Reduced neutralizing antibody response in naïve Covishield vaccinees against Omicron emphasizes booster vaccination

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Letter to editor

Reduced neutralizing antibody response in naïve Covishield vaccinees against Omicron emphasizes booster vaccination

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Running title: Neutralizing antibody response in Covishield vaccinees against Omicron

Highlights

- Immune response was assessed in the sera of Covishield vaccinees
- IgG response in naïve vaccinees was lesser than recovered and breakthrough cases
- Neutralizing antibody titre for naïve vaccinees was lowest with Omicron
- Breakthrough cases demonstrated highest neutralizing antibody titre with Omicron
- The study demonstrated need for booster dose in naïve vaccinees

Dear Editor,

In this journal, Yang *et al.,* demonstrated significant increase in neutralizing antibody response against Alpha, Beta, Gamma, Delta and Omicron variant post homologous booster vaccination of BBIBP-CorV.[1] Many studies have proven the importance of regular and booster vaccination in protecting the human population from serious disease and mortality from SARS-CoV-2. India has severely affected with emerging SARS-CoV-2 Variants of Concern (VOCs) during several waves of the COVID-19 pandemic. In fight against SARS-CoV-2, India has initiated national COVID-19 vaccination program on 16 January 2021. A major part of the population in India have been administered with the first/second dose of Covishield vaccine (1,51,12,99,993). However, small population has received the first/second dose of Covaxin, an indigenously developed inactivated vaccine (30,69,67,102). Even with the high vaccination coverage in the country, large number of the breakthrough cases were reported and created hesitancy for vaccination. The waning

immune response post vaccination is the probable cause and important factor associated with these breakthrough infections.

The recently emerged highly transmissible SARS-CoV-2 Omicron variant has also caused exponential rise in Covid-19 cases with breakthrough infection and re-infection worldwide including India.[2-5] The Omicron variant have been evolved into 21 sub lineages namely BA.1, BA.1.1, BA.1.2, BA.1.3, BA.1.4, BA.1.5, BA.1.6, BA.1.7, BA.1.8, BA.1.9, BA.1.10, BA.1.12, BA.1.13, BA.1.13.1, BA.1.14, BA.1.15, BA.2, BA.3. These sub lineages have been detected from 164 countries and BA.1.1 and BA.2 found to be dominating the other sub lineages of Omicron.[6] Recently, the World health organization has also warned about XE variant which is mutant hybrid of BA.1 and BA.2. The Omicron has also altered pathogenesis due to change in cellular tropism which could be the reason for the milder disease.[7] It has been reported that the Omicron variant significantly evades immune response generated with therapeutic monoclonal antibodies and the vaccine-elicited neutralizing antibodies after two doses of COVID-19 vaccine.[8] Andrews and Rossler et al., demonstrated limited protection against severe disease caused by the Omicron variant in individuals vaccinated with two doses of ChAdOx1 nCoV-19.[9-10] Besides this, few studies have also reported reduced neutralization of Omicron variant with the sera of ChAdOx1 nCoV-19 vaccinees.[11-12] Apparently, it has been found that the booster dose of mRNA vaccine boosts the immune response which protects against Omicron but immunity wanes over time.[13]

Globally, various research groups are studying the vaccine effectiveness against the VOCs and the rate of breakthrough post vaccination. Here, we report the IgG and neutralizing antibody response in individuals vaccinated with two doses of Covishield vaccine against B.1, Delta, Beta and Omicron variant.

Briefly, the sera were collected from COVID-19 naïve individuals vaccinated with two doses of Covishield (n=24; 180 days post second vaccination), COVID-19 recovered cases vaccinated with two doses of Covishield (n=17; 180 days post second vaccination) and individuals with SARS-CoV-2 breakthrough infection post vaccination with two doses of Covishield (n=46; 14-30 days post infection). All the recovered cases (n=17) were infected with prototype B.1 variant. Of the 46 breakthrough cases, complete genome could be retrieved only from 21 cases. Seventeen cases were found to be affected with Delta variant, while four with Kappa variant. All the serum samples were screened for IgG antibodies using S1-RBD and N-protein ELISA. Besides this, the neutralization potential of these sera was assessed against B.1, Delta, Beta and Omicron variant with plaque reduction neutralization test (PRNT).

The geometrical mean titre (GMT) of IgG antibodies with S1-RBD ELISA was lesser in naïve vaccinees (147.5; 95% CI: 92.4–235.4) compared to the recovered cases (634.2; 95% CI: 406.1–990.6) and breakthrough cases (1683; 95% CI: 1119–2553). Similar decreasing trend in GMT titres was observed with N protein ELISA for naïve vaccinees (77.2; 95% CI: 55.1–109.6) with respect to recovered cases (112.1; 95% CI: 69.9–179.9) and breakthrough infection (594.1; 95% CI: 349.9–1009) (Figure 1 A-B).

Neutralization studies demonstrated reduction in the GMT titre of neutralizing antibodies (NAb) against Omicron with sera of naïve vaccinees (32.81-fold; 95% CI: 14.7–

73.2), recovered cases (28.13-fold; 95% CI: 75.9–10.4) and breakthrough cases (46.86-fold; 95% CI: 74.1–29.6) compared to prototype B.1 variant. All the three groups effectively neutralized the B.1, Beta and Delta variants than Omicron (Figure 2 A-G). The GMT titre of NAb was lowest for Omicron with the sera of naïve vaccinees (0.11; 95% CI: 0.07–0.19) than the recovered cases (11.28; 95% CI: 2.63–51.1) and breakthrough cases (26.25; 95% CI: 8.5–81.4) (Figure 2 G). With highest mutations in spike region, omicron variant clearly showed immune escape against respective neutralizing antibodies induced with Delta variant infection in breakthrough cases than B.1, Delta and Beta variant. Even though highest fold-reduction amongst breakthrough cases was observed with Omicron variant, it also had highest NAb titre than the recovered cases and naïve vaccinees. Breakthrough cases also represented maximum NAb response against all the variants than naïve vaccines and recovered cases.

Despite the fact that vaccines are effective against severe SARS-CoV-2 infection, many breakthrough and re-infection cases were observed during the pandemic. The shifting paradigm would be mainly due to the reducing/waning immune responses post either natural infection or vaccinations, emergence of the new SARS-CoV-2 variant and its immune escape potential. In summary, our study demonstrated lowest IgG and NAb response in naïve vaccinees than other groups. This emphasizes the waning immune response in naïve vaccinees post second dose and warrants the administration of precautionary dose to boost the immunity.

Conflicts of Interest

Authors do not have a conflict of interest among themselves.

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Legends to figures

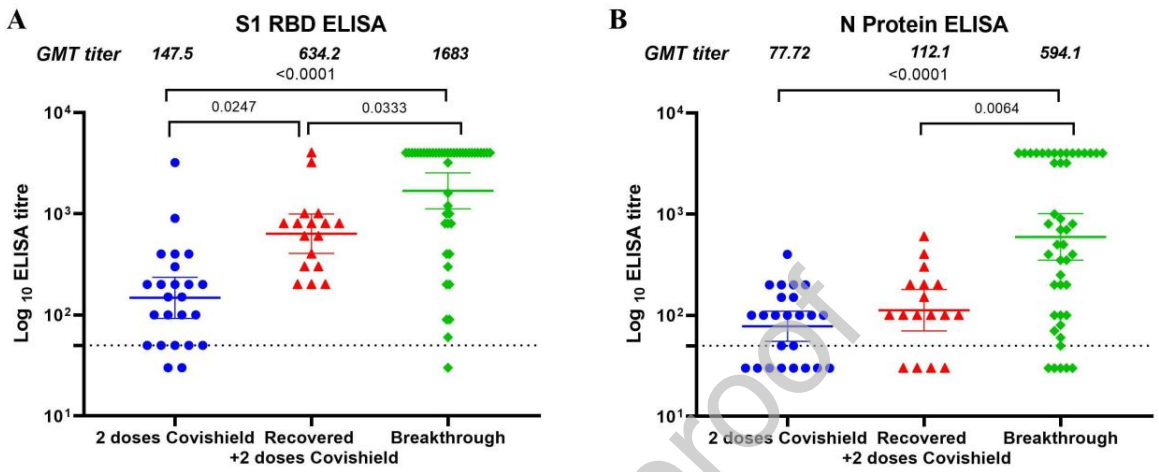

Figure 1. Anti SARS-CoV-2 IgG antibody response in sera of individuals vaccinated with two doses of Covishield (blue), recovered cases with Covishield vaccination (red) and breakthrough cases with Covishield vaccination (green) (A) IgG antibody response with S1-RBD ELISA (B) IgG antibody response with N protein ELISA. A two-tailed pair-wise comparison was performed using the Kruskal Wallis test with a p-value of 0.05. The dotted line on the figures indicates the limit of detection of the assay. Data are presented as geometric mean titer values with 95% confidence interval.

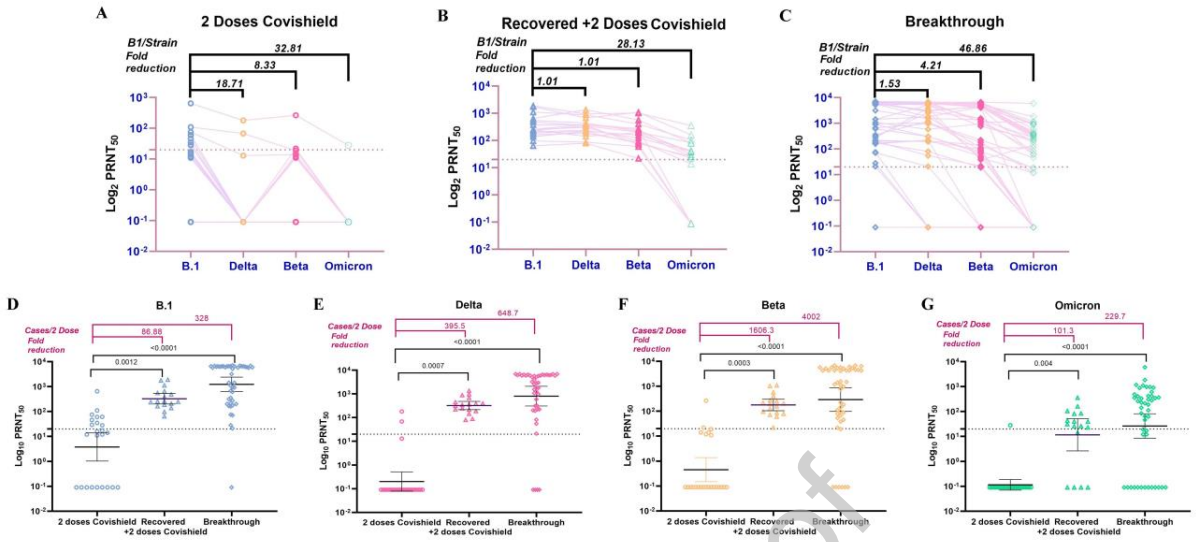

Figure 2. Neutralizing antibody (NAb) response in sera of individuals vaccinated with (A) two doses of Covishield; (B) recovered cases with Covishield vaccination and (C) breakthrough cases with Covishield vaccination against Delta, Beta and Omicron variants compared to B.1. NAb tires in three groups against B.1, Delta, Beta, Omicron variants with respect to vaccinated individuals with two doses. A two-tailed pair-wise comparison was performed using the Kruskal Wallis test with a p-value of 0.05. The dotted line on the figures indicates the limit of detection of the assay. Data are presented as geometric mean titer values with 95% confidence interval.