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Research Paper

Research Report of Pacific Study Group on Immune Response of Covishield Vaccination among Health Care Subjects

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ABSTRACT

SARS CoV-2 is the causative agent of novel corona virus disease 2019 (COVID -19) which has captured the entire world as pandemic leading to huge death toll. Till the end of 2020, some vaccines against COVID -19 were developed. Sputnik, COVISHIELD, COVAXIN, Pfizer, Moderna are some of them. In India, vaccination program was started on 18 January, 2021 and COVISHIELD and COVAXIN were part of this. COVISHIELD Vaccine is produced by Serum Institute of India, Pune and said to provide 70% efficacy against all strains of SARS-CoV-2 found till date.

An attempt was made to find efficacy of COVISHIELD vaccine in health-care workers including faculty members, residents and nursing staff of Pacific Medical College and Hospital, Udaipur, Rajasthan. Pacific Study Group was constituted incorporating departments of Medicine, Biochemistry and Microbiology for proper execution of the study. After institutional ethical approval (PMU/PMCH/IEC/184/2021/Dated 12.02.2021), 50participants who were never affected by COVID-19 and received first dose of COVISHIELD vaccine were enrolled in the study. Out of 50, 40 participants were from age group of 20-40 Years and rest 10 was from 41-70 years age group. COVID antibody IgG was evaluated by recombinant protein by CLIA using ICMR approved kid representing SARS CoV-2 S1 RBD antigens.

After four weeks of receiving a single dose of COVISHIELD, 80% participants out of 50 developed IgG antibodies. Among those 80% participants, 34% developed 1-10 units, 4% developed 10-20 units and 42% developed more than 20 units of antibodies indicating potent efficacy of vaccine. However, 20% of total participants did not develop any antibodies against SARS CoV-2 out of which 17.5% were from 20-40 age group, and 30% were from 40-70 years age group. There was no observed side effect after receiving single dose of COVISHIELD amongst the participants. Negative control group of five participants who were non-vaccinated and non-COVID affected showed no development of antibodies whereas positive control group of non-vaccinated by COVID affected participants (n=5) showed development of more than 20 units of IgG antibodies reflecting development of natural immunity against SARS CoV-2. The immune status increased further in the study subjects (87%) after second dose. But, with the passage of time, the immunity reduced and only 72% of

participants were positive for IgG antibodies after six months of the first dose of vaccination. This highlights the need of booster dose. The study is in-progress and results of antibody status after the booster vaccination are being evaluated.

KEYWORDS: SARS CoV-2, Sputnik, Pandemic, Efficacy, IgG, S1 RBD

INTRODUCTION

The world woke up to a dreadful pandemic in the year 2019-20, and before we can take action the dreadful virus quickly caught the entire globe within its paw. Since the first reported incident, we have been trying to come out of this wildfire. The world came together for once, trying to find out a way with vaccines against the virus as the only ray of hope. Before the pandemic set in, we already knew about the structure and functioning of these Coronaviruses due to the previous outbreaks of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). This pre-existing information fuelled the development process with more pace[1]. In the beginning the primary goal for a COVID-19 vaccine was to prevent progression of the disease towards severe form[2]. Phased distribution has been done in countries in a manner where higher priority corresponding to increased risk of receiving the infection such as Health Care Workers, and increased risk of complications such as elderly persons[3].

As of the date 22/04/2023, worldwide 13.37Billion doses of COVID-19 Vaccines have been administered (Based on reports from National Public Health Agencies)[4]. And in India around 2.21 billion doses have been administered. Observational and Case control studies have been come in to use to asses Real-World Vaccine Effectiveness, as multiple COVID-19 vaccines have been authorised[5]. There is an ongoing study which is investigating the long term effect of mRNA vaccines in protection against the SARS-Cov2[6].

As of today, there are around 22 potential vaccines which have received authorisation for use by National Agencies. Around 6 vaccines are authorised for Emergency or Full Use by Stringent Regulatory Authority, out of these six, five of them are in phase IV. In total 330 vaccines are in different stage of development , out of them 102 are still in clinical research phase, with Phase I and Phase II trials comprising of 30-30 each, Phase II trial including 25 and 8 vaccines in Phase IV development[7]. Phase II trials showed promising results for several vaccines with efficacy touching 95% in preventing COVID-19 infection, especially symptomatic infections.

The table below enlists various vaccines with their type[8,9].

Table 1: Various COVID Vaccines

Type Of Vaccine	Manufacturer
DNA Vaccine	ZyCoV-D
RNA Vaccine	Pfizer-BioNTech, Moderna
Viral Vector	Oxford-AstraZeneca (COVISHIELD), Sputnik V, Jansen
Conventional Inactivated	Chinese Academy of Medical Sciences, BBIBP-CorV, Covaxin, CoronaVac, CoviVac, COVIran Barekar, QazVac, WIBP0CorV, FAKHRAVAC, Minhai-Kangtai
Protein Subunit Vaccine	EpiVacCorona, MVC-COV1901, Soberana 02, Abdala, ZF2001

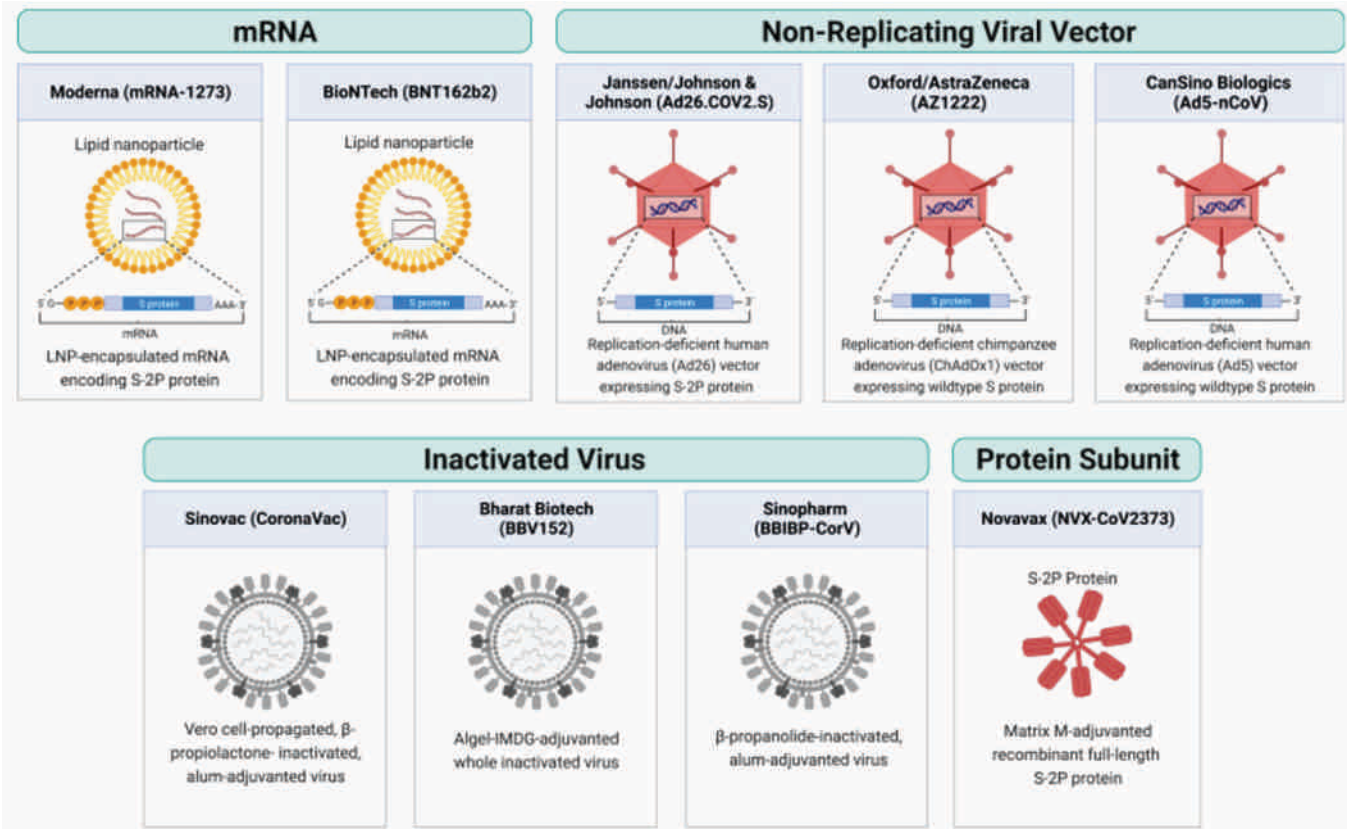


Figure 1: Various COVID-19 vaccines approved by WHO[23]

The Oxford/AstraZeneca vaccine – branded as COVISHIELD in India is produced and distributed by Serum Institute of India (Cyrus Poonawala Group) for the nation. The vaccine is supposed to give immunity against the B1.1.7 (UK)[10], B1.167.1$_{11}$ and P.1 (Brazil)[12] variant of the SARS-CoV-2. The vaccine is a recombinant, replication – deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein.

Preliminary efficacy data shows the vaccine gives 66.7% protection against a symptomatic COVID-19 infection after more than 14 days after the administration of 2nd Dose. (Data from UK and Brazil[13]

METHODOLOGY

Study Centre: Pacific Medical College and Hospital, Udaipur, Rajasthan, India

Pacific Study Group: Departments of Medicine, Microbiology and Biochemistry

Study Population: Health Care Subjects of Pacific Medical College and Hospital

Sample Size: 162 Subjects

Study Design: A Prospective Observational Study

Study Duration: 6 months

Inclusion Criteria:

- All healthcare individuals who had received at least a single dose of COVISHIELD vaccine

Exclusion Criteria:

- Individuals who were tested positive for COVID-19 at any point of time
- Age <18 Years and >70 Years
- All unvaccinated healthcare workers
- Individuals with comorbid illness (E.g. DM-2, HTN, on lifelong immunosuppression etc.)

Parameters:

IgG Antibody against the SARS-CoV-2 was evaluated by recombinant protein by CLIA using ICMR approved kid representing SARS CoV-2 S1 RBD antigens.

After institutional ethical approval (PMU/ PMCH /IEC/ 184/ 2021/ Dated 12.02.2021), 50 participants who were never affected by COVID-19 and received first dose of COVISHIELD vaccine were enrolled in the study. The IgG antibody titre was evaluated after 4 weeks of receiving the 1st dose of COVISHIELD vaccine.

Following up, 61participants who had received the second dose of COVISHIELD vaccine and was never affected with

COVID-19 infection were enrolled in the second phase of the study, and the IgG antibody titre was evaluated.

In the final phase, 50 participants were enrolled who had received the first dose and second dose of the vaccine and the IgG antibody was evaluated after 6 months of set time of receiving the first dose.

RESULTS

The study was carried in a phased manner, consisting of three phases. We initiated the First phase of the study after 4 Weeks after the Government of India commenced the first round of vaccination amongst healthcare professionals. In the first phase 50 individuals (never affected with COVID-19) were enrolled who had received the first dose of the vaccine. The second phase was carried out 4 weeks after the second dose of the vaccine (The 2nd Dose was given 4 weeks after the 1st Dose). 61 Participants were enrolled in this phase, and their Antibody titre was evaluated. In the third and final phase there were again 51 participants, and the phase was carried at 6 months after the 1st Dose of Vaccination. Total 10 Dropouts were observed in the third phase. Hence, a total of 162 participants were enrolled in the study.

Basic Demography

The participants were predominantly Males (127) and a much smaller fraction were females (35). The Individual demography according to phases has been shown below (Table

Table 2: Phases of Study

Phase	Time Frame
Phase – I	4 Weeks after 1st Dose
Phase – II	4 Weeks after 2nd Dose
Phase – III	6 Months after 1st Dose

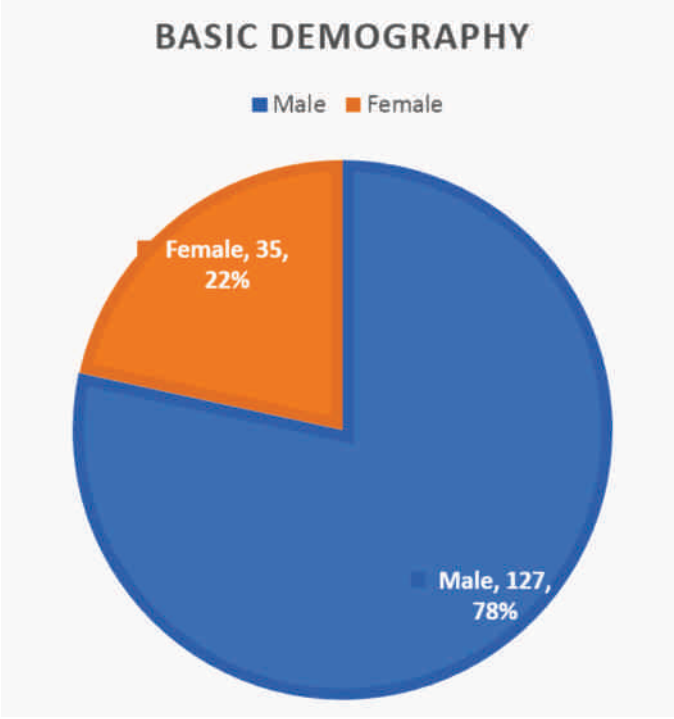


Figure 2: Total Gender Distribution

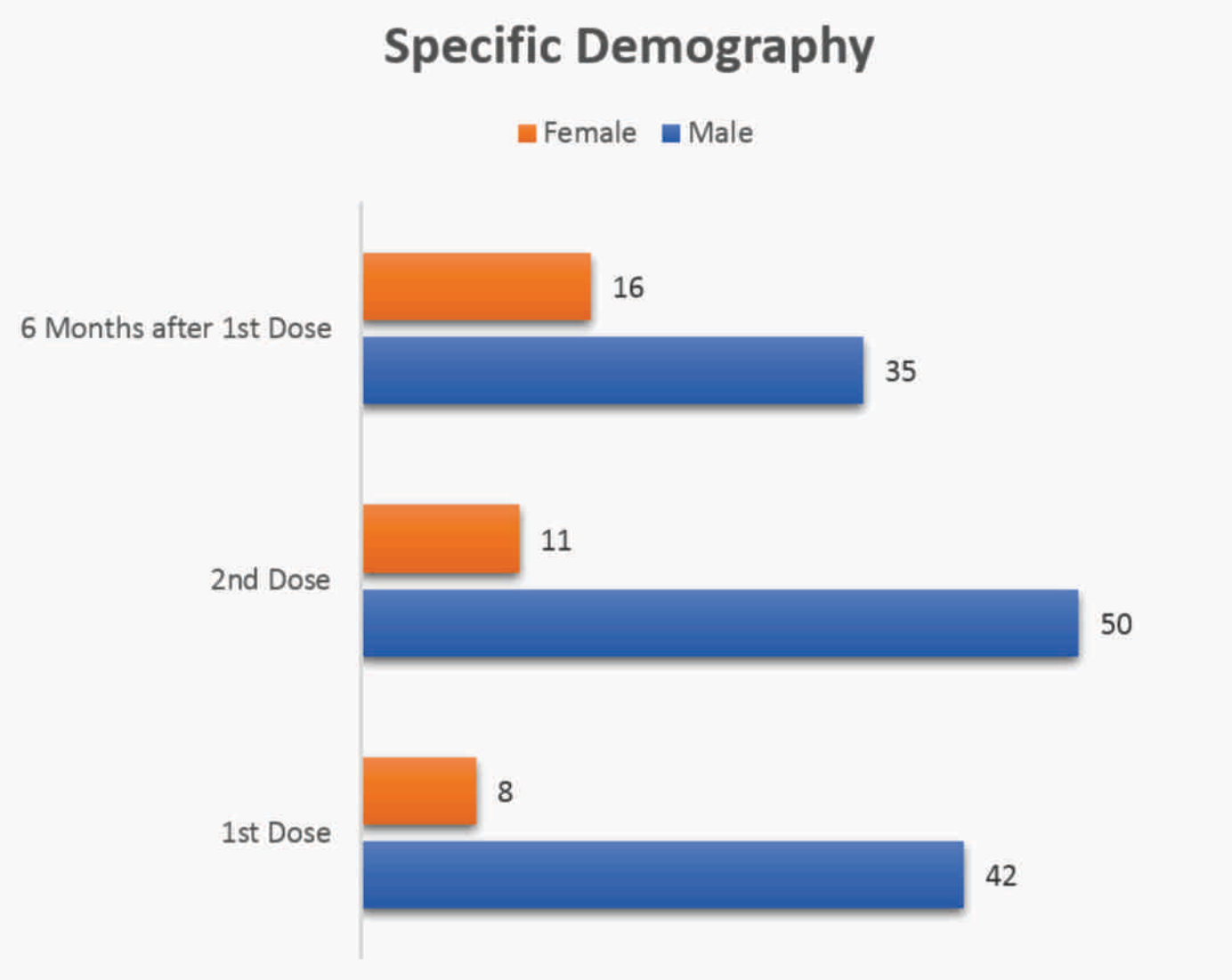


Figure 3: Specific Gender Distribution in Different Phases

Results of IgG Titre

Out of the entire study population, 81% (131) tested positive for Anti SARS CoV -2 antibody, giving a good immune response to the vaccine, remaining 19% (31) tested negative. (A positive titre was considered IgG level of >1.00, and negative response was considered when IgG <1.00)

The antibody response in the different phases is as seen in Figure 5.

In the first phase, 82% (41) were positive and 18% (9) were negative (n=50), and subsequently in the second phase86.88% (53) were positive and 13% (8) were negative (n=61), following up in the final phase (6 Months after the 1st dose of vaccination) only 37(72.54%) were positive and 14 (27.45%) were negatives (n=51).

For those who developed no response to the vaccines (n=31), 23 of them were 20-40 years of age and 8 belonged to elderly age group of 40-70 Years. The breakdown of the age group in various phases is as seen in Figure 6.

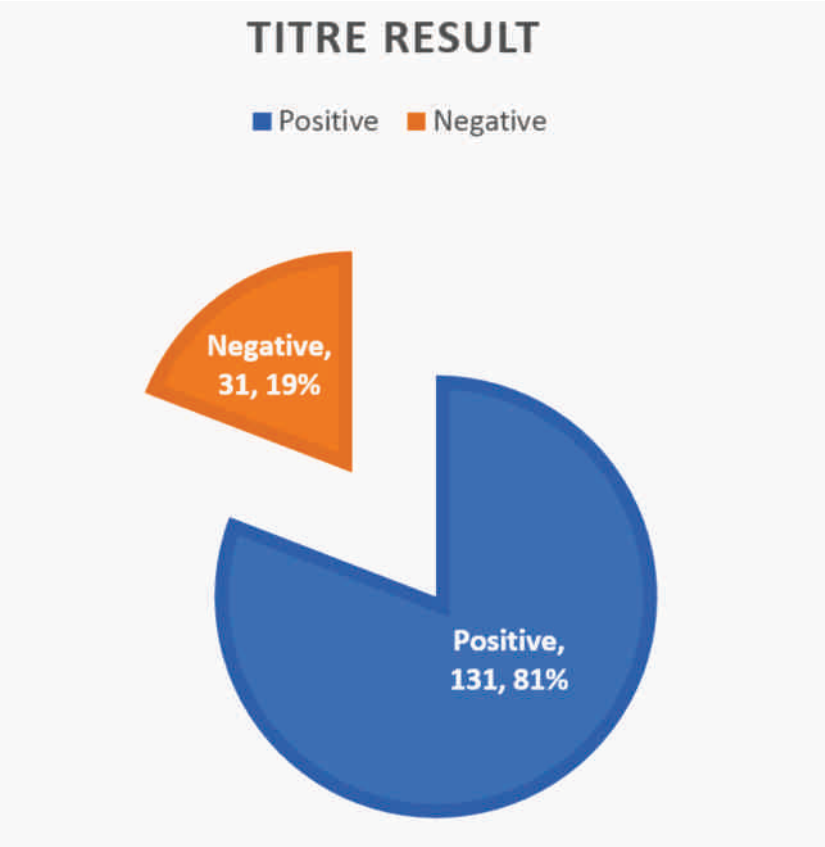
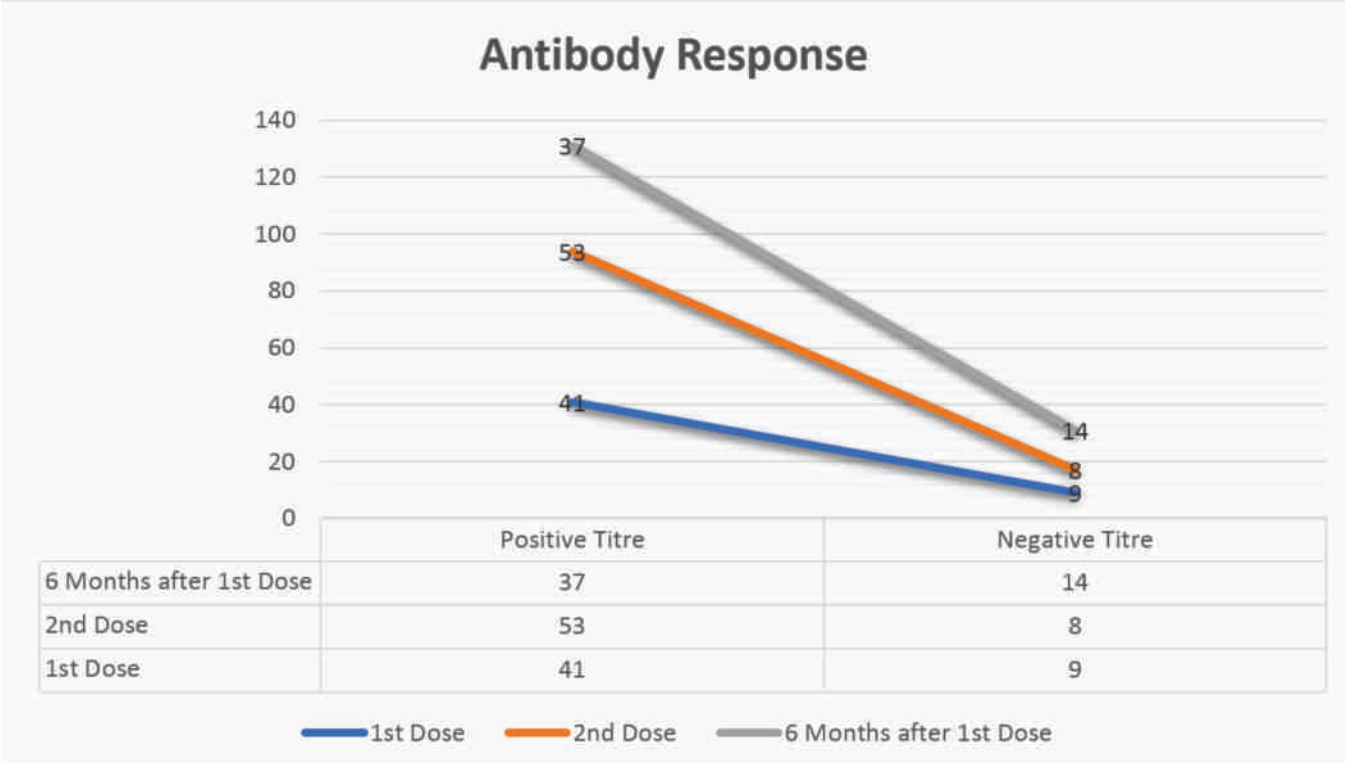


Figure 4: Result of IgG Titre



	Positive Titre	Negative Titre
6 Months after 1st Dose	37	14
2nd Dose	53	8
1st Dose	41	9

Figure 5: Antibody Response in different phases

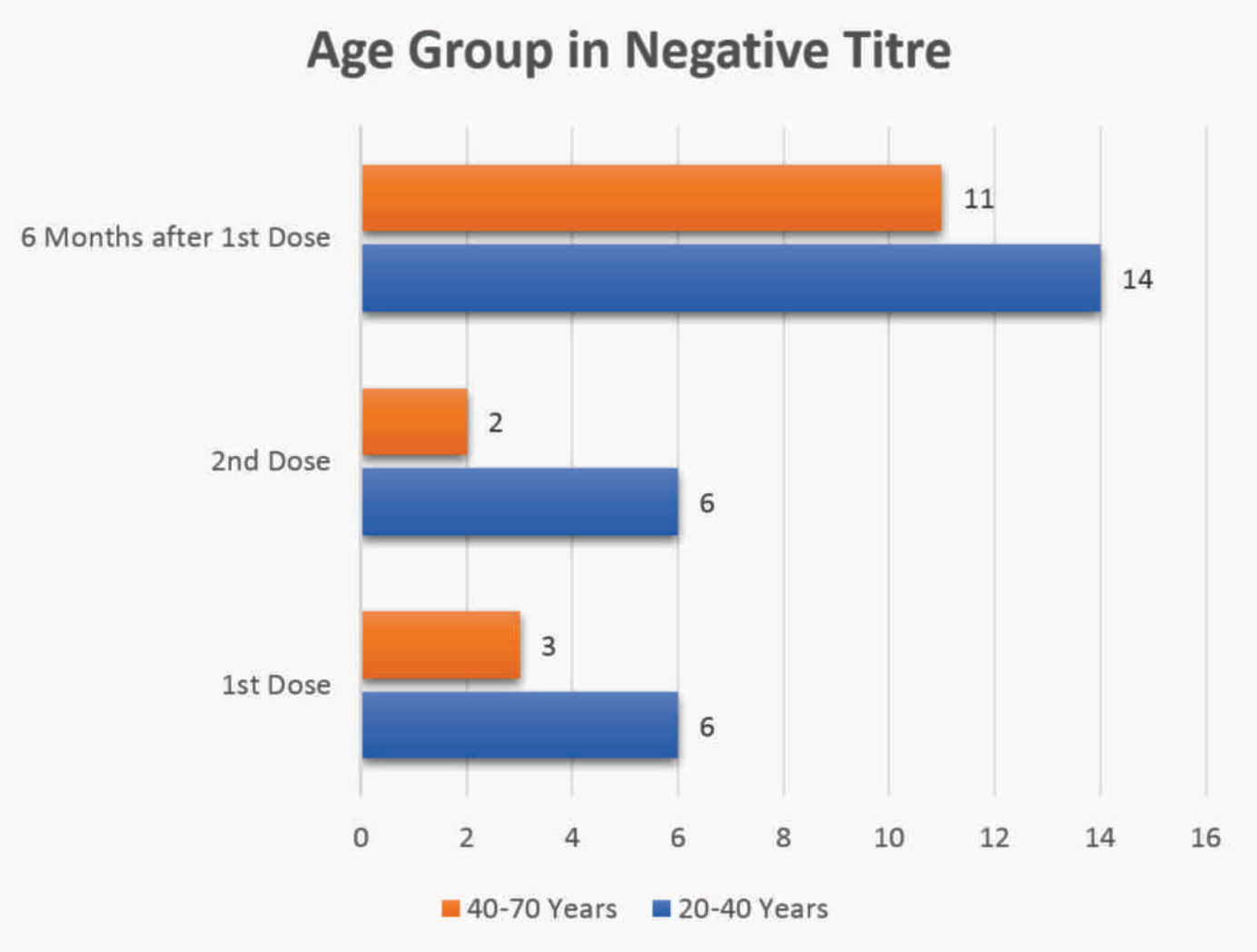


Figure 6: Age Distribution in antibody negative participants

Positive Response

A total of 131 (81%) participants had a positive response to the vaccine (Figure 4 and Figure 5) A titre of >1 was considered as positive response. The antibody level was divided into three sub-groups;

- Mild (1-10 Units)
- Moderate (10-20 Units)
- Strong Response (>20 Units).

Total 43 (32%) participants developed a mild response, 13 (9.92%) developed a moderate response, and 75 (57.25%) developed a strong immune response (Figure 7). The highest number of strong response was seen in the Phase 2 (After the 2nd Dose) (Figure 8).

The younger age group (20-40 Years) were amongst the most (51 out of 75) to develop a strong immune response (Figure 9), and the mean IgG level was 9.95, however highest mean was observed in the Phase – II of the study (13.81) (Figure 10).

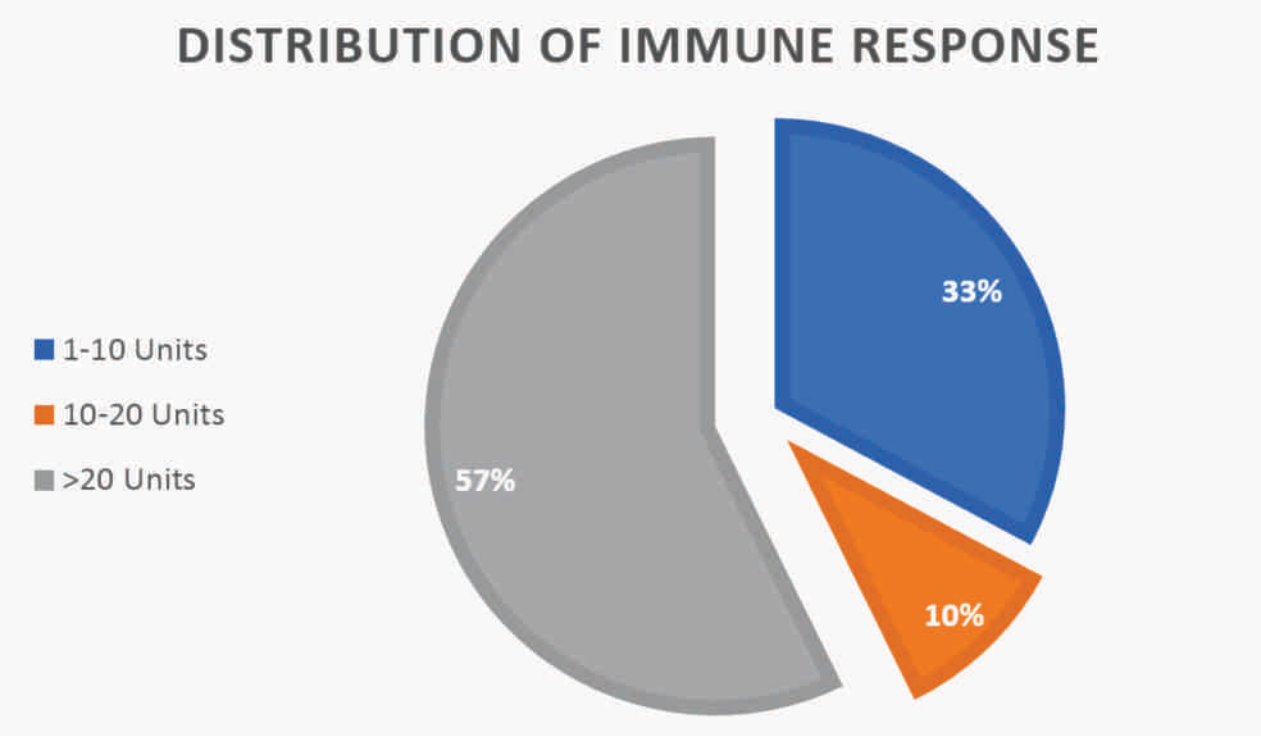


Figure 7: Immune Response amongst positive titre

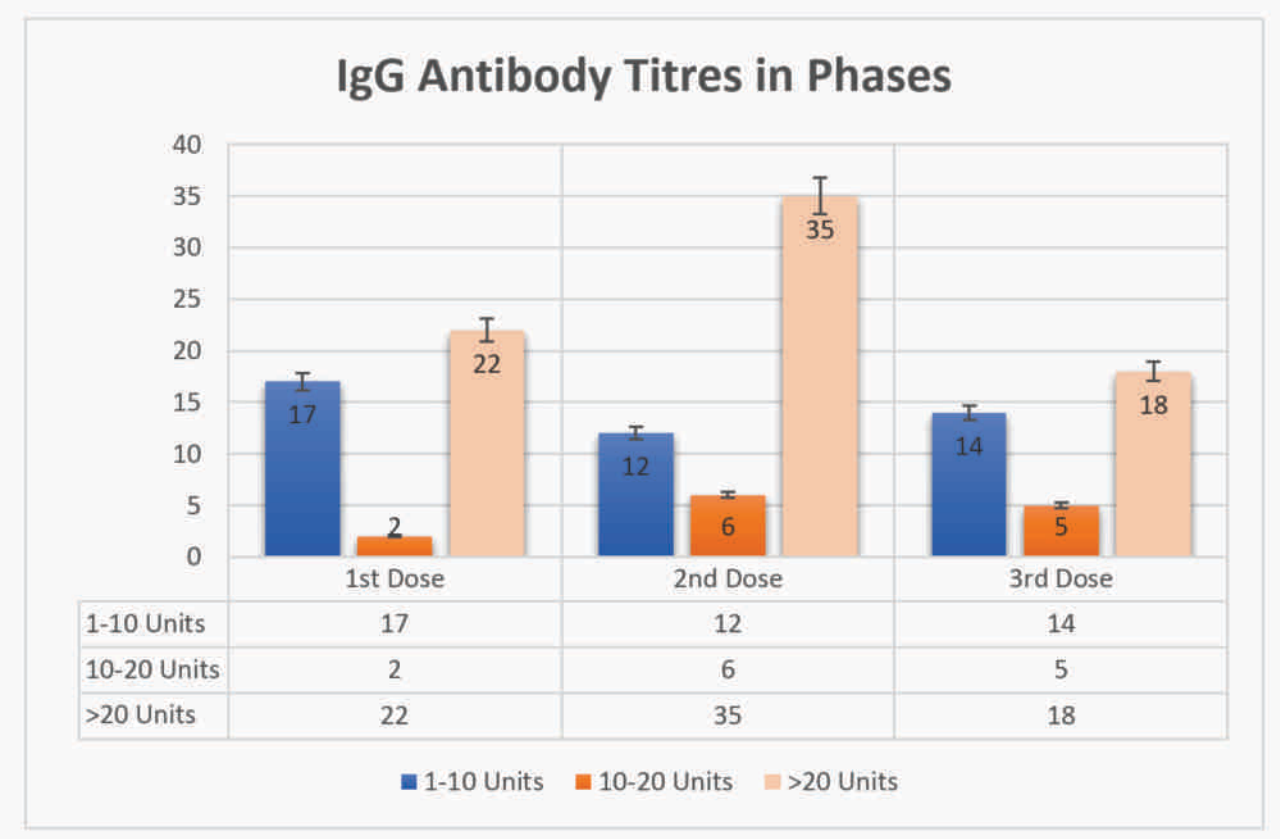


Figure 8: Level of IgG titre in different phases

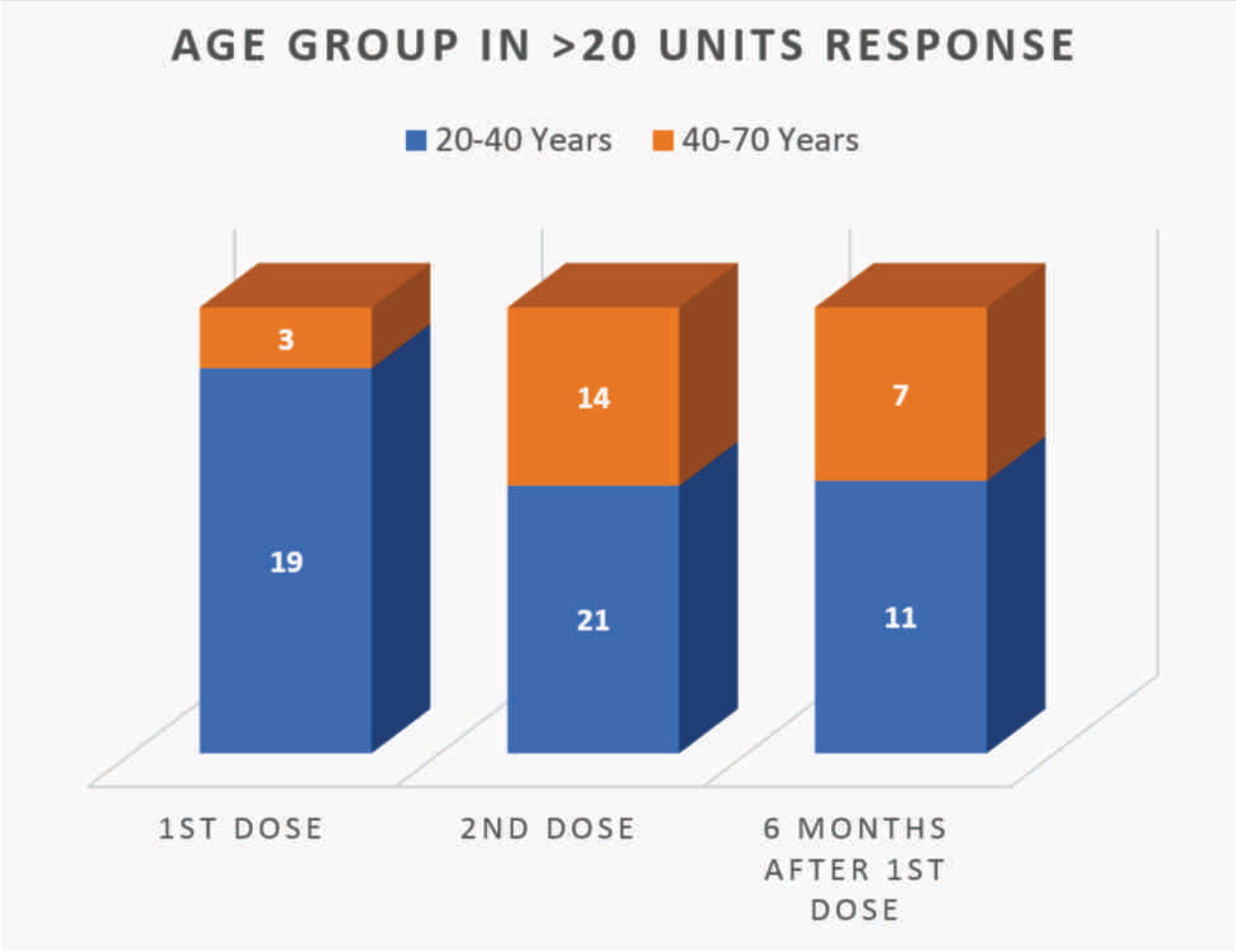


Figure 9: Age distribution in strong response group

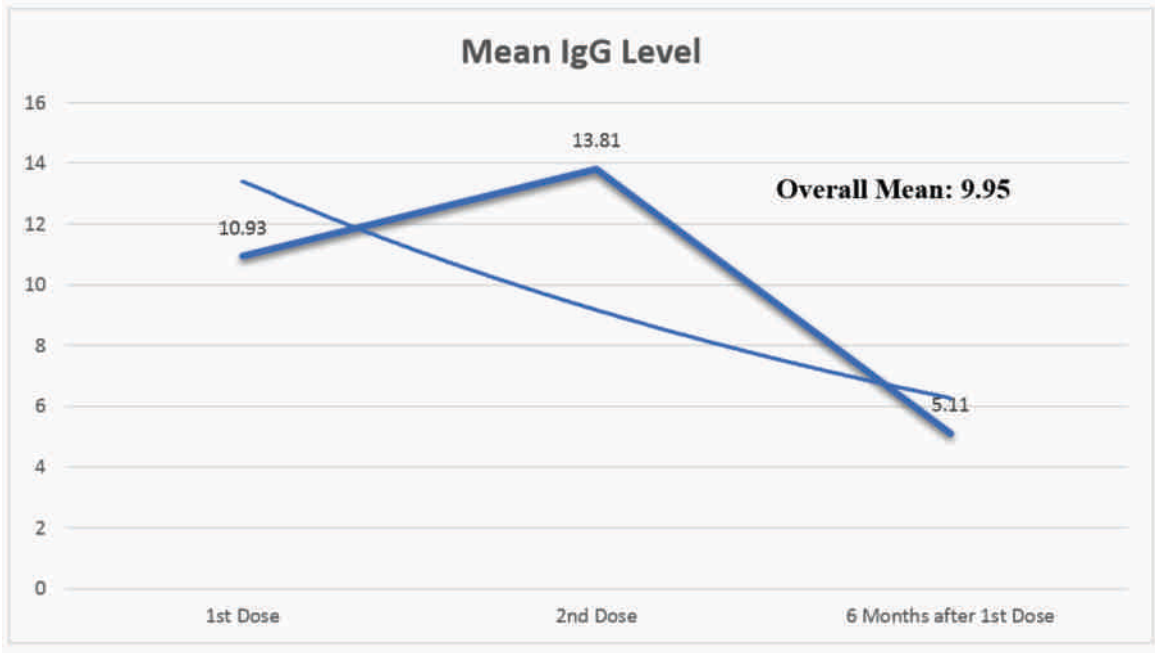


Figure 10: Mean IgG Level

Table 3: Compiled Data

Complete Data					
Data	Variables	1st Dose	2nd Dose	6 Months Interval	Total
Gender	Total	50	61	51	162
	Male	42	50	35	127
	Female	8	11	16	35
Negative Titre	Total	9	8	14	31
	20-40 Years	6	6	11	23
	40-70 Years	3	2	3	8
Positive Titre	Total	41	53	37	131
	1-10 Units	17	12	14	43
	10-20 Units	2	6	5	13
	>20 Units	22	35	18	75
>20 Titre Distribution	20-40 Years	19	21	11	51
	40-70 Years	3	14	7	24
Mean IgG Level		10.93	13.81	5.11	9.95

Analysis for Negative and Positive participants:

- χ^2 Value : 3.75
- P Value (Chi-Squared Test): 0.153
- P Value (Fisher's Exact Test): 0.162

Table 3 depicts the crux of the study, showing general distribution and division of all the participants and their response divided into the Phases of the study.

DISCUSSION

Since the world quickly got engulfed in the deadly flame of the pandemic, the need of a vaccine was probably never this high in the history of mankind. The Astra-Zeneca vaccine was the quickest and the first vaccine to be developed and deployed worldwide including India. Our findings talk about a very interesting but pertinent question that arose along with the Great Indian Vaccination Drive, The decrementing nature of immune response.

Our results for identifying vaccine efficacy (V_E)are purely based on IgG Antibody levels. However, the JIPMER vaccine effectiveness study group[14] tried a different manner to establish V_E, via a Test negative case control study. The manner to evaluate the efficacy was divided in similar phases (After Dose -1 and After Dose -2). The authors used a test – negative case control pairs of 360 patients. Compared to this study, our result was significantly higher (81% positive response overall), however due to variable statistical analysis a formal comparison cannot be made.

Another study from Vellore[15] showed that out of the 7080 fully vaccinated HCWs, 679 developed COVID-19 infection after 47 days of second dose. But the severity and even incidence was much lower in the vaccinated group as compared to non-vaccinated individuals.

However, the reason for higher percentage of positive response in our study cannot be attributed to a single cause. Probably it can be due to recruitment of apparently healthy individuals, and participants who were not previously infected with COVID-19. However, in stark contrast, a study done in Malawi16showed almost 2-3-fold rise in IgG antibody levels after a single shot AstraZeneca vaccine following a mild COVID-19 infection.

As seen in *Figure 5* the vaccine induced a good immune response upon administration of first dose, where 41 out of 50 (82%) had positive titre, and this result rose even further upon 2nd dose and 86.8% participants had a positive response. However, as time passed the immunity reduced exponentially, when 6 months after the 1st dose of vaccine, positive titre was seen in only 72.5% of the participants, which is even lesser than in the first phase.

Parallel studies have shown similar findings that the vaccine effects do actually wane, especially against moderate to severe infections of COVID 19 in a 6-9 months time frame[17]. A North Carolina study[18] saw a substantial decline in vaccine effectiveness after 5 months of the initial dose, they commented that the waning of efficacy can be because of decremental immunity and also emergence of new mutated variants of the virus (E.g. Delta, Omicron).

However, those who did not develop any immune response at all were predominantly in the 20-40 years of age group (Figure 6). This is in contrast of a general consensus that the vaccine effectiveness is inversely proportional to age[19].

Amongst the participants who developed a positive IgG titre, a major percentage (57.25%) of them had a strong response (Tire >20 Units). This shows that COVISHIELD vaccine is quite effective in developing sufficient immunity and preventing severe disease. The highest number of participants having >20 Units of Titre were in the Phase – 2 of the study (35/61), and the lowest was in the third phase (18/51). The waning immunity again comes into play here. The age group to develop a strong response was again the younger (20-40 Years) bracket. The mean IgG level showed a triangular response with titre being the highest (13.81) in the second phase and lowest (5.11) in the third phase.

The waning immunity of the vaccine shows an ardent need of a booster dosing. At the time of our study, no such booster dose provisions were available, although published data shows similar conclusion and an appeal for a booster vaccination is called upon worldwide. Studies are being done to pin-point the timing for administration of a prime booster. The results are more encouraging to prime a booster at least after 12 weeks interval for dramatically better results[13].The numbers show that vaccine effectiveness for booster doses after the primary vaccination is in the high 90%, and no significant adverse reactions are seen[20].

The declining mean titre levels along with lowest positive response in Phase – III, require us to bat an eye for a booster dose. This numbers could prove beneficial in overcoming Vaccine hesitancy and vaccine denial. Wheeler SE *et al.*[21] studied that even in COVID -19 recovered individuals, the IgG against the Spike protein shows a decline after no booster priming. In that study similar to our findings, IgG titre had its peak after the 2nd Dose and had a statistically significant decline after 75 days. Again, a moderate decline was seen in RBD spike protein antibody after 8 months of infection and/or vaccination. However, following an infection the immune memory generated is quite substantial and remains significant till around 6 months[22].

We observed no significant adverse reaction to the vaccine, and around 81% of participants developed a positive response. Hence, COVISHIELD is effective in developing immunity against COVID-19.

Despite this there are some key limitations in our study. Our study population is extremely specific and consisting all healthy individuals. People with managed or unmanaged comorbidities have had a worse outcome of COVID-10 infection and that can trickle down to vaccine effectiveness as well. We have only tested for S1 RBD IgG for the spike protein, there can be extremely varied but ultimately effective immune response which may not pertain to Spike protein alone[21]. We have excluded previously infected COVID – 19 and also dropped those who caught the infection midway of the study. And the vaccine has proven to generate substantial response after administering following a mild infection[16].

CONCLUSION

Regardless of the shortcomings or lack of data thereof, our study shows a steep decline in vaccine derived immunity against COVID-19 with increasing time. As with all viral vaccines, during an outbreak or with time there is a great need for a booster immunisation. Two doses are simply not enough, and it can lead to another catastrophic wave of the pandemic with countless loss of human life. Booster immunisation may not curb the rapid spread, but it has proven that vaccines do help in keeping the infections mild, manageable at home. Thus in turn not stressing the healthcare system, leaving the vital resources free and at bay to help the severe infections effectively and reducing the disease impact on morbidity and mortality.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

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