Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

COVID-19 vaccination and booster induced authentic-virus neutralizing antibody response is superior to SARS-CoV-2 natural infection induced response

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Understanding of antibody responses to SARS-CoV-2 natural infection (NI) and/or vaccination is constantly evolving, with most researchers reporting waning immune responses between six to eleven months [1–4]. Studies have previously investigated antibody kinetics following COVID-19 and/or vaccination in various cohorts and at different periods during the pandemic. However, these studies have primarily relied on binding antibody responses, or pseudovirus-based neutralization assays, rather than authentic-virus neutralization assays evaluating functional antibody responses. Here we characterize neutralizing antibody (NAb) responses using authentic-virus plaque reduction neutralization test (PRNT) among individuals with SARS-CoV-2 NI and/or vaccination.

A total of 449 blood samples were collected from 222 human subjects after obtaining informed consent between July 2020 and December 2021 in Honolulu, Hawaii, USA (IRB#2020-00406). An additional 44 de-identified blood samples were collected from individuals with history of SARS-CoV-2 NI (Table 1).

PRNTs were conducted as previously described using the SARS-CoV-2 isolate USA-WA1/2020 [5]. Sigmoidal-dose-response-logistic-regression model was used to determine PRNT titers at 50% neutralization. All calculations were conducted using GraphPad(v9.0).

Functional neutralization assay, expressed as median NAb titers and IQR, revealed significantly lower titers among individuals with history of NI alone (608, IQR:241-1,256) compared to NAb titers among individuals with history of NI after at least one dose of COVID-19 vaccination (5,347, IQR:1,433-12,723; $p<0.001$) or individuals without history of NI after complete COVID-19 vaccination (1,766, IQR:606-4,219; $p<0.001$). History of previous SARS-CoV-2 NI provided a moderate increase in NAb titers compared to that among SARS-CoV-2 naive individuals following complete COVID-19 vaccination ($p=0.033$). NAb titers after two dose COVID-19 vaccination series were significantly higher (3,785, IQR:1,837-6,770; $p<0.001$) than after one dose (310, IQR:93-588), which was further enhanced following booster dose (16,715, IQR:6,671-33,930; $p<0.001$) (Fig. 1A). Longitudinal analysis following SARS-CoV-2 NI revealed that NAb titers declined most dramatically within the first six weeks (851 at two weeks vs. 341 at six weeks) after NI. Longitudinal analysis in COVID-19 vaccinated individuals without history of NI showed the largest decline in NAb titers at three- and six-months following completion of primary vaccination (3,785 at two weeks vs. 627 at three months, $p<0.001$; 557 at six months, $p<0.001$), which was restored after booster dose administration ($p<0.001$) (Fig. 1B). Similar findings were observed in the longitudinal cohort analysis among individuals for which multiple blood draws were obtained (Fig. 1C).

Based on functional neutralization assay, we report **(i)** potent COVID-19 vaccine-induced NAb responses are superior to responses following NI ($p<0.001$); **(ii)** NI followed by vaccination has a modest advantage in NAb levels when compared to administration of two-dose vaccine series ($p=0.033$); **(iii)** NAb responses decline at three- and six-months following the second dose of COVID-19 vaccine ($p<0.001$); and **(iv)** NAb responses are restored within two weeks following booster dose of COVID-19 vaccine ($p<0.001$). SARS-CoV-2 antibody responses characterized in this and other studies are similar to those observed following common cold coronavirus infection, which produces waning antibody responses that results in frequent re-infection [6]. These data paired with morbidity and mortality data associated with the onslaught of new SARS-CoV-2 variants will help guide the administration of future booster vaccination.

Abbreviations: NAb, neutralizing antibodies; NI, naturally infected; PRNT, plaque reduction neutralization test.

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Table 1
Clinicoepidemological characteristics of individuals with a history of SARS-CoV-2 natural infection and/or COVID-19 vaccination.

	NI (n = 125)			VX (n = 129)		
De-Identified[a]	n =	44	(35%)	—		
	NI (n = 81)			VX (n = 129)		
Gender						
Male	n =	35	(43%)	n =	54	(42%)
Female	n =	46	(57%)	n =	75	(58%)
Age in years						
Mean ± SD (range)	47.35 ± 15.78 (20 - 83)			44.86 ± 19.45 (20 - 85)		
Median (IQR)	48.00 (34.50 - 59.25)			40.00 (27.00 - 60.00)		
Days Post Symptom Onset[b]						
	n =	67	(83%)	—		
Mean ± SD (range)	122.51 ± 125.24 (13 - 558)			—		
Median (IQR)	75.00 (24.00 - 175.50)			—		
Days Post SARS-CoV-2 PCR Positivity[b]						
	n =	64	(79%)	—		
Mean ± SD (range)	93.09 ± 84.43 (11 - 348)			—		
Median (IQR)	53.50 (22.00 - 150.75)			—		
COVID-19 Vaccination with and without History of Natural Infection						
	n =	42	(52%)	n =	129	(100%)
Pfizer-BioNTech	n =	28	(67%)	n =	66	(51%)
Moderna	n =	12	(29%)	n =	59	(46%)
J&J/Janssen	n =	2	(5%)	n =	3	(2%)
Days Post COVID-19 Vaccination						
No. Samples	n =	61		n =	271	
Dose 1 (≥ 10 and ≤ 42 days)	n =	20	(33%)	n =	56	(21%)
Mean ± SD (range)	18.60 ± 8.45 (10 - 39)			19.61 ± 6.07 (13 - 41)		
Median (IQR)	15.50 (14.00 - 21.00)			19.00 (14.00 - 23.25)		
Dose 2[c] (≥ 10 days)	n =	41	(67%)	n =	199	(73%)
Mean ± SD (range)	41.88 ± 42.28 (10 - 212)			87.96 ± 81.87 (10 -323)		
Median (IQR)	26.00 (16.00 - 48.00)			47.00 (19.00 - 145.00)		
Dose 3 (≥ 10 days)	n =	0	(0%)	n =	16	(6%)
Mean ± SD (range)	—			32.13 ± 31.05 (13 - 135)		
Median (IQR)	—			20.00 (17.00 - 28.00)		

NI = history of SARS-CoV-2 natural infection; VX = COVID-19 vaccination without a history of SARS-CoV-2 natural infection; SD = standard deviation; IQR = interquartile range. [a]De-identified/anonymized medical waste with clinical history of SARS-CoV-2 natural infection, with no associated clinicoepidemiological data were available. [b]Varied reporting for days post symptom onset and days post PCR positivity due to asymptomatic infection, and lack of access to SARS-CoV-2 testing. [c]Dose 2 = complete COVID-19 vaccinaton, two doses of a Pfizer-BioNTech or Moderna COVID-19 vaccine or one dose of J&J/Janssen COVID-10 vaccine.

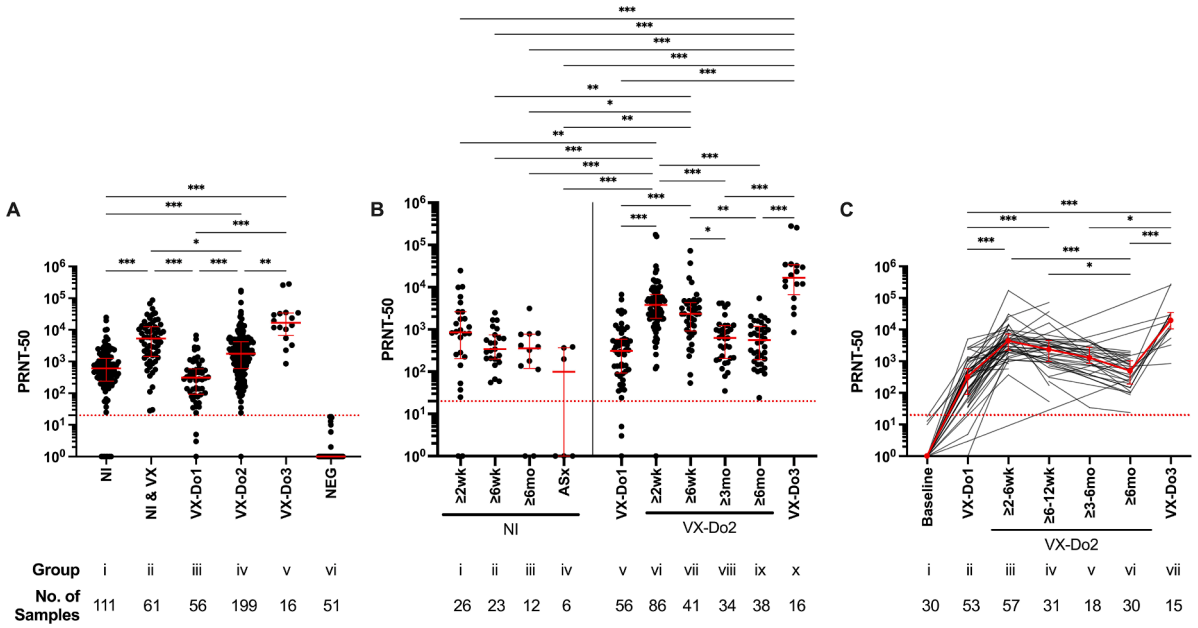

Fig. 1. SARS-CoV-2 PRNT-50 antibody titers. (A) Group comparisons among, i) individuals with a history of SARS-CoV-2 natural infection prior to COVID-19 vaccination (NI); ii) individuals with a history of SARS-CoV-2 natural infection and ≥ 10 days following at least one dose of a COVID-19 vaccine (NI & VX); iii) individuals without a history of SARS-CoV-2 natural infection, ≥ 10 and ≤ 42 days following one dose of a mRNA COVID-19 vaccine (VX-Do1), iv) individuals without a history of SARS-CoV-2 natural infection, ≥ 10 days following two doses/complete COVID-19 vaccination (VX-Do2), v) individuals without a history of SARS-CoV-2 natural infection, ≥ 10 days following booster dose (VX-Do3); and vi) SARS-CoV-2 naïve individuals (NEG). (B) Longitudinal analysis among individuals with a history of SARS-CoV-2 natural infection (left) or COVID-19 vaccination without a history of SARS-CoV-2 natural infection (right). Intervals for the SARS-CoV-2 naturally infected individuals (left) were as follows: i) ≥ 10 days to 6 weeks (NI, ≥ 2wk), ii) ≥ 6 weeks to 6 months (NI, ≥ 6wk), iii) ≥ 6 months (NI, ≥ 6mo) following symptom onset and/or PCR positivity, and iv) asymptomatic SARS-CoV-2 natural infection (ASx). Intervals for the individuals without a history of SARS-CoV-2 natural infection following COVID-19 vaccination (right) were as follows: v) ≥ 10 and ≤ 42 days following one dose of a COVID-19 vaccine (VX-Do1), vi) ≥10 days to 6 weeks (VX-Do2, ≥ 2wk), vii) ≥ 6 weeks to 3 months (VX-Do2, ≥ 6wk), viii) ≥ 3 months to 6 months (VX-Do2, ≥ 3 mo), ix) ≥ 6 months (VX-Do2, ≥ 6 months) following two doses/complete COVID-19 vaccination; and x) with complete COVID-19 vaccination and ≥10 days following booster dose (VX-Do3), without a history of SARS-CoV-2 infection. (C) Longitudinal cohort analysis among the individuals following COVID-19 vaccination without a history of SARS-CoV-2 infection for which multiple blood draws (n = 64) were obtained (two blood draws/collection points, n = 16; three blood draws, n = 22; four blood draws, n = 8; five blood draws, n = 7; six blood draws, n = 8; seven blood draws, n = 3). Samples were collected at i) baseline, ii) ≥ 10 and ≤ 42 days following one dose of a mRNA COVID-19 vaccine (VX-Do1), iii) ≥10 days to 6 weeks (VX-Do2, ≥ 2wk), iv) ≥ 6 weeks to 3 months (VX-Do2, ≥ 6wk), v) ≥ 3 months to 6 months (VX-Do2, ≥ 3mo), vi) ≥ 6 months (VX-Do2, ≥ 6 months) following two doses/complete COVID-19 vaccination; or vii) after complete COVID-19 vaccination and ≥10 days following booster/third dose (VX-Do3). Kruskal-Wallis ANOVA test for non-parametric data was used to evaluate group differences. Dotted red line is the limit of detection of the neutralizing antibody titer (PRNT ≥ 20). *p≤0.033, **p≤0.002, ***p<0.001.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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