Original Article

DOI: 10.7860/JCDR/2022/57170.16856

Safety and Immunogenicity Outcomes of an Inactivated Viral Vaccine against SARS-CoV-2 (Covaxin®)

Microbiology Section

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ABSTRACT

Introduction: Bharat Biotech International Ltd in partnership with National Institute of Virology (NIV), has developed an indigenous whole virion inactivated Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) viral vaccine BBV-152 (Covaxin®), formulated with Toll Like Receptors 7/8 agonist Imidazoquinoline (IMDG) molecule adsorbed to alum (Algel). Variety of factors other than environmental ones can affect vaccines efficiency outside the strict setting of clinical trials, like how the vaccine is stored or transported, and even how patients are vaccinated. In addition, the intrinsic capacity of the recipient to respond to a vaccine which is determined by sex, genetic factors, age, psychological stress, nutrition and other diseases are also likely to have an impact.

Aim: To determine the safety, reactogenicity and immunogenicity of an inactivated whole virus vaccine (Covaxin®) amongst hospital-based population groups.

Materials and Methods: The prospective analytical study was conducted in the Department of Microbiology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India, from January 2021 to March 2021. The study primarily included Healthcare Workers (HCWs) employed at SMS Medical college and attached hospitals. In-vitro quantitative Immunoglobin G (IgG) antibodies against SARS-CoV-2 spike Receptor Binding Domain (RBD) were measured using Chemiluminescence Immunoassay (CLIA) based Advia centaur SARS-CoV-2 IgG, manufactured by Siemens Pvt. Ltd., Munich, Germany, as per manufacture's instructions.

Results: Out of total 223 individuals, 61.88 % (138/223) showed neutralising antibody titre of >1 index value by CLIA, rest 38.12% (85/223) were non reactive i.e., titre <1 index value, after four weeks of receiving first dose of Covaxin®. After 2 to 4 weeks of receiving second dose 84.30% (188/223) showed neutralising antibody titre of >1 index value by CLIA, rest 15.70% (35/223) were non reactive i.e., titre <1 index value. After receiving first dose, 100% (223/223) of the participants developed localised pain and bodyache 33.63% (75/223). None of the participants showed any anaphylactic reaction or any emergency condition just after vaccination.

Conclusion: Covaxin® is a well-tolerated vaccine, and induces good humoral response against SARS-CoV-2 with a significant rise in the neutralising antibody titres.

Keywords: Coronavirus disease-2019, Neutralising antibody, Titres

INTRODUCTION

It has been troublesome months since Coronavirus Disease-2019 (COVID-19) caused by SARS-CoV-2 virus was first observed in Wuhan, China in late December 2019 [1]. The outbreak of SARS-CoV-2 infection has spread over more than 216 countries across with nearly 79 million confirmed cases and approximately 1.7 million deaths [2]. In India, around 10 million cases and 150000 deaths have been reported in the year 2020 [2]. In comparison to the present outbreak, earlier outbreaks caused by other members of *Coronaviridae*, like SARS-CoV infected only around 8000 people with death rate of 10% and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infected around about 2000 people with 35% fatality rate [3].

Despite global spread of SARS-CoV-2 virus, a large proportion of the population in many countries is thought to have so far escaped infection and remain non immune to SARS-CoV-2 [4]. Elderly people, frontline workers and people with various co-morbidities are at very high-risk for COVID-19 disease and its complications [5]. The disease is new to mankind and body's immune system is naive against the virus, that's why no vaccine strategy has yet been able to surface, that could guarantee protection [6]. None of us know when the nightmare is going to end up. It has been more than two years without any definitive treatment plans and any efficient COVID-19 vaccine would bring us a step closer to normal life [1]. Conventionally, vaccine development takes on an average of 10-11 years from the scientific bench to being administered to the public [7,8]. However, today many vaccine candidates are there in different stages of development for COVID-19 pandemic. This is perhaps for the first time in history that World Health Organisation (WHO) reports over 163 vaccines in its preclinical evaluation stage and 52 in clinical evaluation stage for COVID-19 (as of December, 2020) [9].

It has been shown that antibodies produced in COVID-19 positive individuals with mild or no symptoms are not long-lasting [10,11] and there are chances of reinfection with the same virus over an extended period of time [12]. Therefore, an effective vaccine against SARS-CoV-2 is urgently needed even for individuals that have been infected previously so as to protect them even when the virus causes seasonal epidemics [13]. Because of the established technology, the manufacturing process for inactivated vaccines is already mature for large scale production in India itself. These vaccines have been known for manifesting moderate immunogenicity and adjuvants as well as booster doses help in improving their immunogenicity, further.

Bharat Biotech International Ltd., in partnership with NIV, a premier institute of Indian Council of Medical Research (ICMR) has developed an indigenous whole virion inactivated SARS-CoV-2 viral vaccine BBV-152 (Covaxin®), formulated with Toll Like Receptors 7/8 agonist IMDG molecule adsorbed to alum (Algel). This has been permitted for restricted use under emergencies in public interest. It comes as a two-dose regimen, recommended to be taken 28 days apart and is available in multidose vials. It does not require storage at subzero temperatures which is difficult to maintain in India's climatic conditions and frequent power cuts. It can be stored at 2-8° C [14]. Variety of factors other than environmental ones can affect vaccine's efficiency

in real world conditions outside the strict setting of clinical trials, like how the vaccine is stored or transported, and even how patients are vaccinated. In addition, the intrinsic capacity of the recipient to respond to a vaccine which is determined by sex, genetic factors, age, psychological stress, nutrition and other diseases are also likely to have an impact [15].

The extent of morbidity and mortality due to infections caused by SARS-CoV-2 has emphasised the urgent need for a safe and effective vaccine. Coronaviruses are enveloped, positive sense single-stranded Ribonucleic Acid (RNA) viruses with a glycoprotein spike on the surface, which mediates receptor binding and cell entry during infection. The roles of the spike protein in receptor binding and membrane fusion make it an attractive vaccine antigen [16]. As reported in other studies, [17,18] experience with other strains of Coronavirus show that spike protein is the target for neutralising antibodies whereas antibodies produced against Nucleocapsid antigens are not neutralising antibodies.

Neutralising antibodies protect the host by binding to specific proteins on the virus thereby neutralising its ability to bind to the Angiotensin Converting Enzyme-2 (ACE-2) cell receptors of the host and its entry into the host cell is hampered. They also facilitate phagocytes in recognition and killing of the virus [17]. Antispike protein assays correlate well with Viral Neutralisation Test (VNT) and can thus provide information about the presence of neutralising antibodies in the individuals. Hence, the present study was aimed to evaluate the safety, reactogenicity and immunogenicity of an inactivated whole virus vaccine (Covaxin®) while the vaccine has been rolled out.

The primary objectives are-

1) To determine the level of antibody titres two weeks after first and two to four weeks after second dose of the inactivated vaccine in HCWs of 18 to 65 years of age.
2) To estimate the proportion of cases who experienced side-effects in first 30 days of vaccination.

The secondary objectives are-

1) To compare and determine the difference in levels of antibody titre as per the age, sex, number of doses and presence of co-morbidity, after two weeks of first dose and 2-4 weeks of second dose of vaccination among HCWs on subgroup analysis.
2) To determine the difference in levels of antibody titre in different comparison groups.

MATERIALS AND METHODS

The prospective observational study was conducted in the Department of Microbiology, Sawai Man Singh Medical College, Jaipur, Rajasthan, India, from January 2021 to March 2021. Written informed consent was obtained from each participant and the study was approved by Office of the Ethics Committee, SMS Medical College and attached hospitals, Jaipur, Rajasthan, India (No.693 MC/EC/2021).

A total of 223 HCWs from Gangauri and Kanwatiya Hospitals allied to Sawai Man Singh Medical College, Jaipur, Rajasthan, India, were selected for the study. The study primarily included HCWs employed at SMS Medical College and attached hospitals. The present study was a preliminary assessment of immunogenicity outcomes (in terms of measuring IgG antibody titres) against Receptor Binding Domain (RBD) proteins (Receptor binding proteins) which can be considered as the basis of protection [18]. Along with this, the immunogenicity outcomes were also studied in those subjects with co-morbidities like diabetes mellitus, hypertension, hypo/hyperthyroidism. Sampling was done four weeks after first dose and 2 to 4 weeks after second dose of Covaxin®. Safety and reactogenicity outcomes were noted just after vaccination and after one week of first and second doses of the vaccine.

Sample size calculation: All the HCWs who got vaccinated at the study centre were taken up in the present study.

Inclusion criteria: Subjects in the age group of 18-65 years, and who received two doses of Covaxin®. Total 223 subjects were enrolled for the study. Apart from 223 subjects in the study group (Case 1 and Case 2), and two control groups were created-

a) Vaccinated with no previous history of COVID-19 infection (n=202) (Case 1)
b) Vaccinated with confirmed previous COVID-19 infection (n=21) (Case 2)
c) Non vaccinated with no previous history of COVID-19 infection (Control group 1) (n=46)
d) Non vaccinated with confirmed previous COVID-19 infection (Control group 2) (n=49)

Exclusion criteria: Participants having fever, history of any allergies, any other serious health-related issues, pregnant or lactating females, or had received any other COVID-19 vaccine were excluded from the study.

All the participants received two doses of Covaxin® injected intramuscularly in the deltoid muscle four weeks apart at SMS Medical college and allied hospitals (proof of vaccination was confirmed by Co-win app certificate) and site staff observed participants for half an hour after vaccination for any acute reactions. All the HCWs were vaccinated in SMS Medical college and it was all done in collaboration with PSM department. As in the initial days only SMS hospital was the centre of vaccination in Jaipur. They were enquired telephonically after one week of the first dose for any sign of reactogenicity. Reactogenicity represents the clinical manifestations observed in inflammatory response to vaccination. The experience of symptoms following vaccination can lead to needle fear, long term negative attitudes and non compliant behaviours that can undermine the public health impact of vaccination [16].

For immunological response assessment, 2 mL blood samples of the study subjects were collected for determining the IgG antibody titers against RBD spike proteins in them just before administration of Covaxin®. After second dose, acute reactions and reactogenicity after one week was noted and blood samples were collected after 2 to 4 weeks for determining antibody titres. In-vitro quantitative IgG antibodies against SARS-CoV-2 spike RBD were measured using CLIA based Advia centaur SARS-CoV-2 IgG, manufactured by Siemens Pvt. Ltd., Munich, Germany, as per manufactures' instructions. This is a fully automated two step Sandwich Immunoassay using indirect chemiluminescent technology. Samples were considered non reactive for SARS-CoV-2 IgG antibodies when the titre <1 index value was given by the system and considered reactive when the result >1 index value was given. Measuring interval was 0.5 to 20. Index value and results were noted as such without testing any further dilutions.

STATISTICAL ANALYSIS

Data were entered on Microsoft excel sheet and analysed using Primer software. Continuous data were summarised in form of mean and standard deviation. Count data were expressed in form of proportions. The difference in proportions was analysed using Chi-square test. The level of significance was kept 95% for all statistical tests.

RESULTS

All 223 participants in the study completed their immunisations and scheduled visits within prescribed time. Total 78 individuals were in the age group of 20 years to 34 years, 103 in age group of 35 years to 49 years and 42 in the age group of 50 years to 65 years [Table/Fig-1]. Out of these, 21 had suffered with COVID-19 illness and 202 were without any previous SARS-CoV-2 infection. The median age was 38 years (SD ±10.63 years). 18.8% (42/223) were older than 50 years and 81.2% (181/223) were below 50 years.

Age (years)	Males	Females
20-34	58	20
35-49	61	42
50-65	23	19

[Table/Fig-1]: Age wise distribution of males and females.

There were 36.3% (81/223) females and 63.7% (142/223) males, 11.21% (25/223) participants had atleast one co-morbidity.

Out of total 223 individuals, 61.88% (138/223) showed neutralising antibody titre of >1 index value by CLIA, rest 38.12% (85/223) came non reactive i.e., titre <1 index value, after four weeks of receiving first dose of Covaxin®. After 2 to 4 weeks of receiving second dose 84.30% (188/223) showed neutralising antibody titre of >1 Index value by CLIA, rest 15.70% (35/223) came non reactive i.e., titre <1 Index value [Table/Fig-2,3].

Level of antibody titre (Index value)	Study groups	RT-PCR positive Non vaccinated (n=49) CONTROL 2	RT-PCR negative Non vaccinated (n=46) CONTROL 1	First dose Covaxin (n=223)	Second dose Covaxin (n=223)	Level of significance
<1		9 (18.37%)	36 (78.26%)	85 (38.12%)	35 (15.70%)	Chi-square=99.251 df=15 p=0.001
1.01-5		11 (22.45%)	7 (15.22%)	49 (21.97%)	73 (32.74%)	
5.01-10		11 (22.45%)	3 (6.52%)	32 (14.35%)	20 (8.97%)	
10.01-15		0	0	11 (4.93%)	21 (9.42%)	
15.01-20		0	0	10 (4.49%)	14 (6.27%)	
>20		18 (36.73%)	0	36 (16.14%)	60 (26.90%)	

[Table/Fig-2]: Comparison of level of IgG antibody titers (after 2-4 weeks of vaccination) against RBD spike proteins.
p-value <0.05 considered significant

Antibody titre	After first dose (n=223)	After second dose (n=223)	Level of significance
<1	85 (38.12%)	35 (15.70%)	Chi-square=38.116 df=5, p=0.001
1.05-5	49 (21.97%)	73 (32.74%)	
5.01-10	32 (14.35%)	20 (8.97%)	
10.01-15	11 (4.93%)	21 (9.42%)	
15.01-20	10 (4.49%)	14 (6.27%)	
>20	36 (16.14%)	60 (26.90%)	

[Table/Fig-3]: Status of IgG antibody titers against RBD spike proteins after first and second dose of Covaxin®.
p-value <0.05 considered significant

Total 9.42% (21/223) were previously known COVID-19 positive individuals. Out of these 85.71% (18/21) developed antibody titre >1 Index value and 33.33% (7/21) of these developed titre of >20 index value after first dose of Covaxin® After the first dose of Covaxin® in previously known Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) positive patients, a titre of >20 was observed in 33.33% (7/21) of subjects which increased to 52.38% (11/21) after the second dose at four weeks, as depicted in [Table/Fig-4]. 80% (20/25) of the participants having one or more co-morbidities like hypertension, diabetes, hypo/hyperthyroidism and others developed reactive titres after receiving second dose [Table/Fig-5].

Antibody titres	Vaccination status (n=21)	
	First dose (n=21)	Second dose (n=21)
<1	3 (14.29%)	1 (4.76%)
1.05-5	5 (23.81%)	4 (19.05%)
5.01-10	2 (9.52%)	1 (4.76%)
10.01-15	3 (14.29%)	3 (14.29%)
15.01-20	1 (4.76%)	1 (4.76%)
>20	7 (33.33%)	11 (52.38%)

[Table/Fig-4]: Change in level of IgG antibody titers against RBD spike proteins after vaccination in RT-PCR positive cases (N=21, Case 2).

Age distribution of people having antibody titres >1 index value after first and second dose is shown in [Table/Fig-6]. Gender-based distribution of people developing antibody titres >1 index value after first dose is shown in [Table/Fig-7]. There was no significant difference in detectable antibody level in male and female groups after first and second dose of vaccination. 59.15% (84/142) of the males and 66.67% (54/81) of the females developed titres >1 index value after first dose and 83.10% (118/142) of males and 86.42% (70/81) of females developed titres >1 index value.

After receiving first dose, 100% (223/223) of the participants developed localised pain [Table/Fig-8]. None of the participants showed any anaphylactic reaction or emergency condition just after vaccination. Age distribution of the adverse events occurring in the participants is depicted in [Table/Fig-9]. Injection site pain was present in all the age groups equally. Fever, bodyache and headache was commoner among people of age group 35-50 years and generalised weakness.

Titres	Co-morbid patients
<1	5/25 (20%)
1.05-5	7/25 (28%)
5.01-10	2/25 (8%)
	2/25 (8%)
15.01-20	1/25 (4%)
>20	8/25 (32%)

[Table/Fig-5]: IgG antibody titers against RBD spike proteins in co-morbid patients (hypertension, diabetes, hypo/hyperthyroidism).

Age (years)	Detectable level of antibodies Index value >1	
	First dose	Second dose
20-34 (n=78)	49 (62.82%)	66 (84.61%)
35-49 (n=103)	65 (63.10%)	90 (87.37%)
50-65 (n=42)	24 (57.14%)	32 (76.19%)
Level of significance	Chi-square=0.495 df=2, p=0.781	Chi-square=2.831 df=2, p=0.243

[Table/Fig-6]: Association of age with detectable level of IgG antibody titers against RBD spike proteins after first and second dose of Covaxin®.

Sex	First dose		Level of significance	Second dose		Level of significance
	>1 titre	<1 titre		>1 titre	<1 titre	
Male (n=142)	84 (59.15%)	58 (40.85%)	Chi-square=0.936 Df=1, p=0.333	118 (83.10%)	24 (16.90%)	Chi-square=0.216 df=1, p=0.642
Female (81)	54 (66.67%)	27 (33.33%)		70 (86.42%)	11 (13.58%)	

[Table/Fig-7]: Association of sex of cases with detectable IgG antibody titers against RBD spike proteins.

Side-effects	Number of cases (N=223)	Percentage (%)
Local Pain	223	100
Fever	32	14.35
Bodyache	75	33.63
Headache	8	3.59
Generalised weakness	9	4.04

[Table/Fig-8]: Side-effects experienced after first dose of Covaxin®.

Side-effects	20-34 years	35-49 years	50-65 years
Body pain	100%	100%	100%
Fever (n=32)	10/32 (31.25%)	19/32 (59.37%)	3/32 (9.37%)
Bodyache (n=75)	25/75 (33.33%)	30/75 (40%)	20/75 (26.66%)
Headache (n=8)	2/8 (25%)	5/8 (62.5%)	1/8 (12.5%)
Generalised Weakness (n=9)	2/9 (22.22%)	2/9 (22.22%)	5/9 (55.55%)

[Table/Fig-9]: Association of age with side-effects experienced after first dose of Covaxin®.

After the first dose of Covaxin® in previously known Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) positive patients, a titre of >20 was observed in 33.33% (7/21) of subjects which increased to 52.38% (11/21) after the second dose at four weeks, as depicted in [Table/Fig-4].

DISCUSSION

In a brief span of time, COVID-19 has become a major cause of concern worldwide ever since its first case was reported in Wuhan, China in December 2019. The pace at which the virus is being transmitted across the globe and sudden upsurge in number of cases is much faster than SARS and MERS [13]. The continuous evolving nature of SARS-CoV-2, makes the task challenging to restrict its spread. One of the prominent approaches for controlling SARS-CoV-2 infection is the development of efficacious vaccines against it [19,20]. Vaccine is being acclaimed as the most potent weapon for inducing immunity with adequate safety, to curtail down the transmission of virus [21]. With use of vaccines, barring individual protection against the virus, pool of immune people is aimed to be created that comprises around 60-70% of entire population leading to herd immunity [22,23]. Apart from development of various vaccines, evaluation of these vaccines for their effectiveness and safety at each step is equally important. This has remained major hurdle for researchers in establishing the vaccine efficiency so far [20]. Live attenuated vaccines closely resemble natural infections and provide higher level of immunogenicity in comparison to other types, but no COVID-19 live attenuated vaccine is in clinical trial mode as of now [21]. Inactivated vaccines have proven their efficacy for many diseases and major advantage with these vaccines is that their productions can be scaled up early [21].

History was taken from the participants for any site-specific adverse reactions (e.g., pain, redness and swelling) and systemic adverse reactions (fever, headache and fatigue) within one week after first dose and two weeks after second dose. The most common reaction was pain at the site of injection site (100%) 223/223 followed by bodyache 33.63% (75/223), fever 14.35% (32/223), and headache 3.59% (8/223) and generalised weakness 4.04% (9/223). It was observed that all reactions were mild, transient and self-limiting and did not require any treatment except taking a tablet of paracetamol within 24 hours of receiving the vaccine shot. There were no unsolicited adverse effects observed in this trial which were unrelated to the vaccination. No major adverse effect was observed within half an hour of injection. Mild to moderate pain at the injection site was present in all the participants irrespective of the age, especially after taking first dose of the vaccine. None of the participants reported injection site redness or swelling. In general, local reactions were mostly mild to moderate in severity and resolved within 3-5 days.

Polack FP et al., have reported that 66-83% of the participants in his study showed manifestations of local reactogenicity with mRNA vaccine by Pfizer. Pain was less frequently reported among participants of older age group [5]. Baden LR et al., have published that 4.2-88.6% participants had localised pain after mRNA-1273 vaccine [24]. Zhang Y et al., have notified that 2-2.5% of participants had localised pain in this study [25]. Both bodyache and headache was reported more by younger adults (<50 years) in comparison to older (>50 years) in the present study. This was very less in comparison to studies done on Pfizer mRNA vaccine in which malaise was reported in 59% participants and headache in 52% [5]. Similar study also has reported more bodyache and headache in younger vaccine recipients. Fever was noted in 16.02% (29/181) of <50 years of age group and in 7.14% (3/42) in older recipients (>50 years) in this study. This finding was similar to what has been notified for mRNA vaccine by Polack FP et al., who have reported 11-16% of recipients developing fever. None of the study participants developed any lymphadenopathy, cardiac arrhythmias or stroke that have been reported with mRNA vaccine though only in 4 participants [5].

Overall, two dose regimen of Covaxin® was found to be very safe and well tolerated by healthy individuals aged between 20-65 years. This clearly suggests a good safety profile of Covaxin®. However, this should be discreetly interpreted because of very small sample size in the present study. As depicted in results 80.43% (37/46) of RT-PCR negative, non vaccinated participants did not have detectable level of antibodies followed by participants who had first dose of Covaxin® 85/223 (38.12%). Moreover, there were 18.37% (9/49) RT-PCR positive and non-vaccinated participants (Control group) and 15.7% (35/223) of participants (test group) with even after second doses did not have detectable antibodies. Higher level (>20 index value) of antibodies were seen maximum in RT-PCR positive but non vaccinated group, followed by person after second dose 26.9% (60/223). 6.5% (3/46) RT-PCR negative non vaccinated cases who had high level (>20) of antibody titre. These observations were statistically significant (p-value=0.001). Data published for other Coronavirus vaccines revealed more than 90% efficacy for the lipid nanoparticle m-RNA vaccine BNT162b2, [26]. About 92% efficacy for sputnik V vaccine (developed at National Research center for Epidemiology and Microbiology) [27], 94.5%for the Moderna lipid nanoparticle m RNA-1273 vaccine [28] and 70.4% for a viral vector Corona vaccine ChAdox1 n CoV-19 and protection of 64.1% after one dose [29].

As recommended in a study, any vaccine with efficacy of 60-80% could allow reduction for physical distancing if high coverage is achieved [30]. The findings in present study clearly indicate that efficacy of Covaxin® against SARS-CoV-2 exceeds this threshold and has a good potential to have impact on public health. The present study showed that four weeks after first dose of Covaxin®, 61.89% (138/223) participants developed neutralising antibodies (>1 index value) and maximum four weeks after second dose, 84.3% (188/223) participants developed reactive titres. A 38% cases did not achieve detectable level of antibodies four weeks after first dose of Covaxin®. However, after second dose this proportion got reduced to 15%. There were around 16% cases who had very high antibody titre (>20) even after first dose. This increased to (27%) after second dose. There were significant proportion (38.11%) of cases who did not show detectable level of antibodies even after 4 weeks of receiving first dose, but 15% of them showed substantial increase in antibody titre after second dose (p-value=0.001). This shows that second dose of Covaxin® is essential to boost up the primed immune system and thus good efficacy is ensured after receiving two doses of Covaxin® as recommended by the manufacturers.

Clinical research on many vaccines has shown that women exhibit a greater immune response, both innate (pattern recognition receptors, cytokines) and adaptive (humoral and cell mediated), that can facilitate vaccine efficienc [30,31]. This difference exists across the entire life span and is related to the presence of two X chromosomes. X chromosomes contain many genes such as ACE-2, which regulate immune and cellular function. MicroRNAs are also present in numerous numbers on X chromosomes and there is incomplete inactivation of some genes too, both of these facilitate immune response. Apart from these, sex steroid hormones also influence the female immune response [30,31]. In the present study, it was noted that the number of females showing

seroconversion was higher after first and second dose {66.67% (54/81) and 86.42% (70/81) respectively in comparison to the males after first and second dose, 59.15% (84/142) and 83.10 (118/142)} respectively as shown in [Table/Fig-7]. But statistically, there was no significant difference in detectable antibody level in male and female groups after first and second dose of vaccination.

Elderly people may have an impaired immune response to primary as well as secondary immunisation due to age related alterations in immune systems due to age related illnesses, infections, drug intake etc [3]. In the present trial, higher percentage of participants under the age of 50 years developed antibodies (62.98% after first dose and 86.18% after second dose) in comparison to the age group of more than 50 years (57.14% after first dose and 76.19% after second dose) as shown in [Table/Fig-6]. But statistically, there was no significant difference in proportion of cases that developed detectable level of antibody titre in different age groups after first dose as well as after second dose of Covaxin®. Thus, age has no significant association with development of detectable level of antibodies between the age groups of 20 to 65 years.

In this study, as depicted in [Table/Fig-3], 11.21% (25/223) participants had one or more co-morbidities like hypertension, diabetes, thyroid disorders, cardiac problems etc., but surprisingly 80% (20/25) of these developed antibodies after second dose of the vaccine and 20% (5/25) of these remained non reactive for IgG antibodies against SARS-CoV-2.

In present study, 9.4% (21/223) participants were known SARS-CoV-2 positive by Reverse Transcription-PCR. Out of these 14.2% (2/21) were non reactive after first dose. Only 4.76% (1/21) remained non reactive for IgG antibodies against SARS-CoV-2, after second dose. Overall, in this group after receiving first dose, 85.71% (18/21) of the participants developed antibodies and out of those 33.33% (7/21) had antibody titres of >20 index value. First dose of the vaccine acted as booster in them as their immune system was already primed by virus due to infection. After second dose 95.24% (20/21) of the participants developed antibodies and 52.38% (11/21) of them were reported to have titres >20 index value. This observation indicates that, a booster dose planned after few months of second dose, can enhance the development of antibodies in upto 95.24% of the people.

Recently an amendment to the protocol of present study was made which will provide additional longitudinal testing of antibodies for a year in participants. The results of which will be published when available.

Limitation(s)

This study reported the reactogenicity, safety and immune response data from a small group of individuals. This study did not include the most susceptible age group (>65 years) with co-morbidities. Therefore, complete analysis of a larger number of participants of all age groups is needed to provide a comprehensive profile of the inactivated vaccine against SARS-CoV-2 in terms of tolerability, immunogenicity and immune persistence. Although Covaxin® elicited good antibody response, whether it could actually protect individuals against COVID-19 remains unknown as the level of protection gained cannot be solely deduced from the antibody titres. T cell-mediated responses on stimulation by the vaccine were not assessed in this study. At last, the duration of the study was short to actually assess the long-term safety and efficacy follow-ups.

CONCLUSION(S)

Covaxin® is well tolerated and induces good humoral response against SARS-CoV-2. It can contribute well in control of the disease during this pandemic together with other public health measures and help in reducing the devastating loss of health, life, social and economic well-being that has resulted from COVID-19. For assessing efficacy, immune persistence and long-term adverse events, further longitudinal studies of longer duration should be conducted.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Apr 21, 2022
- Manual Googling: Aug 07, 2022
- iThenticate Software: Aug 08, 2022 (13%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 19, 2022**
Date of Peer Review: **May 26, 2022**
Date of Acceptance: **Aug 10, 2022**
Date of Publishing: **Sep 01, 2022**