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1 Research Note

2 **Long-term evolution of humoral immune response after SARS-CoV-2 infection**

3

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24 **Abstract**

25 **Objective**

26 We aimed to characterize the evolution of humoral immune response up to one year
27 after SARS-CoV-2 infection in health care workers (HCWs) during the first wave of
28 COVID-19 in Paris.

29 **Methods**

30 Serum samples from 92 HCWs were tested at month 0 (M0), M6 and M12 after
31 SARS-CoV-2 infection for IgG targeting the nucleocapsid (N), IgG targeting the
32 receptor-binding domain (RBD) of spike (S) protein, IgA targeting S, and anti-RBD
33 neutralizing antibodies. After M6, 46 HCWs received a single-dose of COVID-19
34 vaccine.

35 **Results**

36 We observed a significant decrease of all SARS-CoV-2 immunologic markers at M6
37 post-infection: median decreases were 0.26 log binding antibody units (BAU)/mL
38 (M0: 1.9 [interquartile range (IQR) 1.47 – 2.27]; M6: 1.64 [IQR: 1.22 – 1.92]) for anti-
39 RBD IgG, 4.10 (index) (M0: 4.94 [IQR: 2.72 – 6.82]; M6: 0.84 [IQR: 0.25 – 1.55]) for
40 anti-N IgG, 0.64 (index) (M0: 2.50 [IQR: 1.18 – 4.62]; M6: 1.86 [IQR: 0.85 – 3.54]) for
41 anti-S IgA, and 24.4% (M0: 66.4 [IQR: 39.7 – 82.5]; M6: 42.0 [IQR: 16.8 – 68.8])
42 inhibition activity for the RBD neutralizing antibodies. Between M6 and M12, anti-
43 RBD IgG level, anti-S IgA index, and anti-RBD neutralizing activity, significantly
44 increased among COVID-19 vaccinated HCWs, whereas they remained stable
45 among unvaccinated HCWs. Anti-N IgG index significantly decreased between M6
46 and M12 among both vaccinated (median: 0.73 [IQR: 0.23 – 1.11] at M6 and 0.52
47 [IQR: 0.20 – 0.73] at M12) and unvaccinated HCWs (median: 0.79 [IQR: 0.21 – 4.67]
48 at M6 and 0.34 [IQR: 0.24 – 2.78] at M12).

49 **Conclusion**

50 A steady decline in the anti-N IgG response was observed during the first year
51 following SARS-CoV-2 infection among HCWs, whereas the anti-RBD IgG and the
52 anti-S IgA responses remained stable and could be enhanced by COVID-19
53 vaccination.

54

55 **Keywords:** SARS-CoV-2, IgG, IgA, seroneutralization, vaccines

56

57 **Introduction**

58 During the beginning of the COVID-19 pandemic, the contamination risk of health
59 care workers (HCWs) by the SARS-CoV-2 was of major concern. The SEROCOV
60 multicenter cohort study conducted among 1062 frontline HCWs from 5 Parisian
61 hospitals reported a rate of SARS-CoV-2 infection of 14.6% at the end of the first
62 COVID-19 wave by detection of anti-nucleocapsid protein (N) IgG in HCW sera [1].
63 Several studies have shown that anti-SARS-CoV-2 IgG levels decreased after
64 infection throughout time and that COVID-19 vaccination led to a rise of antibodies
65 levels [2,3]. The present retrospective study aimed to characterize the evolution of
66 the humoral immune response among SARS-CoV-2-infected HCWs from the
67 SEROCOV study during the first year post-infection.

68

69 **Methods**

70 For the SEROCOV study, registered on ClinicalTrials.gov: NCT04304690 first
71 registered on 11/03/2020, and approved by the ethics committee (CPP Sud-Ouest et
72 Outre-Mer I, approval no. 2-20-023 id7257), HCWs from Pitié-Salpêtrière, Bichat,
73 Tenon, Trousseau and Saint-Antoine hospitals were included from March 16, 2020 to

74 April 24, 2020 for a 3-month follow-up. HCWs with a positive detection of SARS-CoV-
75 2 anti-N IgG in the serum at the end of the initial 3-month period were included in the
76 present study for an additional 9-month follow-up. Humoral immune responses were
77 evaluated at M0 (corresponding to the time of seroconversion), M6 and M12 (5-6 and
78 11-12 months after seroconversion, respectively). All participant signed an informed
79 consent [1].

80 Semi-quantification (index) of IgG against N and quantification (log binding antibody
81 units [BAU]/mL) of Ig against receptor-binding domain (RBD) of spike (S) protein
82 were assessed by chemiluminescence assay (ALINITY i System, Abbott). Semi-
83 quantitative (index) ELISA assay was performed for anti-S IgA (ELISA Anti-SARS-
84 CoV-2 IgA kit, Euroimmun). Anti-RBD neutralizing activity of sera was measured with
85 a semi-quantitative ELISA assay (SARS-CoV-2 Surrogate Virus Neutralization Test,
86 GenScript) based on the binding inhibition of labelled RBD to angiotensin converting
87 enzyme 2 (ACE2) by the anti-RBD neutralizing antibodies (results expressed in %).
88 For statistical analyses, Mann-Whitney U tests and non-parametric Wilcoxon paired
89 tests were performed with the GraphPad Prism version 8.0.2 software. $p < 0.05$ was
90 considered statistically significant.

91

92 **Results**

93 The study included 92 SARS-CoV-2-infected HCWs from the SEROCOV cohort: 22
94 males, 70 females, median age of 33 years [interquartile range (IQR) 28-41]. A total
95 of 91 and 55 serum samples were available at M6 and M12, respectively. We first
96 evaluated the natural evolution of humoral anti-SARS-CoV-2 immune response
97 between M0 and M6. The anti-RBD IgG median level decreased significantly by 0.26
98 log BAU/mL between M0 (1.90 log BAU/mL [IQR: 1.47 – 2.27]) and M6 (1.64 log

99 BAU/mL [IQR: 1.22 – 1.92]) (Fig.1A). The anti-N IgG median index also significantly
100 decreased by 4.10 during this period: 4.94 [IQR: 2.72 – 6.82] at M0 and 0.84 [IQR:
101 0.25 – 1.55] at M6 (Fig. 1B). We also observed a significant decline by 0.64 of the
102 anti-S IgA median index between M0 (2.50 [IQR: 1.18 – 4.62]) and M6 (1.86 [IQR:
103 0.85 – 3.54]) (Fig. 1C). Considering the anti-RBD neutralizing activity, a median
104 decay of 24.4% of inhibition was observed: 66.4% [IQR: 39.7 – 82.5] at M0 and
105 42.0% [IQR: 16.8 – 68.8] at M6 (Fig. 1D).

106 After M6, 46 (79%) HCWs received a single-dose of COVID-19 vaccine: 35 (76%)
107 Pfizer-BioNTech and 11 (24%) Oxford-AstraZeneca. The anti-SARS-CoV-2 humoral
108 immune response was compared between vaccinated and unvaccinated HCWs. In
109 the unvaccinated group of HCWs, the natural evolution of antibody responses could
110 be analysed. The levels of anti-RBD IgG, anti-S IgA and the anti-RBD neutralizing
111 activity were stable between M6 and M12 (Figs. 2A, 2C and 2D), whereas we
112 observed a significant decrease of the anti-N IgG median index during the same
113 period: 0.79 [IQR: 0.21 – 4.67]) at M6 and 0.34 [IQR: 0.24 – 2.78] at M12 (Fig. 2B). A
114 significant decrease of the anti-N IgG median index was also observed in the
115 vaccinated group of HCWs: 0.73 [IQR: 0.23 – 1.11] at M6 and 0.52 [IQR: 0.20 –
116 0.73]) at M12 (Fig. 2B). However, the single-dose vaccination induced a strong
117 increase of the anti-RBD IgG level (+1.95 log BAU/mL), the anti-S IgA index (+16.30)
118 and the anti-RBD neutralizing activity (+71.4% of inhibition) (Figs. 2A to 2D).

119

120 We also investigated the impact of the COVID-19 vaccine type (Pfizer-BioNTech or
121 Oxford-AstraZeneca) on the humoral immune response of HCWs. No difference was
122 observed between both vaccines at M12 for the anti-N IgG index, the anti-S IgA index
123 and the anti-RBD neutralizing activity between the two vaccines (Fig. 2F to 2H).

124 Conversely, a significantly higher level of anti-RBD IgG was observed in the Pfizer-
125 BioNTech group of HCWs than among in the Oxford-AstraZeneca group of HCWs
126 (median: 3.56 log BAU/mL [IQR: 3.33 - 3.78] versus 2.94 log BAU/mL [IQR: 2.76 –
127 3.14] (Fig. 2E).

128

129 **Discussion**

130 The evolution of the humoral immunity after SARS-CoV-2 infection is an important
131 element to study the dynamic of COVID-19 pandemic. Our study reinforces and
132 brings new evidence to the fact that anti-S antibodies (IgG and IgA) decreased but
133 remained detectable through time, conversely to anti-N antibodies, and can be
134 strongly enhanced after vaccination.

135 As previously shown [3,4], we observed a continuous decrease of the anti-N IgG over
136 1 year. The anti-RBD IgG level also decreased until M6 but remained stable above
137 the positive threshold over a year. These data were consistent with those observed in
138 others European HCWs or in symptomatic/asymptomatic patients [2,3,5–7]. We
139 observed the same pattern of evolution for the anti-S IgA antibodies. Previous works
140 have shown that anti-S IgA levels decreased in a less proportion compared to the
141 anti-RDB IgG levels over a time period of 6 to 9 months [8–10]. The present study
142 confirmed this decrease at M6 but showed that, similarly to the anti-RBD IgG, they
143 remained stable over a year. These patterns of antibody evolution is coherent with
144 the kinetics of B-cells and T-cells expansion after SARS-CoV-2 infection [11] and
145 suggest that active and young adult HCWs could exhibit an efficient immune
146 response in case of virus re-exposure after one year.

147 Moreover, a strong increase of antibodies titers was observed between M6 and M12
148 after one dose of vaccine. Consistent with previous studies [12,13], only one dose of

149 vaccine after SARS-CoV-2 infection was enough to increase strongly immune
150 response makers.

151 One of the limitations of our study it is the low number of available serum samples
152 from SARS-CoV-2-infected HCWs, and particularly for the unvaccinated group and
153 for the Oxford-AstraZeneca group. Indeed, we only observed a lower level of the anti-
154 RBD IgG with the Oxford-AstraZeneca group which is consistent with the literature
155 [13]. No significant differences were observed for the anti-S IgA level and the anti-
156 RDB neutralizing activity. Those results could be explained by the fact that the last
157 two immunologic markers were assessed by semi-quantitative assays, which do not
158 allow a precise quantification.

159

160 **Conclusion**

161 Anti-RBD IgG and anti-S IgA levels decreased until 6 months and then stabilized until
162 12 months post-SARS-CoV-2 infection in HCWs. Anti-N IgG levels showed a
163 continuous decline throughout the study period. COVID-19 vaccination (Pfizer-
164 BioNTech and Oxford-AstraZeneca) led to a strong increase of all anti-SARS-CoV-2
165 immunologic markers, except for the anti-N IgG response.

166

167 **Authors' contribution**

168 DB, AGM and ET planned the study; ET, KZ, SS, SM, MD, CS and BA conducted the
169 experiments; ET and DB analysed the data; ET, DB and AGM wrote the manuscript.
170 ET, DB, AGM, PH and FT reviewed the manuscript. All authors approved the final
171 version.

172

173 **Conflict of Interest**

174 Authors declare that they have no conflict of interest.

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195

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240

241 **Figure legends**

242

243 **Fig. 1.** Natural evolution of humoral immune response after SARS-CoV-2 infection
244 among HCWs.

245 Evolution of antibody response during 6 months for (A) anti-RBD IgG, (B) anti-N IgG,
246 (C) anti-S IgA and (D) anti-RBD neutralizing activity (M0 n=92 and M6 n=91). On
247 each graph, the horizontal dotted line represents the positivity cutoff of the technique:
248 (A) 50 BAU/mL, (B) 0.5 (index), (C) 1.1 (index), (D) 30%. ** p<0.005 **** p<0.0001.

249

250 **Fig. 2.** Evolution of immune response after SARS-CoV-2 infection among COVID-19
251 vaccinated and unvaccinated HCWs.

252 Evolution of antibody response between M6 and M12 among vaccinated (dark grey,
253 n=46) and unvaccinated (light grey n=9) HCWs: (A) anti-RDB IgG, (B) anti-N IgG, (C)
254 anti-S IgA and (D) anti-RBD neutralizing activity.

255 Comparison of antibody response at M12 among HCWs vaccinated with Pfizer-
256 BioNTech vaccine (white, n=35) and with Oxford-AstraZeneca vaccine (grey, n=11):
257 (E) anti-RBD IgG, (F) anti-N IgG, (G) anti-S IgA, and (H) anti-RBD neutralizing
258 activity. On each graph, the horizontal dotted line represents the positivity cutoff of
259 the technique: (A) and (E) 50 BAU/mL, (B) and (F) 0.5 (index), (C) and (G) 1.1
260 (index), (D) and (H) 30%. *p<0.05 ****p<0.001.

261

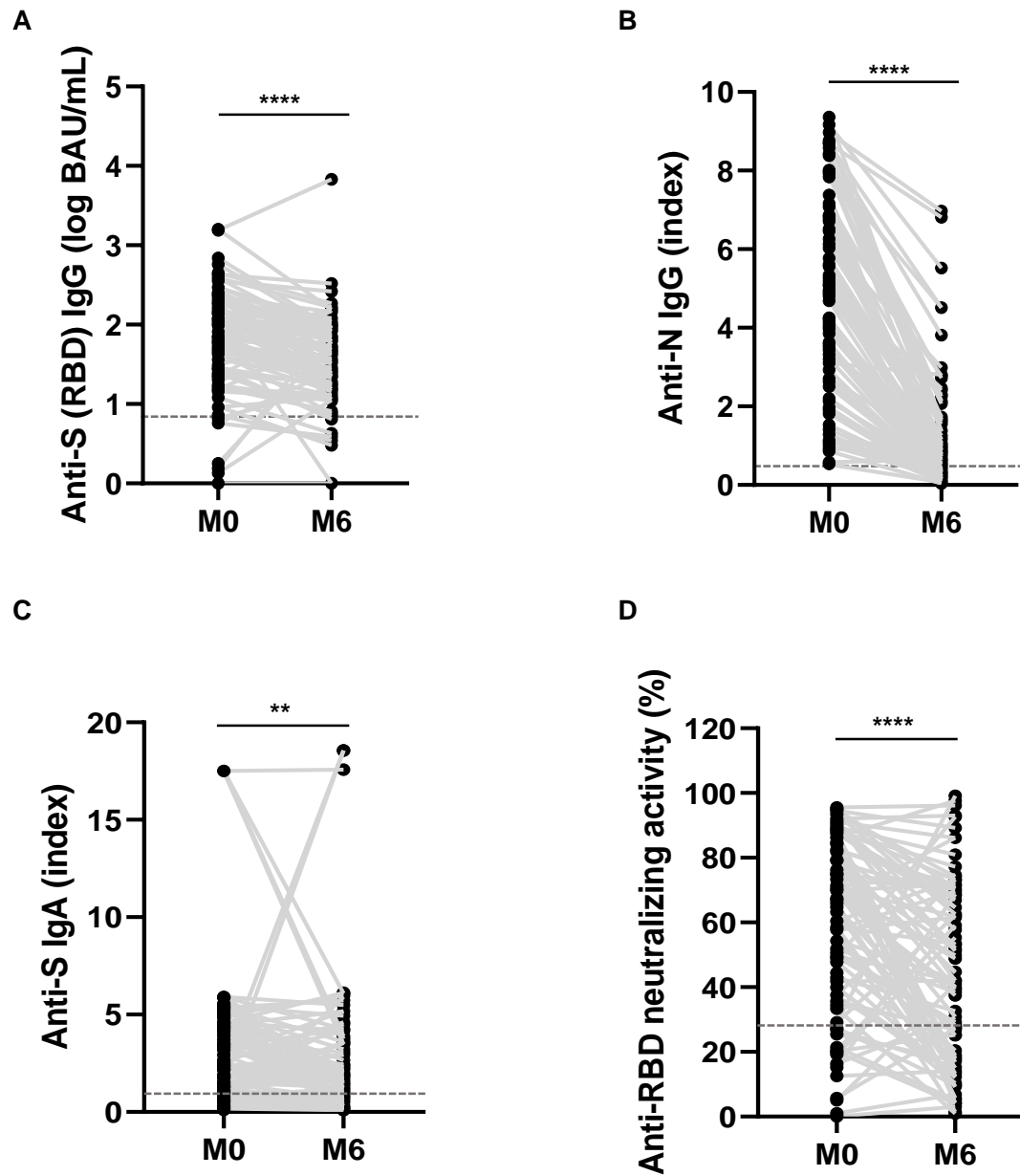


Fig. 1

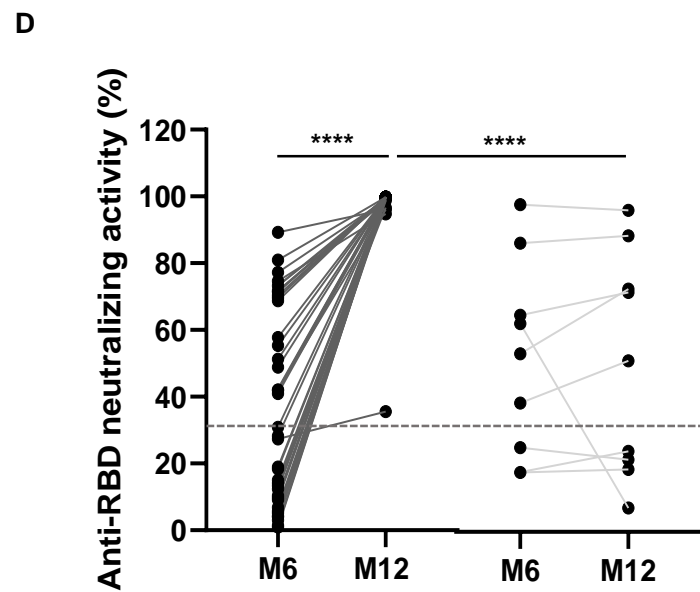
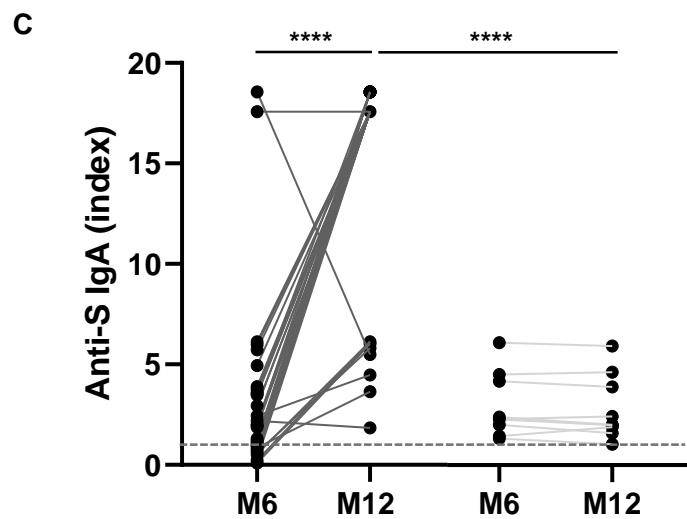
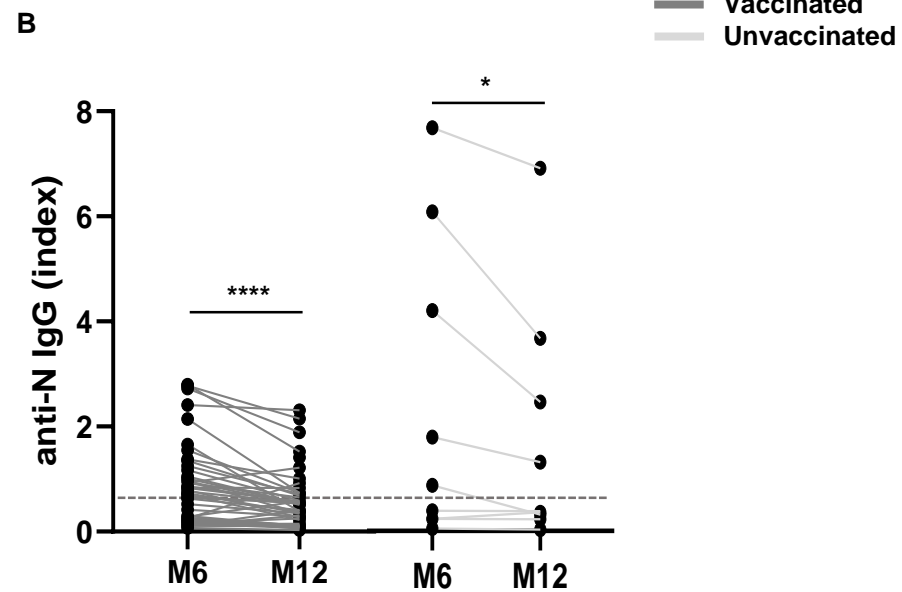
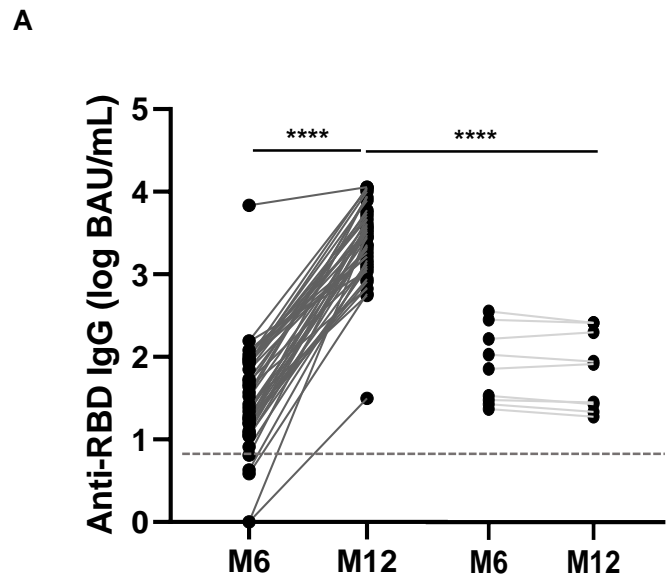
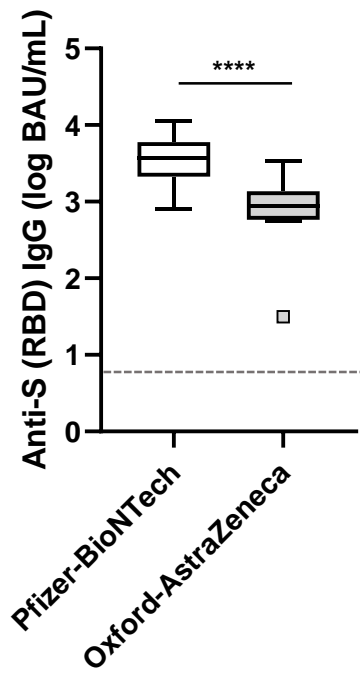
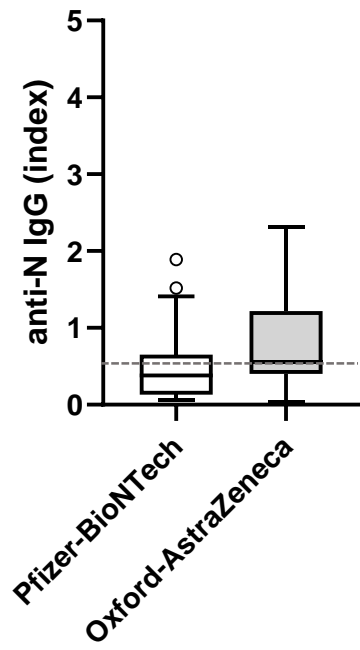
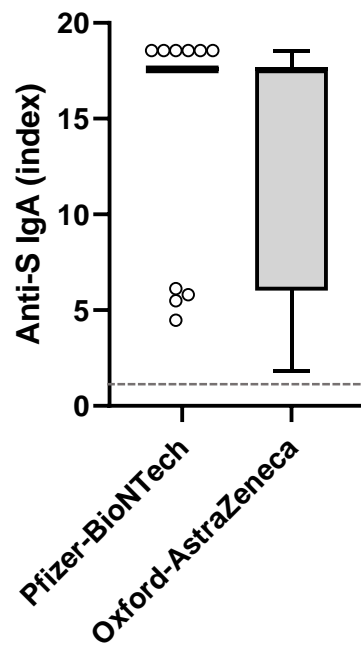
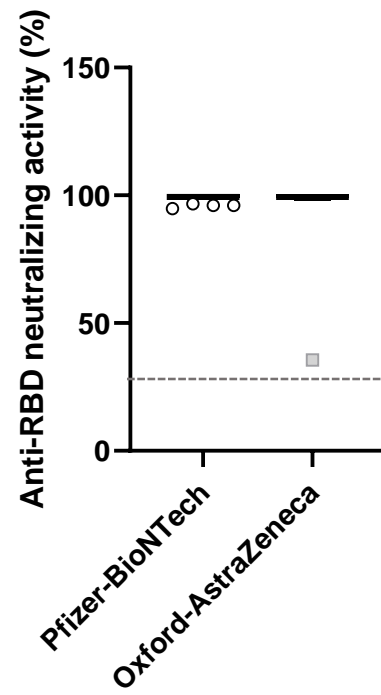


Fig. 2

E**F****G****H****Fig. 2**