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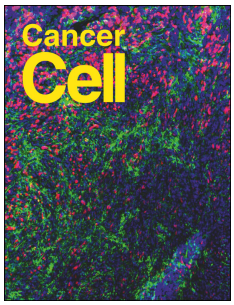

Neutralization breadth of SARS-CoV-2 viral variants following primary series and booster SARS-CoV-2 vaccines in patients with cancer

Vivek Naranbhai, Kerri J. St. Denis, Evan C. Lam, Onosereme Ofoman, Wilfredo-Garcia Beltran, Cristhian Berrios, Atul K. Bhan, Justin F. Gainor, Alejandro B. Balazs, A. John Iafrate, on behalf of the CANVAX team

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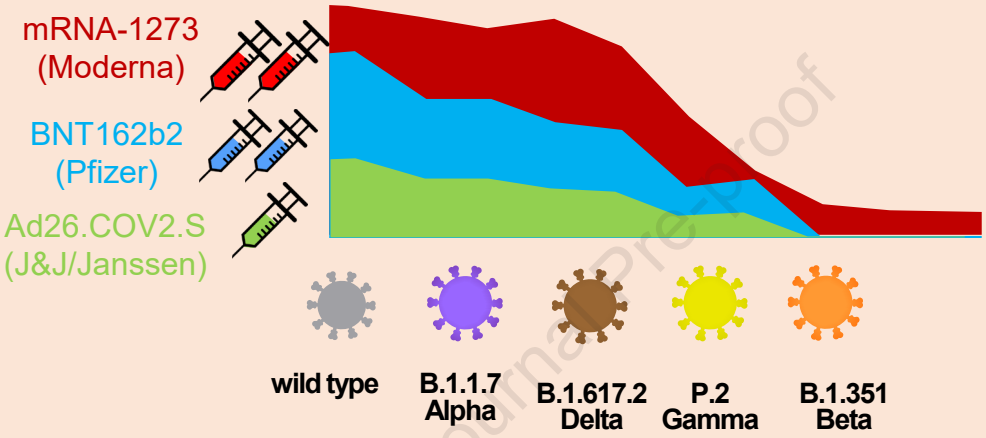
Patients with cancer receiving SARS-CoV-2 vaccines

Substudy of CANVAX cohort study

Pseudovirus neutralization varies by variant and vaccine



Neutralization Breadth * (Number of variants neutralized)

↑ Increases with higher wildtype neutralization

↓ Deceases with older age

↑ Increases with **boosters** (even in individuals with lowest responses)

* predictable by clinically measured serum spike-binding antibodies

REPORT

Neutralization breadth of SARS-CoV-2 viral variants following primary series and booster SARS-CoV-2 vaccines in patients with cancer

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Running header: SARS-CoV-2 vaccines in cancer patients

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Summary (150/150 words)

Patients with cancer are more likely to have impaired immune responses to SARS-CoV-2 vaccines. We study the breadth of responses against SARS-CoV-2 variants followingly primary vaccination in 178 patients with a variety of tumor types, and after booster doses in a subset. Neutralization of alpha, beta, gamma and delta SARS-CoV-2 variants is impaired relative to wildtype, regardless of vaccine type. Regardless of viral variant, mRNA1273 is the most immunogenic, followed by BNT162b2 and then Ad26.COV2.S. Neutralization of more variants (breadth) is associated with higher magnitude of wildtype neutralization, and increases with time since vaccination; increasing age associates with lower breadth. The concentrations of anti-spike protein antibody are a good surrogate for breadth (PPV=90% at >1000U/ml). Booster SARS-CoV-2 vaccines confer enhanced breadth. These data suggest that achieving a high antibody titer is desirable to achieve broad neutralization; a single booster dose with current vaccines increases breadth of responses against variants.

Keywords: SARS-CoV-2, mRNA1273, BNT162b2, Ad26.COV2.S, booster dose, breadth, neutralization, variants

Main text

Introduction

Patients with cancer are at increased risk of severe disease and/or death from severe acute respiratory syndrome coronavirus two (SARS-CoV-2) infection (Bakouny et al., 2020; Kuderer et al., 2020) and vaccination against SARS-CoV-2 is a cornerstone of prevention. The magnitude of anti-SARS-CoV-2 spike protein antibodies, receptor-binding domain (RBD) antibodies and neutralization titer against wildtype SARS-CoV-2 are robust correlates of vaccine-mediated protection (Earle et al., 2021; Khoury et al., 2021), but are not sufficiently validated for use clinically. In the Cancer, COVID and Vaccination study (CANVAX) of more than 750 patients with cancer, we observed lower humoral immune responses than in non-cancer controls (Naranbhai et al., 2021a), consistent with findings from other cohorts (Addeo et al., 2021; Bird et al., 2021; Van Oekelen et al., 2021; Thakkar et al., 2021). In both non-cancer controls and patients with cancer, the magnitude of response was strongly associated with prior SARS-CoV-2 infection and vaccine type: mRNA1273 was the most immunogenic followed by BNT162b2. Both mRNA vaccines were markedly more immunogenic than Ad26.COV2.S. Finally, booster vaccines were able to overcome poor responses in CANVAX (Naranbhai et al., 2021a) and other studies (Greenberger et al., 2021; Shapiro et al., 2021).

Evolution of SARS-CoV-2 variants with mutations that confer higher transmissibility or evasion of immune responses pose an ongoing threat, as exemplified by the rapid rise of the delta variant to global dominance during 2021. We, and others, have previously observed marked variation of *in vitro* neutralization of viral variants in healthy individuals (Garcia-Beltran et al., 2021a; Tada et al., 2021). There are few robust data regarding the degree of protection against each variant following different vaccines in immunocompromised patients, but the frequency of breakthrough infection resulting in hospitalization appears to be markedly higher for immunocompromised patients than in the general population, highlighting the impact of lower immunogenicity and higher risk of severe disease (Hippisley-Cox et al., 2021). Based on these and other data, additional 'booster' vaccine doses have been recommended for immunocompromised patients in many developed countries. Whilst these vaccine

increase the magnitude of response (Greenberger et al., 2021; Shapiro et al., 2021), whether homologous (i.e. wildtype strain based) 'booster' doses enhance the breadth of protection against variants is uncertain (Cho et al., 2021).

Here, we examine the magnitude and breadth of neutralization of SARS-CoV-2 variants following the primary series, and after booster doses of vaccination in patients with cancer who received one of the SARS-CoV-2 Federal Drug Administration (FDA) Emergency Use Authorized (EUA) vaccines in the United States.

Results

The CANVAX study is an ongoing prospective cohort study of SARS-CoV-2 vaccines in patients with cancer. For this report, we selected 178 participants of CANVAX without prior SARS-CoV-2 infection who were sampled >=14 days after vaccination stratifying by vaccine type: 58 mRNA1273 (Moderna), 60 BNT162b2 (Pfizer/BioNTech) and 60 Ad26.COV2S (J&J/Janssen). The baseline participant characteristics known to affect immunogenicity are shown according to vaccine type in **Table 1**, and recapitulate those of the overall CANVAX study: Ad26.COV2.S recipients were slightly older but the sex, cancer type, and therapy types were similar between groups.

Neutralization of alpha, beta, gamma and delta SARS-CoV-2 variants is impaired in vaccine recipients

We assessed *in vitro* neutralization of wildtype SARS-CoV-2 (ancestral strain) and four viral variants (alpha, beta, delta and gamma strains) using an extensively validated high-throughput pseudovirus neutralization assay (Garcia-Beltran et al., 2021a, 2021b). These variants represent recent waves of the pandemic, and harbor both shared and distinct mutations (Table S1) that are targeted by immune responses induced by vaccination with current vaccines, which all encode wildtype SARS-CoV-2 spike protein. We quantified the serum pseudovirus neutralization titer (pNT50) associated with 50% reduction in viral entry into ACE2-expressing 293T-cells.

Consistent with the overall CANVAX population and other studies (Naranbhai et al., 2021b; Tada et al., 2021), neutralization of wildtype SARS-CoV-2 was highest for

mRNA1273 recipients, followed by BNT162b2 and lowest amongst Ad26.COV2.S recipients. Adjusting for covariates, neutralization was lower among BNT162b2 recipients than mRNA1273 for alpha, gamma and delta variants (Figure 1 and Table S2).

We observed marked and significantly neutralization of alpha, beta, delta and gamma variants for most vaccine groups (Figure 1). The differences were most striking for the beta variant, where fewer than half of all evaluated donors (41% of mRNA1273, 30% of BNT162b and 18% of Ad26.COV2.S recipients) had neutralization measurable above the assay limit of detection. Few patients with cancer in this study had measurable neutralization against wildtype SARS-CoV-2 and the four variants tested following receipt of Ad26.COV2.S were 43% against wildtype, 30% against alpha, 18% against beta, 12% against gamma and 15% against delta.

Neutralization breadth is associated with wildtype neutralization titer, time since vaccination and is reduced with age

Next, we sought to identify correlates of vaccine breadth. In multivariate regression, the magnitude of neutralization of wildtype SARS-CoV-2 was the strongest correlate of breadth (effect estimate 1.4 additional variants neutralized per $\log_{10}$ increase in neutralization titer, 95% CI 1.1:1.6, adjusted p<0.001; **Table 2**). Vaccine type did not independently associate with breadth of neutralization (p>0.1 for each vaccine). Older age was associated with narrower breadth of response (effect estimate per 5 year increase in age -0.09, 95% CI -0.17:-0.01, adjusted p=0.029) . Breadth of response tended to increase with time after vaccination, even adjusting for the expected initial increase and later waning in the magnitude of response (effect estimate per week after vaccination 0.04, 95% CI 0:0.08, adjusted p=0.061).

Anti-spike binding antibody concentrations are a surrogate for breadth

We measured total binding antibodies against SARS-CoV-2 spike protein (combined IgA/M/G) with Roche Elecsys assay (FDA & EUA approved) and specific isotypes (IgA, IgG, IgM and combined IgA/M/G) of antibodies binding the receptor-binding domain (RBD) with a validated assay we previously developed (Garcia-Beltran et al., 2021a).

Anti-RBD responses were dominated by IgG isotype responses, and responses varied by vaccine as previously reported (Figure S1). Wildtype neutralization was more robustly correlated with anti-RBD concentrations (Pearson R=0.63, 95% CI 0.53-0.71, p<0.001) than overall anti-spike responses (Pearson R=0.53, 95% CI 0.41-0.63, p<0.001) but both correlations were modest (Figure S2). A response comprised of more isotypes was not associated with greater breadth after adjusting for neutralization titer against wildtype virus as having a more isotype diverse response was associated with neutralization titer (p<0.001), as in other studies (Noval et al., 2021).

Anti-spike IgA/M/G total antibodies are easily measured in clinical practice, whereas neutralization is not. An anti-spike IgA/G/M titer >1000 U/ml on the Roche Elecsys FDA EUA assay was predictive of neutralization breadth (positive predictive value for neutralization of >2 variants at a titer >20 90%, negative predictive value 88%, overall sensitivity 95%, overall specificity 78%; Figure S3).

Additional 'booster' SARS-CoV-2 vaccines confer enhanced variant neutralization breadth

Since the magnitude of wildtype response associated with breadth, and booster doses increase the magnitude of wildtype response, we hypothesized that an additional homologous vaccine dose (or 'booster') elicits enhanced heterologous breadth. The safety of additional doses in this cohort was comparable to the primary series (Naranbhai et al., 2021a). In 13 participants with low baseline response (Table S3), booster doses enhanced neutralization of alpha, beta, gamma and delta variants (Figure 2). Notwithstanding that these participants had low pre-booster titers (only 1 had measurable neutralization of any strain), the magnitude of neutralization of alpha, beta, gamma and delta variants was numerically higher post-booster doses than the overall evaluated population who had received the full vaccine series. In this subset of participants with poor pre-booster responses, neutralization breadth increased from median 0 (IQR 0-0) variants neutralized pre-booster to a median of 2 (IQR 1-4) variants neutralized post-booster.

Discussion

SARS-CoV-2 vaccination induces lower antibody responses in patients with cancer. Here we studied the breadth of response against SARS-CoV-2 variants as these represent the leading threat to vaccinated individuals. As in patients without cancer, vaccination with SARS-CoV-2 vaccines induces lower neutralization of variants, particularly beta, than wildtype. The vaccine types varied in magnitude of response but crucially, the magnitude of wildtype neutralization response was the primary correlate of breadth of neutralization. As predicted and concordant with another small study of four individuals (Iketani et al., 2021), booster doses even with wildtype vaccines increase breadth against viral variants.

These data have several potential clinical implications. First, to achieve the greatest neutralizing breadth, the most immunogenic vaccine may be preferred as the primary series for patients at high risk, where feasible. Second, the hierarchy of effectiveness of the three FDA EUA vaccines in preventing breakthrough infection by variants, where mRNA1273 provides the highest protection, followed by BNT162b2 and then Ad26.COV2.S (Naranbhai et al., 2021b) are likely accounted for by differences in immunogenicity against wildtype SARS-CoV-2. Finally, booster doses with wildtype vaccines would be expected to increase protection against variants in patients with cancer even as we await the next generation of vaccines. This observation is likely because of boosting of polyclonal responses capable of binding conserved sites in current and predicted future variants. The magnitude of increase in variant naturalization appears to be robust, even when responses to initial vaccination are poor, suggesting a single booster dose may be adequate for most patients to overcome the apparent reduced priming of responses. Whether these patients may require additional doses due to waning responses remains unclear.

There are several additional noteworthy observations. Increasing age was associated with reduced breadth of neutralization (independent of magnitude of response), consistent with impaired immune functions such as decline in somatic hypermutation with age (Troutaud et al., 1999). Interestingly we observed a trend towards enhanced breadth over time, but this is likely small and likely not at the magnitude seen in individuals with natural infection who continue to accrue increased breadth over time potentially because of antigen persistence (Cho et al., 2021).

Interestingly, an anti-spike antibody titer higher than 1000 U/ml on the Roche Elecsys assay, an assay that is widely available in clinical practice, was a good surrogate for breadth. This may be a helpful threshold in counselling patients regarding need for boosters, notwithstanding limitations of inferring clinical protection from immunologic measures.

A key limitation of this study is the focus on in vitro immunogenicity. Effectiveness of vaccines against variants is likely to be more complex involving differences in viral infectivity, exposure rates, transmissibility and possibly virulence in combination with largely humoral immune responses and cellular responses. This is illustrated by the exceptional success of the delta variant in transmission, but its relatively modest escape of neutralization. The number of individuals evaluated after booster doses is modest, but these represent the extra tail of the curve of patients who failed to make adequate responses after initial vaccination.

In conclusion, while current wildtype-based SARS-CoV-2 vaccines induce lower magnitude responses in patients with cancer that show impaired neutralization of viral variants, boosting these responses can safely restore breadth against current viral variants.

Acknowledgments

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Author Contributions

Conceptualization, V.N., A.J.I.

Methodology, V.N., J.F.G., A.B.B, A.J.I., W.F.G.B.,

Formal Analysis V.N., K.J.S.D, E.C.L

Investigation V.N. K.J.S.D, E.C.L, O.O., W.F.G.B., C.B., A.B.B.

Data Curation V.N.

Writing-Original Draft V.N.

Writing-Review & Editing V.N., K.J.S.D, E.C.L, O.O., W.F.G.B., C.B., A.B., J.F.G., A.B.I., A.J.I.

Visualization V.N.

Supervision J.F.G., A.B.B, A.J.I.

Funding acquisition J.F.G., A.B.B, A.J.I.

Declaration of Interests

JFG has served as a compensated consultant or received honoraria from Bristol-Myers Squibb, Genentech, Ariad/Takeda, Loxo/Lilly, Blueprint, Oncorus, Regeneron, Gilead, Moderna, AstraZeneca, Pfizer, Novartis, Merck, and GlydeBio; research support from Novartis, Genentech/Roche, and Ariad/Takeda; institutional research support from Bristol-Myers Squibb, Tesaro, Moderna, Blueprint, Jounce, Array Biopharma, Merck, Adaptimmune, Novartis, and Alexo; and has an immediate family member who is an employee with equity at Ironwood Pharmaceuticals. AJI has served as a compensated consultant for Oncoclinicas Brasil, Kinnate, Repare, and Paige.ai.

Inclusion and Diversity Statement

We worked to ensure gender balance in the recruitment of human subjects. We worked to ensure ethnic or other types of diversity in the recruitment of human subjects. One or more of the authors of this paper self-identifies as an underrepresented ethnic minority in science. One or more of the authors of this paper self-identifies as a member of the LGBTQ+ community. While citing references scientifically relevant for this work, we also actively worked to promote gender balance in our reference list.

Figure Legends

Figure 1: Neutralization of SARS-CoV-2 variants following vaccination with mRNA1273 (n=58), BNT162b2 (n=60) or Ad26.COV2.S (n=60) in patients with cancer.

The y-axis shows pseudovirus neutralization titer 50 (pNT50, defined as the titer at which the serum achieves 50% neutralization of SARS-CoV-2 wildtype pseudovirus entry into ACE2-expressing 293T cells). Briefly, lentiviral particles encoding both luciferase and ZsGreen reporter genes were pseudotyped with the SARS-CoV-2 spike protein from the strain indicated (see Table S1 for sequences) and produced in 293T cells, titered using ZsGreen expression by flow cytometry and used in an automated neutralization assay with 50–250 infectious units of pseudovirus co-incubated with three-fold serial dilutions of serum for 1 h. Neutralization was determined on 293T-ACE2 cells. A horizontal dotted line is shown at a pNT50 titer of 12 which is the lower limit of detection (LLOD) of this assay; a pNT50 titer of 20 corresponds with the clinical threshold for positivity defined previously(Garcia-Beltran et al., 2021a). The geometric mean titer, proportion positive (at a threshold of 1:12). Statistical comparison of neutralization titers against each strain between recipients of different vaccines is details in Table S2 and denoted by * on the graph where p-value are adjusted for covariates previously shown to be associated with wildtype virus neutralization namely age, chemotherapy, immunotherapy, timing after vaccination, and cancer type. Comparison of neutralization titers for recipients of each vaccine type, against different strains is shown as the fold change in neutralization, and corresponding p-value (based on a dunnet's test conducted in GraphPad Prism v9.0). Horizontal lines denote geometric mean titers, whiskers extend to 2.5th and 97.5th centiles to encompass the 95% confidence interval.

Figure 2: Effect of booster doses on neutralization of SARS-CoV-2 viral variants in patients with cancer (n=13). The color of each dot indicates the initial vaccine series and additional vaccine as indicated in legend. The geometric mean titer (GMT) and proportion above the lower limit of detection (LLOD=12) is shown.

Tables

Table 1: Baseline characteristics of participants in this study

Characteristic	Overall (n=178)	mRNA1273 (n=58)	BNT162b2 (n=60)	Ad26.CoV2.S (n=60)	p-value
Age (IQR)	68 (61, 72)	66 (61, 71)	64 (57, 71)	69 (67, 73)	0.014
Sex					0.9
Female	109 (61%)	34 (59%)	38 (63%)	37 (62%)	
Male	69 (39%)	24 (41%)	22 (37%)	23 (38%)	
Chemotherapy*	59 (33%)	21 (36%)	19 (32%)	19 (32%)	0.8
Immunotherapy*	29 (16%)	8 (14%)	11 (18%)	10 (17%)	0.8
Time after 1st dose (days (IQR)	68 (55, 93)	67 (62, 86)	74 (51, 111)	65 (42, 86)	0.054
Cancer type					0.13
Solid	141 (79%)	41 (71%)	50 (83%)	50 (83%)	
BMT	23 (13%)	13 (22%)	6 (10%)	4 (6.7%)	
Hematologic	14 (7.9%)	4 (6.9%)	4 (6.7%)	6 (10%)	

*Within 12 months of vaccination

Table 2: Multivariate regression analysis to identify correlates of breadth of neutralization.

	Effect estimate *	95% CI	p-value
Neutralization titer against wildtype SARS-CoV-2	1.4	1.1, 1.6	<0.001
Age (per 5 year increase)	-0.09	-0.17, -0.01	0.029
Vaccine type			
mRNA1273		Ref	
BNT162b2	-0.16	-0.57, 0.25	0.4
Ad26.COV2.S	-0.29	-0.77, 0.18	0.2
Chemotherapy	-0.14	-0.50, 0.22	0.4
Immunotherapy	0.16	-0.30, 0.62	0.5
Time after 1st dose (per week)	0.04	0.00, 0.08	0.061
Cancer type			
Solid		Ref	
Bone marrow transplanted	-0.04	-0.55, 0.47	0.9
Hematologic	0.2	-0.42, 0.81	0.5

*Effect estimates shown are per additional variant neutralized at measurable levels (above lower limit of detection).

STAR Methods

RESOURCE AVAILABILITY

Lead Contact:

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, A. John Iafrate (aiafrate@partners.org).

Materials Availability:

The study did not generate new unique reagents.

Data and Code Availability:

- Code for computing and analyzing neutralization breadth measures is available in the supplementary appendix
- Any additional information required to reanalyze the data reported in this work paper is available from the Lead Contact upon request

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Patients

The CANVAX study enrolled consenting adult patients at the Massachusetts General Hospital Cancer Center between April 21 through July 21, 2021. Recruitment and enrolment procedures have been previously described. For this analysis we randomly selected participants without prior SARS-CoV-2 infection (confirmed by anti-nucleocapsid antibody testing) who had received each of the three FDA EUA vaccines (by allocating random numbers to each participant and selecting the first 60). Participants were samples >=14 days after their final dose of vaccine. This study was approved by the Mass General Brigham Human Research Committee (2021P000746). Adult participants provided written (or in exceptional cases verbal) informed consent to participation in this study.

METHOD DETAILS

Neutralization assays

We used pseudovirus neutralization assay that we have previously described in detail elsewhere. In brief, pseudovirus neutralization titer 50 (pNT50) was calculated by taking the inverse of the serum concentration that achieved 50% neutralization of SARS-CoV-2 pseudotyped lentivirus particles entry into ACE2-expressing 293T cells. We introduced mutations corresponding to the SARS-CoV-2 variants of concern shown in Supplementary Table 1 by site directed mutagenesis, and confirmed clones by sequencing.

Binding antibody assays

We measured antibodies against the spike protein with the Roche Elecsys Anti-SARS-CoV-2 S assay (Roche Diagnostics, Indianapolis, USA), at the MGH Core Clinical laboratory, a CLIA lab. Anti-receptor binding domain antibodies were measured with an enzyme-linked immunosorbent assay (ELISA)(Garcia-Beltran et al., 2021a, 2021b).Briefly, we used an indirect ELISA with a standard consisting of anti-SARS-CoV and -CoV-2 monoclonal antibody (CR3022) (IgG1 isotype). 96-well ELISA plates were coated with purified wild-type SARS-CoV-2 RBD. Plates were blocked with BSA and washed. A seven-point standard curve was created using CR3022-IgG1 starting at 2 µg/mL by performing 1:3 serial dilutions with dilution buffer, and serum samples were diluted 1:100 with dilution buffer. Diluted samples and standards were added to corresponding wells and incubated for 1 h at 37°C, followed by washing. Total antibodies were detected with anti-human IgG+IgA+IgM (H+L)-HRP (Bethyl) diluted 1:25,000 for a 30 min incubation at room temperature. After washing, TMB substrate (Inova) was added to each well and incubated for 5-15 min before stopping with 1 M H_2SO_4. Optical density (O.D.) was measured at 450 nm with subtraction of the O.D. at 570 nm as a reference wavelength on a SpectraMax ABS microplate reader. Anti-RBD antibody levels were calculated by interpolating onto the standard curve and correcting for sample dilution; one unit per mL (U/mL) was defined as the equivalent reactivity seen by 1 µg/mL of CR3022.

QUANTIFICATION AND STATISTICAL ANALYSIS

Analyses were performed in R (v4.05) using the *gtsummary* packages and lm() functions. Details are provided in the figure legends and below. We modelled log_{10} transformed pseudovirus neutralization titers as the dependent variable. We selected covariates found to associated with neutralization of wildtype SARS-CoV-2 in the overall CANVAX study comprising >600 individuals these were: age, days post-vaccination, vaccine type, cancer type (categorized into solid, bone-marrow transplant or hematologic), receipt of chemotherapy in prior year and receipt of immunotherapy in prior year as the independent variables. Statistical comparisons in Figure 1 are shown relative to either mRNA1273 for each comparison of neutralization response between vaccine groups for each variant, or relative to wildtype virus for each comparison of neutralization response between variants for each vaccine group. The distribution of the data after log_{10} transformation was visually assessed in R to confirm suitability for linear regression. Comparisons between vaccine groups were performed by linear regression adjusting for all the above covariates in R (as detailed in Table S2). Comparisons between variants were performed by dunnet's test in GraphPad Prism v9.0.Figures were made in Graphpad Prism.

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Antibodies		
CR3022-IgG1	Obtained from the lab of Dr. Aaron Schmidt	IEDB Cat# CR3022, RRID:AB_2848080
Anti-human IgG+IgM+IgA (H+L) HRP	Bethyl	Cat# A80-152P
Polyclonal human sera	This study	N/A
Bacterial and Virus Strains		
SARS-CoV-2 ΔC18 (wild type) pseudotyped pHAGE-CMV-Luc2-IRES-ZsGreen-W lentivirus	Garcia-Beltran Cell, 2021	N/A
SARS-CoV-2 ΔC18 B.1.1.7 pseudotyped pHAGE-CMV-Luc2-IRES-ZsGreen-W lentivirus	Garcia-Beltran Cell, 2021	N/A
SARS-CoV-2 ΔC18 B.1.351 v1 pseudotyped pHAGE-CMV-Luc2-IRES-ZsGreen-W lentivirus	Garcia-Beltran Cell, 2021	N/A
SARS-CoV-2 ΔC18 P2 pseudotyped pHAGE-CMV-Luc2-IRES-ZsGreen-W lentivirus	Garcia-Beltran Cell, 2021	N/A

SARS-CoV-2 ΔC18 B.1.617.2 v1 pseudotyped pHAGE-CMV-Luc2-IRES-ZsGreen-W lentivirus	This study	N/A
Chemicals, Peptides, and Recombinant Proteins		
SARS-CoV-2 receptor binding domain protein	Obtained from the lab of Dr. Aaron Schmidt	N/A
Experimental Models: Cell Lines		
293T/ACE2.MF	Obtained from the lab of Dr. Michael Farzan	N/A

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GMT	191.4	85.4	22.2	94.7	48.1	18.9	33.1	18.4	13.2	76.2	33.2	15.2	72.1	32.7	14.7
% >LLOD	85	75	43	72	65	30	40.7	30	18	62	47	12	63	53	15

Comparisons:

between vaccine

adjusted p-value*

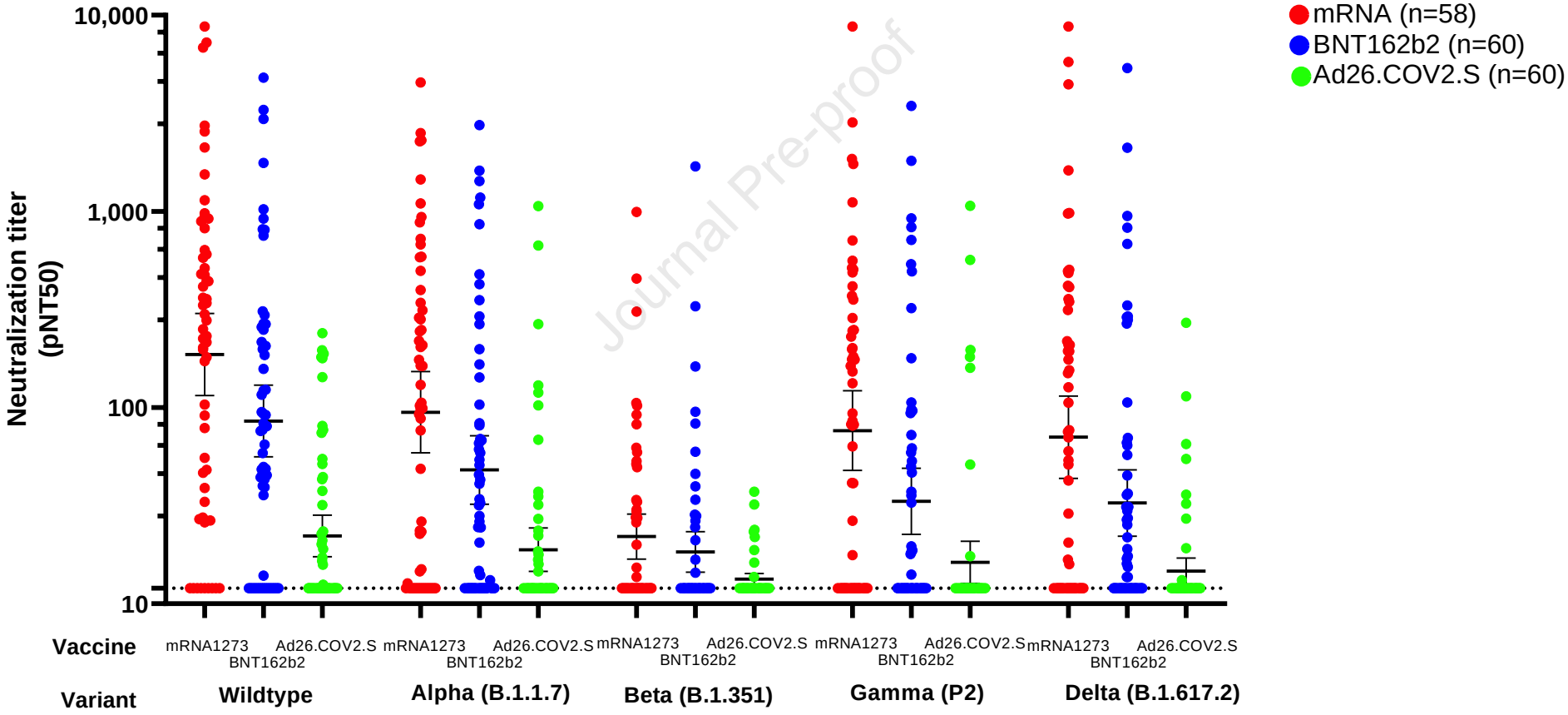
Ref	**	***	*Ref*	**	***	*Ref*	*ns*	**	*Ref*	***	***	*Ref*	**	***

between variants

fold-change

p-value

Ref	*Ref*	*Ref*	*2*	*1.8*	*1.2*	*4.6*	*8.7*	*1.7*	*2.5*	*2.6*	*1.4*	*2.7*	*2.6*	*1.5*
			***	**	*ns*	***	***	***	***	***	*ns*	***	***	*



Highlights and eTOC Blurb

Highlights

- Neutralization of variants is diminished, especially in Ad26.COV2.S recipients
- Neutralization breadth is associated with wildtype neutralization titer
- Anti-spike binding antibody concentrations >1000U/ml predict breadth
- Booster vaccines confer enhanced variant neutralization breadth

eTOC Blurb

Naranbhai et al. examine how well current wildtype-based SARS-CoV-2 vaccines perform in patients with cancer in neutralizing viral variants. The findings support preferring the most immunogenic wildtype vaccines (i.e. mRNA1273 or BNT162b2) for patients at high risk, to generate breadth against variants.