Analysis of SARS-CoV-2 Omicron Neutralization Data up to 2022-01-28

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Abstract

The rapid spread of the Omicron BA.1 (B.1.1.529) SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) variant in 2021 resulted in international efforts to quickly assess its escape from immunity generated by vaccines and previous infections. Numerous laboratories published Omicron neutralization data as preprints and reports. Here, we use forest plots and antigenic cartography to analyze aggregated Omicron neutralization data from 49 reporting laboratories up to 2022-01-28. We found that, in twice vaccinated individuals, titer fold drop of Omicron relative to wild type is more than 17x, likely substantially higher given the number of measurements below the assay detection limit. Moreover, after a third dose with an mRNA vaccine, the titer fold drop to Omicron is considerably less at 7x, and triple vaccination reduces fold drops across SARS-CoV-2 variants. We demonstrate that it is possible to build reliable antigenic cartography maps from this collated data.

Introduction

The Omicron BA.1 variant (B.1.1.529) was first reported to WHO on November 24, 2021 and has quickly replaced Delta as the world-wide dominant variant. To assess the utility of vaccines existing at the time (wild type based, monovalent) and analyse the requirement of a vaccine strain update with respect to Omicron BA.1 as an example of a novel emerging virus strain, it is important to describe its ability to escape immunity acquired through vaccination, factoring in different vaccine types and vaccination strategies. Multiple laboratories have rapidly produced data with diverse serum panels and variants to hand and released them, mostly as preprints or preliminary reports, for public use. This manuscript demonstrates a proof-of-concept study in which we analyze the available data up to the end of January 2021 to identify trends in Omicron BA.1's escape across laboratories and assays which might be explained by infection and vaccination history. Our analysis suggests that collated data from different sources can be used to produce reliable vaccine escape and antigenic analysis as a first response to emergencies. We present our results as forest plot-based visual analysis to facilitate their joint interpretation. We also show antigenic cartography maps and antibody landscapes from the aggregated data. The aggregated data which we used for our analysis is available as a publicly accessible google sheet document[1].

Results

We analyzed Omicron virus neutralization data from 49 laboratories which at the time of analysis (May 2022) were either in preprint form or otherwise in the public domain. These data include neutralization of Omicron (B.1.1.529, BA.1 and BA.1+R346K (BA.1.1)) as well as ancestral and other SARS-CoV-2 variants by different vaccine sera and sera of individuals infected with the wild type (WT), Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) or Delta (B.1.617.2) variant. An

overview of neutralization assays and cell types used by the different laboratories is given in Table 1.

The majority of available data was generated using the Omicron BA.1 sublineage. Some research groups indicated that the virus they used had the R346K mutation (BA.1.1, BA.1+R346K). To identify whether this substitution impacted neutralization, we split the data into two groups, one that assayed BA.1 and the other that assayed BA.1+R346K and calculated WT and Omicron Geometric Mean Titers (GMTs) for these groups (Supplementary Table 11). This revealed better neutralization of BA.1+R346K in double vaccinated individuals. However, to avoid biases caused by different group sizes, we next looked at serum samples that were titrated against both Omicron sublineages and found no substantial difference of GMTs and fold drops from WT. Hence in this study, we did not distinguish the two sub lineages based on the 346 position amino acid.

We categorized the serum panels used by the different laboratories by their infection or vaccination history into different serum groups. In the “2x Vax” group (n=107) we included double vaccinated individuals, independent of vaccine type, and single dose Johnson & Johnson (J&J) vaccinated individuals, as a single J&J dose is the recommended vaccination regime. The “3x Vax” (n=48) group consisted of triple vaccinated sera, or sera that received a combination of J&J and mRNA vaccines[2]. We summarized individuals with either infection and then vaccination as “Inf + 2x Vax” (n=36), since the majority received two vaccine doses, or vaccination and breakthrough infection as “2x Vax + Inf” (n=12), again the majority had received two doses. Finally, convalescent “conv” sera were categorized by the infecting SARS-CoV-2 variant (n(WT)=33, n(Alpha)=5, n(Beta)=5, n(Gamma)=3, n(Delta)=6).

We analyzed Omicron's escape in fold changes of titers relative to WT and the three VoCs Alpha, Beta and Gamma. The numerical data is summarized in Table 2. Fold drops in neutralization titers of Omicron compared to wild type-like antigens (Wu-1, WA1, B.1) in different vaccine sera are shown in Figure 1, grouped by serum type and ordered by decreasing fold drop. Some of the data we used are estimates as numerical data or individual repeat data was not available at the time of data analysis. In such cases we extracted individual data points from figures using Webplotgitizer[3]. In the majority of serum groups, we found no significant differences between fold changes and titers obtained by digitization or directly from the manuscript (Supplementary Figure 29), and in no serum group did we detect significant differences in both titers and fold changes. Although digitization can introduce some inaccuracies, we conclude that these do not differ substantially from measurement noise across reporting laboratories and have included both types of acquired data in our analyses.

Omicron fold drops relative to wild type titers in the double and triple vaccinated serum groups

The double and triple vaccinated serum groups constituted the majority of the data that have been reported and consequently analyzed here, and were the most relevant from a public health perspective at the time of analysis. The 2x Vax serum group contained the highest number of individual measurements and exhibited the widest spread and largest uncertainty in fold drops of Omicron neutralization compared to WT. We found an average fold drop of 17x in this serum group (Table 2) when treating measurements below an assay's limit of detection (LOD) in the usual manner as 2-fold lower than the LOD. However, the majority of fold drops were likely greater than the point estimate due to many Omicron titers being below LOD. Consequently the average fold drop is likely substantially greater than 17x.

There were three studies[456] that had only a 2-fold drop from WT to Omicron; in all three cases the titers to WT were unusually low. Low titers against the reference antigen limit the amount of further reduction until an assay's detection limit is reached, resulting in LOD censoring of titers and seemingly low fold drops.

In the 3x Vax group we found an average fold drop of 7x. Here, almost all Omicron titers were detectable and fold drops lower and more narrowly distributed than in 2x Vax. Due to this, the estimate of average fold drop for this group will be more reliable compared to the 2x Vax group.

In addition to the fold drop from WT to Omicron, we further found that in 3x Vax the fold drop from titers against variants of concerns (VoC) to Omicron was remarkably reduced compared to 2x Vax (Table 2). To quantify this reduction, we calculated the 2x Vax/3x Vax ratio of mean fold drops from WT and the VoCs Alpha, Beta, and Delta to Omicron (Supplementary Figures 1-4). We found the highest ratio of 5.7 relative to the Alpha variant, indicating the strongest reduction of fold drops from titers measured against Alpha to titers measured against Omicron after three doses. For WT, fold drops after three doses were reduced by 2.5 compared to two doses. For Beta and Delta variants, the 2x Vax/3x Vax ratio was surprisingly similar at 1.7 and 1.6, respectively. Interestingly, the ratio of fold drop from WT to the Beta variant, the most antigenically distant variant compared to WT after Omicron, was reduced by a similar amount of 1.8, indicating that a third encounter of the original Wu-1 spike increases cross-reactivity to other variants.

Omicron fold drops relative to wild type titers in groups with combinations of infection and vaccination

The Inf + 2x Vax group was closest to the triple vaccinated in mean fold drop, with the majority of Omicron titers above the detection threshold and an average fold drop from WT of 10x. We found substantial heterogeneity within the 2x Vax + Inf group depending on the infecting variant. Fold drops from WT around the group's average of 12x were reported after infection with the Delta or Alpha variants, whereas breakthrough infections with Omicron elicited higher titers against Omicron than against the WT variant[7] (Supplementary Tables 1-7).

Omicron fold drops in convalescent serum groups

Omicron fold drops were largest when comparing them to titers against the infecting antigen (Supplementary Figures 1-4, Table 2). For WT and Alpha infections, high titers against the homologous or antigenically similar WT variant with low to non-detectable Omicron titers resulted in the largest mean fold drops from WT of 18x and 28x, respectively. Fold reductions relative to Beta and Delta were similar at 21x and 28x in the corresponding convalescent serum groups. Compared to WT serum, these sera exhibited much lower mean drops from WT to Omicron due to lower WT titers.

The variability in fold drop data

We saw high variability of fold drop data within all serum groups, likely owing to several factors such as age of participants, serum collection times, and different assays and cell types used to assess serum neutralization ability by different laboratories (SOM extended analysis Sections 1-2). The 2x Vax group showed the most variability in fold reduction data. This is likely because of a wide range of reported WT titers, most likely due to serum collection times from two weeks to nine months post second dose, and LOD censoring of low to non-detectable Omicron titers. An analysis of reported titers over time for the different serum groups, demonstrating the effect of LOD censoring on fold drops, is given in the SOM (extended analysis section 2, Supplementary

Figures 30-31). In contrast to the 2x Vax group, the majority of sera in the 3x Vax group were collected within one month post third dose, and Omicron and WT titers were reported in a similar range resulting in a smaller range of fold drops.

The Inf + 2x Vax group had a spread similar to 3x Vax with again a narrow range of serum collection times. The 2x Vax + Inf group contained the two most extreme values, the highest fold drop from WT recorded three days after hospitalization, and the lowest fold drop reported after an Omicron breakthrough infection. The heterogeneity of infecting variants and low number of data points refrain us from making a definitive statement about the variability of fold reductions in this group. The subgroup which consisted of individuals infected with WT showed somewhat higher variability than the 3x Vax group but not as much as the 2x Vax group. Notably, this was the serum group with the widest spread of sample collection times.

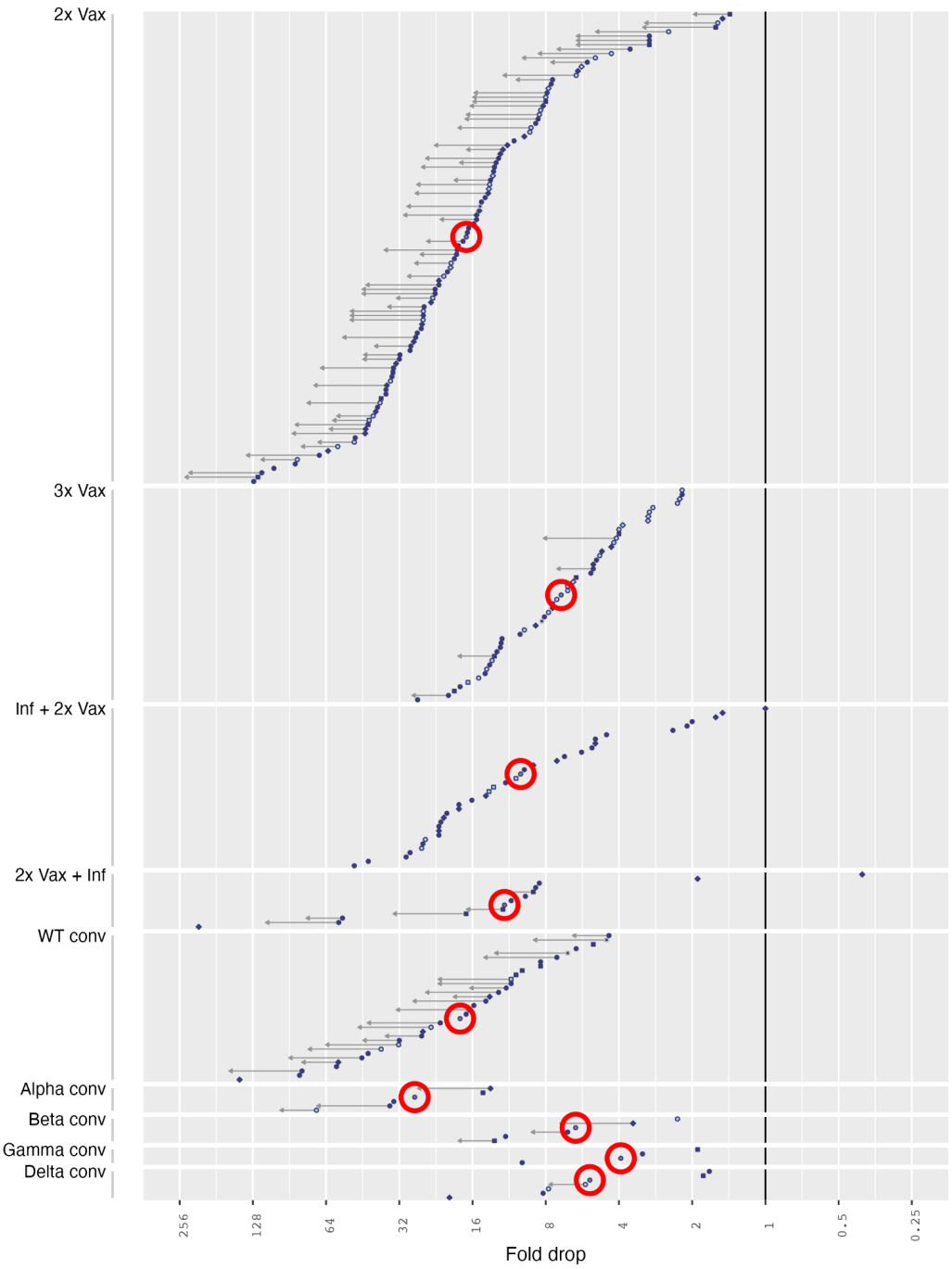

Figure 1: Omicron fold drops relative to wild type. The red circle indicates the mean value for each group. Arrows indicate uncertainties in the point estimate due to titers below the limit of detection (LOD) of the assay. A short arrow marks measurements with more than half of Omicron titers below the assay's limit of detection (LOD), or conversely reference antigen titers at or lower than the LOD. Long arrows mark measurements with more than approximately 80% of Omicron titers below the LOD. Light blue dots show NIH SAVE laboratories, grey dots mark data points for which the reference antigen was not stated in the manuscript and is here assumed to be Wu-1. The solid vertical line marks no fold change. Shapes indicate type of data acquisition (sphere: manuscript; square: fold drops from manuscript, titers by Webplotdigitizer[3]; diamond: fold drops and titers by Webplotdigitizer[3]). A version of this plot with labels per study can be found in Supplementary Figure 1, Supplementary Figures 5-13.

Omicron titers and geometric mean titers (GMT) relative to wild type titers

In addition to fold drops relative to WT titers, we report Omicron titers obtained by applying the fold drops shown in Figure 1 to the WT titers. We estimated GMTs over serum groups as described in the Methods section. The titers grouped by serum type and ordered by decreasing WT titer are presented in Figure 2 and the numerical data is summarized in Table 2.

The highest GMTs against both WT and Omicron were recorded in the Inf + 2x Vax serum group (estimated WT GMT: 2249, Omicron GMT: 240) (Table 2). Second highest GMTs were found in the 3x Vax group, with mean titer estimates against WT and Omicron at 1575 and 233, respectively. In both serum groups, the majority of Omicron titers were above the assay detection threshold and hence Omicron GMT estimates are largely reliable. In line with the reduced fold drops across variants, we found that a third vaccine dose increased GMTs against all variants compared to two doses only (ratio GMT(3x Vax)/GMT(2x Vax) WT: 5.1, Alpha: 4.1, Beta: 6.3, Delta: 4.3) (Supplementary Figures 14-17). The highest titer increase occurred for Omicron, with the GMT estimate in the 3x Vax group being 13x higher than in the 2x Vax group.

Omicron titer point estimates and GMTs in the remaining groups are likely to be lower than reported due to many titers below the limit of detection. Although WT titers in the group of 2x Vax + Inf sera were well detectable (WT GMT: 1598), in five out of nine studies half or more of all samples did not have detectable titers against Omicron. Hence, the GMT estimate for Omicron of 128 is likely inflated. Similar patterns of detectable WT titers but low to non-detectable titers against Omicron were present in the 2x Vax and convalescent serum groups.

Investigating the existence of an upper limit of detection

It might be suspected that the substantially lower fold drop in 3x Vax compared to 2x Vax is because higher titers in 3x Vax were underreported, either by laboratories not titrating to the endpoint, or because of a high-titer non-linearity in the assay. However, the data as presented in Figure 2 demonstrates that the fold drop from WT to Omicron was independent of titer magnitude against WT, as evident by horizontal bars of similar length between WT and Omicron point estimates. Thus the substantially lower fold drop in 3x Vax is unlikely to be an assay endpoint issue.

The impact of live-virus or pseudotype on neutralization titers

Comparing pseudovirus (PV) and live-virus (LV) neutralization assays, our GMT estimates for titers obtained by pseudovirus assays exceeded live-virus GMTs by approximately 2-fold in the 2x Vax group (BA.1 LV GMT: 11 vs PV GMT: 23 and WT LV GMT: 199 vs PV GMT: 395) and we found a 4-fold higher Omicron PV GMT in 3x Vax (BA.1 LV GMT: 90 vs PV GMT: 399 and WT LV GMT: 964 vs PV GMT: 2080) (Supplementary Figure 37, Supplementary Table 9). The WT GMT increase from 2x Vax to 3x Vax was approximately 5-fold for both antigen types. For Omicron, the increase after a third vaccination amounted to 8-fold for LV and 17-fold for PV neutralization assays. We further investigated whether the type of pseudovirus had an impact on measured neutralization titers and found similar titers for lentiviral and VSV pseudotypes, whereas HIV-1 pseudotypes resulted in the highest WT titers (Supplementary Figure 38, Supplementary Table 10). This, however, could be a lab-effect, as all except one data point using HIV-1 pseudotypes were produced by one research group[8].

Analyzing the mean fold drop from WT to Omicron in those two serum groups revealed no substantial difference between LV and PV neutralization assays in the 2x Vax, but approximately two times higher LV than PV fold drops in the 3x Vax serum group (2x Vax LV: 16.9x vs PV: 17x

and 3x Vax LV: 10.9x vs PV: 5.3x) (Supplementary Figure 34, Supplementary Table 9). Looking for trends based on pseudotype, we found higher fold drops when using HIV-1 pseudotypes than in lentiviral or VSV pseudotypes (Supplementary figure 35.1).

We next investigated whether this trend of lower fold drops from infecting antigen to Omicron in PV neutralization assays is observable in other serum groups too. For that, we split the data into LV-assessed neutralization and PV-assessed neutralization serum samples, excluding HIV-1 pseudotypes due to our observations described above. For these subgroups, we calculated the fold drop from the homologous (infecting) variant to the Alpha, Beta, Gamma, Delta and Omicron variants in 2x Vax, 3x Vax, and the different convalescent serum groups (Supplementary Figure 35.2). In most serum groups, the order of variant escape was the same for LV and PV. In most cases, we again found less pronounced drops in PV- than LV-assessed neutralization across the different variants (Supplementary Figure, 35.2). The extent to which PV and LV fold drops differed depended on the serum group and was inconsistent across antigens, but LV fold drops from homologous were not larger than twice the PV fold drops. In Beta and Gamma conv, different patterns can be explained by small sample sizes due to the low number of studies reporting variant titers in those serum groups. Although this suggests a systemic bias towards less pronounced fold drops and thus seemingly more cross-reactivity in pseudovirus neutralization assays, the variety in the number of laboratories titrating multiple variants in different serum group prevents us from making a definite statement.

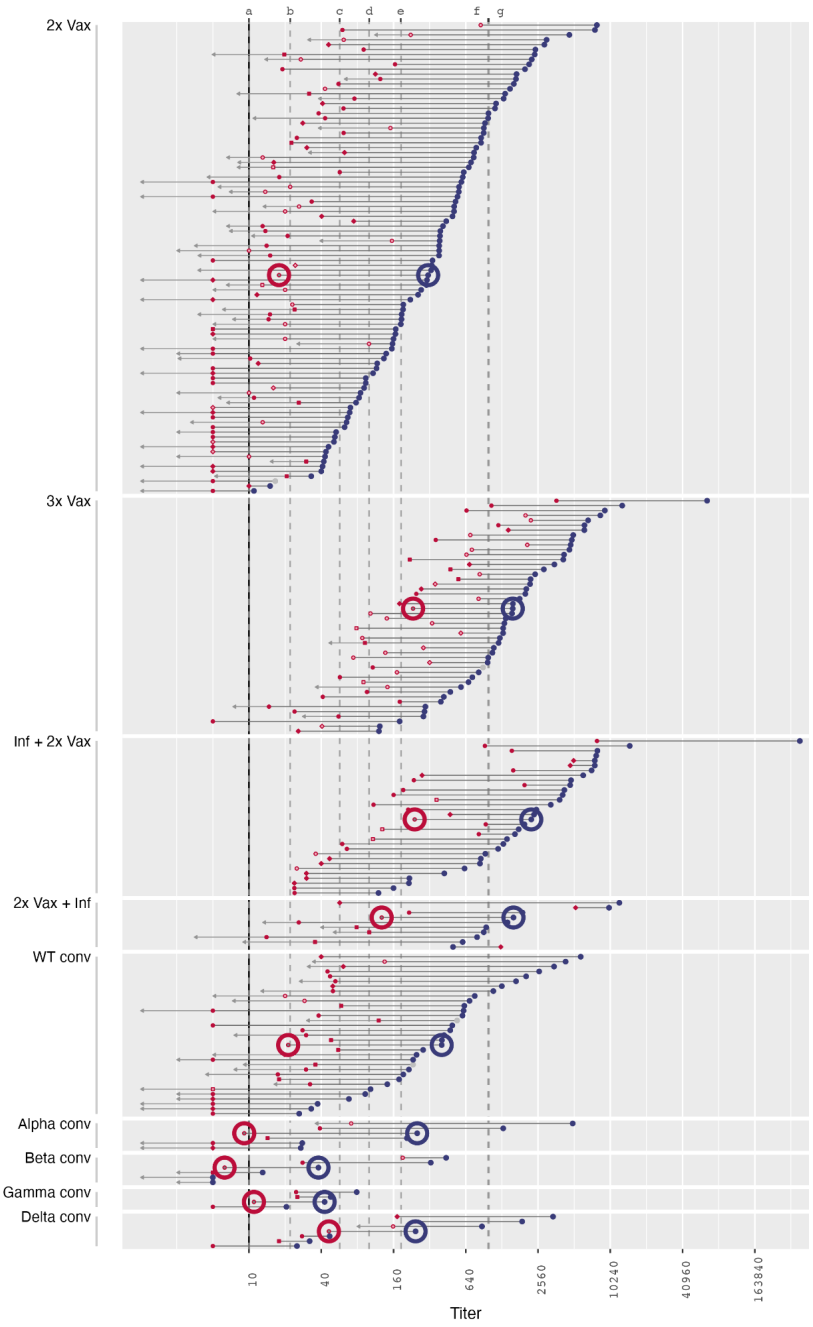

Figure 2: Omicron titers relative to wild type ordered by decreasing wild type titers. Red dots indicate Omicron titers and small blue dots indicate wild type titers, the big circles indicate geometric mean titers per grouping. Omicron titers were obtained by applying the fold drop given in Figure 1 to wild type titers, corresponding to the horizontal bar connecting wild type and Omicron point estimates. Arrows indicate uncertainties in the point estimate. A short arrow marks measurements with more than half of Omicron titers below the assay's limit of detection (LOD), or conversely reference antigen titers at or lower than the LOD. Long arrows mark measurements with more than approximately 80% of Omicron titers below the LOD. Dashed lines mark thresholds of protection against symptomatic disease after vaccination with two doses of Moderna (a,d,f,g)[9] or AstraZeneca (b,c,e,f)[10] assessed by pseudovirus neutralization assay (a 78% VE, b 60% VE, c 70% VE, d 91% VE, e 80% VE, f 90% VE, g 96% VE). Pink dots show NIH SAVE laboratories. Shapes indicate type of data acquisition (sphere: manuscript; square: fold drops from manuscript, titers by Webplotdigitizer [3]; diamond: fold drops and titers by Webplotdigitizer [3]). A version of this plot with labels per study can be found in Supplementary Figure 14, Supplementary Figures 18-26.

Relating titers to protection against symptomatic disease

To estimate the protection against symptomatic disease, we compared the titers here to correlates of protection against symptomatic disease as determined by pseudovirus neutralization studies after two doses of AstraZeneca[10] or Moderna[9]. Other studies employed logistic models to infer the relationship between variant neutralizing antibodies and vaccine efficacy [11–13]. Based on the logistic models between fold-drops and vaccine efficacy, the fold drop of 17x in doubly vaccinated individuals would predict a VE of 42% whereas the fold drop of 7x in triply vaccinated individuals predicts a VE of 90% against symptomatic infection (the parameters used for the logistic expression were as in [11].

Antigenic cartography of Omicron's immune escape

To visualize Omicron's escape in antigenic space we applied antigenic cartography[14] to the titer data aggregated here. In an antigenic map virus variants are positioned based on their antigenic properties inferred by fold drops in serum reactivity. Variants that elicit similar titers in the same sera are positioned at small distances from each other, and vice versa. We have represented this dataset in a two dimensional map since the existence of many sera with titers measured against only two variants makes maps with higher dimensions unnecessary. Further information about the goodness of fit and map validation is given in the SOM, map verification section.

Figure 3A shows the antigenic map created from only convalescent serum data. Usually antigenic cartography maps are constructed from neutralization data originating from a single source as the variability one observes in such data can lead to incompatibilities in map geometry. Despite the fact that this map was created from data with quite variable assay conditions, serum collection dates and even differing virus types (pseudo and live), the general topology of the map is surprisingly similar to previous maps [15–17]. Maps constructed using only live-virus or

pseudovirus neutralization data resulted in very similar variant positions for variants with sufficient titrations in the different serum groups (Supplementary Figure 28.1).

We show a comparison of the first map to the map by Wilks *et al.*[16] in Supplementary Figure 28.2. In both the map by Wilks *et al.*[16] and the map presented here, variants other than Omicron occupied a relatively small space, and Omicron's substantial escape in all serum groups resulted in its positioning to the far right of the map. WT convalescent sera were close to the antigenically similar or homologous WT, D614G and Alpha variants (Figure 3A). This serum group also exhibited medium titers against the Delta variant, while Delta sera showed low reactivity against other variants compared to the Delta variant (Table 2, Supplementary Figure 17). The Beta variant showed the second biggest escape after Omicron, which was also found in independent studies by Wilks *et al.*[16], and van der Straten *et al.*[15].

Whereas antigenic maps show individual sera as points based on their reactivity, antibody landscapes show the distribution of reactivities for individual sera against multiple strains as a surface in a third dimension above an antigenic map[18]. To illustrate the effect of a third vaccination and natural infection we constructed antibody landscapes for the WT conv, 2x Vax and 3x Vax serum groups (Figure 3B-E). We additionally show immune profiles after Omicron breakthrough infections (Figure 3B, 3F). The method for creating the landscapes is outlined in the SOM.

While we found considerable variation in the individual sera landscapes, in line with the spread we observed for the titer data, the GMT landscapes demonstrated the beneficial effect of a third vaccine dose on titer levels across antigenic space. Immune profiles after natural WT infection or double vaccination were almost identical, both in titer magnitude and reactivity decrease

towards other variants, indicated by the slope of each surface. Notably, a third dose not only resulted in an approximately 4-fold increase of titers against WT-similar variants, but the titer difference across other variants was reduced by 30%, illustrating the lower fold drop to Omicron compared to 2x Vax and WT conv sera. While two doses elicited well detectable titers against all variants other than Omicron, a third dose was required to lift Omicron titers to an illustrative protective level indicated by the grey plane positioned at the titer value of 50. Infection with Omicron after vaccination lifted antibody levels across antigenic space, resulting in even broader immune profiles than 3x Vax.

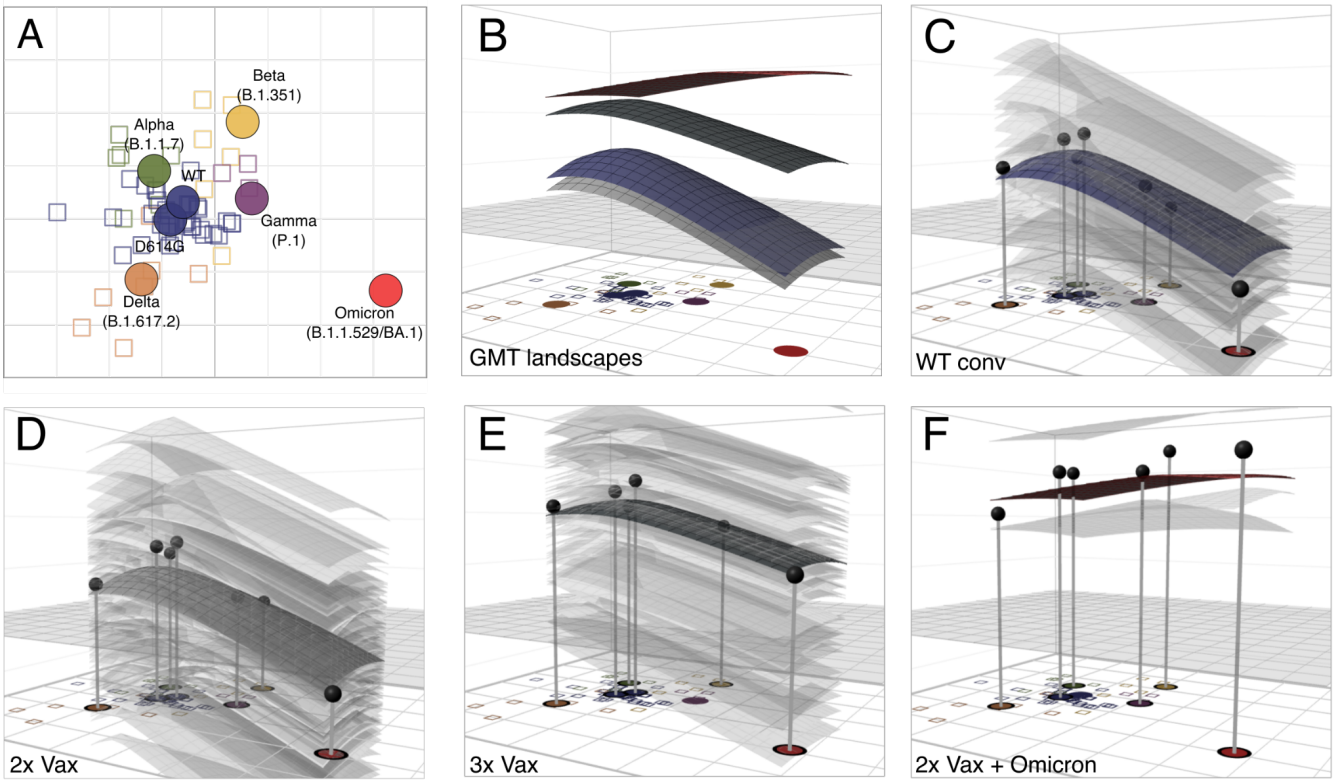

Figure 3: Antigenic cartography. A) Antigenic map from only convalescent serum groups. Variants are shown as colored circles and labeled, sera are shown as open squares with the color indicating the serum group. WT indicates the GMT of data over the antigens Wu-1 and WA1. The x- and y-axes correspond to relative antigenic distances, each grid line reflects an additional 2-fold dilution in the neutralization assay. As relative distances are shown the map's orientation is free. Antigenic maps were constructed as detailed in [14,16]. **B)** GMT antibody landscapes for the WT conv (blue), 2x Vax (grey), 3x Vax (dark grey) serum groups and Omicron breakthrough infections (red) are shown. The antigenic map given in **A** serves as the base plane. Titers are plotted on the z-axis, starting at a titer of 20 with each line corresponding to a two-fold increase. The grey plane at titer 50 serves as reference for correlates of protection as shown in Fig. 2. **C-F)** Individual (transparent) and GMT (coloured) landscapes for the serum groups in **B**. GMTs against variants are indicated by impulses and were adjusted as

described by [16] to account for reactivity biases against variants titrated in more laboratories. Antigenic landscapes were constructed as detailed in the SOM.

Discussion

Some definitive statements can be made from the aggregation of Omicron virus neutralization data. Sera from individuals who have been vaccinated twice or infected once show generally more than a 17x fold drop of titers from wild type, whereas people who have been vaccinated three times or have experienced a breakthrough infection show average fold drops of 7x and 10x, respectively. This reduced titer drop in triple vaccinated individuals appears to be real and not an artifact of an upper limit of detection of the assay. Moreover, the infected and twice vaccinated group showed the highest overall titers against WT and Omicron, 2249 and 240 respectively. We found evidence for pseudovirus titers being generally higher than live-virus titers across all serum groups. The relation for fold-drop patterns were more complicated; the 2x Vax and WT conv serum groups displayed similar fold drop patterns (with the exception of respectively Beta and Delta antigens) however in the 3x Vax group, live-virus fold drops were generally higher than pseudovirus drops.

Censored titers below an assay's detection threshold can result in a deflation of fold drops when titers against the reference antigen are low. The mean fold drop for the 2x Vax group, for example, is likely substantially greater than our 17x numeric estimate. On the other hand since there were almost no thresholded titers in the 3x Vax group, the fold drop of 7x is more reliable. A deflation of fold drops due to wild type titers at or above an assay's upper limit of detection is unlikely, as visible in Figure 2. The differences between Omicron and WT titers were roughly consistent across studies in the 3x Vax and 2x Vax + Inf cohort and were not influenced by the absolute magnitude of WT titers.

The topology of the map constructed from data collated across different laboratories, sampling time points, and assay types, is consistent with the map constructed in studies based on data from more controlled serum groups, single assay and virus types [16,15]. The titer magnitude differences between LV and PV did not impact the positioning of antigen variants in the map made with convalescent sera since fold-drops were generally similar for convalescent sera. Note that the higher fold drop of live-virus Delta in the WT conv serum group did translate into the map as a larger distance between Delta and WT antigens. We further found that adding data published in 2022 did only marginally influence mean drops and GMTs we reported based on data published in 2021, and that the type of data acquisition did not result in significant differences in GMTs and fold drops across serum groups. This indicates that the data we used here are a representative sample of the true distribution of titers against Omicron after vaccination and infection.

We used antibody landscapes to illustrate the combined effect of lower fold drops and increased titers after three vaccine doses on Omicron's escape from vaccine sera. Landscapes generated from WT convalescent sera and 2x Vax sera were almost identical both in magnitude and shape similar to what has been observed in [16] . Antibody landscapes from GMTs and individual study-based titer data show that a third vaccination not only elicited a considerable increase of titers against Omicron but also against other variants (Figure 3). The increase of antibody level magnitude across antigenic space was even more pronounced after Omicron breakthrough infection.

While these aggregate results suggest that a third vaccine dose results in substantially higher neutralizing titers against Omicron (and lower fold drops compared to WT, therefore likely a

higher VE) independent of first infecting/vaccinating variant, it needs to be noted that almost all of the data in the 3x Vax group are from sera taken within one month of the last vaccination. Pajon *et al.* reported data one and six months after the third dose[20]. While the fold drop they found six months after vaccination fell in the middle of the 3x Vax distribution we show here and was still lower than the majority of 2x Vax drops, the fold drop one month post vaccination was at the lower end, suggesting that vaccine-elicited immunity against Omicron wanes quicker than against the WT variant. Indeed, whereas WT titers dropped only to approximately half their value after six months, titers against Omicron were reduced by 6.25-fold. A less substantial reduction of 1.6-fold for WT and 2-fold for Omicron was found by Xia *et al.* from one to three months post third Pfizer dose[21]. However, more data is needed to make inferences about the longevity of immunity against Omicron after vaccination. Still, the substantially lower fold drop and a shift from mostly undetectable titers to mostly detectable titers after a third vaccination are strong evidence for the utility of booster vaccination at increasing virus neutralization titers against Omicron, and thus potentially at increasing vaccine efficacy.

The lower fold drops and higher titers after a third vaccine dose could be the result of ongoing affinity maturation in germinal centers after a second vaccination, and a recall of affinity matured B cells upon the third dose. Kim *et al.*[22] reported the persistence of germinal centers after mRNA vaccination for more than six months after mRNA vaccination, and found that antibodies derived from plasma cells with high levels of somatic hypermutation exhibited higher neutralization capacity against the D614G variant. Sokal *et al.*[23] found that memory B cell-derived monoclonal antibodies of vaccinated individuals could maintain binding capacity to the Beta variant during affinity maturation. This, in combination with broader antibody landscapes, suggests that repeated vaccination with the original spike protein has the potential to boost cross-reactive immunity across antigenic space.

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Table 1: **List of included studies.**

Study	Date of publication	Antigen type	Cell type	R346K
Sigal[11]	2021-12-6 & 15	Live-virus	H1299 ACE2	Yes
Sheward[29]	2021-12-7	Lentiviral Pseudotype	HEK293T ACE2	No
Ciesek[30]	2021-12-8	Live-virus	Caco2	No
Kimpel[31]	2021-12-8	Live-virus	Unknown	No
Schmidt[8]	2021-12-12	HIV-1 Pseudotype	HT1080 ACE2	No
Israel MoH[32]	2021-12-12	Live-virus	Unknown	NA
Zhang[33]	2021-12-10	VSV Pseudotype	Huh 7	No
HKU[34]	2021-12-12	Live-virus	Unknown	NA
Balazs[4]	2021-12-14	Lentiviral Pseudotype	HEK293T ACE2	No
Gruell[35]	2021-12-14	Lentiviral Pseudotype	HEK293T ACE2	No
Corti[36]	2021-12-14	VSV Pseudotype	VeroE6/VeroE6-TMPRSS2	No
Poehlmann[37]	2021-12-13	VSV Pseudotype	Vero Cells	No
Montefiori/Doria-Rose[38]	2021-12-15	Lentiviral Pseudotype	Unknown	No
Ho[6]	2021-12-15	VSV Pseudovirus	VeroE6	Yes
Schwartz[39]	2021-12-14	Live-virus	S-Fuse cells	NA
Gupta[40]	2021-12-20	Lentiviral Pseudovirus	293T TMPRSS2*	NA
Snape[41]	2021-12-11	Live-virus	Vero Cells	NA
Liu[42]	2021-12-20	Lentiviral Pseudotype	HEK293T ACE2	NA
Krammer[43]	2021-12-20	Live-virus	VeroE6 TMPRSS2	NA
Chen[44]	2021-12-22	Lentiviral Pseudotype	HEK293T-ACE2	NA
Gao[45]	2021-12-22	VSV Pseudotype	Vero	NA
Veesler[46]	2021-12-22	VSV Pseudotype	VeroE6 TMPRSS2	NA
Suthar[47]	2021-12-22	Live-virus	VeroE6 TMPRSS2	No
Sahin[48]	2021-12-23	VSV pseudotype	Vero76	No
Weiss[49]	2021-12-28	Lentiviral Pseudotype	293T ACE2/TMPRSS2	No
Screaton[50]	2021-12-29	Live-virus	Vero	No
Sanders[15]	2022-01-03	Lentiviral Pseudotype	293T ACE2	No
Arien[51]	2021-12-24	Live-virus	Vero	No
Shi[52]	2021-12-22	Live-virus	VeroE6	No
Barouch[53]	2022-01-03	Lenti-CMV Pseudotype	HEK293T-hACE2	NA
Suzuki[54]	2022-01-01	Live/ VSV pseudovirus	VeroE6-TMPRSS2	Yes/No
Wang[55]	2021-12-27	VSV Pseudotype	VeroE6	NA
Landau[56]	2021-12-30	Lentiviral Pseudotype	293T ACE2/VERO	No
Eckerle[17]	2021-12-31	Live-virus	VeroE6	NA
Cicin-Sain[57]	2021-12-21	VSV Pseudotype	VeroE6	NA
Haveri[58]	2021-12-24	Live-virus	VeroE6	NA
Bailey[59]	2021-12-24	Lentiviral Pseudotype	HEK293T-hACE2	No
Chen(HKU)[7]	2021-12-28	HIV-1 Pseudotype	HEK293T-hACE2	NA
Iwasaki[5]	2021-12-29	Live-virus	VeroE6-TMPRSS2	No
Wang (CDC)[60]	2022-01-05	Live-virus	VeroE6-TMPRSS2	NA

Garg[61]	2022-01-05	Live-virus	VeroE6	NA
Lyke/Atmar[2]	2022-01-14	Lentiviral Pseudotype	293T ACE2	No
Münch/Schrezenmeier[62]	2022-01-17	VSV Pseudovirus	VeroE6	No
Takahashi[63]	2021-12-26	VSV Pseudovirus	VeroE6/TMPRSS2	No
Xia/Swanson/Shi[21]	2022-01-22	Pseudovirus	VeroE6	No
Pajon/Doria-Rose[20]	2022-01-22	Lentiviral Pseudotype	293T ACE2	No
Mizukami[64]	2022-01-22	Live-virus	VeroE6/TMPRSS2	Yes/No
Gintsburg[65]	2022-01-19	Live-virus	VeroE6	No
Poovorawan[66]	2022-01-18	Live-virus	NA	NA
Protzer[67]	2022-01-28	Live-virus	MDA-MB-231-hACE2	No

*293T TMPRSS2 ACE2 transfected- NA in Column R346K was used when no information on this substitution was available- Supplementary Tables 1-7 have further details on these studies.

Table 2: Geometric Mean Titers (GMT) and mean fold drops by serum group. Mean fold drops were calculated from fold drops per study. Studies reporting fold drops but not GMTs result in a discrepancy between GMT based mean fold drop and individual study based mean fold drop. 95%CI are given in parentheses. NA as CI indicates that only one measurement was available in this group (conv = convalescent).

Serum group	GMT						Mean Omicron fold drop from					Mean fold drop to WT			
	WT	Alpha	Beta	Gamma	Delta	Omicron	WT	Alpha	Beta	Gamma	Delta	Alpha	Beta	Gamma	Delta
2x Vax	311 (234; 413)	308 (174; 546)	71 (47; 105)	74 (26; 211)	120 (84; 172)	18 (14; 23)	17 (14.1; 20.4)	15.9 (9.6; 26.4)	4.5 (3.5; 5.7)	5.1 (3; 8.8)	7 (5.7; 8.6)	1.2 (0.8; 1.8)	5.8 (4.7; 7.1)	3 (1.4; 6.5)	2.8 (2.3; 3.3)
3x Vax	1575 (1099; 2257)	1272 (311; 5196)	449 (246; 817)		518 (278; 965)	233 (156; 346)	6.9 (5.7; 8.4)	2.8 (1.6; 5.1)	2.7 (2; 3.7)	4.8 (NA; NA)	4.3 (2.9; 6.3)	1.4 (1.1; 1.9)	3.1 (2.3; 4.1)		2.4 (1.9; 3.1)
Inf + 2x Vax	2249 (1299; 3894)	621 (356; 1081)	468 (241; 908)	148 (43; 508)	829 (406; 1693)	240 (126; 458)	10.1 (7.2; 14.3)	4.3 (1.8; 10.2)	4.8 (2.3; 10)	3.5 (2.7; 4.6)	3.6 (2; 6.4)	1.5 (0.9; 2.6)	3.4 (1.9; 6.1)	3.4 (2.3; 5.2)	2.4 (1.5; 4)
2x Vax + Inf	1598 (778; 3280)	3737 (1540; 9070)	2803 (848; 9262)	2195 (585; 8243)	638 (368; 1108)	128 (39; 418)	11.8 (4.3; 32.9)	6.9 (0.1; 468.9)	4.8 (0.6; 41.8)	0.8 (0; 20.4)	5.1 (1.4; 18.2)	0.9 (0.3; 2.4)	1.2 (0.2; 5.7)	1 (0; 1000.5)	2.6 (1.5; 4.6)
WT conv	403 (252; 647)	153 (35; 667)	34 (14; 79)	30 (7; 137)	167 (75; 373)	21 (14; 33)	18 (13.1; 24.8)	11.3 (4; 32.1)	3.4 (1.6; 7.6)	5.4 (0.7; 43.6)	11.6 (5.7; 23.8)	1.9 (1.3; 2.7)	7.4 (3.8; 14.3)	2.7 (0.1; 124.9)	2.2 (1.6; 3)
Alpha conv	252 (41; 1553)	209 (71; 614)	41 (8; 202)	24 (2; 300)	71 (10; 506)	9 (2; 41)	27.7 (11.8; 64.9)	35.4 (19.4; 64.7)	7 (2.1; 22.9)	7 (0.1; 977.6)	8 (2.3; 27.3)	0.6 (0.2; 2.3)	4.1 (1.4; 11.9)	3.2 (0; 117496)	3.4 (1.1; 10.4)
Beta conv	38 (7; 200)	32 (6; 182)	69 (15; 312)	8 (2; 37)	20 (5; 82)	6 (1; 40)	6 (2.4; 15.3)	9.7 (3.3; 28.5)	20.8 (8.1; 53.3)	8.3 (0; 5781282.2)	3.1 (1.1; 8.5)	0.9 (0.3; 2.7)	0.5 (0.2; 1)	1.1 (0; 11152.9)	2.3 (1; 5.4)
Gamma conv	43 (23; 80)	47 (16; 136)	63 (23; 173)	92 (46; 185)	14 (4; 43)	11 (3; 41)	3.9 (0.5; 32.4)	4.3 (0.9; 19.2)	5.8 (2.2; 15.2)	12.6 (0; 157172.1)	1.2 (0.8; 2)	0.9 (0.3; 2.9)	0.7 (0.2; 2.1)	0.3 (0.1; 0.9)	3.1 (0.6; 17)

Delta conv	244 (48; 1242)	103 (26; 409)	47 (13; 167)	16 (14; 19)	1018 (231; 4482)	46 (13; 160)	5.3 (1.9; 14.3)	5.6 (1.5; 21.1)	2.6 (0.4; 15.8)	2.2 (0; 49263.1)	28.2 (12.3; 65)	1.2 (0.5; 2.9)	3.2 (1; 10.3)	1.7 (1.2; 2.5)	0.2 (0.1; 0.5)

Methods

Data collection

Omicron neutralization data from publicly available preprints, reports or tweets were collected and categorized according to antigen type, vaccine and convalescent sera tested, and the presence of the R346K substitution in the spike in addition to the common set of Omicron spike substitutions. In most cases, datasets are named after the corresponding author. A full list of all studies considered is shown in Table 1, detailed metadata in Supplementary Tables 1-7.

Geometric Mean Titer and fold drop calculation

We used numerical data on geometric mean titers (GMT) and Omicron titer fold drops to a reference antigen as stated in each study. In case of missing GMT data, GMTs were either directly extracted from the manuscripts' figures using Webplotdigitizer[3] or individual data points were extracted by the same method and GMTs subsequently calculated with the meantiter R package[68] (method = "truncated_normal", dilution_stepsize = 0), which performs a Bayesian statistics analysis to correctly handle thresholded values. In such cases of calculating GMTs from individual data points we did not add uncertainty arrows to plot or tables, except if all data points were below an assay's detection threshold. Thresholded titers for individual data were set to "<Limit of Detection (LOD)" prior to GMT calculation via the meantiters package. In case of thresholded GMTs directly available or extracted from the manuscript, we set the GMT estimates to LOD/2. When data points needed to be extracted from figures, individual measurements were often overlapping and difficult to distinguish. Hence, in some cases the sample number given in the manuscript differs from the number of data points used to calculate the GMT in this analysis. If numerical data on fold drops but not GMTs were available, we used

the fold drops as given in the manuscript and determined GMTs as described above. Otherwise fold drops were calculated by dividing the reference antigen GMT by the Omicron GMT. Omicron GMTs were obtained by applying the fold drop from wild type to the wild type GMT. GMTs and 95% confidence intervals per serum group were calculated using the meantiter R package[68] with the same parameters as before.

Mean fold drops and 95% confidence intervals as reported in Table 2 and Supplementary Tables 8-9 were obtained by calculating the mean of reported fold drops in each study using Rmisc's CI function [69]. Some studies reported fold drops but not titers or variant titers resulting in discrepancies between individual study based mean fold drops and GMT based fold drops.

Webplotdigitizer[2] was used for the following studies: GMTs for[11] Sheward[29], Balazs (Delta titers) [70], Ciesek[30], Zhang[33] (subset), Krammer[43], Sanders [15] and Wang (CDC)[60] were obtained by Webplotdigitizer. GMTs and fold changes were obtained by Webplotdigitzer for Sigal[11], Veesler[46], Kimpel[31], Corti[36] (subset), Gupta[40] and Liu[42]

The remaining data[45] were directly obtained from the respective manuscripts or reports.

Dataset availability

The aggregate dataset is available as a publicly accessible google sheets document[1].

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Supplementary Information is available for this paper.

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