1 **SARS-CoV-2 Omicron neutralization by therapeutic antibodies, convalescent**

2 **sera, and post-mRNA vaccine booster**

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5 **One Sentence Summary:** Third dose of Pfizer/BioNTech COVID-19 vaccine significantly

6 boosts neutralizing antibodies to the Omicron variant compared to a second dose, while

7 neutralization of Omicron by convalescent sera, two-dose vaccine-elicited sera, or therapeutic

8 antibodies is variable and often low.

9

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47

48   **Abstract:**

49   The rapid spread of the highly contagious Omicron variant of SARS-CoV-2 along with its high

50   number of mutations in the spike gene has raised alarm about the effectiveness of current

51   medical countermeasures. To address this concern, we measured neutralizing antibodies against

52   Omicron in three important settings: (1) post-vaccination sera after two and three immunizations

53   with the Pfizer/BNT162b2 vaccine, (2) convalescent sera from unvaccinated individuals infected

54   by different variants, and (3) clinical-stage therapeutic antibodies. Using a pseudovirus

55   neutralization assay, we found that titers against Omicron were low or undetectable after two

56   immunizations and in most convalescent sera. A booster vaccination significantly increased titers

57   against Omicron to levels comparable to those seen against the ancestral (D614G) variant after

58   two immunizations. Neither age nor sex were associated with differences in post-vaccination

59   antibody responses. Only three of 24 therapeutic antibodies tested retained their full potency

60   against Omicron and high-level resistance was seen against fifteen. These findings underscore

61   the potential benefit of booster mRNA vaccines for protection against Omicron and the need for

62   additional therapeutic antibodies that are more robust to highly mutated variants.

63   **Main Text:**

64   **INTRODUCTION**

65   In November 2021 a new SARS-CoV-2 variant, named Omicron (Pango lineage B.1.1.529),

66   was identified as a variant of concern (VOC). Its rapid spread in Africa and unusually high

67   number of mutations, especially in the spike gene, has triggered intense international efforts to

68   track the variant's spread and evaluate its effects on the potency of therapeutics and vaccines.

69   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.

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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)

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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

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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

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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)

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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

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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.

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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

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References and Notes

1. D. Corti, L. A. Purcell, G. Snell, D. Veesler, Tackling COVID-19 with neutralizing monoclonal antibodies. *Cell* **184**, 3086-3108 (2021).

2. Y. Cao, J. Wang, F. Jian, T. Xiao, W. Song, A. Yisimayi, W. Huang, Q. Li, P. Wang, R. An, J. Wang, Y. Wang, X. Niu, S. Yang, H. Liang, H. Sun, T. Li, Y. Yu, Q. Cui, S. Liu, X. Yang, S. Du, Z. Zhang, X. Hao, F. Shao, R. Jin, X. Wang, J. Xiao, Y. Wang, X. S. Xie, B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. *bioRxiv*, 2021.2012.2007.470392 (2021).

3. A. Rössler, L. Riepler, D. Bante, D. v. Laer, J. Kimpel, SARS-CoV-2 B.1.1.529 variant (Omicron) evades neutralization by sera from vaccinated and convalescent individuals. *medRxiv*, 2021.2012.2008.21267491 (2021).

4. L. Lu, B. W.-Y. Mok, L. Chen, J. M.-C. Chan, O. T.-Y. Tsang, B. H.-S. Lam, V. W.-M. Chuang, A. W.-H. Chu, W.-M. Chan, J. D. Ip, B. P.-C. Chan, R. Zhang, C. C.-Y. Yip, V. C.-C. Cheng, K.-H. Chan, I. F.-N. Hung, K.-Y. Yuen, H. Chen, K. K.-W. To, Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients. *medRxiv*, 2021.2012.2013.21267668 (2021).

5. N. Ikemura, A. Hoshino, Y. Higuchi, S. Taminishi, T. Inaba, S. Matoba, SARS-CoV-2 Omicron variant escapes neutralization by vaccinated and convalescent sera and therapeutic monoclonal antibodies. *medRxiv*, 2021.2012.2013.21267761 (2021).

6. E. Cameroni, C. Saliba, J. E. Bowen, L. E. Rosen, K. Culap, D. Pinto, A. De Marco, S. K. Zepeda, J. di Iulio, F. Zatta, H. Kaiser, J. Noack, N. Farhat, N. Czudnochowski, C. Havenar-Daughton, K. R. Sprouse, J. R. Dillen, A. E. Powell, A. Chen, C. Maher, L. Yin, D. Sun, L. Soriaga, C. Gustafsson, H. Chu, N. M. Franko, J. Logue, N. T. Iqbal, I. Mazzitelli, J. Geffner, R. Grifantini, A. Gori, A. Riva, O. Giannini, A. Ceschi, P. Ferrari, A. Franzetti-Pellanda, C. Garzoni, C. Hebner, L. Purcell, L. Piccoli, M. S. Pizzuto, A. C. Walls, A. Telenti, H. W. Virgin, A. Lanzavecchia, D. Veesler, G. Snell, D. Corti, Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *bioRxiv*, 2021.2012.2012.472269 (2021).

7. S. Cele, L. Jackson, K. Khan, D. Khoury, T. Moyo-Gwete, H. Tegally, C. Scheepers, D. Amoako, F. Karim, M. Bernstein, G. Lustig, D. Archary, M. Smith, Y. Ganga, Z. Jule, K. Reedoy, J. E. San, S.-H. Hwa, J. Giandhari, J. M. Blackburn, B. I. Gosnell, S. A. Karim, W. Hanekom, NGS-SA, C.-K. Team, A. von Gottberg, J. Bhiman, R. J. Lessells, M.-Y. S. Moosa, M. Davenport, T. de Oliveira, P. L. Moore, A. Sigal,

347   SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization

348   and requires ACE2 for infection. *medRxiv*, 2021.2012.2008.21267417 (2021).

349   8.   C. I. Kaku, E. R. Champney, J. Normark, C. E. Johnson, C. Ahlm, M. Sakharkar, M. E. Ackerman, M. N.

350   E. Forsell, L. M. Walker, Broad anti-SARS-CoV-2 antibody immunity induced by heterologous

351   ChAdOx1/mRNA-1273 prime-boost vaccination. *medRxiv*, 2021.2012.2013.21267598 (2021).

352   9.   W. F. Garcia-Beltran, K. J. St Denis, A. Hoelzemer, E. C. Lam, A. D. Nitido, M. L. Sheehan, C. Berrios, O.

353   Ofoman, C. C. Chang, B. M. Hauser, J. Feldman, D. J. Gregory, M. C. Poznansky, A. G. Schmidt, A. J.

354   Iafrate, V. Naranbhai, A. B. Balazs, mRNA-based COVID-19 vaccine boosters induce neutralizing

355   immunity against SARS-CoV-2 Omicron variant. *medRxiv*, 2021.2012.2014.21267755 (2021).

356 10.   H. Gruell, K. Vanshylla, P. Tober-Lau, D. Hillus, P. Schommers, C. Lehmann, F. Kurth, L. E. Sander, F.

357   Klein, mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2

358   Omicron variant. *medRxiv*, 2021.2012.2014.21267769 (2021).

359 11.   F. Schmidt, F. Muecksch, Y. Weisblum, J. D. Silva, E. Bednarski, A. Cho, Z. Wang, C. Gaebler, M.

360   Caskey, M. C. Nussenzweig, T. Hatziioannou, P. D. Bieniasz, Plasma neutralization properties of the

361   SARS-CoV-2 Omicron variant. *medRxiv*, 2021.2012.2012.21267646 (2021).

362 12.   K. Basile, R. J. Rockett, K. McPhie, M. Fennell, J. Johnson-Mackinnon, J. E. Agius, W. Fong, H. Rahman,

363   D. Ko, L. Donavan, L. Hueston, C. Lam, A. Arnott, S. C.-A. Chen, S. Maddocks, M. V. O'Sullivan, D. E.

364   Dwyer, V. Sintchenko, J. Kok, Improved neutralization of the SARS-CoV-2 Omicron variant after Pfizer-

365   BioNTech BNT162b2 COVID-19 vaccine boosting. *bioRxiv*, 2021.2012.2012.472252 (2021).

366 13.   I. Nemet, L. Kliker, Y. Lustig, N. S. Zuckerman, O. Erster, C. Cohen, Y. Kreiss, S. Alroy-Preis, G. Regev-

367   Yochay, E. Mendelson, M. Mandelboim, Third BNT162b2 vaccination neutralization of SARS-CoV-2

368   Omicron infection. *medRxiv*, 2021.2012.2013.21267670 (2021).

369 14.   A. Wilhelm, M. Widera, K. Grikscheit, T. Toptan, B. Schenk, C. Pallas, M. Metzler, N. Kohmer, S. Hoehl,

370   F. A. Helfritz, T. Wolf, U. Goetsch, S. Ciesek, Reduced Neutralization of SARS-CoV-2 Omicron Variant

371   by Vaccine Sera and monoclonal antibodies. *medRxiv*, 2021.2012.2007.21267432 (2021).

372 15.   N. Doria-Rose, X. Shen, S. D. Schmidt, S. O'Dell, C. McDanal, W. Feng, J. Tong, A. Eaton, M. Maglinao,

373   H. Tang, R. L. Atmar, K. E. Lyke, L. Wang, y. Zhang, M. R. Gaudinski, W. P. Black, I. Gordon, M. Guech,

374   J. E. Ledgerwood, J. N. Misasi, A. Widge, P. C. Roberts, J. Beigel, B. Korber, R. Pajon, J. R. Mascola, D.

375   C. Montefiori, Booster of mRNA-1273 Vaccine Reduces SARS-CoV-2 Omicron Escape from Neutralizing

376   Antibodies. *medRxiv*, 2021.2012.2015.21267805 (2021).

377   16.   J. M. Carreño, H. Alshammary, J. Tcheou, G. Singh, A. Raskin, H. Kawabata, L. Sominsky, J. Clark, D. C.

378   Adelsberg, D. Bielak, A. S. Gonzalez-Reiche, P. P. S. Group, K. Srivastava, E. M. Sordillo, G. Bajic, H.

379   van Bakel, V. Simon, F. Krammer, Activity of convalescent and vaccine serum against a B.1.1.529 variant

380   SARS-CoV-2 isolate. *medRxiv*, 2021.2012.2020.21268134 (2021).

381   17.   B. M. Jackson-Thompson, E. Goguet, E. D. Laing, C. H. Olsen, S. Pollett, K. M. Hollis-Perry, S. E.

382   Maiolatesi, L. Illinik, K. F. Ramsey, A. E. Reyes, Y. Alcorta, M. A. Wong, J. Davies, O. Ortega, E.

383   Parmelee, A. R. Lindrose, M. Moser, E. Graydon, A. G. Letizia, C. A. Duplessis, A. Ganesan, K. P. Pratt,

384   A. M. Malloy, D. W. Scott, S. K. Anderson, A. L. Snow, C. L. Dalgard, J. H. Powers, 3rd, D. Tribble, T. H.

385   Burgess, C. C. Broder, E. Mitre, Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) study:

386   an observational cohort study of SARS-CoV-2 infection and vaccination in healthcare workers. *BMC Infect*

387   *Dis* **21**, 544 (2021).

388   18.   E. D. Laing, C. D. Weiss, E. C. Samuels, S. A. A. Coggins, W. Wang, R. Wang, R. Vassell, S. L. Sterling,

389   M. A. Tso, T. Conner, E. Goguet, M. Moser, B. M. Jackson-Thompson, L. Illinik, J. Davies, O. Ortega, E.

390   Parmelee, M. Hollis-Perry, S. E. Maiolatesi, G. Wang, K. F. Ramsey, A. E. Reyes, Y. Alcorta, M. A.

391   Wong, A. R. Lindrose, C. A. Duplessis, D. R. Tribble, A. M. W. Malloy, T. H. Burgess, S. D. Pollett, C. H.

392   Olsen, C. C. Broder, E. Mitre, Durability of antibody responses and frequency of clinical and subclinical

393   SARS-CoV-2 infection six months after BNT162b2 COVID-19 vaccination in healthcare workers.

394   *medRxiv*, 2021.2010.2016.21265087 (2021).

395   19.   S. A. Richard, S. D. Pollett, C. A. Lanteri, E. V. Millar, A. C. Fries, R. C. Maves, G. C. Utz, T. Lalani, A.

396   Smith, R. M. Mody, A. Ganesan, R. E. Colombo, C. J. Colombo, D. A. Lindholm, C. Madar, S. Chi, N.

397   Huprikar, D. T. Larson, S. E. Bazan, C. English, E. Parmelee, K. Mende, E. D. Laing, C. C. Broder, P. W.

398   Blair, J. G. Chenoweth, M. P. Simons, D. R. Tribble, B. K. Agan, T. H. Burgess, E. C.-C. S. Group,

399   COVID-19 Outcomes Among US Military Health System Beneficiaries Include Complications Across

400   Multiple Organ Systems and Substantial Functional Impairment. *Open Forum Infect Dis* **8**, ofab556 (2021).

17

401   20.   S. Lusvarghi, W. Wang, R. Herrup, S. N. Neerukonda, R. Vassell, L. Bentley, A. E. Eakin, K. J. Erlandson,

402   C. D. Weiss, Key substitutions in the spike protein of SARS-CoV-2 variants can predict resistance to

403   monoclonal antibodies, but other substitutions can modify the effects. *J Virol*, JVI0111021 (2021).

404   21.   M. Schubert, F. Bertoglio, S. Steinke, P. A. Heine, M. A. Ynga-Durand, F. Zuo, L. Du, J. Korn, M.

405   Milošević, E. V. Wenzel, H. Maass, F. Krstanović, S. Polten, M. Pribanić-Matešić, I. Brizić, A. Piralla, F.

406   Baldanti, L. Hammarström, S. Dübel, A. Šustić, H. Marcotte, M. Strengert, A. Protić, Q. Pan

407   Hammarström, L. Čičin-Šain, M. Hust, Human serum from SARS-CoV-2 vaccinated and COVID-19

408   patients shows reduced binding to the RBD of SARS-CoV-2 Omicron variant in comparison to the original

409   Wuhan strain and the Beta and Delta variants. *medRxiv*, 2021.2012.2010.21267523 (2021).

410   22.   E. D. Laing, S. L. Sterling, S. A. Richard, N. J. Epsi, S. Coggins, E. C. Samuels, S. Phogat, L. Yan, N.

411   Moreno, C. L. Coles, M. Drew, J. Mehalko, S. Merritt, K. Mende, V. Munster, E. de Wit, K. K. Chung, E.

412   V. Millar, D. R. Tribble, M. P. Simons, S. D. Pollett, D. Esposito, C. Lanteri, G. T. Clifton, E. Mitre, T. H.

413   Burgess, C. C. Broder, Antigen-based multiplex strategies to discriminate SARS-CoV-2 natural and

414   vaccine induced immunity from seasonal human coronavirus humoral responses. *medRxiv*, (2021).

415   23.   S. Jangra, C. Ye, R. Rathnasinghe, D. Stadlbauer, g. Personalized Virology Initiative study, F. Krammer,

416   V. Simon, L. Martinez-Sobrido, A. Garcia-Sastre, M. Schotsaert, SARS-CoV-2 spike E484K mutation

417   reduces antibody neutralisation. *Lancet Microbe*, (2021).

418   24.   S. N. Neerukonda, R. Vassell, S. Lusvarghi, R. Wang, F. Echegaray, L. Bentley, A. E. Eakin, K. J.

419   Erlandson, L. C. Katzelnick, C. D. Weiss, W. Wang, SARS-COV-2 Delta variant displays moderate

420   resistance to neutralizing antibodies and spike protein properties of higher soluble ACE2 sensitivity,

421   enhanced cleavage and fusogenic activity. *bioRxiv*, (2021).

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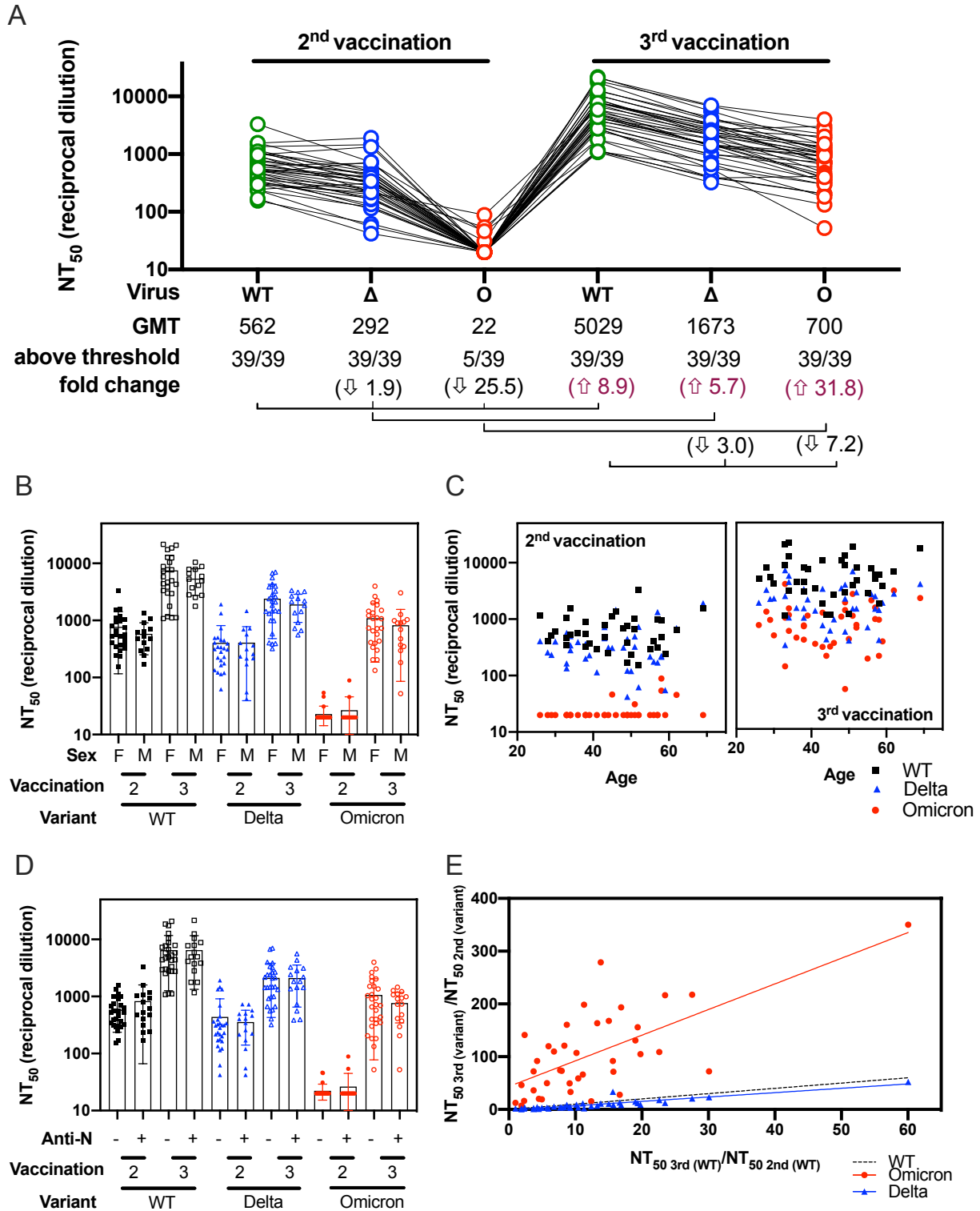
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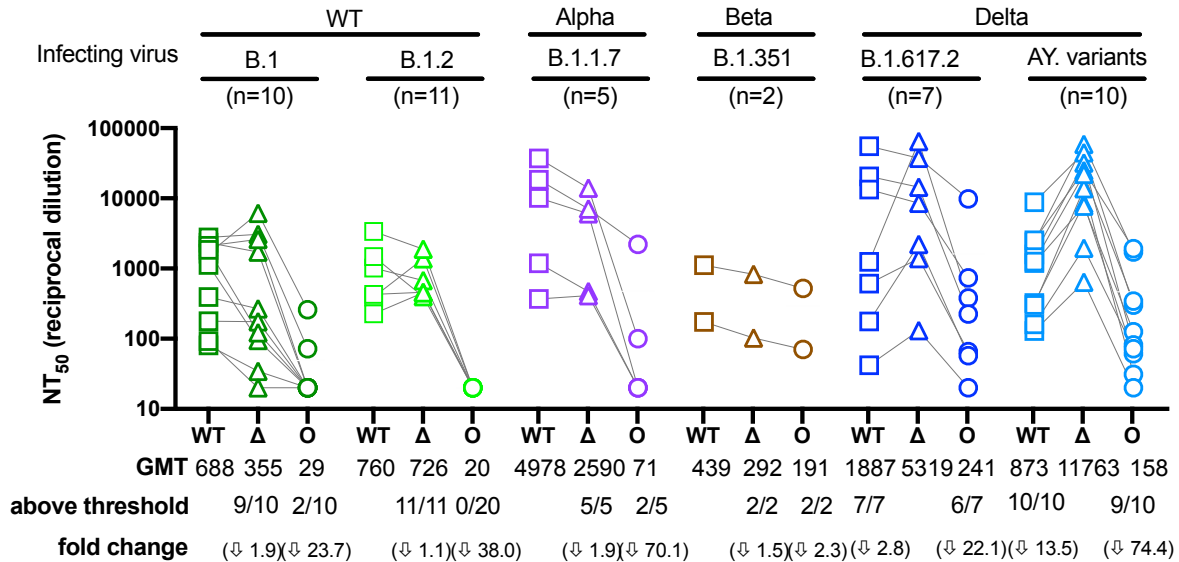
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560 **Fig. 1. Sensitivity of the Omicron variant to neutralization by Pfizer/BNT162b2 vaccinee**

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.

26

	WT				Alpha	Beta	Delta	
Infecting virus	B.1 (n=10)		B.1.2 (n=11)		B.1.1.7 (n=5)	B.1.351 (n=2)	B.1.617.2 (n=7)	AY. variants (n=10)
	WT Δ O		WT Δ O		WT Δ O	WT Δ O	WT Δ O	WT Δ O
GMT	688 355 29		760 726 20		4978 2590 71	439 292 191	1887 5319 241	873 11763 158
above threshold	9/10 2/10		11/11 0/20		5/5 2/5	2/2 2/2	7/7 6/7	10/10 9/10
fold change	(⇓ 1.9)(⇓ 23.7)		(⇓ 1.1)(⇓ 38.0)		(⇓ 1.9)(⇓ 70.1)	(⇓ 1.5)(⇓ 2.3) (⇓ 2.8)	(⇓ 22.1)(⇓ 13.5)	(⇓ 74.4)

**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.

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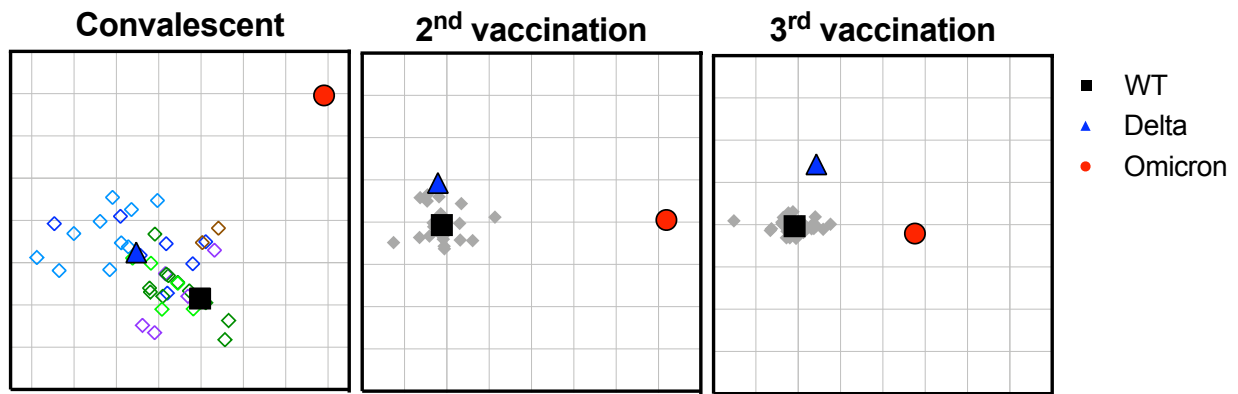
Fig. 3. Antigenic cartography of convalescent and vaccinee sera against WT, Delta and Omicron. Antigenic maps were separately generated from convalescent (left panel), 2nd vaccination (middle panel) or 3rd vaccination (right panel) sera. Convalescent sera are shown in diamonds as follows: B.1 (dark green), B.1.2 (light green), B.1.1.7 (purple), B.1.351 (brown), AY variants (light blue), and B.1.617.2 (dark blue). Gray diamonds correspond to post-vaccination sera. Each grid square corresponds to 2-fold dilution in the neutralization assay. Black squares correspond to WT variant. Blue triangles correspond to Delta variant. Red circle corresponds to Omicron variant.
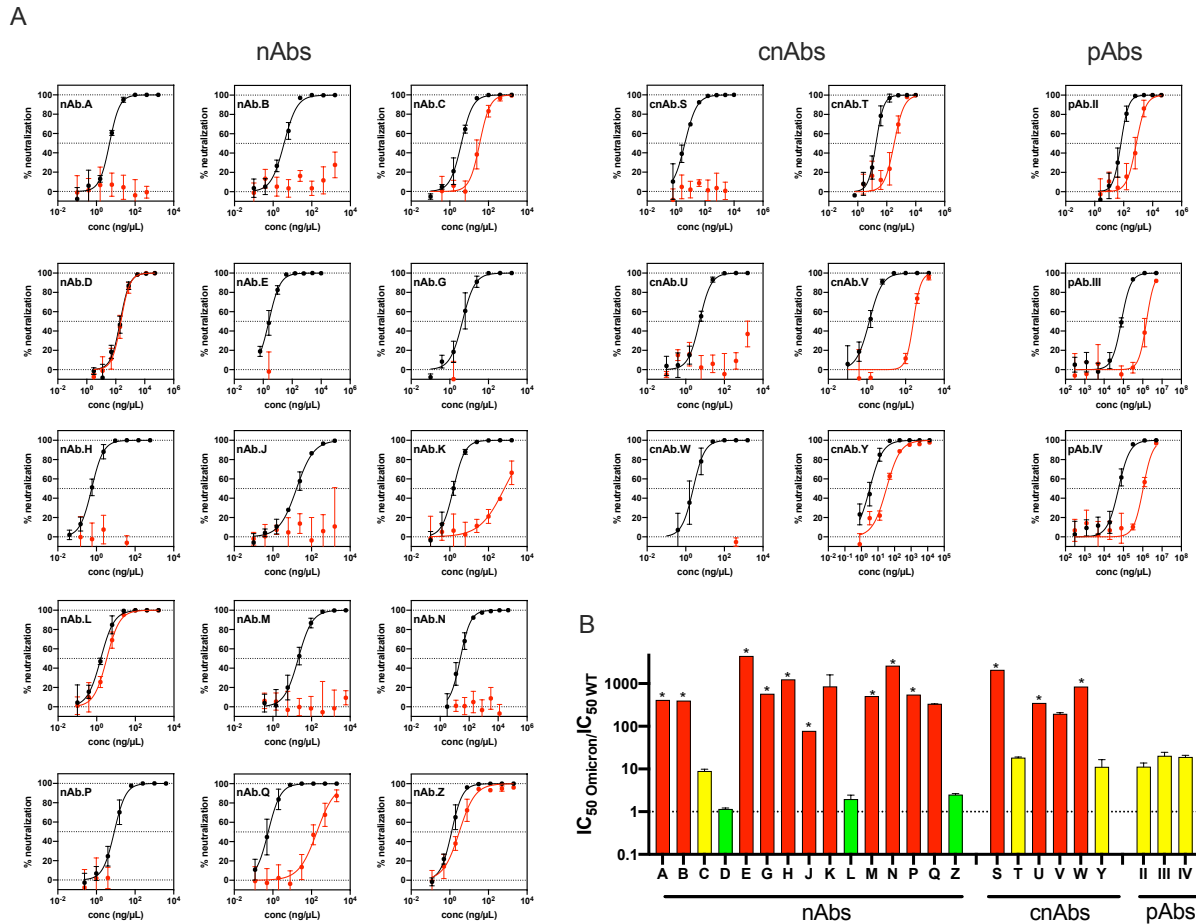
Fig. 4. Neutralization of Omicron by therapeutic antibodies. (A) Neutralization curves for each one of the 24 therapeutic antibody products against WT (black) and Omicron (red). (B) Bar graph showing the ratio between the IC_{50} of Omicron and WT for all the antibody products. The sensitivity of the 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)

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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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