Safety and Immunogenicity of Mix-Match of Vaccines -Covishield and Covaxin – a Pilot Study

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Short Report

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SAFETY AND IMMUNOGENICITY OF MIX-MATCH OF VACCINES - COVISHIELD AND COVAXIN – A PILOT STUDY

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Abbreviations: S-spike protein, RBD –Receptor binding domain

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Abstract:

This single-center prospective observational study was conducted to assess the safety and immunogenicity of combination vaccines AstraZeneca's ChAdOx1-nCov-19 (Covishield in India) and inactivated whole virion BBV152 (Covaxin). A total of 330 unvaccinated healthy volunteers were screened for SARS-COV2 seropositivity. RT PCR tests were conducted for seronegative volunteers (n =44). They were randomly assigned to four groups and given either same or mixed vaccines at an interval of 4 weeks between the two doses. Mix and match of vaccines did not evoke any adverse events. Combination of vaccines elicited similar immune responses in 4 groups. They were further studied dividing into homologous and heterologous vaccine groups. In Conclusion, Combination vaccines are safe and immunogenic and heterologous vaccines elicit better immunogenic response.

INTRODUCTION:

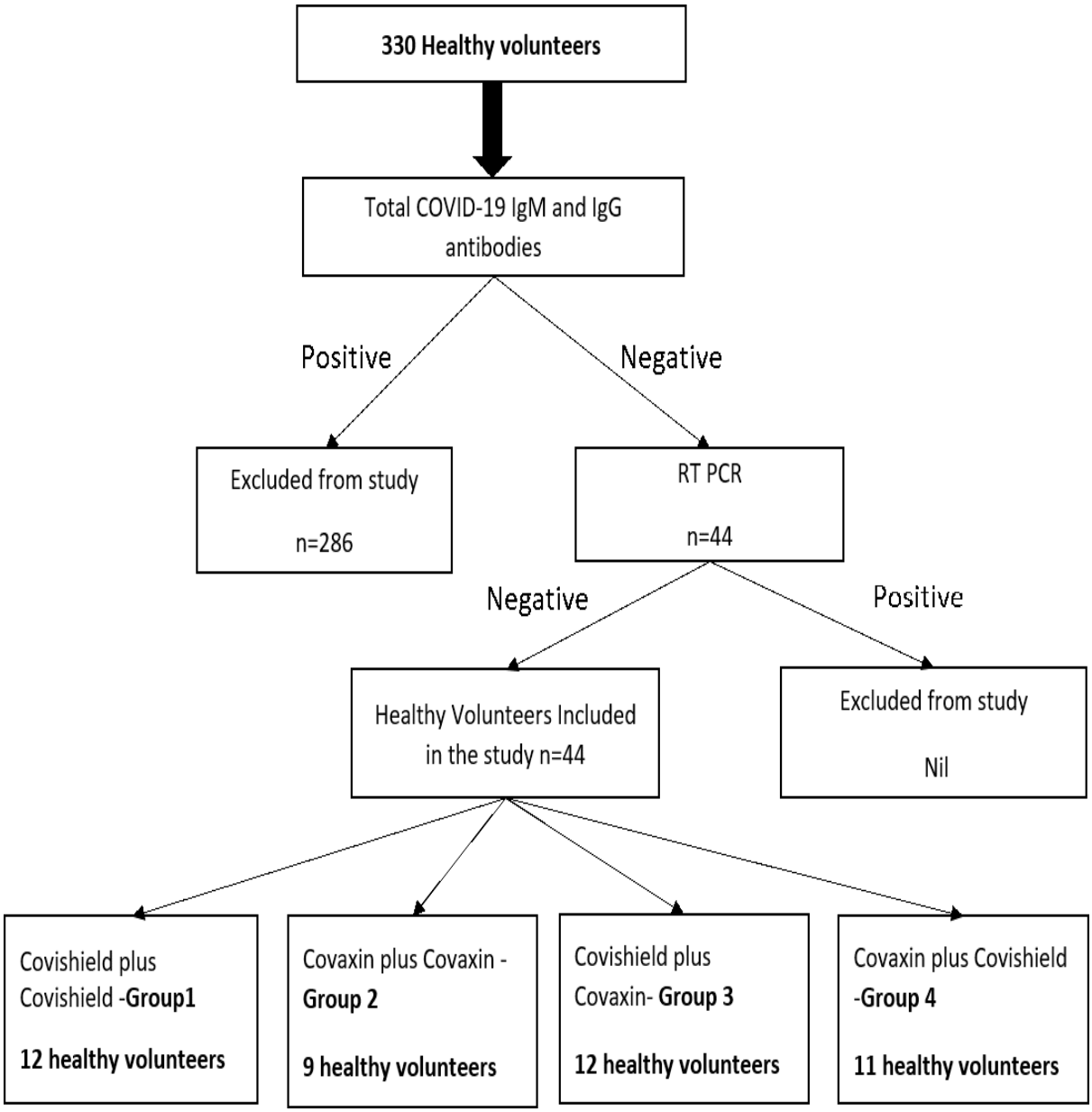
Vaccination has been shown to be protective against severe COVID-19 disease by various studies[1,2,3,4]. However, the vaccine efficacy was demonstrated to be less effective against the emerging variants of SARS-CoV-2[5]. Recent studies by Kant R et al.,[6] Com- COV study[7], Combi Vacs trial[8], ChAdOx1 nCoV-19, and BNT162b2[9] have all demonstrated greater immunogenic response and increased protective efficacy with combination of vaccines. All these studies mainly focussed on Pfizer (BNT162b2), Moderna (mRNA-1273) and AstraZeneneca (ChAdOx1-nCov-19). We aimed to assess the safety and immunogenicity of combination of AstraZeneca's ChAdOx1-nCov-19 (Covishield in India) and inactivated whole virion BBV152 (Covaxin) with 4 weeks' interval. This study was conducted to reduce various difficulties in vaccinating populations across the world specially to mitigate vaccine deficit.

Materials and Methods:

This is a single-centre prospective observational study conducted at AIG Hospitals, Hyderabad, India. The study protocol was approved by the Institutional ethics committee (AIG/IEC-CT 51/08.2021-01). We recruited 330 healthy volunteers and screened for seronegativity for SARS-CoV-2 antibodies (IgM and IgG by chemiluminiscence; Roche Cobas e 601) and SARS-CoV2 negative report by RT-PCR. 3 ml of blood was drawn for screening SARS-COV2 antibodies. Nasopharyngeal swabs were collected from individuals who were seronegative (n=44) for SARS-CoV RT-PCR employing Taq path kits (Thermoscientific, USA). All the volunteers have provided written informed consent. Eligible participants (n=44) were divided randomly into four groups. **(Figure 1)**. Group1- Covishield –Covishield group (homologous), Group 2 Covaxin –Covaxin group (homologous), Group 3 – Covishield –Covaxin group (heterologous), Group 4 –Covaxin –Covishield group (heterologous). Healthy volunteers were

given 1st dose of Covishield (0.5 ml of intramuscular in deltoid) in group 1 and group 3 while volunteers in group 2 and group 4 received Covaxin (0.5 ml of intramuscular in deltoid) as 1st dose. After 4 weeks of 1st dose, groups 1 and 4 received Covishield as 2nd dose while groups 2 and 3 received Covaxin as 2nd dose respectively. Further, the volunteers were divided into homologous (similar vaccines for two doses; group A) and heterologous (mix-match of vaccines for two doses; group B) vaccination groups and their antibody titers were evaluated to assess the immunogenic response. S1/S2 neutralizing antibodies titers and RBD specific antibody titers were evaluated at day 28 after the 1st dose and day 15 after the second dose (45 days of first dose) of vaccination; Sera were tested for S1/S2 antibody titers using chemiluminiscence assays (automated Diasorin Liaison XL, Italy) and electro-chemiluminescent assays for RBD specific antibody titer (Cobas e 601,Roche Diagnostics, Basel, Switzerland).They were carefully monitored for any adverse events for 60 days. The data including demographics were entered in MS-excel and analyzed using SPSS version 23. Categorical variables were expressed in percentages (frequency distribution) and continuous variables as mean and standard deviation (SD), median and range wherever required. Chi-square tests, student t-test and ANOVA were used appropriately.

Figure 1 : Flow chart of the mix –vac study



Results:

A total of 44 participants out of 330 healthy volunteers were eligible for mix and match vaccine study (mix–vac study). Among 44 volunteers, 21 received the homologous vaccines and 23 received the heterologous vaccines. The mean age in Covishield homologous vaccine group was 34.83±7.58 years, and Covaxin homologous vaccine group was 31.33±5.20 years, Covishield followed by Covaxin heterologous group is 31.58±5.32 years and Covaxin followed by Covishield heterologous group was 32.27±5.26 years with no significant difference (p=0.49). There is no significant difference between the groups with respect to comorbidities like hypertension (Table-1) and none of them had diabetes or other comorbidities. The antibody titers (median) of S1/S2-IgG and RBD specific IgG 15 days after 2nd dose of vaccination in Covishield homologous group is 841.5 (24.0-3985)AU/ml and 9823.5 (858-42800)IU/ml, Covaxin homologous group is 68.4 (3.8-1850)AU/ml and 951 (0.4-13710)IU/ml, Covishield followed by Covaxin heterologous group is 1195 (5.21-3981) AU/ml and 11554.5 (10.8-30740) IU/ml and Covaxin followed by Covishield heterologous group is 1250 (12.8-4225)AU/ml and 3247 (0.75-23290)IU/ml respectively. There is no significant difference (p= 0.08) in antibody titers between the groups. The volunteers experienced fever, injection site pain, and mild headache in all the groups with no significant difference between the groups (Table-1). There are no major adverse events noted in the mix-match vaccine groups.

TABLE -1: **Demographic and clinical profile of participant's mix-vac study.**

	Both Covishield Group -1 N=12	**Both Covaxin Group -2 N=9**	**First Covishield then Covaxin Group -3 N=12**	**First Covaxin then Covishield Group -4 N=11**	**P value***
Age	34.83±7.58	31.33±5.20	31.58±5.32	32.27±5.26	0.49
28th Day after 1st dose S1/S2 -IgG Antibodies	605 (48.4-3330) AU/ml	112 (37.6-1450) AU/ml	633(8.68-3981) AU/ml	109 (5.24-3970) AU/ml	0.17
28th Day after 1st dose RBD – IgG Antibodies	5242 (96.5-13370) IU/ml	843(0.4-19320) IU/ml	. 6254.5(71.3-23290) IU/ml	747(0.75-41340) IU/ml	0.43
15th Day after 2nd dose S1/S2 - IgG Antibodies	841.5 (24.0-3985) AU/ml	68.4 (3.8-1850) AU/ml	1195(5.21-3981) AU/ml	1250 (12.8-4225) AU/ml	0.08
15th Day after 2nd dose RBD specific IgG Antibodies	9823.5 (858-42800) IU/ml	951(0.4-13710) IU/ml	11554.5(10.8-30740) IU/ml	3247(0.75-23290) IU/ml	0.08
Smoking (Yes)	2 (16.67%)	1 (11.11%)	1 (8.33%)	2 (18.18%)	0.89
Alcohol intake	2 (16.67%)	3 (33.33%)	2 (16.67%)	5 (45.45%)	0.33
Comorbidities (Hypertension)	2 (16.67%)	4 (44.44%)	2 (16.67%)	6 (54.54%)	0.12
1st Visit dose 1					
Fever (yes)	4 (33.33%)	3 33.33%)	4 (33.33%)	4 (36.36%)	0.99
Headache (yes)	5 (41.67%)	4 (44.44%)	7 (58.33%)	5 (45.45%)	0.85
Pain at site (Yes)	9 (75.00%)	5 (55.55%)	3 (25.00%)	6 (54.54%)	0.10
2nd Visit dose 2					
Fever (Yes)	2 (16.67%)	2 (22.22%)	1 (8.33%)	4 (36.36%)	0.40
Headache (Yes)	8 (66.67%)	4 (44.44%)	8 (66.67%)	5 (45.45%)	0.55
Pain at site (Yes)	5 (41.67%)	5 (55.55%)	6 (50.00%)	4 (36.36%)	0.82

*Chi-square test and One-Way ANOVA were used

The data were then analyzed between homologous (group-A) and heterologous groups (group-B). The mean age in homologous vaccine group was 33.3 $\pm$ 6.75 and heterologous vaccine group was 31.91 $\pm$ 5.18 with no significant difference (p= 0.44). The median antibody titers of S1/S2-IgG and RBD specific IgG at 15 days after 2nd dose of vaccine in homologous groups is 290 (3.8-3985) AU/ml and 7568 (0.4-42800) IU/ml, and heterologous group is 1250(5.21-4225) AU/ml and 6427(0.075-30740) IU/ml respectively. A significant difference (p= 0.02) in S1/S2 -IgG antibody titers was observed after 15 days of 2nd dose vaccination between homologous and heterologous groups, while there was no significant difference (p=0.97) in RBD specific-IgG antibody titers between the groups (Table-2, Figure 3; Figure 4).

TABLE -2: **Antibody titres of homologous and heterologous groups study at 28 and 45 days after vaccination.**

	Homologous vaccine group. (n=21) Group A	**Heterelogous vaccine group (n=23) Group B**	**P value***
Age (years)	33.3 + 6.75	31.91 + 5.18	0.44
28th Day after 1st dose S1/S2-IgG Antibodies	181 (37.6-3330) AU/ml	373 (5.24-3981) AU/ml	0.272
28th Day after 1st dose RBD –IgG Antibodies	1769 (0.4-19320) IU/ml	3383 (0.075-41340) IU/ml	0.111
15th Day after 2nd dose S1/S2- IgG Antibodies	290(3.8-3985) AU/ml	1250 (5.21-4225) AU/ml	**0.022**
15th Day after 2nd dose RBD- IgG Antibodies	7568 (0.4-42800) IU/ml	6427 (0.075-30740) IU/ml	0.976

*Student paired t-test

Figure 2: Simple box plot of S1/S2 IgG antibodies 15 days after 2nd dose of vaccination

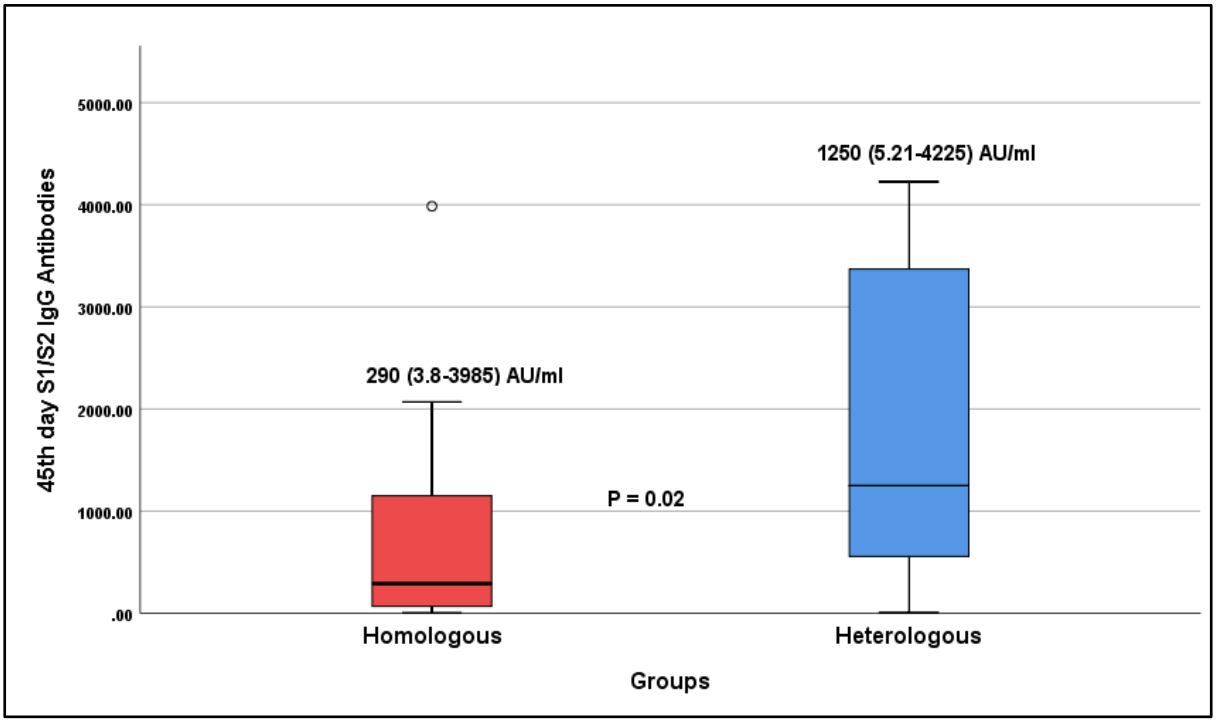
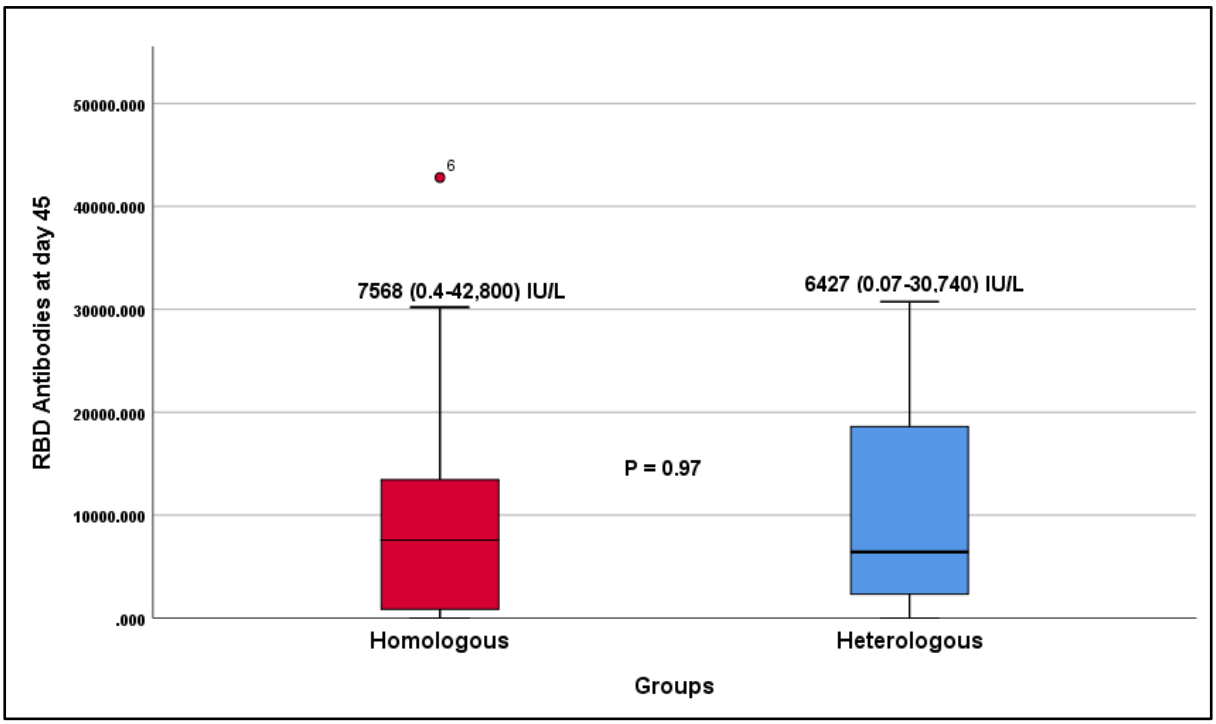


Figure 3: Simple box plot of RBD specific IgG antibodies after 15 days of 2nd dose of vaccination



Discussion:

Our study is the first Indian prospective pilot study demonstrating the safety and immunogenicity of mix-match vaccines with Covaxin and Covishield in healthy volunteers. These results are similar to those conducted by Kant R et al(n=18)[6] which included only Covishield first dose followed by Covaxin, while our study included both Covishield followed by Covaxin and Covaxin followed by Covishield groups. The major limitation of the study was the smaller number (n=44). Despite the small number, our study included two groups with two combination of vaccines that are in use in this part of the world. However, these results need to be assessed in larger cohorts. Since the number is small in this study, our results do not interpret the best combination but it helps to answer the apprehensions among the general public about combination vaccine and prevent vaccine hesitancy.

Conclusion:

Our results show safety and immunogenicity of mix-match of COVID-19 vaccination (Covishield followed by Covaxin, and Covaxin followed by Covishield) and demonstrate enhanced antibody response with heterologous vaccines than homologous vaccines.

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