Plasma after both SARS-CoV-2 boosted vaccination and COVID-19 potently neutralizes BQ1.1 and XBB.

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Abstract

Background

The SARS-CoV-2 Omicron variants, dominating in the late 2022 COVID-19 waves, have acquired resistance to most neutralizing anti-Spike monoclonal antibodies authorized so far, and the BQ.1.* sublineages, dominant in the western countries, are notably resistant to all authorized monoclonal antibodies. Polyclonal antibodies from individuals both with at least 3 vaccine doses and also recently recovered from Omicron COVID-19 (VaxCCP) could retain neutralizing activity against such new Omicron lineages.

Methods

Here we reviewed BQ.1.1 virus neutralization data from 652 individual patient samples from 32 separate cohorts defined by boosted vaccinations with or without recent Omicron COVID-19, as well as infection without vaccination.

Findings

More than 97% of the plasma samples from individuals in the recently (within 6 months) boosted VaxCCP study cohorts neutralized BQ.1.1, XBB and BF.7 with 100% neutralization of WA-1, BA.4/5, BA.4.6 and BA.2.75. The geometric mean of the geometric mean 50% neutralizing titers (GMT(GMT_{50}) were 201, 52 and 204 for BQ.1.1, XBB and BF.7, respectively. Compared to VaxCCP, plasma sampled from COVID-19 naïve subjects who also recently within 6 months received at least a third vaccine dose had about half of the GMT(GMT_{50}) for all viral variants with percent neutralizations of 82%, 60% and 94% for BQ.1.1, XBB and BF.7, respectively.

Interpretation

Boosted VaxCCP characterized by either recent vaccine dose or infection event within 6 months represents a robust, variant-resilient, passive immunotherapy against the new Omicron BQ.1.1, XBB and BF.7 variants.

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Research in Context

Evidence before this study

Passive antibody therapy is necessary for both prophylaxis and therapy of immunocompromised COVID-19 patients. The currently dominant SARS-CoV-2 Omicron BQ.1.1 variant is now resistant *in vitro* to all clinically authorized monoclonal antibodies making COVID-19 convalescent plasma the only remaining option for passive immunotherapy in the immunocompromised. There is scattered data about the efficacy of convalescent plasma at neutralizing BQ.1.1. The few prepublished manuscripts individually have limited numbers (less than 100) in subject cohorts, making systematic reviews necessary to draw robust conclusions. We searched PubMed, medRxiv and bioRxiv for manuscripts reporting virus neutralizations for BQ.1.1 using English language as a restriction. Articles lacking plasma BQ.1.1 virus neutralizations were excluded.

Added value of this study

Plasma collected from donors both recently (within 6 months) vaccine boosted and convalescent from COVID-19 (VaxCCP) neutralizes BQ.1.1, XBB and BF.7 in more than 95% of cases, and with high neutralizing titers.

Implications of all the available evidence

Boosted VaxCCP remains active against BQ.1.1 and other recent Omicron variants dominating the 2022-2023 Winter wave and represents a robust COVID-19 passive immunotherapy for immunocompromised patients.

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Introduction

In immunocompromised (IC) patients both passive immunotherapies and small molecule antivirals are often necessary to treat COVID-19 or eliminate persistently high SARS-CoV-2 viral load. Chronic, persistent viral loads increase both transmission and mutation risk, and prevent administration of the required immunosuppressive/antineoplastic therapies[1]. Small molecule antivirals have not been formally validated for IC patients, who often have contraindications, and the convergent evolution of the Omicron variant of concern (VOC) has led to inefficacy of all the anti-Spike monoclonal antibodies (mAbs) authorized so far for both treatment or prevention, e.g. in the highly prevalent BQ.1.* sublineages[2]. The other rapidly growing XBB.* and BF.7 sublineages are also highly resistant to anti-Spike mAbs[3]. Polyclonal plasma from individuals who are both vaccinated and had COVID-19 (VaxCCP) has more than ten times the antibody levels capable of neutralizing pre-Omicron variants as well as Omicron variants BA.1 through BA.4/5[4,5]. Polyclonal COVID-19 convalescent plasma (CCP) has thousands of distinct antibody specificities of different isotypes, including many capable of SARS-CoV-2 neutralization. High-titer pre-Omicron CCP contains Omicron neutralizing activity despite being collected before variant appearance[4,5].

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

Results

Seven articles were included (**Figure 1**) which contained virus neutralizations with WA-1, BQ.1.1, BA.4/5, BA.4.6, XBB and BF.7, assessed with either live authentic SARS-CoV-2 or SARS-CoV-2 pseudovirus neutralization assays and represented data from 652 patients (**Supplementary Table 1**). Qu *et al*. in the USA reported on Spring and Summer 2022 breakthrough infections with BA.1 and BA.4/5 in two sampled cohorts with predominantly unvaccinated individuals, as well as a third cohort of healthcare workers after a single monovalent booster vaccination in the Fall of 2021[8] (**Table 1**). Zou *et al*. in the USA in the Summer and Fall of 2022 sampled individuals who had already received 3 mRNA BNT162b2 vaccinations with or without previous COVID-19, both before and about 4 weeks after a 4th monovalent or bivalent vaccine booster vaccination[9]. Miller *et al*. also in the USA sampled both before the 3rd vaccination dose and about 4 weeks after monovalent mRNA vaccination in the Fall of 2021, as well as with the 4th vaccine dose in the Summer or Fall of 2022, with either monovalent or bivalent booster vaccinations in Fall of 2022 in those with no documented COVID-19[10]. Cao *et al*. in China investigated BQ.1.1 neutralizations from plasma of 4 cohorts after 3 doses of CoronaVac (Fall 2021) without COVID-19 or 2-12 weeks after BA.1, BA.2 and BA.5 infection[3]. Planas *et al*. in France evaluated at plasma from individuals both 4 and 16 weeks after a third monovalent mRNA vaccine dose in the Fall of 2021 as well as 12 and 32 weeks after vaccine breakthrough BA.1/2 or BA.5 infection[11]. Davis *et al* in the USA sampled after the 3rd mRNA vaccine monovalent dose in the Fall of 2021 and also after either a 4th monovalent mRNA dose or a bivalent (wild-type + BA.4/5) vaccine dose in the Summer and Fall of 2022[12]. Kurhade *et al* in the USA also compared after the 4th monovalent vaccine dose or 3 mRNA doses with the 4th the bivalent dose without COVID-19 and also after bivalent boost with recent COVID-19[13].

These diverse cohorts were assembled into 3 groups, 1) plasma after both 3-4 vaccine doses and COVID-19 (VaxCCP); 2) plasma from subjects after administration of 3-4 vaccine doses (i.e. boosted), but either self-reported as COVID-19-*naïve* or anti-nucleocapsid negative; and 3) Omicron infection without vaccination (CCP) as well as participants sampled 6 to 11 months after previous vaccine dose and before the booster vaccination. Boosted VaxCCP neutralized BQ.1.1, XBB and BF.7 with approximately 2 to 3 times the dilutional potency of the vaccine-only or CCP/pre-boost vaccination groups for all viral variants (**Table 2 and Figure 2**). Importantly, while there was a 25-fold reduction in neutralization by boosted VaxCCP against BQ.1.1 compared to WA-1, more than 97% of the boosted VaxCCP samples neutralized BQ.1.1 as well as XBB and BF.7 (**Table 2 and Figure 2c**). The single cohort within the boosted VaxCCP group which was at 85% neutralization was sampled late, 8 months after BA.1/2 breakthrough infection[11] (**Supplementary Table 2 and 3**). Except for the GMT (GMT_{50}) against XBB at 52, the other viral variant neutralizations were in the same range as pre-Alpha CCP neutralizing WA-1 (i.e., 311)[4]. By comparison the large randomized clinical trial which effectively reduced outpatient COVID-19 progression to hospitalizations had a GMT_{50} of 80 for WA-1 with pre-Alpha CCP[14]. Boosted vaccinations at 3-4 doses without COVID-19, showed GMT(GMT_{50}) of 83 for BQ.1.1, with only 4 of 13 cohorts over 95% neutralizations, for 82% overall (i.e. 182 of 221 individuals). Four separate studies[8,13,12,10] characterized BQ.1.1 virus neutralizations with plasma after the new bivalent (wild-type + BA.4/5) mRNA vaccine booster in the Fall of 2022, with 92% (69 of 75 samples) neutralization activity within 4 weeks of bivalent booster (**Supplementary Table 3**).

Many studies performed virus neutralizations on samples drawn before the 3rd or 4th vaccine dose which were 6 to 11 months after last vaccine dose. The GMT(GMT_{50})'s were about 4 times reduced compared to VaxCCP even though the fold reductions were similar (**Figure 3**, **Table 2**). In agreement with lower GMT_{50} for neutralizations was the low percent neutralizing BQ.1.1 (60%), XBB (46%), and BF.7 (75%) at 6 to 11 months after vaccination (**Figure 3, Table 2 and Supplementary Table 3**).

Three studies used the lentiviral pseudovirus assays, with diverse Spike proteins cloned in, while the other four were live virus assays using different cell types (**Supplementary Table 1**). Notably, Planas *et al* employed the IGROV-1 cell type for better growth of Omicron sublineages[11]. While the single study fold reductions (FR) and percent neutralizations normalize the results between studies, the GMT_{50} can vary between studies even amongst the live authentic viral neutralization studies (e.g. mNeongreen reporter assays versus cytopathic effects)[9,13]. We sorted the live authentic viral neutralizations from the pseudoviral neutralizations, plotting also the minimum and maximums (**Supplementary Figures 1-3**). In general, the live authentic SARS-CoV-2 neutralization assays for VaxCCP appeared to have a ten-fold more antibody neutralization levels, most likely due to the single study by Cao et al[3] employing lentiviral pseudovirus. In contrast, the GMT_{50} achieved with pseudoviral assays in the boosted vaccinations without COVID-19 appeared slightly higher than the ones achieved with authentic virus.

Discussion

The FDA deemed CCP safe and effective for both immunocompetent and IC COVID-19 outpatients[6,7,15], and further extended its authorized use in the IC patient population in December 2021[7,15], at a time when oral antiviral therapy promised a no transfusion outpatient solution and many anti-Spike mAbs were still effective.

Up until the present, CCP remained a backup bridge for IC patients, durable against the changing variants and as a salvage therapy in seronegative IC patients. With the recent advent of Omicron XBB.* and BQ.1.* defeating the remaining anti-Spike mAbs, boosted VaxCCP, recently collected within the last 6 months of either a vaccine dose or SARS-CoV-2 is likely to be the only viable remaining passive antibody therapy in the 2022-23 Winter for IC patients who have failed to make antibodies after vaccination and still require B-cell depleting drugs or immunosuppressive therapy. In a literature review of CCP from diverse VOC waves as well as boosted vaccinees and VaxCCP up to BA-1, VaxCCP showed higher neutralization titers against Omicron at levels above 300 dilutional GMT_{50}[4].

The accelerated evolution of SARS-CoV-2 VOCs has created the problem that the pharmaceutical development of additional mAbs is not worth the effort and cost given their expected short useful clinical life expectancy, so the anti-Spike mAb pipeline has remained stuck in 2022. High levels of antibodies in donor plasma from both boosted vaccinations and COVID-19 convalescent plasma (VaxCCP) neutralize more than 95% of BQ.1.1, XBB and BF.7. Recently collected plasma within a 6 month window from those boosted vaccinees without prior documented COVID-19 had a 20% to 30% reduction in neutralization percent and half of the neutralizing antibody levels compared to VaxCCP. In those vaccinated with last dose more than 6 months prior to sample collection both the neutralization percent and neutralizing antibody titers fell further compared to the recently boosted VaxCCP group. Four studies (Planas[11], Zou[9], Cao[3] and Kurhade[13]) had directly comparative cohorts in the three groups which increases the robustness reduction in neutralizations with the vaccine only or more than 6 months to last vaccine or infection event compared to VaxCCP. The main limitation of our systematic review is the small number of studies reporting virus neutralization with BQ.1.1 with most available as pre-preprints without peer-review yet. However, we note that peer-review itself does not change GMT_{50} or neutralization numbers and the authors of these papers have considerable expertise in the topic.

Boosted VaxCCP has full potential to replace anti-Spike mAbs for passive antibody therapy of IC patients against recent Omicron sublineages, in the meanwhile polyclonal IgG formulations can be manufactured. VaxCCP qualification in the real-world will likely remain constrained on high-throughput serology, whose correlation with GMT_{50} is not perfect[16,17]. Nevertheless, the very high prevalence (97%) of Omicron-neutralizing antibodies and the high GMT(GMT_{50}) in recently boosted VaxCCP reassure about its potency, and further confirm that exact donor-recipient VOC matching is dispensable. Overall, our findings urge WHO to revise its guidelines and recommend boosted VaxCCP for therapy of COVID-19 in IC patients.

Search strategy and selection criteria

On November 19, 2022 we searched PubMed, medRxiv and bioRxiv for manuscripts reporting BQ.1.1 neutralization, using English language as a restriction. Search of bioRxiv with same keywords yielded 14 records of which only 7 contained plasma viral neutralization data. Search of medRxiv produced 3 records which did not have BQ.1.1 neutralizations. PubMed retrieved 3 entries using ("BQ.1.1") and ("neutralization"), one of which was focused on anti-Spike mAb alone[2] and the other 2 were duplicates from bioRxiv[8,12]. Articles underwent evaluation for data extraction by two assessors (DS and DF) with disagreements resolved by third assessor (AC).

Articles lacking plasma BQ.1.1 virus neutralizations were excluded. The process of study selection is represented in the PRISMA flow diagram (**Figure 1**).

The type of viral assay (live or pseudovirus), time interval to blood sample, GMT_{50}, minimum and maximum neutralizing 50% dilutional titer for WA-1 (pre-Alpha wild-type) and Omicron sublineages BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB and BF.7 and number out of total that neutralized Omicron were abstracted from study text, graphs and tables. Prism v. 9.4 (GraphPad Software, San Diego, CA, USA) was used for data analysis. While all manuscripts included neutralization data against WA-1, BQ1.1, BA.4/5 and BA.2.75, only a subset of manuscripts included neutralization data for BA.4.6, XBB and BF.7 which were assembled for relevance to present circulating variants. Historic early Omicron partial neutralization data on variants like BA.1 or BA.2 were excluded because of the full set data with BA.4/5 and BA.2.75.

Statistical significance between $\log_{10}$ transformed $GMT_{50}$was investigated using Tukey's test. The multiple comparison test was a two-way ANOVA with Alpha 0.05 on log transformed GMT_{50}. The log normal test was performed on WA-1, BQ.1.1, BA.4/5, BA.4.6, XBB and BF.7 virus GMT_{50}. Two studies[10,11] reported the median titer rather than the GMT_{50}. Compiled data abstracted from the published studies is available in the supplementary dataset.

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Conflict of interest disclosure
DJS reports AliquantumRx Founder and Board member with stock options (macrolide for malaria), Hemex Health malaria diagnostics consulting and royalties for malaria diagnostic test control standards to Alere- all outside of submitted work. AC reports being part of the scientific advisory board of SabTherapeutics and has received personal fees from Ortho Diagnostics, outside of the submitted work. All other authors report no relevant disclosures.

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Table 1

Synopsis of included studies, reporting plasma sources, epoch of sampling, region, time since vaccination/infection to plasma sampling, and sample size. The cohorts were split into three groups-1) boosted vaccinations and recent COVID-19 (vaxCCP), 2) boosted vaccines only without documented COVID-19 (Vac only) and 3) infection alone or pre-boosted sampling 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
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]	CorVacx3	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
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 BTI (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	reboost 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

Table 2

GMT(GMT_{50}) 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**	**BF.7**
Post COVID-19/vaccine (study cohorts)	9	9	9	9	9	6	7
GMT(GMT_{50})	4983*	201	719	352	303	52	204
Fold reduction from WA-1	ref	25	7	14	16	96	24
Samples tested	231	231	231	106	231	62	148
Samples neutralizing	231	103**	230	106**	230	60	146
Percent neutralizing	100	97	100	100	100	97	99
Boosted vaccine (study cohorts)	14	14	14	8	14	5	4
GMT(GMT_{50})	3436	83	281	123	107	25	357
Fold reduction from WA-1	ref	41	12	28	32	137	10
Samples tested	260	261	260	136	261	93	158
Samples neutralizing	260	97	241	126	231	56	149
Percent neutralizing	100	75	93	93	89	60	94
Infection only or preboosted vaccine (study cohorts)	9	9	9	6	9	4	2
GMT(GMT_{50})	1022	41	101	117	57	22	110
Fold reduction from WA-1	ref	25	10	9	18	47	9
Samples tested	161	162	161	113	162	78	84
Samples neutralizing	159	98	123	85	104	36	63
Percent neutralizing	99	60	76	75	64	46	75

*Pre-Alpha CCP from 27 different studies had a GMT(GMT_{50}) of 311 from 707 samples with 315 or 45% neutralizing omicron BA.1[4].

** percent neutralizations after CoronaVac and Omicron COVID-19 in the paper by Cao *et al* could not be retrieved from the manuscript. 106 samples from the 6 other cohorts were used for percent neutralization.

Figure 1

PRISMA flowchart for the current study. Number of records identified from various sources, excluded by manual screening, found eligible and included according to subgroup analyses.

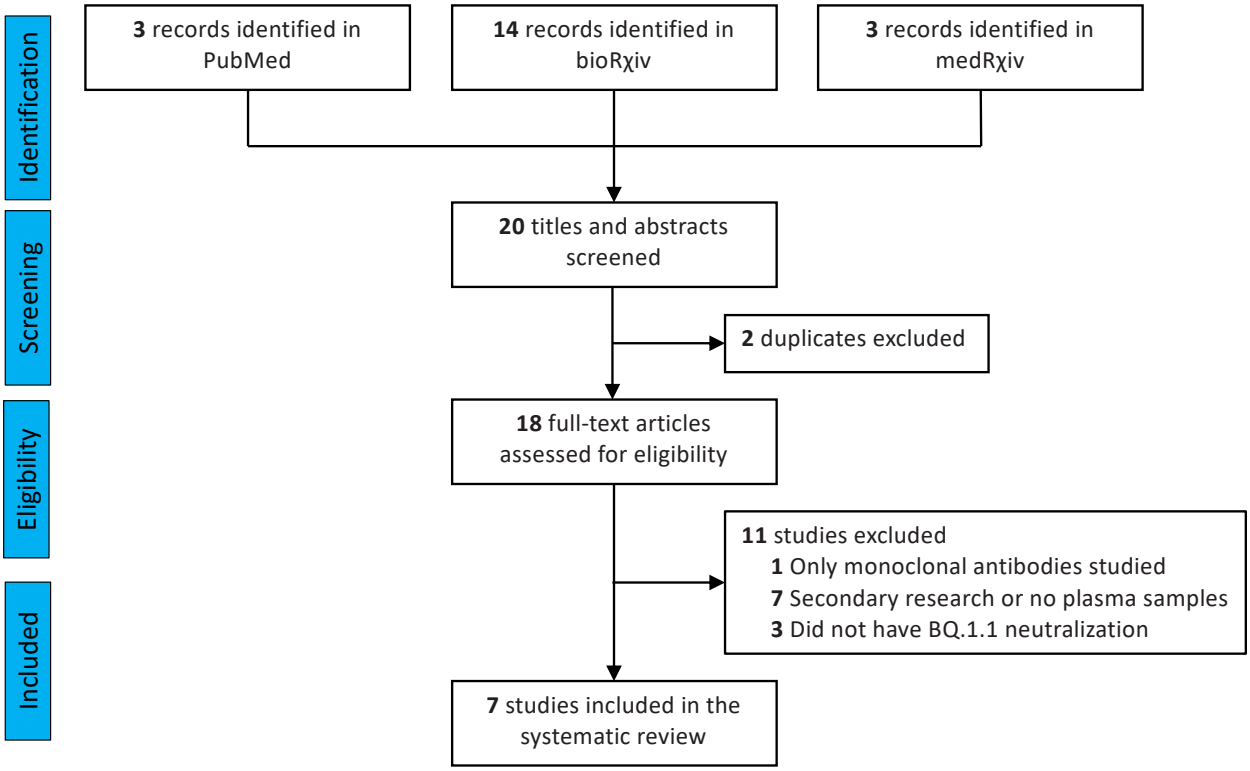


Figure 2

Neutralizing GMT (GMT_{50}) against WA-1, BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB, BF.7. A) post boosted vaccinations and COVID-19 and B) boosted vaccinated plasma without COVID-19. Geometric standard deviation for error bars, fold reduction (FR) below data, and number of studies above x-axis. Geomeans statistically significant in difference by multiple comparison in Tukey's test are indicated. C) The percent of total samples within a study which neutralized Omicron BQ.1.1 graphed in increasing percentages on left y axis with the total number of samples tested on the right y axis.

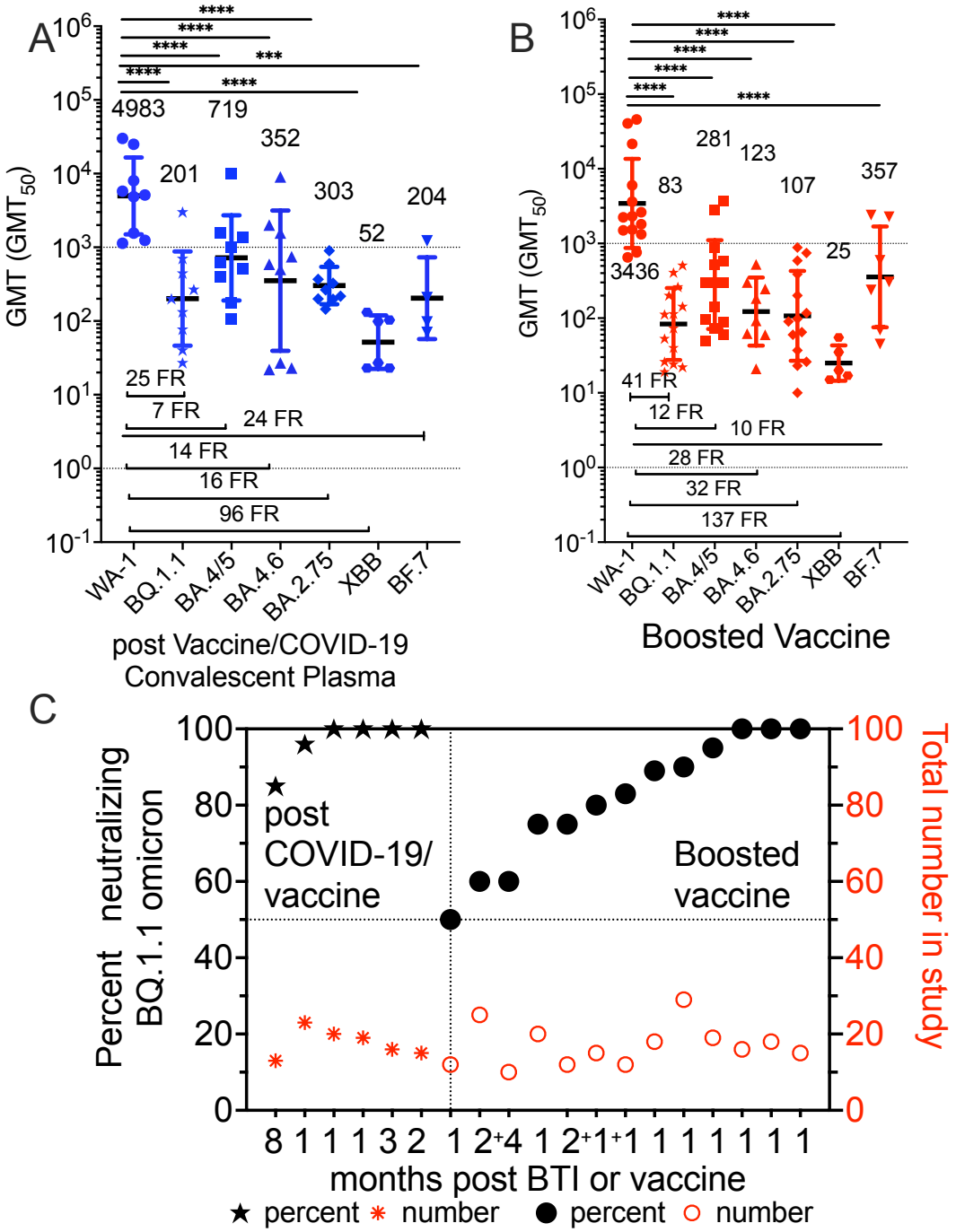
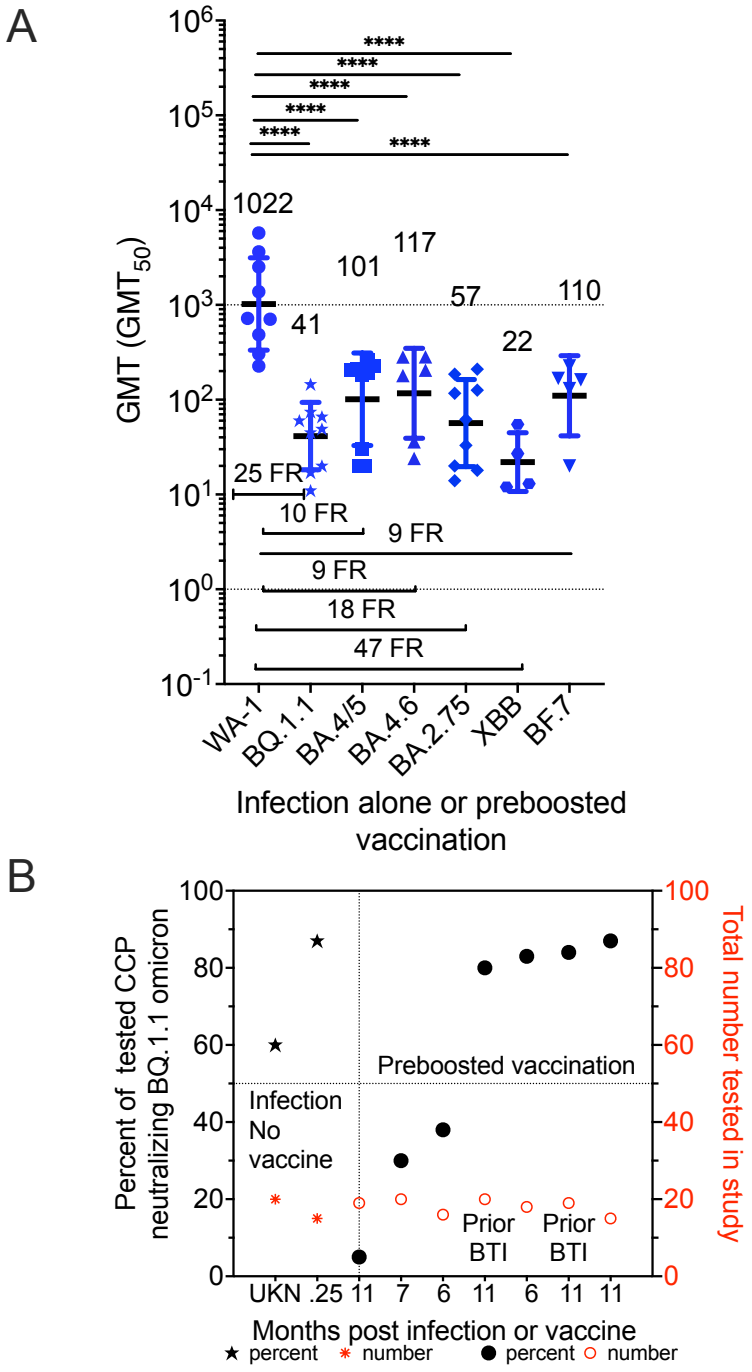


Figure 3

Geometric mean neutralizing titers (GMT_{50}) against WA-1, BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB, BF.7 A) plasma Omicron infection alone or pre-boosted-6 to 11 months after last vaccine dose sampled in 2021 or 2022. Geometric standard deviation for error bars, fold reduction (FR) above data, and number of studies above x-axis. GMT(GMT_{50}) statistically significant in difference by multiple comparison in Tukey's test are indicated. B). The percent of total samples within a study which neutralized Omicron BQ.1.1 graphed in increasing percentages on left y-axis with the total number of samples tested on the right y-axis.



Supplementary Table 1

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
Davis[12]	Live virus	Live authentic SARS-CoV-2	VeroE6-TMPRSS2	20
Kurhade[13]	Live virus	mNeonGreen (mNG) 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 (mNG) reporter USA-WA1/2020 SARS-CoV-2	Vero E6-TMPRSS2	20

Supplementary Table 2

GMT_{50} of different plasma sources against BQ.1.1, BA.4/5, BA.4.6, BA.2.75, XBB and BF.7 and fold-reductions (FR) compared to 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 GMT_{50}	FR XBB	BF.7 GMT_{50}	FR BF.7
Cao[3]	3xCorVac+BA.1 inf	VaxCCP	50	1557	27	58	107	15	23	68	197	8	23	68	70	22
Cao[3]	3xCorVac +BA.2 inf	VaxCCP	39	1245	40	31	175	7	22	57	217	6	23	54	97	13
Cao[3]	3xCorVac +BA.5 inf	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]	mRNAvacx3+ BA.1/2 inf	VaxCCP	13	8000	200	40	400	20	500	16	200	40				
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 inf	VaxCCP	16	25000	700	36	1000	25	2000	13	600	42				
Planas[11]	3xmRNAvac+ BA.5 inf	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]	CorVacx3	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				
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	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 BTI (17-unvac)	Inf only	20	707	66	11	190	4	180	4	210	3			162	4
Qu[8]	Hosp BA.1 (6-unvac;5-2xmRNAvac)	Inf only	15	720	145	5	263	3	205	4	186	4			227	3

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

Supplementary Table 3

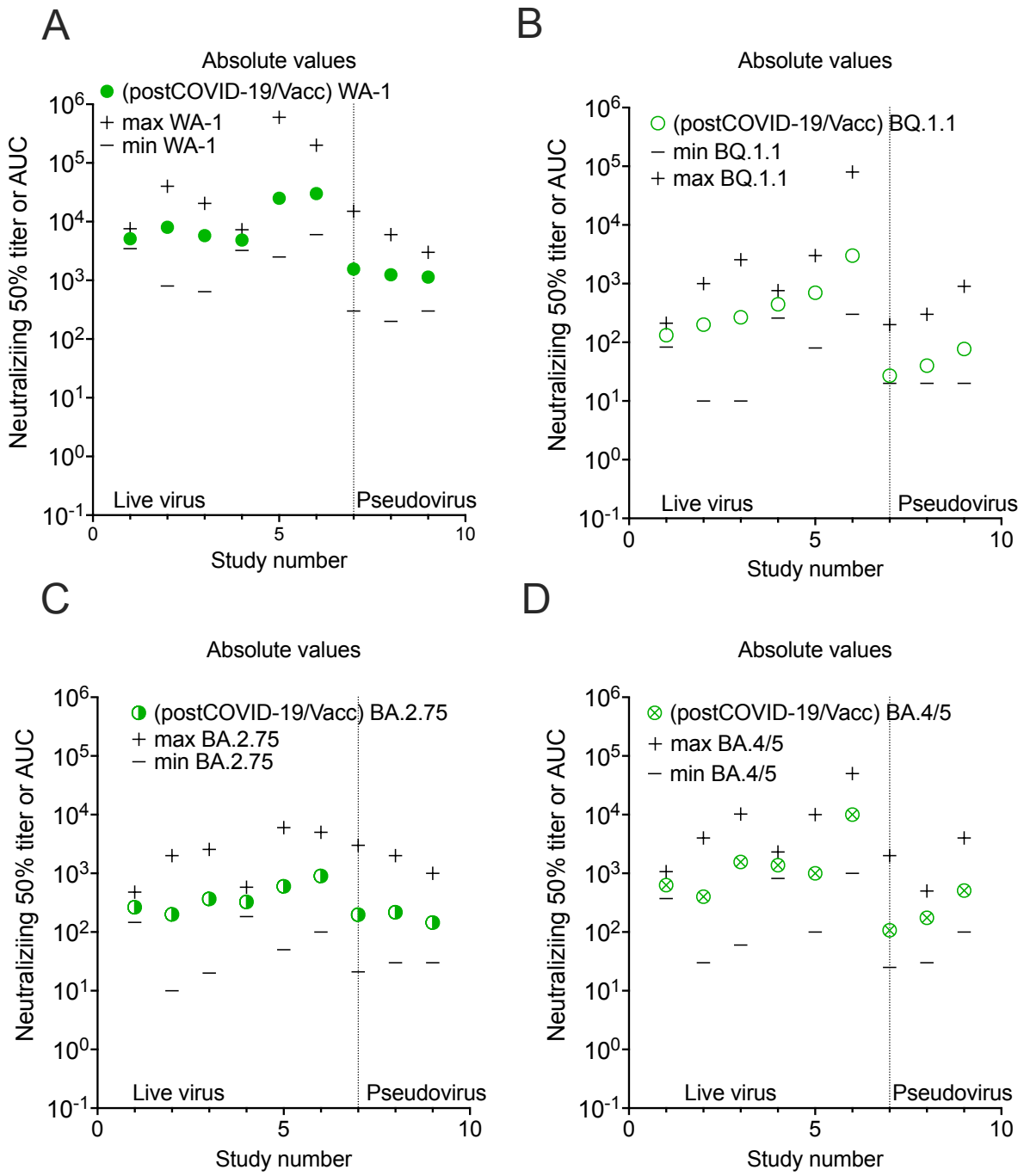
Neutralizing activity numbers (#) by study cohort.

	Vaccine and COVID-19 history at sample time	**Group**	WA-1 #	WA-1 neutral-izing #	BQ.1.1 #	BQ.1.1 neutral-izing #	BA.4/5 #	BA.4/5 neutral-izing #	BA.4.6 #	BA.4.6 neutral-izing #	BA.2.75 #	BA.2.75 neutral-izing #	XBB.1 #	XBB.1 neutral-izing #	BF.7 #	BF.7 neutral-izing #
Cao[3]	3xCorVac+BA.1 inf	VaxCCP	50	50			50	50			50	50			50	49
Cao[3]	3xCorVac +BA.2 inf	VaxCCP	39	39			39	39			39	39			39	38
Cao[3]	3xCorVac +BA.5 inf	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]	mRNAvacx3+ BA.1/2 inf	VaxCCP	13	13	13	11	13	12	13	13	13	11				
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 inf	VaxCCP	16	16	16	16	16	16	16	16	16	16				
Planas[11]	3xmRNAvac+ BA.5 inf	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]	CorVacx3	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				
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	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 BTI (17-unvac)	Inf only	20	20	20	12	20	15	20	14	20	15			20	14
Qu[8]	Hosp BA.1 (6-unvac;5-2xmRNAvac)	Inf only	15	14	15	13	15	11	15	12	15	8			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

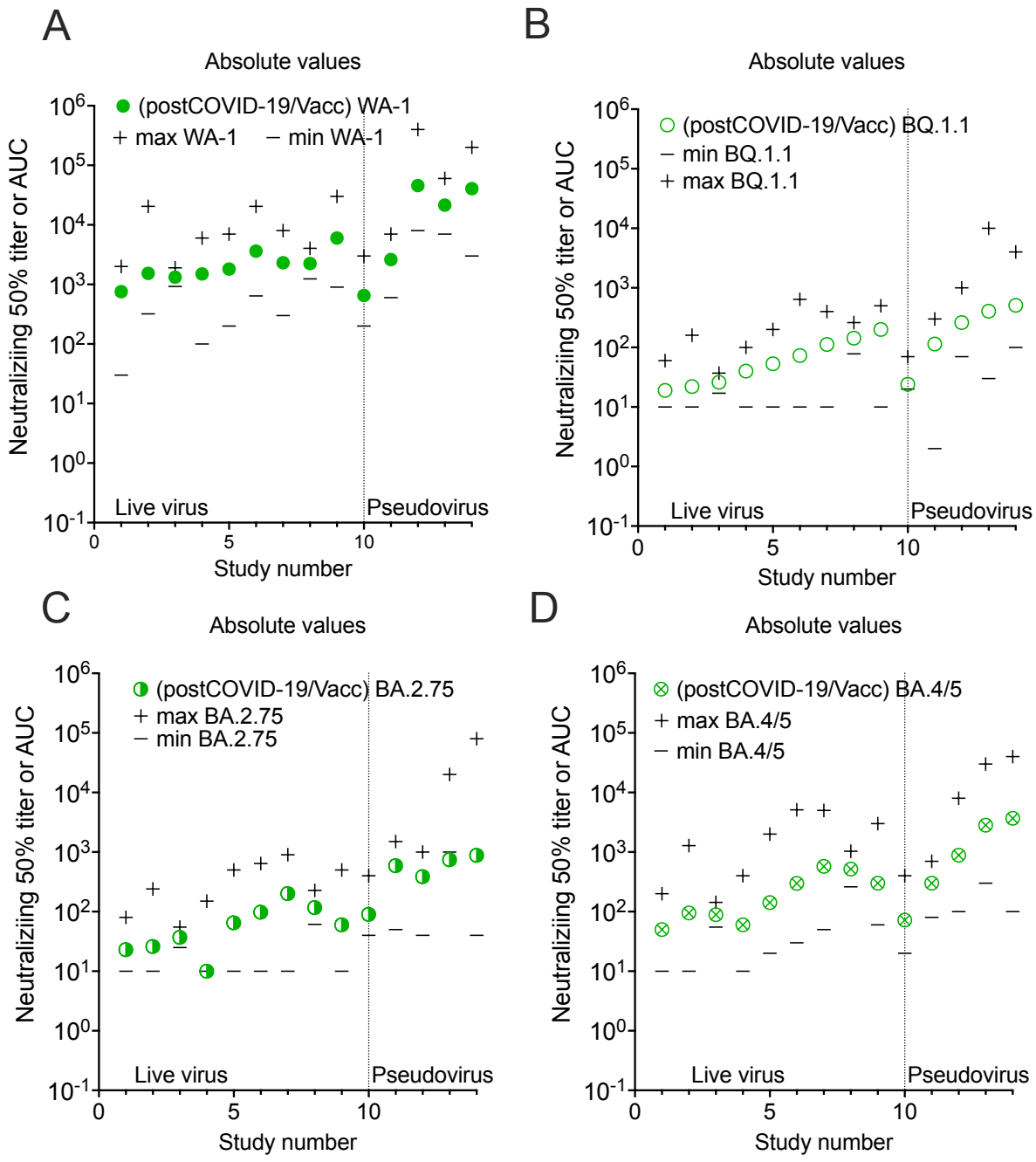
Supplementary Figure 1

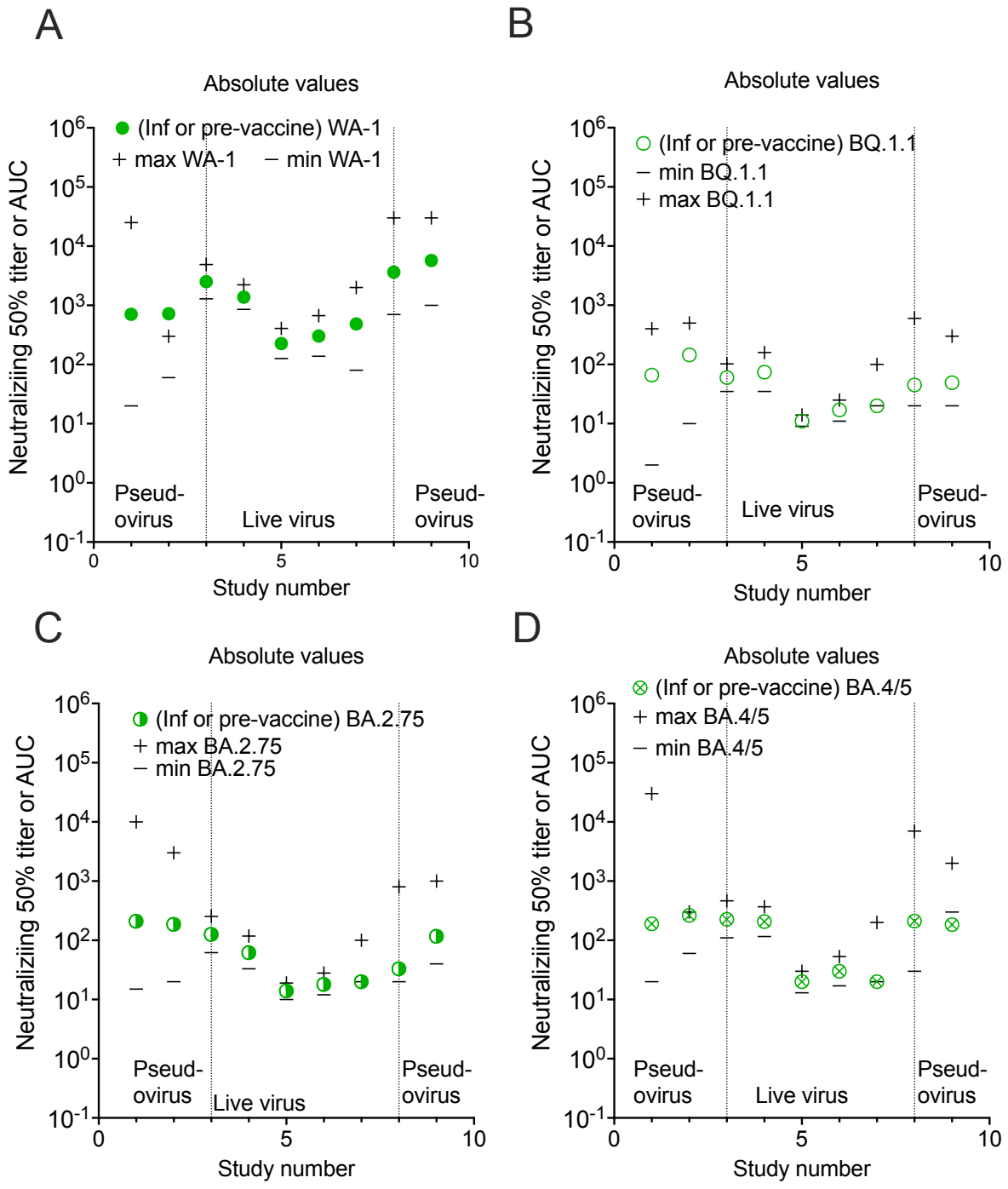
Plasma GMT_{50} from post boosted vaccinations and COVID-19 sorted by study cohort with live virus assays on the left and pseudovirus on right, with individual sample minimum and maximum dilution titer also shown. A) WA-1; B) BQ.1.1; C) BA.2.75; D) BA.4/5.



Supplementary Figure 2

Plasma GMT_{50} from boosted vaccinations only without COVID-19 sorted by study cohort with live virus assays on the left and pseudovirus on right with with individual sample minimum and maximum dilution titer also shown. A) WA-1; B) BQ.1.1; C) BA.2.75; and D) BA.4/5.



Supplementary Figure 3

Plasma GMT_{50} from Omicron infection alone and also pre-boosted in 2021 or 2022 6 to 11 months after last vaccine dose sampled sorted by study cohort with live virus assays on the left and pseudovirus on right with minimum and maximum dilution titer also shown. A) WA-1; B) BQ.1.1; C) BA.2.75; and D) BA.4/5.