

1 Plasma after both SARS-CoV-2 boosted vaccination and COVID-19 potentially neutralizes BQ.1.1
2 and XBB.1

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15
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31 Abstract

32 The SARS-CoV-2 Omicron variants, dominating in the late 2022 COVID-19 waves, have acquired
33 resistance to most neutralizing anti-Spike monoclonal antibodies authorized so far, and the BQ.1.*
34 sublineages, dominant in the western countries, are notably resistant to all authorized monoclonal
35 antibodies. Polyclonal antibodies from individuals both with at least 3 vaccine doses and also
36 recently recovered from Omicron COVID-19 (VaxCCP) could retain neutralizing activity against
37 such new Omicron lineages. Here we reviewed BQ.1.1 virus neutralization data from 740
38 individual patient samples from 37 separate cohorts defined by boosted vaccinations with or
39 without recent Omicron COVID-19, as well as infection without vaccination. More than 96% of
40 the plasma samples from individuals in the recently (within 6 months) boosted VaxCCP study
41 cohorts neutralized BQ.1.1, XBB.1 and BF.7 with 100% neutralization of WA-1, BA.4/5, BA.4.6
42 and BA.2.75. The geometric mean of the geometric mean 50% neutralizing titers (GM(GMT₅₀)
43 were 334, 72 and 204 for BQ.1.1, XBB.1 and BF.7, respectively. Compared to VaxCCP, plasma
44 sampled from COVID-19 naïve subjects who also recently within 6 months received at least a third
45 vaccine dose had about half of the GM(GMT₅₀) for all viral variants with percent neutralizations
46 of 79%, 52% and 94% for BQ.1.1, XBB.1 and BF.7, respectively. Boosted VaxCCP characterized
47 by either recent vaccine dose or infection event within 6 months represents a robust, variant-
48 resilient, passive immunotherapy against the new Omicron BQ.1.1, XBB.1 and BF.7 variants.

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53	Table of contents	
54	Introduction.....	4
55	Results.....	4
56	Discussion.....	6
57	Search strategy and selection criteria.....	7
58	References.....	9
59	Table 1	11
60	Table 2	13
61	Figure 1	14
62	Figure 2	15
63	Figure 3	16
64	Supplementary Table 1	17
65	Supplementary Table 2	18
66	Supplementary Table 3	21
67	Supplementary Figure 1	23
68	Supplementary Figure 2.....	24
69	Supplementary Figure 3.....	25
70		
71		

72 Introduction

73 In immunocompromised (IC) patients both passive immunotherapies and small molecule antivirals
74 are often necessary to treat COVID-19 or eliminate persistently high SARS-CoV-2 viral load.
75 Chronic, persistent viral loads increase both transmission and mutation risk, and prevent
76 administration of the required immunosuppressive/antineoplastic therapies¹. Small molecule
77 antivirals have not been formally validated for IC patients, who often have contraindications, and
78 the convergent evolution of the Omicron variant of concern (VOC) has led to inefficacy of all the
79 anti-Spike monoclonal antibodies (mAbs) authorized so far for both treatment or prevention, e.g.
80 in the highly prevalent BQ.1.* sublineages². The other rapidly growing XBB.* and BF.7
81 sublineages are also highly resistant to anti-Spike mAbs³. Polyclonal plasma from individuals who
82 are both vaccinated and had COVID-19 (VaxCCP) has more than ten times the antibody levels
83 capable of neutralizing pre-Omicron variants as well as Omicron variants BA.1 through BA.4/5^{4,5}.
84 Polyclonal COVID-19 convalescent plasma (CCP) has thousands of distinct antibody specificities
85 of different isotypes, including many capable of SARS-CoV-2 neutralization. High-titer pre-
86 Omicron CCP contains Omicron neutralizing activity despite being collected before variant
87 appearance^{4,5}.

88
89 Given that CCP remains a recommended therapy for IC^{1,6,7}, we systematically reviewed recent
90 primary research for neutralization results against BQ.1.1 by plasma collected from vaccinated
91 subjects with or without COVID-19 or after recent Omicron infection alone.

92

93 Results

94 Eight articles were included (**Figure 1**) which contained virus neutralizations with WA-1, BQ.1.1,
95 BA.4/5, BA.4.6, XBB.1 and BF.7, assessed with either live authentic SARS-CoV-2 or SARS-
96 CoV-2 pseudovirus neutralization assays and represented data from 652 patients (**Supplementary**
97 **Table 1**). Qu *et al.* in the USA reported on Spring and Summer 2022 breakthrough infections with
98 BA.1 and BA.4/5 in two sampled cohorts with predominantly unvaccinated individuals, as well as
99 a third cohort of healthcare workers after a single monovalent booster vaccination in the Fall of
100 2021⁸ (**Table 1**). Zou *et al.* in the USA in the Summer and Fall of 2022 sampled individuals who
101 had already received 3 mRNA BNT162b2 vaccinations with or without previous COVID-19, both
102 before and about 4 weeks after a 4th monovalent or bivalent vaccine booster vaccination⁹. Miller
103 *et al.* also in the USA sampled both before the 3rd vaccination dose and about 4 weeks after
104 monovalent mRNA vaccination in the Fall of 2021, as well as with the 4th vaccine dose in the
105 Summer or Fall of 2022, with either monovalent or bivalent booster vaccinations in Fall of 2022
106 in those with no documented COVID-19¹⁰. Cao *et al.* in China investigated BQ.1.1 neutralizations
107 from plasma of 4 cohorts after 3 doses of CoronaVac (Fall 2021) without COVID-19 or 2-12 weeks
108 after BA.1, BA.2 and BA.5 infection³. Planas *et al.* in France evaluated GMT₅₀ in plasma from
109 individuals both 4 and 16 weeks after a third monovalent mRNA vaccine dose in the Fall of 2021
110 as well as 12 and 32 weeks after vaccine breakthrough BA.1/2 or BA.5 infection¹¹. Davis *et al.* in
111 the USA sampled after the 3rd mRNA vaccine monovalent dose in the Fall of 2021 and also after
112 either a 4th monovalent mRNA dose or a bivalent (wild-type + BA.4/5) vaccine dose in the
113 Summer and Fall of 2022¹². Kurhade *et al.* in the USA also compared GMT₅₀ after the 4th
114 monovalent vaccine dose or 3 mRNA doses with the 4th the bivalent dose without COVID-19 and
115 also after bivalent boost with recent COVID-19¹³. Wang *et al.* in the USA compared GMT₅₀ after
116 three vaccine doses, the 4th monovalent vaccine dose or 3 mRNA doses with the 4th the bivalent

117 dose without COVID-19, and also after 2-3 vaccine doses and recent BA.2 breakthrough infection
118 or 3-4 mRNA vaccine doses and recent BA.4/5 breakthrough infection¹⁴.

119
120 These diverse cohorts were assembled into 3 groups, 1) plasma after both 2-4 vaccine doses and
121 COVID-19 (VaxCCP); 2) plasma from subjects after administration of 3-4 vaccine doses (i.e.
122 boosted), but either self-reported as COVID-19-*naïve* or anti-nucleocapsid negative; and 3)
123 Omicron infection without vaccination (CCP) as well as participants sampled 6 to 11 months after
124 previous vaccine dose and before the booster vaccination. Boosted VaxCCP neutralized BQ.1.1,
125 XBB.1 and BF.7 with approximately 3 times the dilutional potency of the vaccine-only or 2-6
126 times CCP/pre-boost vaccination groups for all viral variants (**Table 2 and Figure 2**). Importantly,
127 while there was a 20-fold reduction in neutralization by boosted VaxCCP against BQ.1.1 compared
128 to WA-1, more than 96% of the boosted VaxCCP samples neutralized BQ.1.1 as well as XBB.1
129 and BF.7 (**Table 2 and Figure 2c**). The single cohort within the boosted VaxCCP group which
130 was at 85% neutralization was sampled late, 8 months after BA.1/2 breakthrough infection¹¹
131 (**Supplementary Table 2 and 3**). Except for the GMT (GMT₅₀) against XBB.1 at 72, the other
132 viral variant neutralizations were in the same range as pre-Alpha CCP neutralizing WA-1 (i.e.,
133 311)⁴. By comparison the large randomized clinical trial which effectively reduced outpatient
134 COVID-19 progression to hospitalizations had a GMT₅₀ of 80 for WA-1 with pre-Alpha CCP¹⁵.
135 Boosted vaccinations at 3-4 doses without COVID-19, showed GM(GMT₅₀) of 123 for BQ.1.1,
136 with only 6 of 21 cohorts over 90% neutralizations, for 82% overall (i.e. 272 of 344 individuals).
137 Four separate studies^{8,13,12,10} characterized BQ.1.1 virus neutralizations with plasma after the new
138 bivalent (wild-type + BA.4/5) mRNA vaccine booster in the Fall of 2022, with 88% (103 of 117
139 samples) neutralization activity within 4 weeks of bivalent booster (**Supplementary Table 3**).

140
141 Many studies performed virus neutralizations on samples drawn before the 3rd or 4th vaccine dose
142 which were 6 to 11 months after last vaccine dose. The GM(GMT₅₀)'s for BQ.1.1 and BA.2.75
143 were about 6 times reduced compared to VaxCCP even though the fold reductions were similar
144 (**Figure 3, Table 2**). In agreement with lower GMT₅₀ for neutralizations was the low percent
145 neutralizing BQ.1.1 (60%), XBB.1 (46%), and BF.7 (75%) at 6 to 11 months after vaccination
146 (**Figure 3, Table 2 and Supplementary Table 3**).

147
148 Four studies used the lentiviral pseudovirus assays, with diverse Spike proteins cloned in, while
149 the other four were live virus assays using different cell types (**Supplementary Table 1**). Notably,
150 Planas *et al* employed the IGROV-1 cell type for better growth of Omicron sublineages¹¹. While
151 the single study fold reductions (FR) and percent neutralizations normalize the results between
152 studies, the GMT₅₀ can vary between studies even amongst the live authentic viral neutralization
153 studies (e.g., mNeonGreenTM reporter assays versus cytopathic effects)^{9,13}. We sorted the live
154 authentic viral neutralizations from the pseudoviral neutralizations, plotting also the minimum and
155 maximums (**Supplementary Figures 1-3**). In general, the live authentic SARS-CoV-2
156 neutralization assays for VaxCCP appeared to have similar antibody neutralization levels, with the
157 single study by Cao *et al*³ employing lentiviral pseudovirus with lower dilutional titers. In contrast,
158 the GMT₅₀ achieved with pseudoviral assays in the boosted vaccinations without COVID-19
159 appeared slightly higher than the ones achieved with authentic virus.

160

161 **Discussion**

162 The FDA deemed CCP safe and effective for both immunocompetent and IC COVID-19
163 outpatients^{6,7,16}, and further extended its authorized use in the IC patient population in December
164 2021^{7,16}, at a time when oral antiviral therapy promised a no transfusion outpatient solution and
165 many anti-Spike mAbs were still effective.

166
167 Up until the present, CCP remained a backup bridge for IC patients, durable against the changing
168 variants and as a salvage therapy in seronegative IC patients. With the recent advent of Omicron
169 XBB.* and BQ.1.* defeating the remaining anti-Spike mAbs, boosted VaxCCP, recently collected
170 within the last 6 months of either a vaccine dose or SARS-CoV-2 is likely to be the only viable
171 remaining passive antibody therapy in the 2022-23 Winter for IC patients who have failed to make
172 antibodies after vaccination and still require B-cell depleting drugs or immunosuppressive
173 therapy. In a literature review of CCP from diverse VOC waves as well as boosted vaccinees and
174 VaxCCP up to BA-1, VaxCCP showed higher neutralization titers against Omicron at levels above
175 300 dilutional GMT₅₀⁴.

176
177 The accelerated evolution of SARS-CoV-2 VOCs has created the problem that the pharmaceutical
178 development of additional mAbs is not worth the effort and cost given their expected short useful
179 clinical life expectancy, so the anti-Spike mAb pipeline has remained stuck in 2022. High levels
180 of antibodies in donor plasma from both boosted vaccinations and COVID-19 convalescent plasma
181 (VaxCCP) neutralize more than 95% of BQ.1.1 and BF.7 with XBB.1 at 85%. Recently collected
182 plasma within a 6 month window from those boosted vaccinees without prior documented COVID-
183 19 had a 20-30% reduction in neutralization percent for BQ.1.1 and XBB.1 with 10% reduction for
184 the others and a third of the GM(GMT₅₀) neutralizing antibody levels compared to VaxCCP. In
185 those vaccinated with last dose more than 6 months prior to sample collection both the
186 neutralization percent and neutralizing antibody titers fell further compared to the recently boosted
187 VaxCCP group. Four studies (Planas¹¹, Zou⁹, Cao³ and Kurhade¹³) had directly comparative
188 cohorts in the three groups which increases the robustness reduction in neutralizations with the
189 vaccine only or more than 6 months to last vaccine or infection event compared to VaxCCP. The
190 main limitation of our systematic review is the small number of studies reporting virus
191 neutralization with BQ.1.1 with most available as pre-preprints without peer-review yet. However,
192 we note that peer-review itself does not change GMT₅₀ or neutralization numbers and the authors
193 of these papers have considerable expertise in the topic.

194
195 Boosted VaxCCP has full potential to replace anti-Spike mAbs for passive antibody therapy of IC
196 patients against recent Omicron sublineages, in the meanwhile polyclonal IgG formulations can
197 be manufactured. VaxCCP qualification in the real-world will likely remain constrained on high-
198 throughput serology, whose correlation with GMT₅₀ is not perfect^{17,18}. Nevertheless, the very high
199 prevalence (96%) of Omicron-neutralizing antibodies and the high GM(GMT₅₀) in recently
200 boosted VaxCCP reassure about its potency, and further confirm that exact donor-recipient VOC
201 matching is dispensable. Overall, our findings urge WHO to revise its guidelines and recommend
202 boosted VaxCCP for therapy of COVID-19 in IC patients.

203
204

205 Search strategy and selection criteria

206 On November 19, 2022 we initially searched PubMed, medRxiv and bioRxiv for manuscripts
207 reporting BQ.1.1 neutralization, using English language as a restriction. Search of bioRxiv with
208 same keywords yielded 15 records of which only 8 contained plasma viral neutralization data.
209 Search of medRxiv produced 3 records which did not have BQ.1.1 neutralizations. PubMed
210 retrieved 3 entries using (“BQ.1.1”) and (“neutralization”), one of which was focused on anti-
211 Spike mAb alone² and the other 2 were duplicates from bioRxiv^{8,12}. Articles underwent evaluation
212 for data extraction by two assessors (DS and DF) with disagreements resolved by third assessor
213 (AC). Articles lacking plasma BQ.1.1 virus neutralizations were excluded. The process of study
214 selection is represented in the PRISMA flow diagram (**Figure 1**).

215
216 The type of viral assay (live or pseudovirus), time interval to blood sample, GMT₅₀, minimum and
217 maximum neutralizing 50% dilutional titer for WA-1 (pre-Alpha wild-type) and Omicron
218 sublineages BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB.1 and BF.7 and number out of total that
219 neutralized Omicron were abstracted from study text, graphs and tables. Two studies (Wang¹⁴ and
220 Qu⁸) reported BQ.1 and those were separate cohorts in addition to BQ.1.1. Prism v. 9.4 (GraphPad
221 Software, San Diego, CA, USA) was used for data analysis. While all manuscripts included
222 neutralization data against WA-1, BQ.1.1, BA.4/5 and BA.2.75, only a subset of manuscripts
223 included neutralization data for BA.4.6, XBB.1 and BF.7 which were assembled for relevance to
224 present circulating variants. Historic early Omicron partial neutralization data on variants like
225 BA.1 or BA.2 were excluded because of the full set data with BA.4/5 and BA.2.75.

226
227 Statistical significance between log₁₀ transformed GMT₅₀ was investigated using Tukey’s test. The
228 multiple comparison test was a two-way ANOVA with Alpha 0.05 on log transformed GMT₅₀.
229 The log normal test was performed on WA-1, BQ.1.1, BA.4/5, BA.4.6, XBB.1 and BF.7 virus
230 GMT₅₀. Two studies^{10,11} reported the median titer rather than the GMT₅₀. Compiled data abstracted
231 from the published studies is available in the supplementary dataset.

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304

305 **Table 1**

306 Synopsis of included studies, reporting plasma sources, epoch of sampling, region, time since
 307 vaccination/infection to plasma sampling, and sample size. The cohorts were split into three
 308 groups-1) boosted vaccinations and recent COVID-19 (VaxCCP), 2) boosted vaccines only
 309 without documented COVID-19 (Vac only) and 3) infection alone or pre-boosted sampling
 310 before 3rd or 4th vaccine dose (Infection only or pre-boost)

Study	Vaccine and COVID-19 history at sample time	Group	Time period of plasma sampling	Geography	Sampling time mean or median (min-max)	Sample number
Cao ³	3xCorVac+BA.1 inf	VaxCCP	Spring 2022	China	5-7 weeks post hosp admit (42 weeks avg)	50
Cao ³	3xCorVac +BA.2 inf	VaxCCP	Summer 2022	China	3-11 weeks post hosp admit (8 weeks mean)	39
Cao ³	3xCorVac +BA.5 inf	VaxCCP	Summer/Fall 2022	China	2-11 weeks (mean 5 weeks)	36
Zou ⁹	4xBNT162b2+BTI	VaxCCP	Summer/Fall 2022	USA	4 week post dose	20
Planas ¹¹	mRNAvacx3+ BA.1/2 inf	VaxCCP	Spring/Fall 2022	France	32 weeks post BTI BA.1/2	13
Wang ¹⁴	2-3xmRNAvac+ BA.2 BTI	VaxCCP	Spring/Fall 2022	USA	2-23 weeks (mean 6 wk (3over 90 days))	14
Wang ¹⁴	3-4xmRNAvac+ BA.4/5 BTI	VaxCCP	Summer/Fall 2022	USA	2-8 weeks (mean 4 weeks)	20
Kurhade ¹³	3xmRNAvac+bivalent+BTI	VaxCCP	Fall 2022	USA	4 weeks post with infection history	23
Zou ⁹	3xBNT162b2+bivalent+BTI	VaxCCP	Summer/Fall 2022	USA	4 week post dose	19
Planas ¹¹	3xmRNAvac+ BA.1/2 inf	VaxCCP	Spring/Fall 2022	France	12 weeks post BTI BA.1/2	16
Planas ¹¹	3xmRNAvac+ BA.5 inf	VaxCCP	Fall 2022	France	8 weeks post BTI BA.5	15
Davis ¹²	3xmRNAvac	Vac only	Fall 2021	USA	1-4 weeks post boost	12
Kurhade ¹³	4xmRNAvac	Vac only	Summer 2022	USA	4-12 weeks	25
Cao ³	3xCorVac	Vac only	Fall 2021	China	4 weeks	40
Zou ⁹	4xBNT162b2	Vac only	Summer/Fall 2022	USA	4 weeks post dose	20
Planas ¹¹	3xmRNAvac	Vac only	Winter 2021/2022	France	16 weeks post 3rd dose	10
Wang ¹⁴	3xmRNAvac	Vac only	Fall 2021	USA	2-12 weeks (mean 5 weeks)	14
Wang ¹⁴	3xmRNAvac+monovalent	Vac only	Summer/Fall 2022	USA	3-4 weeks	19
Wang ¹⁴	3xmRNAvac+bivalent	Vac only	Summer/Fall 2022	USA	3-4 weeks	21
Davis ¹²	3xmRNAvac+monovalent	Vac only	Summer/Fall 2022	USA	10-15 weeks post boost	12
Kurhade ¹³	3xmRNAvac+bivalent	Vac only	Fall 2022	USA	4 weeks post	29
Davis ¹²	3xmRNAvac+bivalent	Vac only	Summer/Fall 2022	USA	2-6 weeks post booster (8 no vacc. 10 no infection)	12
Qu ⁸	3xmRNAvac	Vac only	Fall 2021	USA	2-13 weeks	15
Zou ⁹	3xBNT162b2+bivalent	Vac only	Summer/Fall 2022	USA	4 week post dose	18
Planas ¹¹	3xmRNAvac	Vac only	Fall/Winter 2021	France	4 weeks post 3rd dose	18
Miller ¹⁰	3xBNT162b2	Vac only	Fall 2021	USA	2-4 weeks	16

Miller ¹⁰	3xmRNA+ monovalent	Vac only	Spring/Fall 2022	USA	2-9 weeks	18
Miller ¹⁰	3xmRNA +bivalent	Vac only	Fall 2022	USA	2-3 weeks	15
Qu ⁸	BA.4/5 inf (17-unvac)	Inf only	Summer 2022	USA	not stated	20
Qu ⁸	Hosp BA.1 (6-unvac;5-2xmRNAvac)	Inf only	Spring 2022	USA	1 week post hospitalization	15
Zou ⁹	3xBNT162b2+BTI	preboost with BNT162b	Summer/Fall 2022	USA	preboost with BNT162b (6-11 months post last dose)	20
Zou ⁹	3xBNT162b2 +BTI	preboost with bivalent	Summer/Fall 2022	USA	preboost with bivalent (6-11 months post last dose)	19
Zou ⁹	3xBNT162b2	preboost with bivalent	Summer/Fall 2022	USA	preboost with bivalent (6-11 months post last dose)	18
Zou ⁹	3xBNT162b2	preboost with BNT162b	Summer/Fall 2022	USA	preboost with BNT162b (6-11 months post last dose)	20
Miller ¹⁰	2xBNT162b2	preboost with BNT162b	Fall 2021	USA	preboost (6-11 months post last dose)	16
Miller ¹⁰	3xmRNA	preboost with bivalent	Fall 2022	USA	preboost with bivalent (6-11 months post last dose)	15
Miller ¹⁰	3xmRNA	preboost with monovalent	Spring/Fall 2022	USA	preboost with monovalent (6-11 months post last dose)	18

311

312 **Table 2**

313 GM(GMT₅₀) of plasma from three different sources against recent Omicron sublineages.

Neutralization virus	WA-1	BQ.1.1	BA.4/5	BA.4.6	BA.2.75	XBB.1	BF.7
Post COVID-19/vaccine (study cohorts)	11	13	11	6	9	8	4
GM(GMT ₅₀)	6561*	334	1005	352	303	72	204
Fold reduction from WA-1	ref	20	7	19	22	91	32
Samples tested	265	265	265	106	231	96	148
Samples neutralizing	265	167**	264	106**	230	82	146
Percent neutralizing	100	96	100	100	100	85	99
Boosted vaccine (study cohorts)	17	21	17	7	14	7	7
GM(GMT ₅₀)	4350	123	362	123	107	47	357
Fold reduction from WA-1	ref	35	12	35	41	93	12
Samples tested	314	344	314	136	261	147	158
Samples neutralizing	314	272	295	126	231	76	149
Percent neutralizing	100	79	94	93	89	52	94
Infection only or preboosted vaccine (study cohorts)	9	11	9	6	9	4	5
GM(GMT ₅₀)	1022	48	101	117	57	22	110
Fold reduction from WA-1	ref	21	10	9	18	47	9
Samples tested	161	197	161	113	162	78	84
Samples neutralizing	159	123	123	85	104	36	63
Percent neutralizing	99	62	76	75	64	46	75

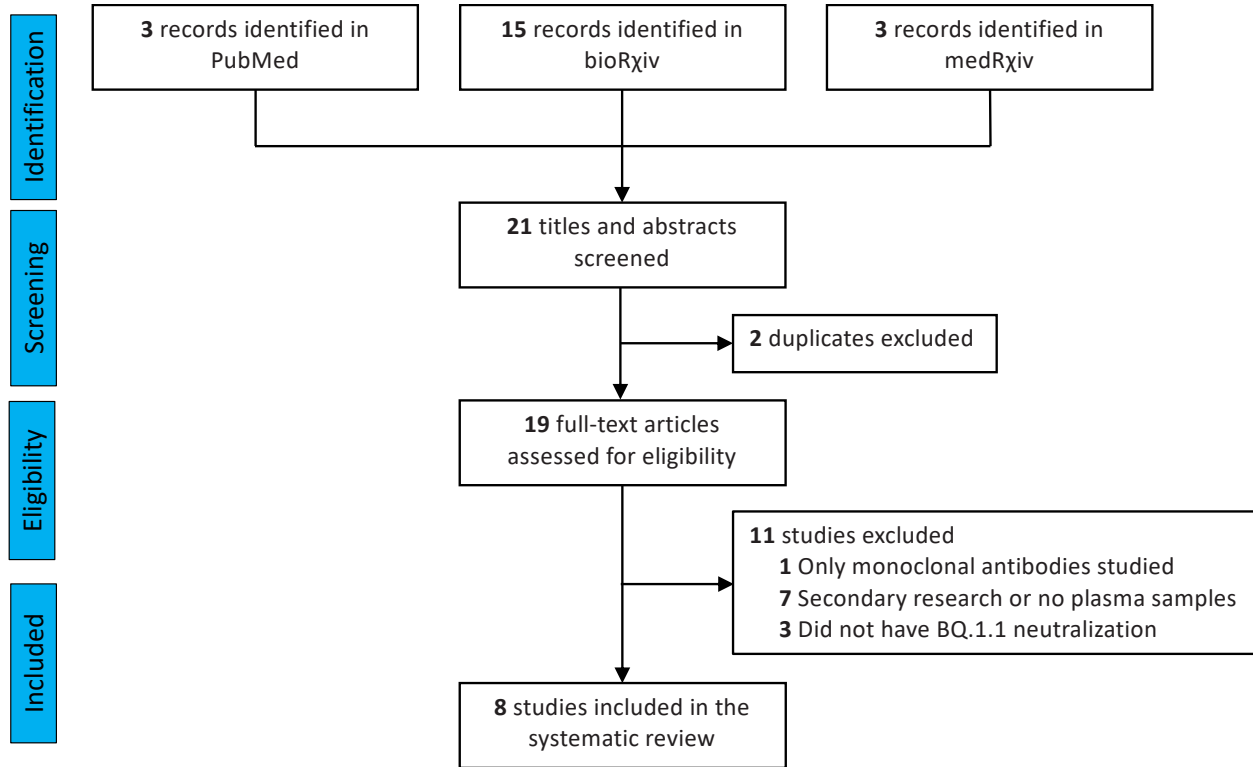
314 *Pre-Alpha CCP from 27 different studies had a GM(GMT₅₀) of 311 from 707 samples with 315
315 or 45% neutralizing omicron BA.1⁴.

316 ** percent neutralizations after CoronaVac and Omicron COVID-19 in the paper by Cao *et al*
317 could not be retrieved from the manuscript. 174 samples from the 6 other cohorts were used for
318 percent neutralization.

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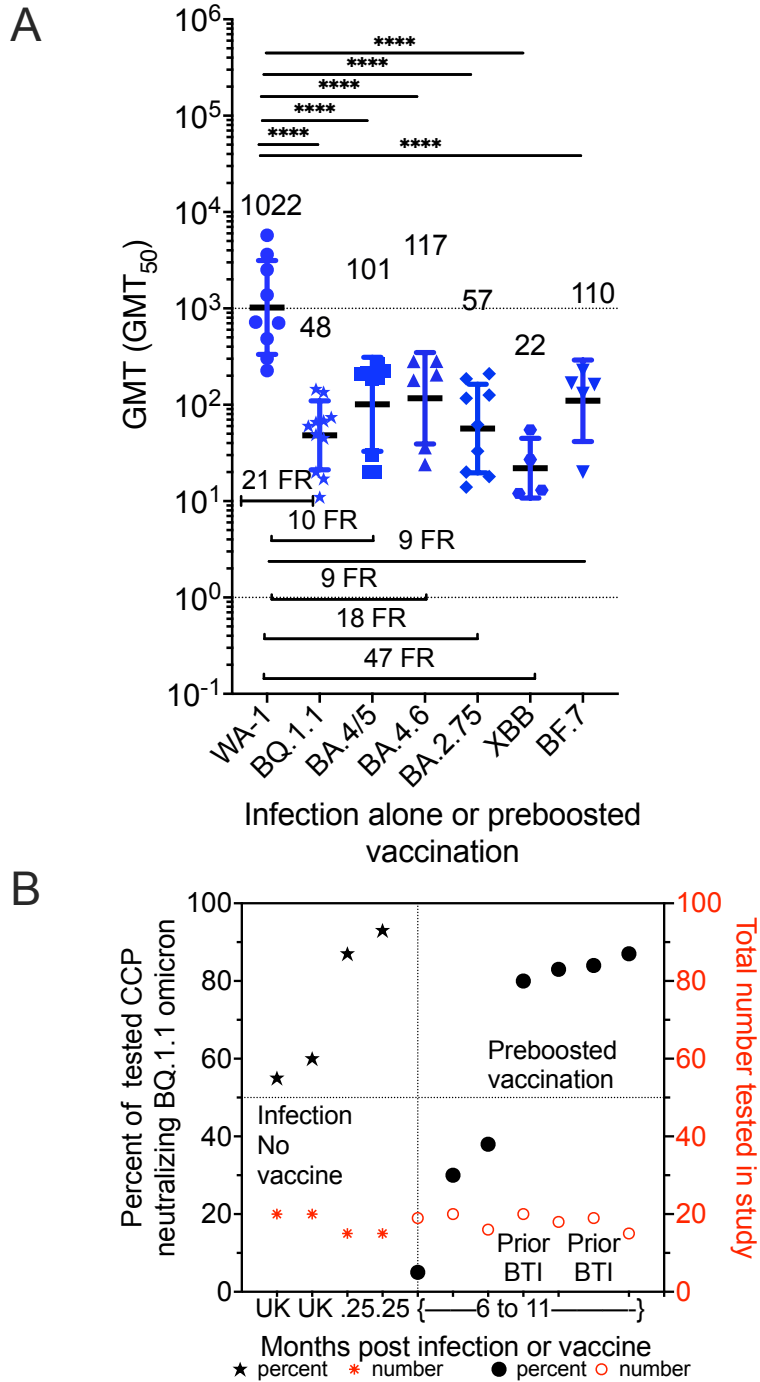
321 **Figure 1**
322 PRISMA flowchart for the current study. Number of records identified from various sources,
323 excluded by manual screening, found eligible and included according to subgroup analyses.
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336 **Figure 3**

337 Geometric mean neutralizing titers (GMT₅₀) against WA-1, BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB, BF.7
 338 A) plasma Omicron infection alone or pre-boasted-6 to 11 months after last vaccine dose sampled in 2021
 339 or 2022. Geometric standard deviation for error bars, fold reduction (FR) above data, and number of studies
 340 above x-axis. GM(GMT₅₀) statistically significant in difference by multiple comparison in Tukey's test are
 341 indicated. B). The percent of total samples within a study which neutralized Omicron BQ.1.1 graphed in
 342 increasing percentages on left y-axis with the total number of samples tested on the right y-axis.



343

344

345 **Supplementary Table 1**

346 Virus neutralization assays.

Reference	Assay	Virus	Replication-competent cells	neutralization threshold
Qu ⁸	Pseudovirus	Lentiviral pseudovirus	HEK293T-ACE-2	80
Miller ¹⁰	Pseudovirus	Lentiviral pseudovirus	HEK293T-ACE-2	20
Cao ³	Pseudovirus	VSV pseudovirus	HEK293T-ACE-2	20
Wang ¹⁴	Pseudovirus	VSV pseudovirus	VeroE6-	100
Davis ¹²	Live virus	Live authentic SARS-CoV-2	VeroE6-TMPRSS2	20
Kurhade ¹³	Live virus	mNeonGreen reporter USA-WA1/2020 SARS-CoV-2	Vero E6-TMPRSS2	20
Planas ¹¹	Live virus	Live authentic SARS-CoV-2	IGROV-1 or Vero E6-TMPRSS2	30
Zou ⁹	Live virus	mNeonGreen reporter USA-WA1/2020 SARS-CoV-2	Vero E6-TMPRSS2	20

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350 Supplementary Table 2

351 GMT₅₀ of different plasma sources against BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB.1 and BF.7 and fold-reductions (FR) compared to
 352 WA-1.

papers	Vaccine and COVID-19 history at sample time	Group	#	WA-1 GMT ₅₀	BQ.1.1 GMT ₅₀	FR BQ.1.1	BA.4/5 GMT ₅₀	FR BA.4/5	BA.4.6 GMT ₅₀	FR BA.4.6	BA.2.75 GMT ₅₀	FR BA.2.75	XBB.1 GMT ₅₀	FR XB B	BF.7 GMT ₅₀	FR BF.7
Cao ³	3xCorVac+BA.1 BTI	VaxCCP	50	1557	27	58	107	15	23	68	197	8	23	68	70	22
Cao ³	3xCorVac +BA.2 BTI	VaxCCP	39	1245	40	31	175	7	22	57	217	6	23	54	97	13
Cao ³	3xCorVac +BA.5 BTI	VaxCCP	36	1136	77	15	508	2	27	42	145	8	27	42	208	5
Zou ⁹	4xBNT162b2+BTI	VaxCCP	20	5120	132	39	629	8	587	9	265	19	99	52		
Planas ¹¹	3xmRNAvac+ BA.1/2 BTI	VaxCCP	13	8000	200	40	400	20	500	16	200	40				
Wang ¹⁴	2-3xmRNAvac+ BA.2 BTI	VaxCCP	14	24970	849	29	3727	7					186	134		
Wang ¹⁴	2-3xmRNAvac+ BA.2 BTI--BQ.1	VaxCCP	14		1250	20										
Wang ¹⁴	3-4xmRNAvac+ BA.4/5 BTI	VaxCCP	20	20507	671	31	5541	4					214	96		
Wang ¹⁴	3-4xmRNAvac+ BA.4/5 BTI--BQ.1	VaxCCP	20		1644	12										
Kurhade ¹³	3xmRNAvac+bivalent+BTI	VaxCCP	23	5776	267	22	1558	4	744	8	367	16	103	56	1223	5
Zou ⁹	3xBNT162b2+bivalent+BTI	VaxCCP	19	4847	444	11	1377	4	1564	3	326	15	131	37		
Planas ¹¹	3xmRNAvac+ BA.1/2 BTI	VaxCCP	16	25000	700	36	1000	25	2000	13	600	42				
Planas ¹¹	3xmRNAvac+ BA.5 BTI	VaxCCP	15	30000	3000	10	10000	3	9000	3	900	33				
Davis ¹²	3xmRNAvac	Vac only	12	758	19	40	50	15			23	33				
Kurhade ¹³	4xmRNAvac	Vac only	25	1533	22	70	95	16	62	25	26	59	15	102	69	22
Cao ³	3xCorVac	Vac only	40	652	24	27	72	9	21	31	90	7	20	33	45	14
Zou ⁹	4xBNT162b2	Vac only	20	1325	26	51	89	15	92	14	37	36	17	78		
Planas ¹¹	3xmRNAvac	Vac only	10	1500	40	38	60	25	60	25	10	150				
Wang ¹⁴	3xmRNAvac	Vac only	14	7687	139	55	628	12					108	71		
Wang ¹⁴	3xmRNAvac--BQ.1	Vac only	14		208	37										
Wang ¹⁴	3xmRNAvac+monovalent	Vac only	19	21182	261	81	1540	14					137	155		
Wang ¹⁴	3xmRNAvac+monovalent--BQ.1	Vac only	19		496	43										

Wang ¹⁴	3xmRNAvac+bivalent	Vac only	21	13736	337	41	1688	8					162	85		
Wang ¹⁴	3xmRNAvac+bivalent--BQ.1	Vac only	21		568	24										
Davis ¹²	3xmRNAvac+monovalent	Vac only	12	1812	53	34	142	13			65	28				
Kurhade ¹³	3xmRNAvac+bivalent	Vac only	29	3620	73	50	298	12	183	20	98	37	35	103	305	12
Davis ¹²	3xmRNAvac+bivalent	Vac only	12	2312	112	21	576	4			201	12				
Qu ⁸	3xmRNAvac--BQ.1	Vac only	15		140	19										
Qu ⁸	3xmRNAvac	Vac only	15	2616	114	23	300	9	246	11	589	4			238	11
Zou ⁹	3xBNT162b2+bivalent	Vac only	18	2237	143	16	518	4	524	4	117	19	55	41		
Planas ¹¹	3xmRNAvac	Vac only	18	6000	200	30	300	20	300	20	60	100				
Miller ¹⁰	3xBNT162b2	Vac only	16	45695	261	175	887	52			387	118			595	77
Miller ¹⁰	3xmRNA+monovalent	Vac only	18	21507	406	53	2829	8			745	29			2276	9
Miller ¹⁰	3xmRNA +bivalent	Vac only	15	40515	508	80	3693	11			883	46			2399	17
Qu ⁸	BA.4/5 inf (17-unvac)	Inf only	20	707	66	11	190	4	180	4	210	3			162	4
Qu ⁸	BA.4/5 inf (17-unvac)--BQ.1	Inf only	20		68	10										
Qu ⁸	Hosp BA.1 (6-unvac;5-2xmRNAvac)	Inf only	15	720	145	5	263	3	205	4	186	4			227	3
Qu ⁸	Hosp BA.1 (6-unvac;5-2xmRNAvac)--BQ.1	Inf only	15		135	5										
Zou ⁹	3xBNT162b2+BTI	reboost with BNT162b	20	2516	60	42	226	11	283	9	126	20	55	46		
Zou ⁹	3xBNT162b2 +BTI	preboost with bivalent	19	1377	74	19	207	7	282	5	62	22	27	51		
Zou ⁹	3xBNT162b2	preboost with bivalent	18	226	11	21	20	11	24	9	14	16	12	19		
Zou ⁹	3xBNT162b2	Preboost with BNT162b	20	303	17	18	30	10	36	8	18	17	13	23		
Miller ¹⁰	2xBNT162b2	Preboost with BNT162b	16	484	20	24	20	24			20	24			20	24

Miller ¹⁰	3xmRNA	preboost with bivalent	15	3633	45	81	211	17			33	110			131	28
Miller ¹⁰	3xmRNA	preboost with monovalent	18	5731	49	117	184	31			117	49			168	34

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380 Supplementary Table 3

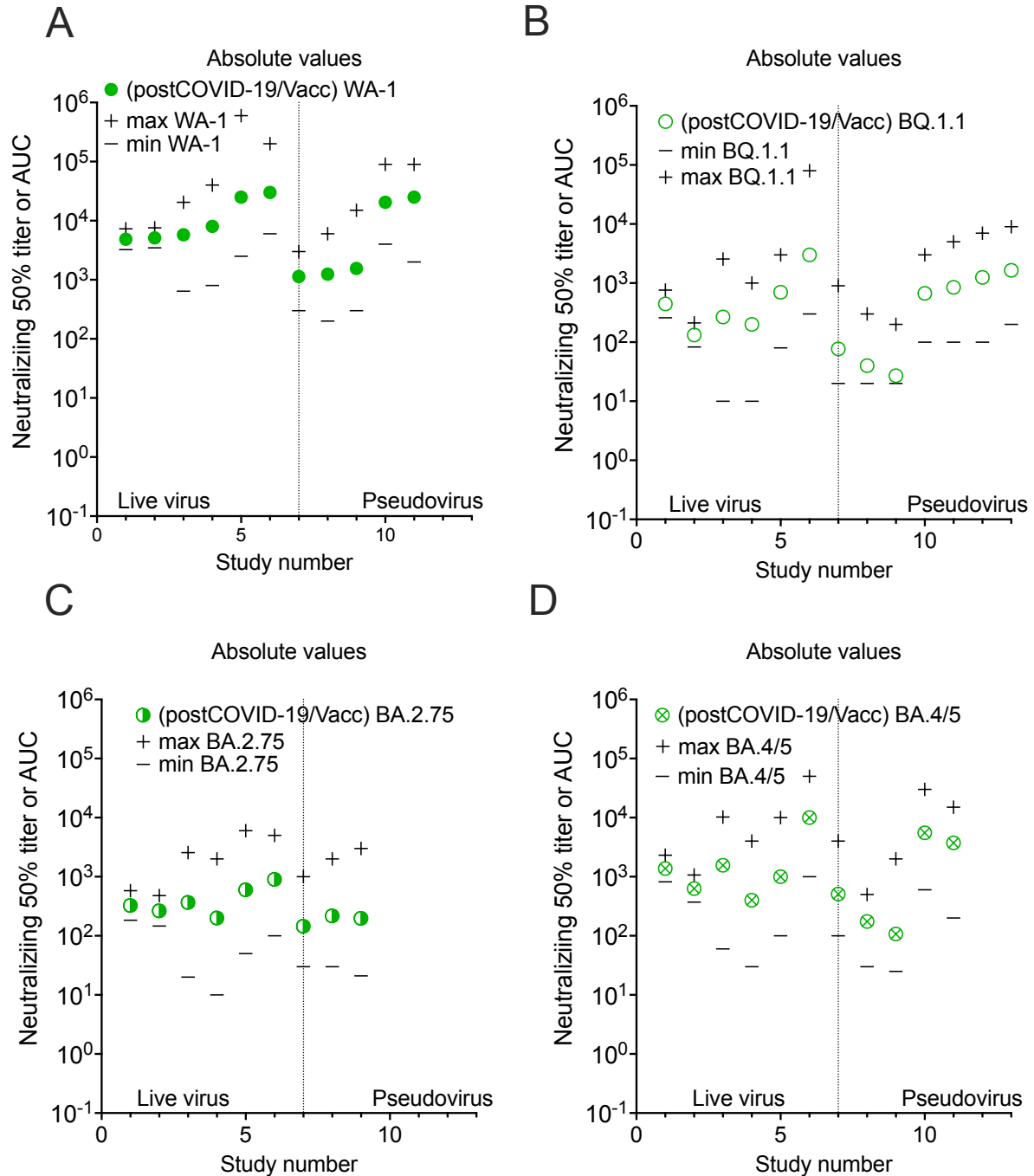
381 Neutralizing activity numbers (#) by study cohort.

	Vaccine and COVID-19 history at sample time	Group	WA-1 #	WA-1 neutralizing #	BQ.1.1 #	BQ.1.1 neutralizing #	BA.4/5 #	BA.4/5 neutralizing #	BA.4.6 #	BA.4.6 neutralizing #	BA.2.75 #	BA.2.75 neutralizing #	XB B.1 #	XBB.1 neutralizing #	BF.7 #	BF.7 neutralizing #
Cao ³	3xCorVac+BA.1 BTI	VaxCCP	50	50			50	50			50	50			50	49
Cao ³	3xCorVac +BA.2 BTI	VaxCCP	39	39			39	39			39	39			39	38
Cao ³	3xCorVac +BA.5 BTI	VaxCCP	36	36			36	36			36	36			36	36
Zou ⁹	4xBNT162b2+BTI	VaxCCP	20	20	20	20	20	20	20	20	20	20	20	19		
Planas ¹¹	3xmRNAvac+ BA.1/2 BTI	VaxCCP	13	13	13	11	13	12	13	13	13	11				
Wang ¹⁴	2-3xmRNAvac+ BA.2 BTI	VaxCCP	14	14	14	13	14	14					14	8		
Wang ¹⁴	2-3xmRNAvac+ BA.2 BTI--BQ.1	VaxCCP			14	13										
Wang ¹⁴	3-4xmRNAvac+ BA.4/5 BTI	VaxCCP	20	20	20	18	20	20					20	14		
Wang ¹⁴	3-4xmRNAvac+ BA.4/5 BTI--BQ.1	VaxCCP			20	20										
Kurhade ¹³	3xmRNAvac+bivalent+BTI	VaxCCP	23	23	23	22	23	23	23	23	23	23	23	22	23	23
Zou ⁹	3xBNT162b2+bivalent+BTI	VaxCCP	19	19	19	19	19	19	19	19	19	20	19	19		
Planas ¹¹	3xmRNAvac+ BA.1/2 BTI	VaxCCP	16	16	16	16	16	16	16	16	16	16				
Planas ¹¹	3xmRNAvac+ BA.5 BTI	VaxCCP	15	15	15	15	15	15	15	15	15	15				
Davis ¹²	3xmRNAvac	Vac only	12	12	12	6	12	11			12	9				
Kurhade ¹³	4xmRNAvac	Vac only	25	25	25	15	25	23	25	22	25	17	25	8	25	21
Cao ³	3xCorVac	Vac only	40	40			40	39			40	40			40	37
Zou ⁹	4xBNT162b2	Vac only	20	20	20	15	20	8	20	19	20	19	20	10		
Planas ¹¹	3xmRNAvac	Vac only	10	10	10	6	10	7	10	5	10	3				
Wang ¹⁴	3xmRNAvac	Vac only	14	14	14	5	14	14					14	3		
Wang ¹⁴	3xmRNAvac--BQ.1	Vac only			14	6										
Wang ¹⁴	3xmRNAvac+monovalent	Vac only	19	19	19	15	19	19					19	8		
Wang ¹⁴	3xmRNAvac+monovalent--BQ.1	Vac only			19	16										
Wang ¹⁴	3xmRNAvac+bivalent	Vac only	21	21	21	16	21	21					21	9		
Wang ¹⁴	3xmRNAvac+bivalent--BQ.1	Vac only			21	18										
Davis ¹²	3xmRNAvac+monovalent	Vac only	12	12	12	9	12	12			12	10				
Kurhade ¹³	3xmRNAvac+bivalent	Vac only	29	29	29	26	29	29	29	28	29	28	29	20	29	28
Davis ¹²	3xmRNAvac+bivalent	Vac only	12	12	12	10	12	12			12	11				
Qu ⁸	3xmRNAvac--BQ.1	Vac only			15	14										
Qu ⁸	3xmRNAvac	Vac only	15	15	15	12	15	15	15	15	15	14			15	14

Zou ⁹	3xBNT162b2+bivalent	Vac only	18	18	19	18	18	18	19	19	19	18	19	18		
Planas ¹¹	3xmRNAvac	Vac only	18	18	18	16	18	18	18	18	18	13				
Miller ¹⁰	3xBNT162b2	Vac only	16	16	16	16	16	16			16	16			16	16
Miller ¹⁰	3xmRNA+ monovalent	Vac only	18	18	18	18	18	18			18	18			18	18
Miller ¹⁰	3xmRNA +bivalent	Vac only	15	15	15	15	15	15			15	15			15	15
Qu ⁸	BA.4/5 inf (17-unvac)	Inf only	20	20	20	12	20	15	20	14	20	15			20	14
Qu ⁸	BA.4/5 inf (17-unvac)-- BQ.1	Inf only			20	11										
Qu ⁸	Hosp BA.1 (6-unvac;5- 2xmRNAvac)	Inf only	15	14	15	13	15	11	15	12	15	8			15	14
Qu ⁸	Hosp BA.1 (6-unvac;5- 2xmRNAvac)--BQ.1	Inf only			15	14										
Zou ⁹	3xBNT162b2+BTI	reboost with BNT162b	20	20	20	16	20	19	20	19	20	17	20	17		
Zou ⁹	3xBNT162b2 +BTI	preboost with bivalent	19	19	19	16	19	19	19	19	19	17	19	12		
Zou ⁹	3xBNT162b2	preboost with bivalent	18	18	19	1	18	9	19	9	19	5	19	2		
Zou ⁹	3xBNT162b2	Preboost with BNT162b	20	19	20	6	20	12	20	12	20	8	20	5		
Miller ¹⁰	2xBNT162b2	Preboost with BNT162b	16	16	16	6	16	5			16	7			16	4
Miller ¹⁰	3xmRNA	preboost with bivalent	15	15	15	13	15	15			15	9			15	14
Miller ¹⁰	3xmRNA	preboost with monovalent	18	18	18	15	18	18			18	18			18	17

383 Supplementary Figure 1

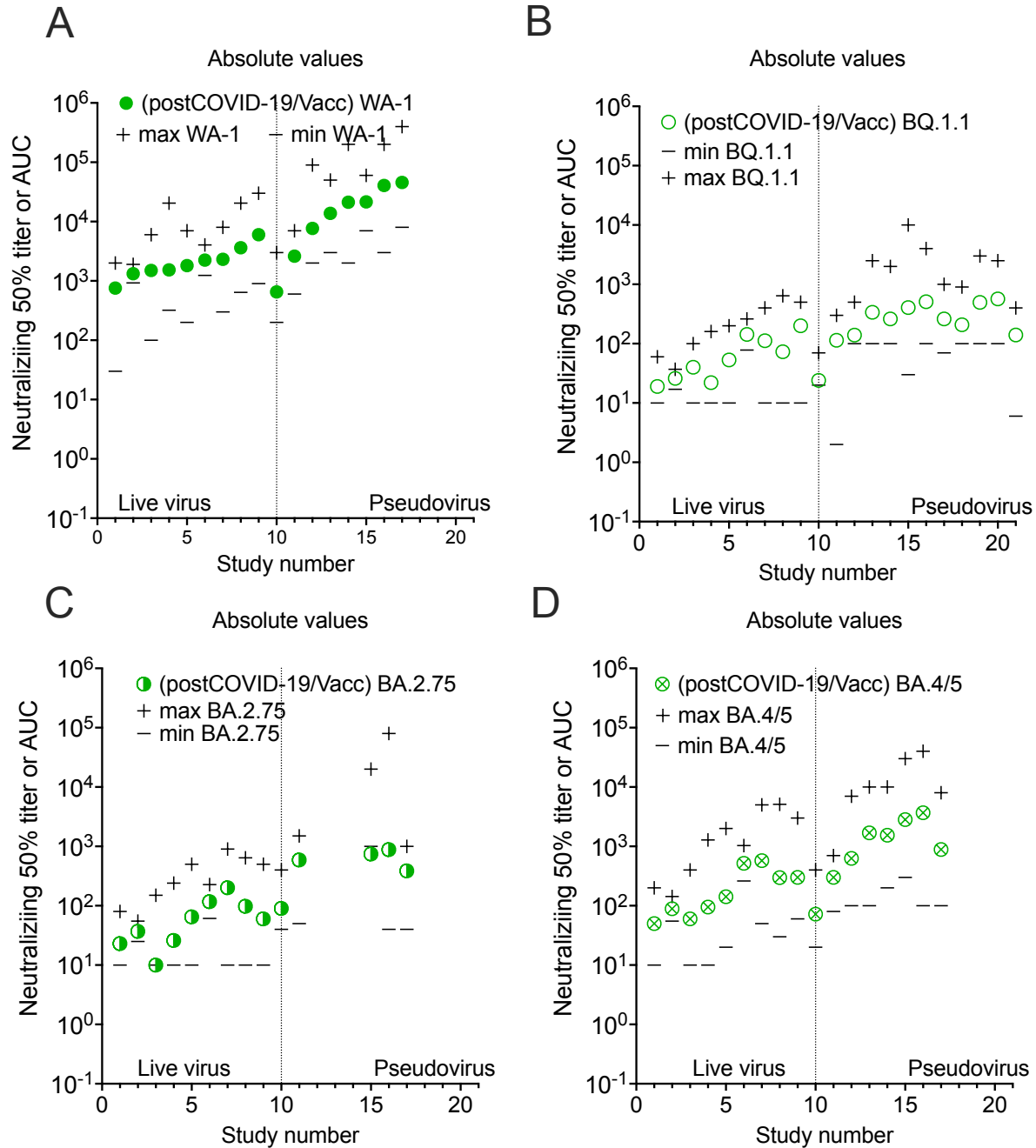
384 Plasma GMT₅₀ from post boosted vaccinations and COVID-19 sorted by study cohort with live virus
385 assays on the left and pseudovirus on right, with individual sample minimum and maximum
386 dilution titer also shown. A) WA-1; B) BQ.1.1; C) BA.2.75; D) BA.4/5.



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390 **Supplementary Figure 2**

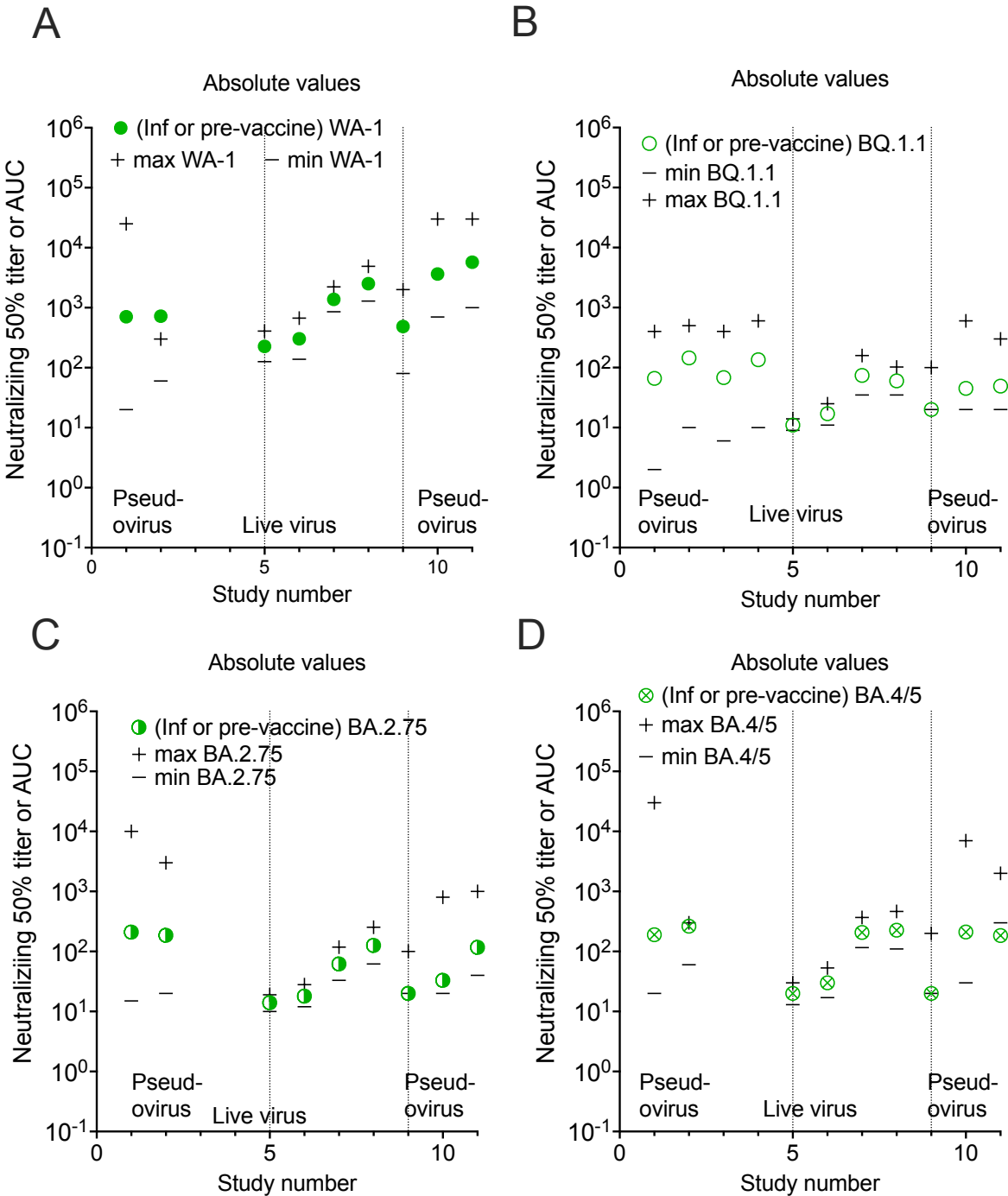
391 Plasma GMT₅₀ from boosted vaccinations only without COVID-19 sorted by study cohort with
392 live virus assays on the left and pseudovirus on right with with individual sample minimum and
393 maximum dilution titer also shown. A) WA-1; B) BQ.1.1; C) BA.2.75; and D) BA.4/5.



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400 **Supplementary Figure 3**

401 Plasma GMT₅₀ from Omicron infection alone and also pre-boosted in 2021 or 2022 6 to 11 months
 402 after last vaccine dose sampled sorted by study cohort with live virus assays on the left and
 403 pseudovirus on right with minimum and maximum dilution titer also shown. A) WA-1; B) BQ.1.1;
 404 C) BA.2.75; and D) BA.4/5.
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