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5 Antibody Resistance of SARS-CoV-2 Variants 6 B.1.351 and B.1.1.7

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37 **The COVID-19 pandemic has ravaged the globe, and its causative agent, SARS-**
38 **CoV-2, continues to rage. Prospects of ending this pandemic rest on the**
39 **development of effective interventions. Single and combination monoclonal**
40 **antibody (mAb) therapeutics have received emergency use authorization¹⁻³, with**
41 **more in the pipeline⁴⁻⁷. Furthermore, multiple vaccine constructs have shown**
42 **promise⁸, including two with ~95% protective efficacy against COVID-19^{9,10}.**
43 **However, these interventions were directed toward the initial SARS-CoV-2 that**
44 **emerged in 2019. The recent emergence of new SARS-CoV-2 variants B.1.1.7 in the**
45 **UK¹¹ and B.1.351 in South Africa¹² is of concern because of their purported ease of**
46 **transmission and extensive mutations in the spike protein. We now report that**
47 **B.1.1.7 is refractory to neutralization by most mAbs to the N-terminal domain (NTD)**
48 **of spike and relatively resistant to a few mAbs to the receptor-binding domain**
49 **(RBD). It is not more resistant to convalescent plasma or vaccinee sera. Findings**
50 **on B.1.351 are more worrisome in that this variant is not only refractory to**
51 **neutralization by most NTD mAbs but also by multiple individual mAbs to the**
52 **receptor-binding motif on RBD, largely due to an E484K mutation. Moreover,**
53 **B.1.351 is markedly more resistant to neutralization by convalescent plasma (9.4**
54 **fold) and vaccinee sera (10.3-12.4 fold). B.1.351 and emergent variants^{13,14} with**
55 **similar spike mutations present new challenges for mAb therapy and threaten the**
56 **protective efficacy of current vaccines.**

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58 Considerable SARS-CoV-2 evolution has occurred since its initial emergence, including
59 variants with a D614G mutation¹⁵ that have become dominant. Viruses with this mutation

60 alone do not appear to be antigenically distinct, however¹⁶. SARS-CoV-2 B.1.1.7, also
61 known as 501Y.V1 in the GR clade (Fig. 1a), emerged in September 2020 in South East
62 England and rapidly became the dominant variant in the UK, possibly due to its enhanced
63 transmissibility¹¹. This strain has now spread to over 50 countries, and there are
64 indications that it may be more virulent¹⁷. B.1.1.7 contains 8 spike mutations in addition
65 to D614G, including two deletions (69-70del & 144del) in NTD, one mutation (N501Y) in
66 RBD, and one mutation (P681H) near the furin cleavage site (Fig. 1b). SARS-CoV-2
67 B.1.351, also known as 501Y.V2 in the GH clade (Fig. 1a), emerged in late 2020 in
68 Eastern Cape, South Africa (SA)¹². This variant has since become dominant locally,
69 raising the specter that it too has enhanced transmissibility. B.1.351 contains 9 spike
70 mutations in addition to D614G, including a cluster of mutations (e.g., 242-244del &
71 R246I) in NTD, three mutations (K417N, E484K, & N501Y) in RBD, and one mutation
72 (A701V) near the furin cleavage site (Fig. 1b). There is a growing concern that these new
73 variants could impair the efficacy of current mAb therapies or vaccines, because many of
74 the mutations reside in the antigenic supersite in NTD^{18,19} or in the ACE2-binding site
75 (also known as the receptor-binding motif—RBM) that is a major target of potent virus-
76 neutralizing antibodies. We therefore addressed this concern by assessing the
77 susceptibility of authentic B.1.1.7 and B.1.351 viruses to neutralization by 30 mAbs, 20
78 convalescent plasma, and 22 vaccinee sera. In addition, we created VSV-based SARS-
79 CoV-2 pseudoviruses that contain each of the individual mutations as well as one with all
80 8 mutations of the B.1.1.7 variant (UKΔ8) and another with all 9 mutations of the B.1.351
81 variant (SAΔ9). A total of 18 mutant pseudoviruses were made as previously

82 described^{20,21}, and each was found to have a robust titer (Extended Data Fig. 1) adequate
83 for neutralization studies.

84

85 **Monoclonal antibodies**

86 We first assayed the neutralizing activity of 12 RBD mAbs against authentic B.1.1.7 and
87 B.1.351 viruses, as compared to the original SARS-CoV-2 strain (WT), in Vero E6 cells
88 as previously described^{20,21}. Three mAbs target the “inner side”, four target RBM, and
89 five target the “outer side”. The footprints of these mAbs on RBD are shown in Fig. 2a,
90 and their neutralization profiles are shown in Fig. 2b. For neutralization of B.1.1.7, only
91 the activities of 910-30²² and S309⁵ are significantly impaired. For neutralization of
92 B.1.351, however, the activities of 910-30, 2-15²⁰, LY-CoV555 (bamlanivimab)^{1,23},
93 C121²⁴, and REGN10933 (casirivimab)² are completely or markedly abolished. The four
94 mAbs that target RBM are among the most potent SARS-CoV-2-neutralizing antibodies
95 in clinical use or development. Note that mAbs directed to lower aspects of the “inner
96 side” (2-36²⁰ & COVA1-16^{25,26}) or to the “outer side” retain their activities against B.1.351,
97 including 2-7²⁰, REGN10987 (imdevimab)², C135²⁴, and S309 that are in clinical use or
98 development. The results on the neutralization of B.1.1.7 and B.1.351 by these 12 mAbs
99 are summarized in Fig. 2c as fold increase or decrease in IC50 neutralization titers relative
100 to the WT. To understand the specific spike mutations responsible for the observed
101 changes, we also tested the same panel of mAbs against pseudoviruses UKΔ8 and SAΔ9,
102 as well as those containing only a single mutation found in B.1.1.7 or B.1.351. The results
103 are displayed, among others, in Extended Data Fig. 2 and summarized in Fig. 2c. There
104 is general agreement for results between B.1.1.7 and UKΔ8, as well as between B.1.351

105 and SA Δ 9. Against B.1.1.7, the decreased activity of 910-30 is mediated by N501Y,
106 whereas the slightly impaired activity of S309 is unexplained. Against B.1.351, the
107 complete loss of activity of 2-15, LY-CoV555, and C121 is mediated by E484K; the
108 complete loss for 910-30 is mediated by K417N; and the marked reduction for
109 REGN10933 is mediated by K417N and E484K, as has been reported²⁷. A structural
110 explanation on how E484K disrupts the binding of 2-15, LY-CoV555, and REGN10933 is
111 presented in Extended Data Fig. 3a.

112

113 We also assessed the neutralizing activity of six NTD mAbs against B.1.1.7, B.1.351, and
114 WT viruses. Both B.1.1.7 and B.1.351 are profoundly resistant to neutralization by our
115 antibodies 5-24 and 4-8²⁰, as well as by 4A8²⁸, all of which target the antigenic supersite
116 in NTD¹⁸ (Insert in Fig. 2d). The activities of 2-17, 4-19, and 5-7²⁰ are variably impaired,
117 particularly against B.1.351. To understand the specific mutations responsible for the
118 observed changes, we then tested these mAbs against pseudoviruses containing only a
119 single mutation found in B.1.1.7 or B.1.351 (Extended Data Fig. 2). The results are
120 summarized in Fig. 2c as fold increase or decrease relative to the WT (D614G). It is
121 evident that the resistance of B.1.1.7 to most NTD mAbs is largely conferred by 144del,
122 whereas the resistance of B.1.351 is largely conferred by 242-244del and/or R246I.
123 Amino-acid residues 144, 242-244, and 246 all fall within the NTD supersite^{18,19} (Insert in
124 Fig. 2d; details in Extended Data Fig. 3b).

125

126 We next tested the neutralizing activity of 12 additional RBD mAbs, including ones from
127 our own collection (1-20, 4-20, 2-4, 2-43, 2-30, & 2-38)²⁰ as well as CB6 (etesevimab)^{3,6},

128 COV2-2196 & COV2-2130⁷, Brii-196 & Brii-198⁴, and REGN10985. The results against
129 B.1.1.7, B.1.351, and WT are highlighted in Extended Data Fig. 4a, and the detailed
130 findings against the single-mutation pseudoviruses are shown in Extended Data Fig. 2.
131 The fold changes in neutralization IC50 titers relative to the WT are tabulated in Extended
132 Data Fig. 4b. Here, we only comment on results for mAbs in clinical development. The
133 activity of CB6 is rendered inactive against B.1.351 because of K417N. Brii-196 and
134 COV2-2130 are essentially unaffected by the new variants; the activities of Brii-198 and
135 COV2-2196 are diminished 14.6 fold and 6.3 fold, respectively, against B.1.351 but not
136 against B.1.1.7.

137

138 Lastly, we examined, in a single experiment, the neutralizing activity of mAb therapies in
139 clinical use or under clinical investigation against B.1.1.7, B.1.351, and WT viruses, as
140 well as against UKΔ8, SAΔ9, and WT pseudoviruses. The results for single mAb LY-
141 CoV555 and S309, as well as for combination regimens REGN10933+REGN10987, LY-
142 CoV555+CB6, Brii-196+Brii-198, and COV2-2196+COV2-2130, are shown in Extended
143 Data Fig. 5 and summarized in Fig. 2e. Note that LY-CoV555, alone or in combination
144 with CB6, is no longer able to neutralize B.1.351. While REGN10933+REGN10987 and
145 COV2-2196+COV2-2130 are seemingly unaffected against variant pseudoviruses, there
146 are noticeable decreases in their activity against B.1.351 authentic virus. Although S309
147 and the Brii-196+Brii-198 combination are not significantly impaired, their potencies are
148 noticeably lower (Fig. 2e). These findings suggest that antibody treatment of this virus
149 might need to be modified in localities where B.1.351 and related variants^{13,14} are

150 prevalent, and highlight the importance of combination antibody therapy to address the
151 expanding antigenic diversity of SARS-CoV-2.

152

153 **Convalescent plasma**

154 We obtained convalescent plasma from 20 patients more than one month after
155 documented SARS-CoV-2 infection in the Spring of 2020. Each plasma sample was then
156 assayed for neutralization against B.1.1.7, B.1.351, and WT viruses. Fig. 3a shows that
157 most (16 of 20) plasma samples lost >2.5-fold neutralizing activity against B.1.351, while
158 maintaining activity against B.1.1.7. Only plasma from P7, P10, P18, and P20 retain
159 neutralizing activities similar to those against the WT. These results are summarized as
160 fold increase or decrease in plasma neutralization IC50 titers in Fig. 3b. Furthermore, the
161 magnitude of the drop in plasma neutralization is better seen in Fig. 3c, showing no loss
162 of activity against B.1.1.7 but substantial loss against B.1.351 (9.4 fold).

163

164 Every plasma sample was also tested against each mutant pseudovirus, and those
165 findings are shown in Extended Data Fig. 6 and summarized in Figs. 3b & 3c. Eight
166 samples show >2.5-fold decrease in neutralizing activity against UKΔ8, in contrast to the
167 results for B.1.1.7 neutralization. These discrepant results highlight our previous
168 observation²⁰ that pseudovirus neutralization does not always faithfully recapitulate live
169 virus neutralization. The loss of plasma neutralizing activity against B.1.351 could be
170 largely attributed to E484K (Fig. 3b), which has been shown to attenuate the neutralizing
171 activity of convalescent sera²⁹. Our findings here suggests that this RBM mutation is
172 situated in an immunodominant epitope for most infected persons. It is also interesting

173 to note that cases such as P7, P10, and P18 have neutralizing antibodies that are
174 essentially unperturbed by the multitude of spike mutations found in these two new
175 variants (Fig. 3b). A detailed analysis of their antibody repertoire against the viral spike
176 could be informative.

177

178 **Vaccinee Sera**

179 Sera were obtained from 12 participants of a Phase 1 clinical trial of Moderna SARS-Co-
180 2 mRNA-1273 Vaccine⁹ conducted at the NIH. These volunteers received two
181 immunizations with the vaccine (100 µg) on days 0 and 28, and blood was collected on
182 day 43. Additional vaccinee sera were obtained from 10 individuals who received the
183 Pfizer BNT162b2 Covid-19 Vaccine¹⁰ under emergency use authorization at the clinical
184 dose on days 0 and 21. Blood was collected on day 28 or later.

185

186 Each vaccinee serum sample was assayed for neutralization against B.1.1.7, B.1.351,
187 and WT viruses. Fig. 4a shows no loss of neutralizing activity against B.1.1.7, whereas
188 every sample lost activity against B.1.351. These results are quantified and tabulated as
189 fold increase or decrease in neutralization IC50 titers in Fig. 4b, and the extent of the
190 decline in neutralization activity is more evident in Fig. 4c. Overall, the neutralizing activity
191 against B.1.1.7 was essentially unchanged, but significantly lower against B.1.351 (12.4
192 fold, Moderna; 10.3 fold, Pfizer).

193

194 Every vaccinee serum was also tested against each mutant pseudovirus, and the results
195 are presented in Extended Data Fig. 7 and summarized in Figs. 4b & 4c. No single

196 mutation in B.1.1.7 has an appreciable impact on the neutralizing activity of vaccinee
197 sera. The loss of neutralizing activity against SAΔ9 is largely consistent with the loss in
198 B.1.351 live virus neutralization. A major contributor to the neutralization resistance of
199 this variant virus appears to be E484K (Fig. 4b), indicating that this RBM mutation is
200 situated in an immunodominant epitope recognized by all vaccinees studied.

201

202 **Discussion**

203 Both SARS-CoV-2 variants B.1.1.7 and B.1.351 are raising concerns not only because of
204 their increase transmissibility but also because of their extensive mutations in spike that
205 could lead to antigenic changes detrimental to mAb therapies and vaccine protection. It
206 is of equal concern that another variant known as P.1 or 501Y.V3 is increasing rapidly in
207 Brazil and spreading far beyond^{13,14}. P.1 contains three mutations (K417T, E484K, and
208 N501Y) at the same RBD residues as B.1.351. Much of our findings on B.1.351 would
209 likely be similar for this emergent variant. N501Y is shared among viruses in these three
210 lineages; while this mutation may confer enhanced binding to ACE2³⁰, its antigenic impact
211 is limited to a few mAbs (Fig. 2c & Extended Data Fig. 4b), with no pronounced effects
212 on the neutralizing activity of convalescent plasma or vaccinee sera (Figs. 3b & 4b), as
213 others are reporting³¹⁻³³.

214

215 Our findings have relevance to the use of mAb to treat or prevent SARS-CoV-2. Both
216 B.1.1.7 and B.1.351 are resistant to neutralization by mAbs directed to the NTD supersite
217 (Figs. 2c, 2d, & Extended Data Fig. 3b). More importantly, B.1.351 is resistant to a major
218 group of potent mAbs that target the RBM, including three regimens authorized for

219 emergency use (Fig. 2c). LY-CoV555 alone and in combination with CB6 are inactive
220 against B.1.351, and the activity of REGN10933 is impaired (Fig. 2b) while its combination
221 with REGN10987 retains much of the activity (Fig. 2e). Several other mAbs in
222 development are similarly impaired (Figs. 2c, 2e, & Extended Data Fig. 4b) against this
223 variant. Decisions on the use of these mAbs will depend heavily on the local prevalence
224 of B.1.351 or variants with an E484K mutation, thus highlighting the importance of viral
225 genomic surveillance worldwide and proactive development of next-generation antibody
226 therapeutics, including combinations that target antigenically distinct epitopes.

227

228 Convalescent plasma from patients infected with SARS-CoV-2 from early in the pandemic
229 show no significant change in neutralizing activity against B.1.1.7, but the diminution
230 against B.1.351 is remarkable (Figs. 3b &3c). This relative resistance is largely due to
231 E484K, a mutation shared by B.1.351 and P.1¹²⁻¹⁴. Again, in areas where such viruses
232 are common, one would have a concern about re-infection, as other studies are also
233 suggesting^{34,35}. This apprehension is heightened by the recent observation from the
234 Novavax vaccine trial in South Africa that placebo recipients with prior SARS-CoV-2
235 infection were not protected against a subsequent exposure to B.1.351^{36,37}. Even more
236 disturbing is the situation in Manaus, Brazil where a second wave of infection due to P.1
237 is sweeping through a population that was already 76% seropositive due to prior infection
238 in the Spring of 2020³⁸.

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240 As for the ramifications of our findings for the protective efficacy of current SARS-CoV-2
241 vaccines, the neutralizing activity of vaccinee sera against B.1.1.7 is largely intact and no

242 adverse impact on current vaccines is expected (Fig. 4c), consistent with conclusions
243 being reached by others^{33,39,40}. On the other hand, the loss of 10.3-12.4 fold in activity
244 against B.1.351 is larger than results being reported using mutant pseudoviruses^{33,41,42}
245 or live virus⁴³. Taken together, the overall findings are worrisome, particularly in light of
246 recent reports that both Novavax and Johnson & Johnson vaccines showed a substantial
247 drop in efficacy in South Africa^{36,37,44}.

248

249 The recent emergence of B.1.1.7, B.1.351, and P.1 marks the beginning of SARS-CoV-
250 2 antigenic drift. This conclusion is supported by data presented herein, illustrating how
251 so many of these spike changes conferred resistance to antibody neutralization, and by
252 studies reporting similar spike mutations selected by antibody pressure in vitro or in vivo⁴⁵⁻
253 ⁴⁹. Mutationally, this virus is traveling in a direction that could ultimately lead to escape
254 from our current therapeutic and prophylactic interventions directed to the viral spike. If
255 the rampant spread of the virus continues and more critical mutations accumulate, then
256 we may be condemned to chasing after the evolving SARS-CoV-2 continually, as we have
257 long done for influenza virus. Such considerations require that we stop virus transmission
258 as quickly as is feasible, by redoubling our mitigation measures and by expediting vaccine
259 rollout.

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383 **Figure legends**

384 **Fig. 1 | Emerging SARS-CoV-2 variants identified in the United Kingdom and South**
385 **Africa. a,** Phylogenetic tree of SARS-CoV-2 variants, with B.1.351 and B.1.1.7
386 highlighted. **b,** Mutations in the viral spike identified in B.1.351 (SA) and B.1.1.7 (UK) in
387 addition to D614G.

388

389 **Fig. 2 | Susceptibility of B.1.1.7 and B.1.351 to neutralization by mAbs. a,** Footprints
390 of neutralizing mAbs on the RBD. Left panel, top view of SARS-CoV-2 spike with one
391 RBD in the “up” conformation (pdb: 6zgg). RBD and NTD are colored green and peach,
392 respectively. The positions of ‘inner’ and ‘outer’ sides are indicated on the “up” RBD with
393 the ACE2-binding site colored yellow. The three panels to the right show the antibody
394 footprints on RBD. **b,** Neutralization of B.1.1.7, B.1.351, and WT viruses by select RBD
395 mAbs. **c,** Fold increase or decrease in IC50 of neutralizing mAbs against B.1.1.7 and
396 B.1.351, as well as UKΔ8, SAΔ9, and single-mutation pseudoviruses, relative to WT,
397 presented as a heatmap with darker colors implying greater change. MPI↓ denotes that
398 maximum percent inhibition is substantially reduced, confounding IC50 calculations. **d,**
399 Neutralization of B.1.1.7, B.1.351, and WT viruses by NTD-directed mAbs, the footprints
400 of which are delineated by the color tracings in the insert. **e,** Changes in neutralization
401 IC50 of authorized or investigational therapeutic mAbs against B.1.1.7, B.1.351, WT
402 (WA1) viruses as well as UKΔ8, SAΔ9, and WT (D614G) pseudoviruses. Data in **b** and **d**
403 are mean ± SEM of technical triplicates, and represent one of two independent
404 experiments.

405

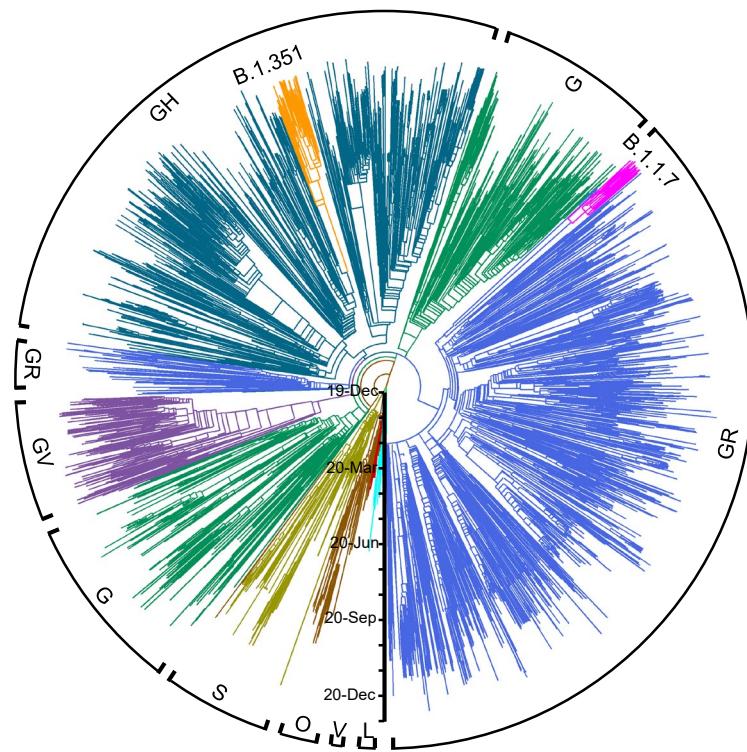
406 **Fig. 3 | B.1.351 is more resistant to neutralization by convalescent plasma from**
407 **patients. a,** Neutralization results for 20 convalescent plasma samples (P1-P20) against
408 B.1.1.7, B.1.351, and WT viruses. Data represent mean \pm SEM of technical triplicates. **b,**
409 Fold increase or decrease in neutralization IC50 of B.1.1.7 and B.1.351, as well as UK Δ 8,
410 SA Δ 9, and single-mutation pseudoviruses, relative to the WT presented as a heatmap
411 with darker colors implying greater change. **c,** Change in reciprocal plasma neutralization
412 IC50 values of convalescent plasma against B.1.1.7 and B.1.351, as well as UK Δ 8 and
413 SA Δ 9, relative to the WT. Mean fold changes in IC50 values relative to the WT are written
414 above the *p* values. Statistical analysis was performed using a Wilcoxon matched-pairs
415 signed rank test. Two-tailed p-values are reported.

416

417 **Fig. 4 | B.1.351 is more resistant to neutralization by vaccinee sera. a,**
418 Neutralization profiles for 22 serum samples obtained from persons who received SARS-
419 CoV-2 vaccine made by Moderna (V1-V12) or Pfizer (V13-V22) against B.1.1.7, B.1.351,
420 and WT viruses. Data are mean \pm SEM of technical triplicates, and represent one of two
421 independent experiments. **b,** Fold change in serum neutralization IC50 of B.1.1.7 and
422 B.1.351, as well as UK Δ 8, SA Δ 9, and single-mutation pseudoviruses, relative to the WT,
423 presented as a heatmap with darker colors implying greater change. **c,** Change in
424 reciprocal serum IC50 values for Moderna and Pfizer vaccinees against B.1.1.7 and
425 B.1.351, as well as UK Δ 8 and SA Δ 9, relative to the WT. Mean fold change in IC50 relative
426 to the WT is written above the *p* values. Statistical analysis was performed using a
427 Wilcoxon matched-pairs signed rank test. Two-tailed p-values are reported.

Fig. 1

a



b

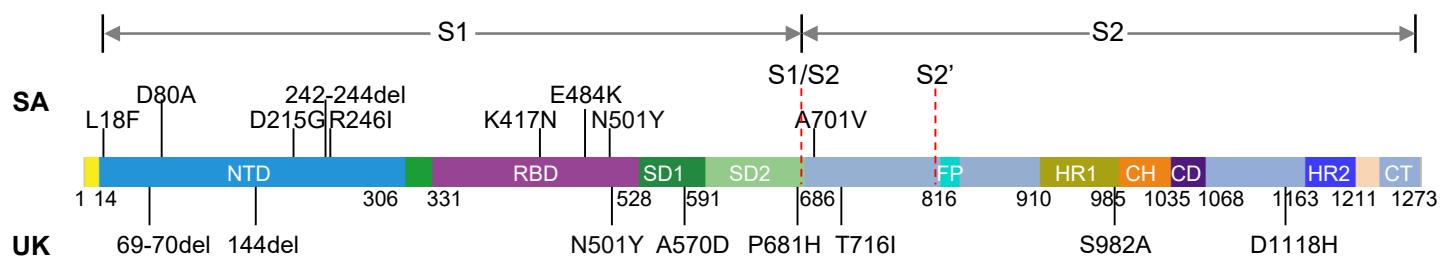
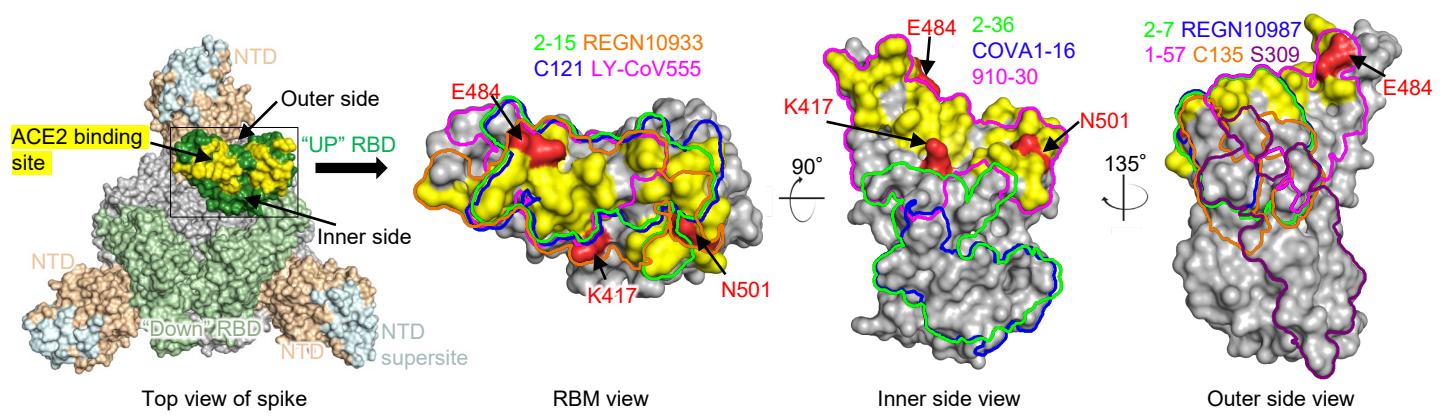
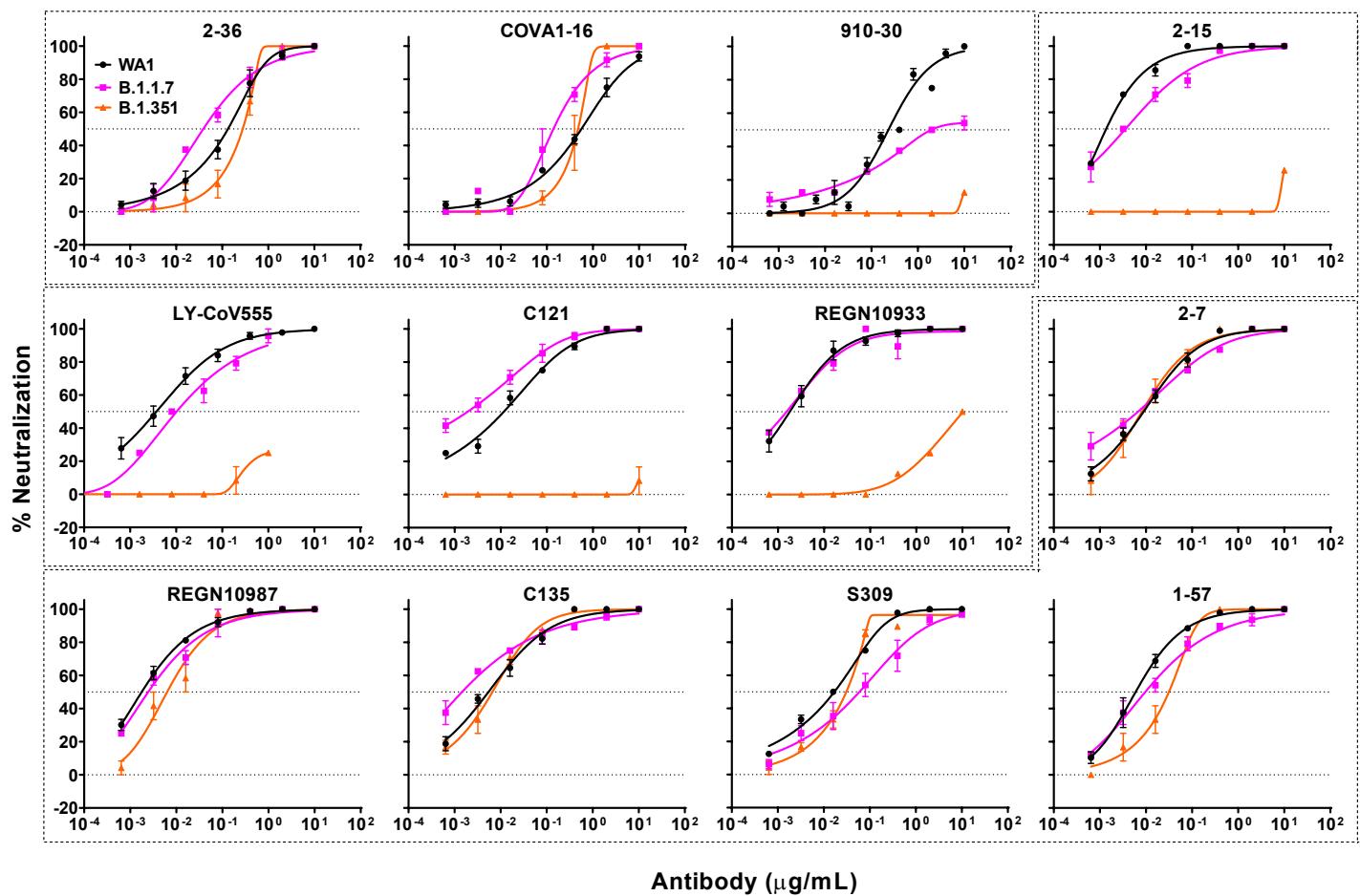


Fig. 2

a



b



C

Fold Change of IC50 from WT	RBD-directed mAbs												NTD-directed mAbs						
	Inner side			RBM				Outer side					Supersite			Others			
	2-36	COVA1-16	910-30	2-15	LY-CoV555	C121	REGN10933	2-7	REGN10987	C135	S309	1-57	5-24	4-8	4A8	2-17	4-19	5-7	
UK	B.1.1.7	3.4	3.4	-10.3	-3.0	-2.8	4.0	1.0	1.5	1.0	3.0	-4.0	-1.5	-330.2	<-1000	<-1000	-42.6	-29.2	-7.5
	UKΔ8	1.2	1.3	-14.0	2.2	1.7	2.3	2.5	1.4	2.1	-1.4	-3.1	2.1	<-1000	<-1000	<-1000	-121.2	-20.5	-11.9
	69-70del	-1.0	1.1	2.7	1.2	1.1	1.7	1.3	-1.2	1.2	1.8	-1.6	1.1	1.1	1.1	1.5	-1.1	-3.6	-4.0
	144del	1.5	-1.3	2.3	1.3	1.1	1.7	1.3	1.2	-1.4	1.4	1.4	1.1	<-1000	<-1000	<-1000	-80.7	1.6	-3.7
	N501Y	-1.2	-1.4	-12.7	1.5	-1.0	1.5	-1.4	-1.0	1.3	1.2	1.2	3.6	-2.9	-6.7	MPI↓	-12.0	-1.4	-3.2
	A570D	4.1	1.9	6.7	1.4	1.7	1.7	4.7	-2.3	-1.6	1.1	-1.2	2.2	1.1	-15.1	-2.9	-4.8	-1.9	-2.2
	P681H	2.0	1.5	2.5	3.1	2.3	-1.0	1.6	-1.4	-1.9	1.3	-1.2	2.9	-1.5	-2.8	1.1	-4.7	-1.2	1.8
	T716I	4.3	3.9	3.9	3.1	3.5	2.0	3.6	-1.1	-1.6	1.2	-1.6	2.9	-3.5	-5.5	MPI↓	-2.6	1.2	-1.0
	S982A	-3.9	-3.0	-2.4	1.1	-2.0	1.4	-2.3	-2.2	-1.2	1.6	-1.0	-1.5	-1.1	-1.1	-2.9	-4.3	1.2	-1.3
	D1118H	-1.1	-3.1	1.0	1.2	1.0	1.7	-1.3	-1.4	-1.7	1.2	1.5	1.1	-1.3	-3.1	1.4	-1.1	-1.1	-1.8
SA	B.1.351	-2.1	1.0	-456.6	<-1000	<-1000	<-1000	<-1000	1.1	-3.5	1.0	-2.2	-5.2	<-1000	<-1000	<-1000	-456.4	-595.2	-84.8
	SAΔ9	-2.0	1.3	<-1000	<-1000	<-1000	<-1000	-58.8	1.3	1.8	1.2	1.3	3.3	<-1000	<-1000	<-1000	-406.6	<-1000	-18.1
	L18F	1.5	1.9	2.8	3.0	1.0	1.8	1.4	-1.4	-1.8	1.1	1.2	-1.6	-2.2	1.3	MPI↓	-107.2	<-1000	-8.9
	D80A	-1.4	1.2	2.1	2.0	1.5	2.0	1.4	-2.2	-2.2	1.0	2.2	-2.7	2.3	2.0	-1.0	-2.0	<-1000	-9.8
	D215G	1.9	1.6	1.5	1.8	1.5	2.1	1.5	-1.8	-2.1	-1.2	1.0	2.2	-1.1	-1.8	-2.3	-6.0	1.1	1.1
	242-244del	-1.4	1.2	-1.2	1.4	-1.1	1.1	1.0	-1.2	-3.2	1.8	1.2	-1.3	<-1000	<-1000	<-1000	<-1000	<-1000	-20.7
	R246I	1.3	1.7	2.2	2.4	1.4	2.1	2.2	1.4	-2.1	1.1	2.3	1.7	<-1000	<-1000	<-1000	-2.8	<-1000	-9.2
	K417N	3.2	3.3	<-1000	3.3	8.4	1.2	-13.1	2.1	-1.2	2.9	1.6	7.8	2.9	-1.6	1.7	-1.5	1.2	-1.2
	E484K	-1.2	-1.0	4.3	<-1000	<-1000	<-1000	-10.5	-3.4	-1.1	2.3	2.5	-1.1	-1.6	-3.2	MPI↓	-2.8	-1.1	-1.4
	N501Y	-1.2	-1.4	-12.7	1.5	-1.0	1.5	-1.4	-1.0	1.3	1.2	1.2	3.6	-2.9	-6.7	MPI↓	-12.0	-1.4	-3.2
	A701V	1.9	1.4	2.1	2.8	2.0	1.6	2.3	-1.8	-2.6	1.5	1.1	2.5	-3.3	-2.0	MPI↓	-3.3	-1.2	-1.3

Red: resistance >3 fold; Green: sensitization >3 fold

d

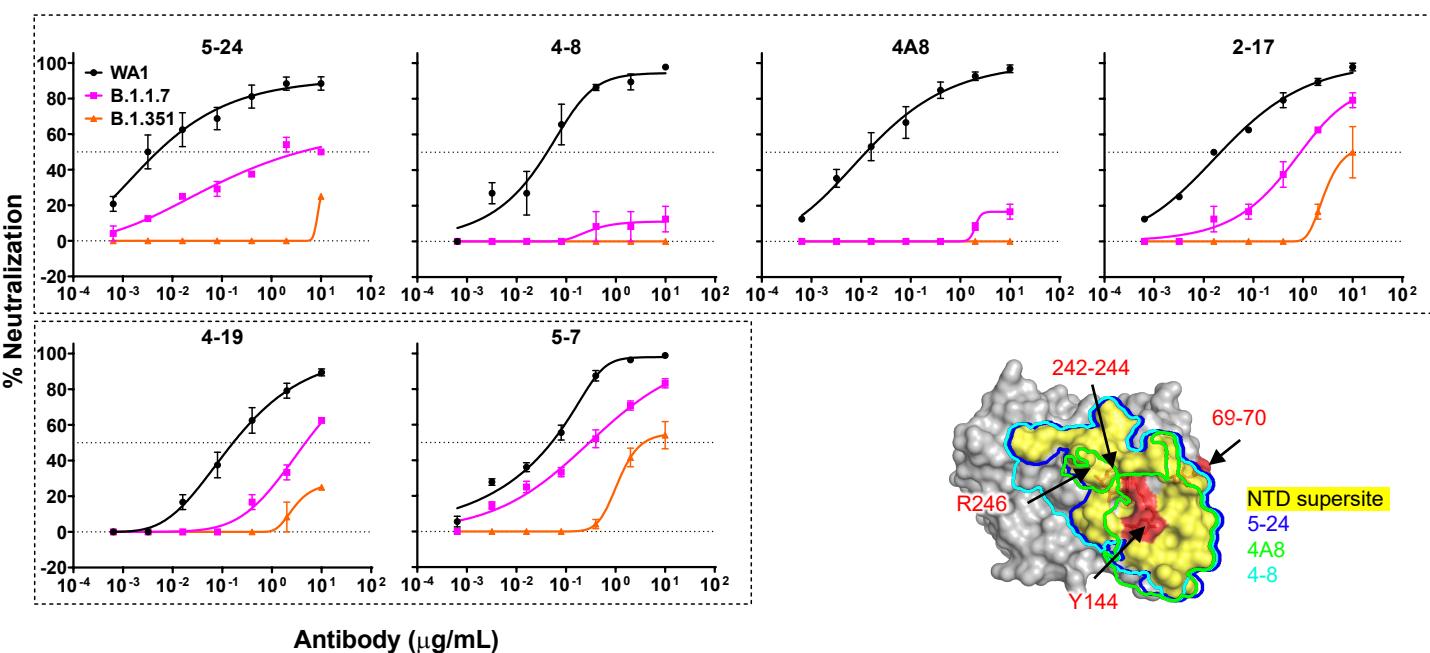


Fig. 2

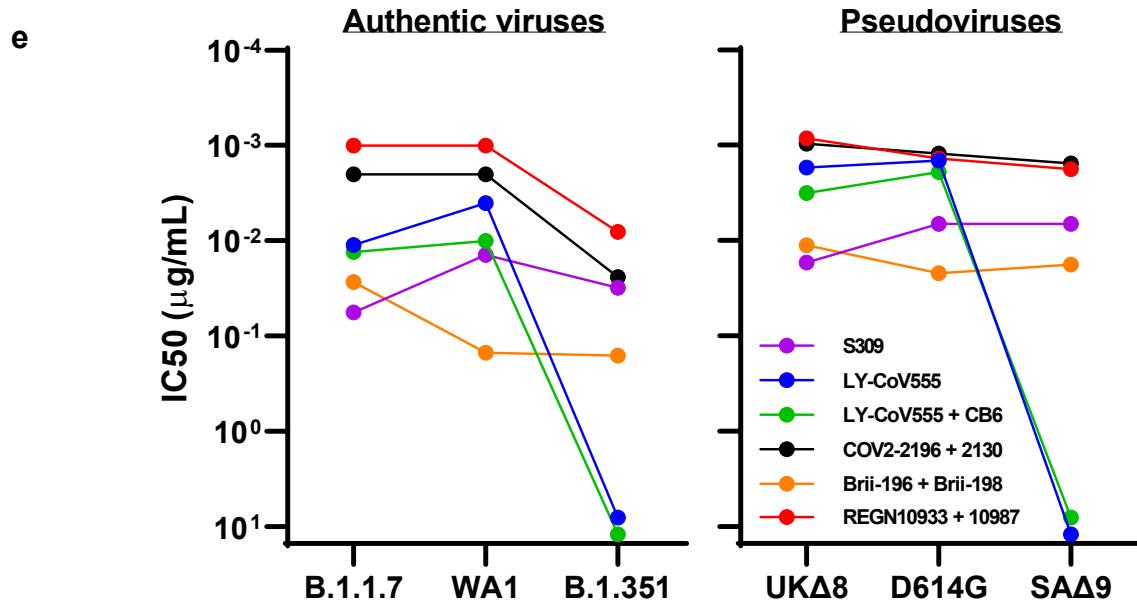
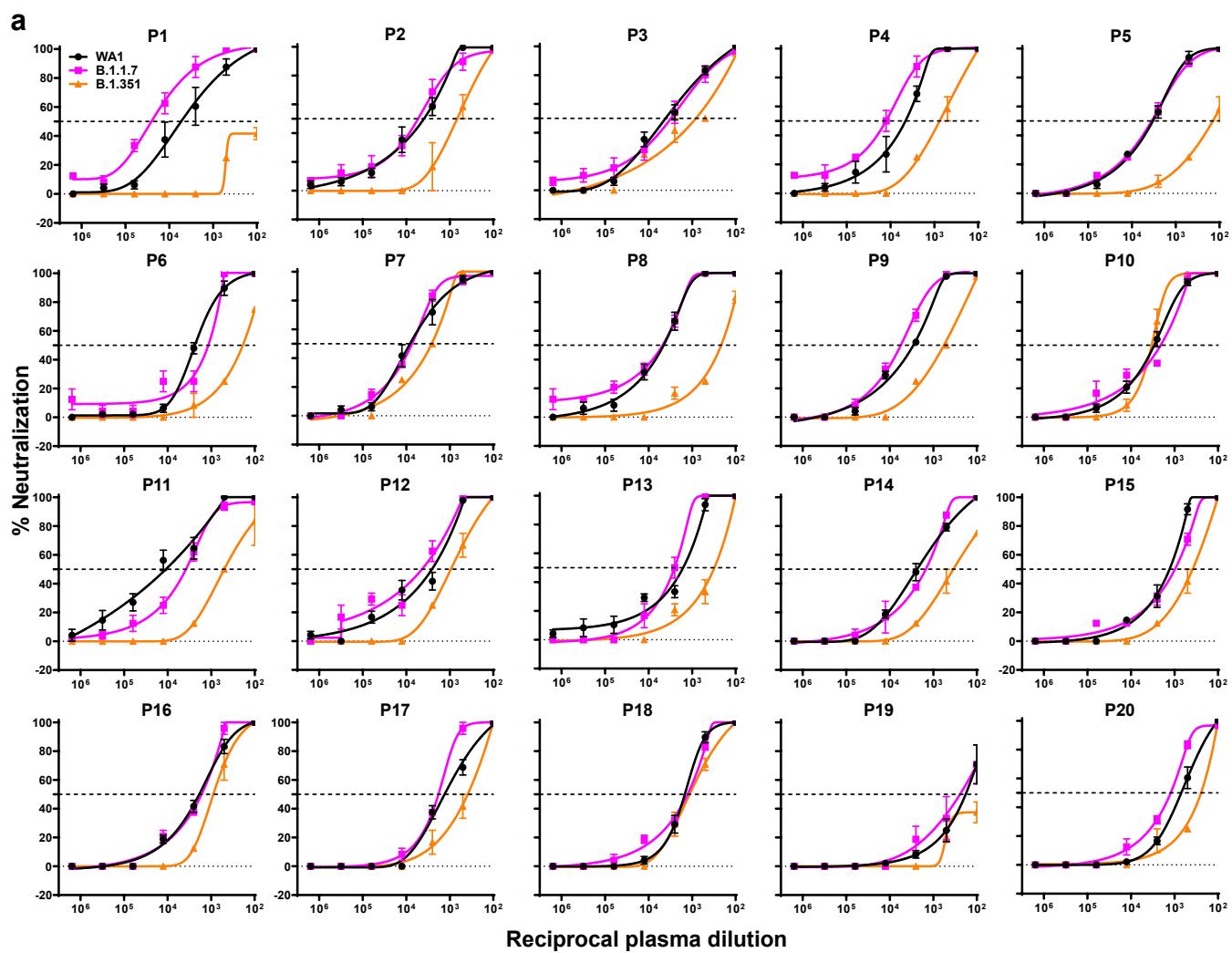


Fig. 3



b

Fold change of IC50 from WT		Convalescent plasma																			
		P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20
UK	B.1.1.7	4.8	1.4	-1.3	2.8	1.1	-2.0	-1.1	1.1	1.9	-1.4	-2.9	1.7	1.6	-1.6	-1.3	-1.1	1.4	-1.2	1.4	1.7
	UKΔ8	-4.4	-6.2	-2.0	-4.6	-2.6	-16.7	1.3	-2.7	1.7	-1.4	-2.5	-4.2	-4.7	-1.9	-2.2	1.8	-1.8	-1.2	-2.3	-1.5
	69-70del	-1.9	-1.8	2.3	1.8	-1.8	-1.5	1.4	-1.3	1.2	1.6	-1.9	1.7	-2.0	1.5	1.2	-1.1	-1.8	1.0	-1.1	1.2
	144del	1.3	2.8	1.4	2.6	-1.4	-4.5	-1.1	-1.5	1.0	-1.1	-4.5	-1.1	-2.2	-1.4	1.1	-1.6	-2.0	-1.5	-2.0	-1.4
	N501Y	-1.6	-2.3	1.9	1.0	-1.1	-3.6	1.0	-2.4	1.5	1.2	-2.0	-2.1	-3.1	-1.3	-1.7	-1.3	-1.5	1.0	-1.3	1.4
	A570D	1.0	4.3	1.9	5.1	-1.1	-3.2	1.4	-1.6	1.5	1.4	-2.7	1.4	-3.1	1.1	-1.1	-1.1	-1.2	-1.1	-1.0	-1.0
	P681H	-1.8	-1.5	-1.6	1.1	-1.9	-2.3	1.0	-1.7	1.0	1.3	-2.6	-1.5	-4.1	1.1	-1.4	-1.3	-1.8	-1.3	-1.9	1.0
	T716I	-1.1	1.3	1.9	1.9	1.6	-3.7	-1.4	-2.5	-1.1	-1.0	-2.8	-1.4	-6.4	1.0	-2.0	-1.9	-2.3	-2.0	-1.8	-1.4
	S982A	-5.0	-9.3	1.2	-1.5	-2.5	-2.8	1.0	-3.0	1.2	1.1	-2.2	-2.7	-3.7	-1.4	-1.4	-1.1	-2.0	1.2	-2.4	-1.7
	D1118H	-2.1	-1.9	2.0	1.1	-1.5	-2.6	1.0	-3.1	1.2	-1.1	-2.6	-1.4	-3.0	1.0	-1.7	-1.3	-1.7	-1.1	-1.5	1.0
SA	B.1.351	-53.3	-5.8	-5.0	-6.1	-23.4	-12.5	-3.2	-20.9	-5.1	1.1	-21.9	-2.7	-5.2	-6.8	-3.4	-2.1	-3.4	-1.3	-1.8	-2.9
	SAΔ9	-260.6	-5.1	-4.1	-11.1	-22.8	-40.4	1.6	-21.4	-15.5	-1.4	-8.7	-5.2	-9.3	-12.5	-7.7	-4.0	-3.9	1.0	-3.7	-1.6
	L18F	-1.2	1.0	1.9	3.0	-1.9	1.7	1.5	-1.1	1.5	1.1	1.9	-1.1	-1.5	1.3	-1.2	2.1	1.3	-1.1	1.8	1.0
	D80A	1.0	-2.3	-1.4	-1.0	-1.5	-2.8	1.8	-2.3	2.2	1.5	-1.8	1.0	-2.0	2.2	-1.3	2.0	1.4	4.2	-1.2	1.3
	D215G	-1.9	-2.3	1.0	1.3	-1.8	-4.4	1.1	-3.1	1.3	-1.5	-3.3	-2.2	-4.5	-2.4	-2.6	-1.4	-2.9	-1.6	-2.3	-2.0
	242-244del	-1.1	-2.6	-2.0	-1.5	2.1	-9.3	-1.3	-4.6	2.3	2.4	-2.2	-2.6	-6.8	-1.3	-3.0	-1.2	-3.1	-2.6	-2.1	-1.5
	R246I	1.4	-1.2	1.3	1.3	-1.8	-4.0	-1.4	-1.1	1.1	1.3	-4.9	-1.1	-2.1	-1.0	-1.2	-1.3	-1.8	-1.1	-1.8	1.5
	K417N	-1.3	1.4	6.6	2.5	-1.1	-2.0	1.8	1.0	1.8	1.2	-1.6	-1.4	-2.1	1.8	-1.2	1.3	-1.1	1.2	-1.2	1.5
	E484K	-25.4	-4.7	-1.3	-2.6	-7.6	-9.6	-1.6	-10.8	-9.1	-1.3	-8.1	-3.5	-9.8	-2.3	-6.3	-4.3	-3.3	-1.5	-4.0	-3.5
	N501Y	-1.6	-2.3	1.9	1.0	-1.1	-3.6	1.0	-2.4	1.5	1.2	-2.0	-2.1	-3.1	-1.3	-1.7	-1.3	-1.5	-1.0	-1.3	1.4
	A701V	-1.3	-3.8	-1.1	-1.2	-1.9	-2.3	-1.0	-2.1	1.4	1.1	-2.9	-1.5	-2.3	-1.1	-1.8	-1.7	-1.7	-1.7	-1.9	-1.1

Red: resistance >2.5 fold; Green: sensitization >2.5 fold

Fig. 3

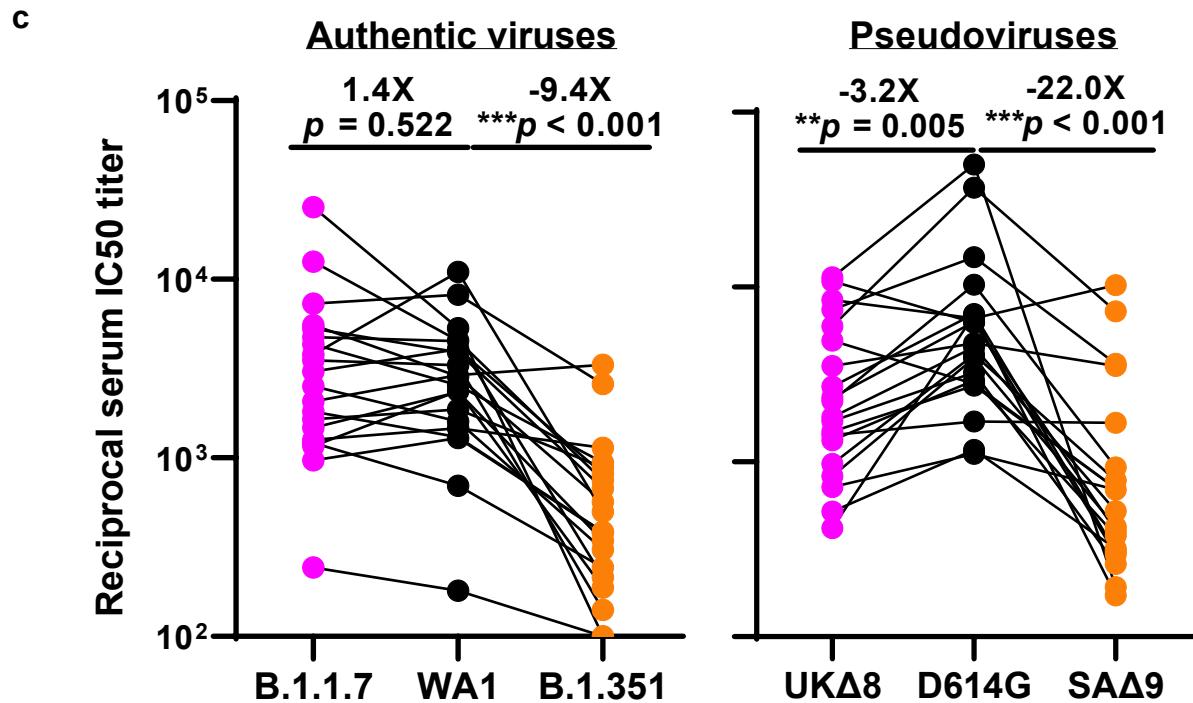
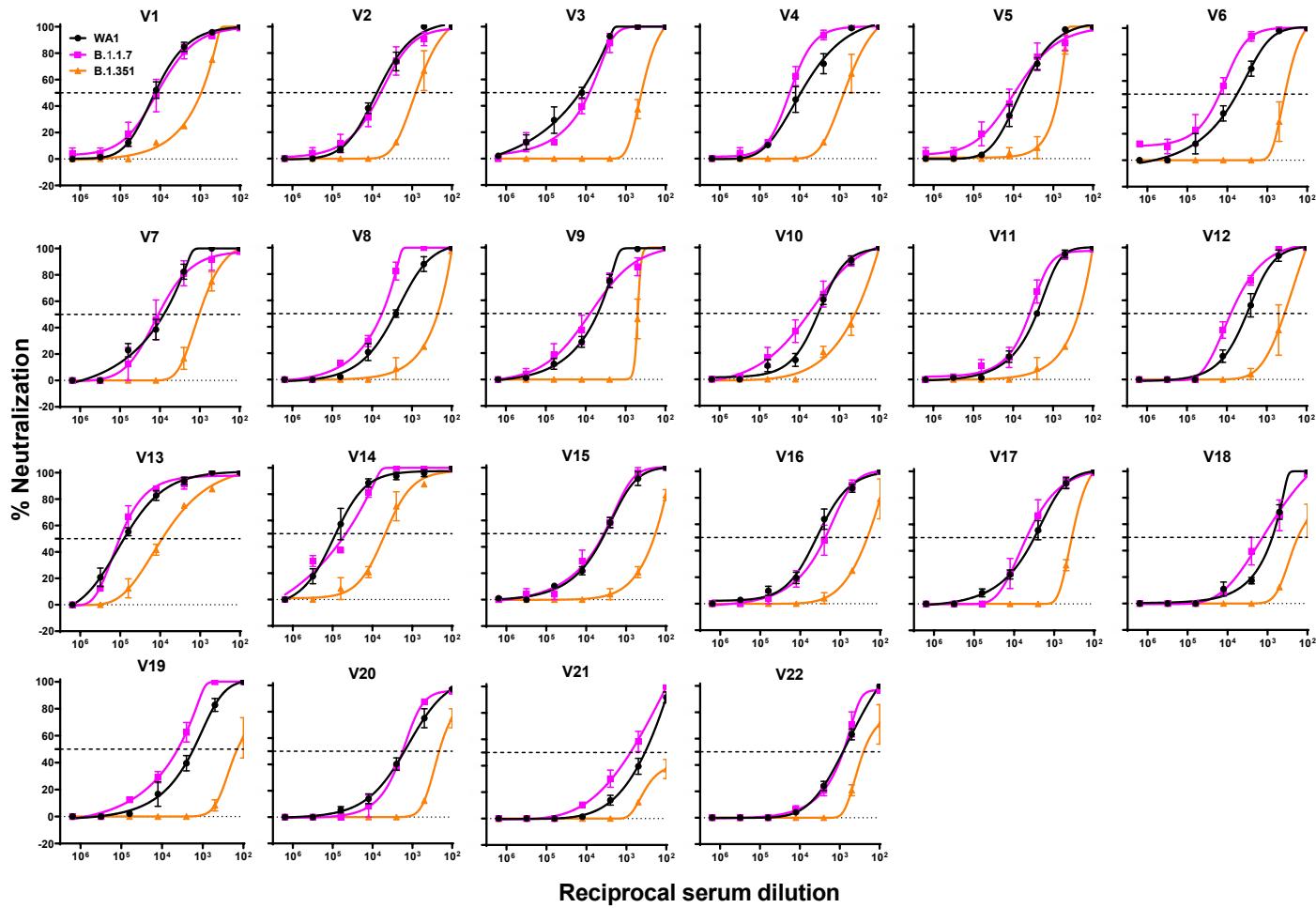


Fig. 4

a



Reciprocal serum dilution

b

Fold change of IC50 from WT		Moderna vaccinee sera												Pfizer vaccinee sera											
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22		
UK	B.1.1.7	-1.1	-1.2	-1.7	1.9	1.5	2.7	1.4	2.1	1.5	1.7	1.5	2.5	1.3	-1.8	1.1	-1.7	1.6	1.7	2.4	1.1	2.3	-1.0		
	UKΔ8	-2.7	-2.2	-3.0	-1.2	-1.7	-1.9	-1.2	-1.9	-1.4	1.0	-1.2	-1.8	-1.6	-1.9	-2.1	-1.8	1.1	-2.4	-2.3	-3.2	-1.1	1.1		
	69-70del	1.4	1.4	-1.3	1.2	-1.3	-1.1	1.9	1.1	1.5	-1.4	1.3	1.3	-1.4	1.3	-1.0	-1.0	-1.5	-1.3	1.3	1.3	-1.4	2.1		
	144del	-1.1	-1.2	-1.4	2.1	-1.2	-1.2	-1.1	-1.2	-1.2	-1.1	1.1	-1.3	-1.2	-1.7	-1.2	-1.2	-1.3	1.1	-1.2	-1.6	1.1	-1.3		
	N501Y	1.5	1.1	-1.8	1.6	-2.0	1.9	2.2	-2.0	-1.2	4.6	2.9	-1.2	-1.2	1.2	-2.1	-1.6	-1.6	-1.5	-1.1	-2.4	-1.4	1.0		
	A570D	1.4	2.2	1.2	2.4	1.7	1.6	2.2	1.5	1.0	1.5	1.4	1.6	1.2	1.5	1.5	2.6	1.2	1.3	1.8	1.1	-1.2	1.4		
	P681H	2.2	1.2	-1.7	-1.5	-1.5	1.0	1.1	-1.4	1.0	-1.1	1.1	1.1	1.2	1.2	-1.3	1.1	-1.1	-1.1	-1.0	-2.1	-1.3	-1.0		
	T716I	1.1	-1.1	-1.1	1.6	1.3	1.3	1.8	1.1	1.0	1.6	1.2	1.4	1.7	1.4	1.3	1.1	1.1	1.3	1.1	1.6	1.1	1.1		
	S982A	-2.3	-1.5	-2.6	-1.8	-2.0	-1.6	-1.3	-2.5	-1.7	-1.5	-1.5	-1.5	-1.2	-1.6	-1.6	-1.7	-1.5	-1.9	-1.6	-2.4	-2.0	-1.3		
	D1118H	-1.2	1.1	-1.2	-1.4	1.1	1.0	1.0	-1.5	-1.2	-1.1	1.0	1.1	-1.2	-1.2	-1.6	-1.6	-1.2	-1.5	-1.2	-1.3	-1.7	-1.3		
SA	B.1.351	-14.4	-9.4	-28.8	-12.1	-8.7	-17.0	-7.7	-11.6	-10.2	-8.4	-11.1	-8.8	-9.0	-17.5	-18.4	-18.5	-9.3	-4.3	-11.9	-7.4	<-3.4	-3.7		
	SAA9	-6.9	-8.4	-22.7	-11.0	-6.1	-7.7	-2.9	-10.0	-4.8	-3.2	-13.0	-6.6	-3.0	-2.2	-9.2	-3.5	-2.5	-7.5	-10.4	-4.5	<-4.5	-2.5		
	L18F	1.9	1.0	-1.8	-1.1	-1.3	1.0	3.3	-1.5	1.0	1.2	1.8	1.0	1.2	-1.3	1.2	1.2	1.0	-1.4	1.4	-1.4	-1.5	1.4		
	D80A	1.2	1.5	-1.1	2.1	1.1	1.5	1.8	-1.5	1.4	3.0	1.3	1.1	1.8	1.0	1.2	1.4	-1.5	-1.8	1.0	-1.8	-1.3	1.1		
	D215G	-1.3	1.1	1.1	-1.2	1.3	1.2	-1.1	-2.9	-1.1	2.7	1.1	-1.3	-1.1	1.1	-1.8	-2.0	-1.2	-1.8	-1.3	1.0	-1.2	1.1		
	242-244del	-3.6	1.0	-1.3	-1.8	-1.7	-1.3	-1.7	-1.7	-1.4	-1.5	-1.6	-1.6	-1.4	-1.9	-1.4	-1.3	1.5	1.1	-1.3	-2.6	-1.6	-1.8		
	R246I	-1.6	1.1	-2.0	-1.1	-1.7	-1.2	1.1	-2.1	-1.3	-1.1	1.0	-1.7	-1.5	-1.2	1.6	1.0	1.3	2.0	2.9	-4.0	1.0	-1.1		
	K417N	1.6	1.4	-1.1	1.0	1.0	-1.2	1.7	-1.3	1.1	1.4	-1.3	1.5	1.4	1.8	1.2	1.4	-1.5	1.9	2.0	1.0	-1.8	1.6		
	E484K	-3.0	-2.3	-3.9	-4.0	-1.4	-2.8	-1.3	-3.3	-2.2	-2.6	-3.2	-1.8	-1.9	-2.7	-2.1	-1.6	-2.9	-11.3	-3.3	-3.2	-3.1	-1.8		
	N501Y	1.5	1.1	-1.8	1.6	-2.0	1.9	2.2	-2.0	-1.2	4.6	2.9	-1.2	-1.2	1.2	-2.1	-1.6	-1.5	-1.1	-2.4	-1.4	1.0			
	A701V	-1.1	-1.2	-1.9	-2.2	-1.7	-1.6	-1.4	-1.7	+1.2	1.1	2.1	-1.1	-1.2	-1.3	-1.2	-1.1	-2.1	-1.5	-1.4	1.1	-2.2	-1.5		

Red: resistance >2.5 fold; Green: sensitization >2.5 fold

Fig. 4

c

