Analysis of anti-Omicron neutralizing antibody titers in different convalescent plasma sources.

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Abstract

The latest SARS-CoV-2 variant of concern Omicron, with its immune escape from therapeutic anti-Spike monoclonal antibodies and vaccine-elicited sera, demonstrates the continued relevance of COVID19 convalescent plasma (CCP) therapies. Lessons learnt from previous usage of CCP suggests focusing on outpatients and immunocompromised recipients, with high neutralizing antibody (nAb) titer units. In this analysis we systematically reviewed Omicron neutralizing plasma activity data, and found that approximately 50% (426/911) of CCP from unvaccinated donors neutralizes Omicron with a very low geometric mean of geometric mean titers for 50% neutralization (GM(GMT_{50})) of about 17, representing a more than 24-fold reduction from paired WA-1 neutralization. Two doses of mRNA vaccines in nonconvalescent subjects had a similar 50% percent neutralization with Omicron neutralization GM(GMT_{50}) about 24. However, CCP from vaccinees recovered from previous variants of concern or third-dose uninfected vaccinees was nearly 100% neutralizing with Omicron GM(GMT_{50}) over 200, a 12-fold Omicron neutralizing antibody increase compared to unvaccinated convalescents from former VOCs. These findings have implications for both CCP stocks collected in prior pandemic periods and plans to restart CCP collections. Thus, CCP from vaccinated donors provides an effective tool to combat variants that defeat therapeutic monoclonal antibodies.

Introduction

The SARS-CoV-2 Omicron variant of concern (VOC) (originally named VUI-21NOV-01 by Public Health England and belonging to GISAID clade GRA(B.1.1.529+BA.*) was first reported on November 8, 2021 in South Africa , and shortly thereafter was also detected all around the world. Omicron mutations impact 27% of T cell epitopes [1] and 31% of B cell epitopes of Spike, while percentages for other VOC were much lower [2]. The Omicron variant has further evolved to several sublineages which are named by PANGO phylogeny using the BA alias: the BA.1 wave of Winter 2021-2022 has been suddenly replaced by BA.2 and BA.2.12.1 in Spring 2022, and by the BA.4 and BA.5 waves in Summer 2022..

The VOC Omicron is reducing the efficacy of all vaccines approved to date (unless 3 doses are delivered) and is initiating an unexpected boost in COVID19 convalescent plasma (CCP) usage, with Omicron being treated as a shifted novel virus instead of a SARS-CoV-2 variant drift. Two years into the pandemics, we are back to the starting line for some therapeutic classes. Specifically, Omicron escapes viral neutralization by most monoclonal antibodies (mAbs) authorized to date with the lone exception of bebtelovimab [3]. Despite the development of promising oral small-chemical antivirals (molnupiravir and nirmatrelvir), the logistical and economical hurdles for deploying these drugs worldwide has prevented their immediate and widespread availability, and concerns remain regarding both molnupiravir (both safety[4] and efficacy [5]) and nirmatrelvir (efficacy), expecially in immunocompromised subjects. COVID19 convalescent plasma (CCP) was used as a frontline treatment from the very beginning of the pandemic. Efficacy outcomes have been mixed to date, with most failures explained by low dose, late usage, or both, but efficacy of high-titer CCP has been definitively proven in outpatients with mild disease stages [6, 7]. Neutralizing antibody (nAb) efficacy against VOC remains a prerequisite to support CCP usage, which can now be collected from vaccinated convalescents, including donors recovered from breakthrough infections (so-called “hybrid” or “VaxCCP”)[8]: pre-Omicron evidence suggest that those nAbs have higher titers and are more effective against VOCs than those from unvaccinated convalescents [9, 10]. From a regulatory viewpoint, to date, plasma from vaccinees that have never been convalescent does not fall within the FDA emergency use authorization

There are tens of different vaccine schedules theoretically possible according to EMA and FDA approvals, including a number of homologous or heterologous boosts, but the most commonly delivered schedules in the western hemisphere have been: 1) BNT162b2 or mRNA-1273 for 2 doses eventually followed by a homologous boost; 2) ChAdOx1 for 2 doses eventually followed by a BNT162b2 boost; and 3) Ad26.COV2.S for 1 dose eventually followed by a BNT162b2 boost [11]. Many more inactivated vaccines have been in use in low-and-middle income countries (LMIC), which are target regions for CCP therapy: this is feasible given the lower number of patients at risk for disease progression there (lower incidences of obesity, diabetes, and hypertension, and lower median age) and the already widespread occurrence of collection and transfusion facilities. Most blood donors there have already received the vaccine schedule before, after or without having been infected, with a nAb titer generally declining over months [12]. Hence identifying the settings where the nAb titer is highest will definitively increase the efficacy of CCP collections. Variations in nAb titers against a given SARS-CoV-2 strain are usually reported as fold-changes in geometric mean titer of antibodies neutralizing 50% of cytopathic effect or foci (GMT_{50}) compared to wild-type strains: nevertheless, fold-changes for groups that include non-responders can lead to highly artificial results and possibly over-interpretation. Rigorous studies have hence reported the percentage of

86 responders as primary outcome and provided fold-changes of GMT_{50} where calculation is reasonable
87 (100% responders in both arms) [13].

88 To date the most rigorous data repository for SARS-CoV-2 sensitivity to antivirals is the Stanford
89 University Coronavirus Antiviral & Resistance Database, but as of July 24, 2022 the tables there
90 summarizing "Convalescent plasma" and "Vaccinee plasma" (https://covdb.stanford.edu/search-
91 drdb/?form_only) do not dissect the different heterologous or homologous vaccination schemes, the
92 simultaneous occurrence of vaccination and convalescence, or the time from infection/vaccine to
93 neutralization assay. Consequently, a more in-depth analysis is needed to better stratify CCP types.

94

95 Methods

96 On July 23, 2022, we searched PubMed, medRxiv and bioRxiv for research investigating the efficacy of
97 CCP (either from vaccinated or unvaccinated donors) against SARS-CoV-2 VOC Omicron for article
98 (pre)published after December 1, 2019, using English language as the only restriction. In PubMed we
99 used the search query "("convalescent plasma" or "convalescent serum") AND ("neutralization" or
100 "neutralizing") AND "SARS-CoV-2"", while in bioRxiv and medRxiv we searched for abstract or title
101 containing "convalescent, SARS-CoV-2, neutralization" (match all words). When a preprint was published,
102 the latter was used for analysis. We also screened the reference lists of reviewed articles for additional
103 studies not captured in our initial literature search. Articles underwent evaluation for inclusion by two
104 assessors (D.F. and D.S.) and disagreements were resolved by a third senior assessor (A.C.). We excluded
105 review articles, meta-analyses, studies reporting antibody levels by serological assays other than
106 neutralization, as well as studies exclusively analyzing nAbs in vaccine-elicited plasma/serum from non-
107 convalescent subjects. In unvaccinated subjects, convalescence was annotated according to infecting
108 sublineage (pre-VOC Alpha, VOC Alpha, VOC Beta, VOC Delta, or VOC Omicron sublineages). Given the
109 heterologous immunity that develops after vaccination in convalescents, the infecting lineage was not
110 annotated in vaccine recipients. In vaccinees, strata were created for 2 homologous doses, 3 homologous
111 doses, or post-COVID-19 and post-vaccination (Vax-CCP). The mean neutralizing titer for WA-1 (pre-Alpha
112 wild-type), Omicron and number out of total that neutralized Omicron was abstracted from studies.

113 Statistical significance between means was investigated using Tukey's test.

114

115 Results

116 Our literature search identified 29 studies dealing with the original Omicron lineage (BA.1), that were
117 then manually mined for relevant details : the PRISMA flowchart for study selection is provided in Figure
118 1. Given the urgency to assess efficacy against the upcoming VOC Omicron, most studies (with a few
119 exceptions[14, 15, 16, 17]) relied on Omicron pseudovirus neutralization assays, which, as opposed to live
120 authentic virus, are scalable, do not require BSL-3 facilities, and provide results in less than 1 week.
121 GMT_{50} of nAb and fold-reduction (in GMT_{50} against Omicron compared to wild-type SARS-CoV-2 (e.g.,
122 WA-1) were the most common ways of reporting changes, which reduces variability due to difference in
123 neutralization assays used.

Figure 2 and Table 1 summarize that neutralizing activity to WA-1 from CCP collected from subjects infected with pre-Alpha SARS-CoV-2 (Supplementary Table 1), Alpha VOC (Supplementary Table 2), Beta VOC (Supplementary Table 3), Delta VOC (Supplementary Table 4) or plasma from nonconvalescent subjects vaccinated with 2 mRNA vaccine doses (Supplementary Tables 5 and 6) The same plasma types computed a geometric mean of multiple GMT_{50} from many studies with about a 21-fold reduction against BA.1 geomeans compared to wild-type SARS-CoV-2 geomeans. CCP from uninfected vaccinees receiving a third vaccine dose registered geomean of the $GMT_{(50)}$ of 2,723 (or 10- fold higher nAb geomean of the GMT_{50}) to wild-type viral assays: in this group the nAb geomean of the GMT_{50} fold-reduction against BA.1 was 9, but importantly the geomean of the $GMT_{(50)}$ was close to 291 again. The approximately 21-fold reduction in nAb geomean of the $GMT_{(50)}$ from wild-type to BA.1 was reversed by the 10-15-fold increase in nAb geomean of the $GMT_{(50)}$ from either boosted vaccination or VaxCCP.

In addition to the nAb GMT_{50} levels showing potency, the percentage of individuals within a study cohort positive for any level of BA.1 neutralization shows the likelihood of a possible donation having anti-BA.1 activity. All studies but one tested a limited number of 20 to 40 individuals. The pre-Alpha CCP showed that most (18 of 27 studies) had less than 50% of individuals tested within a study with measurable BA.1 neutralizing activity: only 2 out of 27 studies indicated 100% of individuals tested showed BA.1 neutralization (Figure 3). Likewise, most of the studies investigating Alpha and Beta CCP showed similar percent with nAb. Delta CCP had 6 of 7 studies with more than 50% BA.1 neutralization. The plasma from studies of the 2-dose mRNA vaccines indicated a more uniform distributive increase in percent of individual patients with measurable Omicron nAb's. The stark contrast is Vax-CCP, where 16 of 19 studies had 100% of individuals tested with anti-BA.1 nAb. The 3-dose vaccinee studies similarly had 12 of 17 studies with 100% measurable nAb.

There were 5 studies which directly compared anti-WA-1 versus BA.1 nAb titers in nonvaccinated pre-Alpha, Alpha, Beta, and Delta CCP, and vaccinated plasma with the same nAb assay (Figure 4). nAb GMT_{50} against WA-1 was higher for Alpha and Delta CCP but lower for Beta CCP. nAb geomean of the $GMT_{(50)}$ against BA.1 was actually highest for Beta CCP 13 geomean with geomean levels of 9, 8, 10 for pre-Alpha, Alpha and Delta (Figure 4, panel A). In these 5 studies, nAb geomean of the $GMT_{(50)}$ rose from 2-dose vaccinations to VaxCCP to the 3-dose boosted vaccination. Importantly, for nAb geomean of the $GMT_{(50)}$ against BA.1 were 13 to 103 to 223, respectively representing a 8 to 17-fold rise (Figure 4, panel B).

Another set of 9 matched vaccination studies inclusive of plasma collected after 2- and 3-dose schedules, as well as Vax-CCP depicted a 23-fold rise in geomean of the $GMT_{(50)}$ of anti-BA.1 nAb from the 2-dose vaccine to post COVID-19 vaccinees, and a 21-fold increase after the third vaccine dose. The pattern was similar for nAb geomean of the $GMT_{(50)}$ against WA-1 (Figure 4, panel C).

The AZD1222, 3-dose mRNA-1273 and Ad26.COV2 vaccines were understudied, with 3 or less independent studies at different time points, reported in Table 10. The GMT_{50} nAb to BA.1 after 3-mRNA-1273 doses ranged 60 to 2000, with a 5 to 15 fold reduction compared with WA-1. GMT_{50} of anti-BA.1 nAbs after AZD1222 vaccine was modest (~10 to 20), as with Ad26.COV2 vaccine (~20 to 40). Two studies reported on post-COVID-19/post-mRNA-1273 with nAb GMT_{50} against BA.1 of 38 and 272. Studies with 100% of individual patient samples neutralizing BA.1 included 2 3-dose mRNA-1273 studies, one AZD1222 study, and one post-COVID-19/post-mRNA-1273 study.

Few data exist for comparisons among different vaccine boosts. For CoronaVac® (SinoVac), three doses led to 5.1 fold reduction in anti-BA.1 nAb GMT_{50} compared to wild-type [18], while for Sputnik V nAb titer moved from a 12-fold reduction at 6-12 months up to a 7-fold reduction at 2-3 months after a boost with Sputnik Light [19, 20]. These *in vitro* findings have been largely confirmed *in vivo*, where prior heterologous SARS-CoV-2 infection, with and without mRNA vaccination, protects against BA.1 re-infection [21].

Seventeen studies analyzed the efficacy of CCP and VaxCCP against Omicron sublineages other than BA.1 (summarized in Table 2). Those studieslargely confirmed that Omicron CCP *per se* is poorly effective against the cognate or other Omicron sublineages[22] (with the lone exception of cross-reactions among lineages sharing L452 mutations[23] and broad-spectrum nAbs elicited by BA.5[24]). On the contrary, both homologous and heterologous efficacy of Omicron VaxCCP is again universally preserved [15, 25]. Despite evidences that concentrated pooled human IgG from convalescent and vaccinated donors has 5-fold reduced potency against BA.5 compared to wild-type SARS-CoV-2 [26], such VaxCCP derivative is devoid of IgA and IgM nAbs. These findings have important implications if a VaxCCP program is going to be re-launched at the time of BA.2 and BA.4/5 waves.

Discussion

Since nAbs are by definition antiviral, CCP with a high nAb GMT_{50} is preferable, , and there is now strong clinical evidence that nAb titers correlate with clinical benefit in randomized clinical trials[6, 7]. Although nAb titers correlate with vaccine efficacy[27, 28], it is important to keep in mind that SARS-CoV-2-binding non-neutralizing antibodies can similarly provide protection via Fc-mediated functions [29, 30]. However, such functions are harder to measure and no automated assay exist for use in clinical laboratories. Hence, whereas the presence of a high nAb GMT_{50} in CCP is evidence for antibody effectiveness *in vitro*, the absence of nAb titer does not imply lack of protection *in vivo* where Fc effects mediate protection by other mechanisms such as antibody-dependent cell-mediated cytotoxicity , complement activation and phagocytosis.

The mechanism by which CCP from vaccinated COVID-19 convalescent individuals better neutralizes Omicron lineagesis probably a combination of higher amounts of nAb and broader antibody specificity. Higher amounts of antibody could neutralize antigenically different variants through the law of mass action [31] whereby even lower affinity antibodies elicited to earlier variants would bind to the Omicron variant as mass compensates for reduced binding strength to drive the reaction forward. In addition, vaccinated COVID-19 convalescent individuals would have experienced SARS-CoV-2 protein in two antigenically different forms: as part of intact infective virions generated *in vivo* during an infectious process and as antigens in vaccine preparations. As the immune system processes the same antigen in different forms, there are numerous opportunities for processing the protein in different manners that can diversity the specificity of the immune response and thus increase the likelihood of eliciting antibodies that react with variant proteins. Structurally, it has been shown that third dose mRNA vaccination induces mostly class 1/2 antibodies encoded by IGHV1-58;IGHJ3-1 and IGHV1-69;IGHJ4-1 germlines, but not the IGHV2-5;IGHJ3-1 germline, broadly cross-reactive Class 3 antibodies seen after infection [32].

Our analysis provides strong evidence that, unlike what has been observed in Syrian hamster models [33], CCP from unvaccinated donors is unlikely (less than 50%) to have any measurable Omicron neutralization. Although the nAb GMT_{50} threshold for clinical utility remains poorly defined, it is noticeable that low BA.1 nAb GMT_{50} were generally detected in CCP after infection from pre-Omicron VOCs.

On the contrary, despite the huge heterogeneity of vaccine schedules, CCP from vaccinated and COVID-19 convalescent individuals (Vax-CCP) consistently harbors high nAb titers against BA.1 and novel sublineages if collected up to 6 months since last event (either vaccine dose or infection). These Omicron neutralizing levels are comparable in dilutional titers to that of WA-1 CCP neutralizing WA-1, but their prevalence is much higher at this time, facilitating recruitment of suitable donors. Pre-Omicron CCP boosted with WA-1-type vaccines induces heterologous immunity that effectively neutralizes Omicron in the same assays which rule in or out therapeutic anti-Spike monoclonal antibodies. Consequently, prescreening of Vax-CCP donors for nAb titers is not necessary, and qualification of Vax-CCP units remains advisable only within clinical trials. A more objective way to assess previous infection (convalescence) would be measuring anti-nucleocapsid (N) antibodies, but unfortunately these vanish quickly [34, 35]. Previous symptomatic infection and vaccination can be established by collecting past medical history (PMH) during the donor selection visit, which is cheaper, faster, and more reliable than measuring rapidly declining anti-N antibodies. Although there is no formal evidence for this, it is likely that asymptomatic infection (leading to lower nAb levels in pre-Omicron studies) also leads to lower nAb levels after vaccination compared to symptomatic infection, given that disease severity correlates with antibody titer [36, 37]: hence those asymptomatically infected donors missed by investigating PMH are also less likely to be useful.

The same reasoning applies to uninfected vaccinees receiving third dose boosts, but several authorities, including the FDA, do not currently allow collection from such donors for CCP therapy on the basis that the convalescent polyclonal and poly-target response is a prerequisite for efficacy and superior to the polyclonal anti-Spike-only response induced by vaccinees. This may be a false premise for recipients of inactivated whole-virus vaccines (e.g., BBIBP-CorV or VLA2001): for BBIBP-CorV, the efficacy against Omicron is largely reduced [18, 20, 38], but the impact of boost doses is still unreported at the time of writing. Table 1 and Table 9 clearly show that 3-doses of BNT162b2 are enough to restore nAb levels against Omicron in the absence of SARS-CoV-2 infection.

Another point to consider is that information on nAb levels after the third vaccine dose has been almost exclusively investigated for only 1 month of follow-up, while studies on convalescents extend to more than 6 months: to date it seems hence advisable to start from convalescent vaccinees rather than uninfected 3-dose vaccinees. This is also confirmed by immune escape reported *in vivo* after usage of vaccine (non-convalescent) plasma [39] despite very high nAb titres, likely due to restricted antigen specificity. Vaccine schedules with a delayed boost seem to elicit higher and broader nAb levels than the approved, short schedules[40, 41, 42, 43], but this remain to be confirmed in larger series. The same is true for breakthrough infections from Alpha or Delta VOC in fully BNT162b2 vaccinated subjects[44], although variation in time from infection due to successive waves is a major confounder.

With the increase of Omicron seroprevalence in time, polyclonal intravenous immunoglobulins collected from regular donors could become a more standardized alternative to CCP, but their efficacy to date (at the peak of the vaccinations campaign) is still 16-fold reduced against Omicron compared to wild-type

SARS-CoV-2[45], and such preparations include only IgG and not IgM and IgA, which have powerful SARS-CoV-2 activity [46, 47]. Nevertheless, FDA recently reported efficacy of hyperimmune serum against BA.1, BA.2, BA.3, BA.2.12.1, and BA.4/5 [48].

CCP collection from vaccinated convalescents (regardless of infecting sublineage, vaccine type and number of doses) is likely to achieve high nAb titer against VOC Omicron, and, on the basis of lessons learnt with CCP usage during the first 2 years of the pandemic. Although in ideal situations one would prefer RCT evidence of efficacy against Omicron before deployment, there is concern that variants are generated so rapidly that by the time such trials commenced this variant could be replaced for another. Given the success of CCP in 2 outpatient RCTs reducing hospitalization[6, 7] and the loss of major mAb therapies due to Omicron antigenic changes, the high titers in CCP collected from vaccinated convalescents provides an immediate option for COVID-19, especially in LMIC. Given the reduced hospitalization rate with Omicron compared to Delta [49], it is even more relevant to identify patient subsets at risk of progression in order to minimize the number needed to treat to prevent a single hospitalization: moving from the same criteria used for mAb therapies while using the same (now unused) in-hospital facilities seems a logical approach.

We declare we have no conflict of interest related to this manuscript.

References

1. Ahmed SF, Quadeer AA, McKay M. SARS-CoV-2 T cell responses are expected to remain robust against Omicron. *Viruses* **14**, 79 (2022).

2. Bernasconi A, *et al.* Report on Omicron Spike mutations on epitopes and immunological/epidemiological/kinetics effects from literature. Accessed at https://virological.org/t/report-on-omicron-spike-mutations-on-epitopes-and-immunological-epidemiological-kinetics-effects-from-literature/770 on July 23, 2022.) (2021).

3. Focosi D, McConnell S, Casadevall A, Cappello E, Valdiserra G, Tuccori M. Monoclonal antibody therapies against SARS-CoV-2. *Lancet Infect Dis*, (2022).

4. Zhou S, *et al.* β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. *The Journal of Infectious Diseases* **224**, 415-419 (2021).

5. Jayk Bernal A, *et al.* Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med* **386**, 509-520 (2022).

6. Libster R, *et al.* Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. *N Engl J Med* **384**, 610-618 (2021).

7. Sullivan D, *et al.* Early Outpatient Treatment for Covid-19 with Convalescent Plasma. *N Engl J Med*, (2021).

8. Vickers MA, *et al.* Exponential increase in neutralizing and spike specific antibodies following vaccination of COVID-19 convalescent plasma donors. *Transfusion* **61**, 2099-2106 (2021).

9. Schmidt F, *et al.* High genetic barrier to SARS-CoV-2 polyclonal neutralizing antibody escape. *Nature* **600**, 512-516 (2021).

10. Di Germanio C, *et al.* Vaccination of COVID-19 Convalescent Plasma Donors Increases Binding and Neutralizing Antibodies Against SARS-CoV-2 Variants. *Transfusion* **62**, 563-569 (2021).

11. Munro APS, *et al.* Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *The Lancet* **398**, 2258-2276 (2021).

12. Franchini M, *et al.* Neutralizing antibody levels against SARS-CoV-2 variants of concern Delta and Omicron in vaccine breakthrough-infected blood donors. *Transfusion* **62**, 1171-1176 (2022).

13. Jacobsen H, *et al.* Diminished neutralization responses towards SARS-CoV-2 Omicron VoC after mRNA or vector-based COVID-19 vaccinations. 2021.2012.2021.21267898 (2021).

14. Planas D, *et al.* Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature* **602**, 671-675 (2022).

15. Bekliz M, *et al.* Neutralization of ancestral SARS-CoV-2 and variants Alpha, Beta, Gamma, Delta, Zeta and Omicron by mRNA vaccination and infection-derived immunity through homologous and heterologous variants. 2021.2012.2028.21268491 (2021).

16. Rossler A, Riepler L, Bante D, von Laer D, Kimpel J. SARS-CoV-2 Omicron Variant Neutralization in Serum from Vaccinated and Convalescent Persons. *N Engl J Med* **386**, 698-700 (2022).

17. Muik A, *et al.* Neutralization of SARS-CoV-2 Omicron by BNT162b2 mRNA vaccine-elicited human sera. *Science (New York, NY)* **375**, 678-680 (2022).

18. Zhao X, *et al.* Reduced sera neutralization to Omicron SARS-CoV-2 by both inactivated and protein subunit vaccines and the convalescents. 2021.2012.2016.472391 (2021).

19. Dolzhikova IV, *et al.* Sputnik Light booster after Sputnik V vaccination induces robust neutralizing antibody response to B.1.1.529 (Omicron) SARS-CoV-2 variant. 2021.2012.2017.21267976 (2021).

20. Bowen JE, *et al.* Omicron BA.1 and BA.2 neutralizing activity elicited by a comprehensive panel of human vaccines. 2022.2003.2015.484542 (2022).

21. Carazo S, *et al.* Protection against Omicron re-infection conferred by prior heterologous SARS-CoV-2 infection, with and without mRNA vaccination. 2022.2004.2029.22274455 (2022).

22. Turelli P, *et al.* Omicron infection induces low-level, narrow-range SARS-CoV-2 neutralizing activity. 2022.2005.2002.22274436 (2022).

23. Qu P, *et al.* Differential Evasion of Delta and Omicron Immunity and Enhanced Fusogenicity of SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 Subvariants. 2022.2005.2016.492158 (2022).

24. Richardson SI, *et al.* SARS-CoV-2 BA.4 infection triggers more cross-reactive neutralizing antibodies than BA.1. 2022.2007.2014.500039 (2022).

25. Zhou R, *et al.* Vaccine-breakthrough infection by the SARS-CoV-2 Omicron variant elicits broadly cross-reactive immune responses. *Clin Transl Med* **2**, e720 (2022).

26. Aggarwal A, *et al.* SARS-CoV-2 Omicron BA.5: Evolving tropism and evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern. 2022.2007.2007.22277128 (2022).

27. Khoury DS, *et al.* Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* **27**, 1205-1211 (2021).

28. Feng S, *et al.* Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* **27**, 2032-2040 (2021).

29. Gilbert PB, *et al.* Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science*, eab3435 (2021).

30. Earle KA, *et al.* Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* **39**, 4423-4428 (2021).

31. Tyrrell DA. Neutralization of viruses by homologous immune serum. II. Theoretical study of the equilibrium state. *The Journal of experimental medicine* **97**, 863-870 (1953).

32. Andreano E*, et al.* COVID-19 mRNA third dose induces a unique hybrid immunity-like antibody response. 2022.2005.2009.491201 (2022).

33. Ryan KA*, et al.* Convalescence from prototype SARS-CoV-2 protects Syrian hamsters from disease caused by the Omicron variant. 2021.2012.2024.474081 (2021).

34. Krutikov M*, et al.* Prevalence and duration of detectable SARS-CoV-2 nucleocapsid antibodies in staff and residents of long-term care facilities over the first year of the pandemic (VIVALDI study): prospective cohort study in England. *The Lancet Healthy Longevity*, (2021).

35. Amjadi MF*, et al.* Anti-membrane and anti-spike antibodies are long-lasting and together discriminate between past COVID-19 infection and vaccination. 2021.2011.2002.21265750 (2021).

36. Klein S*, et al.* Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *The Journal of clinical investigation* **130**, 6141-6150 (2020).

37. Focosi D, Franchini M. Clinical predictors of SARS-CoV-2 neutralizing antibody titers in COVID-19 convalescents: Implications for convalescent plasma donor recruitment. *European journal of haematology* **107**, 24-28 (2021).

38. Yu X*, et al.* Pseudotyped SARS-CoV-2 Omicron variant exhibits significant escape from neutralization induced by a third booster dose of vaccination. 2021.2012.2017.21267961 (2021).

39. Gachoud D*, et al.* Antibody response and intra-host viral evolution after plasma therapy in COVID-19 patients pre-exposed or not to B-cell depleting agents. 2022.2004.2024.22274200 (2022).

40. Chatterjee D*, et al.* SARS-CoV-2 Omicron Spike recognition by plasma from individuals receiving BNT162b2 mRNA vaccination with a 16-week interval between doses. *Cell Rep* **38**, 110429 (2022).

41. Grunau B*, et al.* Immunogenicity of Extended mRNA SARS-CoV-2 Vaccine Dosing Intervals. *JAMA* **327**, 279-281 (2022).

42. Tauzin A, *et al.* A single BNT162b2 mRNA dose elicits antibodies with Fc-mediated effector functions and boost pre-existing humoral and T cell responses. *medRxiv [Preprint]*, 2021.2003.2018.435972 (2021).

43. Skowronski DM, *et al.* Two-dose SARS-CoV-2 vaccine effectiveness with mixed schedules and extended dosing intervals: test-negative design studies from British Columbia and Quebec, Canada. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, ciac290 (2022).

44. Miyamoto S, *et al.* Vaccination-infection interval determines cross-neutralization potency to SARS-CoV-2 Omicron after breakthrough infection by other variants. 2021.2012.2028.21268481 (2022).

45. Focosi D, Franchini M. Passive immunotherapies for COVID-19: The subtle line between standard and hyperimmune immunoglobulins is getting invisible. *Rev Med Virol*, e2341 (2022).

46. Klingler J, *et al.* Role of IgM and IgA Antibodies in the Neutralization of SARS-CoV-2. *J Infect Dis* **223**, 957-970 (2020).

47. Wang Z, *et al.* Enhanced SARS-CoV-2 neutralization by dimeric IgA. *Science translational medicine*, (2020).

48. Awasthi M, Golding H, Khurana S. SARS-CoV-2 hyperimmune intravenous human immunoglobulins neutralizes Omicron subvariants BA.1, BA.2, BA.2.12.1, BA.3 and BA.4/BA.5 for treatment of COVID-19. *Clinical Infectious Diseases*, (2022).

49. Wolter N, *et al.* Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa. *Lancet* **399**, 437-446 (2022).

50. Iketani S, *et al.* Antibody Evasion Properties of SARS-CoV-2 Omicron Sublineages. *Nature* **604**, 553-556 (2022).

51. Cao YR, *et al.* BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. *Nature*, (2022).

52. Tuekprakhon A, *et al.* Further antibody escape by Omicron BA.4 and BA.5 from vaccine and BA.1 serum. *Cell* **185**, 2422-2433.e2413 (2022).

53. Tjan LH, *et al.* As well as Omicron BA.1, high neutralizing activity against Omicron BA.2 can be induced by COVID-19 mRNA booster vaccination. *J Infect Dis*, jiac159 (2022).

54. Khan K, *et al.* Omicron sub-lineages BA.4/BA.5 escape BA.1 infection elicited neutralizing immunity. 2022.2004.2029.22274477 (2022).

55. Willett BJ, *et al.* Distinct antigenic properties of the SARS-CoV-2 Omicron lineages BA.4 and BA.5. 2022.2005.2025.493397 (2022).

56. Muik A, *et al.* Omicron BA.2 breakthrough infection enhances cross-neutralization of BA.2.12.1 and BA.4/BA.5. 2022.2008.2002.502461 (2022).

57. Yu J, *et al.* Comparable Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants. 2022.2002.2006.22270533 (2022).

58. Seaman MS, *et al.* Vaccine Breakthrough Infection with the SARS-CoV-2 Delta or Omicron (BA.1) Variant Leads to Distinct Profiles of Neutralizing Antibody Responses. 2022.2003.2002.22271731 (2022).

59. Zou J, *et al.* Cross neutralization of Omicron BA.1 against BA.2 and BA.3 SARS-CoV-2. *Nat Commun* **13**, 2956 (2022).

60. Lapointe HR, *et al.* Serial infection with SARS-CoV-2 Omicron BA.1 and BA.2 following three-dose COVID-19 vaccination. 2022.2005.2019.22275026 (2022).

61. Hachmann NP, *et al.* Neutralization Escape by the SARS-CoV-2 Omicron Variants BA.2.12.1 and BA.4/BA.5. *N Engl J Med* **387**, 86-88 (2022).

62. Wang Q, *et al.* SARS-CoV-2 Omicron BA.2.12.1, BA.4, and BA.5 subvariants evolved to extend antibody evasion. 2022.2005.2026.493517 (2022).

63. Planas D, *et al.* Duration of BA.5 neutralization in sera and nasal swabs from SARS-CoV-2 vaccinated individuals, with or without Omicron breakthrough infection. 2022.2007.2022.22277885 (2022).

64. Zeng C, *et al.* Neutralization and Stability of SARS-CoV-2 Omicron Variant. *bioRxiv*, (2021).

65. Liu L, *et al.* Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature* **602**, 676-681 (2022).

66. Schmidt F, *et al.* Plasma Neutralization of the SARS-CoV-2 Omicron Variant. *N Engl J Med* **386**, 599-601 (2022).

67. Arien KK, *et al.* Three doses of BNT162b2 vaccine confer neutralising antibody capacity against the SARS-CoV-2 Omicron variant. *NPJ Vaccines* **7**, 35 (2022).

68. Lusvarghi S, *et al.* SARS-CoV-2 BA.1 variant is neutralized by vaccine booster-elicited serum, but evades most convalescent serum and therapeutic antibodies. *Sci Transl Med*, eabn8543 (2022).

69. Hoffmann M, *et al.* The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. *Cell* **185**, 447-456 e411 (2022).

70. Zou J, *et al.* Neutralization against Omicron SARS-CoV-2 from previous non-Omicron infection. *Nat Commun* **13**, 852 (2022).

71. Zhang L, *et al.* The significant immune escape of pseudotyped SARS-CoV-2 variant Omicron. *Emerging microbes & infections* **11**, 1-5 (2022).

72. Gruell H, *et al.* mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. *Nat Med* **28**, 477-480 (2022).

73. Dejnirattisai W, *et al.* SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. *Cell* **185**, 467-484 e415 (2022).

74. Sheward DJ, *et al.* Variable loss of antibody potency against SARS-CoV-2 B.1.1.529 (Omicron). *bioRxiv*, 2021.2012.2019.473354 (2021).

75. Tada T, *et al.* Increased resistance of SARS-CoV-2 Omicron variant to neutralization by vaccine-elicited and therapeutic antibodies. *EBioMedicine* **78**, 103944 (2022).

76. Aggarwal A, *et al.* SARS-CoV-2 Omicron: evasion of potent humoral responses and resistance to clinical immunotherapeutics relative to viral variants of concern. *medRxiv*, 2021.2012.2014.21267772 (2021).

77. Zhao X, *et al.* Effects of a Prolonged Booster Interval on Neutralization of Omicron Variant. *N Engl J Med* **386**, 894-896 (2022).

78. Bowen JE, *et al.* Omicron BA.1 and BA.2 neutralizing activity elicited by a comprehensive panel of human vaccines. *bioRxiv*, (2022).

79. Carreno JM, *et al.* Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. *Nature* **602**, 682-688 (2022).

80. Syed AM, *et al.* Omicron mutations enhance infectivity and reduce antibody neutralization of SARS-CoV-2 virus-like particles. *medRxiv*, (2022).

81. Haveri A, *et al.* Neutralizing antibodies to SARS-CoV-2 Omicron variant after third mRNA vaccination in health care workers and elderly subjects. *Eur J Immunol*, (2022).

82. Li M, *et al.* Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern. *Blood advances*, 2022.2003.2001.22271662 (2022).

83. Kurahashi Y, *et al.* Cross-neutralizing activity against Omicron could be obtained in SARS-CoV-2 convalescent patients who received two doses of mRNA vaccination. *medRxiv*, 2022.2002.2024.22271262 (2022).

84. Lechmere T, *et al.* Broad Neutralization of SARS-CoV-2 Variants, Including Omicron, following Breakthrough Infection with Delta in COVID-19-Vaccinated Individuals. *mBio* **13**, e0379821 (2022).

85. Edara VV, *et al.* mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant. *Cell Rep Med* **3**, 100529 (2022).

86. Cele S, *et al.* Omicron extensively but incompletely escapes Pfizer BNT162b2 neutralization. *Nature* **602**, 654-656 (2022).

87. Wilhelm A, *et al.* Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and Monoclonal Antibodies. *medRxiv*, 2021.2012.2007.21267432 (2021).

88. Doria-Rose NA, *et al.* Booster of mRNA-1273 Strengthens SARS-CoV-2 Omicron Neutralization. *medRxiv*, 2021.2012.2015.21267805 (2021).

89. Kawaoka Y, *et al.* Characterization and antiviral susceptibility of SARS-CoV-2 Omicron/BA.2. *Res Sq*, (2022).

90. Dejnirattisai W, *et al.* Reduced neutralisation of SARS-COV-2 Omicron-B.1.1.529 variant by post-immunisation serum. *Lancet* **399**, 234-236 (2022).

Figure 1

PRISMA flowchart for the current study.

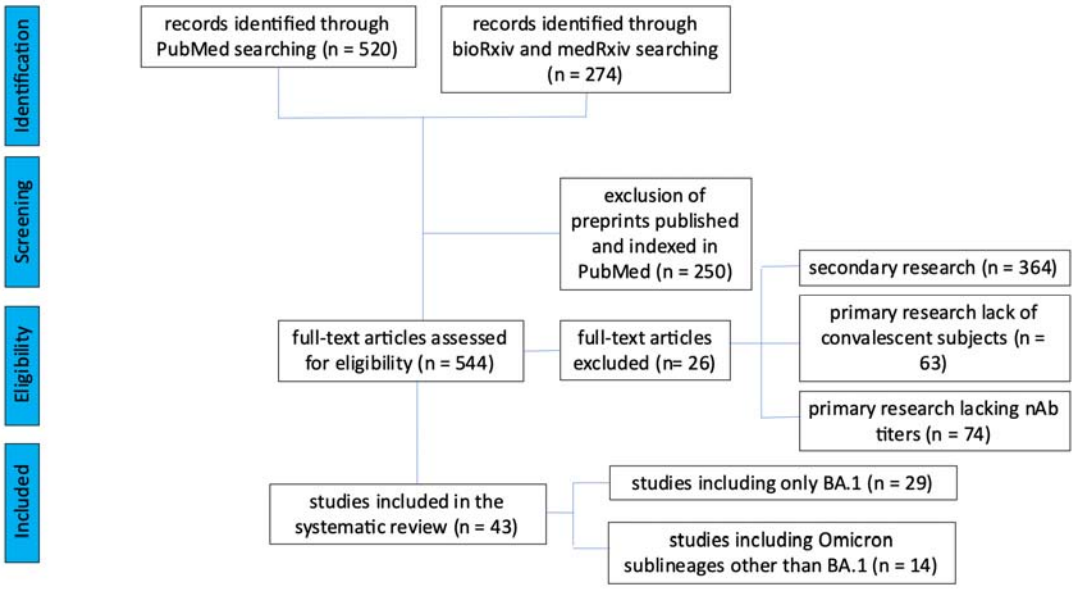

Figure 2

Geometric mean neutralizing titers (GMT_{50}) against WA-1 versus Omicron BA.1 by study for A) unvaccinated convalescent plasma and B) vaccinated plasma with or without COVID-19. Geomeans for entire study groups with neutralization of WA-1 in filled circles with Omicron in empty circles with geomeans and fold reduction (FR) above data and number of studies above x-axis. All geomeans are not statistically significant in difference by multiple comparison in Tukey's test.

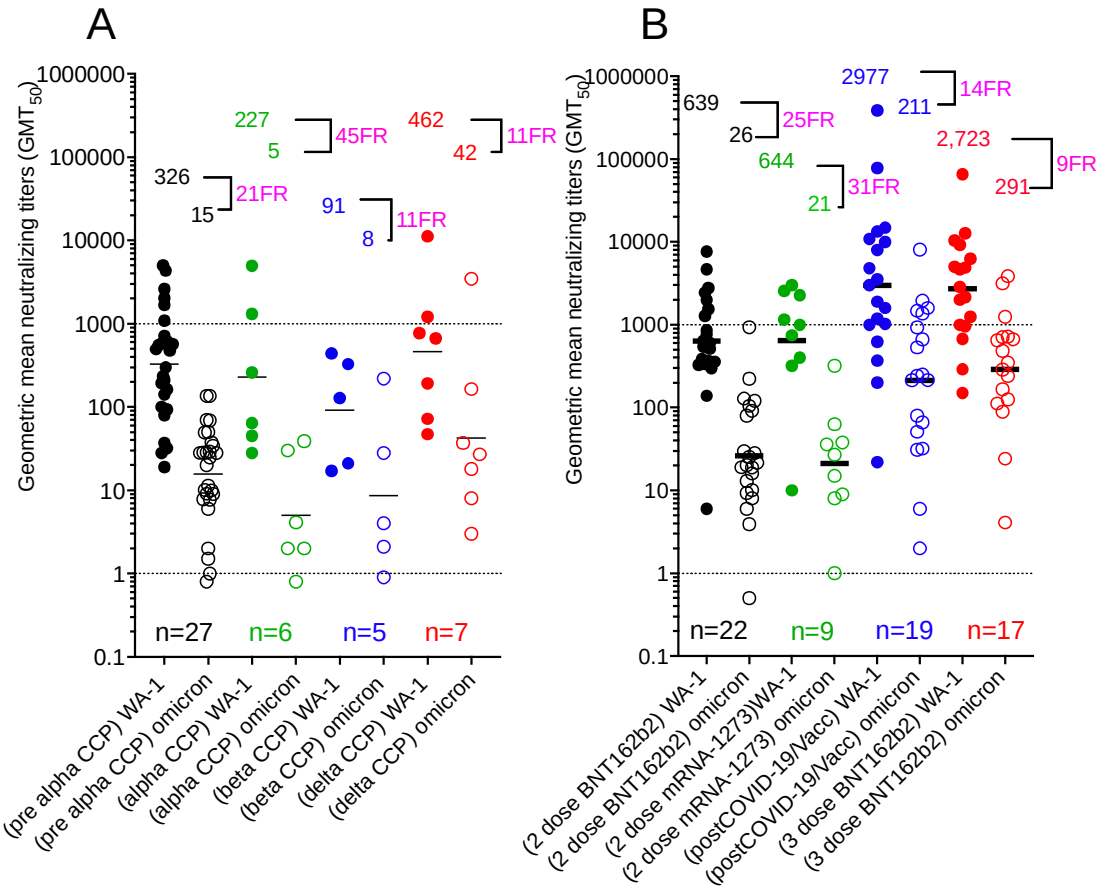

Figure 3

Percent of individual plasma samples in each study showing any titer of Omicron BA.1 neutralization. The percent of samples within a study condition which neutralized Omicron graphed in increasing percentages with the number of samples tested on the right y axis. A) pre-Alpha CCP neutralization of Omicron; B) Alpha, Beta and Delta CCP neutralization of Omicron C) 2 dose mRNA vaccines neutralization of Omicron D) post-COVID-19/post-vaccine (VaxCCP) and uninfected 3-dose vaccine neutralization of Omicron.

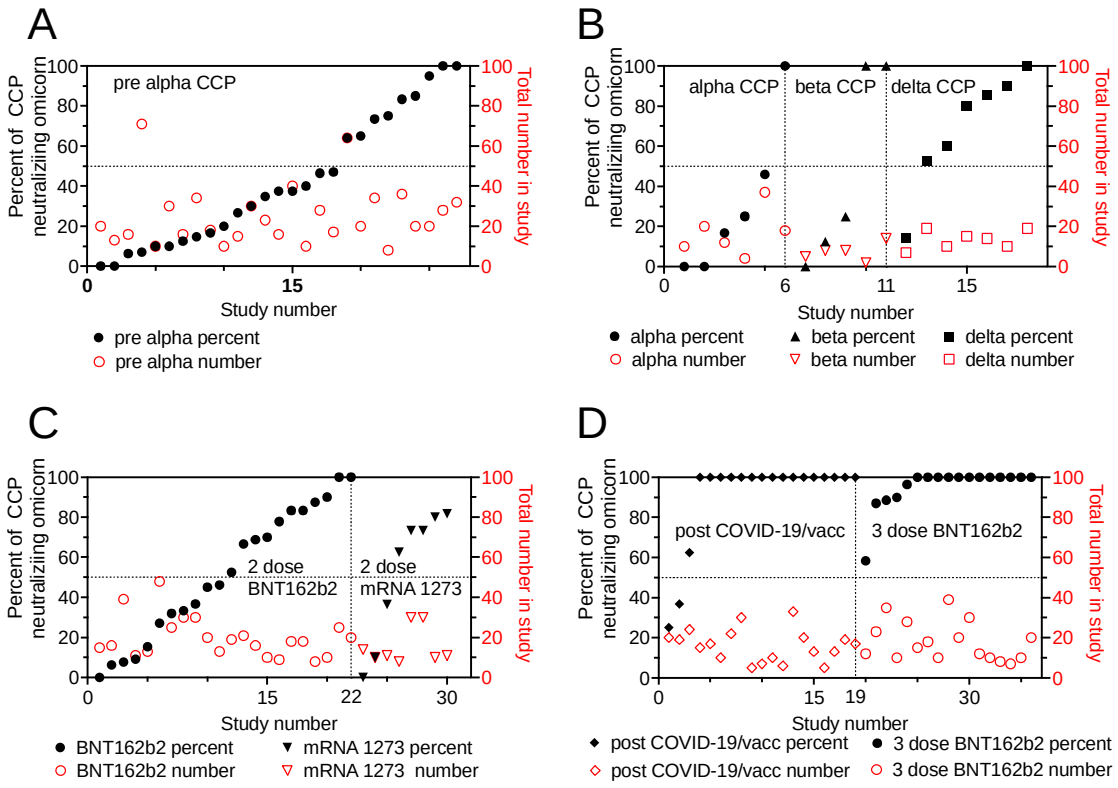

Figure 4

Geometric mean neutralizing titers (GMT_{50}) of anti-WA.1 or anti-Omicron BA.1 neutralizing antibodies in plasma samples from 5 studies investigating diverse SARS-CoV-2 infecting lineage or vaccination status. 5 studies characterized A) pre-Alpha, Alpha, Beta and Delta CCP for Omicron nAb compared to WA-1, and also B) 2 or 3 doses BNT162b plasma, as well as post-COVID-19 plus BNT162b vaccine (VaxCCP). C) 9 additional studies looked at the same vaccine conditions in the first 5 comparing WA-1 nAb to Omicron nAb.

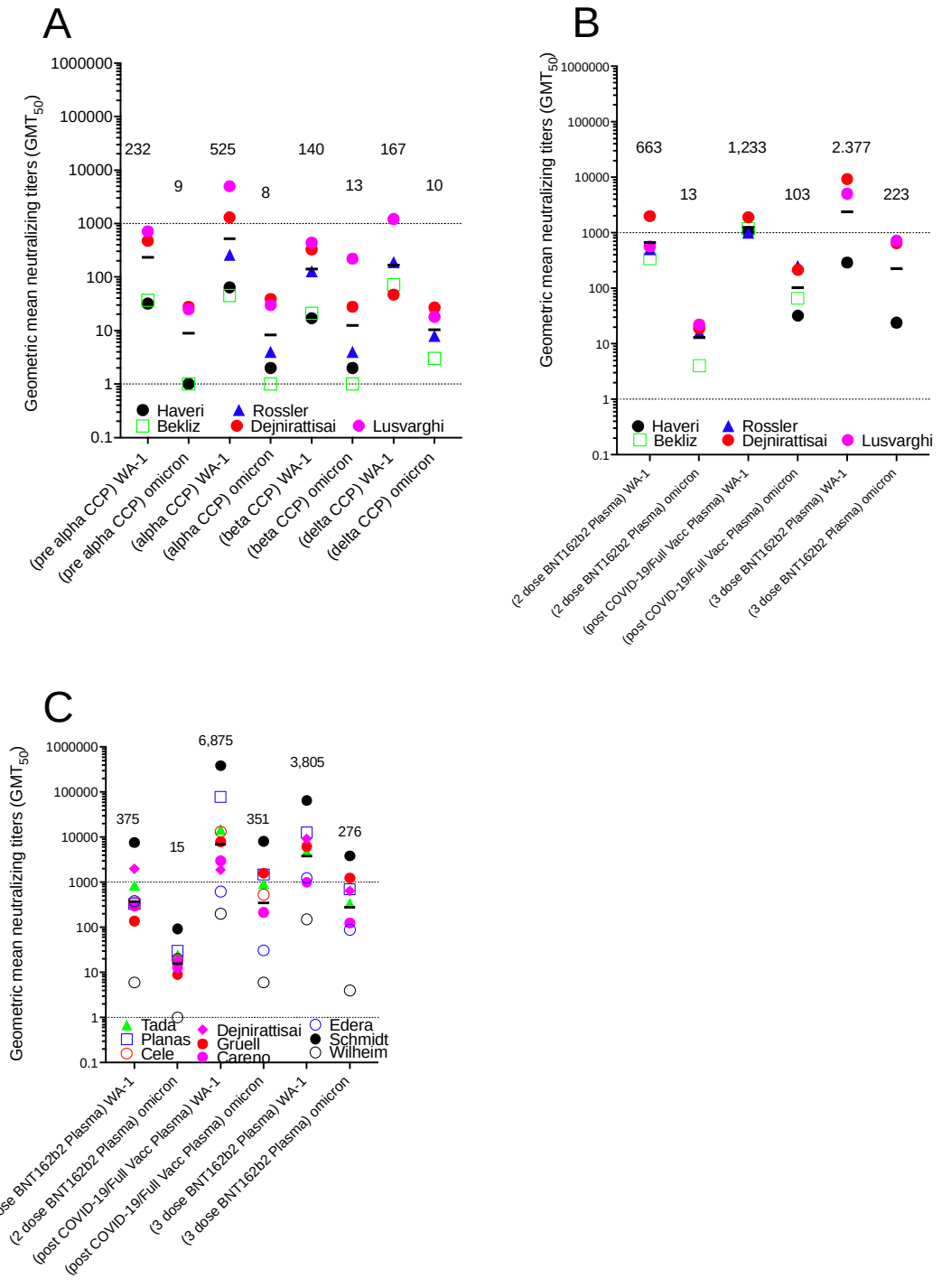

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Table 1

Comparison of WA-1 to Omicron BA.1 nAb and percent with any Omicron BA.1 nAb amongst VOC CCP and vaccination status.

plasma type	number of studies	WA-1 nAb GMT_{50}	Omicron BA1 nAb GMT_{50}	fold reduction in nAb GMT_{50} vs. Omicron BA.1	total number individuals in all studies	total Omicron BA.1 neutralizing number	Omicron BA.1 neutralizing percent
pre-Alpha	27	326	15	21	679	300	44
Alpha	6	227	5	45	101	38	38
Beta	5	91	8	11	37	19	51
Delta	7	462	42	11	94	69	73
2 dose BNT162b2 plasma	22	639	26	25	434	204	47
2 dose mRNA-1273 plasma	9	644	21	31	134	81	60
post-COVID-19/full vacc plasma	19	2977	211	14	305	269	88
3 dose BNT162b2 plasma	17	2,723	291	9	307	293	95

Table 2

Efficacy of CCP, vaccinee plasma and VaxCCP expressed as GMT_{50} against Omicron sublineages.

CCP source	target Omicron sublineage			
	BA.1	**BA.2**	**BA.2.12.1**	**BA.4/5**
wild-type CCP (unvaccinated)	↓[50] (including BA.1.1)	↓[50]	no data	no data
uninfected 3-dose mRNA vaccinee plasma	↓[50] (including BA.1.1) [15, 25]	↓[50]	no data	stronger escape than BA.2[23, 51, 52]
any pre-Omicron VOC VaxCCP	no data	=[53]	no data	[24]
Delta VaxCCP	no data	no data	[23]	[23]
BA.1 CCP	↓[22]	no data	no data	7.5-7.6-fold lower than against BA.1[23, 51, 52, 54, 55]
BA.1 VaxCCP	1:2929 at 9-12 days[15, 25, 48, 56]	1.3 to 1.8-fold lower [50, 57, 58] 4.2-fold lower[59] than against the parental BA.1 sublineage; no neutralization[60] [48]	1.8-fold lower than against BA.2[23, 51 61, 62] > 5-fold lower compared to wild-type[56] [48]	2.6-3.2-fold lower than against BA.1[54, 55, 61, 63] 4.5-fold lower than against BA.2[55] > 5-fold lower compared to wild-type[56] [48]
BA.2 CCP	no data	no data	no data	poor[55] [63]
BA.2 VaxCCP	1.2-fold lower compared to wild-type[56]	1.5-fold lower compared to wild-type[56]	2.5-fold lower compared to wild-type[56]	2.5-fold lower compared to wild-type[56]
BA.2.12.1 CCP	no data	no data	no data	no data
BA.2.12.1 VaxCCP	no data	no data	no data	no data
BA.4/ 5 CCP	557 (2-FR) [24]	884 (1-FR)[24]	no data	1,047[24]
BA.4/5 VaxCCP	2,785 (2-FR)[24]	4244 (1-FR)[24]	no data	3,779[24]

Supplementary table 1

Synopsis of *in vitro* studies investigating the efficacy of pre-Alpha CCP against Omicron

reference	Time since infection	(pre-Alpha CCP) WA-1 GMT_{50}	(pre-Alpha CCP) fold drop vs. BA.1	(pre-Alpha CCP) BA.1 GMT_{50}	(pre-Alpha CCP) number in study	(pre-Alpha CCP) BA.1 neutralizing number	(pre-Alpha CCP) BA.1 neutralizing percent
Zeng[64]		4980	177	28	18	3	17
Liu[65]		4344	32	136	10	2	20
Schmidt[66]	1.2 mo	2616	38	69	20	19	95
Schmidt[66]	12 mo	2037	15	136	20	17	85
Schmidt[66]	6 mo	1678	49	34	20	13	65
Arien[67]		1086	22	49	10	1	10
Lusvarghi[68]		715	29	25	16	2	13
Hoffman[69]		614	80	8	17	8	47
Zou[70]		601	16	38	64	41	64
Planas[14]	6 mo	569	20	28	16	6	38
Planas[14]	12 mo	580	20	29	23	8	35
Zhang[71]		556	8	70	28	28	100
Gruell[72]	1.5 mo	494	82	6	30	3	10
Gruell[72]	12 mo	93	12	8	30	9	30
Dejnirattisai[73]		475	17	28	32	32	100
Sheward[74]		300	6	50	34	25	74
Tada[75]		233	26	9	10	4	40
Aggerwal[76]		210	21	10	20	0	0
Zhao[77]		193	17	11	16	1	6
Bowen[78]		162	16	10	28	13	46
Zou[70]		142	5	28	36	30	83
Carreno[79]		100	11	9	15	4	27
Syed[80]		80	4	20	8	6	75
Bekliz[15]		37	45	1	34	5	15
Haveri[81]		32	32	1	13	0	0
Li[82]		28	14	2	71	5	7
Kurahashi[83]		19	13	2	40	15	38
GM (GMT_{50})		326	21	15			44
total					679	300	

Supplementary table 2

Synopsis of *in vitro* studies investigating the efficacy of Alpha CCP against Omicron

reference	Time since infection	(Alpha CCP) WA-1 GMT_{50}	(Alpha CCP) fold reduction vs. BA.1	(Alpha CCP) BA.1 GMT_{50}	(Alpha CCP) number	(Alpha CCP) BA.1 neutralizing number	(Alpha CCP) BA.1 neutralizing percent
Lusvarghi[68]		4978	166	30	4	1	25
Dejnirattisai[73]		1313	34	39	18	18	100
Rossler[16]		260	64	4	10	0	0
Haveri[81]		64	32	2	20	0	0
Bekliz[15]		45	56	1	12	2	17
Li[82]		28	14	2	37	17	46
GM (GMT_{50})		525	65	8			38
total					101	38	

Supplementary table 3

Synopsis of *in vitro* studies investigating the efficacy of Beta CCP against Omicron.

reference	Time since infection	(beta CCP) WA-1 GMT_{50}	(beta CCP) fold reduction vs. BA.1	(beta CCP) BA.1 GMT_{50}	(beta CCP) number	(beta CCP) BA.1 neutralizing number	(beta CCP) BA.1 neutralizing percent
Lusvarghi[68]		439	2	220	2	2	100
Dejnirattisai[73]		327	12	28	14	14	100
Rossler[16]		128	32	4	8	1	13
Bekliz[15]		21	23	1	8	2	25
Haveri[81]		17	8	2	5	0	0
GM (GMT_{50})		140	11	13			51
Total					37	19	

Supplementary table 4

Synopsis of *in vitro* studies investigating the efficacy of Delta CCP against Omicron.

reference	Time since infection	(Delta CCP) WA-1 GMT_{50}	(Delta CCP) fold drop vs. BA.1	(Delta CCP) BA.1 GMT_{50}	(Delta CCP) number	(Delta CCP) BA.1 neutralizing number	(Delta CCP) BA.1 neutralizing percent
Zeng[64]		11200	3	3733	19	10	53
Lechmere[84]		4751	28	170	14	12	86
Lusvarghi[68]		1211	66	18	15	12	80
Aggerwal[76]		770	21	37	10	9	90
Rossler[16]		192	25	8	7	1	14
Bekliz[15]		72	24	3	10	6	60
Dejnirattisai[73]		47	2	27	19	19	100
GM (GMT_{50})		167	17	10			73
Total					94	69	

Supplementary table 5

Synopsis of *in vitro* studies investigating the efficacy of plasma from uninfected recipients of 2 BNT162b2 doses against Omicron.

reference	Time since second BNT162b2 dose	(2 dose BNT162b2 plasma) WA-1 GMT_{50}	(2 dose BNT162b2 plasma) fold reduction vs. BA.1	(2 dose BNT162b2 plasma) BA.1 GMT_{50}	(2 dose BNT162b2 plasma) number	(2 dose BNT162b2 plasma) BA.1 neutralizing number	(2 dose BNT162b2 plasma) BA.1 neutralizing percent
Schmidt[66]	1 mo	7627	83	92	18	15	83
Liu[65]		4669	21	222	13	6	46
Zeng[64]		2769	23	120	48	13	27
Schmidt[66]	5 mo	2435	19	128	18	15	83
Dejnirattisai[73]		1993	105	19	20	20	100
Chatterjee[40]		1544	2	935	25	25	100
Syed[80]		1280	16	80	21	14	67
Tada[75]		859	34	25	9	7	78
Bowen[78]		764	27	28	10	9	90
Chatterjee[40]		641	6	105	19	10	53
Hoffman[69]	3 mo	604	60	10	11	1	9
Lusvarghi[68]		562	26	22	39	3	8
Gruell[72]	1 mo	546	68	8	30	10	33
Rossler[16]	1 mo	512	32	16	20	9	45
Edara[85]	1 mo	384	19	20	13	2	15
Muik[17]		368	61	6	25	8	32
Cele[86]		359	19	19	8	7	88
Bekliz[15]		338	86	4	16	11	69
Planas[14]	5 mo	329	11	30	16	1	6
Carreno[79]		300	23	13	10	7	70
Gruell[72]	5 mo	139	15	9	30	11	37
Wilheim[87]		6	11	1	15	0	0
GM (GMT_{50})		639	25	26			47
Total					1319	35	

Supplementary table 6

Synopsis of *in vitro* studies investigating the efficacy of plasma from uninfected recipients of 2 mRNA-1273 doses against Omicron.

reference	time since second RNA-1273 dose	(2 dose mRNA-1273 plasma) WA-1 GMT_{50}	(2 dose mRNA-1273 plasma) fold drop vs. BA.1	(2 dose mRNA-1273 plasma) BA.1 GMT_{50}	(2 dose mRNA-1273 plasma) number	(2 dose mRNA-1273 plasma) BA.1 neutralizing number	(2 dose mRNA-1273 plasma) BA.1 neutralizing percent
Doria-Rose[88]		3016	48	63	30	22	73
Syed[80]		2560	8	320	10	8	80
Doria-Rose[88]		2269	84	27	30	22	73
Bowen[78]		1155	32	36	11	9	82
Tada[75]		999	26	38	8	5	63
Edara[85]	1 mo	745	50	15	11	4	36
Carreno[79]		400	43	9	10	10	100
Rossler[16]	5 mo	320	40	8	10	1	10
Wilheim[87]		10	20	1	14	0	0
GM (GMT_{50})		644	31	21			60
Total					134	81	

Supplementary table 7

Synopsis of *in vitro* studies investigating the efficacy of plasma from infected and vaccinated (2 BNT162b2 doses) subjects (VaxCCP) against Omicron.

reference	month since last event (either infection or vaccination)	(post-COVID-19/full vacc plasma) WA-1 GMT_{50}	(post-COVID-19/full vacc plasma) fold drop vs. BA.1	(post-COVID-19/full vacc plasma) BA.1 GMT_{50}	(post-COVID-19/full vacc plasma) number	(post-COVID-19/full vacc plasma) BA.1 neutralizing number	(post-COVID-19/full vacc plasma) BA.1 neutralizing percent
Schmidt[66]		388872	48	8102	17	17	100
Planas[14]		78162	53	1475	22	22	100
Tada[75]		14868	16	929	7	7	100
Cele[86]		13333	25	533	13	13	100
Kawoaka[89]		10863	16	665	5	5	100
Kawoaka[89]		10002	7	1369	13	13	100
Lechmere[84]		8843	5	1769	15	15	100
Gruell[72]		7997	5	1599	30	30	100
Arien[67]		4822	20	241	10	10	100
Carreno[79]		3000	14	214	10	10	100
Dejnirattisai[73]		1899	9	215	17	17	100
Li[82]		1598	20	80	20	20	100
Bekliz[15]		1190	18	66	6	6	100
Haveri[81]		1024	32	32	33	33	100
Rossler[16]		1000	4	250	5	5	100
Edara[85]		625	20	31	24	15	63
Kurahashi[83]	12 mo	369	7	51	19	19	100
Wilheim[87]		200	32	6	20	5	25
Kurahashi[83]	1 mo	22	14	2	19	7	37
GM (GMT_{50})		3124	15	210			88
total					305	269	

Supplementary table 8

Synopsis of *in vitro* studies investigating the efficacy of plasma from uninfected subjects vaccinated with 3 BNT162b2 doses against Omicron.

reference	Time since third BNT162b2 vaccine dose	(3 dose BNT162b2 plasma) WA-1 GMT_{50}	(3 dose BNT162b2 plasma) fold drop vs. BA.1	(3 dose BNT162b2 plasma) BA.1 GMT_{50}	(3 dose BNT162b2 plasma) number	(3 dose BNT162b2 plasma) BA.1 neutralizing number	(3 dose BNT162b2 plasma) BA.1 neutralizing percent
Schmidt[66]	1 mo	65617	17	3860	18	18	100
Planas[14]		12739	18	708	20	20	100
Zeng[64]		10412	3	3155	23	20	87
Dejnirattisai[73]		9219	14	649	20	20	100
Gruell[72]	1 mo	6241	5	1248	30	30	100
Lusvarghi[68]		5029	7	718	39	39	100
Tada[75]		4892	14	349	12	12	100
Liu[65]		4673	7	668	15	15	100
Kawoaka[89]		2866	6	485	10	10	100
Arien[67]		2157	13	166	10	10	100
Hoffman[69]	1 mo	2006	7	287	10	9	90
Edara[85]		1247	14	89	35	31	89
Carreno[79]		1000	8	125	10	10	100
Syed[80]		960	4	240	8	8	100
Muik[17]		673	6	112	28	27	96
Haveri[81]		290	12	24	7	7	100
Wilheim[87]	0.5 mo	150	37	4	12	7	58
GM (GMT_{50})		2723	9	291			95
total					307	293	

Supplementary table 9

Synopsis of *in vitro* studies investigating the efficacy of plasma from uninfected subjects vaccinated with 3 doses of mRNA-1273, AZD-1222 or Ad26.COV2 against BA.1. Because of diversity of vaccines the geomeans and sums were not computed.

reference	vaccine type	WA-1 GMT_{50}	fold drop vs. BA.1	BA.1 GMT_{50}	number	BA.1 neutralizing number	BA.1 neutralizing percent
Careno[79]	COVID19 + mRNA-1273	3000	11	272	10	10	100
Edara[85]	COVID19 + mRNA-1273 6 mo	931	25	38	13	9	69
Careno[79]	3 dose mRNA-1273	1000	17	60	10	10	100
Doria-Rose[88]	3 dose mRNA-1273	8457	4	2002	30	30	100
Doria-Rose[88]	3 dose mRNA-1273	4216	6	650	30	30	100
Edara[85]	3 dose mRNA-1273	1395	15	96	17	16	94
Dejnirattisai[90]	AZD1222	390	19	21	41	41	100
Rossler[16]	AZD1222	250	25	10.0	20	0	0
Planas[14]	AZD1222 5 mo	187	18	10	18	2	10
Syed[80]	Ad26.COV2	28	1	20.0	9	2	22
Schmidt[66]	Ad26.COV2 1 mo	588	24	25	19	2	11
Schmidt[66]	Ad26.COV2 6 mo	982	23	43	19	11	58

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