaccine, COVISHIELD™, COVID-19 vaccine AZD1222, Janssen Ad26.COV2.S vaccine, Sputnik V (Gam-COVID-Vac), Covaxin, Novavax, Sinopharm etc. The article reveals the characteristics, interim analysis of clinical study, safety and efficacy of covid 19 vaccines evaluated during phase I/II/III and storage conditions for vials.

INTRODUCTION:

It is important to understand first how to spread transmission of SARS-CoV-2 at work between people and in the environment. The World Health Organization (WHO) interim guidance provides an overview of transmission of SARS-CoV-2 and allusion for the prevention of covid 19 in the community.[1] According to current knowledge, the SARS-CoV-2 virus transmits between people and when an infected person coughs or sneezes, sings, breathes deeply or talks and is in close contact with another person, it significantly binds mostly to epithelial cells at the site of respiratory tract and starts replicating. There is Angiotensin-Converting Enzyme 2 (ACE2) is the major receptor sites for infection of both SARS-CoV-2 and SARS-CoV. There is inadequate substantiation of transmission of SARS-COV-2 through fomites (objects or materials may be infected with viable corona virus, such as equipment, material or work surfaces) around the infected person milieu. Such transmission can be occurring due to touching the fomites and after followed by touching to the mouth, nose and or eyes. Transmission of coronavirus can occur where infected persons spend long periods of time with others such as in surroundings of medical facilities, mostly in indoor, crowded, and inefficiently ventilated places.[1,2] The virus can be detected by nasal swabs, sputum, RT-PCR value for the viral RNA might be useful to detect the viral load as well as the early markers of the innate immune response. The symptoms of covid 19 infection appear after an incubation period of ~5 days and the period from the onset of SARS-CoV-2 illness symptoms like fever, cough, and fatigue, sputum production, headache, hemoptysis, diarrhea, dyspnoea, and lymphopenia and in some cases recent onset anosmia and/or ageusia to death ranged from 6 to 41 days with a median of 14 days. This period is shorter among patients >70 years old compared with those under the age of 70 and it depends on the age of the patient and patient's immune system. [2,3]

The outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or COVID-19 pandemic has led to globally as on 26th May 2021 167,423,479 confirmed cases of COVID-19, including 3,480,480 deaths spreads worldwide.[3] The COVID-19 pandemic is an infectious disease caused by a newly discovered coronavirus SARS-cov-2 consists of viral envelope having three structural proteins as the virus assembly is included with the membrane protein (M) and the envelope protein (E), whereas the entry of the virus to the host cell arbitrated by spike protein (S). Among these structural proteins, the spike forms large protrusions from the virus surface, giving coronaviruses the appearance of having crowns.[2]

There are a few provisionally licensed vaccines which are critical new tool in the battle against covid 19 according to urgent global need for safe and effective vaccines showing broad immune response for prevention of covid 19 infection. As per to the WHO draft landscape about COVID-19 vaccines, 153 vaccines are in clinical estimation and 196 vaccines are in preclinical assessment as on day 1 April 2022. The phase 3 / phase 4 vaccine candidates include a variety of vaccine platforms and WHO is listed in EUL and allowing emergency use in prophylaxis tool in a pandemic of covid 19.[5] As on 4 April 2022, a total of 11,250,782,214 vaccine doses have been administered.[3] Safe and effective vaccines works for reactive use and its immunizations gives durable and long-lasting immune response vaccines and are suitable candidates for the WHO target product profiles in outbreak settings with rapid onset of immunity and for long term protection of persons at high ongoing risk of covid 19.[6]

A) COVID-19 vaccine ChAdOx1-S [recombinant][7-12]:

Introduction:

The COVID-19 vaccine ChAdOx1-S [recombinant] vaccine against COVID-19 infection is developed by Oxford University in United Kingdom and AstraZeneca. It is manufactured by M/s. SK Bioscience Co. Ltd. As COVID-19 Vaccine (ChAdOx1-S [recombinant]); M/s. Serum Institute of India Pvt. Ltd. Pune, Maharashtra India manufactures vaccine as COVISHIELD™ ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) and M/s. AstraZeneca AB, EU approved nodes as COVID-19 Vaccine (ChAdOx1-S [recombinant])]. And WHO has listed this vaccine in Emergency Use Listing (EUL) recommendations as on 15th Feb 2021 for COVID-19 Vaccine (ChAdOx1-S [recombinant]), SK Bioscience Co-operative Ltd. and for COVISHIELD™ ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant); and as on 15 April 2021 for COVID-19 Vaccine (ChAdOx1-S [recombinant])], AstraZeneca AB.

It is a monovalent liquid vaccine; preservative free multi dose suspension and is composed of replication deficient of chimpanzee adenovirus (ChAdOx1) vector which is single recombinant and expressing glycoprotein S of corona virus SARS-CoV-2 and generate cellular immune responses which preserve that data in order to memory of immune cells. Vaccine is clear or slightly opaque or colorless to slightly brown in color free from particle with a pH of 6.6 and one single dose 0.5ML of vaccine is composed of : ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) 5 × 1010 viral particles (vp). It contains Genetically

Modified Organisms (GMOs) as it is produced in genetically modified Human Embryonic Kidney (HEK) 293 cells. It contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free' and 2 mg of alcohol (ethanol) and other excipients are L-histidine, magnesium chloride, disodium edetate (dihydrate) etc., it also contains other excipients like L-histidine hydrochloride monohydrate, hexahydrate, Tween 80 or polysorbate 80 (E 433), sucrose and vehicle as water for injections.

Manufacturers of M/s. SK biosciences produces multiple dose vial as 10 doses per vial each dose contains 0.5mL dose; while covishield^{TM} and AstraZeneca AB Vaccine contains two multiple dose vials as 2 doses per vial and 10 doses per vial each dose contains 0.5mL dose, respectively. Two doses (each dose is 0.5mL) can be administered with an interval of 4 to 12 weeks and WHO has recommended the interval period is 8 to 12 weeks. The study of immunization course reveals that vaccine is safe and well tolerated in clinical trial conducted for the prevention of corona virus disease 2019 (COVID-19); however there are some site reactions may occur such as pain, redness, itching, swelling and induration; and systemic reactions such as headache, increasing body temperature, fatigue, depression, arthralgia and myalgia, There is no any unsolicited adverse events and Serious Adverse Events (SAEs) was caused by the study vaccine. However, it is recommended that both doses are administered with ChAdOx1-S/nCoV-19 [recombinant] vaccine products for protection of Covid 19 infection, and although ChAdOx1-S/nCoV-19 [recombinant] vaccine products are produced at different manufacturing sites or assigned different product names, even if interchangeable for both doses are considered fully equivalent.

COVID-19 Vaccine AZD1222 (ChAdOx1-S [recombinant])] (AstraZeneca):

Study Design & Participants:

COVID-19 Vaccine is recombinant ChAdOx1 nCoV-19 Corona Virus Vaccine of Astra Zeneca. It has been estimated on the basis of an interim analysis of four controlled clinical trials were conducted randomized. The four controlled clinical trials are as in that first trial is a Phase I/II Study conducted in United Kingdom on healthy adults of age 18 to 55 years registered as COV001 (trial registration no.: NCT04324606); second trial is a Phase II/III Study conducted in United Kingdom on adults of age≥18 years (containing elderly) and trial is registered as COV002 (trial registration No.:NCT04400838); whereas third trial is a Phase III Study conducted in Brazil on adults of age ≥18 years (consisting the elderly) registered as COV003 (trial registration No.: ISRCTN89951424); and fourth trial is a Phase I/II study

conducted in South Africa on adults of age 18 to 65 years and trial is registered as COV005 (trial registration no.: NCT04444674).

The interim analysis has shown the evaluation study on ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2 to asses safety and efficacy conducted in four clinical trials at various countries as Brazil, South Africa, and the United Kingdom. (refer table 1). The AZD1222 vaccine has an efficacy of 63.09% (95% CI 51.81; 71.73) against symptomatic SARS-CoV-2 infection, have been shown by the primary analysis of data irrespective of interdose interval (data cut 7th December 2020) from trial conducted on volunteers in the United Kingdom, Brazil and South Africa who has received 2 standard doses. The vaccine efficacy obtained from the participants who have received two standard doses as in UK (participants has received the booster or second dose more than 12 weeks after the first dose administration) as 60.3%, while in Brazil (most participants has received the booster dose or second dose within 6 weeks after the first dose administration) as 64.2% obtained against primary symptomatic COVID-19 infection. It has showed that there is no any significant difference in efficacy estimates and it showed similar findings while comparing the interval time as 8 weeks in between two doses. From April 23rd to Nov 4 th, 2020, 23,848 participants were involved and vaccinated across the four studies i.e. total 1077 participants in COV001 (UK), COV002 (UK) involves overall 10,673 participants in, COV003 (Brazil) contains total 10,002 participants and COV005 (South Africa) consists of total 2096 participants. The primary efficacy from total 131 cases of symptomatic COVID-19 in Low Dose (LD)/Standard dose (SD) or SD/SD recipients was analysed for greater than 14 days after the administration of booster dose of the vaccine. There were total 30 (0·5%) cases in the vaccine group involved among 5807 participants and in the control group total 101 (1·7%) cases were involved among 5829 participants resulting into vaccine efficacy as 70·4% (95·8% CI). Vaccine efficacy is calculated as 62·1% (95% CI) from the trial in which participants who have received two Standard Doses (SD) of vaccines. whereas vaccine efficacy was higher as 90·0% in those participants with low dose administration considering as first dose of vaccine. For the results of subgroup comparison (refer table 2) conducted in UK cohort those participants of age from 18 to 55 years have received SD/SD dose, 49 cases were observed and vaccine efficacy as 65.6% was estimated as 59·3% (95% CI). Total 33 cases were involved in vaccination in which the participants who have received vaccines as standard dose/standard dose analysis more than 8 weeks. The vaccine efficacy was similar at United Kingdom and Brazil in the standard dose (SD) / standard dose (SD) cohort study.

Table 1: Vaccine efficacy against covid 19 for more than 14 days after the administration of a second dose of covid 19 vaccine (AstraZeneca)

	Total No. of subjects involved	ChAdOx1nCOV-19 covid 19 vaccine Group		Control group		Vaccine efficacy (%) (95%CI)
		No. of covid 19 cases	No. of cases	No. of risk	No. of cases	
All Low Dose prime (LD)/Standard Dose boost Recipient	131	30	5807	101	5829	70.4
COV002 (United Kingdom)	86	18	3744	68	3804	73.5
Low Dose prime (LD)/Standard Dose boost Recipient	33	3	1367	30	1374	90.0
Standard dose/ Standard dose Recipient (Two standard dose vaccine given)	53	15	2377	38	2430	60.3
COV003 (Brazil) with Standard dose/Standard dose)	45	12	2063	33	2025	64.2
All Standard dose/ Standard dose Recipient (Two standard dose vaccine given)	98	27	4440	71	4455	62.1
Other non-primary symptomatic study	18	7	5807	11	5829	36.4
Any symptomatic study	149	37	5807	112	5829	67.1
Asymptomatic study (COV002)	69	29	3288	40	3350	27.3
Low Dose prime (LD)/Standard Dose boost Recipient	24	7	1120	17	1127	58.9
Standard dose/ Standard dose Recipient (Two standard dose vaccine given)	45	22	2168	23	2223	3.8
Nucleic acid amplification positive swab	221	68	5807	153	5829	55.7

Table 2: Group evaluation of vaccine efficacy against covid 19 more than 14 days after an administration second dose of covid 19 vaccine (AstraZeneca)

	Total No. of cases	ChAdOx1nCOV-19 vaccine group (%)	Control group (%)	Vaccine efficacy (VE)%	pValue obtained
COV002 age group from 18 to 55 years* **UK**					
Low Dose prime (LD)/Standard Dose boost Recipient	33	3/1367	30/1374 (2.2)	90.0	0.019
Standard dose/ Standard dose Recipient (Two standard dose vaccine given)	49	14/1879	35/1922 (1.8)	59.3	
COV002 age group from 18 to 55 years > 8 weeks interval both vaccine doses **UK**					
Low Dose prime /Standard Dose boost Recipient	33	3/1357	30/1362 (2.2)	90.0	0.082
Standard dose/ Standard dose Recipient (Two standard dose vaccine given)	34	8/1407	26/1512 (1.7)	65.6	
All Standard dose/ Standard dose Recipient (Two standard dose vaccine given)** **UK & Brazil**					
< 6 weeks interval both vaccine doses*	28	9/1702	19/1698 (1.1)	53.4	0.557
> 6 weeks interval both vaccine doses*	70	18/2738	52/2757 (1.9)	65.4	

Storage of Vials:

Store the original carton in a refrigerator at temperature 2°C to 8°C. Do not freeze the vaccine. Protect from light. When the vial opens (first needle puncture) for administration store the vial for not more than 48 hours in a refrigerator (2°C to 8°C). In this time period the vaccine may be kept and used at temperatures up to 30°C for a single period of up to 6 hours. After this time period, the vial of vaccine must be discarded. Do not return the vial of vaccine to the refrigerator. Vial should be discarded if the suspension is discoloured or particles are observed in the vial. Do not shake it. Dispose any unused vaccine or waste material in compliance with the local guidance for genetically modified organisms or biohazardous waste. Disinfect the spills by using agents with activity against adenovirus.

COVISHIELD™ (Serum Institute):[13]

Study Design & Participants:

COVISHIELD™ vaccine is manufactured by Serum Institute of India Pvt. Ltd, Pune. The clinical trial Phase II/III type. Total 1600 healthy volunteers of age 18 years and older were involved and randomized in this clinical trial study of which observer-blind type and controlled conducted in India. Of which 400 volunteers were randomly assigned as in 3:1 ration for immunogenicity study to receive either COVISHIELD vaccine or Oxford/AZ-ChAdOx1 nCoV-19 vaccine, respectively. The balancing 1200 volunteers were randomly assigned for safety evaluation as in a 3:1 ratio to receive either COVISHIELD vaccine or Placebo, respectively. An interim analysis reveals the data till 14 Dec 2020 on all 1600 participants distributed as 1200 participants in COVISHIELD™ group, 100 participants in Oxford/AstraZeneca-ChAdOx1 nCoV-19 vaccine group and 300 in Placebo group.

The study of immunogenicity has conducted in India and the obtained data is comparable with anti-S IgG antibody titers and seroconversion proportion (seroconversion 100%) in between COVISHIELD™ vaccine and Oxford/AstraZeneca/AZ-ChAdOx1 nCoV-19 vaccine (refer Tables 3).

Table 3: Comparison of Immunogenicity data of in between Covishield™ and ChAdOx1nCOV-19 vaccine

Time point	Covishield Vaccine Total No. of subjects=291)		Oxford /AstraZeneca/ ChAdOx1nCOV-19 vaccine (Total No. of Subjects = 97)	
	Anti-s IgG antibodies	Seroconversion rate	Anti-s IgG antibodies	Seroconversion rate
Baseline	291	-	291	-
Day 29 (+14) Visit 3	289	279	97	89
Day 57(+14) Visit 4	140 (100%)	140 (100%)	46 (100%)	46 (100%)

Storage of vials:

Store vials in a refrigerator at 2ºC to 8ºC. Do not freeze the vials and protect it from light. Discard all opened multidose vials of COVISHIELD™ within 6 hours or at the closing of vaccination whichever is come first.

B) Moderna COVID-19 vaccine or mRNA vaccine:[14,15]

Introduction:

The mRNA-1273 vaccine against COVID-19 developed by Moderna and National Institute of Allergy and Infectious Diseases center in United States of America (USA). The mRNA vaccine is an LNP-encapsulated vaccine. It contains synthetic mRNA which is single-stranded, 5'-capped and expressing the perfusion-stabilized spike (s) glycoprotein of coronavirus SARS-CoV-2.[3] The mRNA-1273 vaccine is not a live virus vaccine, and does not enter the nucleus of the cell and is degraded quickly.[2] The vaccine is composed of ingredients such as lipids (SM-102 and 1,2-dimyristoyl-rac-glycero-3-methoxy); polyethylene glycol-2000; 2-distearoyl-sn-glycero-3-phosphocholine (DSPC)), cholesterol and other ingredients like acetic acid, tromethamine, tromethamine hydrochloride, sodium acetate, and sucrose.[3] The pivotal phase 3 registration trial of the mRNA-1273 vaccine against COVID-19 was conducted in 99 centers across the United States of America and about 30,000 healthy or had stable pre-existing medical conditions participants were involved in the age group of 18 years or older with no known history of SARS-CoV-2 infection.[3] The Moderna vaccine mRNA-1273 can be administered through intramuscularly (0.5 mL), given 28 days apart.[3] The available data from the phase 3 trials reveals that the mRNA-1273 vaccine is safe in people with evidence of prior SARS-CoV-2 infection. There is an insufficient data available on mRNA-1273 vaccination of pregnant women, immunocompromised persons in severely to evaluate vaccine efficacy or vaccine-associated risks. Currently there is no any efficacy or safety data has been available for children or adolescents below the age of 18 years; also for the lactating women or the effects of mRNA vaccines on breastfed children, or in persons with autoimmune conditions. [2]

Study Design & Participants:

The vaccine was highly efficacious against laboratory-confirmed COVID-19 infection from 14 days after the administration of second vaccine dose until the end of the follow-up stage. About 30,000 participants (healthy and stable medical conditions) of age 198 years and older

were involved in the pivotal phase 3 trial of the vaccine was conducted in 99 centers across the United States of America. Overall about 25% (7512 of 30 351) were aged of 65 years and 16.7% (5065 of 30 351) were under 65 years and at risk of severe COVID-19 illness. The primary endpoint efficacy was estimated as 94.1% (95% Confidence Interval (CI) against symptomatic COVID-19 was started 14 days after the administration of second dose at 2 to 42 days after the administration of first dose. There were total 196 cases as 11 cases were involved in the vaccinated group and 185 cases were involved in the placebo group. To estimate efficacy against severe covid 19 total 30 cases of severe COVID-19were analysed in trial 14 or more days after the administration of second dose in placebo group and the vaccine efficacy was analysed high as 100% (95%CI).

The safety concern of the mRNA-1273 COVID-19 vaccine (Moderna) which is favorable safety profile and data were evaluated from 30,351 participants who have received at least one dose of the vaccine in the vaccine group (n = 15,185) and in the placebo group (n = 15 166). 87.9% of study participants were followed up for at least 28 days after dose 2, and the median follow-up time for all participants was 9 weeks after dose 2.

Storage of Vials:

The Moderna COVID-19 vaccine is multidose vial (10 doses) sterile, preservative-free, white to off-white in color, frozen suspension, stored at at between –25 ºC and –15 ºC (–13 ºF and 5 ºF), Store the vials in refrigerator at temperature between 2° C to 8 °C for up to 30 days preceding to first use. Store the unopened vials at temperature 8°C to 25 °C for up to 12 hours. The vials should be stored at temperature between 2°C to 25°C and should be discarded after 6 hours after the first dose of vaccine has been withdrawn.

C) Janssen Ad26.COV2.S vaccine (Johnson & Johnson):[16-18]

Introduction:

The Janssen COVID-19 Ad26.COV2.S vaccine is also known as Ad26COVS1 against SARS-COV-2 infection is a recombinant, replication-incompetent human adenoviral serotype 26 (Ad26) vectored monovalent vaccine encoding a full-length and stabilized SARS-CoV-2 spike (s) protein. The acute oral toxicity estimated for the product was greater than 5000mg/kg (>5000mg/kg). This vaccine is free from adjuvants, preservatives and materials of animal origin, or fetal tissue. The recommended dose is one dose (0.5 ml) given by intramuscularly into the deltoid muscle. The vector does not replicate in human cells because

the E1 gene is deleted from the genome. To manufacture vaccines a specific cell line is used which was created by transformation of the primary cells using the Adenovirus E1 gene that constitutively expresses E1 and this cell line is derived from a single human primary cell and it was that complements for the missing E1 gene. The vaccine is manufactured through various purification steps after the proliferation of expression of Ad26 vector to the spike (s) protein which was grown in PER.C6G TetR named cell line with media, several amino acids and non animal ensuing proteins and then filled into vials. One dose of 0.5 ml Janseen vaccine is composed of 5 x 1010 AD26.COV2.S viral particles and with ingredients are citric acid monohydrate (C6H8O7·H2O), ethanol, 2-hydroxypropyl-beta-cyclodextrin (HBCD), it contains also other excipients like sodium citrate dihydrate, polysorbate 80 or Tween 80, sodium chloride (NaCl), sodium hydroxide (NaOH), and hydrochloric acid (HCl). It does not contain preservatives and administered through intramuscularly. The minimum interval is 14 days between administration of this vaccine and any other vaccine against other conditions.

Study Design & Participants:

The pivotal safety, efficacy and immunogenicity study is derived from five ongoing clinical study batches as first is COV1001 having study on healthy adults ages 18 to 55 in the United States and Belgium which includes a phase 1/2 trial in 1045 adults (1-dose and 2-dose regimens, with booster in 1 cohort) showing an acceptable safety and reactogenicity profile in adults aged 18 years and above and no any safety concerns has raised in assigned populations; second phase 2a randomized, double blinded and placebo controlled type of study was evaluated in COV1002 and conducted at various sites as Germany, Spain, Netherlands in healthy volunteers of age more than 18 years and older of which includes a phase 1 safety and immunogenicity study in 250 adults (2-dose regimen); third as COV2001 which include a phase 1a safety and immunogenicity study involving 550 adults and 660 adolescents (1-dose and 2-dose regimens) (enrolment of adolescents has not yet started); fourth randomized phase 3 study as in COV3001 which is multicentre, double blinded and placebo controlled to evaluate safety, efficacy and immunogenicity study of a single dose (5×1010 vp) of Janseen Ad26.COV2.S vaccine. The study is being conducted in various countries like Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa and USA. A total of 44 325 participants were randomized, of whom 43 783 were given either Ad26.COV2.S or placebo. which include a phase 3 efficacy and safety trial in 40 000 adults (1-dose regimen); and fifth as COV3009 which includes a phase 3 efficacy and safety trial in 30 000 adults (2-dose regimen). The concern of efficacy against new variants was evaluated

in the USA, VE against moderate to severe/critical COVID-19 and against severe/critical COVID-19 was consistent with the global VE findings. In South Africa, vaccine was observed with highly efficacious against severe infection of COVID-19 (VE: 81.7% (95%CI)) and robust VE 64.0% (95%CI) was observed for moderate to severe condition of COVID-19 after 28 days of vaccination) as where the 20H/501Y.V2 variant (B.1.351 lineage) was the predominant variant (96.3% of sequenced cases thus far),. Whereas in Brazil, the variant from the P.2 lineage was the predominant strain (70.7% of sequenced cases thus far), VE was similar to the USA and South Africa. The participants from Brazil, South Africa, and the USA has not shown any differences in S-specific binding antibody levels and responder rates induced by Ad26.COV2.S vaccine. (refer Table 4)

Table 4: Vaccine efficacy regarding severity endpoint (USA, Brazil, South Africa)

Name of Country	Disease severity condition	No. of risk / Total Number of subjects(N)		Vaccine Efficacy (%) for more than Day 28 (95%CI)
		Vaccine group Total subjects (N) = 19,306	Placebo group Total subjects (N) =19,178	
United States of America (USA)	Moderate to severe or critical condition	32/8958	112/8835	72.0
	severe or critical condition	1/8958	7/8835	85.9
Brazil (Efficacy results)	Moderate to severe or critical condition	24/3354	74/3312	68.1
	severe or critical condition	1/3354	8/3312	87.6
South Africa (Efficacy results)	Moderate to severe or critical condition	23/2449	64/2463	64.0
	severe or critical condition	4/2449	22/2463	81.7

Storage of Vials:

The vaccine is provided to countries at -20°C with a shelf life of 24 months. Vaccine can be stored at 2°C to 8°C for 3 months. Don't re-freeze the vaccine once thawed. The vials should be protected from light. Store the vials at temperature between 2°C to 8°C after the first dose of vaccine has withdrawn for not longer than 6 hours in compliance with the WHO Multidose open vial policy. Any remaining doses in an opened vial must be discarded after 6 hours or at the end of the immunization session, whichever comes first.

D) Sputnik V (Gam-COVID-Vac) (Gamaleya national Centre):[19]

Introduction:

Gam-COVID-Vac or sputnik V is a combined vector vaccine approved in Russia and developed by The Gamaleya national Centre. It is based on rAd type 26 (rAd26) vector and rAd type 5 vector (rAd5). These two vectors lugs gene with glycoprotein S (rAd26-S and rAd5-S) for coronavirus SARS-CoV-2 The vaccination of rAd26-S and rAd5-S are through intramuscularly separately with interval of 21 days.

Study design and participants:

Study type is a randomized, double-blind, placebo-controlled, multicentre. Phase 1/2 clinical trials of the vaccine were conducted and completed in 12th August 2020. Phase 3 trial of the Sputnik V (Gam-COVID-Vac) vaccine was conducted in adults at 25 hospitals and polyclinics in Moscow, Russia to appraise efficacy, immunogenicity, and safety The results have shown that it was well tolerated and highly immunogenic in healthy participants. Also, with enhanced pharmacovigilance a post-marketing efficacy study is carried out and vaccine is allowed to use in high-risk groups for the prevention of COVID-19 infection.

The interim analysis of the randomized, controlled, phase 3 trial of Gam-COVID-Vac in Russia which is highly efficacious has shown efficacy as 91·6% (95% CI 85·6–95·2) against COVID-19 (from day 21 after first dose, the day of receiving second dose) and 100% (95% CI 94·4–100) efficacious against severe COVID-19; immunogenicity, and a good tolerability profile in participants aged 18 years or older and in parallel with implementation of multiple clinical trials (in Russia, Belarus, United Arab Emirates, and India). Overall 16,427 participants and 5435 participants were involved in the vaccine group and placebo group respectively for preliminary analysis, and all of these participants were received at least one

dose of vaccine reporting serious adverse events (4 deaths were reported but it was not due to vaccine administration: three (<0·1%) of 16 427 participants in the vaccine group (one death was associated with fracture of the thoracic vertebra and the other two were associated with COVID-19 (one patient with a severe cardiovascular background who developed symptoms on day 4 after first dose and one patient with a background of endocrinological comorbidities who developed symptoms on day 5 after first dose)) and one (<0·1%) in the placebo group of 5435 participants. However, vaccine group with 14,964 participants and placebo group with 4902 participants were studied and clinical data has evaluated at the time of database lock (Nov 24, 2020); From days 21 after the vaccination of first dose (the day of dose 2), there were 16 COVID-19 cases were confirmed in the vaccine group (of 14 964 participants; 0·1%) and 62 cases were confirmed in the placebo group (of 4902 participants; 1·3%); vaccine efficacy was estimated as91·6% (95% CI). (refer Table 5).

Table 5: Vaccine Efficacy (VE%) on the basis of Interim analysis

	No. of Total cases	**Vaccine group (%)**	**Placebo group (%)**	**Efficacy of vaccine (95%CI)**	**pValue obtained**
First covid 19 incidence from 21 days after administration of first dose (Day of dose 2)*					
Overall	78	6/14964 (0.1)	62/4902 (1.3)	91.6 (85-95.2)	<0.0001
Age group (years)					
18-30	5	1/1596 (0.1)	4/521 (0.8)	91.9 (51.2-99.3)	0.0146
31-40	17	4/3848	13/1559 (1.0)	90.0 (71.1-96.5)	<0.0001
41-50	19	4/4399	15/1443 (1.0)	91.3 (73.7-96.9)	<0.0001
51-60	27	5/3510	22/1146 (1.9)	92.7 (81.1-97.0)	<0.0001
>60	10	2/1611(0.1)	8/533 (1.5)	91.8 (67.1-98.3)	0.0004
Sex					
Female	32	9/5821(0.2)	23/1887(1.2)	87.5(73.4-94.2)	<0.0001
Male	46	7/9143(0.1)	39/3015(1.3)	94.2(87.2-97.4)	<0.0001
Moderate or severe cases	20	0/14964	20/4902(0.4)	100(94.4-100.4)	<0.0001
First covid 19 occurrence after administration of dose 1#					
Any time after dose1	175	79/16427(0.5)	96/5435(1.8)	73.1(63.7-80.8)	<0.001
From 14 days after dose 1	109	30/14999(0.2)	79/4950(1.6)	87.6(81.1-91.8)	<0.0001
First Covid 19 occurrence after dose 2 (28 days after dose 1)*					
All	60	13/14094(0.1)	87/4601(1.0)	91.1(83.8-95.1)	<0.0001

* It includes participants who received both doses.

- # It includes participants who received at least one dose.

Storage of Vials:

Vaccine developed in two forms: liquid (which is stored at –18°C) and freeze dried (which is stored at 2–8°C). Store liquid form of the vaccine at –18°C.

E) COVID-19 vaccine or BNT162b2 (Pfizer and BioNTech):[20-22]

Introduction:

The COVID-19 vaccine BNT162b2 (Pfizer–BioNTech) is an mRNA vaccine instructing a P2 mutant spike (s) protein (PS 2) and synthesized as an RNA–LNP of nucleoside modified mRNA (modRNA). After administration of vaccine it is encapsulated into Lipid nanoparticles (LNPs) and it consent to transfection of the mRNA into host cells and RNA is released into the cytosol by taking LNPs into the cells, and then it expresses the encoded viral protein. At the time of mixing of RNA and dissolved lipids, the lipids outline the nanoparticles encapsulating the RNA. After vaccination mRNA is rapidly degraded in intracellular region, as a result the peptides on cell surface triggers a particular humoral T-cell arbitrate immune response against the spike (s) protein.

WHO has listed the COVID-19 mRNA vaccine BNT162b2 as on 31 December 2020 for emergency use. mRNA vaccine BNT162b2 developed by the M/s. BioNTech and Pfizer and have shown a high efficacy as 95%. It is first vaccine that it receives emergency validation by WHO since the outbreak commenced a year prior. The vaccine can be administered through intramuscularly into the deltoid muscle with two doses (30 microgram, 0.3 ml each) between an interval of 21 to 28 days.

Study Design and Participants:

The pivotal phase II/III trial of the vaccine BNT162b2 was conducted in six countries as Argentina, South Africa, Brazil, Turkey , Germany, and USA. About 43,000 healthy and stable medical condition participants (white (83%) and from sites of USA (77%)) of age 16 to 85 years were involved in this trial, uniformly randomized between vaccine group and placebo groups. The vaccination was in two doses separated by interval of 21 days. The primary evaluation of vaccine efficacy in vaccine group was analysed as 94.6% (95% CI)

against covid 19 from 178 cases of symptomatic signs and 169 cases from the placebo group. After confirmation of analysis the Vaccine efficacy was estimated of 95.0% (95% CI); as there were 8 cases in vaccine group and 162 cases in placebo group without evidence of a prior SARS-CoV-2 infection. The vaccine efficacy is as 52.4% (95% CI) between both the first and second doses and 90.5% (95% CI) between the second dose and 7 days after the administration of second dose. There were no any significant variation in vaccine efficacy in primary analysis were evaluated accordingly to age, ethnicity, race, country and obesity. The efficacy against severe COVID-19 was estimated as 88.9% (95% CI) accordingly to total 10 severe COVID-19 cases observed in trial i.e. 1 case was in the vaccinated group and 9 in the placebo group. Out of 10 cases, 5 cases observed in 7 or more days after the administration of second vaccine dose, 1 case was observed in the vaccine group and 4 cases were observed in the placebo group.

Storage of Vials:

Store the vials at ultra low temperature freezer up to 6 months, it requires temperature controlled thermal shippers (with Global Positioning System (GPS) temperature-monitoring device) using dry ice for maintaining the recommended temperature as –70 °C ± 10°C for up to 10 days will be needed for transportation purpose. When the doses arrives thermal shippers can be refilled with dry ice and keep for temporary storage units up to 15 days. And after 15 days, transfer the vials to refrigerator at temperature 2°C to 8°C for five days, it gives a total storage time of 20 days. Store the vials at 2°C to 8↑8C once it is thawed. There are various storage conditions permit evenhanded access to the Pfizer vaccine for different areas with varying infrastructure.

F) Sinopharm, BIBP (Beijing Bio-Institute)[23,24]

Introduction

The Sinopharm vaccine is formed by Beijing Bio-Institute of Biological Products Co Ltd, subsidiary of China National Biotech Group (CNBG) and WHO listed the Sinopharm COVID-19 vaccine for emergency use in Emergency Use Listing (EUL). The Sinopharm product is also named as SARS-CoV-2 Vaccine (Vero Cell) which is inactivated. It is aluminium hydroxide adjuvanted and β-propiolactone inactivated SARS-CoV-2 Vaccine (Vero Cell) vaccine based on the HB02 strain i.e. 19nCOV-CDC-TAN-HB02.

Study Design and Participants:

On the basis of all available evidence, WHO recommends the vaccine for adults 18 years and older, in a two-dose schedule with a spacing of three to four weeks. Vaccine efficacy for symptomatic and hospitalized disease was estimated to be 79%, all age groups combined. Few older adults (over 60 years) were enrolled in clinical trials, so efficacy could not be estimated in this age group. Nevertheless, WHO is not recommending an upper age limit for the vaccine because preliminary data and supportive immunogenicity data suggest the vaccine is likely to have a protective effect in older persons. There is no theoretical reason to believe that the vaccine has a different safety profile in older and younger populations. WHO therefore recommends that countries using the vaccine in older age groups conduct safety and effectiveness monitoring to make the recommendation more robust. The EUL pathway involves a rigorous assessment of late phase II and phase III clinical trial data as well as substantial additional data on safety, efficacy, quality and a risk management plan. These data are reviewed by independent experts and WHO teams who consider the current body of evidence on the vaccine under consideration, the plans for monitoring its use, and plans for further studies.

There are three ongoing pivotal studies for safety, efficacy (refer table 7) and immunobridging consistency as first is COVIV-01 : it is a phase I/II clinical trial which is conducted in China; whereas second is COVIV-02: it is a phase 3 trial for efficacy & conducted in Baharain, Jorden, United Arab Emirates and Egypt; while third is COVIV-05: it is a phase 3 commercial trial for immunogenicity study conducted in China.

Other studies are there but still reports are awaiting as COVIV-03: it is a phase 3 study trial is ongoing in Peru; whereas COVIV-04: it a phase 3 ongoing study in Argentina; while COVIV-PPV23-IIV4 is ongoing phase 4 study and used in combine with a pneumococcal polysaccharide and inactivated influenza vaccine.(for details refer table 6)

Table 6. Clinical study database overview of covid 19 vaccine BIBP, Sinopharm clinical database as of 20 April 2021

Name of Trial Batch	Phase (study)	Site	No. of volunteers or participants involved	Dosing schedule	Status of Interim Results
COVIV-01 Trial registration No. ChiCTR2000032459	Phase I/II (Safety)	China	2128 (more than 3 years)	Multiple*	Available for participants for more than 18 years
COVIV-02 Trial registration No. NCT04510207	Phase III (Efficacy)	Baharain, Jorden, United Arab Emirates and Egypt	45,000 (more than 18 years	2 dose schedule (0-21days)	Available
COVIV-03 Trial registration No. NCT04612972	Phase III (efficacy)	Peru	12,000 (more than 18 years)	2 dose schedule (0-21days)	Under Recruiting
COVIV-04 Trial registration No. NCT04560881	Phase III (efficacy)	Argentina	3000 (greater than 18 years)	2 dose schedule (0-21days)	Under Recruiting
COVIV-05 Trial registration No. CTR20201998	Phase III (immuno-bridging and consistency of commercial product)	China	2100 (aged 18-59 years)	2 dose schedule (0-21days)	Available
COVIV-PP-V23-IIV4-combine Trial registration No. NCT04790851	Phase IV (combine study)	China	1152	2 dose schedule	Under Recruiting

*** It contains 1 dose schedule, 2 dose schedule and 3 dose schedule of combination of low dose (2 microgram), medium dose (4microgram) and high dose (8 microgram)**

Table 7: Vaccine Efficacy data of BIBP, Sinopharm (COVIV-02) (32 December 2020)

	Vaccine Group No. at risk causes/ No. of subjects	**Placebo group No. at risk causes/ No. of subjects**	**Vaccine efficacy (%) (95%CI)**
Total estimation	21/13765	95/13765	78.1
Severe condition	0/13765	2/13765	Not estimated
Sex criteria			
Male	18/11598	83/11642	78.4
Female	3/2167	12/2123	75.5
Age			
18 to 59 years	20/13556	94/13559	78.1
More than 60 years	0/209	0/206	Not estimated
Comorbidities			
Hypertension	0/374	4/367	Not estimated
Diabetic condition	2/300	6/308	63.7
BMI based	7/3040	36/3080	80.7
Baseline of SARS-Cov-2			
Baseline Positive values	0/Not reported	1/Not reported	Not estimated
Baseline negative values	16/Not reported	83/Not reported	80.8

Storage condition for vials:

Store the vials in a refrigerator at 2°C to 8 °C). Protect from light.

G) Covaxin (Bharat Biotech)[2,25,26]

Introduction:

Covaxin vaccine is an an inactivated whole virion COVID-19 vaccine, COVAXIN™ has been developed by Bharat Biotech International Limited and in collaboration with Indian Council of Medical Research (ICMR). The COVAXIN™ has been evaluated for its safety, reactogenicity and immunogenicity in phase 1 and 2 clinical trials and the trial reports were submitted to the Central Drugs Standard Control Organization (CDSCO) India. COVAXIN™ has been approved under emergency use authorization with permission number

MF/BIO/21/000002, dated 03.01.2021, F. No: BIO/MA/20/000103. This permission is given for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode, where COVAXIN^{TM} vaccine will be administered to the vaccine recipients and they will be followed up for safety. M/s. Bharat Biotech has developed a Whole Virion Inactivated Corona Virus Vaccine (Covaxin) in collaboration with ICMR and National Institute of Virology NIV (Pune), from where they received the virus seed strains. This vaccine is developed on Vero cell platform, which has well established track record of safety and efficacy in the country & globally.

Study Design & Participants:

The firm has produced clinical data in various animal species (mice, rats, rabbits, Syrian hamster, non-human primates (Rhesus macaques), hamsters etc.). The firm has submitted all these data to CDSCO. The clinical trials in Phase I and Phase II were conducted on overall 800 participants and vaccine safety, efficacy and evaluation data was demonstrated to give strong immune response. In India total 25,800 volunteers are involved in conduction of the Phase III efficacy trial and the vaccine has been found to be safe as per the data available till date. The ongoing phase 3 trial in 25,800 volunteers resulting interim analysis and showing 81% efficacy for covaxin vaccine.

H) Novavax (NVX-CoV2373) COVID-19 Vaccine[25]

Introduction:

Novavax vaccine is protein-based COVID-19 vaccine candidate contains a prefusion spike (s) protein. It developed by Novavax. The purified protein is fixed to the genetic sequence of the coronavirus SARS-COV-2 spike (S) protein and is formed in insect cells.

Study Design and Participants:

Novavax demonstrates strong efficacy as 89.3% in Phase 3 trial was conducted in United Kingdom (UK) and clinical efficacy was demonstrated in phase 2b was conducted in South Africa. There were total 20,000 participants involved in phase 1, 2 and 3 trials. In UK phase 3 study were enrolled more than 15,000 participants of age 18 to 84 years.

The first interim analysis of Novavax estimated the vaccine efficacy as 89.3% based on observed cases of covid 19 as 6 and 56 cases in vaccine group and placebo group, respectively, out of total 62 cases. From this total 62 cases, 61 cases were observed in mild or

moderate condition while 1 was observed in severe condition in the in placebo group. Efficacy was calculated based on PCR analysis on strains of 56 from the 62 cases as 95.6%, 85.6% against the original COVID-19 strain and United Kingdom variant strain respectively.

Novavax demonstrates strong efficacy as 90% in Phase 3 trial was conducted in South Africa. There were total 4400 participants involved at the beginning in August 2020, with COVID-19 cases. Preliminary analysis data has shown vaccine efficacy as 92.6% (25 out of 27 cases) for 27 of 44 COVID-19. South Africa escape variant. The vaccine efficacy has shown as 60% (95%CI) in the phase 2b trial conducted in South Africa. The clinical trial phase 3 (randomized, placebo controlled, observer blinded) with 30,000 subjects of age 18 years and older has conducted in US and Mexico to assess the efficacy study, safety and immune-genicity evaluation of Novavax (NVX-CoV2373) vaccine having a significant progress on covid-19.

Storage of Vials:

Sore the vials in refrigerator at temperature 2°C to 8°C.

DISCUSSION

The immunization approaches are considered in account for a number of concerns regarding the superiority of COVID-19 vaccine access by considering risk assessment of adverse effects of vaccination in population groups with increased risk of severe COVID-19 (older adults and individuals with comorbidities), vaccine logistics (cold chain supply), sufficient coverage of vaccination, and duration of protective immune response. According to WHO target product profiles for COVID-19 vaccines, some characteristics required for emergency use during an outbreak include efficacy of at least 50%, for suitability of use in older adults, maximum of two dose procedure, and prevention for at least 6 months.

Now a days, the pharmaceutical companies are investigating a single dose regimen of the vaccine for the prevention of covid 19 infection.

Currently there is no any efficacy or safety data has been available for children or adolescents below the age of 18 years; also for the lactating women or the effects of vaccines on breastfed children, or in persons with autoimmune conditions. There is an insufficient data available on vaccination of pregnant women, immunocompromised persons in severely to evaluate vaccine efficacy or vaccine-associated risks.

All vaccines such as vector vaccines or sputnik V (Gamaleya National Research Centre for Epidemiology and Microbiology [NRCEM]; Oxford/AstraZeneca/ChAdox1ncov-19, Sinopharm or BIBP (Beijing Bio-Institute of Biological Products), and Janseen Ad26.COV2.S vaccine (Johnson & Johnson), mRNA-based vaccines or mRNA-1273 (Moderna), Novavax vaccine (Novavax), Covaxin (Bharat Biotech) and BNT162b2 (Pfizer/BioNTech) etc. have shown promising results in parallel with implementation of multiple clinical trials.

WHO has listed the vaccines in Emergency Use list (EUL) such as BNT162b2 (Pfizer/BioNTech) vaccine on 31 December 2020; ChAdOx1-S [recombinant] (AstraZeneca/Oxford) COVID-19 vaccines on 15 February 2021 (AstraZeneca & SKBioscience (Republic of Korea)) and the Serum Institute Ltd. of India; covid 19 vaccine ChAdOx1-S [recombinant] (AstraZeneca AB) on 15 April 2021 and COVID-19 vaccine Janseen Ad26.COV2.S (Johnson & Johnson) on 12 March 2021; and Sputnik V (Russia) on as of Jan 23, 2021.[27]

Until the widespread immunity stop the progress of the spreading of coronavirus SARS-COV-2, physical distancing measures and novel therapies are required to control covid 19 infection. In the period in-between, if an efficacious vaccine used in cohort at risk of severe disease has the potential to boast a major impact on the pandemic of covid 19.

ANNEXURE:

Annexure1: Covid 19 Vaccines (Clinical Assessment Phase 4/3 as on Date 26th May 2021)

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Annexure 1

COVID 19 VACCINES (Clinical Assessment Phase 4/3 as on Date 26th May 2021)

Sr. No.	Name of Lead Candidate (Manufacturer)	Type of trial	Type of Study	Study Design	Health Condition	Phase of Trial	Dose	Route of drug Administration	Dose Interval	Storage Condition	Efficacy
1.	mRNA-1273 mRNA-1283 **(Moderna)**	Interventional	mRNA based vaccine encapsulated in lipid nanoparticle (LNP)	Randomized, Stratified, Observer-Blind, Placebo-Controlled Study	Prevention of covid 19 infection	Phase 4	25 µg, 100 µg and 250 µg	Intramuscular (IM)	On Day 1 and On Day 29	In between –25 °C and –15°C	94.1%
2.	Covishield ™ ChAdOx1 nCoV- 19 or covid 19 vaccine **(Serum Institute of India)**	Interventional	adenoviral vector expressing spike (s) protein antigen of SARS-COV-2	Randomized, Parallel Group Trial	Prevention of covid 19 infection	Phase 4	0.5mL	Intramuscular (IM)	On Day 1 And On day 29	2°C to 8 °C	73.43%
3.	AZD1222 **(Oxford University and AstraZeneca)**	Interventional	Recombinant replication defective chimpanzee adenovirus	Prospective, multicentre, open-label, non-	Prevention of covid 19 infection	Phase 4	0.5mL	Intramuscular (IM)	On Day 0 And On day 28	2°C to 8 °C	63.09%

			expresses SARS-cov-2 s surface glycoprotein	comparative clinical study							
4.	mRNA Vaccine BNT162b2/COMIRNATY (INN Tozinameran) **Pfizer Biontecha**	Observational	Nucleoside modified mRNA vaccine	Test - negative case-control design and a retrospective cohort design	Prevention of covid 19 infection	Phase 4	30 microgram, 0.3 ml each	Intramuscular (IM)	On Day 0 And On day 21	-70°C	95%
5.	Sinopharm or BIBP **(China National Biotec Group and Beijing Institute of Biological Products)**	Interventional	Inactivated SARS-CoV-2 vaccine	randomized, double-blinded, and placebo-controlled study	Prevention of covid 19 infection	Phase 4	2 dose	Intramuscular (IM)	On Day 0 And On day 21	2°C to 8 °C	78.1%
6.	Sputnik V (**The Gamaleya national Centre)**	Observational	Human adenovirus vector based covid-19 vaccine	Randomized Double-blind Placebo-controlled Multi-center Clinical Trial	Prevention of covid 19 infection	Phase 3	0.5mL	Intramuscular (IM)	On Day 0 And On day 21	2°C to 8 °C	91.8%
7.	Covaxin (BBV152) **Bharat Biotech International Limited**	Interventional	Whole - Virion Inactivated SARS-CoV-2 Vaccine	Randomized, Double-blind, Multicenter study	Prevention of covid 19 infection	Phase 3	0.5mL	Intramuscular (IM)	On Day 1 And On day 14	2°C to 8 °C	81%
8.	Ad26.COV2.S (COVID-19) vaccine **(Janssen**	Observational	Recombinant, replication-incompetent	Randomized ,Double-	Prevention of covid 19	Phase 3	0.5mL	Intramuscular (IM)	Day 0 or Day 0 +56	-20°C	Different for different

	Pharmaceuticals)		human adenoviral vector type 26 (Ad26) vaccine encoding the (SAR-COV-2) spike s protein	blind, Placebo – controlled, Multicenter study	infection						conditions *
9.	NVX-CoV2373 **Novavax**	Interventional	recombinant SARS CoV-2 glycoprotein nanoparticle vaccine) Protein subunit	Randomized, Observer-Blinded, Placebo-Controlled crossover assignment Study	SARS-CoV Infection Covid19	Phase 3	0.5mL	Intramuscular (IM)	On Day 0 And On day 21	2°C to 8 °C	89.3%