

## Los anticuerpos ampliamente neutralizantes superan el cambio antigénico de la variante Ómicron del SARS-CoV-2

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## RESUMEN

La recientemente surgida variante Ómicron del SARS-CoV-2 alberga 37 sustituciones de aminoácidos en la proteína pico (S), 15 de las cuales están en el dominio de unión al receptor (RBD, *receptor binding domain*), lo que aumenta las preocupaciones sobre la eficacia de las vacunas disponibles y la terapéutica de anticuerpos.

Aquí nosotros mostramos que el Ómicron RBD se une al ACE2 humano con mayor afinidad, en relación con la cepa original (Wuhan-Hu-1 RBD), y que adquiere unión al ACE2 de ratón.

Se observaron reducciones severas de la actividad neutralizante del plasma contra Ómicron, en comparación con el pseudovirus ancestral, para personas vacunadas y convalecientes.

La mayoría (26 de 29) de los anticuerpos monoclonales (mAb, *monoclonal antibody*) dirigidos a los motivos de unión al receptor (RBM, *receptor binding motif*) perdieron actividad neutralizante in vitro contra Ómicron, con solo 3 mAb, incluido el mAb1S2K146, que imita a ACE2, reteniendo su potencia inalterada.

Además, una fracción de los mAbs fueron ampliamente neutralizantes contra los sarbecovirus, al reconocer sitios antigénicos fuera del RBM, incluido el sotrovimab<sup>2</sup>, S2X2593 y S2H974, neutralizaron Ómicron.

La magnitud de la evasión inmune mediada por Ómicron y la adquisición de la unión al ACE2 de ratón marca un importante cambio mutacional del SARS-CoV-2. En general, los mAb ampliamente neutralizantes del sarbecovirus, que reconocen los epítomos conservados entre las variantes del SARS-CoV-2 y otros sarbecovirus, pueden resultar clave para controlar la pandemia en curso y sus futuros efectos secundarios zoonóticos.

## INTRODUCCIÓN

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La evolución de los virus de ARN puede resultar en un escape inmunológico y la modulación de la unión a los receptores del huésped.<sup>5</sup> Las variantes de preocupación (VOC, *variant of concern*) del SARS-CoV-2 anteriores han desarrollado resistencia a los anticuerpos neutralizantes, incluidos algunos anticuerpos clínicos utilizados como terapéuticos<sup>6-9</sup>.

La VOC B.1.351 (Beta) demostró la mayor magnitud de evasión inmune de la neutralización de los anticuerpos del plasma<sup>6,7</sup>, mientras que B.1.617.2 (Delta) superó rápidamente a todos los demás virus aislados circulantes a través de adquisición de mutaciones que mejoraron la transmisión y la patogenicidad<sup>10-13</sup> y erosionaron las respuestas de neutralización de los anticuerpos.<sup>10</sup>

La variante Ómicron (B.1.1.529.1) se detectó por primera vez en noviembre de 2021, después de lo cual fue declarada inmediatamente por la OMS como un VOC y rápidamente aumentó en frecuencia en todo el mundo (**Datos extendidos Fig.1**). Sorprendentemente, el análisis de las sustituciones dentro de la variante Ómicron mostró cambios sustanciales de cualquier otro SARS-CoV-2 aislado descrito anteriormente, incluidas 37 mutaciones en la proteína S, en el haplotipo predominante (**Fig. 1a-b y Datos extendidos Fig. 1-5**). Quince de las mutaciones de Ómicron se agrupan en el RBD (*receptor binding domain*), que es el principal objetivo de los anticuerpos neutralizantes tras la infección y la vacunación<sup>14,15</sup>, lo que sugiere que Ómicron puede escapar de los anticuerpos neutralizantes generados tras la infección y por la vacunación, así como de las terapias con anticuerpos monoclonales. Nueve de estas mutaciones se asignan al motivo de unión al receptor (RBM), que es el subdominio del RBD que interactúa directamente con el receptor del huésped, ACE2<sup>16</sup>.

Los informes preliminares indicaron que la actividad neutralizante del plasma de las personas vacunadas con Pfizer-BioNTech BNT162b2 está severamente reducida contra Ómicron<sup>17,18</sup>, documentando un escape sustancial, aunque no completo, de los anticuerpos neutralizantes generados por las vacunas ARNm. Otro informe también mostró que la eficacia de la vacuna contra la enfermedad sintomática con la variante Ómicron es significativamente menor que contra la variante Delta<sup>19</sup>. El potencial de las dosis de refuerzo, para mejorar esta disminución en la neutralización, aún se están explorando. Además, se demostró que la actividad neutralizante de varios anticuerpos monoclonales terapéuticos disminuye o se elimina contra Ómicron<sup>18,20</sup>.

Para comprender las consecuencias del número sin precedentes de mutaciones encontradas en la proteína S de Ómicron, empleamos un ensayo de pseudovirus para estudiar la neutralización mediada por anticuerpos monoclonales y policlonales, así como resonancia de plasmón de superficie para medir la unión de RBD a receptores ACE2 humanos y de animales.

## RESULTADOS

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### ***El RBD de Ómicron se une con mayor afinidad al ACE2 humano y gana en unión al ACE2 de ratón***

El número sin precedentes de sustituciones encontradas en el genoma de Ómicron plantea interrogantes sobre su origen. 23 de las 37 mutaciones de aminoácidos de la proteína S de Ómicron han sido previamente observadas individualmente en las variantes de interés (VOI) del SARS-CoV-2, VOC u otros *sarbecovirus*, mientras que las 14 sustituciones restantes no se han descrito antes en ningún aislamiento del SARS-CoV-2 (**Datos extendidos Fig. 6a**). El análisis de la base de datos GISAID21 indica que rara vez hubo más de 10-15 mutaciones en la proteína S de Ómicron, presentes en un haplotipo no Ómicron dado o linaje Pango (**Datos extendidos Fig. 6b, c y d**). Si bien no hemos evaluado formalmente la posibilidad de eventos de recombinación, la replicación persistente en individuos inmunodeprimidos o la transmisión de

ping-pong entre especies<sup>5</sup> son posibles escenarios para la rápida acumulación de mutaciones que podrían haber sido seleccionadas en función de la aptitud y la evasión inmunológica.

Para evaluar este último escenario, investigamos si las mutaciones RBD encontradas en Ómicron pueden haber resultado de la adaptación del SARS-CoV-2 a los receptores animales. Con este fin, probamos la Unión de RBD a receptores ACE2 de ratón, de visón americano y de pangolín, mediante una resonancia de plasmón de superficie (SPR) (**Fig. 1c y datos extendidos Fig. 7**). Ómicron se unió al ACE2 de ratón, pero no al de visón ni de pangolín, mientras que los RBD de Wuhan-Hu-1, Beta, Alpha y K417N no reconocieron ninguno de estos 3 ACE2 en nuestro ensayo. Es probable la adquisición de unión a ACE2 de ratón sea explicada por la sustitución Q493R, que es muy similar a la mutación Q493K aislada sobre la adaptación de ratón del SARS-CoV-2<sup>22</sup>.

Varias de las mutaciones del RBD de Ómicron se encuentran en posiciones que son sitios de contacto clave con el ACE2 humana, como K417N, Q493K y G496S<sup>23,24</sup>. Excepto N501Y, que aumenta la afinidad de unión de ACE2 se multiplicó por 6<sup>25</sup>, todas las demás sustituciones se mostraron mediante un escaneo mutacional profundo (DMS) para reducir la unión a ACE2 humana individualmente<sup>26</sup>, lo que resulta en una marcada disminución prevista la de afinidad (**Tabla de datos ampliados 1**). Sin embargo, encontramos que el RBD de Ómicron tiene un aumento de 2,4 veces de la afinidad de unión a la ECA2 humana (**Fig. 1d**), lo que sugiere la interacción de la constelación completa de mutaciones RBD.

En conjunto, estos hallazgos sugieren, que las mutaciones en el RBD de Ómicron, puede haber permitido la adaptación a los roedores, así como contribuyó a un aumento potencial de la transmisión en los humanos.

### ***Ómicron escapa a los anticuerpos neutralizantes del plasma policlonal***

Para investigar la magnitud de la evasión inmune mediada por las 37 mutaciones presentes en la proteína S de Ómicron, determinamos la actividad neutralizante del plasma frente a las proteínas S de Wuhan-Hu-1 y el Pseudovirus VSV de Ómicron en diferentes cohortes de pacientes convalecientes o individuos vacunados con 6 de las principales vacunas COVID-19 (ARNm-1273, BNT162b2, AZD1222, Ad26.COVS, Sputnik V y BBIBP-CorV) (**Fig. 2, Figura de datos extendidos 8-9 y Tabla de datos extendidos 2**).

Los pacientes convalecientes, y los individuos vacunados con Ad26.COVS (dosis única), Sputnik V o BBIBP-CorV no tenían actividad neutralizante contra Ómicron, excepto por un vacunado con Ad26.COVS y 3 vacunados BBIBP-CorV (**Fig. 2a-b**).

Los individuos vacunados con ARNm-1273, BNT162b2 y AZD1222 mostraron una mayor neutralización contra Wuhan-Hu-1 y retuvieron la actividad contra Ómicron con una disminución de 33, 44 y 36 veces, respectivamente (**Fig. 2a**).

Curiosamente, esta disminución fue menos pronunciada para las personas vacunadas que habían estado infectadas anteriormente (5 veces) (**Fig. 2b**) consistente con la ampliación de las respuestas de anticuerpos como consecuencia de la maduración de la afinidad impulsada por múltiples estimulaciones antigénicas<sup>27-29</sup>. Colectivamente, estos hallazgos demuestran una reducción sustancial y sin precedentes en la actividad neutralizante del plasma contra Ómicron, versus virus ancestral, que en varios casos puede caer por debajo de títulos protectores<sup>30</sup>.

## Los anticuerpos contra el sarbecovirus ampliamente neutralizantes conservan la actividad contra Ómicron

Los anticuerpos monoclonales neutralizantes con eficacia in vivo demostrada en la prevención o el tratamiento del SARS-CoV-2<sup>31-41</sup> se puede dividir en 2 grupos según su capacidad para bloquear la unión de S a ACE2.

De los 8 anticuerpos monoclonales actualmente autorizados o aprobados, 7 (bamlanivimab, etesevimab, casirivimab, imdevimab, cilgavimab, tixagevimab y regdanvimab) bloquean la unión de S a ACE2 y a menudo se utilizan en combinación.<sup>9</sup> Estos anticuerpos monoclonales se unen a epítomos que se superponen con el RBM (**Fig. 3a**) que es estructural y evolutivamente plástico<sup>42</sup>, como lo ilustra la acumulación de mutaciones a lo largo de la pandemia y la diversidad de este subdominio entre los *sarbecovirus* que utilizan ACE2.<sup>43</sup> La combinación de 2 anticuerpos monoclonales de este tipo de bloqueo del ACE2, proporciona una mayor resistencia a las variante virus que portan mutaciones en el RBM<sup>32</sup>.

La segunda clase de anticuerpos monoclonales, representada por sotrovimab, no bloquean la unión de ACE2, pero neutralizan el SARS-CoV-2 al dirigirse a los epítomos que no son RBM, compartidos a través muchos *sarbecovirus*, incluido el SARS-CoV<sup>4,44</sup>.

Aquí, comparamos la actividad neutralizante in vitro de los anticuerpos monoclonales terapéuticos de estos 2 grupos contra las proteínas S de las variantes Wuhan-Hu-1 y Ómicron, utilizando un pseudovirus VSV.

Aunque sotrovimab tenían una potencia reducida 3 veces contra Ómicron, todos los demás anticuerpos monoclonales (específicos del RBM), perdieron completamente su actividad neutralizante, con la excepción del cóctel de cilgavimab y tixagevimab, para el cual determinamos una potencia reducida ~ 200 veces (**Fig. 3b-c**). Estos hallazgos son consistentes con 2 informes recientes<sup>18,20</sup> y, junto con los datos serológicos, apoyan la noción de un cambio antigénico con Ómicron.

A continuación, probamos un panel más grande de 36 anticuerpos monoclonales neutralizantes específicos de NTD o RBD, para los cuales el epítomo se ha caracterizado estructuralmente, o asignado a un sitio antigénico dado, a través de estudios de competición<sup>3,4,10,14,45,46</sup> (**Fig. 4a, Tabla 2 de datos extendidos y Fig. 10 de datos extendidos**).

Cuatro anticuerpos específicos de NTD perdieron completamente su actividad contra Ómicron, en consonancia con la presencia de varias mutaciones y deleciones en el supersitio antigénico NTD<sup>8,25</sup>. 3 de los 22 anticuerpos monoclonales dirigidos al sitio antigénico I de RBD (RBM) retuvieron una potente actividad neutralizante contra Ómicron, incluido S2K146, que se une al RBD del SARS-CoV-2, SARS-CoV y otros sarbecovirus a través del mimetismo molecular ACE2<sup>1</sup>.

De los nueve anticuerpos monoclonales específicos para el sitio II4 del RBD conservado (anticuerpos monoclonales de clase 4), solo S2X2593 retuvo actividad contra Ómicron, mientras que la neutralización disminuyó en más de 10 veces o se suprimió para los anticuerpos monoclonales restantes. Finalmente, la neutralización de Ómicron también se retuvo con el anticuerpo monoclonal S2H97, que reconoce el sitio crítico V, altamente conservado.

El panel de los 44 anticuerpos monoclonales probados en este estudio, representa a los miembros de cada una de las 4 clases de anticuerpos monoclonales de sarbecovirus ampliamente neutralizantes, definidos por sus sitios de unión RBD afines (sitio I, II, IV y V).

Nuestros hallazgos muestran que los miembros de cada una de las 4 clases pueden retener capacidad neutralizante contra Ómicron: S2K146, S2X324 y S2N28 en sitio de destino I, S2X259 en el sitio de destino II, sotrovimab en el sitio de orientación IV y el sitio de orientación V de S2H97 (**Fig. 4b**). Varios de estos anticuerpos monoclonales reaccionan de forma cruzada con, y pueden neutralizar, los sarbecovirus, más allá del clado 1b1,3,4 del SARS-CoV-2, lo que confirma la noción de que dirigirse a epítomos conservados puede resultar no solo en amplitud, sino también en protección, contra la evolución del virus.

## DISCUSIÓN

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El asombroso número de sustituciones presentes en la proteína S de Ómicron marca un cambio dramático en la antigenicidad, y se asocia con una evasión inmune de una magnitud sin precedentes para el SARS-CoV-2, y una supuesta ampliación del tropismo.

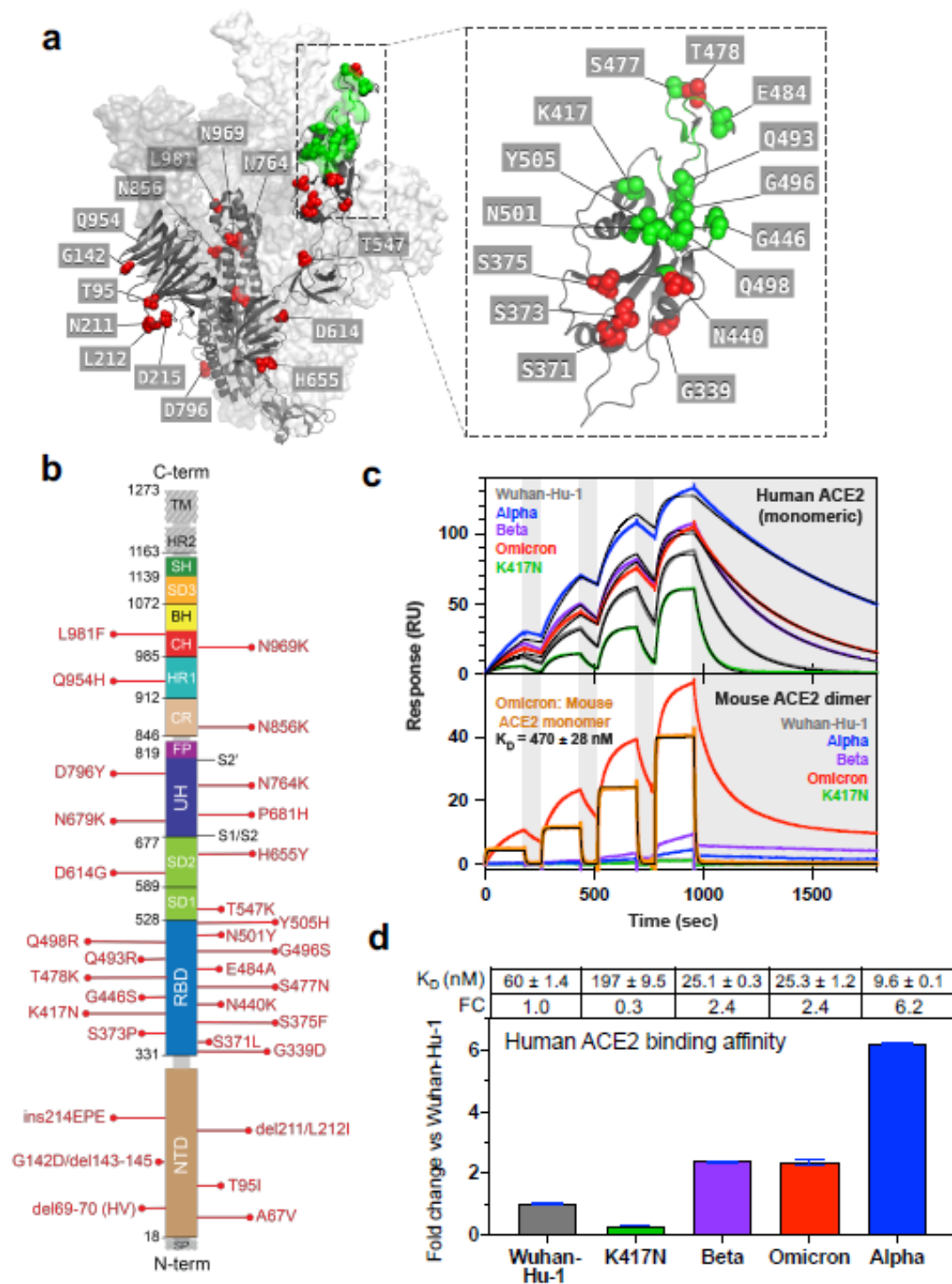
Si bien el cambio antigénico de la influenza se define como un reordenamiento genético de los segmentos del genoma de ARN, el mecanismo de acumulación de un gran número de mutaciones en la proteína S del SARS-CoV-2 Ómicron, aún no se ha establecido.

Aunque los eventos de recombinación son un sello distintivo del coronavirus<sup>47</sup>, nosotros y otros<sup>48</sup> proponemos que el cambio de Ómicron puede resultar de replicación viral extensa en huéspedes inmunodeficientes<sup>49-51</sup> o del ping-pong de la transmisión entre especies,<sup>5</sup> entre humanos y roedores, como se describió anteriormente para los visones.<sup>52,53</sup>

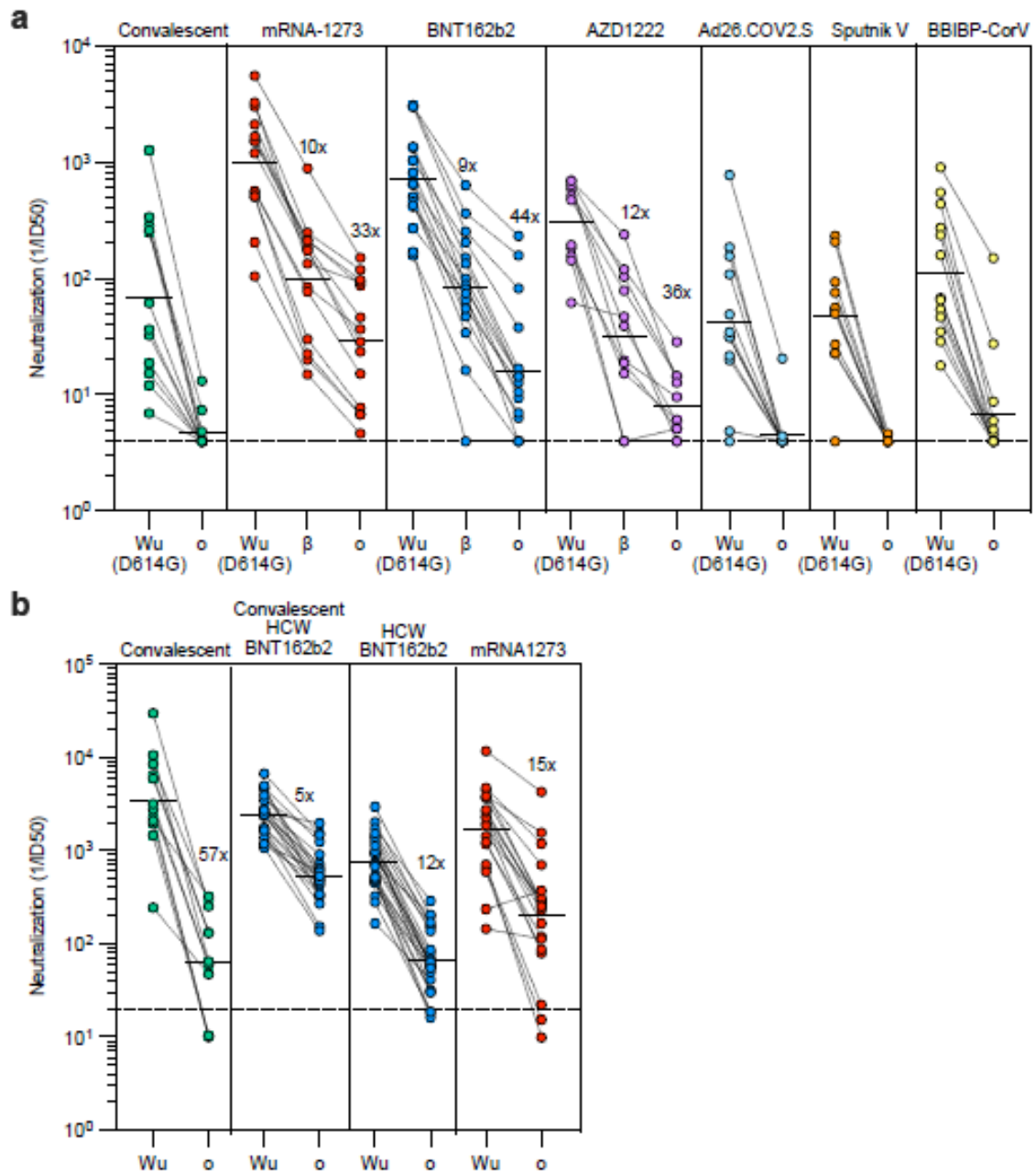
De acuerdo con la disminución variable en los títulos de anticuerpos neutralizantes en plasma, encontramos que sólo 6 de un panel de 44 anticuerpos monoclonales neutralizantes retuvieron una potente actividad neutralizante contra Ómicron.

Estos anticuerpos monoclonales reconocen 4 sitios antigénicos en el RBD, que se conservan en Ómicron y otros sarbecovirus. Sorprendentemente, encontramos 3 potentes anticuerpos monoclonales neutralizantes que se unen al RBM, que no se ven afectados por las mutaciones de Ómicron, incluida una imitación molecular del receptor ACE2 (S2K146).<sup>1</sup>

En conjunto, estos datos pueden orientar los esfuerzos futuros para desarrollar vacunas y terapias contra el SARS-CoV-2 para contrarrestar el cambio antigénico y los futuros derrames zoonóticos del sarbecovirus.

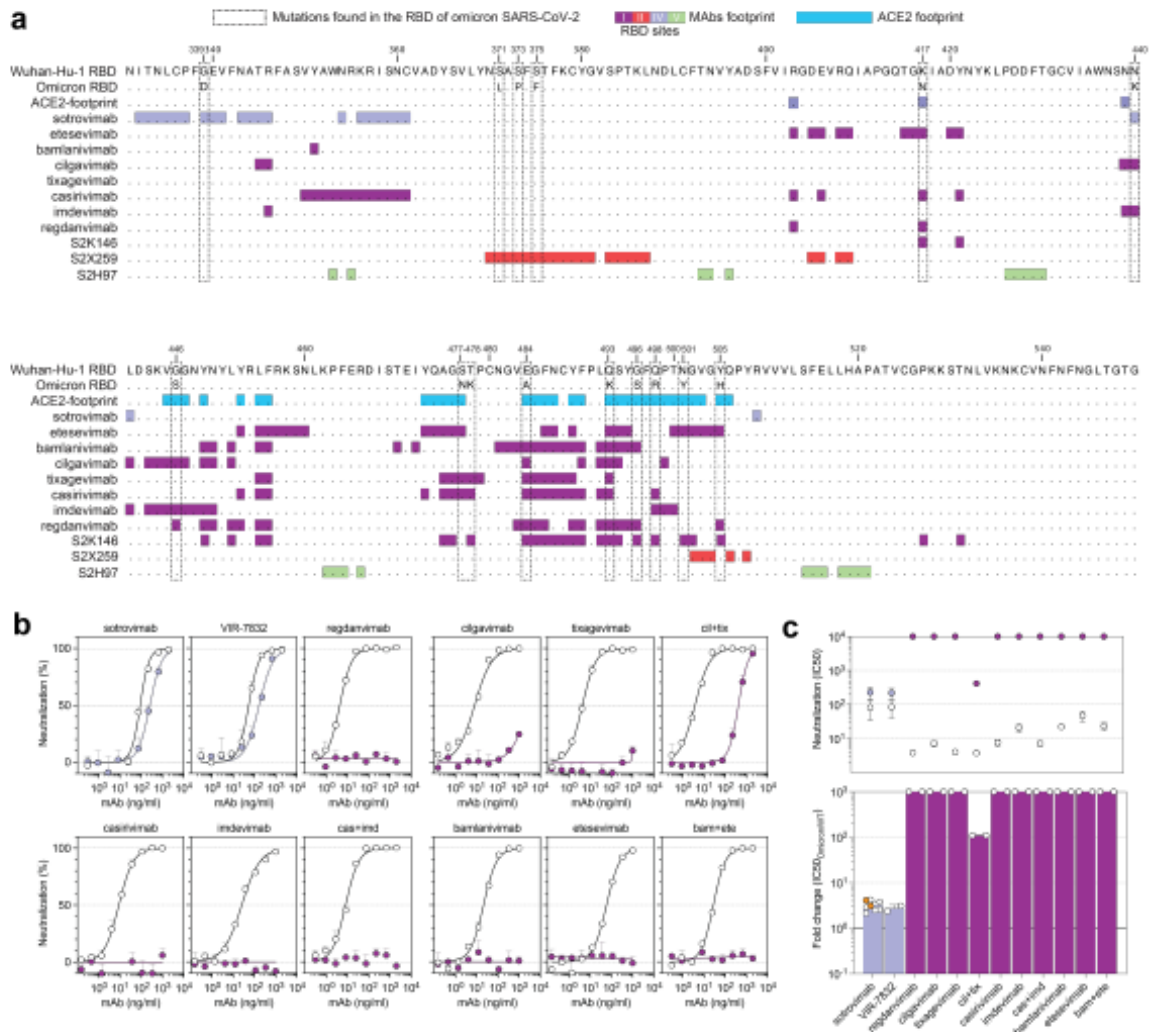


**Fig. 1. Omicron RBD shows increased binding to human ACE2 and gains binding to murine ACE2.** **a**, SARS-CoV-2 S in fully open conformation (PDB: 7K4N) with positions of mutated residues in Omicron highlighted on one protomer in green or red spheres in or outside the ACE2 footprint (ACE2), respectively. RBM is defined by a 6 Å cutoff in the RBD-ACE2 interface<sup>42</sup>. **b**, Omicron mutations are shown in a primary structure of SARS-CoV-2 S with domains and cleavage sites highlighted. **c**, Single-cycle kinetics SPR analysis of ACE2 binding to five RBD variants. ACE2 is injected successively at 11, 33, 100, and 300 nM (human) or 33, 100, 300, and 900 nM (mouse); monomeric and dimeric mouse ACE2 were tested. Black curves show fits to a 1:1 binding model. White and gray stripes indicate association and dissociation phases, respectively. **d**, Quantification of human ACE2 binding data. Reporting average  $\pm$  standard deviation of three replicates.

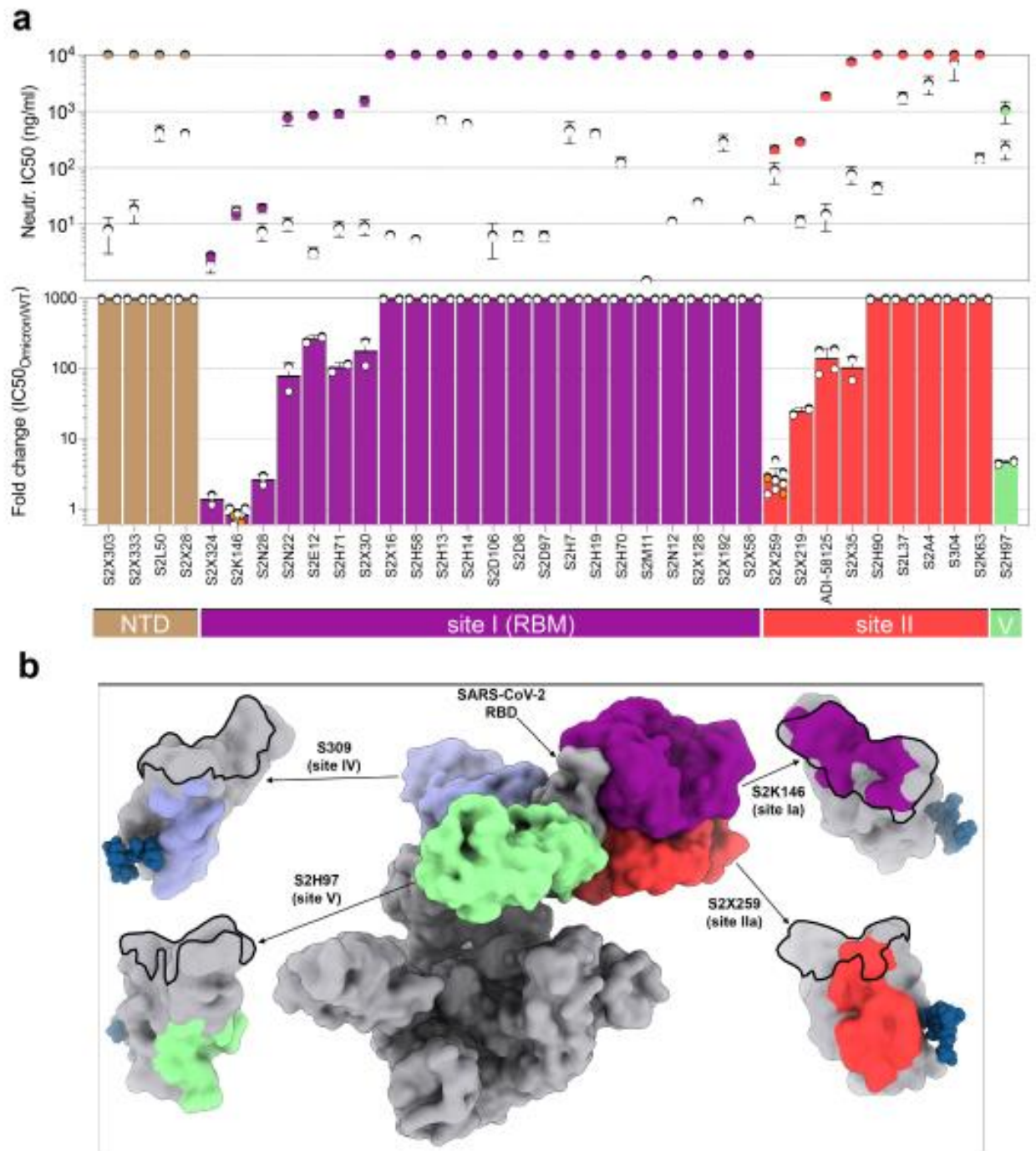


**Fig. 2. Neutralization of Omicron SARS-CoV-2 VSV pseudovirus by plasma from COVID-19 convalescent and vaccinated individuals.** Plasma neutralizing activity in COVID-19 convalescent or vaccinated individuals (mRNA-1273, BNT162b2, AZD1222, Ad26.COV2.S (single dose), Sputnik V and BBIBP-CorV). **a**, Pairwise neutralizing antibody titers (ID<sub>50</sub>) against Wuhan-Hu-1 (D614G), Beta and Omicron VOC. Vero E6-TMPRSS2 used as target cells. Shown one representative experiment out of 2. **b**, Pairwise neutralizing antibody titers of plasma (ID<sub>50</sub>) against Wuhan-Hu-1 and Omicron VOC. 11 out of 12 convalescent donors were hospitalized for COVID-19. Vero E6 used as target cells. Data are average of  $n = 2$  replicates. Line, geometric mean of 1/ID<sub>50</sub> titers. HCW, healthcare workers; Wu, Wuhan-Hu-1; o, Omicron VOC,  $\beta$ , Beta VOC. Enrolled donors' demographics provided in **Extended Data Table 2**.





**Fig. 3. Neutralization of Omicron SARS-CoV-2 VSV pseudovirus by clinical-stage mAbs. a,** RBD sequence of SARS-CoV-2 Wuhan-Hu-1 with highlighted footprints of ACE2 (light blue) and mAbs (colored according to the RBD antigenic site recognized). Omicron RBD is also shown, and amino acid substitutions are boxed. **b,** Neutralization of SARS-CoV-2 VSV pseudoviruses carrying Wuhan-Hu-1 (white) or Omicron (colored as in Fig. 4b) S proteins by clinical-stage mAbs. Data are representative of one independent experiment out of two. Shown is the mean  $\pm$  s.d. of 2 technical replicates. **c,** Mean IC<sub>50</sub> values for Omicron (colored as in Fig. 4b) and Wuhan-Hu-1 (white) (top panel), and mean fold change (bottom panel). Vero E6 used as target cells. Non-neutralizing IC<sub>50</sub> titers and fold change were set to 10<sup>4</sup> and 10<sup>3</sup>, respectively. Orange dots for sotrovimab indicate neutralization of Omicron carrying R346K. Data are representative of n = 2 to 6 independent experiments.



**Fig. 4. Neutralization of Omicron SARS-CoV-2 VSV pseudovirus by monoclonal antibodies.** **a**, Mean IC<sub>50</sub> values for Omicron (colored as in **b**) and Wuhan-Hu-1 (white) (top panel), and mean fold change (bottom panel) for 4 NTD mAbs and 32 RBD mAbs. Non-neutralizing IC<sub>50</sub> titers and fold change were set to 10<sup>4</sup> and 10<sup>3</sup>, respectively. Orange dots for S2K146 and S2X259 indicate neutralization of Omicron carrying R346K. Vero E6 used as target cells. Data are representative of *n* = 2 to 6 independent experiments. **b**, The RBD sites targeted by 4 mAbs cross-neutralizing Omicron are annotated and representative antibodies (the Fv region) bound to S are shown as a composite. Colored surfaces on the RBD depict the epitopes and the RBM is shown as a black outline.

**Extended Data Table 1. Characteristics of single point mutations present in Omicron RBD relative to Wuhan-Hu-1 RBD.**

|                                    | RBD expr.                | ACE2 binding             |               |
|------------------------------------|--------------------------|--------------------------|---------------|
|                                    |                          | FACS                     | SPR           |
|                                    | log fold-change          | log fold-change          | fold-change   |
| G339D                              | 0.3                      | 0.06                     |               |
| S371L                              | -0.61                    | -0.14                    |               |
| S373P                              | -0.22                    | -0.08                    |               |
| S375F                              | -1.81                    | -0.55                    |               |
| K417N                              | 0.1                      | -0.45                    | 0.3           |
| N440K                              | -0.12                    | 0.07                     | 1.2           |
| G446S                              | -0.4                     | -0.2                     |               |
| S477N                              | 0.06                     | 0.06                     |               |
| T478K                              | 0.02                     | 0.02                     | 1.2           |
| E484A                              | -0.23                    | -0.07                    | 1.0 for E484K |
| Q493K                              | 0.03                     | 0.05                     |               |
| G496S                              | 0.12                     | -0.63                    |               |
| Q498R                              | -0.1                     | -0.06                    |               |
| N501Y                              | -0.14                    | 0.24                     | 6.2           |
| Y505H                              | 0.16                     | -0.71                    |               |
| <b>Total:</b>                      | -2.84<br>(692-fold loss) | -2.39<br>(245-fold loss) |               |
| <b>K417N/<br/>E484K/<br/>N501Y</b> |                          |                          | 2.4           |

Expression and FACS ACE2 binding data from<sup>26</sup>

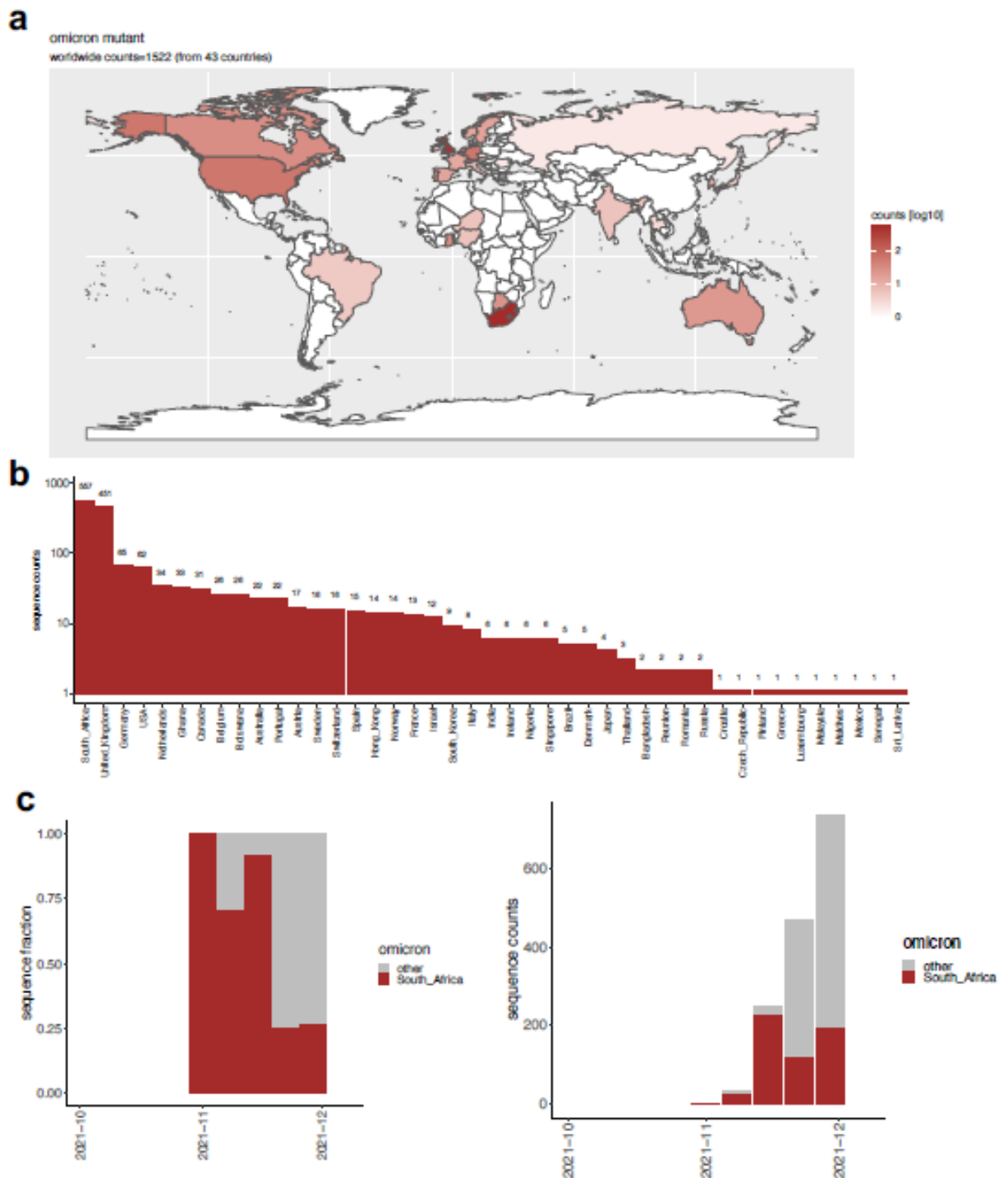
**Extended Data Table 2. Enrolled donors' demographics.**

| <b>2-4 weeks after infection/2<sup>nd</sup> vaccine dose</b>           | <b>Figure</b> | <b>Nr.</b> | <b>Females</b> | <b>Males</b> | <b>Age (average, range)</b> |
|--|---------------|------------|----------------|--------------|-----------------------------|
| <b>Wild type SARS-CoV-2-infected convalescent</b>                      |               | <b>24</b>  | <b>9</b>       | <b>15</b>    | <b>56, 34-73</b>            |
| Ospedale Luigi Sacco   | 2b            | 11         | 1              | 10           | 56, 34-73                   |
| Swiss volunteers   | 2b            | 1          |                | 1            | 52, 52-52                   |
| HAARVI (University of Washington)                                      | 2a            | 12         | 8              | 4            |                             |
| <b>Previously infected BNT162b2-vaccinated</b>                         |               | <b>22</b>  | <b>17</b>      | <b>5</b>     | <b>39, 26-56</b>            |
| Clinica Luganese Moncucco  | 2b            | 4          | 3              | 1            | 38, 27-54                   |
| Ente Ospedaliero Cantonale   | 2b            | 18         | 14             | 4            | 39, 26-56                   |
| <b>Naïve BNT162b2-vaccinated</b>                                       |               | <b>42</b>  | <b>27</b>      | <b>15</b>    | <b>43, 24-67</b>            |
| Clinica Luganese Moncucco  | 2b            | 7          | 4              | 3            | 42, 28-50                   |
| Ente Ospedaliero Cantonale   | 2b            | 18         | 13             | 5            | 43, 24-67                   |
| HAARVI (University of Washington)                                      | 2a            | 17         | 10             | 7            | 45, 22-76                   |
| <b>Naïve mRNA-1273-vaccinated</b>                                      |               | <b>34</b>  | <b>23</b>      | <b>11</b>    |                             |
| Innovative Research, Novi Michigan (1 week after 2 <sup>nd</sup> dose) | 2b            | 20         | 14             | 6            | 58, 34-74                   |
| HAARVI (University of Washington)                                      | 2a            | 14         | 9              | 5            | 47, 23-79                   |
| <b>Naïve ChAdOx1-vaccinated</b>  |               |            |                |              |                             |
| INGM, Ospedale Maggiore Policlinico of Milan                           | 2a            | 12         | 10             | 2            | 38, 29-51                   |
| <b>Naïve Sputnik V-vaccinated</b>                                      |               |            |                |              |                             |
| Hospital de Clínicas José de San Martín, Buenos Aires                  | 2a            | 11         | 7              | 4            | 42, 30-58                   |
| <b>Naïve BBIBP-CorV-vaccinated</b>                                     |               |            |                |              |                             |
| Aga Khan University  | 2a            | 13         | 9              | 4            | 30, 25-39                   |
| <b>1-19 weeks after 1st vaccine dose</b>                               |               | <b>Nr.</b> | <b>Females</b> | <b>Males</b> | <b>Age (average, range)</b> |
| <b>Naïve Ad26.COVS.S-vaccinated</b>                                    |               |            |                |              |                             |
| HAARVI (University of Washington)                                      | 2a            | 12         | 6              | 6            | 33, 23-60                   |
| <b>Total</b>   |               | <b>170</b> | <b>108</b>     | <b>62</b>    |                             |

**Extended Data Table 3. Properties of tested mAbs.**

| mAb          | Domain (site) | VH usage | Source (DSO)              | IC50 Wuhan-Hu-1 (ng/ml) | IC50 Omicron (ng/ml) | PDB/EMD    | Ref.            |
|--------------|---------------|----------|---------------------------|-------------------------|----------------------|------------|-----------------|
| sotrovimab   | RBD (IV)      | 3-23     | SARS-CoV immune donor     | 90.6                    | 260.1                | 6WPS, 7JX3 | 2-4,10,44,59,60 |
| VIR-7832*    | RBD (IV)      | 3-23     | SARS-CoV immune donor     | 53.2                    | 164.6                | 6WPS, 7JX3 | 2-4,10,44,59,60 |
| regdanvimab  | RBD (I/RBM)   | N/A      | SARS-CoV-2 immune donor   | 4.3                     | und.                 | 7CM4       | 61,62           |
| cilgavimab   | RBD (I/RBM)   | 3-15     | SARS-CoV-2 immune donor   | 8.1                     | 2772                 | 7L7E       | 39,41           |
| fixagevimab  | RBD (I/RBM)   | 1-58     | SARS-CoV-2 immune donor   | 4.3                     | und.                 | 7L7E, 7L7D | 39,41           |
| casirivimab  | RBD (I/RBM)   | 3-11     | SARS-CoV-2-imm. huIg mice | 8.9                     | und.                 | 6XDG       | 31-35           |
| imdevimab    | RBD (I/RBM)   | 3-30     | SARS-CoV-2 immune donor   | 25.1                    | und.                 | 6XDG       | 31-35           |
| bamlanivimab | RBD (I/RBM)   | 1-69     | SARS-CoV-2 immune donor   | 21.3                    | und.                 | 7KMG       | 37,38,63,64     |
| etelevimab   | RBD (I/RBM)   | 3-66     | SARS-CoV-2 immune donor   | 59.2                    | und.                 | 7C01       | 36              |
| S2D106       | RBD (I/RBM)   | 1-69     | Hosp. (98)                | 9.1                     | und.                 | 7R7N       | 4,42            |
| S2D8         | RBD (I/RBM)   | 3-23     | Hosp. (49)                | 7.3                     | und.                 |            | 42              |
| S2D97        | RBD (I/RBM)   | 2-5      | Hosp. (98)                | 5.3                     | und.                 |            | 42              |
| S2E12        | RBD (I/RBM)   | 1-58     | Hosp. (51)                | 3.7                     | 896                  | 7K4N, 7R6X | 4,42,44,45      |
| S2H14        | RBD (I/RBM)   | 3-15     | Sympt. (17)               | 624.8                   | und.                 | 7JX3       | 4,14,42         |
| S2H19        | RBD (I/RBM)   | 3-15     | Sympt. (45)               | 361.1                   | und.                 |            | 42              |
| S2H58        | RBD (I/RBM)   | 1-2      | Sympt. (45)               | 5.4                     | und.                 |            | 4,42            |
| S2H7         | RBD (I/RBM)   | 3-66     | Sympt. (17)               | 607                     | und.                 |            | 42              |
| S2H70        | RBD (I/RBM)   | 1-2      | Sympt. (45)               | 145                     | und.                 |            | 42              |
| S2H71        | RBD (I/RBM)   | 2-5      | Sympt. (45)               | 10.6                    | 993                  |            | 42              |
| S2M11        | RBD (I/RBM)   | 1-2      | Hosp. (46)                | 1.0                     | und.                 | 7K43       | 31,42,45        |
| S2N12        | RBD (I/RBM)   | 4-39     | Hosp. (51)                | 11.8                    | 10.8                 |            | 42              |
| S2N22        | RBD (I/RBM)   | 3-23     | Hosp. (51)                | 8.4                     | 919                  |            | 42              |
| S2N28        | RBD (I/RBM)   | 3-30     | Hosp. (51)                | 5.8                     | 17.1                 |            | 42              |
| S2X128       | RBD (I/RBM)   | 1-69-2   | Sympt. (75)               | 23.2                    | und.                 |            | 42              |
| S2X16        | RBD (I/RBM)   | 1-69     | Sympt. (48)               | 6.2                     | und.                 |            | 4,42            |
| S2X192       | RBD (I/RBM)   | 1-69     | Sympt. (75)               | 223.3                   | und.                 |            | 42              |
| S2X30        | RBD (I/RBM)   | 1-69     | Sympt. (48)               | 7.2                     | 1750                 |            | 42              |
| S2X324       | RBD (I/RBM)   | 2-5      | Sympt. (125)              | 2.6                     | 3.0                  |            | 25              |
| S2X58        | RBD (I/RBM)   | 1-46     | Sympt. (48)               | 11.1                    | und.                 | EMD-24607  | 4,42            |
| S2K146       | RBD (I/RBM)   | 3-43     | Sympt. (35)               | 14.2                    | 12.6                 | pending    | 1               |
| S2H13        | RBD (I/RBM)   | 3-7      | Sympt. (17)               | 628.3                   | und.                 | 7JV4       | 4,14            |
| ADI-58125    | RBD (II)      | 3-23     | SARS-CoV immune donor     | 9.3                     | 1703                 |            | 65              |
| S2H90        | RBD (II)      | 4-61     | Sympt. (81)               | 37.3                    | und.                 |            | 42              |
| S2K63v2      | RBD (II)      | 3-30     | Sympt. (118)              | 129.1                   | und.                 |            | 25              |
| S2L37        | RBD (II)      | 3-13     | Hosp. (51)                | 1496                    | und.                 |            | 25              |
| S2X259       | RBD (II)      | 1-69     | Sympt. (75)               | 81.8                    | 193.6                | 7RA8, 7M7W | 3               |
| S2X35        | RBD (II)      | 1-18     | Sympt. (48)               | 58.6                    | 7999                 | 7R6W       | 4,14            |
| S2X219       | RBD (II)      | 3-53     | Sympt. (75)               | 9.8                     | 268.3                |            |                 |
| S304         | RBD (II)      | 3-13     | SARS-CoV immune donor     | 4603                    | und.                 | 7JX3       | 4,14            |
| S2A4         | RBD (II)      | 3-7      | Hosp. (24)                | 2285                    | und.                 | 7JVC       | 14              |
| S2H97        | RBD (V)       | 5-51     | Sympt. (81)               | 279.7                   | 1368                 | 7M7W       | 4               |
| S2L50        | NTD (i)       | 4-59     | Hosp. (52)                | 337.9                   | und.                 |            | 46              |
| S2X28        | NTD (i)       | 3-30     | Sympt. (48)               | 422.7                   | und.                 | EMD-23584  | 46              |
| S2X303       | NTD (i)       | 2-5      | Sympt. (125)              | 4.5                     | und.                 | 7S0F, 7S0E | 10,46           |
| S2X333       | NTD (i)       | 3-33     | Sympt. (125)              | 13                      | und.                 | 7LXW, 7LXY | 31,44,46        |

DSO, days after symptom onset. N/A, not available. \* VIR-7832 is derived from sotrovimab, Fc further engineered to carry GAALIE<sup>66</sup>



**Extended Data Fig. 1. Geographic distribution and evolution of incidence over time of the SARS-COV-2 Omicron VOC.** **a**, World map showing the geographic distribution and sequence counts of Omicron as of December 9, 2021. **b**, Total number of Omicron sequences deposited by country as of December 9, 2021. **c**, Fraction (left) and total number (right) of sequences deposited on a weekly basis worldwide (grey) or in South Africa (red).

|        | PANGO     | WHO label   | Signal peptide and NTD  | RBM  | S1/S2                                    | S2   |
|--------|-----------|-------------|---|--|--|--|
| VOC    | B.1.1.7   | Alpha (α)   | H89-V70-Y144-   | N501Y  | A570D/D614G/P681H                        | T716I/S982AD1118H                                |
|        | B.1.351   | Beta (β)    | L18F/D80A/D215G/242-244 del                                     | K417N/E484K/N501Y  | D614G                                    | A701V  |
|        | P.1       | Gamma (γ)   | L18F/T20M/P269D/I38Y/R190S                                      | K417T/E484K/N501Y  | D614G/H655Y                              | T1027I/V1178F                                    |
|        | B.1.617.2 | Delta (δ)   | T19R/G142D/E156G/F157-R158-                                     | L452R/T478K  | D614G/P681R                              | D950N  |
| Former | B.1.1.529 | Omicron (ο) | A67V / Δ69-70 / T95I / G142D/Δ143-145<br>Δ211A,212I / ins214EPE | G339D / S371L / S373P / S375F /<br>K417N / N440K / G446S / S477N /<br>T478K / E484A / Q493R / G496S /<br>Q498R / N501Y / Y505H | T547K / D614G / H655Y /<br>N679K / P681H | N764K / D796Y / N856K / Q954H /<br>N969K / L981F |
|        | C.37      | Lambda (λ)  | G75V/T76I/246-252del  | L452Q/F490S  |  | T859N  |
|        | B.1.621   | Mu (μ)      | T95I/Y144T/Y145S/ins146N  | R346K/E484K/N501K  | D614G/P681H                              | D950N  |
|        | B.1.617.1 | Kappa (κ)   | T95I/G142D/E154K  | L452R/E484Q  | D614G/P681R                              | Q1071H   |
|        | B.1.526   | Iota (ι)    | LSF/T95I/D253G  | E484K  | D614G                                    | A701V  |
|        | B.1.525   | Eta (η)     | Q52R/A67V/H89-N70-Y144-   | E484K  | D614G/Q677H                              | F888L  |
|        | B.1.429   | Epsilon (ε) | S13I/W152C  | L452R  | D614G                                    |  |
|        | P.2       | Zeta (ζ)    |   | E484K  | D614G                                    |  |
|        | P.3       | Theta (θ)   | 141-143del/242-244del   | E484K/N501Y  | P681H                                    | S1101Y/E1092K/V1178F                             |

**Extended Data Fig. 2. Schematic of mutations landscape in each current and former SARS-CoV-2 VOC, VOI and VUM (Variant Under Monitoring). Δ, deletion; ins, insertion.**

| Sum of counts (N=1503) | G339 | R346 | S371 | S373 | S375 | K417 | N440 | G446 | L452 | S477 | T478 | E484 | Q493 | G496 | Q498 | N501 | Y505 | WU-1                                |
|------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|-------------------------------------|
| 436                    | D    |      | L    | P    | F    | N    | K    | S    |      | N    | K    | A    | R    | S    | R    | Y    | H    | Omicron VOC, as of December 9, 2021 |
| 435                    | D    |      | L    | P    | F    |      |      |      |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 106                    | D    |      | L    | P    | F    |      |      |      |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 79                     | D    |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |
| 48                     | D    | K    | L    | P    | F    | N    | K    | S    |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 46                     | D    | K    | L    | P    | F    |      |      |      |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 42                     | D    |      |      |      |      |      |      | K    | S    | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 40                     |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |
| 19                     |      |      |      |      |      | N    | K    | S    |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 15                     | D    |      |      |      |      |      |      | K    | S    | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 11                     | D    |      | L    | P    | F    | N    |      |      |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 10                     | D    |      | L    | P    | F    |      |      |      |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 9                      | D    |      | L    | P    | F    |      |      |      | R    | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| 8                      | D    | K    |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |
| 7                      | D    |      | L    | P    | F    | N    |      |      |      | N    | K    | A    | R    | S    | R    | Y    | H    |                                     |
| prevalence (%)         | 99   | 8.2  | 98   | 98   | 97   | 92   | 97   | 97   | 2.1  | 99   | 100  | 99   | 99   | 99   | 99   | 99   | 98   |                                     |
| Alpha (α)              |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      | Y    |      | VOC                                 |
| Beta (β)               |      |      |      |      |      | N    |      |      |      |      |      | K    |      |      |      | Y    |      |                                     |
| Gamma (γ)              |      |      |      |      |      | T    |      |      |      |      |      | K    |      |      |      | Y    |      |                                     |
| Delta (δ)              |      |      |      |      |      | N    |      |      | R    |      | K    |      |      |      |      |      |      |                                     |
| Epsilon (ε)            |      |      |      |      |      |      |      |      | R    |      |      |      |      |      |      |      |      |                                     |
| Zeta (ζ)               |      |      |      |      |      |      |      |      |      |      |      | K    |      |      |      |      |      | VOI                                 |
| Eta (η)                |      |      |      |      |      |      |      |      |      |      |      | K    |      |      |      |      |      |                                     |
| Theta (θ)              |      |      |      |      |      |      |      |      |      |      |      | K    |      |      | Y    |      |      |                                     |
| Iota (ι)               |      |      |      |      |      |      |      |      |      |      |      | K    |      |      |      |      |      |                                     |
| Kappa (κ)              |      |      |      |      |      |      |      |      | R    |      | Q    |      |      |      |      |      |      |                                     |
| Lambda (λ)             |      |      |      |      |      |      |      |      | Q    |      |      |      |      |      |      |      |      |                                     |
| Mu (μ)                 |      | K    |      |      |      |      |      |      |      |      |      | K    |      |      | Y    |      |      |                                     |

**Extended Data Fig. 3. Amino acid substitutions and their prevalence in the Omicron RBD sequences reported in GISAID as of December 9, 2021; (ambiguous amino acid substitutions are indicated with strikethrough cells). Shown are also the substitutions found in other variants. K417N mutation in Delta is found only in a fraction of sequences. K417N mutation in Delta is found only in a fraction of sequences.**

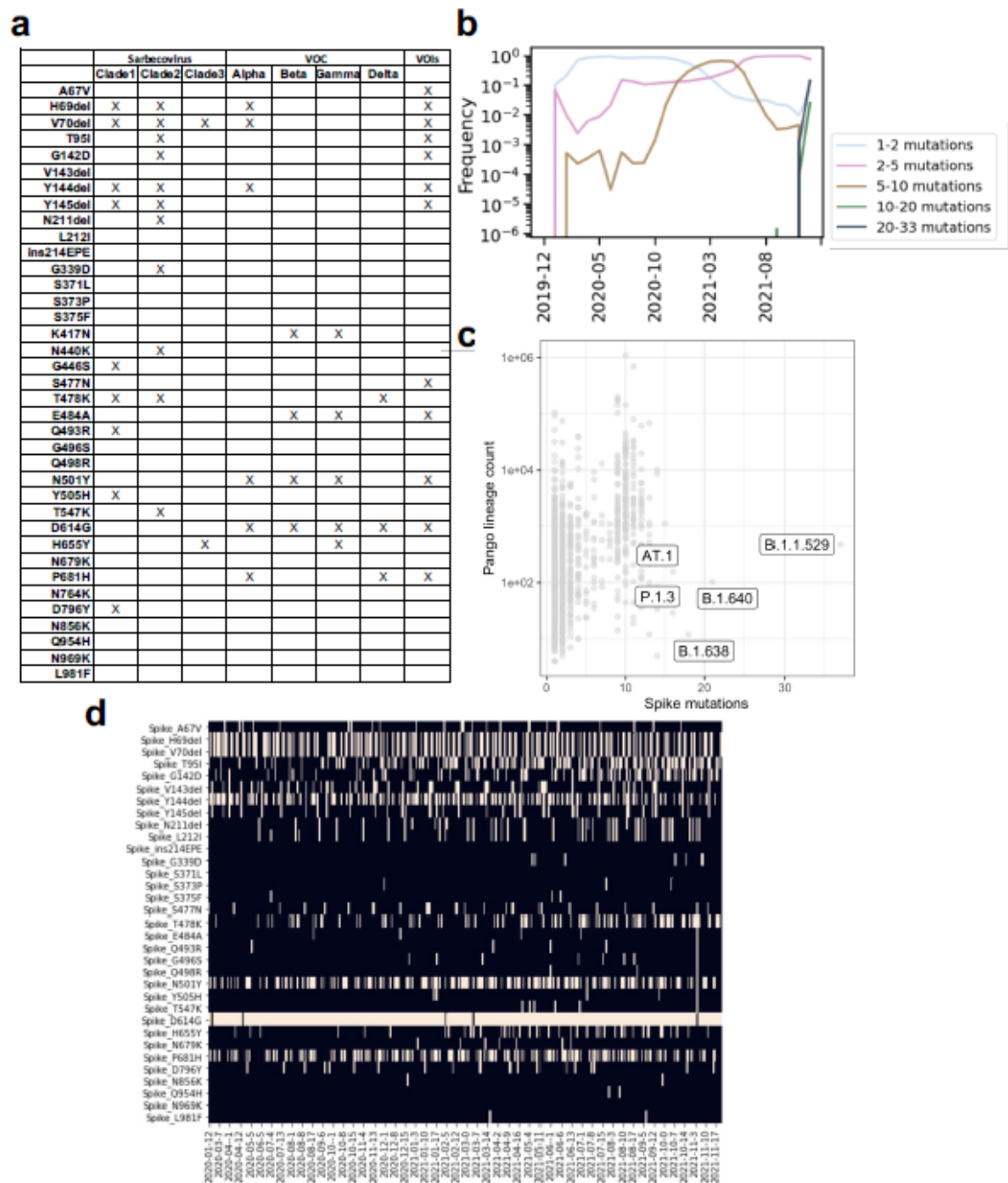
| Sum of counts (N=1503) | A67  | H69  | V70  | T95  | L141 | G142 | V143 | Y144 | Y145 | I210 | N211 | L212 | R214 | Wu-1                                |  |  |
|------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|-------------------------------------|--|--|
| 1039                   | V    | -    | -    | I    |      | D    | -    | -    | -    |      | -    | I    | REPE | Omicron VOC, as of December 9, 2021 |  |  |
| 90                     | V    | -    | -    | I    |      | D    | -    | -    |      |      |      |      |      |                                     |  |  |
| 37                     | V    | -    | -    | I    |      | D    | -    | -    |      |      | -    | I    |      |                                     |  |  |
| 25                     | V    | -    | -    | I    | F    |      |      |      |      |      | -    | I    | REPE |                                     |  |  |
| 17                     | V    | -    | -    | I    |      | D    | -    | -    |      |      |      |      |      |                                     |  |  |
| 16                     | V    | -    | -    | I    |      | D    | -    | -    |      |      |      |      |      |                                     |  |  |
| 10                     | V    | -    | -    | I    |      | D    | -    | -    |      |      |      |      |      |                                     |  |  |
| 10                     | V    | /    | /    | I    |      | /    | /    | /    |      |      |      |      |      |                                     |  |  |
| 8                      | V    | -    | -    | I    |      | D    | -    | -    |      |      | -    | I    | REPE |                                     |  |  |
| 8                      | V    | -    | -    | I    |      | D    | -    | -    |      |      | -    | I    | REPE |                                     |  |  |
| 8                      | V    | -    | -    | I    |      | D    | -    | -    |      |      | /    | /    | /    |                                     |  |  |
| 7                      | V    | -    | -    | I    |      | D    | -    | -    |      | IV   | R    |      |      |                                     |  |  |
| 7                      | V    | -    | -    | I    | /    | /    | /    | /    |      |      | -    | I    | REPE |                                     |  |  |
| 7                      | V    | -    | -    | I    |      | D    | -    | -    |      |      | -    | I    | REPE |                                     |  |  |
| prevalence (%)         | 99.9 | 99.9 | 99.9 | 99.6 | 2.0  | 96.9 | 99.4 | 99.8 | 99.6 | 0.9  | 99.2 | 99.3 | 92.0 |                                     |  |  |
| Alpha ( $\alpha$ )     |      | -    | -    |      |      |      |      |      |      |      |      |      |      | VOC                                 |  |  |
| Beta ( $\beta$ )       |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |  |  |
| Gamma ( $\gamma$ )     |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |  |  |
| Delta ( $\delta$ )     |      |      |      | /    |      | D    |      |      |      |      |      |      |      |                                     |  |  |
| Epsilon ( $\epsilon$ ) |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |  |  |
| Zeta ( $\zeta$ )       |      |      |      |      |      |      |      |      |      |      |      |      |      | VOI                                 |  |  |
| Eta ( $\eta$ )         | V    | -    | -    |      |      |      | -    |      |      |      |      |      |      |                                     |  |  |
| Theta ( $\theta$ )     |      |      |      |      |      |      | -    |      |      |      |      |      |      |                                     |  |  |
| Iota ( $\iota$ )       |      |      |      | I    |      |      |      |      |      |      |      |      |      |                                     |  |  |
| Kappa ( $\kappa$ )     |      |      |      | I    |      | D    |      |      |      |      |      |      |      |                                     |  |  |
| Lambda ( $\lambda$ )   |      |      |      |      |      |      |      |      |      |      |      |      |      |                                     |  |  |
| Mu ( $\mu$ )           |      |      |      | I    |      |      |      | T    |      |      |      |      |      |                                     |  |  |

**Extended Data Fig. 4.** Amino acid substitutions and their prevalence in the Omicron NTD sequences reported in GIAID as of December 9, 2021; (ambiguous amino acid substitutions are marked with strikethrough cells). Shown are also the substitutions found in other variants.

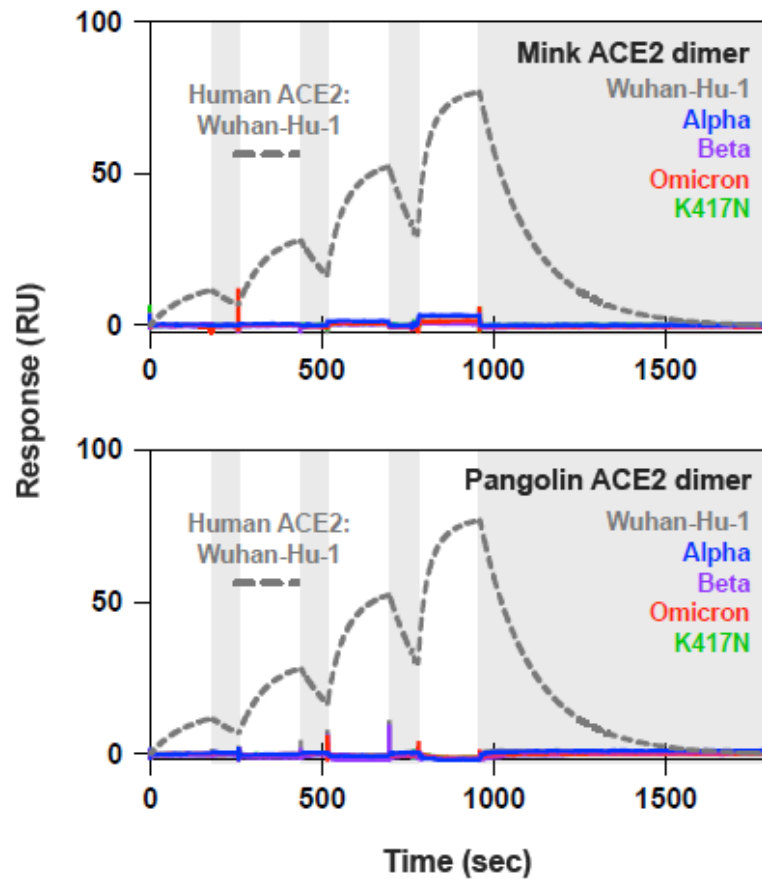


| Sum of counts<br>(N=1503) | N679 | P681 | A701 | T716 | N764 | D796 | N856 | D950 | Q954 | N969 | L981 | I1081 | Wu-1                                |
|---------------------------|------|------|------|------|------|------|------|------|------|------|------|-------|-------------------------------------|
| 940                       | K    | H    |      |      | K    | Y    | K    |      | H    | K    | F    |       | Omicron VOC, as of December 9, 2021 |
| 84                        | K    | H    | V    |      | K    | Y    | K    |      | H    | K    | F    |       |                                     |
| 78                        | K    | H    |      |      | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 66                        | K    | H    |      |      | K    | Y    | K    |      | H    | K    | F    |       |                                     |
| 60                        | K    | H    | /    | /    | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 45                        | K    | H    | /    | /    | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 18                        | K    | H    | V    |      | K    | Y    | K    |      | H    | K    | F    |       |                                     |
| 17                        | K    | H    |      |      | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 17                        | K    | H    | V    |      | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 12                        | K    | H    | /    | /    | K    | Y    | K    |      | H    | K    | F    |       |                                     |
| 9                         | K    | H    | /    | /    | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 7                         | K    | H    | /    | /    | /    | /    | /    | /    | /    | /    | /    | /     |                                     |
| 6                         | K    | H    |      |      | K    | Y    | K    | /    | H    | K    | F    |       |                                     |
| 6                         | K    | H    | /    |      | K    | Y    | K    |      | H    | K    | F    |       |                                     |
| 6                         | K    | H    | /    |      | /    | Y    | K    |      | H    | K    | F    |       |                                     |
| 5                         | K    | H    |      |      | K    | Y    | K    |      | H    | K    | F    | V     |                                     |
| 4                         | K    | H    |      |      |      |      |      | N    |      |      |      |       |                                     |
| 4                         | K    | H    |      |      | /    | /    | K    |      | H    | K    | F    |       |                                     |
| 4                         | K    | H    |      | I    | K    | Y    | K    |      | H    | K    | F    |       |                                     |
| prevalence (%)            | 99.8 | 99.9 | 9.5  | 0.4  | 98.9 | 99.3 | 99.2 | 0.6  | 99.2 | 99.2 | 98.9 | 0.5   |                                     |
| Alpha ( $\alpha$ )        | H    |      | I    |      |      |      |      |      |      |      |      |       | VOC                                 |
| Beta ( $\beta$ )          |      | V    |      |      |      |      |      |      |      |      |      |       |                                     |
| Gamma ( $\gamma$ )        |      |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Delta ( $\delta$ )        | R    |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Epsilon ( $\epsilon$ )    |      |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Zeta ( $\zeta$ )          |      |      |      |      |      |      |      |      |      |      |      |       | VOI                                 |
| Eta ( $\eta$ )            | H    |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Theta ( $\theta$ )        |      |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Iota ( $\iota$ )          |      | V    |      |      |      |      |      |      |      |      |      |       |                                     |
| Kappa ( $\kappa$ )        | R    |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Lambda ( $\lambda$ )      |      |      |      |      |      |      |      |      |      |      |      |       |                                     |
| Mu ( $\mu$ )              | H    |      |      |      |      |      |      |      |      |      |      |       |                                     |

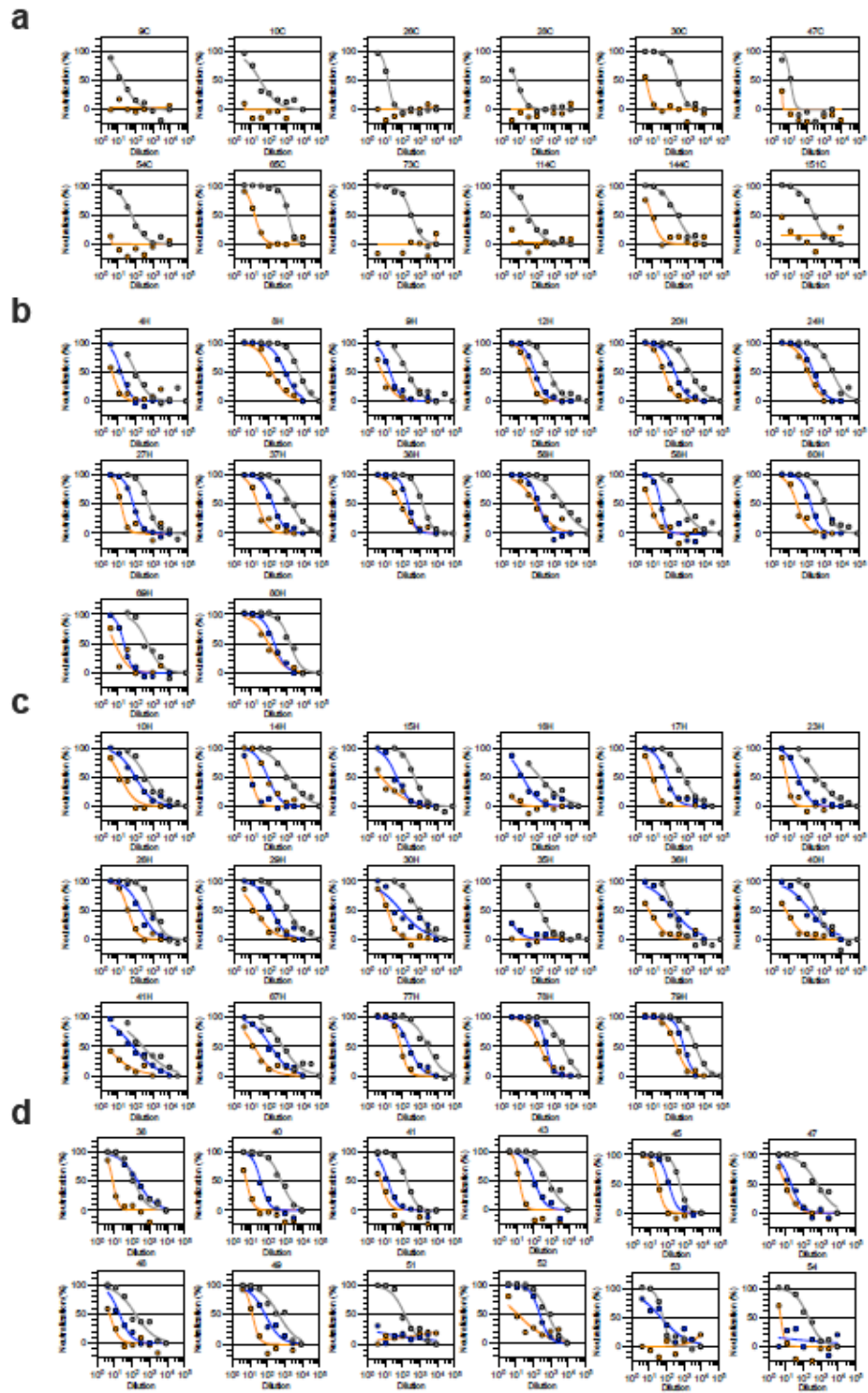
**Extended Data Fig. 5.** Amino acid substitutions and their prevalence in the Omicron S2 sequences reported in GISAID as of December 9, 2021; (ambiguous amino acid substitutions are marked with strikethrough cells). Shown are also the substitutions found in other variants.

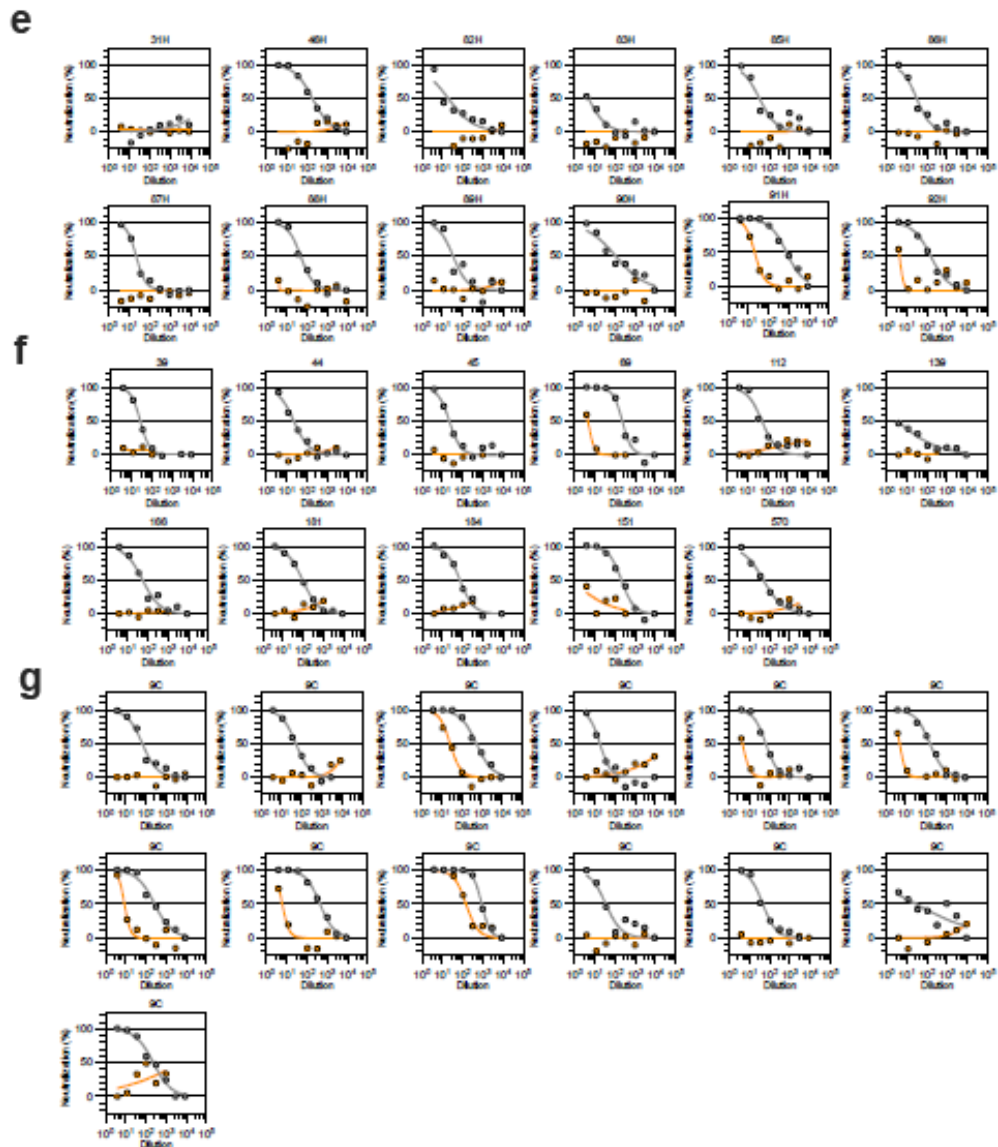


**Extended Data Fig. 6. Characteristics of emergent mutations of Omicron.** **a**, Shared mutations of micron with other sarbecovirus and with VOCs. **b**, Since the beginning of the pandemic there is a progressive coalescence of Omicron-defining mutations into non-Omicron haplotypes that may carry as many as 10 of the Omicron-defining mutations. **c**, Pango lineages (dots) rarely carry more than 10-15 lineage-defining mutations. **d**, Exceptionally, some non-Omicron haplotypes may carry up to a maximum 19 Omicron-defining mutations. Shown are selected exceptional haplotypes. Spike G142D and Y145del may also be noted as G142del and Y145D.

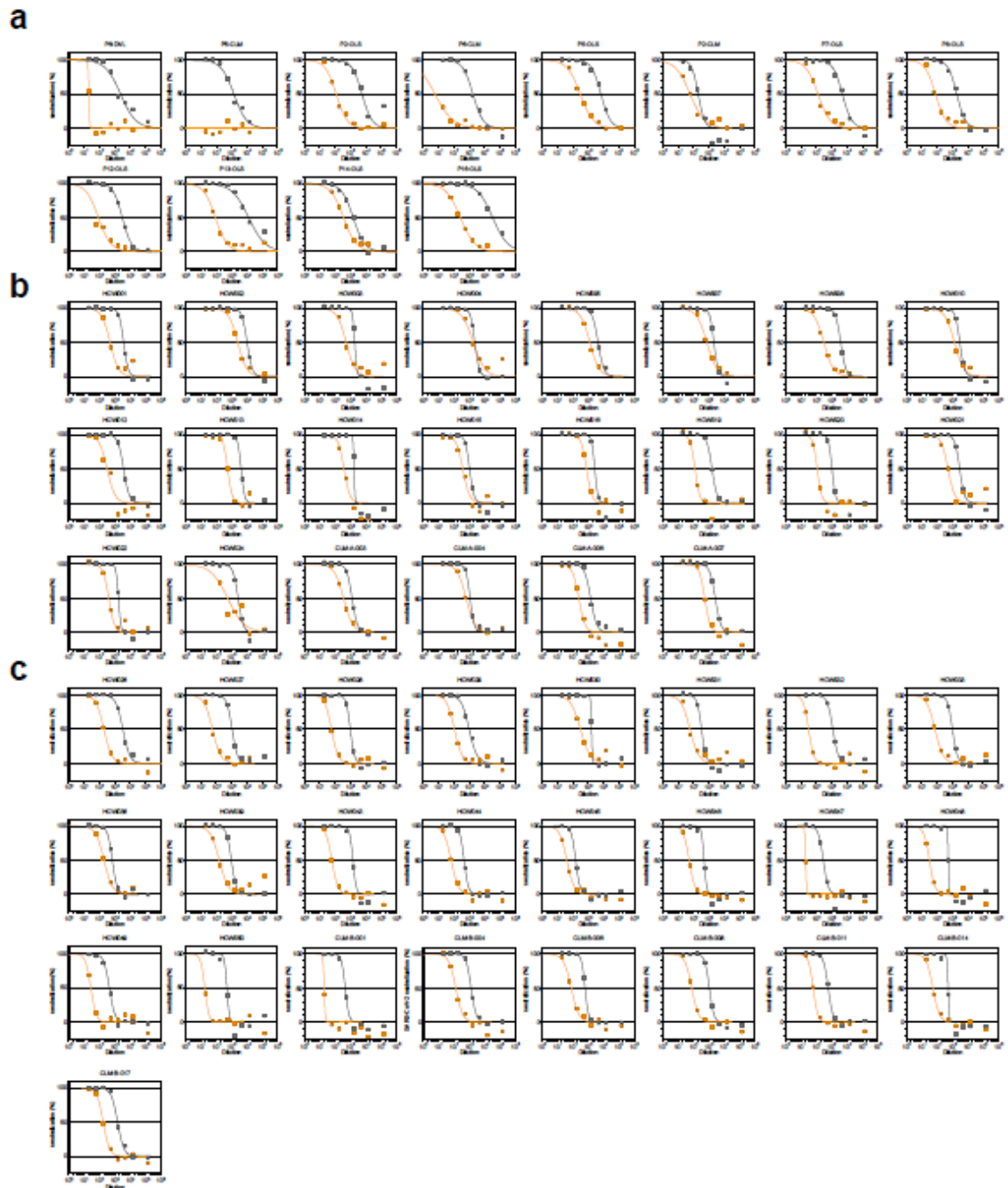


**Extended Data Fig. 7. SPR analysis of pangolin and mink ACE2.** Single-cycle kinetics SPR analysis of ACE2 binding to five RBD variants. Dimeric mink or pangolin ACE2 is injected successively at 33, 100, 300, and 900 nM. White and gray stripes indicate association and dissociation phases, respectively. Monomeric human ACE2 binding to Wuhan-Hu-1 RBD (ACE2 concentrations of 11, 33, 100, and 300 nM) shown for comparison.

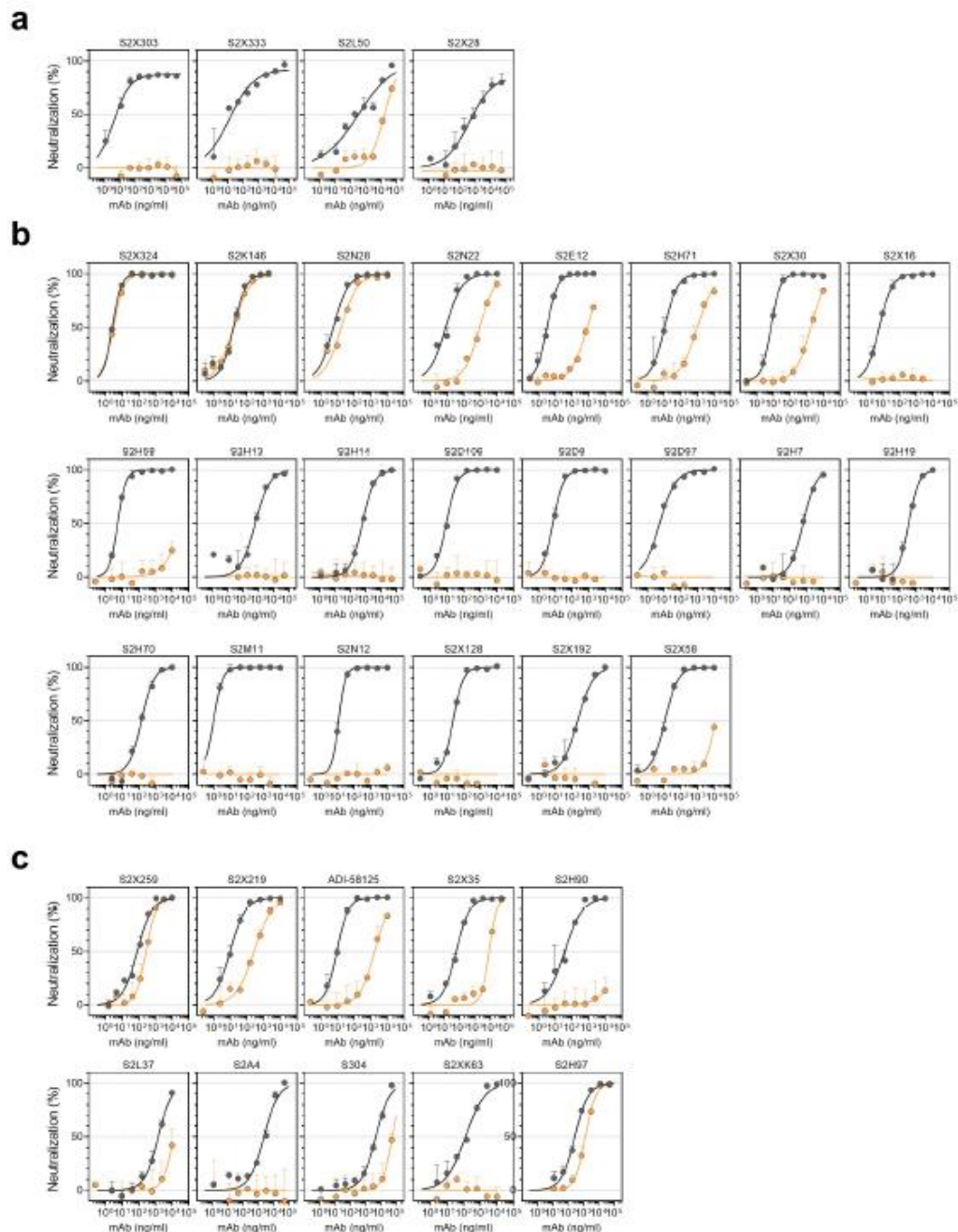




**Extended Data Fig. 8. Neutralization of WT and Omicron S pseudotyped SARS-CoV-2 virus neutralization by plasma from COVID-19 convalescent and vaccinated individuals.** Neutralization of SARS-CoV-2 pseudotyped VSV carrying Wuhan-Hu-1 D614G (grey), Beta (blue) or Omicron (orange) S protein by plasma from convalescent (a) or vaccinated individuals (b, mRNA-1273; c, BNT162b2; d, ChAdOx1; e, Ad26.COV2.S; f, Sputnik V; g, BBIBP-CorV) as shown in Fig. 2a. Data are representative of  $n = 2$  independent experiments.



**Extended Data Fig. 9. Neutralization of WT and Omicron S pseudotyped SARS-CoV-2 virus neutralization by plasma from COVID-19 convalescent and vaccinated individuals.** a-c, Neutralization of SARS-CoV-2 pseudotyped VSV carrying Wuhan-Hu-1 or Omicron S protein by plasma from convalescent individuals 2-4 weeks after infection by WT SARS-CoV-2 (a, 11 out of 12 individuals were hospitalized for COVID-19), and previously infected (b) or naïve (c) individuals, 2-4 weeks after receiving the second dose of BNT162b2 mRNA vaccine. Data are representative of  $n = 2$  independent experiments.



**Extended Data Fig. 10. Neutralization of WT (D614) and Omicron SARS-CoV-2 Spike pseudotyped virus by a panel of 36 mAbs. a-c, Neutralization of SARS-CoV-2 VSV pseudoviruses carrying wild-type D614 (grey) or Omicron (orange) S protein by NTD-targeting (a) and RBD-targeting (b-c) mAbs (b, site I; c, sites II and V). Data are representative of one independent experiment out of two. Shown is the mean  $\pm$  s.d. of 2 technical replicates.**

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