Previously infected vaccinees broadly neutralize SARS-CoV-2 variants

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Abstract

We compared the serum neutralizing antibody titers before and after two doses of the BNT162b2 COVID-19 vaccine in ten individuals who recovered from SARS-CoV-2 infection prior to vaccination to 20 individuals with no history of infection, against clinical isolates of B.1.1.7, B.1.351, P.1, and the original SARS-CoV-2 virus. Vaccination boosted pre-existing levels of anti-SARS-CoV-2 spike antibodies 10-fold in previously infected individuals, but not to levels significantly higher than those of uninfected vaccinees. However, neutralizing antibody titers increased in previously infected vaccinees relative to uninfected vaccinees against every variant tested: 5.2-fold against B.1.1.7, 6.5-fold against B.1.351, 4.3-fold against P.1, and 3.4-fold against original SARS-CoV-2. Our study indicates that a first-generation COVID-19 vaccine provides broad protection from SARS-CoV-2variants in individuals with previous infection.

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44 In recent months, multiple coronavirus disease 2019 (COVID-19) vaccine candidates have
45 successfully concluded phase 3 trials[1], with the three candidates authorized for emergency
46 use by the U.S. Food and Drug Administration reporting efficacies of 95% (BNT162b2
47 [Pfizer-BioNTech]), 94% (mRNA-1273 [Moderna]), and 66% (Ad26.COV2.S [Janssen])[2-4].
48 When combined with the substantial portion of many communities estimated to have
49 gained natural immunity through infection with severe acute respiratory syndrome
50 coronavirus 2 (SARS-CoV-2)[5], the rollout of safe and effective vaccines has raised the
51 possibility that high levels of population immunity could soon be reached. Clouding this
52 prospect is the emergence and global spread of SARS-CoV-2 variants of concern (VOCs),
53 such as those first identified in the United Kingdom (lineage B.1.1.7)[6], South Africa
54 (B.1.351)[7], Brazil (P.1)[8], and California (B.1.429)[9]. Most VOCs possess partially
55 overlapping combinations of spike mutations that enhance binding to the SARS-CoV-2
56 cellular receptor angiotensin-converting enzyme 2 (ACE2), increasing transmissibility[10]
57 (Supplementary Table 1). More concerning has been the emergence of spike mutations
58 with the potential to escape neutralizing antibodies raised against earlier lineages of
59 SARS-CoV-2 through infection with an original linage or by first-generation COVID-19
60 vaccines[11-13]. Recent population studies have validated these findings, showing surges of
61 reinfections in regions with extensive transmission of B.1.35[17,14] and P.1[8], and large
62 declines in vaccine efficacy against B.1.351[14-16].

63 To investigate whether vaccination of individuals previously infected by SARS-CoV-2
64 confers greater protection from VOCs than vaccination of individuals with no evidence of

previous infection, in a cohort of BNT162b2 vaccinees (Supplementary Table 2) we identified a group of 10 study participants who had received a positive COVID-19 PCR test result prior to vaccination, along with an age- and sex-balanced group of 20 participants who had not. While vaccination of previously infected individuals boosted the 50% maximal effective concentration (EC50) of antibodies against the immunodominant SARS-CoV-2 spike receptor-binding domain (RBD) ten-fold (pre-vaccination geometric mean titer [GMT], 82.15; post-vaccination GMT, 823.3), the vaccine-elicited antibody titers of uninfected individuals (GMT, 699.5) were not significantly lower (Fig. 1A). Similarly, post-vaccination levels of RBD-binding IgG (Fig. 1B) and IgA (Fig. 1C) did not differ significantly between the two groups.

We then measured the pre- and post-vaccination neutralizing activity of the two groups of sera against an early SARS-CoV-2 isolate (USA-WA1/2020) and isolates of B.1.1.7, B.1.351, and P.1 (Fig. 2). Pre-vaccination sera from previously infected participants provided higher levels of neutralization against USA-WA1/2020 (GMT, 39.0) than against the three VOCs (GMT, 25.7 for B.1.1.7; GMT<20 for B.1.351; GMT, 31.2 for P.1), consistent with previous reports of convalescent sera[12,17]. Similarly, post-vaccination sera from uninfected participants showed greater neutralization of USA-WA1/2020 than of the VOCs (GMT, 578.6 for USA-WA1/2020; 223.0 for B.1.1.7; 47.5 for B.1.351; 171.9 for P.1). However, post-vaccination serum from previously infected individuals possessed significantly higher neutralizing activity against every SARS-CoV-2 lineage relative to post-vaccination serum from uninfected participants: neutralizing antibody titers increased by a factor of 3.5 against USA-WA1/2020 (95% confidence interval [CI], 2.8 to 4.0); by a factor of 5.2 against B.1.1.7 (95% CI, 2.37 to 9.8); by a factor of 6.5 against B.1.351 (95% CI, 3.4 to 12.3); and by a factor of 4.3 against P.1 (95% CI, 2.8 to 6.5). Notably, there was no

significant difference (P=0.2736, Wilcoxon rank-sum test) between the post-vaccination neutralizing antibody titers of previously infected participants against B.1.351 (GMT, 307.3; 95% CI, 91.0 to 1038) and those of uninfected participants against USA-WA1/2020 (GMT, 578.6; GMT, 332.5 to 1007), suggesting that first-generation COVID-19 vaccines could retain near-complete efficacy against even the most resistant VOCs when administered following natural infection.

Overall, our findings provide important evidence for broad and potent neutralizing antibody responses against emerging SARS-CoV-2 variants, even with exposure to only wildtype SARS- CoV-2 antigen. This reinforces a recent report that natural infection with B.1.351 elicits a similar cross-reactive neutralizing antibody response against B.1.351, P.1, and original SARS-CoV-2[18]. While these and other laboratory results must be validated by ongoing population-level studies, they indicate a novel role for COVID-19 vaccines in protecting hard-hit populations from future waves of the pandemic.