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Safety, efficacy, and immunogenicity of COVAXIN: A review

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ABSTRACT

COVAXIN was granted restricted emergency approval based on safety and immunogenicity studies alone. The approval was heavily questioned leading to controversy regarding safety concerns and unethical trial allegations resulting in lack of trust and vaccine hesitancy among common people. In this article, we aimed to review the scientific evidence regarding the safety and immunogenicity of COVAXIN. Adverse events reported in phase-I/II COVAXIN trials were mild to moderate with no serious adverse events. The incidence of adverse events due to COVAXIN was comparable to other inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines like BBIBP-CorV and CoronaVac. COVAXIN has also demonstrated a similar immunogenicity profile and enhanced immune response as reported by other inactivated vaccines. COVAXIN has demonstrated an enhanced humoral and cell-mediated immune response among vaccine recipients. COVAXIN vaccinated human serum has also shown comparable antibody neutralization activity against SARS-CoV-2 variant B.1.1.7, B.1.617, and other heterologous strains. Evidence suggests that COVAXIN is a safe, well-tolerated, and immunogenic coronavirus disease 2019 vaccine. Its stated efficacy of 77.8% significantly exceeds the World Health Organization's recommendations. However, the COVAXIN phase-III clinical trial data need to be peer reviewed for better transparency and building public confidence in indigenously developed vaccine and shedding COVAXIN hesitancy among common masses.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has turned into a global health, social, and economic crisis. It was first reported and identified in Wuhan, China, in December 2019 as a cluster of pneumonia cases of unknown etiology (Lu *et al*., 2020). Initially referred to as 2019 novel coronavirus (2019-nCoV), the disease spread rapidly, causing millions of deaths across the world. In January 2020, the World Health Organization (WHO) declared the outbreak as a public health emergency of international concern (Sohrabi *et al*., 2020). Subsequently, after due research and analysis, this nCoV was named SARS-CoV-2 and the associated disease was referred to as COVID-19 (WHO, 2021a). With the global spread and increasing severity of the disease, the WHO characterized COVID-19 as a pandemic on March 11, 2020, and called it COVID-19/coronavirus pandemic (Cucinotta and Vanelli, 2020). As of June 10, 2021, more than 174 million confirmed cases and 3.7 million deaths have been reported worldwide. To this day, the USA is the worst hit country with more than 33 million confirmed cases and 0.59 million deaths, followed by India with 29.1 million confirmed cases and 0.36 million deaths (WHO, 2021b, COVID-19 dashboard).

India started the COVID-19 vaccination program on January 16, 2021 and currently three vaccines have been approved for emergency public use, including COVAXIN, Covishield, and recently approved Sputnik-V. The emergency restricted use

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approval of COVAXIN was questioned due to lack of proper safety and efficacy data leading to lack of confidence and distrust among common people for indigenously developed vaccine. Moreover, COVAXIN trials also came under heavy scrutiny with unethical trial allegations. The approval was highly criticized by media and the public. People were hesitant in receiving COVAXIN and some Indian states delayed the vaccination drive owing to safety and lack of efficient data. In this article, we have made an effort to review the safety, immunogenicity, and efficacy of COVAXIN.

COVID-19 VACCINES

Vaccines represent a key weapon in fighting against COVID-19 for saving lives and ending this pandemic. Vaccines help human bodies to develop immunity against SARS-CoV-2 through T and B lymphocytes. Being an nCoV, vaccine development presented with considerable challenges. However, researchers all over the globe have carried out a commendable job in developing novel, safe, and effective COVID-19 vaccines in a limited timeline with extraordinary international collaborations.

Currently, a broad range of COVID-19 vaccines are in the clinical development process for evaluation of quality, safety, and efficacy. As of June 10, a total of 287 vaccines were currently in the developmental process, of which 102 vaccine candidates are in clinical development and 185 vaccine candidates are in the pre-clinical development phase (WHO, 2021c. Draft landscape of COVID-19 vaccines). Fifteen COVID-19 vaccine candidates have been approved for emergency public use. COVID-19 vaccines are classified into different platforms including mRNA, replicating viral vector, non-replicating viral vector, DNA, inactivated virus, live attenuated virus, and other protein subunit vaccines. The 16 COVID-19 vaccines authorized for the public use includes 7 inactivated vaccines (COVAXIN, BBIBP-CorV, WIBP-CorV, CoronaVac, CoviVac, QazVac, and 1 unnamed by Minhai Biotechnology Co.), 2 RNA-based vaccines (BNT162b2 and mRNA-1,273), 4 viral vector vaccines (AZD1222-Covishield, Ad26.COV2.S, Sputnik-V, and Ad5-nCoV), and 2 protein subunit vaccines (EpiVacCorona and RBD-Dimer) (WHO, 2021c. Draft landscape of COVID-19 vaccines).

COVAXIN

Inactivated vaccines are traditional vaccines in which the pathogens are killed/modified rendering the pathogen unable to replicate but retaining its immunogenicity so that the immune system can detect it and produce an immune response against such pathogens. The advantages of inactivated vaccines include better safety in populations with the compromised immune system, ease and low cost of production (Iversen and Bavari, 2021). Bharat Biotech in collaboration with the Indian Council of Medical Research and National Institute of Virology (NIV) developed India's first indigenous COVID-19 vaccine called COVAXIN (BBV152). COVAXIN is a whole-virion β-propiolactone inactivated SARS-CoV-2 vaccine formulated with an imidazoquinoline molecule (Algel-IMDG), which is a toll-like receptor (TLR 7/8) agonist (Ella *et al.*, 2021a).

In public interest, COVAXIN was granted restricted emergency approval by the Central Drugs Standard Control Organization on January 3, 2021, based on phase-I/II safety and immunogenicity clinical trials only (Mohapatra and Mishra, 2021).

India started one of the world's largest vaccination programs for COVID-19 on January 16, 2021, despite controversy and safety concerns (Bagcchi 2021; Bhuyan 2021). COVAXIN is a two-dose regimen administered 28 days apart and is supplied as ready to use liquid formulation in multi-dose vials stable at 2°C–8°C. Table 1 provides the list of preclinical and clinical research studies of COVAXIN published in various peer-reviewed journals.

The clinical trials were initiated after establishing the safety and protective efficacy in preclinical trials conducted in hamsters and non-human primates. The results of preclinical studies were published in nature communications and iScience–CellPress journals. The vaccine candidates successfully induced significant titers of SARS-CoV-2-specific IgG and neutralizing antibodies (Mohandas *et al.*, 2020; Yadav *et al.*, 2021a). Ganneru *et al.* (2021) also reported Th1 skewed antibody responses with an elevated IgG2a/IgG1 ratio and increased levels of SARS-CoV-2-specific IFN-γ^+ CD4$^+$ T-lymphocyte response induced due to inactivated vaccine formulation (Ganneru *et al.*, 2021). The results of pre-clinical studies confirmed the safety and immunogenic potential of the vaccine candidates and supported human clinical trials.

Phase-I clinical trial

The results of the double-blind, randomized phase-I trial for safety and immunogenicity of inactivated SARS-CoV-2 vaccine, COVAXIN, were published in *The Lancet* on January 21, 2021 (Ella *et al.*, 2021b). A total of 375 participants aged 18–55 years were randomized into four groups, three groups ($n = 100$ each) to be administered one of the three test vaccine formulations: 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, 6 μg with Algel, and an Algel only control arm ($n = 75$). Two intramuscular (deltoid muscle) doses (0.5 ml/dose) of COVAXIN were administered on day 0 and day 14 to each participant. The primary outcome was an assessment of local and systemic reactogenicity events and secondary outcome was seroconversion rates. The study reported a good safety profile with pain at injection site, headache, fatigue, and fever as most common adverse events and no serious adverse events were observed. Overall, the incidence of adverse events reported was 14%–25%. The observed adverse events were mild (69%) and moderate (31%) in nature. Based on the micro-neutralization test (MNT$_{50}$), seroconversion rates of 87.9%, 91.9%, and 82.8% were reported in 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, and 6 μg with Algel groups, respectively. Based on the plaque-reduction neutralization test (PRNT$_{50}$), seroconversion rates of 93.4%, 86.4% and 86.6% were reported in 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, 6 μg with Algel groups respectively. Algel-IMDG based 3 and 6 μg formulations of COVAXIN enhanced the humoral and cellular immune response in study participants and both were selected for phase-II clinical trial (Ella *et al.*, 2021b).

Phase-II clinical trial

The results of the double-blind, randomized phase-II trial evaluating safety and immunogenicity of COVAXIN were published on March 8, 2021, in *The Lancet* along with 3-month follow-up of phase-I trial (Ella *et al.*, 2021a). In this study, a total of 380 participants aged 12–65 years were randomly assigned into two groups of 3 μg with Algel-IMDG ($n = 190$) and 6 μg with Algel-IMDG ($n = 190$). Two intramuscular (deltoid muscle) doses

Table 1. Published clinical and pre-clinical research studies of COVAXIN.

S.no	Authors	Study title	Published on	Journal	Reference/DOI
1	Ella R, Vadrevu KM, Jogdand H, *et al.*	Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomized, phase 1 trial.	January 21, 2021	The Lancet Infectious Diseases	(Ella *et al.*, 2021b) https://doi.org/10.1016/S1473-3099(20)30942-7
2	Ella R, Reddy S, Jogdand H, *et al.*	Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomized, multicenter, phase 2 trial, and 3-month follow-up of a double-blind, randomized phase 1 trial.	March 08, 2021	The Lancet Infectious Diseases	(Ella *et al.*, 2021a) https://doi.org/10.1016/S1473-3099(21)00070-0
3	Sapkal GN, Yadav PD, Ella R, *et al.*	Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B.1.1.7 variant of SARS-CoV-2.	March 27, 2021	Journal of Travel Medicine	(Sapkal *et al.*, 2021b) https://doi.org/10.1093/jtm/taab051
4	Yadav PD, Sapkal GN, Abraham P, *et al.*	Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees.	May 07, 2021	Clinical Infectious Diseases	(Yadav *et al.*, 2021b) https://doi.org/10.1093/cid/ciab411
5	Sapkal G, Yadav PD, Ella R, *et al.*	Neutralization of B.1.1.28 P2 variant with sera of natural SARS-CoV-2 infection and recipients of inactivated COVID-19 vaccine COVAXIN.	May 17, 2021	Journal of Travel Medicine	(Sapkal *et al.*, 2021a) https://doi.org/10.1093/jtm/taab077
6	Ganneru B, Jogdand H, Daram VK, *et al.*	Th1 Skewed immune response of whole virion inactivated SARS-CoV-2 vaccine and its safety evaluation.	March 09, 2021	iScience	(Ganneru *et al.*, 2021) https://doi.org/10.1016/j.isci.2021.102298
7	Yadav PD, Ella R, Kumar S, *et al.*	Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques.	March 02, 2021	Nature Communications	(Yadav *et al.*, 2021a) https://doi.org/10.1038/s41467-021-21639-w
8	Mohandas S, Yadav PD, Shete-Aich A, *et al.*	Immunogenicity and protective efficacy of BBV152, whole virion inactivated SARS-CoV-2 vaccine candidates in the Syrian hamster model.	January 08, 2021	iScience	(Mohandas *et al.*, 2021) https://doi.org/10.1016/j.isci.2021.102054

(0.5 ml/dose) of COVAXIN were administered to each participant on day 0 and day 28. Both vaccine formulations were well tolerated and showed similar safety profiles with no serious adverse events. The primary outcome of the phase-II immunogenicity study was Anti-IgG responses against spike protein (S1) glycoprotein, receptor-binding domain, and nucleocapsid protein of SARS-CoV-2 expressed as geometric mean titers (GMTs). MNT_{50} and $PRNT_{50}$ were used to assess neutralizing antibody titers in serum samples (Ella *et al.*, 2021a).

The researchers reported a seroconversion rate of 92.9% in 3 µg with Algel-IMDG group and 98.3% in 6 µg with Algel-IMDG group based on $PRNT_{50}$. Based on MNT_{50}, a seroconversion rate of 88.0% and 96.6% was reported in 3 µg with Algel-IMDG group and 98.3% in 6 µg with Algel-IMDG group, respectively. GMTs ($PRNT_{50}$ and MNT_{50}) were significantly higher in 6 µg with Algel-IMDG group than 3 µg with Algel-IMDG group. Both the study groups elicited T-cell response biased to Th1 phenotype. Three-month post-second dose follow-up results reported by Ella *et al.* (2021) showed that GMTs (MNT_{50}) were 39.9, 69.5, and 53.3 in 3 µg with Algel-IMDG, 6 µg with Algel-IMDG, and 6 µg with Algel groups, respectively. Based on the interim results of phase-II clinical trial, researchers selected COVAXIN 6 µg with Algel-IMDG formulation for phase-III efficacy trial (Ella *et al.*, 2021a).

Both phase-I and phase-II clinical trials of inactivated SARS-CoV-2 vaccine demonstrate that COVAXIN is safe and well tolerated with no serious adverse effects and significant neutralizing antibody response. The phase-I/II trials reported no association between the dose of vaccine and observed adverse events (Ella *et al.*, 2021a, 2021b). However, evaluation of long-term safety outcomes needs phase-III trials. The phase-II trial reported better reactogenicity and more enhanced humoral and cell-mediated immune responses as compared to phase-I trial. The 3-month post-second dose follow-up showed that neutralizing antibody responses persisted and T-cell memory responses were more pronounced in 6 µg with Algel-IMDG group (Ella *et al.*, 2021a). Phase-I trial also established that COVAXIN induced T-cell memory responses (antigen recall memory) as demonstrated by increased antigen-specific CD4^{+} T cells supporting the results of phase-I trial.

The phase-I/II safety and immunogenicity clinical trials of COVAXIN vaccine were based on NIV-2020-770 homologous and two heterologous strains. However, Sapkal *et. al*. (2021b) demonstrated a comparable neutralization activity of COVAXIN vaccinated human serum against SARS-CoV-2 variant B.1.1.7 (UK-variant) and other heterologous strains (Bharat Biotech, 2021).

Phase-III clinical trial

COVAXIN is currently undergoing randomized, double-blind, and placebo controlled phase-III clinical trial. Bharat Biotech announced the first interim analysis of phase-III results. According to the report posted on Bharat Biotech's official website, the phase-III trial involved 25,800 participants aged 18–98 years (including 2,433 above the age of 60 and 4,500 with comorbidities). The report states that COVAXIN has demonstrated an efficacy of 77.8% against symptomatic COVID-19 disease and 93.4% effective against severe COVID-19 disease (Bharat Biotech, 2021).

Table 2. Description of the results from published phase-I/II safety and immunogenicity studies of inactivated COVID-19 vaccines.

Study	Methodology	Adverse events (safety)	Immunogenicity
Ella R, Vadrevu KM, Jogdand H, *et al.* Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomized, phase 1 trial. *Lancet Infect Dis* 2021; published online Jan 21. https://doi.org/10.1016/S1473-3099(20)30942-7 COVAXIN (BBV152)	Double-blind randomized phase-I clinical trial No. of participants (age group): 375 (18–55 years) Participants were randomly assigned to receive: 3 μg with Algel-IMDG (*n* = 100), 6 μg with Algel-IMDG (*n* = 100), 6 μg with Algel (*n* = 100), or Algel only control arm (*n* = 75). Vaccine administration: day 0 and day 14	Incidence of local and systemic adverse reactions 17% in 3 μg with Algel-IMDG 21% in 6 μg with Algel-IMDG 14% in 6 μg with Algel 13% in Algel only Common adverse drug reactions: pain at injection site, headache, fatigue, fever, nausea, and vomiting	Seroconversion rates (MNT_{50}) 87.9% in 3 μg with Algel-IMDG 91.9% in 6 μg with Algel-IMDG 82.8% in 6 μg with Algel Seroconversion rates ($PRNT_{50}$) 93.4% in 3 μg with Algel-IMDG 86.4% in 6 μg with Algel-IMDG 86.6% in 6 μg with Algel
Ella R, Reddy S, Jogdand H, *et al.* Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomized, multicenter, phase 2 trial, and 3-month follow-up of a double-blind, randomized phase 1 trial. *Lancet Infect Dis* 2021; published online March 21. https://doi.org/10.1016/S1473-3099(21)00070-0 COVAXIN (BBV152)	Double-blind randomized phase-II clinical trial No. of participants (age group): 380 (12–65 years) Participants were randomly assigned to receive: 3 μg with Algel-IMDG (*n* = 190) 6 μg with Algel-IMDG (*n* = 190) Vaccine administration: day 0 and day 14	Incidence of local and systemic adverse reactions 20% in 3 μg with Algel-IMDG 21.1% in 6 μg with Algel-IMDG No serious adverse reactions were reported.	Seroconversion rates ($PRNT_{50}$) 92.9% in 3 μg with Algel-IMDG 98.3% in 6 μg with Algel-IMDG Seroconversion rates (MNT_{50}) 88.0% in 3 μg with Algel-IMDG 96.6% in 6 μg with Algel-IMDG
Xia S, Zhang Y, Wang Y, *et al.* Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomized, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis* 2021; 21(1):39-51. https://doi.org/10.1016/s1473-3099(20)30831-8 (BBIBP-CorV)	Double-blind randomized phase-I clinical trial No. of participants (age group): 192 (18–80 years) Participants were separated into two age groups: 18–59 years (*n* = 96) ≥60 years (*n* = 96) Participants in each age group were randomized to: 2 μg group (*n* = 24) or placebo group (*n* = 8), 4 μg group (*n* = 24) or placebo group (*n* = 8), 8 μg group (*n* = 24), or placebo group (*n* = 8) Vaccine administration: day 0 and day 28	Incidence of adverse reactions in 18–59 age group 46% in 2 μg group versus 38% in placebo group 33% in 4 μg group versus 25% in placebo group 46% in 8 μg group versus 13% in placebo group Incidence of adverse reactions in ≥60 years age group 4% in 2 μg group versus 13% in placebo group 25% in 4 μg group versus 0% in placebo group 21% in 8 μg group versus 13% in placebo group Common adverse events were fever and pain at injection site No serious adverse events were reported	Seroconversion rates (Both 18–59 years and ≥60 years age groups) 100% 2 μg group 100% 4 μg group 100% 8 μg group Neutralizing antibodies in placebo groups were negative
	Double-blind randomized phase-II clinical trial No. of participants (age group): 448 (18–59 years) Participants were randomly assigned to: 8 μg group on day 0 (*n* = 84) versus placebo (*n* = 28), 4 μg group on days 0 and 14 (*n* = 84) versus placebo (*n* = 28), 4 μg group on days 0 and 21 (*n* = 84) versus placebo (*n* = 28), and 4 μg group on days 0 and 28 (*n* = 84) versus placebo (*n* = 28)	Incidence of adverse reactions 39% in 8 μg (day 0) group versus 11% in placebo group 21% in 4 μg (days 0 and 14) group versus 18% in placebo group 18% in 4 μg (days 0 and 21) group versus 18% in placebo group 12% in 4 μg (days 0 and 28) group versus 21% in placebo group Common adverse reactions were pain at injection site and fever No serious adverse events were reported	Neutralizing antibody GMTs 14.7% in 8 μg (day 0) group 169.5% in 4 μg (days 0 and 14) group 282.7% in 4 μg (days 0 and 21) group 218% in 4 μg (days 0 and 28) group

Continued

Study	Methodology	Adverse events (safety)	Immunogenicity
Zhang Y, Zeng G, Pan H, *et al.* Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomized, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; 21(2):181-192. https://doi.org/10.1016/S1473-3099(20)30843-4 (CoronaVac)	Double-blind randomized phase-I clinical trial No. of participants (age group): 144 (18–59 years) Participants were assigned to: Days 0 and 14 cohort ($n = 72$) Days 0 and 28 cohort ($n = 72$) Participants in each cohort were randomized to: 3 µg group ($n = 24$) or placebo ($n = 12$) and 6 µg group ($n = 24$) or placebo ($n = 12$)	Incidence of adverse reactions 29% in 3 µg (days 0 and 14) group 38% in 6 µg (days 0 and 14) group 8% in placebo group 13% in 3 µg (days 0 and 28) group 17% in 6 µg (days 0 and 28) group 13% in placebo group	Seroconversion rates in phase-I trial 46% in 3 µg (days 0 and 14) group 50% in 6 µg (days 0 and 14) group 0% in placebo group 83% in 3 µg (days 0 and 28) group 79% in 6 µg (days 0 and 28) group 4% in placebo group
	Double-blind randomized phase-II clinical trial No. of participants (age group): 600 (18–59 years) Participants were assigned to: Days 0 and 14 cohort ($n = 300$) Days 0 and 28 cohort ($n = 300$) Participants in each cohort were randomized to: 3 µg group ($n = 120$) 6 µg group ($n = 120$) Placebo group ($n = 60$)	Incidence of adverse reactions 33% in 3 µg (days 0 and 14) group 35% in 6 µg (days 0 and 14) group 22% in placebo group 19% in 3 µg (days 0 and 28) group 19% in 6 µg (days 0 and 28) group 18% in placebo group Common adverse event was pain at injection site Most of the adverse events were mild with no serious events	Seroconversion rates in phase-II trial 92% in 3 µg (days 0 and 14) group 98% in 6 µg (days 0 and 14) group 3.0% in placebo group 97% in 3 µg (days 0 and 28) group 100% in 6 µg (days 0 and 28) group 0.0% in placebo group
Wu Z, Hu Y, Xu M, *et al.* Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomized, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis* 2021; published online Feb 3. https://doi.org/10.1016/S1473-3099(20)30987-7 (CoronaVac)	Double-blind randomized phase-I clinical trial No. of participants (age group): 72 (≥60 years) Participants were allocated to two blocks: Block-1: 3 µg group ($n = 24$) or placebo ($n = 12$) Block-2: 6 µg group ($n = 24$) or placebo ($n = 12$) Vaccine administration: day-0 and day-28 Double-blind randomized phase-II clinical trial No. of participants (age group): 350 (≥60 years) Participants were randomized into four groups: 1.5 µg group ($n = 100$), 3 µg group ($n = 100$), 6 µg group ($n = 100$), Placebo group ($n = 50$) Vaccine administration: day 0 and day 28	Incidence of adverse reactions in both phase-I/II trials 20% in 1.5 µg group 20% in 3 µg group 22% in 6 µg group 21% in placebo group All the adverse events were mild or moderate in nature. Most common adverse event was pain at injection site.	Seroconversion rates in phase-I trial 100·0% in 3 µg group 95·7% in 6 µg group 0% in placebo group Seroconversion rates in phase-II trial 90·7% in 1·5µg group 98.0% in 3 µg group 99·0% in 6 µg group 0% in placebo group

Continued

Study	Methodology	Adverse events (safety)	Immunogenicity
Xia S, Duan K, Zhang Y, *et al*. Effect of an Inactivated Vaccine against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. *JAMA* 2020; 324(10):951-960. https://doi.org/10.1001/jama.2020.15543 (No Name announced)	Double-blind randomized phase-I clinical trial	Incidence of adverse reactions in phase-I trial	Seroconversion rates in phase-I trial
	No. of participants (age group): 96 (18–59 years)	12.5% in 2.5 μg group	100% in 2.5 μg group
	Participants were assigned into three groups:	20.8% in 5 μg group	100% in 5 μg group
	2.5 μg group (*n* = 24),	16.7% in 10 μg group	100% in 10 μg group
	5 μg group (*n* = 24),	25.0% in placebo group	0% in placebo group
	10 μg group (*n* = 24),		
	Placebo group (*n* = 24)		
	Vaccine administration: days 0, 28, and 56		
	Double-blind randomized phase-II clinical trial	Incidence of adverse reactions in phase-II trial	Seroconversion rates in phase-II trial
	No. of participants (age group): 224 (18–59 years)	6% in 5 μg (days 0 and 14) group versus 14.3% in placebo	85.7% in 5 μg (days 0 and 14) group
	Participants were randomized to either:	19% in 5 μg (days 0 and 21) group versus 17.9% in placebo	100% in 5 μg (days 0 and 21) group
	5 μg on days 0 and 14 (*n* = 84) versus placebo (*n* = 28) or	Common adverse events were injection site pain and fever	0% in placebo group
	5 μg on days 0 and 21 (*n* = 84) versus placebo (*n* = 28)	No serious adverse events were reported	

DISCUSSION

COVAXIN, a whole virion inactivated SARS-CoV-2 vaccine was granted restricted emergency approval based on safety and immunogenicity studies only without phase-III clinical trial and evidence on efficacy of the vaccine. The incomplete evidence-based regulatory approval was criticized, leading to controversy regarding safety concerns for the indigenously developed vaccine. The WHO has recommended that a minimum criterion for any acceptable COVID-19 vaccine should be a clear demonstration of efficacy (on a population basis) ideally with ~50% point estimate and the efficacy can be assessed against the "disease, severe disease, shedding or transmission" endpoints (WHO, 2021d. Target product profiles for COVID-19 vaccines).

The safety profile and incidence of adverse events due to COVAXIN were similar to other inactivated SARS-CoV-2 vaccines like BBIBP-CorV and CoronaVac (Xia *et al*., 2021; Zhang *et al*., 2021). However, the local and systemic adverse events due to COVAXIN are lower when compared to other vaccine platforms like mRNA and viral-vector-based vaccines. COVAXIN has also demonstrated a similar immunogenicity profile and enhanced immune response as reported by other inactivated vaccines (Wu *et al*., 2021; Xia *et al*., 2020; Xia *et al*., 2021; Zhang *et al*., 2021). The detailed description of safety and immunogenicity of inactivated COVID-19 vaccine candidates reported in published studies from phase-I/II clinical trials is presented in Table 2.

One of the significant results reported from the phase-I/II trials was demonstration of enhanced humoral as well as cell-mediated immune response among COVAXIN recipients (Ella *et al*., 2021a; Ella *et al*., 2021b). Although CD4+ and CD8+ T-cell responses were reported in a subset of participants only in phase-I trial but phase-II trial reported much enhanced cell-mediated immune response (Ella *et al*., 2021b). COVAXIN enhanced the T-cell memory response as indicated by increased CD4+, CD45RO+, and CD27+ T-cell population confirming the antigen recall memory response (Ella *et al*., 2021b). Again the 3-month follow-up results of phase-I trial reported that the COVAXIN-induced neutralizing antibody response persisted in all study participants after the 3-month follow-up period (Ella *et al*., 2021a). Other inactivated COVID-19 vaccines have not reported any cell-mediated immunity development in their phase-I/II clinical trials. Moreover COVAXIN vaccinated human serum has shown comparable antibody neutralization activity against SARS-CoV-2 variant B.1.1.7, B.1.617, and other heterologous strain (Sapkal *et al*., 2021a; Sapkal *et al*., 2021b; Yadav *et al*., 2021b).

While traditional inactivated vaccines are formulated with alum as an adjuvant, COVAXIN is formulated with a toll-like- receptor (TLR 7/8) agonist adjuvant molecule (Ella *et al*., 2021b). The alum-based inactivated vaccines typically develop Th2 biased responses leading to safety concerns. Th2 cell-mediated response is implicated in the development of eosinophilic lung immunopathology (Bessa and Bachmann, 2010). However, the TLR 7/8 agonist adjuvant in COVAXIN primarily produces Th1 biased response with minimal Th2 response providing protection against vaccine-induced lung pathology (Ella *et al*., 2021a; Ella *et al*., 2021b). Moreover, TLR 7/8 agonist also induces IgA production, thereby contributing to the immunogenicity of the vaccine (Meiler *et al*., 2008; Bessa and Bachmann, 2010).

Bharat Biotech's report states that COVAXIN has demonstrated high clinical efficacy of 78% in preventing COVID-19 among individuals without prior infection after two dose regimen (Bharat Biotech, 2021). The Sinopharm inactivated vaccine (BBIBP-CorV) has reportedly shown an efficacy of 86% in efficacy trials conducted in UAE and Bahrain, but the efficacy data have not been published yet (Cyranoski, 2020). The stated efficacy of CoronaVac developed by Sinovac has reported varying efficacy results. Researchers in Brazil reported that CoronaVac showed an efficacy of 78% which was later revised to 50.4% efficacy in preventing severe and mild COVID-19 in trials conducted in Brazil, which is significantly lower than the reported efficacy of other inactivated vaccines. However, the CoronaVac Turkish trials have reported an efficacy of 91.25% which was again revised to 83.5% in final analysis (Mallapaty, 2020). The efficacy data on

all inactivated vaccines including COVAXIN has not been made public yet and the data needs to be peer-reviewed.

Based on the preliminary results of phase-III trial results, COVAXIN has a lower efficacy (78%) than other types of COVID-19 vaccines mRNA-1,273 (Baden *et al*., 2021) which is mRNA-based COVID-19 vaccine developed by Moderna showing 95% efficacy and Comirnaty (BNT162b2) (Polack *et al*., 2020) which is also an mRNA-based vaccine developed by Pfizer and BioNTech showing 95% vaccine efficacy in two dose regimen in protection against COVID-19 in phase-III safety efficacy trials. However, the stated efficacy of COVAXIN is higher than Covishield (AZD1222) an adenovirus vaccine developed by AstraZeneca and Oxford vaccine group reporting an overall vaccine efficacy of 70.4% after two doses and 64.1% after a single dose (Voysey *et al*., 2021). The safety and efficacy data from Moderna (mRNA-1,273), Comirnaty (BNT162b2), and Covishield (AZD1222) have been published in peer-reviewed journals (Baden *et al*., 2021; Polack *et al*., 2020; Voysey *et al*., 2021).

CONCLUSION

Evidence suggests that COVAXIN is a safe, well-tolerated and immunogenic vaccine. COVAXIN has also demonstrated comparable effectiveness against mutant SARS-CoV-2 strains as well. The safety and immunogenicity of COVAXIN has been demonstrated in adolescents, adults, and elderly people. The preliminary efficacy significantly exceeds the WHO and FDA recommended minimum acceptable criteria for COVID-19 vaccine approval. However, the COVAXIN phase-III clinical trial data needs to be made public and peer reviewed for better transparency and building confidence in indigenously developed vaccine and shedding COVAXIN hesitancy among common masses.

CONFLICTS OF INTERESTS

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Mukhtar Ahmad Dar and Sameer Dhingra designed the review. Mukhtar Ahmad Dar and Priyadarshani Chauhan contributed to the literature review, drafting the manuscript, and editing throughout the process. Pawan Kumar contributed to literature search and manuscript writing. Sameer Dhingra contributed as supervisor, manuscript editing, and revising process. Richa Chauhan, Krishna Murti, Jaykaran Charan, and Velayutham Ravichandiran contributed in manuscript editing, revisions, and proofreading. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines. The final draft of the manuscript was read and approved by all the authors for submission.

REFERENCES

Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med, 2021; 384(5):403–16.

Bagcchi S. The world's largest COVID-19 vaccination campaign. Lancet Infect Dis, 2021; 21(3):323.

Bessa J, Bachmann MF. T Cell-dependent and -independent IgA responses: role of TLR signalling. Immunol Invest, 2010; 39(4-5):407–28.

Bharat Biotech. Bharat Biotech announces phase 3 results of COVAXIN. Bharat Biotech, 2021. Available via https://www.bharatbiotech. com/images/press/covaxin-phase3-efficacy-results.pdf (Accessed 10 June 2021)

Bhuyan A. India begins COVID-19 vaccination amid trial allegations. Lancet, 2021; 397(10271):264.

Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed, 2020; 91(1):157–60.

Cyranoski D. Arab nations first to approve chinese COVID vaccine. Nature, 2020; 588:2.

Ella R, Reddy S, Jogdand H, Sarangi V, Ganneru B, Prasad S, Das D, Raju D, Praturi U, Sapkal G, Yadav P, Reddy P, Verma S, Singh C, Redkar SV, Gillurkar CS, Kushwaha JS, Mohapatra S, Bhate A, Rai S, Panda S, Abraham P, Gupta N, Ella K, Bhargava B, Vadrevu KM. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis, 2021a; 21(7):950–61.

Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, Ganneru B, Sapkal G, Yadav P, Abraham P, Panda S, Gupta N, Reddy P, Verma S, Kumar Rai S, Singh C, Redkar SV, Gillurkar CS, Kushwaha JS, Mohapatra S, Rao V, Guleria R, Ella K, Bhargava B. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis, 2021b; 21(5):637–46.

Ganneru B, Jogdand H, Daram VK, Das D, Molugu NR, Prasad SD, Kannappa SV, Ella KM, Ravikrishnan R, Awasthi A, Jose J. Th1 skewed immune response of whole virion inactivated SARS CoV 2 vaccine and its safety evaluation. iScience, 2021; 24(4):102298.

Iversen PL, Bavari S. Inactivated COVID-19 vaccines to make a global impact. Lancet Infect Dis, 2021; 21(6):746–8.

Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol, 2020; 92(4):401–2.

Mallapaty S. China COVID vaccine reports mixed results — what does that mean for the pandemic? Nature, 2020; 1–6.

Meiler F, Klunker S, Zimmermann M, Akdis CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. Allergy Eur J Allergy Clin Immunol, 2008; 63(11):1455–63.

Mohandas S, Yadav PD, Shete-Aich A, Abraham P, Vadrevu KM, Sapkal G, Mote C, Nyayanit D, Gupta N, Srinivas VK, Kadam M, Kumar A, Majumdar T, Jain R, Deshpande G, Patil S, Sarkale P, Patil D, Ella R, Prasad SD, Sharma S, Ella KM, Panda S, Bhargava B. Immunogenicity and protective efficacy of BBV152, whole virion inactivated SARS-CoV-2 vaccine candidates in the Syrian hamster model. iScience, 2020; 24(2): 1–11.

Mohapatra PR, Mishra B. Regulatory approval of COVID-19 vaccine for restricted use in clinical trial mode. Lancet Infect Dis, 2021; 21(5):599–600.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck Jr RW, Hammitt LL, Türeci O, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC, C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med, 2020; 383(27):2603–15.

Sapkal G, Yadav PD, Ella R, Abraham P, Patil DY, Gupta N, Panda S, Mohan K, Bhargava B. Neutralization of VUI B.1.1.28 P2 variant with sera of COVID-19 recovered cases and recipients of Covaxin an inactivated COVID-19 vaccine. J Travel Med, 2021a; 1–3.

Sapkal GN, Yadav PD, Ella R, Deshpande GR, Sahay RR, Gupta N, Vadrevu KM, Abraham P, Panda S, Bhargava B. Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B.1.1.7 variant of SARS-CoV-2. J Travel Med. 2021b; 28(4):1–3.

Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, Agha R. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int J Surg, 2020; 76(2):71–6.

Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, Briner C, Cicconi P, Collins AM, Colin-Jones R, Cutland CL, Darton TC, Dheda K, Duncan CJA, Emary KRW, Ewer KJ, Fairlie L, Faust SN, Feng S, Ferreira DM, Finn A, Goodman AL, Green CM, Green CA, Heath PT, Hill C, Hill H, Hirsch I, Hodgson SHC, Izu A, Jackson S, Jenkin D, Joe CCD, Kerridge S, Koen A, Kwatra G, Lazarus R, Lawrie AM, Lelliott A, Libri V, Lillie PJ, Mallory R, Mendes AVA, Milan EP, Minassian AM, McGregor A, Morrison H, Mujadidi YF, Nana A, O'Reilly PH, Padayachee SD, Pittella A, Plested E, Pollock KM, Ramasamy MN, Rhead S, Schwarzbold AV, Singh N, Smith A, Song R, Snape MD, Sprinz E, Sutherland RK, Tarrant R, Thomson EC, Török ME, Toshner M, Turner DPJ, Vekemans J, Villafana TL, Watson MEE, Williams CJ, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ,Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet, 2021; 397(10269):99–111.

World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization, Geneva, Switzerland, 2021a. Available via https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (Accessed 08 June 2021)

World Health Organization. WHO coronavirus disease (COVID-19) dashboard. World Health Organization, Geneva, Switzerland, 2021b. Available via https://covid19.who.int/ (Accessed 10 June 2021)

World Health Organization. Draft landscape and tracker of COVID-19 candidate vaccines. World Health Organization, Geneva, Switzerland, 2021c. Available via https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (Accessed 10 June 2021)

World Health Organization (WHO). 2021d. WHO target product profiles for COVID-19 vaccines. World Health Organization, Geneva, Switzerland, 2021d. Available via https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines (Accessed 10 June 2021)

Wu Z, Hu Y, Xu M, Chen Z, Yang W, Jiang Z, Li M, Jin H, Cui G, Chen P, Wang L, Zhao G, Ding Y, Zhao Y, Yin W. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis, 2021; 21(6):803–12.

Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, Li X, Peng C, Zhang Y, Zhang W, Yang Y, Chen W, Gao S, You W, Wang X, Wang Z, Shi Z, Wang Y, Yang X, Zhang L, Huang L, Wang Q, Lu J, Yang Y, Guo J, Zhou W, Wan X, Wu C, Wang W, Huang S, Du J, Meng Z, Pan A, Yuan Z, Shen S, Guo W, Yang X. Effect of an inactivated vaccine against SARS-CoV-2 on safety and immunogenicity outcomes: interim analysis of 2 randomized clinical trials. JAMA - J Am Med Assoc, 2020; 324(10):951–60.

Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, Tan W, Wu G, Xu M, Lou Z, Weijin Huang W, Xu W, Huang B, Wang H, Wang W, Zhang W, Li N, Xie Z, Ding L, You W, Zhao Y, Yang X, Liu Y, Wang Q, Huang L, Yang Y, Xu G, Luo L, Wang W, Liu P, Guo W, Yang X. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis, 2021; 21(1):39–51.

Yadav PD, Ella R, Kumar S, Patil DR, Mohandas S, Shete AM, Vadrevu KM, Bhati G, Sapkal G, Kaushal H, Patil S. Immunogenicity and protective efficacy of inactivated SARS-CoV-2 vaccine candidate, BBV152 in rhesus macaques. Nat Commun, 2021a; 12(1):1–1.

Yadav PD, Sapkal GN, Abraham P, Ella R, Deshpande G, Patil DY, Nyayanit DA, Gupta N, Sahay RR, Shete AM, Panda S, Bhargava B, Mohan VK. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. Clin Infect Dis, 2021b.

Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, Han W, Chen Z, Tang R, Yin W, Chen X, Hu Y, Liu X, Jiang C, Li J, Yang M, Song Y, Wang X, Gao Q, Zhu F. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis, 2021; 21(2):181–92.