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STUDY OF INDIGENOUS COVID-19 VACCINE- "COVAXIN".

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❖ ABSTRACT:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel human coronavirus, has spread across the world. SARS-CoV-2 belongs to b-genus of Sarbecovirus and is a close relative of SARS-CoV with approximately 80% sequence identity. In March 2020, the World Health Organization (WHO) proclaimed the SARS-CoV-2-caused disease coronavirus disease-19 (COVID-19), a pandemic. Therefore, it is imperative to develop effective prophylactic and therapeutic counter measures to prevent and treat COVID-19. Numerous vaccine candidates such as adenovirus-vectored, nucleic-acid-based, recombinant-protein based, and inactivated vaccines are at various stages of developmental phase at either preclinical or clinical trials. However, meeting the global need for billions of doses of COVID-19 vaccines will require collective effort to identify, evaluate, validate, and manufacture effective vaccines. This review article gives detailed information about the study of India's first Indigenous COVID-19 vaccine "COVAXIN". The main objective of this review is to get more information about its preclinical study, formulation, as well as its safety and efficacy in various phases of clinical trials.

❖ KEY WORDS:

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), Pandemic, COVAXIN, Immunogenicity and Safety, Clinical Trials.

❖ INTRODUCTION:

Bharat Biotech has developed COVAXIN, India's indigenous COVID-19 vaccine, 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 BSL-3 (Bio-Safety Level 3) high containment facility. The vaccine is developed using Whole-Virion Inactivated Vero Cell derived platform technology. Because inactivated vaccinations do not multiply, they are unlikely to revert and cause disease. They include dead viruses that are unable to infect humans but can nevertheless instruct the immune system to produce a defensive response in the case of infection.

Why Inactivated Vaccine: Conventionally, inactivated vaccines have been around for decades. Seasonal influenza vaccines, polio vaccines, rabies vaccines, and Japanese encephalitis vaccines all use the same method to manufacture inactivated vaccines with an assured supply of over 300 million doses. It is a well-established and time-tested platform in the world of vaccine technology.[1]

- **IDEAL PROPERTIES OF COVAXIN:**

➢ COVAXIN is included along with immune-potentiators, also known as vaccine adjuvants, which are added to the vaccine to increase and boost its immunogenicity.

➢ It's a two-dose vaccination schedule administered 28 days apart, with no need for sub-zero storage, no reconstitution, and ready-to-use liquid presentation in multi-dose vials that's stable at 2-8^{0}C.

➢ Pre-clinical studies: Demonstrated strong immunogenicity and protective efficacy in animal challenge studies conducted in hamsters & non-human primates.

➢ In July 2020, the vaccine gained DCGI approval for Phase I and II Human Clinical Trials. The Phase 1 study enrolled a total of 375 participants and produced outstanding safety data without any reactogenicity.

➢ With two different SARS-CoV-2 strains, vaccine-induced neutralising antibody titers were found. In symptomatic patients, the cumulative percentage of all side events was barely 15%.

➢ A total of 25,800 subjects have been enrolled and randomized in a 1:1 ratio to receive the vaccine and control in a Event-Driven, randomized, double-blind, placebo-controlled, multicentre phase 3 study.

➢ The purpose of this study is to evaluate the efficacy, safety, and immunogenicity of COVAXIN in volunteers aged above or equal to 18 years.

➢ Of the 25,800 participants, more than 2400 volunteers were above 60 years of age and more than 4500 with comorbid conditions.

➢ COVAXIN demonstrated 81% interim efficacy in preventing COVID-19 in those without prior infection after the second dose. [1]

❖ **Global Acceptance of COVAXIN:**

Bharat biotech claims that it has been approached by several countries across the world for the procurement of COVAXIN. Mongolia, Myanmar, Sri Lanka, the Philippines, Bahrain, Oman, the Maldives, and Mauritius will all receive supplies from the government to the government.[1]

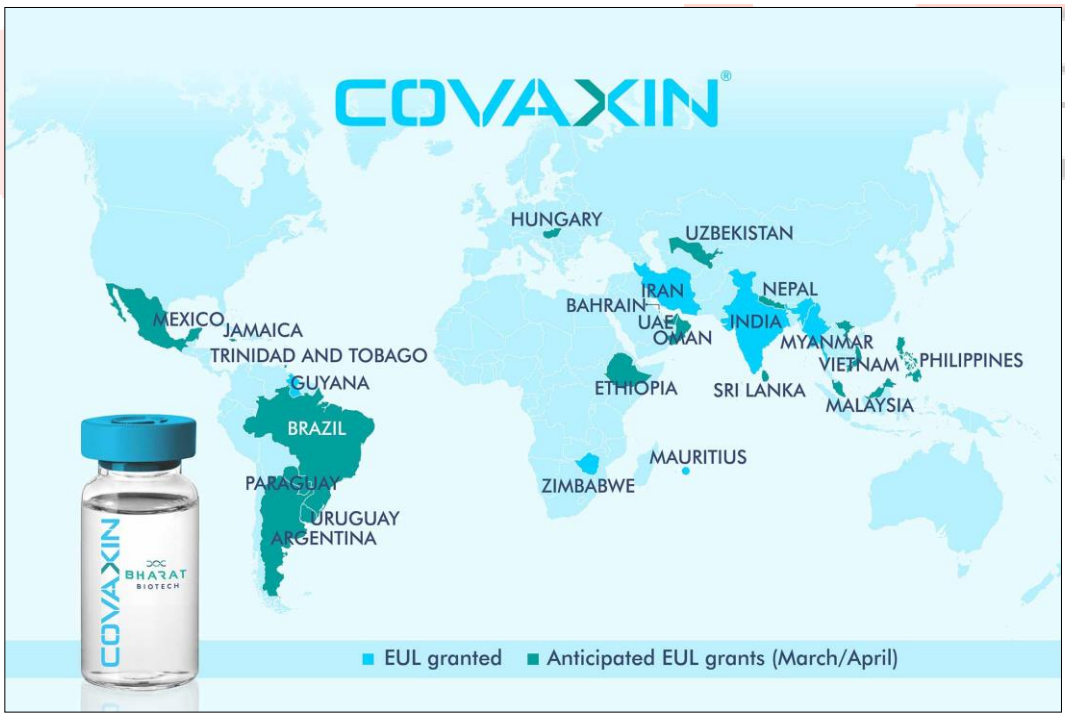


Figure 1: Global acceptance of COVAXIN[1]

❖ VACCINE CANDIDATE PREPARATION :

1. A desirable characteristic for any COVID-19 vaccine candidate is the ability to induce T-helper-1 cell (Th1) responses.[2] Whole-virion inactivated vaccines are usually formulated with Alum, which does not have the ability to induce cell-mediated responses.[3,4] An imidazoquinoline molecule, which is a toll-like receptor (TLR) agonist, has been used to stimulate cell-mediated responses.[5,6] Algel-IMDG (an imidazoquinoline molecule chemisorbed on alum [Algel]) has been designed to traffic vaccine antigen directly to draining lymph nodes without diffusing into the systemic circulation. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine adjuvanted with Algel-IMDG.
2. Inactivated vaccines for viral diseases have been licensed for decades with well-established safety profiles. The availability of well-characterized Vero cell manufacturing platform with proven safety have aided in rapid vaccine development of inactivated vaccines. Some of the most advanced developmental stage vaccine candidates such as the inactivated vaccine (PiCoVacc) and the recombinant vaccine (CoV-RBD219N1) are aluminum adjuvant formulations. These vaccines are shown to generate high levels of NAb titers against SARS CoV 2, which could play an important role in vaccine efficacy. Hence, the development of inactivated vaccines for COVID-19 prevention appears to be a rational approach, while recognizing the fact that such inactivated vaccines with alum adjuvant specifically induce Th2-biased response. For example, inactivated SARS CoV 2 vaccine (CoronaVac, China) formulated with alum-generated Th2 response, but with low levels of Th1 response. Hence, there is no clear indication that CoronaVac induces Th1 response (Zhang et al., 2020)[7]. However, recent literature on SARS and SARS CoV 2 showed the importance of Th1-skewed immune response, in providing the protection against infection and its role in reducing the clinical severity toward subsequent infections (Janice Oh et al., 2012; Jeyanathan et al., 2020; Le Bert et al., 2020).[8,9,10] Further, antigen-specific T cell immune responses live longer than the neutralization antibodies and provide long-term immunity. Hence, SARS CoV 2-specific T cell immunity is found to be critical, while developing a vaccine against SARS CoV 2. Given this, Bharat biotech along with Indian Council of Medical Research (ICMR) - National Institute of Virology (NIV) formulated an inactivated vaccine with an adjuvant (Algel-IMDG) containing TLR agonists molecule, known to induce Th1-biased immunity.
3. Inactivated whole-virion SARS CoV-2 (BBV152) vaccine candidates were formulated with two alum-based adjuvants: Algel (aluminum hydroxide gel) and Algel-IMDG, an imidazoquinoline class molecule (TLR7/ TLR8 agonist, abbreviated as IMDG) chemisorbed onto aluminum hydroxide gel. Three vaccine formulations were prepared: first two contain 3 mg and 6 mg antigen with Algel-IMDG (BBV152A and BBV152B, respectively) and the third one contains 6mg antigen with Algel (BBV152C). To determine the stability of these formulations, Algel-IMDG vaccine formulations (BBV152A and BBV152B) were stored at 37^0C and 2–8^0C temperature for 7 days.[11]
4. Here is the report of the immunogenicity and safety evaluation of the whole-virion inactivated SARS-CoV-2 vaccine candidate (BBV152) formulated in Algel or Algel-IMDG, in animal models.

❖ PRECLINICAL STUDY ON ANIMALS:

Immunogenicity in BALB/c mice:

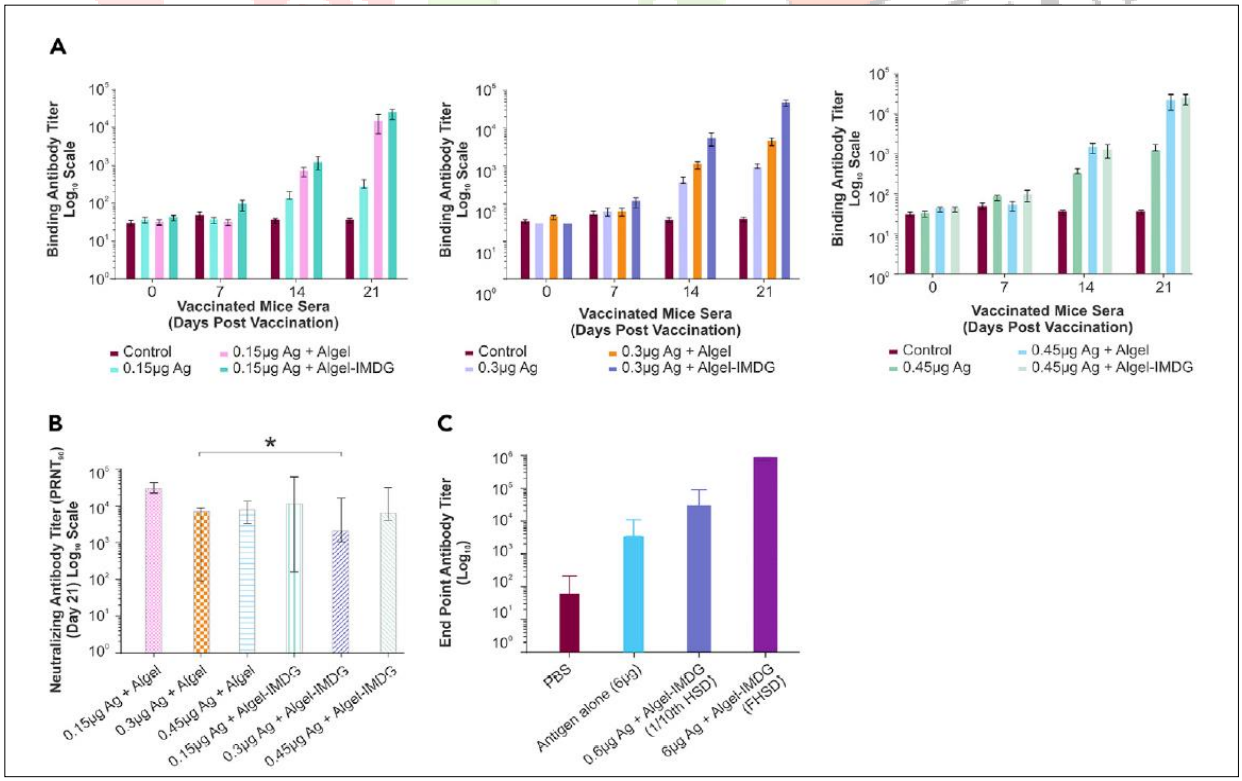
1. Initially, BALB/c mice (n=5/group, female) were administered with adjuvanted vaccine formulations, antigen or adjuvants alone at 1/20th of the intended HSD [Human Single Dose] (i.e.0.15 µg, 0.3 µg, and 0.45 µg /mouse), to determine the optimal dose.
2. ELISA (Enzyme Linked Immunoabsorbent Assay) titers (Figure 2A) and Nab (Neutralizing Antibody) titers (Figure 2B) determined at various time points revealed that immune response elicited against these adjuvanted vaccine formulations tested at three antigen concentrations elicited high levels of binding and Nab titer (Figures 2A and 2B).
3. Antibody response determined on day 7 was found to be less (102 titer) or negligible compared with day 14 and day 21 with a titer of 103 and 104, respectively.
4. Notably, 3 and 6 µg formulations induced high or similar spike-specific antibody titers compared with 9 µg group.
5. Hence, adjuvanted formulation with high antigen dose (9 µg) was eliminated in further studies of the immunogenicity, whereas safety was evaluated in Wistar rats at this high dose.
6. These results also indicated that adjuvanted vaccine formulations either with Algel or Algel-IMDG elicited high spike (S1)-specific antibody binding titers compared with antigen alone tested at all three concentrations (Figure 2A).
7. This was further evaluated by administering BALB/c mice intramuscularly with antigen at actual HSD (6µg Ag) either in the presence or in the absence of adjuvant (Algel-IMDG) and compared with 1/10th HSD of adjuvanted

vaccine formulation (0.6µg Ag and Algel-IMDG). Immune response elicited against adjuvanted vaccine formulation (BBV152B) was significantly higher than the antigen alone (6 µg Ag), which is comparable with 1/10th HSD of adjuvanted vaccine formulation (1/10th of BBV152B).

8. These results suggest the dose-sparing effect of Algel-IMDG (Figure 2C).[11]

❖ IMMUNOGENICITY AND SAFETY:

1. Further, to assess the immunogenicity and safety of clinical batch samples, BALB/c mice (n = 10/group, 5 male and 5 female) were vaccinated via IP route with three adjuvanted vaccine formulations with Algel and Algel-IMDG at 1/10th human intended single dose (0.3 and 0.6 µg /dose with Algel or Algel-IMDG).
2. All adjuvanted vaccine formulations elicited antigen-specific binding antibodies (Figure 2D).
3. Further, sera collected on day 21 were analyzed by ELISA to determine S1, RBD (Receptor Binding Domain: RBD is the key part of virus located on its spike domain that allows it to dock to body receptor to gain entry into cells and lead to infection. These are maily primary targets during the prevention and treatment of viral infection), and N-specific binding titer (Figure E) and showed 100% seroconversion with S1, RBD, and N protein.
4. Analysis of plaque reduction neutralization test (PRNT90)[This test is used to quantify the titer of neutralizing antibody for a virus], performed with individual mice sera, showed high NAbs in all adjuvanted vaccines (Figure 2F).
5. Here also compared different immunization dose schedules (day 7 versus day 14), wherein BALB/c mice were administered intramuscularly with adjuvanted vaccine (full Human Single Dose), with one group receiving second dose on day 7 and the other group on day 14 after initial immunization.
6. The results indicated 8-fold increase in spike-protein-specific antibody titer, when booster dose was given with 14-day interval as compared with that given on day 7 (Figure 2G).
7. In addition, to demonstrate long-lived immune response, BALB/c mice (n = 8/group, 4 male and 4 female) were vaccinated intramuscularly with three adjuvanted vaccine formulations (1/10th HSD 0.3 and 0.6 µg /dose with Algel or Algel-IMDG) on day 0, 7, and 14 and evaluated antibody titer up to 12 weeks after last dose.
8. These results revealed that the spike-specific antibodies reached peak level on day 28, and the antibody titers were sustained up to day 98, i.e., 12 weeks after last dose (Figure 2H).
9. Similarly, here also found sustained NAb titers up to day 98 (Figure 2I), which indicates the BBV152 vaccine candidates were able to produce long-term immunity.[11]



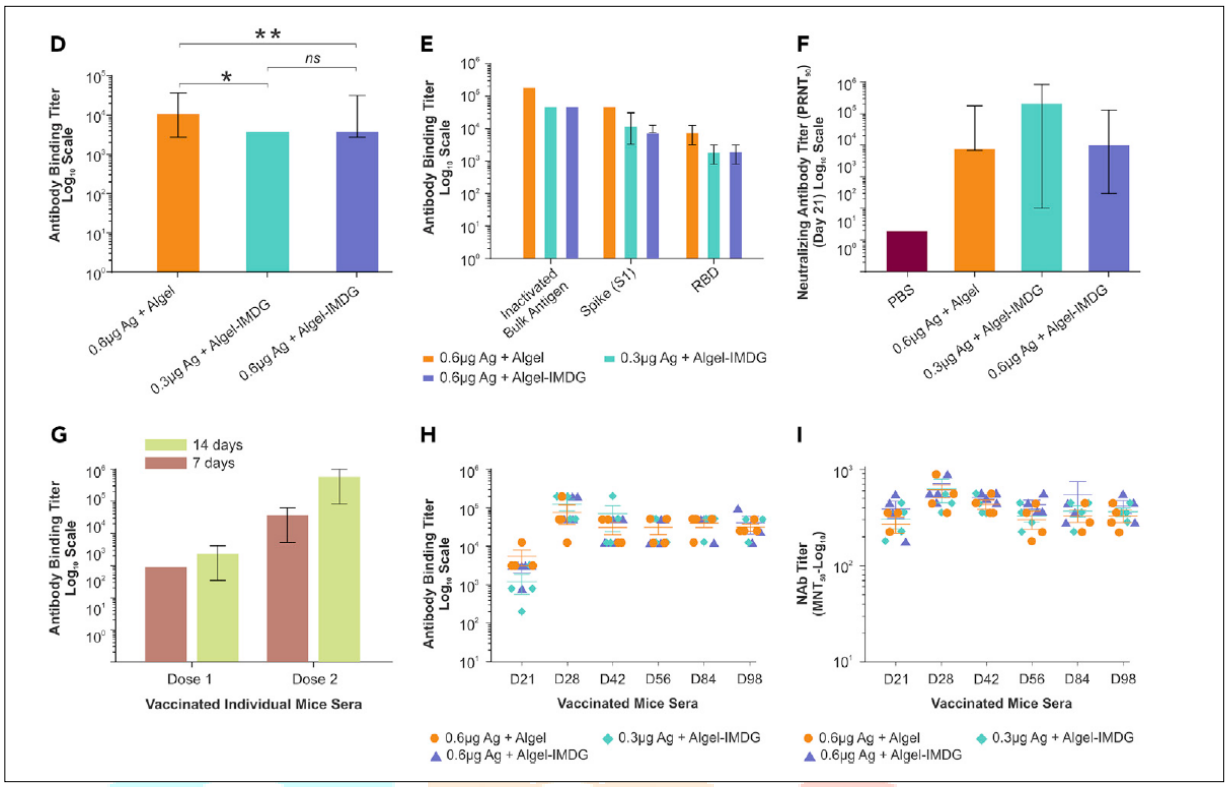


Figure 2: vaccine induces high virus-specific antibody response in mice[11]

i. (A–I) Immune response elicited against antigens at three concentrations of antigen or adjuvanted vaccine formulations in BALB/c mice (n = 5, female) were represented.
ii. Animals were administered via IP route either with 1/20th (Fig A & B) or 1/10th (Fig D, E, & F) human single dose (HSD) or administered via intramuscular route with either full HSD or 1/10th dose (C,G, & H).
iii. S1-specific total IgG antibody binding titers measured using individual sera collected (A) at various time points (day 0, 7, 14, & 21) at 1/20th dose; (D) on day 21 with 1/10th dose; (C) on day 21 either with full HSD or 1/10th dose; (G)on post-dose 1 (on day 7 or 14) and 2 (on day 14 or 28), when BALB/c mice were administered with BBV152B via IM route with different immunization schedule with an interval of 7 or 14 days, and (H) at various time points (day 21, 28, 42, 56, 84, and 98) at 1/10th dose via IM route.
iv. (E) SARS-CoV-2 specific (S1, RBD, N and total inactivated antigen) antibody binding titers elicited against adjuvant vaccines (BBV152A, B & C) on day 21; neutralizing antibody titers performed by PRNT90, using day 21 sera collected from BALB/c mice, when administered via IP route either with 1/20th (B) or 1/10th dose (F) or collected at various time points day 21, 28, 42, 56, 84, and 98 (I), when administered at 1/10th dose via IM route.
v. Antibody binding titers were performed by ELISA and neutralizing antibody titers by PRNT90. Bar graphs representing data represented as mean G SD (G), mean/mean G SEM (A, H, & I) derived from individual mice sera data analysis.
vi. For the long-term immunogenicity study, sera from four animals per group were tested for ELISA and MNT50 analyzed.
vii. Statistical analysis performed by (B) Wilcoxon rank test indicates significant difference between 0.3 µg antigen Algel and 0.3 µg antigen Algel-IMDG at p value < 0.05 and error bars indicate median with 95% CI, whereas in figure D, statistical analysis performed by Mann Whitney test showed significant difference at p value < 0.005 (**) and <0.05 (*), respectively. NS indicates not significant.[1]

❖ **Immunogenicity in New Zealand white rabbits:**

1. To assess the immunogenicity of adjuvanted vaccine formulations at full human single dose (HSD, 3 and 6 µg antigen/dose), rabbits (n = 4) were immunized intramuscularly on days 0, 7, and 14.
2. Similar to mice, immune response in rabbits was also found to be time dependent, and not all animals were seroconverted on day 7 and showed less antibody binding titer ($\geq 10^2$).
3. However, on day 21, they found 100% seroconversion with spike-specific antibody binding titer of greater than or equal to 10^4.
4. All three formulations (BBV152A, B, and C) showed high binding antibody response (Figure 3A), with no statistically significant difference.

5. Similarly, PRNT90 results showed high neutralizing antibody titers in all three adjuvanted vaccine formulations on day 21 (Figure 3B).
6. However, there is no significant difference, and similar results were also observed by MNT50 titers (Figure C).
7. Further, NAb titers determined by MNT50 were slightly higher or comparable with NAb titers of human convalescent sera collected from recovered symptomatic COVID- 19 patients (Figure 3C).[11]

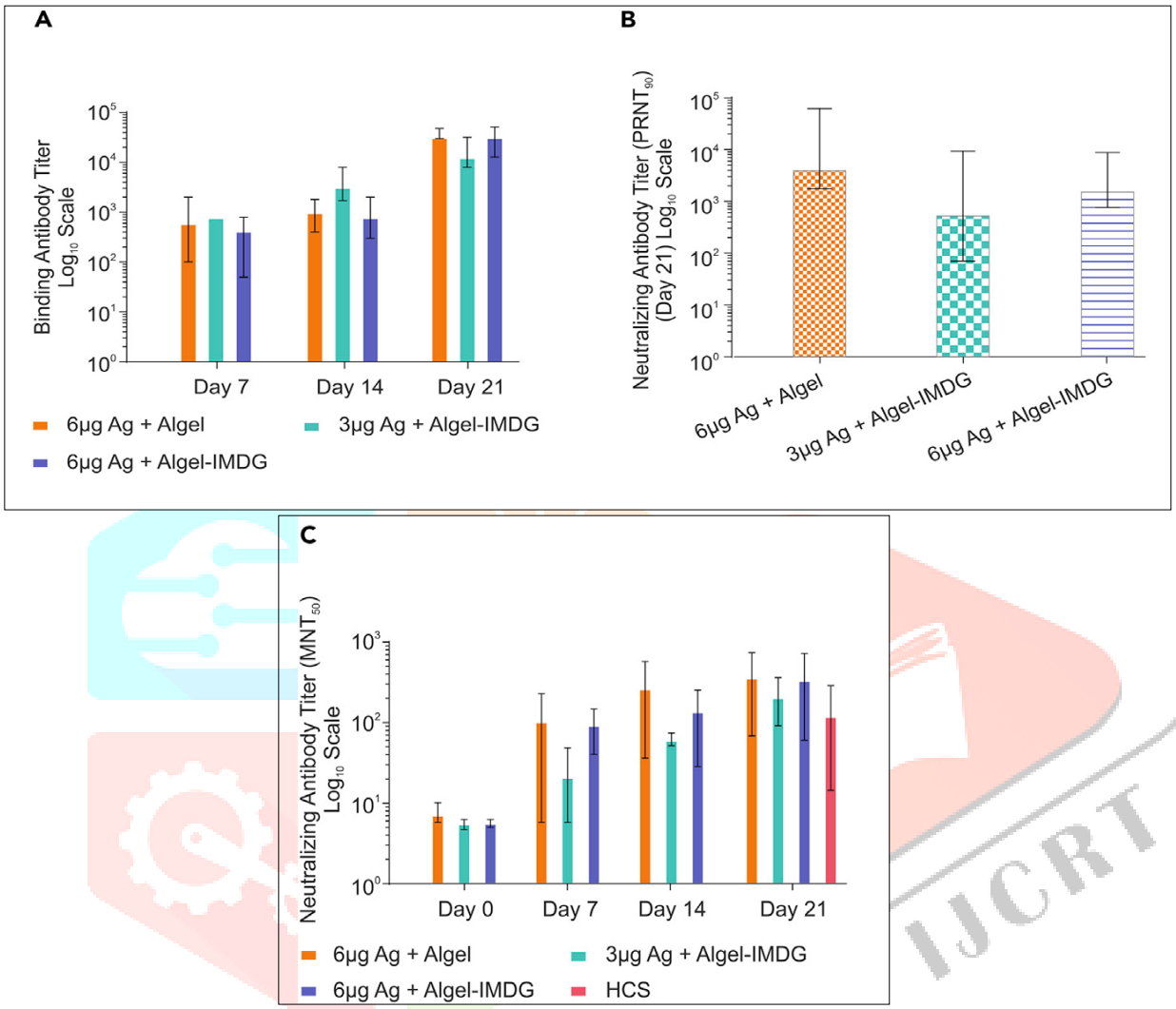


Figure 3. BBV152 induces robust neutralizing antibody response in rabbits

New Zealand white rabbits (n = 4) were administered intramuscularly on days 0, 7, and 14 with full HSD. SARS-CoV-2- specific antibody titers were measured by ELISA. NAb tires were measured by PRNT90 and MNT50.

Data Points represent median/mean of individual animal data.
(A) S1-specific Ab binding titer of sera collected at various time points (day 0, 7, 14, and 21)
(B) PRNT90 neutralizing antibody titers of day 21 sera; error bars indicate median with 95% CI, and statistical analysis performed using Wilcoxon signed rank test found no significant difference among the three adjuvanted vaccine groups.
(C) MNT50 neutralizing antibody titers of sera collected at various time points (day 0, 7, 14, and 21) along neutralizing antibody titer (MNT50) with human convalescent sera (HCS) from recovered COVID-19 patients (n = 15). Samples were collected between 21 and 65 days of virological confirmation. Error bars indicate mean with 95% CI.

❖ **POINTS OF DISCUSSION:**

1. Here is the report of development of a whole-virion inactivated SARS-CoV-2 vaccine candidate (BBV152AC). The strain, used for this vaccine candidate is pathogenic in humans, which is the current predominant circulating strain all over the world. This strain also showed extensive genetic stability and appropriate growth characteristics and thus here NIV-2020-770 strain chosen for further vaccine development.
2. Preclinical toxicity or safety evaluation of either adjuvant-alone (Algel-IMDG) or three formulations did not indicate any undesirable pathological changes and systemic toxicity, except local reactogenicity at the site of injection, which was attributed to the use of adjuvants in the vaccine formulation. Algel (Alum) is the most commonly used adjuvant, known to show depot formation at the site of injection, which helps the antigen for slow release.[12]
3. The microscopic findings at the site of injection in the present study showed the infiltration of macrophages and mononuclear cells indicates the activation of innate immunity. The other adjuvant namely Algel-IMDG, containing TLR7/8 agonist, induced slightly higher reactogenicity. Intra-muscular injection induces a depot effect followed by the passive trafficking of Algel particles via lymphatic flow from the interstitial space to the draining lymph nodes, as revealed by IFN- β/luciferase reporter mice. The lymph node targeting of Algel-IMDG ensures high adjuvant activity in the target organ (lymph nodes) by enabling the induction of a strong, specific, adaptive immune response while minimizing systemic exposure. Further, Algel-IMDG did not show mutagenicity in the five strains of Salmonella typhimurium tested. The local reaction in the studies conducted was consistent with those available in the literature for these adjuvants, which is a physiological reaction to activate immune system rather than any adverse event.[12,13]
4. Results shows that the vaccine formulations induced significantly elevated antigen-binding antibody and NAb responses in the immunized animals, with a distinct Th1 bias observed with Algel-IMDG adjuvanted vaccines. Although the neutralizing antibody titers are not statistically different between the antigen concentration (3 mg and 6 mg) or the nature of adjuvant, all the formulations tested have exhibited excellent immunogenicity. Recently developed, two other inactivated SARS-CoV-2 vaccine candidates (BBIBP-CorV and PiCoVacc) have been shown to induce high levels of NAb titers in mice and rats and showed protection in rhesus macaques against SARS-CoV-2.[14] Reportedly, antibodies raised against PiCoVacc also neutralized 10 representative SARS-CoV-2 strains and indicate possible broader neutralizing ability toward multiple SARS-CoV-2 strains circulating worldwide.[15] The potency results are quite favorably comparable with those reported in the literature for similar COVID-19 vaccines.[14,15]
5. Further, in preclinical studies, it is demonstrated that all the three inactivated whole-virion SARS-CoV-2 vaccine candidates showed 100% seroconversion with high titers of antigen binding and neutralizing antibody responses. Further, the adjuvanted IMDG formulation (BBV152B) showed more than 10 times higher antibody response, compared with antigen-alone, thus Algel-IMDG formulation providing dose-sparing effect. Moreover, these formulations induced immunity that is biased toward Th1-mediated response, as demonstrated by the ratio between IgG2a and IgG1 (greater than 1). In addition, secretion of anti-viral cytokines such as IL-2, IL-4, IL-6, IL-10, IL-17, TNF-alpha, and IFNg observed on days 7 and 14 (7 days after the 1st and 2nd dose) and higher induction of IFN-alpha in Algel- IMDG adjuvanted formulations might have contributed to enhance activation of antigen-presenting cells, such as dendritic cells or macrophages. These results were further supported by our Hamster and non-human primate animal challenge study, wherein Algel-IMDG adjuvanted formulations provided early protection compared with Algel formulation, with the significant reduction in the viral load.[16,17]
6. Although major research is focused on spike as the target protein for SARS CoV-2 vaccine development, there is some attention being paid toward nucleocapsid protein as a target protein, due its 90% amino acid homology and stability with fewer mutations over time. Thus, it is predicted that vaccine strategies with conserved epitope regions could generate cross-protective immunity across beta-corona viruses. [18,19]
7. Further recent research findings based on bioinformatic analysis of epitope mapping revealed that nucleocapsid protein is composed of both T and B cell immunodominant epitopes.[20.21] Earlier, animal studies conducted using DNA vaccine against SARS CoV showed that the nucleocapsid is able to produce enhanced antigen-specific humoral and cellular immune responses.[22.23] It is also to be noted that, though, the earlier immunization studies performed in animal models against nucleocapsid protein reported to cause pneumonia[24,25], yet, there is not much established research evidence so far on the pathogenicity of nucleoprotein in humans.

8. In conclusion of preclinical studies, the ability to induce Th1-skewed immune response and the presence of conserved S and N protein in inactivated vaccine candidate formulated in Algel-IMDG would help to combat other SARS CoV-2 variants. Here also observed that high binding titers with a 100% seroconversion toward S1, RBD, and N protein. Further, high neutralization titers and protective effectiveness of COVAXIN in hamster and non-human primate models might be attributed toward the structural integrity of the inactivated whole-virion vaccine composed of target proteins, both spike and N proteins.

❖ **LIMITATIONS OF STUDY:**

Long-term protective efficacy of these vaccine candidates, cross-neutralization with other SARS CoV 2 variants, and mechanism of action of Algel-IMDG in inducing cell-mediated responses need to be evaluated further.[11]

▪ SAFETY AND IMMUNOGENICITY OF AN INACTIVATED SARS-CoV-2 VACCINE: A DOUBLE BLIND, RANDOMIZED, PHASE 1 TRIAL:

❖ **STUDY DESIGN AND PARTICIPANTS:**

1. A randomised, double-blind, multicenter phase 1 trial was conducted in 11 hospitals across nine Indian states to examine the safety, reactogenicity, tolerability, and immunogenicity of the whole-virion inactivated SARS-CoV-2 vaccine (BBV152).
2. Participants were involved from 18–55 years old and the investigator regarded them healthy at the time of enrolment.
3. At the screening visit, participants were tested with both SARS-CoV-2 nucleic acid and serology tests. They were removed from the experiment if they tested positive for any of the tests.
4. Other key exclusion criteria were an axillary temperature of more than 37·0°C and known allergy to any vaccine component.
5. Participants were assessed for eligibility based on their medical history, laboratory findings, vital signs, and physical examination results, and were enrolled after signing and submitting informed permission forms.
6. The National Regulatory Authority (India) and the respective ethics committees approved the trial, which was carried out in compliance with the International Council for Harmonization Good Clinical Practice guidelines. [26]

❖ **PROCEDURE:**

a. The virus strain containing the Asp614Gly mutation, isolated from a COVID-19 patient and sequenced at the Indian Council of Medical Research National Institute of Virology, was provided to Bharat Biotech.[27] Biosafety level 3 manufacturing facilities and a well established Vero cell manufacturing platform (with proven safety in other licensed live and inactivated vaccines) were used for the rapid development of BBV152.[28-33]

b. BBV152 (manufactured by Bharat Biotech) is a whole-virion β-propiolactone-inactivated SARS-CoV-2 vaccine. The NIV-2020-770 strain contains the Asp614Gly mutation, which is characterised by aspartic acid to glycine shift at the amino acid position 614 of the spike protein.[27]

c. The candidates were formulated with two adjuvants: Algel (alum) and Algel-IMDG, an imidazoquinoline class molecule (TLR7 and TLR8 agonist) adsorbed onto Algel. After their eligibility was established, participants were assigned to the four groups. The control group contained only a sterile phosphate-buffered solution and Algel. Both the vaccine and control were stored at 2–8°C.

d. The vaccine (BBV152) and the control were given as a sterile liquid that was injected intramuscularly (deltoid muscle) at a volume of 0.5 mL/dose on day 0 (day of randomization) and day 14 in a two-dose schedule. This accelerated schedule was chosen given the context of the ongoing pandemic. No onsite dose preparation was required. Each glass vial contained a single dosage of vaccine or control formulation that did not require any further dilution. Before or after vaccination, no prophylactic medication (ibuprofen or acetaminophen) was administered.

e. The follow-up visits were scheduled on days 7, 28, 42, 104, and 194 after vaccination. The study was done in a dose-escalation manner after completing vaccination in the first 50 participants with 3 μg with Algel-IMDG (the lowest antigen concentration) and the control; these participants were monitored for 7 days for safety. The

independent data safety monitoring board reviewed masked safety data and decided whether the trial was allowed to continue with enrolment of the remaining participants into all groups.[26]

❖ RESULTS OBTAINED IN TRIAL:

1. Between July 13 and 30, 2020, 897 individuals were screened and 375 were enrolled. Of the 522 initially screened individuals who were excluded, 133 participants were excluded because they were positive for SARS-CoV-2 by nucleic acid test or serology and 153 were excluded because of abnormal laboratory values (figure 1).
2. The first 50 participants enrolled were monitored for 7 days after vaccination, and on the basis of the independent data safety monitoring board review of masked safety data, the trial was allowed to continue with enrolment of the remaining participants into all groups.
3. Among the enrolled participants, 100 each were randomly assigned to the three vaccine groups, and 75 were randomly assigned to the control group (Algel only). Demographic characteristics of the participants were similar across groups (table 1).
4. After dose 1, solicited local adverse reactions were reported by five participants in the 3 μg with Algel-IMDG group, five in the 6 μg with Algel-IMDG group, one in the 6 μg with Algel group, and three, in the Algel-only control group.
5. Solicited systemic adverse reactions were reported by five participants in the 3 μg with Algel-IMDG group, 14 in the 6 μg with Algel-IMDG group, eight in the 6 μg with Algel group, and seven in the Algel-only group (table 1).
6. Injection site pain (17 of 375 participants), headache (13), exhaustion (11), fever (9) and nausea or vomiting were the most frequently reported side effects (7).
7. All adverse events were mild or moderate in severity and resolved within 24 h of onset.

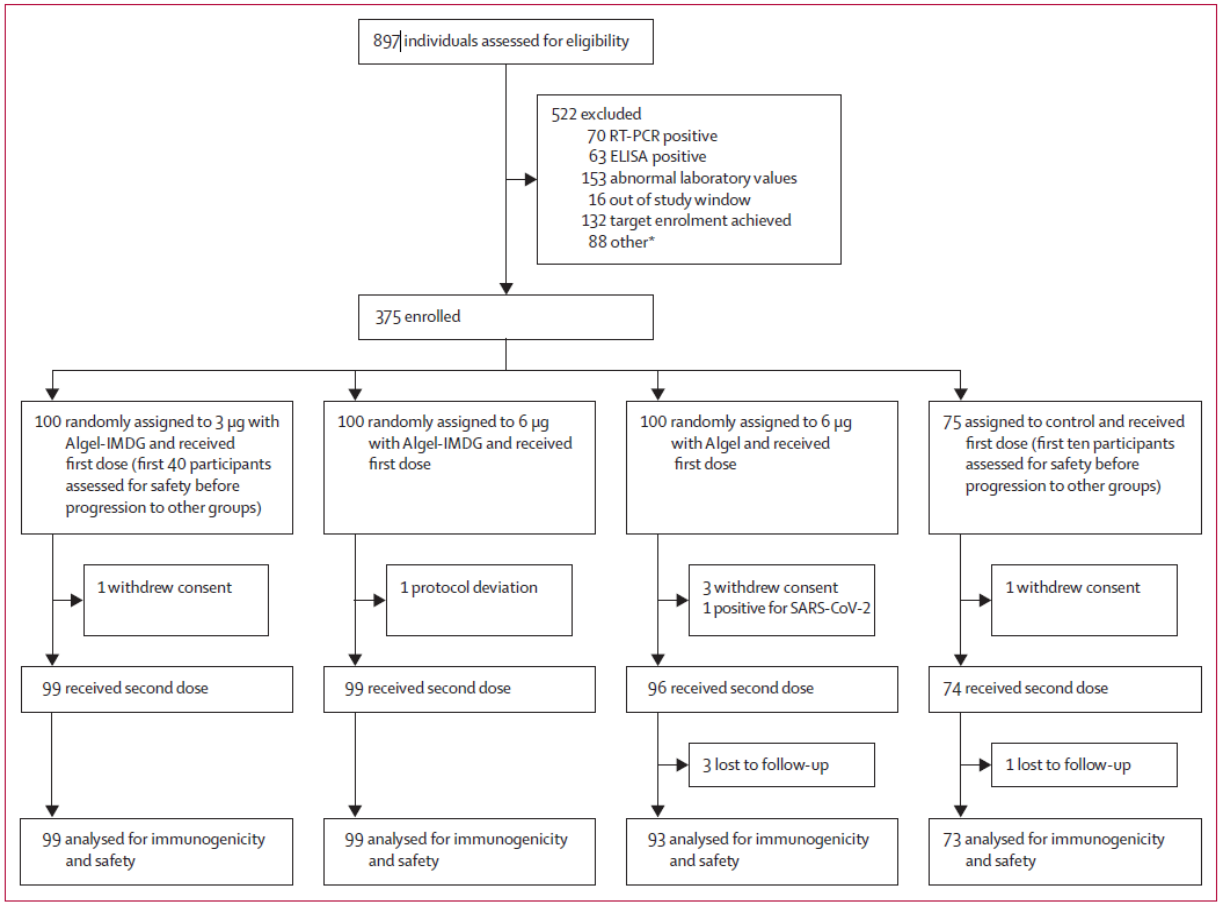


Figure: Trial profile

SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.
*Unable to contact the participant for vaccination or withdrawal of consent.

8. After both doses, solicited local and systemic adverse reactions were reported by 17 participants in the 3 μg with Algel-IMDG group, 21 in the 6 μg with Algel-IMDG group, 14 in the 6 μg with Algel group, and 10 in the Algel-only group.

9. All adverse events were mild (43 [69%] of 62) or moderate (19 [31%]) and were more frequent after the first dose than the second. No significant differences were observed between the vaccinated and control groups.
10. One serious adverse event was reported in the 6 μg with Algel group. The participant was screened on July 25 and vaccinated on July 30. 5 days later, the participant reported fever and headache (initially reported as a solicited adverse event), and on Aug 8 tested positive for SARS-CoV-2 (by a nucleic acid test). The symptoms were initially mild in nature, with the onset of relapsing fever requiring admission to hospital on Aug 15. The participant had stable vital signs (except body temperature) during their hospital stay and did not require supplemental oxygen. The participant was discharged on Aug 22 after a negative nucleic acid test result. The event was not causally associated with the vaccine. No other symptomatic SARS-CoV-2 infections were reported between days 0 and 75. However, follow-up of routine SARS-CoV-2 nucleic acid testing was not done on any scheduled or illness visit.
11. IgG titres (GMTs) to all epitopes (spike protein, receptor-binding domain, and nucleocapsid protein) increased rapidly after the administration of both doses (figure 4A–C). Both 3 μg and 6 μg with Algel-IMDG groups reported similar anti-spike, anti-receptor binding, and anti-nucleoprotein IgG titres (GMTs), adding to the dose-sparing effect of the adjuvant.[26]

Dose 1	3μg+ Algel IMDG (n=100)	6μg+ Algel IMDG (n=100)	6μg+ Algel (n=100)	Algel only (n=75)	Dose 2	3μg+ Algel IMDG (n=100)	6μg+ Algel IMDG (n=100)	6μg+ Algel (n=100)	Algel only (n=75)
Local reactions:									
1. Pain at injection site									
Mild	4	4	1	2		2	1	1	0
Moderate	1	1	0	0		0	0	0	0
2. Swelling									
Mild	0	0	0	1		0	0	0	0
Moderate	0	0	0	0		0	0	0	0
Systemic reaction:									
1. Fever									
Mild	0	1	1	0		2	1	1	0
Moderate	0	1	2	0		0	0	0	0
2. Body ache									
Mild	0	1	0	0		0	0	0	0
Moderate	0	1	1	0		1	0	0	0
3. Fatigue									
Mild	1	0	0	0		1	0	3	0
Moderate	2	3	0	0		1	0	0	0
4. Headache									
Mild	1	2	0	5		0	0	0	0
Moderate	0	3	2	0		0	0	0	0
5. Nausea/ Vomiting									
Mild	1	2	2	2		0	0	0	0
Moderate	0	0	0	0		0	0	0	0

Table 1: Solicited adverse events in the safety set[26]

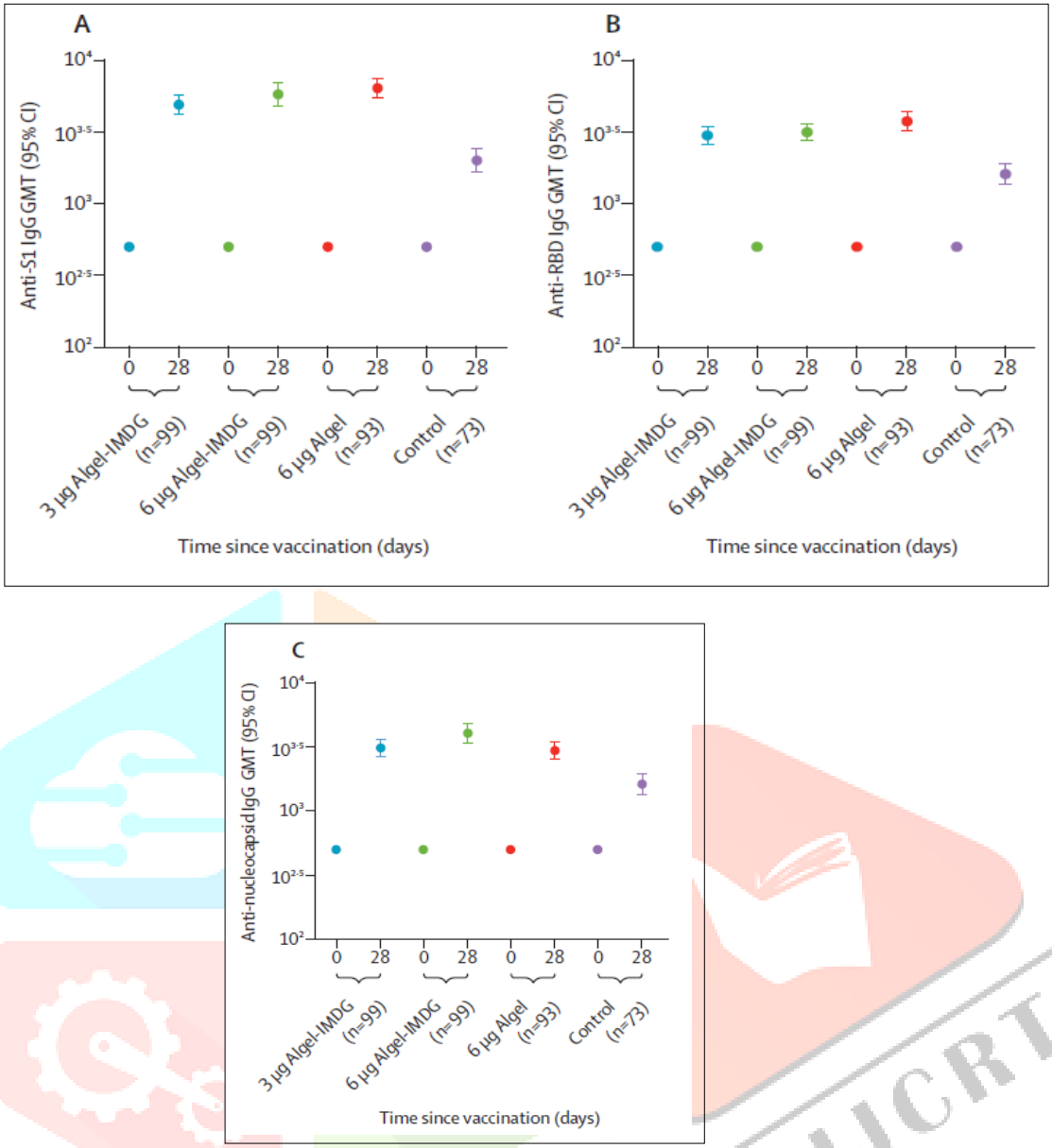


Figure 4: SARS-CoV-2 IgG titres against anti-spike protein (A), receptor-binding domain (B), and nucleocapsid IgG (C)

❖ **POINTS OF DISCUSSION:**

1) The vaccine was well tolerated in all dose groups with no vaccine-related serious adverse events. Both humoral and cell-mediated responses were observed in the recipients of the Algel-IMDG-based vaccines. Pain at the injection site was the most frequent adverse event, followed by headache, tiredness, and fever.
2) The overall incidence of solicited local and systemic adverse events in this study was 14–21% in all vaccine-treated groups, which is noticeably lower than the rates for other SARS-CoV-2 vaccine platform candidates[34-39] and similar to the rates for other inactivated SARS-CoV-2 vaccine candidates.[40,41]
3) One serious adverse event (positive for SARS-CoV-2 by a nucleic acid test) in an individual in the 6 µg with Algel group was not related to vaccination. Because the event occurred in the 5 days after vaccination, the development of a protective immune response was not likely.
4) BBV152 induced binding and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.[40,41] Additionally, cell-mediated responses from other SARS-CoV-2 inactivated vaccine candidates have not been reported thus far.

❖ PHASE II CLINICAL TRIAL STUDY:

BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine (3 g or 6 g) formulated with an alum-adsorbed (Algel) toll-like receptor 7/8 agonist molecule (IMDG).From the Phase I clinical trials reports, the 3 μg and 6 μg with Algel-IMDG formulations were selected for Phase II study. Now below we will see the report of findings of Phase II trail on immunogenicity and safety of BBV152, with first dose administered on day 0 and second on day 28.

❖ STUDY DESIGN AND PARTICIPANTS:

1. The immunogenicity and safety of the whole-virion inactivated SARS-CoV-2 vaccine BBV152 were evaluated in healthy male and female volunteers at nine hospitals throughout nine Indian states in this randomised, multicentre, phase 2 clinical trial.
2. At the time of enrollment, the participants ranged in age from 12 to 65 years old. Participants were tested for SARS-CoV-2 nucleic acid and serology tests at the screening visit, which were performed at a central laboratory using commercially available assays. Individuals who tested positive for any test were removed from the study. The average period between screening and vaccination was three days. Individuals over the age of 65, pregnant or lactating women, and those with comorbidities were excluded from the study.
3. Participants were informed about all research-related activities as well as the option to decline or withdraw from the study. All participants were evaluated for eligibility based on their medical history, vital signs, and physical examination results, and were recruited after signing and dating informed consent forms.
4. The trial was approved by the National Regulatory Authority of India and the ethics committees of each participating institution, and it followed all rules set forth by the International Council for Harmonization for Good Clinical Practice.[42]

❖ RESULTS OBTAINED IN TRIAL:

921 eligible participants were screened between September 5 and 12, 2020, with 380 of them being registered and randomly assigned to either the 3 g with Algel-IMDG group (n=190) or the 6 g with Algel-IMDG group (n=190). There were 48 positive nucleic acid tests and 123 positive serology tests for SARS-CoV-2 among the 541 people who were initially tested but not admitted. Due to competitive recruitment, 190 individuals who were screened and found to be eligible were not enrolled. Other significant exclusions (n=168) were due to RT-PCR results that were inconclusive. At day 56, the 3 g with Algel-IMDG group had a retention rate of 97 percent (184 of 190 participants) while the 6 g with Algel-IMDG group had a retention rate of 93 percent (177 of 190 participants).

❖ POINTS OF DISCUSSION:

1. This report is all about interim findings from the phase 2 clinical trial of BBV152, a whole-virion inactivated SARS-CoV-2 vaccine. The overall participant retention rates were 97% in the 3 μg with Algel-IMDG group and 93% in the 6 μg with Algel-IMDG group. Neutralising antibody titres were similar to a panel of convalescent serum samples. All elicited cytokine responses to BBV152 were biased to Th1 cells. The vaccine was well tolerated in both groups with no serious adverse events. Long-term follow-up of phase 1 trial participants showed that neutralising antibody titres persisted, and T-cell memory responses were more pronounced in the 6 μg with Algel-IMDG group compared with pre-vaccination samples.
2. Pain at the injection site was the most common adverse event in the phase 2 trial, followed by headache, weariness, and fever. There were no severe or life-threatening (grade 4 and 5) adverse events reported. No significant differences in safety were observed between the two groups. However, the study was not powered to compare such differences. After either dose, the combined incidence of local and systemic adverse events in this study is lower than that of other SARS-CoV-2 vaccine platform candidates[43-46], and similar to that of other inactivated SARS-CoV-2 vaccine candidates. [47,48] However, other vaccine studies have enrolled different populations and have employed varying approaches to measure adverse events.
3. BBV152 induced antibody binding (to spike glycoprotein and nucleocapsid protein epitopes) and neutralising antibody responses that were similar to those induced by other SARS-CoV-2 inactivated vaccine candidates.[47,48]

4. A routine schedule, in which the two doses are administered 4 weeks apart, was evaluated in the phase 2 trial of 3 μg with Algel-IMDG and 6 μg with Algel-IMDG. It is found that immune responses (MNT50) were significantly higher with the routine schedule (phase 2) than with the accelerated schedule (phase 1), which is consistent with other reports.[49,50]
5. This study was done at a time when the number of daily diagnosed COVID-19 cases was increasing rapidly. In the Algel-only control group (phase 1 trial), seroconversion was reported in six (8·2%) of 73 participants at day 28, 13 (18·8%) of 69 participants at day 42, and 23 (33·3%) of 69 participants at day 104. These results suggest that both phase 1 and 2 trials are being done during a period of high ongoing SARS-CoV-2 circulation. Since substantial SARS-CoV-2 PCR positivity was observed in the general population during the study period, in the event of natural exposure to SARS-CoV-2, it is possible that post-vaccination antibody titres in vaccinated participants could be slightly inflated. No cases of COVID-19 were reported in either group of the phase 2 trial, whereas one case of symptomatic COVID-19 was reported in the Algel-only control group of the phase 1 trial. However, illness visits were not scheduled, and routine SARS-CoV-2 nucleic acid testing was not done.[42]
6. The findings of this investigation do not allow for efficacy evaluations. Extensive phase 3 clinical trials are required to assess safety outcomes. Due to the small number of convalescent serum samples, they were unable to analyse other immune responses (such as binding antibodies and cell-mediated responses).
7. Furthermore, no additional information on the participant's age or the severity of disease was obtained from symptomatic individuals. Comparisons between phase 1 and 2 trials were not done in a randomised set of participants, and no adjustments on baseline parameters were made. The conclusions should be considered as post-hoc analysis. Despite the fact that direct comparisons between the phase 1 and phase 2 trials are impossible, the reactogenicity assessments reported in this study were significantly better in the phase 2 trial than in the phase 1 trial and other placebo-controlled studies. The study coordinators had verified all source documents to ensure that no data were missing or that errors had occurred. Further corroboration with phase 3 safety results is required.
8. This study enrolled a small number of participants aged 12–18 years and 55–65 years. Follow-on studies are required to establish immunogenicity in children and in those aged 65 years and older. Withdrawals in the 6 μg with Algel-IMDG group were higher than the 3 μg with Algel-IMDG group but were not associated with adverse events. Lastly, this study population lacked ethnic, racial, and gender diversity, further underscoring the importance of evaluating BBV152 in other populations.[42]
9. This study also has several strengths. To ensure generalisability of the results, this study included participants from diverse geographic locations, enrolling 380 participants across nine hospitals across nine states in India. Based on follow-up data from the phase 1 trial, despite a marginal expected decline in neutralising antibody titres at day 104, BBV152 has shown the potential to provide durable humoral and cell-mediated immune responses. Day 56 serum samples from 38 participants in the 6 μg with Algel-IMDG group of the phase 2 trial effectively neutralised a SARS-CoV-2 variant of concern.[52] On the basis of superior cell-mediated responses in the phase 1 trial, the 6 μg with Algel-IMDG formulation was selected for the phase 3 efficacy trial, which involves 25,800 volunteers and is currently underway. BBV152 (COVAXIN) has received emergency use authorisation in India.

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