

Title: Progressive loss of conserved spike protein neutralizing antibody sites in Omicron sublineages is balanced by preserved T-cell recognition epitopes

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25 **Abstract**

The continued evolution of the SARS-CoV-2 Omicron variant has led to the emergence of numerous sublineages with different patterns of evasion from neutralizing antibodies. We investigated neutralizing activity in immune sera from individuals vaccinated with SARS-CoV-2 wild-type spike (S) glycoprotein-based COVID-19 mRNA vaccines after subsequent
30 breakthrough infection with Omicron BA.1, BA.2, or BA.4/BA.5 to study antibody responses against sublineages of high relevance. We report that exposure of vaccinated individuals to infections with Omicron sublineages, and especially with BA.4/BA.5, results in a boost of Omicron BA.4.6, BF.7, BQ.1.1, and BA.2.75 neutralization, but does not efficiently boost neutralization of sublineages BA.2.75.2 and XBB. Accordingly, we found in *in silico* analyses
35 that with occurrence of the Omicron lineage a large portion of neutralizing B-cell epitopes were lost, and that in Omicron BA.2.75.2 and XBB less than 12% of the wild-type strain epitopes are conserved. In contrast, HLA class I and class II presented T-cell epitopes in the S glycoprotein were highly conserved across the entire evolution of SARS-CoV-2 including Alpha, Beta, and Delta and Omicron sublineages, suggesting that CD8⁺ and CD4⁺ T-cell recognition of Omicron
40 BQ.1.1, BA.2.75.2, and XBB may be largely intact. Our study suggests that while some Omicron sublineages effectively evade B-cell immunity by altering neutralizing antibody epitopes, S protein-specific T-cell immunity, due to the very nature of the polymorphic cell-mediated immune, response is likely to remain unimpacted and may continue to contribute to prevention or limitation of severe COVID-19 manifestation.

Main Text

The SARS-CoV-2 Omicron variant of concern (VOC), that emerged in November 2021, contains over 30 amino acid alterations in its spike (S) glycoprotein as compared to the original Wuhan-Hu-1 (wild-type) strain that mediate partial escape from previously established immunity (1-3).

50 Omicron sublineages BA.1, BA.2, BA.4, and BA.5 consecutively dominated the pandemic landscape. Immune escape became pronounced in the more recent sublineages, leading to the authorization of BA.1 and BA.4/BA.5 adapted vaccines (4, 5). While BA.5 has been the globally dominant sublineage since mid-2022, Omicron BA.2.75, BA.2.75.2, BA.4.6, BF.7, BQ.1.1 have locally increased, and XBB has displaced BA.5 in parts of Asia, whereas BQ.1.1 is currently
55 becoming dominant over BA.5 in the United States and parts of Europe (6-8).

Omicron BA.2.75 differs in five amino acids within the N-terminal domain from its parental sublineage BA.2 and previous Omicron VOCs (fig. S1). The receptor-binding domain (RBD) of BA.2.75 has three alterations that are not found in BA.2, of which G446S is shared with BA.1. BA.2.75.2 differs from BA.2.75 in the RBD alterations R346T and F486S. Omicron BA.4.6 and
60 BF.7 are identical in their S glycoprotein sequence (called Omicron BA.4.6/BF.7 S in this study), which bears great similarity to the S glycoprotein sequence of their respective parental sublineages BA.4 and BA.5 (called Omicron BA.4/BA.5 S in this study due to sequence identity). A single R346T change within the RBD that distinguishes BA.4.6/BF.7 S glycoprotein from BA.4/BA.5 S glycoprotein abrogates neutralization by the therapeutic monoclonal antibody
65 (mAb) cilgavimab (9). Cilgavimab in combination with tixagevimab (Evusheld™) is used for pre-exposure COVID-19 prophylaxis in immunocompromised patients. As tixagevimab lacks neutralizing activity against Omicron BA.4/BA.5 and their descendants, this antibody combination therapy is rendered fully ineffective against Omicron BA.4.6, BF.7 (9, 10) and

BQ.1.1 (11), which additionally has a K444T alteration. The S protein of XBB, a recombinant
70 strain (12), is altered at seven amino acid positions (four in NTD, three in RBD) relative to the
main Omicron sublineages BA.1, BA.2, and BA.4/5 and also bears the R346T alteration. It is to
be expected that virus evolution will continue. Real-time understanding of the transmissibility,
pathogenicity, and immune evasion properties of new variants in conjunction with immunity
patterns in the human population that are being shaped through repeated infections with different
75 VOCs, vaccination, and booster cycles with different vaccines, will continue to be critical to
assessing the level of risk to public health going forward.

In the face of this highly dynamic situation, we have set up a COVID-19 pandemic preparedness
and rapid response strategy. Our approach includes the screening of emerging and circulating
variants through an artificial intelligence/machine learning-based early warning system (13),
80 testing prototypical mRNA vaccines adapted to these variants in mouse studies (16), and
mapping SARS-CoV-2 T-cell epitopes recognized by the human T-cell repertoire (19, 20).
Further, studying the neutralizing antibody activity of individuals following breakthrough
infections with the latest circulating variants allows us to detect potential immune escape
patterns early and informs on the need for rapid vaccine adaptation strategies (14-18).

85 In continuation of this work, the current study assessed Omicron sublineages BA.4.6, BF.7,
BA.2.75, BA.2.75.2, BQ.1.1, and XBB, as these sublineages are currently establishing
dominance over BA.5.

We investigated neutralizing activity of immune sera from individuals who received three or four
doses of SARS-CoV-2 wild-type S glycoprotein-based mRNA COVID-19 vaccines
90 (BNT162b2/mRNA-1273 homologous or heterologous regimens) with or without subsequent
breakthrough infection by different Omicron sublineages. Specifically, the following cohorts

were investigated: BNT162b2 triple-vaccinated SARS-CoV-2-naïve individuals (BNT162b2³; n=18; age <55 years), BNT162b2 quadruple-vaccinated SARS-CoV-2-naïve elderly (>60 years) individuals (BNT162b2⁴; n=15), and triple mRNA vaccinated individuals who experienced
95 breakthrough infection with Omicron BA.1 (mRNA-Vax³ + BA.1; n=14), BA.2 (mRNA-Vax³ + BA.2, n=19), or BA.4/BA.5 (mRNA-Vax³ + BA.4/BA.5, n=17) (fig. S2). As a fourth vaccine dose is recommended for the elderly and given the high frequency of breakthrough infections with Omicron sublineages we considered this study population to be representative for a large proportion of the European and North American population. Serum neutralizing activity was
100 tested in a well-characterized pseudovirus neutralization test (pVNT) (14-16) by determining 50% pseudovirus neutralization (pVN₅₀) geometric mean titers (GMTs) for pseudoviruses bearing the S glycoproteins of the SARS-CoV-2 wild-type strain or of Omicron sublineages. In the triple-/quadruple-vaccinated individuals without breakthrough infection, pVN₅₀ GMTs against Omicron BA.4/BA.5 were 5 to 6-fold lower than GMTs against the wild-type strain
105 (GMTs against BA.4/BA.5 were 69 and 121, respectively) (Fig. 1a). GMTs against BA.4/BA.5 were similarly reduced in BA.1 convalescents (GMT 263, 5-fold lower than wild-type), whereas in the BA.2 and BA.4/BA.5 convalescent cohorts, titers against BA.4/BA.5 remained higher (GMTs of 386 and 521, respectively; 3- and 2-fold lower than wild-type). In all three convalescent cohorts, neutralizing titers against Omicron BA.4.6/BF.7 and BA.2.75
110 were robustly above those of triple-/quadruple-vaccinated SARS-CoV-2 naïve individuals (GMT range 239-525 for convalescents as compared to 55-139 for naïves). In the convalescents, Omicron BA.4.6/BF.7 and BA.2.75 GMTs were largely comparable with no significant differences to those against Omicron BA.4/BA.5. In contrast, pVN₅₀ titers against Omicron BQ.1.1, BA.2.75.2, and XBB were significantly lower than those against BA.4/BA.5 across

115 cohorts. Titers against BQ.1.1 were overall very low in the SARS-CoV-2 naïve vaccinated cohorts and BA.1 convalescents (GMTs ≤ 38) and moderately higher in the BA.2 and BA.4/BA.5 convalescent cohorts (GMTs 100 and 154, respectively). Titers against BA.2.75.2 and XBB were low across cohorts (GMTs ≤ 88 and ≤ 33 , respectively).

To assess neutralization breadth irrespective of the magnitude of antibody titers we normalized
120 the Omicron sublineage pVN₅₀ GMTs against those for the wild-type strain. GMT ratios for all Omicron subvariant pseudoviruses were comparable between the BNT162b2³ and BNT162b2⁴ cohorts (Fig. 1b). Hence, both neutralizing antibody titers and variant cross-neutralization were broadly similar in quadruple-vaccinated elderly individuals and triple-vaccinated younger individuals. GMT ratios were in the range of 0.09-0.22 for BA.4/BA.5, BA.4.6/BF.7, and
125 BA.2.75 and ≤ 0.05 for BQ.1.1, BA.2.75.2, and XBB in both cohorts.

Cross-neutralization of BA.4/BA.5 and BA.4.6/BF.7 was significantly ($p < 0.05$) higher in sera from BA.2.convalescents as compared to triple-vaccinated individuals (GMT ratios 0.37 vs 0.17 for BA.4/BA.5, and 0.23 vs 0.12 for BA.4.6/BF.7) and even more so in BA.4/BA.5-convalescents for both the BA.4/BA.5 pseudovirus (GMT ratio 0.48, $p < 0.01$ versus BNT162b2³)
130 and the BA.4.6/BF.7 pseudovirus (GMT ratio 0.41, $p < 0.0001$). Cross-neutralization of BA.4.6/BF.7 was also significantly ($p < 0.0001$) stronger in BA.4/BA.5 convalescents compared to quadruple-vaccinated individuals. While BQ.1.1 was cross-neutralized less efficiently than BA.4/BA.5 in all cohorts (GMT ratios ≤ 0.14), cross-neutralization in BA.4/BA.5 and BA.2 convalescents remained significantly stronger compared to SARS-CoV-2 naïve triple or
135 quadruple-vaccinated and BA.1 breakthrough infected cohorts. Cross-neutralization of BA.2.75, BA.2.75.2, and XBB pseudoviruses was broadly comparable across cohorts. GMT ratios were in the range of 0.20-0.37 for BA.2.75 and ≤ 0.06 for BA.2.75.2 and XBB. Together these data show

that partial neutralization of some Omicron sublineages is retained, being broadest in BA.4/BA.5
convalescent individuals. In contrast, sublineages BA.2.75.2 and XBB have evolved to largely
140 evade neutralizing antibody responses in vaccinated individuals and in those with breakthrough
infections with previous and currently circulating Omicron sublineages.

We next sought to determine whether distinct cross-neutralization of individual SARS-CoV-2
variants is reflected by the degree of B-cell epitope conservation with respect to the wild-type
strain. For this, we analyzed a total of 506 neutralizing B-cell epitopes within the S glycoprotein
145 NTD and RBD, consisting of experimentally confirmed epitopes from the Immune Epitope
Database (IEDB) and epitopes computationally deduced from structures of SARS-CoV-2
neutralizing antibodies from the Coronavirus Antibody Database (CoV-AbDab). Of these 506
epitopes, 462 (91%) included a position that was altered in at least one of the analyzed variants.

We found that B-cell epitopes were partially conserved in the earlier variants Alpha, Beta, and
150 Delta ($\geq 43\%$) (Fig 2, Fig S3, and Table S2), whereas with the occurrence of the heavily RBD-
mutated Omicron BA.1 variant most of these epitopes were altered and remained so for the
Omicron lineage ($\leq 22\%$ conservation). This was particularly the case in BA.2.75.2 and XBB
($\leq 12\%$ conservation), in line with our cross-neutralization data.

Neutralizing antibodies are an important component of immunity against SARS-CoV-2 yet not
155 the only one (17). T cells are known to contribute to the adaptive anti-viral immune response.
Unlike antibodies, which do not require HLA presentation and often depend on specific epitope
conformations, T-cell recognition of the viral proteins is distributed across varying linear
epitopes in different individuals based on their specific composition of HLA class I and II alleles.
This renders T-cell immunity in the population harder to evade through accumulation of
160 mutations. Cytotoxic CD8⁺ T cells that recognize HLA class I presented epitopes play a critical

role in susceptibility to severe COVID-19 disease, hospitalization and death (18, 19). HLA class II dependent CD4⁺ helper T cells typically orchestrate the immune response by their pleiotropic functions and are also considered to have an important role in the prevention of severe disease (20, 21).

165 To estimate the impact of SARS-CoV-2 evolution on T-cell immunity, we assessed the degree of conservation of T-cell epitopes localized in the S glycoproteins of various VOCs. To this aim we filtered experimentally confirmed SARS-CoV-2 epitopes reported for HLA class I and II alleles from the IEDB database. In total, 594 and 559 unique epitopes were collected for HLA class I and class II, respectively. For stringency, in this analysis we only retained experimentally
170 confirmed minimal epitopes of either HLA class I or HLA class II in a human host and removed any inferred or predicted entries. Epitopes were also filtered by length (8-14 for HLA class I and 12-20 for HLA class II). Following filtering, 260 unique HLA class I epitope sequences remained, of which 244 were found in the wild-type strain S glycoprotein. Of these, 71 epitopes (27.3%) included a position reported to be mutated in at least one analyzed variant. Of 468 HLA
175 class II epitopes, 230 (49%) were observed to cover region that contains mutation in at least one analyzed variant. HLA class I and class II epitopes post filtering covered in total 40 unique alleles for both class I and class II.

Approximately 90% of CD8⁺ and CD4⁺ T-cell epitopes of the wild-type S glycoprotein were fully conserved in the Alpha, Beta, and Delta variants (Fig 2, fig S3, Tables S3 and S4) and over
180 80% of CD8⁺ and ~70% CD4⁺ T-cell epitopes were fully conserved in Omicron sublineages including BA.2.75.2, BQ.1.1, and XBB (Fig. 2 and fig. S3), suggesting that T-cell responses against Omicron sublineages may remain largely intact in individuals immunized with wild-type strain-based vaccines.

In summary, our findings provide insights into two mechanisms: firstly, the neutralizing activity
185 of human sera in the context of currently circulating VOCs, and second, the potential of the SARS-CoV-2 S glycoprotein directed CD8⁺ and CD4⁺ T-cell repertoire.

With regard to humoral immunity, we show that exposure of vaccinated individuals to Omicron BA.4/BA.5 refocuses neutralizing antibody responses towards neutralization of BA.4/BA.5 itself, that goes along with partial cross-neutralization of BA.4.6/BF.7, BA.2.75 and at a lower
190 degree of BQ.1.1 but displays poor activity against Omicron BA.2.75.2 and XBB.

That the Omicron BA.4.6/BF.7-neutralizing activity and even more so neutralization of BQ.1.1 by sera from vaccinated individuals and BA.2 convalescents is further reduced as compared to their activity against BA.4/BA.5 suggests that the R346T and the N460K alterations mediate further escape from neutralizing antibodies in human sera. Convergent evolution of the RBD at
195 these critical residues in Omicron BA.4.6, BF.7, BQ.1.1, BA.2.75.2 and XBB (7, 12) suggests that the resulting immune evasion may confer a growth advantage. Reduced neutralization of BA.2.75.2 as compared to BA.2.75 confirms a prominent role of R346T as well as of alterations at F486 in escape from neutralizing antibodies (22).

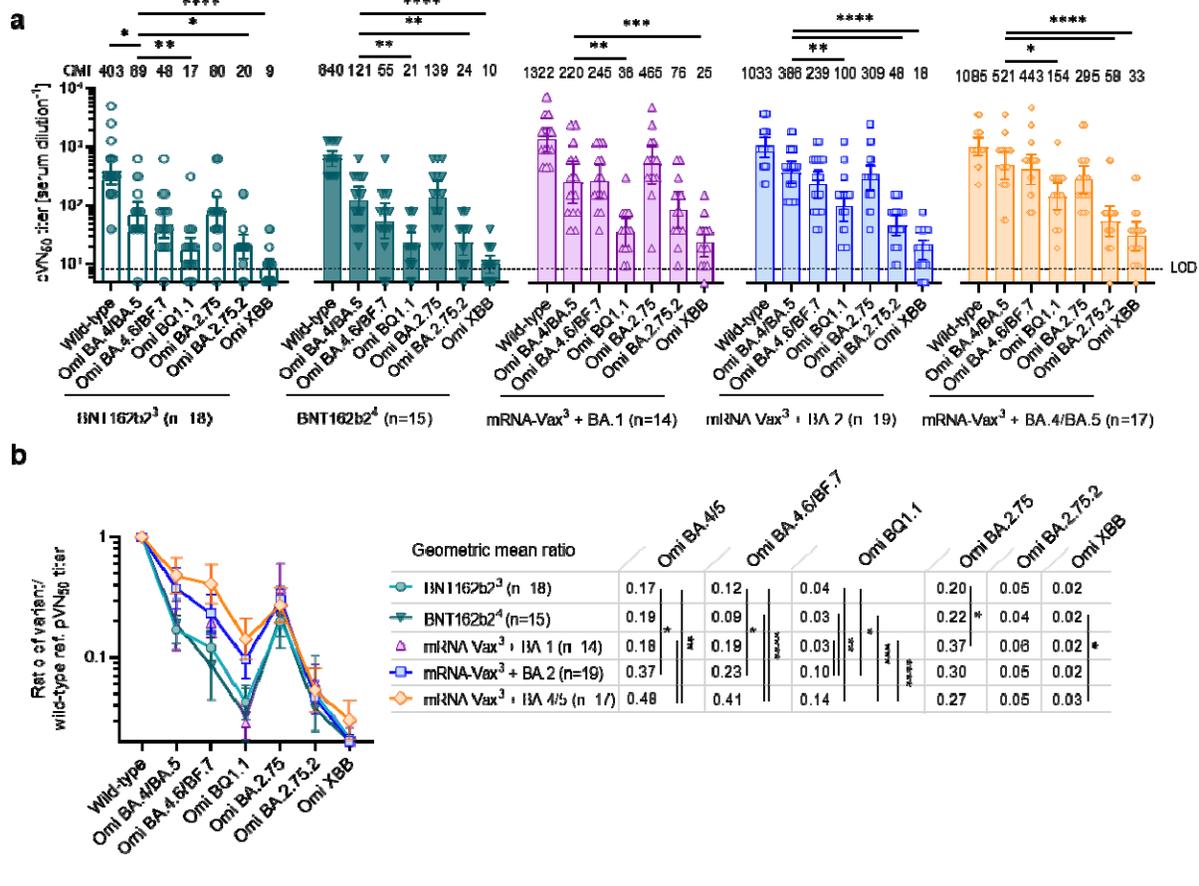
Consistent with previous reports we show that cross-neutralization of Omicron BA.2.75 and
200 BA.4/BA.5 are broadly comparable (10, 23, 24) indicating factors other than immune evasion to be involved in growth advantage of BA.2.75 over BA.5. Minor differences in the sensitivity of Omicron BA.2.75 and BA.4/BA.5 to neutralization by BA.1- and BA.4/BA.5-convalescent sera may indicate amino acid changes with a context-dependent role in immune evasion.

Our findings are supportive for suitability of Omicron BA.4/BA.5-adapted vaccines to boost
205 neutralizing activity against several circulating or emerging variants of potential relevance, such as BA.4.6 and BF.7. They also show that Omicron sublineages continue to accumulate mutations

that disrupt critical B-cell neutralization epitopes, and that further boosters or variant adaptations may be required in future.

With regard to cell-mediated immunity, we show that HLA class I and class II presented T-cell
210 epitopes remained mostly unaltered across the evolution of SARS-CoV-2 including Omicron
sublineages, suggesting that CD8⁺ and CD4⁺ T-cell immunity against Omicron BQ.1.1,
BA.2.75.2, and XBB may be largely intact, despite profound neutralizing antibody evasion. This
fits in with previous reports, e.g. describing the existence of degenerate T-cell epitopes located
within conserved S protein regions (25) and showing that wildtype-strain-vaccinated individuals
215 retain T-cell immunity against Omicron BA.1 (26-28). Indeed, a fundamental difference of T-
cell versus B-cell mediated immunity is that owing to the highly polymorphic nature of HLA
molecules (29-31), the T-cell mediated layer of immunity is more robust against population-level
breaches by VOCs. Our observations indicate that T-cell immunity may mitigate the lack of
neutralizing antibody activity in preventing or limiting severe COVID-19 and further encourages
220 development of vaccine formats that induce functional and broad SARS-CoV-2-directed CD8⁺
T-cell immunity concurrently to boosting antibody responses.

Fig. 1



225 **Fig. 1. Distinct cross-neutralization of Omicron sublineages by vaccine-elicited and convalescent human immune sera**

Cohorts and serum sampling as described in fig. S2. (a) 50% pseudovirus neutralization (pVN₅₀) geometric mean titers (GMTs) against the indicated SARS-CoV-2 wild-type strain or Omicron variants of concern (VOCs). Values above bar graphs represent group GMTs. For titer values below the limit of detection (LOD), LOD/2 values were plotted. The non-parametric Friedman test with Dunn's multiple comparisons correction was used to compare neutralizing titers against the Omicron BA.4/BA.5 pseudovirus (which represents currently dominating BA.5) with titers against the other pseudoviruses. Multiplicity-adjusted p values are shown. (b) SARS-CoV-2

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VOC pVN₅₀ GMTs normalized against the wild-type strain pVN₅₀ GMT (ratio VOC to wild-
235 type). Group geometric mean ratios with 95% confidence intervals are shown. The non-
parametric Kruskal-Wallis test with Dunn's multiple comparisons correction was used to
compare the VOC GMT ratios between cohorts. ****, P<0.0001; ***, p<0.001; **, P<0.01; *,
P<0.05. Serum was tested in duplicate.

240 **Fig. 2**

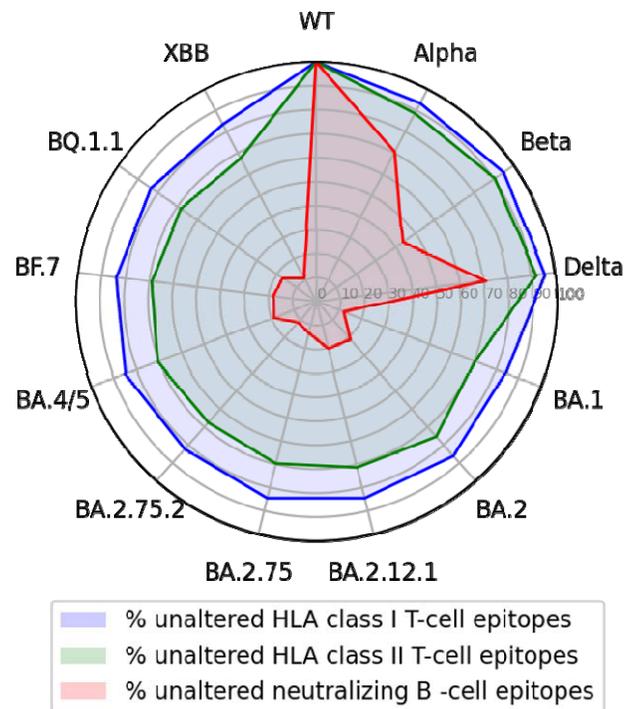


Fig. 2. T-cell epitopes of the wild-type SARS-CoV-2 S glycoprotein but not epitopes for neutralizing antibodies are largely conserved across variants.

Percentages of unaltered neutralizing B-cell epitopes (restricted to NTD and RBD) present in
245 each variant strain compared to SARS-CoV-2 wild-type are represented by the red shaded area.
Percentages of unaltered S glycoprotein linear HLA class I and II T-cell epitopes present in each
variant strain as compared to SARS-CoV-2 S wild-type are shown in blue (HLA class I) and
green (HLA class II) shaded area. The B-cell epitopes were either retrieved from IEDB on
November 25, 2022 or calculated from resolved antigen-antibody protein structures deposited in
250 the Coronavirus antibody database (CoV-AbDab) (32) using a similar computational method to

the one used in our early warning system (13). T-cell epitopes were retrieved from the Immune Epitope Database (IEDB) on November 11, 2022.

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Author contributions:

U.S., Ö.T., and A.M. conceived and conceptualized the work. A.M., A.P., K.B., and B.G.L.
planned and supervised experiments and epitope analyses. G.R.Y., O.O., K.G., J.G., N.K., S.H.
and S.C. coordinated and conducted sample collection. K.G., Y.L., and G.R.Y. coordinated
270 sample shipments and clinical data transfer. B.G.L., and M.B. performed experiments. A.M.,
B.G.L., A.P, Y.F., and H.D. analyzed data. U.S., Ö.T., A.M., A.P., A.T., and B.G.L. interpreted
data and wrote the manuscript. All authors supported the review of the manuscript.

Competing interests:

275 U.S. and Ö.T. are management board members and employees at BioNTech SE. A.M., B.G.L.,
M.B., A.T., J.G. and O.O. are employees at BioNTech SE. A.P. and H.D. are employees at
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employees at the University Hospital, Goethe University Frankfurt. U.S., Ö.T. and A.M. are
inventors on patents and patent applications related to RNA technology and COVID-19 vaccines.
280 Q.Y, H.C., and K.A.S. are inventors on a patent application related to RNA-based COVID-19
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285 **Data and materials availability:**

Materials are available from the authors under a material transfer agreement with BioNTech.

Supplementary materials:

Materials and Methods

290 Figs. S1-S4

Tables S1-S9

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