SARS-CoV-2 Omicron neutralization by therapeutic antibodies, convalescent sera, and post-mRNA vaccine booster

One Sentence Summary: Third dose of Pfizer/BioNTech COVID-19 vaccine significantly boosts neutralizing antibodies to the Omicron variant compared to a second dose, while neutralization of Omicron by convalescent sera, two-dose vaccine-elicited sera, or therapeutic antibodies is variable and often low.

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Abstract:

The rapid spread of the highly contagious Omicron variant of SARS-CoV-2 along with its high number of mutations in the spike gene has raised alarm about the effectiveness of current medical countermeasures. To address this concern, we measured neutralizing antibodies against Omicron in three important settings: (1) post-vaccination sera after two and three immunizations with the Pfizer/BNT162b2 vaccine, (2) convalescent sera from unvaccinated individuals infected by different variants, and (3) clinical-stage therapeutic antibodies. Using a pseudovirus neutralization assay, we found that titers against Omicron were low or undetectable after two immunizations and in most convalescent sera. A booster vaccination significantly increased titers against Omicron to levels comparable to those seen against the ancestral (D614G) variant after two immunizations. Neither age nor sex were associated with differences in post-vaccination antibody responses. Only three of 24 therapeutic antibodies tested retained their full potency against Omicron and high-level resistance was seen against fifteen. These findings underscore the potential benefit of booster mRNA vaccines for protection against Omicron and the need for additional therapeutic antibodies that are more robust to highly mutated variants.

Main Text:

INTRODUCTION

In November 2021 a new SARS-CoV-2 variant, named Omicron (Pango lineage B.1.1.529), was identified as a variant of concern (VOC). Its rapid spread in Africa and unusually high number of mutations, especially in the spike gene, has triggered intense international efforts to track the variant's spread and evaluate its effects on the potency of therapeutics and vaccines. The predominant strain of Omicron has mutations in the spike gene encoding 15 amino acid

70 changes in the receptor binding domain (RBD) of the spike surface protein (G339D, S371L,
71 S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R,
72 N501Y, and Y505H). The RBD mediates virus attachment to the ACE2 receptor on target cells
73 and is the principal target of neutralizing antibodies that contribute to protection against SARS-
74 CoV-2. Many of these RBD changes have been previously reported to reduce the effectiveness
75 of several therapeutic neutralizing antibodies (reviewed in Corti et al(*1*)). A recent study reports
76 that the full complement of RBD substitutions in the Omicron spike compromises the potency of
77 over 85% of 247 anti-RBD monoclonal antibodies (mAbs) tested(*2*). Preliminary reports indicate
78 substantial immune evasion to two-dose vaccine-elicited sera(*3-7*), booster-elicited sera(*8-16*),
79 genotype-varying convalescent sera(*3, 5, 6*), and several mAbs(*2, 6*). However, study
80 populations and methods vary widely among the studies to date, and many lack critical details
81 about host characteristics. Moreover, studies have not examined how host demography predicts
82 these neutralizing humoral responses, and examination of how infection by a broader diversity of
83 SARS-CoV-2 Delta and non-Delta genotypes is important for further insights into how genetic
84 diversity may correlate with cross-neutralizing antibody responses.

85 Here we used a pseudovirus neutralization assay(*16*) to measure antibody neutralization of
86 SARS-CoV-2 Omicron in three important contexts: (1) antibodies induced after two or three
87 doses of the Pfizer-BioNTech Covid-19 (Pfizer/BNT162b2 mRNA) vaccine, (2) antibodies
88 induced from infection by different SARS-CoV-2 variants and (3) therapeutic antibodies under
89 emergency use authorization (EUA) or in later stages of clinical development. We compared the
90 magnitude of neutralization escape by Omicron to D614G (referred to as wild type, WT) and
91 Delta SARS-CoV-2 variants to help inform public health decisions and offer further data toward
92 correlate of protection research.

93 **RESULTS**

94 **Three immunizations of the Pfizer/BNT162b2 mRNA COVID-19 vaccine significantly**
95 **boosts neutralizing antibodies to the Omicron variant compared to two-vaccinations.**

96 The emergence of the Omicron variant coincided with recommendations for booster
97 immunizations, particularly for at risk populations. We studied the neutralization titers of 39
98 generally healthy, adult healthcare workers participating in the Prospective Assessment of
99 SARS-CoV-2 Seroconversion study (PASS study, Table 1)(*17*) who received the full primary
100 series (1st and 2nd) and booster (3rd) immunizations with the Pfizer/BNT162b2 vaccine. We chose
101 to study sera at peak responses after the full primary series vaccination rather than after 6 months
102 because 6-months titers are often very low(*10, 18*).

103 Neutralization activity against Omicron above the threshold of our assay (1:40 dilution) was
104 only observed in 12.8% (5/39) of serum samples obtained at a mean of 30 ± 11 days after the 2nd
105 Pfizer/BNT162b2 vaccination (Figure 1A). After the 2nd vaccination neutralization titers against
106 Omicron (geometric mean titer, GMT 22) were 25.5-fold lower than neutralization titers against
107 WT (GMT 562). By contrast, neuralization titers against Delta (GMT 292) were 1.9-fold lower
108 than WT. Neutralization titers from the same individuals collected 43 ± 17 days after the 3rd
109 Pfizer/BNT162b2 vaccination were 8.9-fold greater against WT (GMT 5029) compared to titers
110 after the 2nd vaccination. The titers against Omicron after the 3rd vaccination (GMT 700) showed
111 31.8-fold increase compared to titers after the 2nd vaccination, whereas titers against Delta after
112 the 3rd vaccination (GMT 1673) were only 5.7-fold higher than the titers after the 2nd
113 vaccination. Importantly, all individuals had measurable neutralizing titers against Omicron after
114 the 3rd vaccination, highlighting the potential for increased protection by a booster vaccine.

115 We also evaluated how sex or age of the individual might affect the titers in sera after
116 vaccination. We did not observe a trend according to sex or age after the 2nd or 3rd vaccination
117 (Figure 1B and 1C, respectively). A total of 17/39 individuals had a positive anti-N (SARS-CoV-
118 2 nucleoprotein) seroconversion during regular scheduled blood sampling between the 2nd and
119 the 3rd immunization(*17*). No symptoms of COVID-19 were reported by the subjects, possibly
120 indicative of silent infection or exposure to SARS-CoV-2 or other coronaviruses. We did not
121 find any trends when comparing differences in neutralizing antibody titers between individuals
122 who had anti-N seroconversion and those who did not (Figure 1D). To assess the breadth of
123 neutralization responses against Omicron induced by boosting, we compared the change in titers
124 against Omicron or Delta relative to WT after the 2nd and 3rd vaccination. To account for
125 variability in the antibody titers from one individual to another, we calculated the ratio between
126 the neutralization titers after the 3rd and the 2nd vaccination for each variant and plotted this ratio
127 for Omicron and Delta against WT (Figure 1E). We observed that the ratios of NT_{50} titer from
128 the 3rd to the 2nd vaccination for Omicron relative to the corresponding ratios for WT were higher
129 than the ratios for Delta relative to WT, suggesting that the 3rd vaccination broadened responses
130 to the distantly-related variant.

131 **Neutralization of Omicron by convalescent sera from individuals infected by different**
132 **variants shows lower neutralization titers compared to the infecting variant.**

133 To investigate the potency of infection-induced neutralizing antibodies against Omicron, we
134 compared neutralization titers against WT, Delta, and Omicron in convalescent sera obtained at a
135 mean of 30.2 ± 9.3 days post-symptom onset from unvaccinated individuals infected with WT,
136 Alpha, Beta, or Delta variants who were enrolled in the Epidemiology, Immunology, and
137 Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC)

138 study(*19*). Genotypes of the infecting variants were sequenced for all cases (Table 2 and
139 Supplementary Table). These convalescent sera were complemented by a Beta-convalescent
140 serum from another protocol.

141 Figure 2 shows that the Delta variant was modestly more resistant to neutralization than WT
142 by sera from most individuals infected with WT, Alpha, or Beta viruses (1.1 to 1.9-fold), while
143 neutralization titers were much more reduced against Omicron (2.3 to 70.1- fold). A total of 2/10
144 and 0/20 individuals infected with WT (B.1 and B.1.2) variants, respectively, had a response
145 above the threshold against Omicron, whereas 2/5 and 2/2 individuals infected with Alpha
146 (B.1.1.7) and Beta (B.1.351) variants, respectively, were above threshold. Convalescent sera
147 from individuals infected with Delta (B.1.617 and AY.14/.25/.44/.47/.62/.74/.119) variants
148 generally had higher neutralization titers against Delta (2.8 to 13.5-fold) compared to WT,
149 indicating more focused antibody responses to epitopes in the Delta spike. Convalescent sera
150 from these Delta-infected individuals showed 22.1 to 74.4-fold lower neutralization titers against
151 Omicron compared to Delta. However, a total of 6/7 individuals infected with the B.1.617.2
152 variant and 9/10 individuals infected with an AY variant had titers above threshold against
153 Omicron.

154 **Boosting reduces apparent antigenic differences between WT and Omicron variants.**

155 We applied antigenic cartography to explore how the convalescent and post-vaccination sera
156 distinguish the different spike antigens. Antigenic maps were made separately using neutralizing
157 antibody titers from individuals infected with the different variants or from individuals after the
158 2nd or 3rd vaccination (Figure 3). Convalescent sera were more heterogeneous compared to the
159 post-vaccination, with each convalescent serum clustering closer to the infecting variant, as
160 expected. The 3rd post-vaccination sera were more tightly clustered around WT compared to the

161 2nd post-vaccination sera. The antigenic distances between Omicron and WT were large for all
162 three sera sets, but the antigenic distance between Omicron and WT were smaller after the 3rd
163 vaccination (7.2-fold drop) compared to either convalescent or the 2nd vaccination sera (49.4-fold
164 drop and 39.4-fold drop, respectively), in agreement with the titer changes in Figure 1A. Small
165 distance changes between WT and Delta were observed for all three sera sets (2.0 to 3.6-fold
166 difference).

167 **The potency of most therapeutic antibody products is compromised against Omicron.**

168 As part of the US government COVID-19 response effort to speed development of
169 therapeutics for COVID-19, we assessed the neutralization of Omicron by 24 therapeutic
170 antibody products currently under EUA or in late stages of clinical development. This panel
171 includes 15 single therapeutic neutralizing antibody products (nAbs), six combination nAbs
172 (cnAbs) and three polyclonal antibody preparations (pAbs). The manufacturers provided these
173 clinical products for side-by-side comparisons of potency against variants but required blind
174 coding of these antibody products for publications. Previously, we reported that several single
175 substitutions in the spike protein of other variants conferred resistance to some of these
176 products(*20*), but a similar assessment has not been performed on the Omicron spike.

177 Figure 4A shows the neutralization curves for each product against WT and Omicron. To
178 quantify the relative drop in nAb potency we calculated ratios between the 50% inhibitory
179 concentration of Omicron to WT (Figure 4B). These ratios do not account for the absolute
180 potencies of the nAbs but do allow for a uniform comparison of the changes in potency against
181 Omicron relative to WT for all the antibody products. We note that the majority of successful
182 clinical trials were performed when predominant strains had a ratio of near 1 compared to WT.
183 However, absolute potency using IC_{50} ng/ml as a measure has not been established as a correlate

184 of protection. We defined ratios between of 5 to 50 as a benchmark for partial or moderate
185 resistance and ratios of > 50 as a benchmark for more complete resistance relative to WT. While
186 the clinical relevance of the IC_{50} changes has not been determined for any *in vitro* assay, these
187 cutoffs were chosen because the therapeutic levels of antibody therapeutics may be high enough
188 to overcome low levels of resistance. By the fold-change measure, only three of 15 nAbs
189 retained near full potency against Omicron compared to WT, and only one retained partial
190 potency. Two cnAbs retained partial potency, while the remaining four cnAbs showed complete
191 loss of neutralization potency. All three pAbs showed reduced neutralization potency (ratios 13-
192 17) against Omicron, in agreement with the data from convalescent and vaccinated individuals.
193 These findings raise concerns that many of the available therapeutic antibody products may not
194 be effective against Omicron.

195 **DISCUSSION**

196 Neutralizing antibodies are widely accepted as an important component of protection against
197 SARS-CoV-2 infection and disease (COVID-19), but efforts to assess antibody titers that
198 correlate with protection are complicated by many factors. These include potential redundancy
199 and synergism of different components of the humoral, cellular, and innate immune system, and
200 differences in variant fitness and host genetics, age, and prior immunity. The risk of infection can
201 also be confounded by human behavior and local public health measures, while measurements of
202 antibody titers can vary with different laboratory methods. Therefore, differences in study
203 populations and laboratory methods are important considerations for assessing the impact of
204 immune evasion by Omicron on medical countermeasures.

205 Here, using the same lentiviral pseudovirus neutralization platform we measured the change
206 in potency of 24 clinical-stage therapeutic antibodies against Omicron compared to WT (D614G)

207 and compared neutralizing antibodies in sera from two well-characterized cohorts of subjects in
208 prospective clinical studies. Our findings show that most vaccinated individuals have low or
209 undetectable titers against Omicron after the second Pfizer/BNT162b2 vaccination, similar to
210 findings reported by others(*3-7*). However, the third vaccination significantly increased
211 neutralizing titers to levels significantly higher than those elicited by the second vaccination, in
212 agreement with other preliminary studies(*8-14*). It is notable that the post-2nd vaccination and
213 post-3rd vaccination sampling times were similar, indicating that this boost does not simply
214 reflect time since last vaccine. We found no association between sex or age with these
215 neutralizing immune responses, although it is important to note that the study samples were from
216 generally healthy adults, and that the post-vaccine-dose sampling time was overall short (43 ± 17
217 days). It has been shown that infection followed by vaccination results in neutralizing antibody
218 titers comparable or higher to titers after two vaccinations(*3, 10, 14, 21*). The PASS study
219 included anti-N antibody testing on all blood samples for detection of silent infections. The
220 neutralizing antibody titers among the 17 asymptomatic individuals who seroconverted for N
221 antibodies between the 2nd and 3rd immunization were not higher than those who did not
222 seroconvert. Other studies have shown high antibody titers in convalescent individuals after the
223 1st or 2nd vaccination(*10, 11*). We did not see an increase after the 3rd vaccination in individuals
224 who seroconverted for N-antibodies. This may be due to reduced antigen load from incident
225 asymptomatic infection or having reached a maximum response after vaccination.
226 The antigenic cartography analysis suggests that the Omicron variant appears to be
227 antigenically distant from WT and Delta, but this distance seems to decrease after the 3rd
228 vaccination. The apparent broadening of responses to Omicron may be due to boosting of titers
229 to cross-reactive epitopes or improved antibody affinity to shared epitopes, or both. For the

230 convalescent sera, high titers generally correlated with the highest cross-neutralization to
231 Omicron. Continued studies of the breadth against multiple variants and duration of responses
232 after booster vaccinations are urgently needed. In both vaccination and convalescent individuals,
233 our studies suggest that booster vaccinations, even with the original ancestral vaccine antigen,
234 could be beneficial in protecting against Omicron, in agreement with the rapidly accumulating
235 data from many sources(*3, 5, 6*).

236 Lastly, nine of the fifteen clinical-grade nAbs under EUA or in late stages of clinical
237 development had no measurable IC_{50} against Omicron compared to WT. Also, while most nAbs
238 and cnAbs lost measurable potency, all polyclonal antibodies retained measurable, though
239 reduced with IC_{50}. Careful selection of therapeutic antibodies is needed according to variant
240 prevalence. As Omicron continues to acquire additional mutations the products that remain
241 effective could be jeopardized, underscoring the risk associated with this variant and its
242 derivatives.

243 In summary, our findings indicate that booster doses of mRNA COVID-19 vaccines may
244 afford an increase in protection against Omicron by inducing higher levels of neutralizing
245 antibodies compared to two vaccine doses or the levels of neutralizing antibodies induced by
246 SARS-CoV-2 infection from different variants. The strengths of this study include representation
247 of a broad diversity of genotypes, including within-Delta diversity, comparable sampling times
248 between convalescent and vaccinated subjects, the use of cartography methods, and the
249 availability of subject demographics to interpret how host characteristics may influence Omicron
250 humoral immunity. The limitations of our study include the relatively small numbers of study
251 subjects, restricted timing of sera collection, and the use of a pseudovirus platform as a surrogate
252 to authentic SARS-CoV-2 viruses. Ultimately neutralization titers need to be tied to clinical

253 outcomes. The rapid and unpredictable evolution of SARS-CoV-2 requires continued
254 development and assessments of medical countermeasures.

255 **MATERIALS AND METHODS**

256 **Vaccinated participants**

257 Details of the PASS study protocol, including the inclusion/exclusion criteria, have been
258 published(*17*). Full details are in the Supplemental Material. Briefly, generally healthy
259 healthcare workers without a history of SARS-CoV-2 infection at screening were enrolled. The
260 study began in August 2020 and involved monthly research clinic visits to obtain serum for
261 longitudinal SARS-CoV-2 antibody testing. The subset of participants included in this study
262 received three doses of Pfizer/BNT162b2 vaccine; none had a PCR-confirmed SARS-CoV-2
263 infection during follow-up. Participants' serially-collected serum samples were screened for
264 immunoglobulin G (IgG) reactivity with SARS-CoV-2 spike protein and nucleocapsid protein
265 (N) using a multiplex microsphere-based immunoassay, as described(*22*).

266 **Unvaccinated infections - study population and general study design**

267 The EPICC study is a cohort study of U.S. Military Health System (MHS) beneficiaries that
268 includes those with a history of SARS-CoV-2 infection, as described previously(*19*). Full details
269 are in Supplemental Material. Enrollment occurred at six Military Treatment Facilities (MTFs).
270 Demographic, comorbidity, COVID illness characteristics, and vaccination status were obtained
271 from the clinical case report form and/or the MHS Data Repository. Biospecimen collection
272 included serial serum samples and upper respiratory specimen swabs.

273

274 **Diagnosis of SARS-CoV-2 infection and genotyping of infections used for convalescent sera**

275 SARS-CoV-2 infection was determined by positive clinical laboratory PCR test performed at the
276 enrolling clinical site, or a follow-up upper respiratory swab collected as part of the EPICC
277 study. The specific clinical PCR assay employed at the MTF varied. The follow-up PCR assay
278 (for EPICC specimens) was the SARS-CoV-2 (2019-nCoV) CDC qPCR Probe Assay research
279 use only kits (IDT, Coralville, IA)(*23*); details are in the Supplemental Material. Whole viral
280 genome sequencing was performed on extracted SARS-CoV-2 RNA from PCR-positive
281 specimens; details are in the Supplemental Material. The Pango classification tool (https://cov-
282 lineages.org/) was used for genotype classification (version 3.1.17).
283
284 **Ethics**
285 The PASS (IDCRP-126) and EPICC (IDCRP-085) studies were approved by the Uniformed
286 Services University of the Health Sciences Institutional Review Board (IRB) in compliance with
287 all applicable Federal regulations governing the protection of human participants. All PASS and
288 EPICC study participants provided informed consent. The convalescent Beta sera, obtained from
289 a traveler who had moderate-severe Covid-19 in the Republic of South Africa during the peak of
290 the Beta (B.1.351) wave in January 2021, was obtained with informed consent and covered
291 under the US Food and Drug Administration IRB approved expedited protocol # 2021-CBER-
292 045.
293
294 **SARS-Cov-2 pseudovirus production and neutralization assays**
295 Lentiviral pseudoviruses were generated and used in neutralization assays, as previously
296 described(*24*). The Omicron spike expression plasmid was generously provided by Nicole Doria-
297 Rose (Vaccine Research Center, National Institutes of Health). Neutralization assays were

298 performed on 293T-ACE2/TMPRSS2 cells stably expressing ACE2 and transmembrane serine
299 protease 2 (BEI # NR-55293). Twenty-four clinical-stage therapeutic antibody products were
300 provided by pharmaceutical companies to support the US government COVID-19 response
301 efforts. The antibody identities are blinded for publications per an agreement with the
302 companies. Neutralization curves were normalized to virus only controls and fitted using
303 nonlinear regression curve (GraphPad Prism, La Jolla, CA). The antibody concentration or sera
304 dilution corresponding to 50% neutralization was defined as NT_{50} for sera or IC_{50} for antibody
305 products. Data reported are averages from at least two independent experiments, each with intra-
306 assay duplicates.

307

308 **Antigenic cartography**

309 ACMACS antigenic cartography software (https://acmacs-web.antigenic-441cartography.org/)
310 was used to create a geometric interpretation of neutralization titers against the WT, Delta, and
311 Omicron variants. Each square in the map indicates one antigenic unit, corresponding to two-fold
312 dilution of the antibody in the neutralization assay. Antigenic distance is measured in any
313 direction of the map.

314

315 **Supplementary Materials**

316 Supplementary materials and methods

317 Table S1: SARS-CoV-2 genotypes for the infecting variants

318

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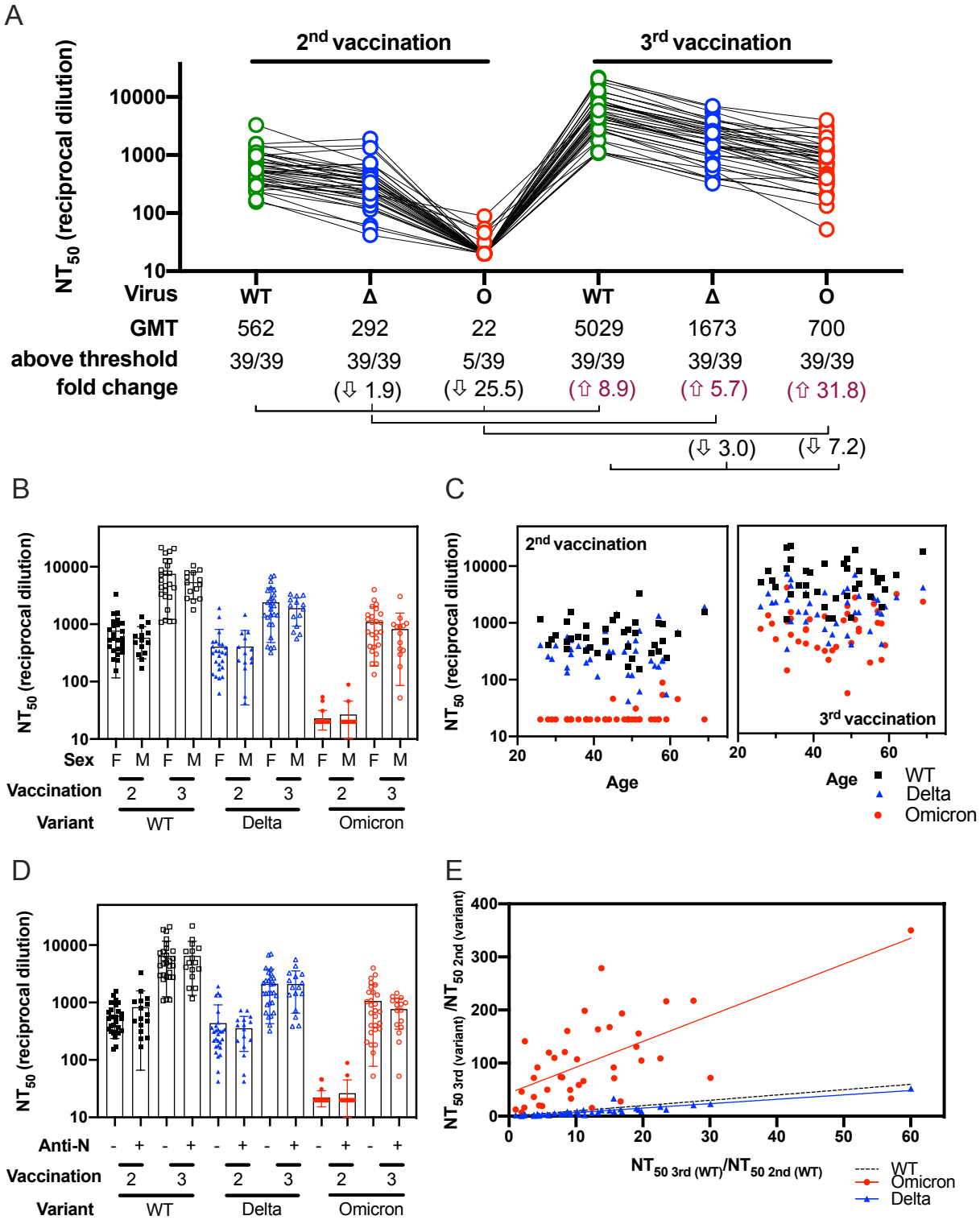
A
2nd vaccination
3rd vaccination
NT50 (reciprocal dilution)
10000
1000
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10
Virus WT Δ O WT Δ O
GMT 562 292 22 5029 1673 700
above threshold 39/39 39/39 5/39 39/39 39/39 39/39
fold change (⇩ 1.9) (⇩ 25.5) (⇧ 8.9) (⇧ 5.7) (⇧ 31.8)
(⇩ 3.0) (⇩ 7.2)
B
Sex F M F M F M F M F M F M
Vaccination 2 3 2 3 2 3
Variant WT Delta Omicron
C
2nd vaccination
3rd vaccination
Age
WT
Delta
Omicron
D
Anti-N - + - + - + - + - + - +
Vaccination 2 3 2 3 2 3
Variant WT Delta Omicron
E
NT50 3rd (variant)/NT50 2nd (variant)
NT50 3rd (WT)/NT50 2nd (WT)
WT
Omicron
Delta

558

559

560 **Fig. 1. Sensitivity of the Omicron variant to neutralization by Pfizer/BNT162b2 vaccinee**
561 **sera. (**A) Neutralization assays were performed using lentiviral pseudoviruses bearing SARS-
562 CoV-2 WT (B.1 lineage, D614G), Delta (Δ, B.1.617.2 lineage, T19R, G142D, E156-, F157-,
563 R158G, L452R, T478K, D614G, P681R and D950N) and Omicron (O, B.1.1.529 lineage, A67V,
564 del69-70, T95I, del142-144, Y145D, del211, L212I, ins214EPE, G339D, S371L, S373P, S375F,
565 K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H,
566 T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K and L981F)
567 with sera from 39 healthcare workers after immunization with two and three doses of
568 Pfizer/BNT162b2 vaccine. Sera was obtained at a mean of 30 ± 11 days after immunization with
569 two doses and at a mean of 43 ± 17 days after booster vaccination. Each serum was run in
570 duplicate in two independent experiments against each pseudovirus to determine the 50%
571 neutralization titer (NT_{50}). The geometric means titers (GMT), the number of NT_{50} above
572 threshold (1:40) and the fold change are indicated. Titers below 1:40 were set at 20 to calculate
573 GMTs. Arrows indicate increase or decrease relative to WT. Connecting lines indicate serum
574 from the same individual. The demographic information for this sera cohort is provided in Table
575 1. (B) NT_{50} by sex after 2nd or 3rd vaccination. (C) NT_{50} by age after 2nd and 3rd vaccination. (D)
576 2nd or 3rd vaccination NT_{50} according to anti-N (nucleocapsid protein) seroconversion between
577 2nd and 3rd vaccination. (E) The ratios between the neutralization titers after the 3rd and the 2nd
578 immunization for Omicron and Delta were plotted against the corresponding ratios for WT. For
579 panels B-E, black squares correspond to WT, blue triangles correspond to Delta and red circles
580 correspond to Omicron.

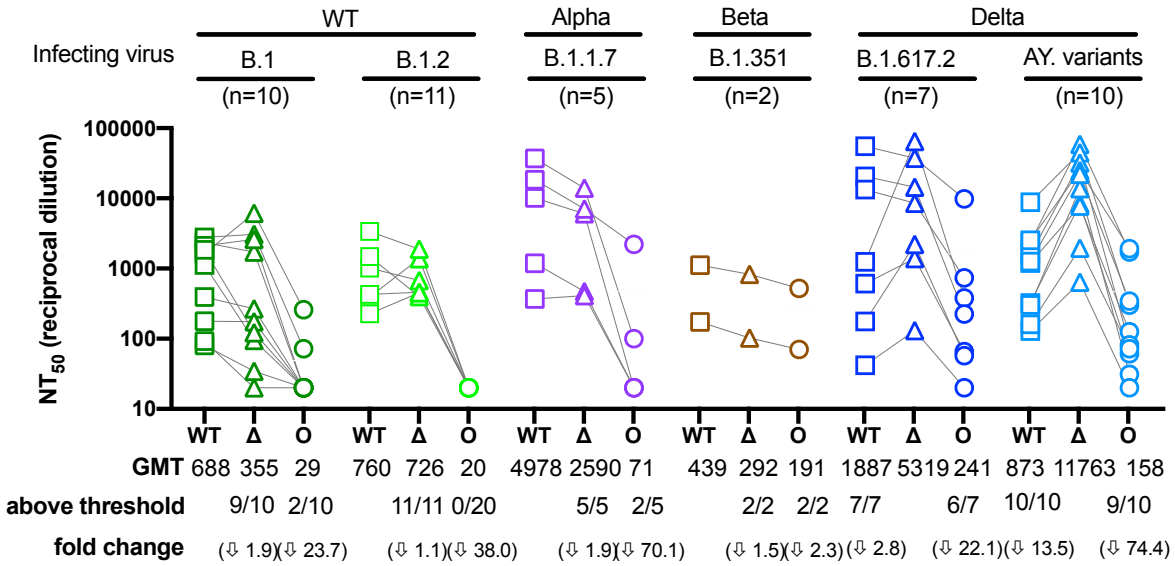
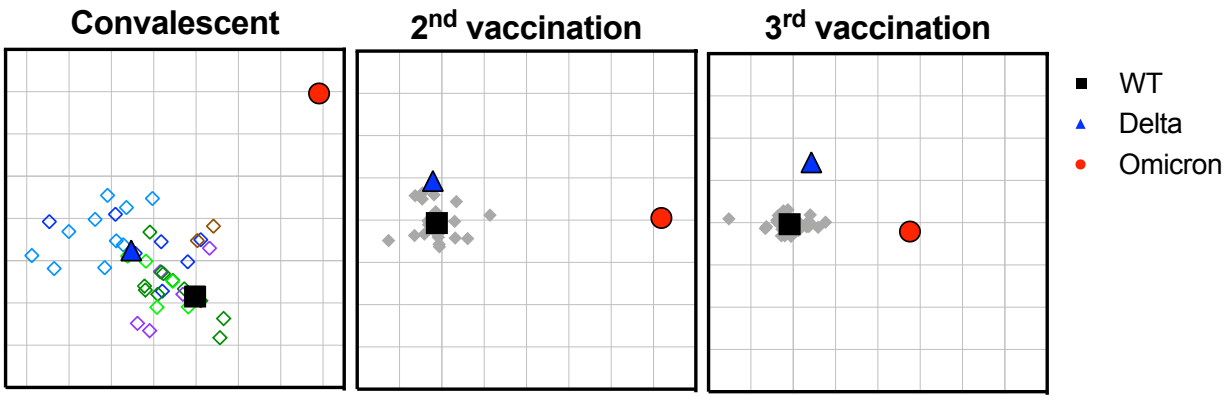


Fig. 2. Sensitivity of the Omicron variant to neutralization by convalescent sera

Neutralization assays were performed using convalescent sera from persons infected with genotyped variants from B.1, B.1.2, B.1.1.7, B.1.351, B.1.617.2, AY.14, AY.25, AY.44, AY.47, AY.62, AY.74 or AY.119 lineages (Table 2 and Supplementary Table). Both B.1 and B.1.2 have no mutations in the receptor binding domain and were therefore considered WT, whereas some of the AY mutants have additional mutations in the RBD relative to B.1.617.2. Each serum was run in duplicate against WT, Delta, and Omicron to determine the NT_{50}. The geometric means (GMT), the number of NT_{50} above threshold (1:40) and the fold change are indicated. Titers that did not inhibit at the lowest dilution tested (1:40) were assigned a titer of 20 for GMT calculations. Arrows indicate decrease relative to the infecting variant. Connecting lines indicate serum from the same individual. Data shown represent two independent experiments each with an intra-assay duplicate. Squares correspond to WT, triangles correspond to Delta, and circles correspond to Omicron.



596

597 **Fig. 3. Antigenic cartography of convalescent and vaccinee sera against WT, Delta and**

598 **Omicron.** Antigenic maps were separately generated from convalescent (left panel), 2nd

599 vaccination (middle panel) or 3rd vaccination (right panel) sera. Convalescent sera are shown in

600 diamonds as follows: B.1 (dark green), B.1.2 (light green), B.1.1.7 (purple), B.1.351 (brown),

601 AY variants (light blue), and B.1.617.2 (dark blue). Gray diamonds correspond to post-

602 vaccination sera. Each grid square corresponds to 2-fold dilution in the neutralization assay.

603 Black squares correspond to WT variant. Blue triangles correspond to Delta variant. Red circle

604 corresponds to Omicron variant.

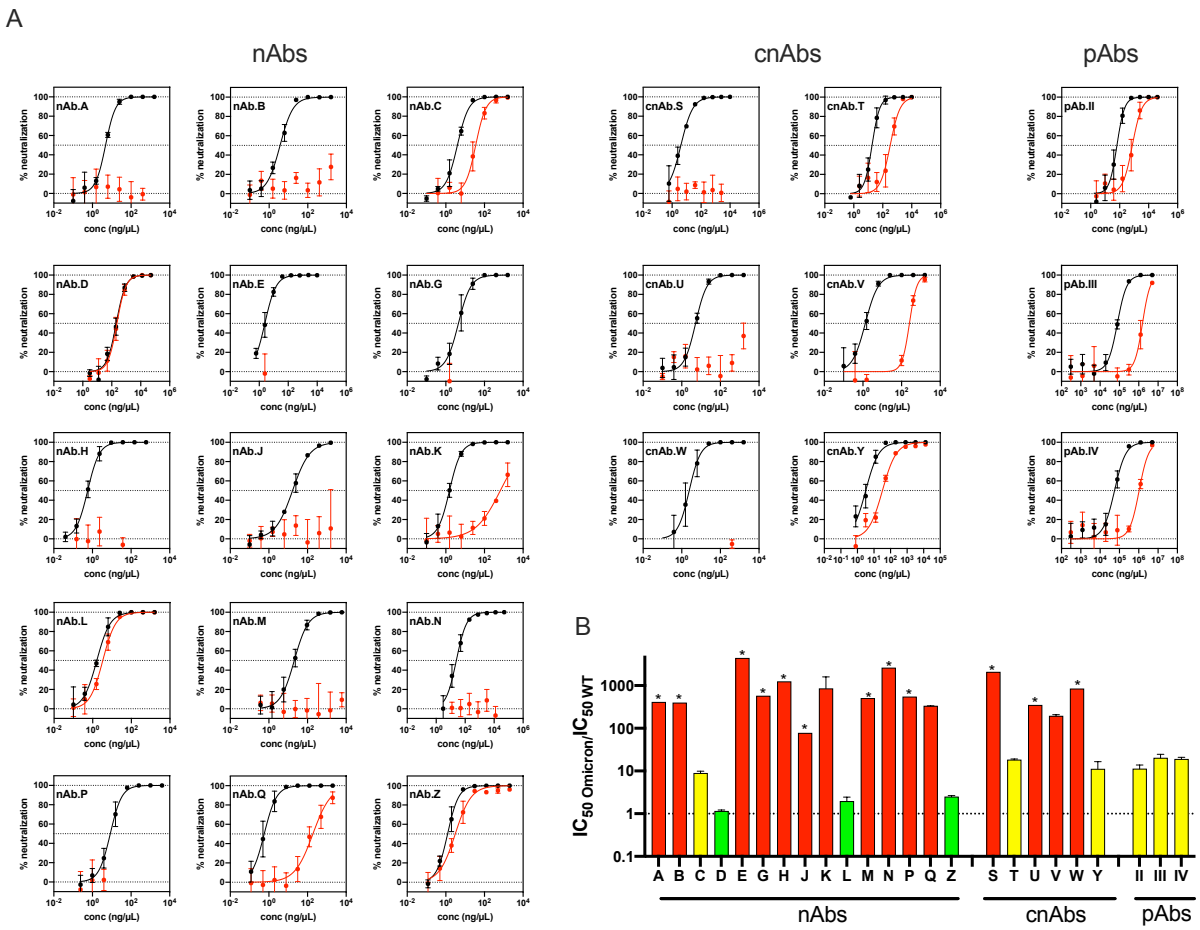


Fig. 4. Neutralization of Omicron by therapeutic antibodies. (A) Neutralization curves for each one of the 24 therapeutic antibody products against WT (black) and Omicron (red). (B) Bar graph showing the ratio between the IC_{50} of Omicron and WT for all the antibody products. The sensitivity of the Omicron variant against 15 monoclonal antibodies (nAbs), 6 combination nAbs products (cnAbs), and 3 polyclonal antibodies (pAbs). Red indicates IC_{50} resistance ratios >50, yellow indicates moderate resistance with IC_{50} ratios between 5-50, and green indicates sensitivity comparable to WT with IC_{50} ratios <5. Antibodies for which complete neutralization was not achieved at the highest concentration tested are denoted by *. Data shown represent two independent experiments each with an intra-assay duplicate.

616 **Table 1. Demographic data for participants receiving Pfizer/BNT162b2 initial vaccine**

617 **series and booster**

	N (%)
Sex	
Female	25 (64.1)
Male	14 (35.9)
Race	
White	26 (66.6%)
Asian	8 (20.5%)
Black	4 (10.3%)
Multiracial	1 (2.6%)
Occupation	
Nurse	11 (28.2%)
Physician	11 (28.2%)
Physical/Occupational/Recreational Therapist	9 (23.1%)
Medical Technician	3 (7.7%)
Lab Personnel	3 (7.7%)
Social Worker	1 (2.6%)
Psychologist	1 (2.6%)
Anti-N seroconversion after vaccination and before boost	
Positive	17 (43.6%)
Negative	22 (56.3%)

Age	
Mean age ± SD (range)	45 ± 11 (26 - 69)
Time between second vaccine and sample collection	
Mean days ± SD (range)	30 ± 11 (28 - 34)
Time between second vaccine and booster dose	
Mean days ± SD (range)	267 ± 14 (218-310)
Time between booster dose and sample collection	
Mean days +/- SD (range)	43 ± 17 (7 - 93)

618

619

Table 2: Characteristics of unvaccinated infections providing convalescent sera

	N = 39
Gender	
Female	14 (35.9%)
Male	25 (64.1%)
Race	
White	29 (74.4%)
Asian	1 (2.6%)
Black	6 (15.4%)
Multiracial	3 (7.7%)
Age	
Mean age ± SD (range)	41.1 ± 20 (1.4 - 73.2)
Charlson comorbidity index	
0	20 (51.3%)
1-2	10 (25.6%)
3-4	5 (12.8%)
>5	4 (10.3%)
Time between infection symptom onset and sample collection	
Mean days ± SD (range)	30.2 ± 9.3 (14.0 - 51.0)
Severity of initial infection	
Outpatient	23 (59.0%)
Hospitalized	16 (41.0%)
Infecting genotype*	

AY.119	1 (2.6%)
AY.14	2 (5.1%)
AY.25	3 (7.7%)
AY.44	1 (2.6%)
AY.47	1 (2.6%)
AY.62	1 (2.6%)
AY.74	1 (2.6%)
B.1	10 (25.6%)
B.1.1.7	5 (12.8%)
B.1.2	6 (15.4%)
B.1.351	1 (2.6%)
B.1.617.2	7 (17.9%)

620 [*] Genotypes assigned based on Pango 3.1.17 (2021-12-06). The genotype of the infecting variant
621 was determined in all cases except for one, a traveler who had moderate-severe Covid-19
622 (outpatient) in the Republic of South Africa during the peak of the Beta (B.1.351) wave in
623 January 2021 (FDA IRB Study # 2021-CBER-045).

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