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Comprehensive mapping of neutralizing antibodies against SARS-CoV-2 variants induced by natural infection or vaccination

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Word count (Abstract): 250

Word count (main text): 3,184

Running Title: Review of neutralizing antibodies against SARS-CoV-2 variants

Keywords: SARS-CoV-2 variants; neutralizing antibodies; natural infection; vaccination

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Research in context

Evidence before this study

Several newly emerged SARS-CoV-2 variants have raised significant concerns globally , and there is concern that SARS-CoV-2 variants can evade immune responses that are based on the prototype strain. It is not known to what extent do emerging SARS-CoV-2 variants escape the immune response induced by previous infection or vaccination. However, existing studies of neutralizing potency against SARS-CoV-2 variants are based on limited numbers of samples and lack comparability between different laboratory methods. Furthermore, there are no studies providing whole picture of neutralizing antibodies induced by prior infections or vaccination against emerging variants. Therefore, we systematically reviewed and quantitively synthesized evidence on the degree to which antibodies from previous SARS-CoV-2 infection or vaccination effectively neutralize variants.

Added value of this study

In this study, 56 studies, including 2,483 individuals and 8,590 neutralization tests, were identified. Antibodies from natural infection or vaccination are likely to effectively neutralize B.1.1.7, but neutralizing titers against B.1.351 and P.1 suffered large reductions. Lineage B.1.351 escaped natural-infection-mediated neutralization the most, with GMT of 79.2 (95% CI: 68.5-91.6), while neutralizing antibody titers against the B.1.1.7 variant were largely preserved (254.6, 95% CI: 214.1-302.8). Compared with

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lineage B, we estimate a 1.5-fold (95% CI: 1.0-2.2) reduction in neutralization against the B.1.1.7, 8.7-fold (95% CI: 6.5-11.7) reduction against B.1.351 and 5.0-fold (95% CI: 4.0-6.2) reduction against P.1. The neutralizing antibody response after vaccinating with non-replicating vector vaccines against lineage B.1.351 was worse than responses elicited by vaccines on other platforms, with levels lower than that of individuals who were previously infected. The neutralizing antibodies induced by administration of inactivated vaccines and mRNA vaccines against lineage P.1 were also remarkably reduced by an average of 5.9-fold (95% CI: 3.7-9.3) and 1.5-fold (95% CI: 1.2-1.9).

Implications of all the available evidence

Our findings indicate that antibodies from natural infection of the parent lineage of SARS-CoV-2 or vaccination may be less able to neutralize some emerging variants, and antibody-based therapies may need to be updated. Furthermore, standardized protocols for neutralizing antibody testing against SARS-CoV-2 are needed to reduce lab-to-lab variations, thus facilitating comparability and interpretability across studies.

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Abstract

Background: Immunity after SARS-CoV-2 infection or vaccination has been threatened by recently emerged SARS-CoV-2 variants. A systematic summary of the landscape of neutralizing antibodies against emerging variants is needed.

Methods: We systematically searched PubMed, Embase, Web of Science, and 3 pre-print servers for studies that evaluated neutralizing antibodies titers induced by previous infection or vaccination against SARS-CoV-2 variants and comprehensively collected individual data. We calculated lineage-specific GMTs across different study participants and types of neutralization assays.

Findings: We identified 56 studies, including 2,483 individuals and 8,590 neutralization tests, meeting the eligibility criteria. Compared with lineage B, we estimate a 1.5-fold (95% CI: 1.0-2.2) reduction in neutralization against the B.1.1.7, 8.7-fold (95% CI: 6.5-11.7) reduction against B.1.351 and 5.0-fold (95% CI: 4.0-6.2) reduction against P.1. The estimated neutralization reductions for B.1.351 compared to lineage B were 240.2-fold (95% CI: 124.0-465.6) reduction for non-replicating vector platform, 4.6-fold (95% CI: 4.0-5.2) reduction for RNA platform, and 1.6-fold (95% CI: 1.2-2.1) reduction for protein subunit platform. The neutralizing antibodies induced by administration of inactivated vaccines and mRNA vaccines against lineage P.1 were also remarkably reduced by an average of 5.9-fold (95% CI: 3.7-9.3) and 1.5-fold (95% CI: 1.2-1.9).

Interpretation: Our findings indicate that the antibody response established by natural infection or vaccination might be able to effectively neutralize B.1.1.7, but

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95 neutralizing titers against B.1.351 and P.1 suffered large reductions. Standardized
96 protocols for neutralization assays, as well as updating immune-based prevention and
97 treatment, are needed.

98 **Funding:** Chinese National Science Fund for Distinguished Young Scholars

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Introduction

Since the first sequence of SARS-CoV-2 was published in January of 2020[1], over 1.1 million strains have been documented in Global Influenza Surveillance and Response System (GISAID)[2], with recent reports of several newly emerged lineages , which has raised significant concerns globally. Of particular concern has been the emergence of lineage B.1.1.7 (UK variant, also known as 501Y.V1), lineage B.1.351 (South Africa variants, 501Y.V2), and lineage P.1 (Brazil variant, 501Y.V3), harboring several significant mutations in spike glycoproteins, which are key domains of virus-neutralizing antibodies[3]. These mutants rapidly became the dominant circulating virus strains in the regions where they were first isolated, and especially for B.1.1.7 and B.1.351, spread globally. Several vital mutations in the receptor-binding domain (RBD), such as N501Y in B.1.1.7 and E484K in B.1.351 and P.1, are associated with increased infectivity and decreased neutralizing potency, with potential to evade humoral immunity from prior infections or vaccinations[4-8]. Another variant of lineage B.1.427/B.1.429, which first emerged in California, was categorized as a Variant of Concern (VOC) in March 2021 according to classification developed by SARS-CoV-2 Interagency Group (SIG) in United States, containing a single L452R mutation in RBD in spike, whose ability of reduced sensitivity to neutralization has yet to be determined[9].

There is concern that SARS-CoV-2 variants can evade immune responses elicited by natural infections and vaccines that are based on the prototype strain (Wuhan-Hu-1). It has been shown that neutralization against variants by convalescent plasma is

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121 remarkably reduced by several mutations, including E484K shared by lineage B.1.351
122 and P.1[10]. Serum collected from recipients of licensed vaccines have a decreased ability
123 to neutralize emerging SARS-CoV-2 mutants to varying degrees, from 1.6-fold reduction
124 for China's protein subunit vaccines to over 6-fold reduction for mRNA vaccines[11-15].
125 Additionally, consistent with immunogenicity results, a major loss of efficacy against
126 B.1.351 was seen in NVX-CoV2373 and ChAdOx1 nCoV-19 vaccines[16,17], though the
127 efficacy was retained against B.1.1.7 for other vaccines[18]. However, existing studies of
128 neutralizing potency against SARS-CoV-2 variants are based on limited numbers of
129 samples and lack comparability between different laboratory methods. Furthermore,
130 there are no studies providing whole picture of neutralizing antibodies induced by prior
131 infections or vaccination against emerging variants.
132
133 Here, we systematically summarize the evidence on neutralization ability against
134 various SARS-CoV-2 variants among those previously-infected with strains from the
135 original SARS-CoV-2 lineage and those who have been vaccinated.

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Methods

Study Selection and Data Extraction

We conducted a systematic search from six databases, including three peer-reviewed databases (PubMed, Embase and Web of Science) and three preprint servers (medRxiv, bioRxiv and Europe PMC), for studies published in English between Sep 1, 2020 and Apr 18, 2021 with predefined search terms **(Table S1)**. We included studies that 1) reported neutralizing antibodies against SARS-CoV-2 variants by using serum or plasma collected from individuals with virologically or serologically-confirmed SARS-CoV-2 infections, and vaccine recipients; and 2) reported or displayed individual antibody titers with summary tables or high-resolution images. Studies that 1) investigated the efficacy of monoclonal and therapeutic antibodies against variants; 2) reported seroprevalence of variants; 3) only detected non-neutralizing antibodies; or 4) reported specific mutation sites from a view of biological mechanism, were excluded. We also excluded abstracts of congress meetings or conference proceedings, study protocols, media news, commentaries, and reviews.

We screened all eligible studies to extract the study characteristics, study participants, types of variants, laboratory methods and antibody titers **(Table S2)**. Data were digitized from the figures in papers by pre-trained investigators with a digital extraction tool if individual titer values were not available in table format[19]. We only extracted the titers expressed as reciprocal dilution of serum that neutralizes or inhibits 50% of the virus (e.g., NT50, PRNT50, etc.). When titers were not explicitly stated, but a category

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158 defined as less than some value exists, we assumed a titer of half of this value (e.g., titer
159 of 10 is assumed when "<20" was present). For individuals with multiple specimens, we
160 only included one sample that most likely to have neutralization antibodies for each
161 study participant to avoid repeated inclusion. The inclusion and exclusion of studies,
162 screening and scrutinization of included studies, data extraction and verification were
163 performed by two independent researchers, a third researcher was consulted when
164 disagreement arose.
165
166 **Data Synthesis and Analysis**
167 The primary outcome variable was a pooled geometric mean titer (GMT), expressing an
168 average level SARS-CoV-2 neutralizing titers for a group of individual titers. To be
169 specific, we calculated lineage-specific GMT with extracted dataset across different study
170 participants and types of neutralization assays, indicating three stratified factors (i.e.,
171 study participants, types of neutralization assays and lineages).
172
173 Individual-level data were classified into four groups **(Table S3)**. Briefly, 1)
174 non-variant-infected individuals, which indicates acutely-infected or convalescent
175 COVID-19 patients infected with parental strains or asymptomatic cases infected with
176 non-variants; 2) variant-infected individuals, which refers to individuals infected with
177 SARS-CoV-2 variants; 3) uninfected vaccine recipients, which refers to healthy vaccines
178 who were not infected with either parental strains or the variants of SARS-CoV-2; 4)
179 previously-infected vaccine recipients, which refers to vaccines who had been infected

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with parental strains.

Among different study participants, we further stratified studies by types of neutralization assays. Multiple neutralization assays used in included studies were classified into three categories based on the type of virus (authentic or pseudo) used and the types of vectors [lentivirus or vesicular stomatitis virus (VSV)] used in pseudovirus neutralization assays, namely, live virus neutralization assays, lentivirus-vector pseudovirus neutralization assays, and VSV-vector pseudovirus neutralization assays.

Within specific study participants and types of neutralization assays, we calculated lineage-specific GMTs. The categories of SARS-CoV-2-variant lineages among included studies was consistent with taxonomy and classification of Phylogenetic Assignment of Named Global Outbreak Lineage (PANGO lineage)[20]. Specifically, lineage B.1.1.117, B.1.1.26, B.1.1.50, and B.1.1.29 served as the reference strains when comparing with SARS-CoV-2 variants in some studies[11,16,21,22], and they were classified as lineage B.1 due to close phylogenetic distance and shared mutation site of 614G[22,23]. Emerging and circulating SARS-CoV-2 variants have been divided into three classes by SIG: variant of interest (VOI), variant of concern (VOC), and variant of high consequence (VOHC)[24]. VOIs include lineage B.1.526, B.1.525 and P.2, with increased transmissibility and disease severity, and VOCs include lineage B.1.1.7, B.1.351, P.1, B.1.427, and B.1.429, with significant reduction in neutralization and increased hospitalizations or deaths[24]. At the time of writing, no variants have been classified as VOHC[24]. The classification of all

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lineages involved in eligible studies were shown in **Table S4**.

For non-variant-infected subjects, we further explored potential determinants affecting the GMT, such as the sampling interval post symptom onset, and disease severity. Disease severity was assessed by classifying individuals as either hospitalized or non-hospitalized, based on World Health Organization COVID-19 Clinical management criteria[25]. We divided the post-symptom-onset sampling interval into three periods (i.e., 0-30 days, 31-90 days, and >90 days) according to the distribution of sampling times in the extracted data **(Figure S9)**. We stratified the uninfected vaccine recipients by vaccine platforms (e.g., non-replicating vector, RNA, inactivated, and subunit protein) and the sampling interval post vaccination (i.e., <14 days, 14-90 days, and >90 days) based on a study that evaluated antibody persistence through 6 months after vaccination[26]. Furthermore, we conducted a matched analysis for samples that had been tested simultaneously against reference strains and variants and calculated the fold changes of GMT.

Statistical Analysis

We first performed univariate subgroup analysis, then used multivariate linear regression models to control for potential confounding among non-variant-infected individuals and uninfected vaccinees to quantitatively explore potential factors that may affect GMT. For the multivariate regression model, we included pango lineage, vaccine platform, sampling interval after last dose, and sampling intervals post symptom onset,

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and disease severity with available data. GMT was calculated as arithmetic mean of log-transformed titer based on natural logarithm form, and t-test 95% CI was estimated. Statistical significance was tested by Kruskal-Wallis rank sum test with Nemenyi's post-hoc test. For paired samples, we used Wilcoxon matched-pairs signed-rank test. Only P-value less than 0.05 were considered statistically significant ($P \leq 0.05$, *; $P \leq 0.01$, **; $P \leq 0.001$, ***). All statistical analyses were done using R (version 4.0.1).

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Results

Study selection and data extraction

We identified a total of 5,182 studies after systematically searching multiple data sources with 2,307 coming from peer-reviewed databases, and 2,875 from preprint severs **(Figure 1)**. After screening title, abstract, and full-text, 56 studies containing a total of 2,483 individuals and 8,590 neutralization measurements were included in our analysis, with previously uninfected vaccine recipients comprising more than half of studies (44 studies; 4,697/8,590 samples, 54.7%), followed by non-variant-infected individuals (41 studies; 3,440/8,590 samples, 40.0%), variant-infected individuals (8 studies; 288/8,590 samples, 3.4%), and previously-infected vaccine recipients (6 studies; 165/8,590 samples, 1.9%) **(Figure 1)**. Live virus neutralization assays were most common (24 studies, 24/56, 42.9%), followed by lentivirus-vector pseudovirus neutralization assay (22 studies, 22/56, 39.3%) and VSV-vector pseudovirus neutralization assay (13 studies, 13/56, 23.2%) **(Table S7)**. The lineage B.1.1.7 and B.1.351 were the two SARS-CoV-2 variants that had been studied the most, comprising more than two third of studies (B.1.1.7: 37 studies, 66.1%; B.1.351: 40 studies, 71.4%) and nearly half of measurements (B.1.1.7: 1,852 measurements, 21.6%; B.1.351: 2,422 measurements, 28.2%) **(Table S7)**. Other VOCs, such as lineage P.1 and B.1.427/B.1.429 were the subject of 20 studies including 863 data points **(Table S7)**.

Level of neutralizing antibodies against SARS-CoV-2 variants among non-variant-infected individuals

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Overall, among studies that evaluated neutralizing antibodies in individuals previously infected with nonvariants, 26.3% (5/19), 95.7% (22/23), and 88.9% (8/9) of the studies found a significant decrease in neutralization against B.1.1.7, B.1.351 and P.1, respectively. The neutralization levels of 6.2% (47/757), 20.0% (204/1,028), and 6.4% (16/249) samples against B.1.1.7, B.1.351 and P.1 were reduced to below the limitation of detection.

In aggregate, neutralizing titers against B.1.351 were significantly reduced, followed by P.1, while titers against B.1.17 were not, when compared to reference lineages titers. With live virus neutralization assays, the pooled GMT was 254.6 (95% CI: 214.1-302.8) for lineage B.1.1.7, 79.2 (95% CI: 68.5-91.6) for B.1.351, 253.1 (95% CI: 194.9-328.8) for P.1, and 275.5 (95% CI: 146.4-518.5) for B.1.427/B.1.429, with an average of 3.4-fold (95% CI: 3.0-4.0) in B.1.351 when comparing to lineage B **(Figure 2A)**. The decrease in neutralization for B.1.351 (3.5, 95% CI: 3.0-4.0) is similar when compared to lineage B.1, which has the 614G mutation. In matched analyses, the reduction in the ability of neutralization against B.1.1.7, B.1.351 and P.1 was 1.5 (95% CI: 1.0-2.2), 8.7 (95% CI: 6.5-11.7) and 5.0-fold (95% CI: 4.0-6.2) compared with lineage B **(Figure S2)**. For lentivirus-vector pseudovirus assays, the average reductions of GMT were 8.1-9.7 fold, 4.2-5.1 fold, and 1.4-1.6 fold for lineage B.1.351, P.1, and B.1.1.7 compared to lineage B/B.1/B+D614G **(Figure 2B)**. In terms of VSV-vector pseudovirus assays, the average reductions of GMT were 2.0-12.3 fold, 1.2-7.9 fold, and 1.2-7.5 fold for lineage B.1.351, P.1, and B.1.1.7 respectively when compared to reference strains **(Figure 2C)**.

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Serum collected from individuals infected with SARS-CoV-2 variants show increased neutralizing antibodies level against corresponding mutant strains **(Figure S3)**. Notably, B.1.1.7-infected persons also show significant decreased neutralizing antibodies titers against B.1.351 **(Figure S3).** Multivariate analysis also indicated B.1.351had significantly reduced neutralizing activity for all three neutralization assays after controlling for sampling intervals post symptom onset and/or clinical severity, compared to reference lineages **(Table S8)**.

Level of neutralizing antibodies against SARS-CoV-2 variants among vaccine recipients

Significant reductions in neutralization against B.1.1.7, B.1.351 and P.1 were found in 48.1% (13/27), 100.0% (26/26) and 66.7% (6/9) of the studies in SARS-CoV-2 naïve vaccine recipients, respectively. Partial reductions reached the background levels, with the proportion of 4.0 (41/1,014), 19.1 (237/1,239), and 11.3 (32/281) against B.1.1.7, B.1.351 and P.1, respectively.

Serum collected from uninfected vaccine recipients had diverse neutralizing antibody levels against SARS-CoV-2 variants across different vaccine platforms. In studies using the live virus neutralization assay, the non-replicating adenoviral vectored vaccine showed generally low GMT against B.1.351 in contrast to other vaccine delivery platforms, with an average of GMTs of 2.1 (95% CI: 1.1-4.1), 70.9 (95% CI: 50.8-98.9),

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296 85.9 (95% CI: 75.9-97.2), and 66.6 (95% CI: 51.0-86.9) for platforms of non-replicating
297 vector, inactivated virus, RNA, and protein subunit, respectively **(Figure 3A)**. Using
298 lineage B as a reference lineage, we found that the average reduction fold of neutralizing
299 antibodies against B.1.351 was 240.2-fold (95% CI: 124.0-465.6) for non-replicating
300 vector platform, 4.6-fold (95% CI: 4.0-5.2) for RNA platform, and 1.6-fold (95% CI:
301 1.2-2.1) for protein subunit platform **(Figure 3A)**. The neutralizing antibodies induced
302 by administration of inactivated vaccines and mRNA vaccines against lineage P.1 were
303 also remarkably reduced by an average of 5.9-fold (95% CI: 3.7-9.3) and 1.5-fold (95% CI:
304 1.2-1.9) **(Figure 3A)**.
305
306 In paired-sample analysis, neutralizing titers induced by mRNA vaccine were reduced
307 3.1-fold (95% CI: 2.4-3.9) against B.1.1.7, 2.7-fold (95% CI: 2.3-3.2) against P.1, and
308 7.4-fold (95% CI: 6.4-8.5) against B.1.351, compared to prototype strain Wuhan-Hu-1
309 that was used for vaccine design **(Figure S4)**. In comparison to lineage B+D614G,
310 significant reductions of antibody levels elicited by all included vaccine platforms
311 against lineage B.1.351 were also found in two pseudovirus neutralization assays
312 ($P<0.05$). Neutralizing antibodies against lentiviral-encapsulated P.1, P.2, and
313 B.1.427/B.1.429 were also significantly reduced when comparing to lineage B+614G
314 ($P<0.01$) **(Figure 3B)**. Additionally, antibodies in serum collected from
315 previously-infected vaccine recipients receiving RNA vaccines or non-replicating-vector
316 vaccines were significantly higher than uninfected vaccine recipients in pseudovirus
317 assays **(Figure S7).** In multivariate regression mode, we found that B.1.351, P.1 and

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B.1.427/1.429 had significant lower GMT of neutralizing antibodies assessed by live virus neutralization assay, and we found that other vaccine platform shows significant higher antibody level than non-replicating-vector vaccine across all included virus strains **(Table S9)**.

Comparison between GMT of neutralizing antibodies induced by natural infection and vaccination

Comparisons of the GMT of neutralizing antibodies induced by natural infections (non-variant-infected individuals) and vaccination (uninfected vaccine recipients) showed that individuals infected with parental strains had similar antibodies titers with individuals vaccinated with mRNA vaccines, but significantly higher antibodies titers than individuals administrated with non-replicating vector vaccines against lineage B.1, B.1.1.7 and B.1.351, when using live virus neutralization assay to detect neutralizing antibodies **(Figure 4A)**. No significant differences between titers were found between non-variant-infected individuals and RNA vaccine-recipients against B.1.1.7, B.1.351 and P.1 tested by VSV-based pseudovirus neutralization assays **(Figure 4C)**.

Discussion

Overall, we comprehensively estimate the antibody levels against preexisting SARS-CoV-2 viruses and recently emerging variants among different study participants using neutralizing antibodies as a protective biomarker. Our analyses found that antibodies in both naturally-infected and vaccine-immune sera/plasma had slightly

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reduced but largely retained neutralizing activity against B.1.1.7. The neutralizing potency against B.1.351 and P.1 was significantly reduced compared to reference lineages. The antibody response after vaccinating with non-replicating vector vaccines against lineage B.1.351 was worse than responses elicited by vaccines on other platforms, and the level of neutralizing antibodies is lower than that of individuals who were previously infected. This finding suggests that immunity derived from natural infection or vaccination might be less able to neutralize some recently emerging variants, and antibody-based therapies may need to be updated.

Neutralizing antibodies titers induced from both natural infections and vaccination against B.1.351 and P.1 were significantly lower than that against other variants or reference strains, mainly due to mutations in spike protein that were associated with decreased neutralizing potency to evade humoral immunity (e.g., E484K) [27]. However, the decrease of neutralizing potency was more obvious in B.1351 than P.1, although both variants shared the E484K mutation, which could be partly explained by the distinct set of other mutations and/or deletions in the NTD region or enhanced neutralization of P.1 by anti-RBD antibodies that bind outside of the RBD[28]. We found that convalescent and vaccine-induced immune sera had neutralizing potency against B.1.1.7 and B.1.427/ B.1.429 that are comparable with reference strains, suggesting that those mutations do not remarkably affect neutralizing activity. While mutations at 501 can increase affinity for angiotensin converting enzyme 2 (ACE2) and enhance transmissibility of B.1.1.7[29-31], variants of B.1.427/B.1.429 bearing spike mutations L452R, S13I, and W152C were only

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362 associated with modest increases in secondary household attack rates, while no
363 evidence of reduced neutralization capacity for these L452R SARS-CoV-2 variants were
364 found[32].However, continued vigilance is warranted given the potential for further
365 mutations that might affect the immunogenicity of the vaccines or reduce the
366 cross-reactivity of previously-induced antibodies by natural infections.
367
368 Both previous infection and vaccination have been shown to provide potent protection
369 against similar strains, but it is unclear how neutralizing antibodies against variants
370 induced by natural infection and vaccination might be different. For the other two most
371 prevalent variants, B.1.1.7 and B.1.351, natural infection-induced sera/plasma had
372 significantly higher neutralizing levels than that attained by those vaccinated with
373 non-replicating vector vaccine in live virus neutralization assay. Additionally, antibodies
374 induced by RNA-vaccine had similar neutralizing level with antibodies derived from
375 naturally-infected individuals against prevalent variants. This suggests that the
376 neutralizing potency elicited by natural infection of previous prototype strains is
377 relatively robust, whereas the immunity induced by vaccination depends on vaccine
378 platform.
379
380 Although some studies have shown that the neutralization levels from live virus and
381 pseudovirus correlate well,[33-35] we stratified the results by each of three neutralization
382 assays to enhance comparability. The results from live virus assays could provide a
383 comprehensive way to assess inherent viral fitness and the potential impact of other

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mutations outside the spike region[6,33-35]. However, even within the same live virus neutralization test, different methods were used for experimental endpoints (e.g., cytopathic effect, fluorescence, etc.), and to report their final individual titers (e.g., NT50, NT80, etc.,). In addition, experimental procedures, such as virus titration, serum dilution, virus-serum neutralization, varied greatly across reports from different laboratories. Thus far, there is no integrated or standardized operation procedure for SARS-CoV-2 neutralization assay (neither live virus nor pseudovirus), making comparison between studies difficult. International efforts to standardize laboratory methods for SARS-CoV-2 neutralization tests are urgently needed. The previous work by WHO in standardizing procedures for avian influenza neutralization assays provides one useful example.[36,37]

Our study has several limitations. First, this study synthesized different neutralization assay results to estimate pooled GMTs. While we stratified analyses by neutralization assays according to virus types and vectors to get the most comparable results, significant variation between assays persists. Second, in many studies, individual-level details were not reported, thus limiting our ability to adjust for potential confounding factors in multivariate regression. We tried to contact study authors, but the response rate was generally low. Thirdly, we did not assess the impact of preexisting cellular immunity, which could provide a degree of protection as reported in previous studies[38].

In conclusion, our study provides a comprehensive mapping of the neutralizing potency against SARS-CoV-2 variants induced by natural infection or vaccination. Our findings

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suggest that immune sera/plasma retained most of its neutralizing potency against B.1.1.7 and B.1.427/ B.1.429 variants, but significantly lost neutralizing potency against B.1.351 and P.1 variants, with B.1.351 having the worst reductions. The evolution of SARS-CoV-2 lineage is still in process, and it's unknown whether long-term accumulation of mutations can erode the neutralizing effectiveness of natural and vaccine elicited immunity, especially in the context of waning immunity. Therefore, longitudinal monitoring of emerging variants and antibody-induced immunity is of high importance, and standardized protocols for neutralizing antibody testing against SARS-CoV-2 are urgently needed.

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Contributors

H.Y. designed and supervised the study. X.C. and Z.C. did the literature search, set up the database and did all statistical analyses. X.C., Z.C., A.S.A., and D.T.L. co-drafted the first version of the article. X.C., Z.C., R.S., W.L., N.Z., J.Z., Q.W., X.D., Z.Z., X.C, S.G., and helped with checking data and did the figures. D.T.L., A.S.A., J.Y, and H.Y. commented on the data and its interpretation, revised the content critically. All authors contributed to review and revision and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of interests

H.Y. has received research funding from Sanofi Pasteur, and Shanghai Roche Pharmaceutical Company; D.T.L. and A.S.A. has received research funding from the US National Institutes of Health. None of those research funding is related to COVID-19. All other authors report no competing interests.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments

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437 We thank Junbo Chen, Qianli Wang, and Yuxia Liang from the Fudan University.

438 This study was funded by the National Science Fund for Distinguished Young
439 Scholars (grant no. 81525023), Program of Shanghai Academic/Technology
440 Research Leader (grant no. 18XD1400300), National Science and Technology
441 Major project of China (grant no. 2018ZX10713001-007, 2017ZX10103009-005,
442 2018ZX10201001-010), the US National Institutes of Health (R01 AI135115 to
443 D.T.L. and A.S.A.)

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Figure legends

Figure 1. Selection flowchart of studies, study participants, and variants studied.

Figure 2. Neutralizing antibodies against SARS-CoV-2 variants in non-variant-infected individuals. Neutralizing antibodies against reference strains (blue dot) and variants of concern (red dot) were determined in **A)** live virus neutralization assay, **B)** lentivirus-vector pseudovirus neutralization assay, and **C)** VSV-vector pseudovirus neutralization assay. The solid point represents the GMT and the error bar represents the 95% confidence interval. The scattering dot represents individual titers. The numbers in the bottom orange rectangle represent the number of studies and sample sizes (no. of studies/no. of samples). Significant statistical differences are indicated by asterisks ($P \leq 0.05$, *; $P \leq 0.01$, **; $P \leq 0.001$, ***).

Figure 3. Neutralizing antibodies against SARS-CoV-2 variants in uninfected vaccine recipients after the administration of different vaccine platforms. Neutralizing antibodies against reference strains (blue dot), variants of concern (red dot), variants of interest (green dot), and other variants (black dot) were determined in **A)** live virus neutralization assay, **B)** lentivirus-vector pseudovirus neutralization assay, and **C)** VSV-vector pseudovirus neutralization assay. The solid point represents the geometric mean titer (GMT) and the error bar

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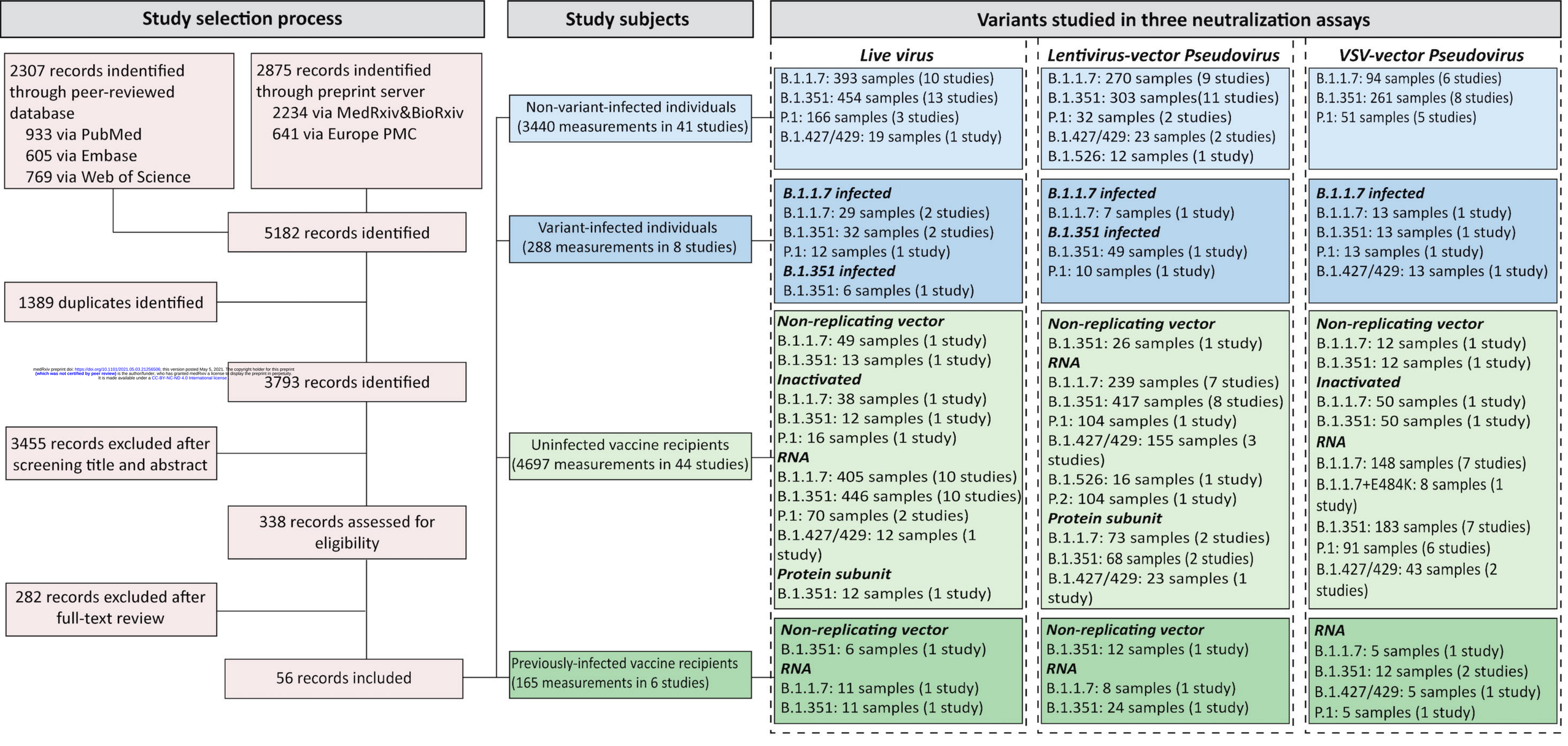
represents the 95% confidence interval. The scattering dot represents individual titers. The numbers in the bottom orange rectangle represent the number of studies and sample sizes (no. of studies/no. of samples). Significant statistical differences are indicated by asterisks (P ≤ 0.05, *; P ≤ 0.01, **; P ≤ 0.001, ***).

Fig 4. Comparison between GMT of neutralizing antibodies induced by natural infection and vaccination by platforms. Neutralizing antibodies comparison were determined in **A)** live virus neutralization assay, **B)** lentivirus-vector pseudovirus neutralization assay, and **C)** VSV-vector pseudovirus neutralization assay. Neutralization against same lineage induced by natural infection and different platforms of vaccination was compared. The solid point represents the GMT and the error bar represents the 95% confidence interval. The scattering dot represents individual titers. The numbers in the bottom orange rectangle represent the number of studies and sample sizes (no. of studies/no. of samples). Significant statistical differences are indicated by asterisks (P ≤ 0.05, *; P ≤ 0.01, **; P ≤ 0.001, ***). N-R vector, non-replicating vector.



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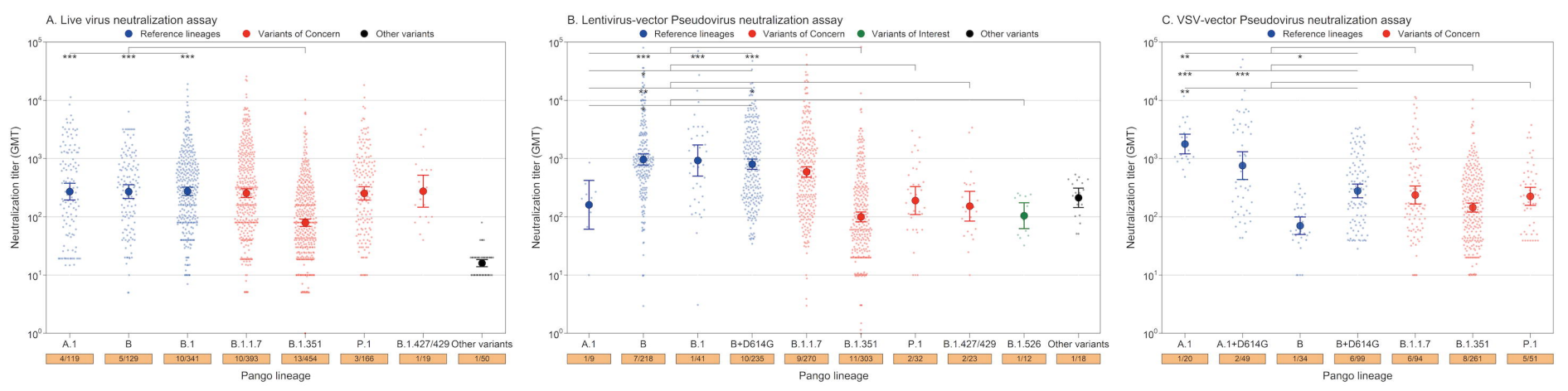
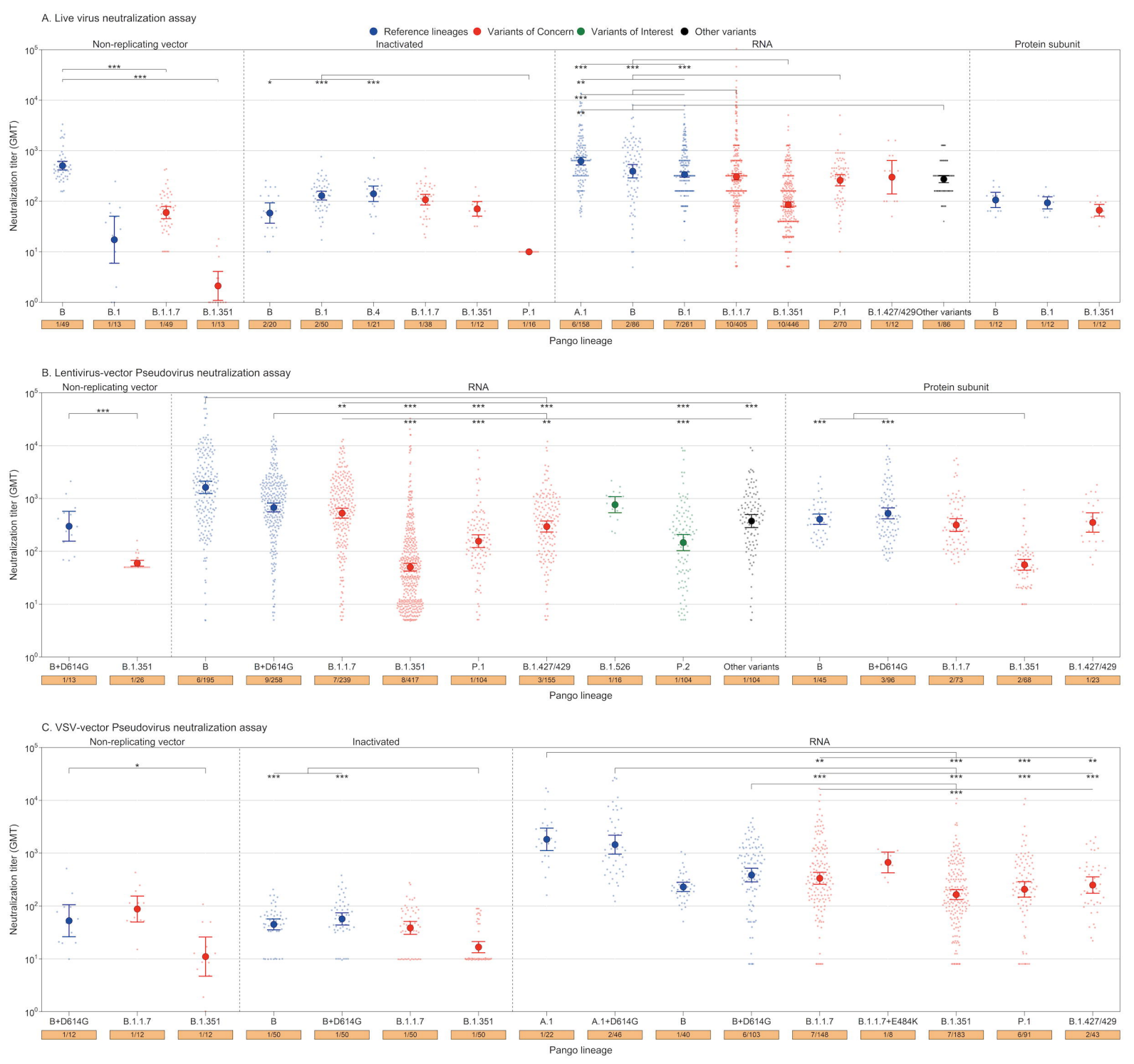

A. Live virus neutralization assay
Reference lineages
Variants of Concern
Other variants
Neutralization titer (GMT)
A.1
B
B.1
B.1.1.7
B.1.351
P.1
B.1.427/429
Other variants
4/119
5/129
10/341
10/393
13/454
3/166
1/19
1/50
Pango lineage
B. Lentivirus-vector Pseudovirus neutralization assay
Reference lineages
Variants of Concern
Variants of Interest
Other variants
Neutralization titer (GMT)
A.1
B
B.1
B+D614G
B.1.1.7
B.1.351
P.1
B.1.427/429
B.1.526
Other variants
1/9
7/218
1/41
10/235
9/270
11/303
2/32
2/23
1/12
1/18
Pango lineage
C. VSV-vector Pseudovirus neutralization assay
Reference lineages
Variants of Concern
Neutralization titer (GMT)
A.1
A.1+D614G
B
B+D614G
B.1.1.7
B.1.351
P.1
1/20
2/49
1/34
6/99
6/94
8/261
5/51
Pango lineage


A. Live virus neutralization assay
Reference lineages
Variants of Concern
Variants of Interest
Other variants
Non-replicating vector
Inactivated
RNA
Protein subunit
Neutralization titer (GMT)
B
B.1
B.1.1.7
B.1.351
B
B.1
B.4
B.1.1.7
B.1.351
P.1
A.1
B
B.1
B.1.1.7
B.1.351
P.1
B.1.427/429
Other variants
B
B.1
B.1.351
1/49
1/13
1/49
1/13
2/20
2/50
1/21
1/38
1/12
1/16
6/158
2/86
7/261
10/405
10/446
2/70
1/12
1/86
1/12
1/12
1/12
Pango lineage
B. Lentivirus-vector Pseudovirus neutralization assay
Non-replicating vector
RNA
Protein subunit
Neutralization titer (GMT)
B+D614G
B.1.351
B
B+D614G
B.1.1.7
B.1.351
P.1
B.1.427/429
B.1.526
P.2
Other variants
B
B+D614G
B.1.1.7
B.1.351
B.1.427/429
1/13
1/26
6/195
9/258
7/239
8/417
1/104
3/155
1/16
1/104
1/104
1/45
3/96
2/73
2/68
1/23
Pango lineage
C. VSV-vector Pseudovirus neutralization assay
Non-replicating vector
Inactivated
RNA
Neutralization titer (GMT)
B+D614G
B.1.1.7
B.1.351
B
B+D614G
B.1.1.7
B.1.351
A.1
A.1+D614G
B
B+D614G
B.1.1.7
B.1.1.7+E484K
B.1.351
P.1
B.1.427/429
1/12
1/12
1/12
1/50
1/50
1/50
1/50
1/22
2/46
1/40
6/103
7/148
1/8
7/183
6/91
2/43
Pango lineage


A. Live virus neutralization assay
Uninfected vaccine recipients
Non-variant-infected individuals
A.1
B
B.1
B.1.1.7
B.1.351
P.1
B.1.427/429
Other variants
Neutralization titer (GMT)
mRNA
Patients
N-R vector
Inactivated
Subunit
6/158
4/119
1/49
2/20
2/86
1/12
5/129
1/13
2/50
7/261
1/12
10/341
1/49
1/38
10/405
10/393
1/13
1/12
10/446
1/12
13/454
1/16
2/70
3/166
1/12
1/19
1/86
1/50
Pango lineage
B. Lentivirus-vector Pseudovirus neutralization assay
B
B+D614G
B.1.1.7
B.1.351
P.1
B.1.427/429
B.1.526
Other variants
6/195
1/45
7/218
1/13
9/258
3/96
10/235
7/239
2/73
9/270
1/26
8/417
2/68
11/303
1/104
2/32
3/155
1/23
2/23
1/16
1/12
1/104
1/18
C. VSV-vector Pseudovirus neutralization assay
A.1
A.1+D614G
B
B+D614G
B.1.1.7
B.1.351
P.1
1/22
1/20
2/46
2/49
1/50
1/40
1/34
1/12
1/50
6/103
6/99
1/12
1/50
7/148
6/94
1/12
1/50
7/183
8/261
6/91
5/51