

1 **FACTORS INFLUENCING SARS-COV-2 IGG**
2 **TEST SENSITIVITY: A BAYESIAN**
3 **ANALYSIS OF SEROCONVERSION AND**
4 **REVERSION BY TIME SINCE INFECTION,**
5 **TEST, AGE AND DISEASE SEVERITY.**

6
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19

1. Abstract

20 1.1. BACKGROUND

21 Antibody testing is commonly used to assess past exposure to pathogens, but the interpretation is
22 complex. We quantified test-specific SARS-CoV-2 seroconversion and reversion by time since PCR-
23 confirmed infection, age and disease severity.

24 1.2. METHODS

25 We used Belgian data from laboratory SARS-CoV-2 testing, prescriptions, contact tracing and hospital
26 surveillance collected between March 2020 and June 2021. Additionally, we gathered data for the
27 Wantai and EuroImmun IgG serological tests from the scientific literature.

28 We used a hierarchical Bayesian model to estimate distributional parameters of a scaled Weibull-bi-
29 exponential distribution for the time-varying sensitivity of qualitative serological test results obtained after
30 PCR-confirmed SARS-CoV-2 infection. We accounted for disease severity (distinguishing between
31 asymptomatic, symptomatic, and hospitalized cases), age (i.e., in terms of age groups 18-49, 50-64,
32 and 65-74 years) and serological test used.

33 1.3. RESULTS

34 We included 44,262 serological test results: 10,864 obtained from published studies, 33,398 from
35 Belgian laboratories. Seroconversion occurred during the six weeks following a PCR-confirmed
36 infection. For the EuroImmun test, 82% (95%CrI: 80%-84%) of symptomatic individuals in the youngest
37 age group seroconverted, compared to 95% (95%CrI: 95%-96%) for the Wantai test. In addition,
38 seroconversion was associated with hospitalization (OR = 6.98, 95%CrI: 4.85-11.37, compared to
39 asymptomatic infection) and older age (OR = 1.67, 95%CrI: 1.43-1.92, for 65-74-year-olds compared to
40 18-49-year-olds). Reversion after initial seroconversion was strongly associated with the test used. At
41 50 weeks, the proportion of symptomatic individuals aged 18-49 years who remained seropositive was
42 63% (95%CrI: 56%-69%) for the EuroImmun test and 95% (95%CrI: 94%-96%) for the Wantai test.
43 Slower reversion was associated with severe infection and older age.

44 **1.4. CONCLUSION**

45 Seropositivity after SARS-CoV-2 infection was significantly associated with the type of test used, age of
46 the case and severity of the infection. More severe infection and older age resulted in increased and
47 prolonged seropositivity.

48

2. Introduction

49 Starting in 2020, numerous seroprevalence studies were conducted to understand the extent of past
50 exposure to SARS-CoV-2 within different populations [1]. These studies used immunoassays,
51 serological tests, capable of directly or indirectly detecting antibodies. These antibodies typically target
52 one of the four structural proteins of the SARS-CoV-2 virus: spike (S), membrane (M), envelope (E), or
53 nucleocapsid (N) protein. The S protein, which is further divided into the N-terminal domain (NTD) and
54 the receptor-binding domain (RBD), along with the N protein, are the primary immunogens and are
55 typically the targets of immunoassays [2]. Assays determine the amount of antibodies and manufacturer
56 suggested threshold values can be used to translate quantitative to qualitative results. Qualitative results
57 are then typically reported as the proportion of positive samples among all samples. The interpretation
58 of such results however is not straightforward as immunoassays are imperfect. Qualitative results are
59 associated with a proportion of false negatives (sensitivity below 100%) and false positives (specificity
60 below 100%) [3]. In addition, the main research interest is often not solely in the presence of antibodies.
61 The main objective of seroprevalence studies, in addition to objectives regarding susceptibility, concerns
62 the proportion of persons previously infected: the cumulative infection rate. The sensitivity with respect
63 to previous infection, as compared to sensitivity to a certain level of antibodies, is a dynamic metric
64 which will depend on the test, but also on antibody kinetics associated with the time since infection and
65 person and disease characteristics [3].

66

67 Quantifying this dynamic sensitivity is difficult as it is affected by different factors. We briefly introduce
68 the three main factors: (A) how infections are diagnosed, (B) which persons are included in the cohort
69 under follow-up and (C) how is time since infection included in the analysis. With respect to (A): studies
70 typically use either a 'gold standard' immunoassay or a combination of immunoassays, neutralization
71 assays or RT-PCR tests to determine 'true' positivity of an individual [4]. The shortcoming of any of
72 these options typically boils down to the gold standard's own sensitivity and specificity. (B) Patients
73 included in longitudinal studies were frequently hospitalized. Hospitalization is typically associated with
74 high antibody titers not reflective of titers in asymptomatic patients [5–7]. Metareviews reported a high
75 risk of patient selection bias in 97-98% of assessments [4,8]. (C) After an initial increase during 3 to 12
76 weeks for SARS-CoV-2 [8], antibody titers will decrease again over time, while antibody avidity and
77 affinity might increase. The decline is not monophasic. An initial strong decrease is followed by a plateau

78 [9,10]. Whether or not this decrease is antigen-specific is still under debate. Antibodies associated with
79 S1 seem more durable than those associated with the N-protein [2,11–16]. Furthermore, the decrease
80 is linked to patient selection. The half-time of IgG S-protein titers associated with asymptomatic cases
81 is less than half of that of mild cases and has been estimated at 55 days [17,18] or even shorter (i.e.,
82 36 days as estimated by Ibarondo et al. [19]). No detectable neutralizing activity was found in 50% of
83 asymptomatic infections 1 year after infection [10]. The role of sex and age is less clear [20]. More stable
84 antibody levels have been reported for females [21]. Studies have reported higher initial titer
85 concentrations in older age groups. Higher initial titers have been linked to extended seropositivity
86 [7,14,21–23]. Typical methods to adjust for the imperfect performance of serological tests, such as a
87 Rogan-Gladen type estimator [24], can be extended to include time-varying sensitivity estimates, but
88 with the exception of some modelling studies, seroprevalence studies typically do not correct for waning
89 of antibodies [25].

90

91 We aim to estimate distributional parameters associated with an underlying parametric distribution for
92 time-varying, test-specific sensitivity in relation to time since infection and to quantify the effect of age
93 and clinical severity on this distribution. While estimating the sensitivity, all available data, including
94 estimates obtained from the literature, will be included. Such an estimate for the time-varying and test-
95 specific sensitivity is necessary for a meaningful interpretation of qualitative individual serological test
96 results and for the translation of population-level seroprevalence results to (cumulative) incidence
97 estimates.

98

3. Methods

99 We used a Bayesian hierarchical model with a binomial likelihood to fit the number of positive serological
100 tests out of all serological tests at week t after PCR-confirmation of SARS-CoV-2 infection. Data on
101 cases was collected from Belgian laboratories and published studies. We first present the distributions
102 for seroconversion and reversion and how these processes result in a temporal state of detectable
103 antibodies, coined seropositivity.

104 3.1. MODEL STRUCTURE

105 We modeled two immunological processes: seroconversion and seroreversion. Seroconversion is the
106 process of reaching a detectable level of antibodies after infection. Seroreversion is the process of losing
107 that detectable level since having first attained it. These processes are represented by two random
108 variables: T_c denotes the time between infection and conversion and T_r is the time between conversion
109 and reversion. T_c is assumed to follow a Weibull distribution. T_r follows a bi-exponential distribution. The
110 Weibull distribution was selected because it can flexibly model time-to-event data. The bi-exponential
111 distribution allowed us to include a mixture of a fast and slow decrease. Four parameters representing
112 different time-to-event processes need to be estimated: a scale and shape parameter for T_c and two
113 exponential parameters for T_r . In addition, we need to estimate the proportion of cases that undergo
114 seroconversion and a parameter that determines the mixture between slow and fast decrease.

115
116 The random variable S_t (with discrete probability density function ($h(S_t)$)) represents the proportion of
117 seropositive cases at week t out of all cases infected at week 1. To account for both the time to
118 seroconversion, the time to seroreversion given seroconversion and the overall proportion that will
119 seroconvert we include $h(S_t)$ as (notation based on Shioda et al. [26]):

$$120$$
$$121 \quad h(S_t) = \sum_{t_c=1}^t \{g(t_c) * Prop * [1 - Z_r(t - (t_c))]\}$$
$$122$$

$$123 \quad Z_r(t - (t_c)) = \sum_{t_r=1}^{t-(t_c)} 1 - (\alpha_r * \exp(-\lambda_{r.fast} * t_r) + (1 - \alpha_r) * \exp(-\lambda_{r.slow} * t_r))$$
$$124$$

125 For a case to be seropositive at week t after infection, it had to undergo seroconversion at week t_c with
126 t_c before or at week t . $g(t_c)$ is the discretized probability density function for T_c . In addition, the case
127 should not have undergone seroreversion during the time interval $t - (t_c)$. Z_r denotes the cumulative
128 density function of T_r . $Z_r(t - (t_c))$ is the proportion of cases seroconverted at week t_c that will have
129 undergone seroreversion by or at week t . Seroreversion will only occur given seroconversion, we
130 therefore have to scale $Z_r(t - (t_c))$: $g(t_c) * Prop * Z_r(t - (t_c))$.

131

132 The parameters for the time-to-event distributions ($scale_c, shape_c, \lambda_{r.fast}, \lambda_{r.slow}$) are global. The
133 proportion, $Prop$, converted and the seroreversion-mixture, α_r , are group-specific with the following
134 linear predictors.

135

$$136 \quad \text{logit}(Prop) = \beta_{pc,0} + \sum_{i=1}^2 \beta_{pc,1i} * severity_i + \sum_{j=1}^2 \beta_{pc,2j} * age_i + u_{pc.test/lab_l}$$

$$137 \quad \text{logit}(\alpha_r) = \beta_{r,0} + \sum_{i=1}^2 \beta_{r,1i} * severity_i + \sum_{j=1}^2 \beta_{r,2j} * age_i + u_{r.test/lab_l}$$

138

139

140 There are three age groups and three severity groups. Coefficients for the first groups are set to zero,
141 leaving two coefficients to be estimated per distributional parameter. u_{test/lab_l} represent the random
142 effect for tests and laboratories. We evaluated multiple approaches for modelling antibody reversion
143 kinetics, including linear decay functions and various time-to-event distributions such as Weibull. After
144 comparative analysis, we selected a bi-exponential distribution. This model optimally captured the
145 biphasic nature of antibody dynamics: an initial rapid decline followed by a slower, plateau-like phase.
146 While α_r was allowed to vary by severity, age group, and test, we determined through model selection
147 that the decay rate parameters $\lambda_{r.fast}$ and $\lambda_{r.slow}$ could be treated as global parameters without
148 significant loss of fit. Multiple model structures were evaluated using Bayesian Information Criterion
149 (BIC) and convergence diagnostics, including interaction terms.

150

151 We used non-informative priors for the model coefficients (i.e., normal distributions with a relatively large
152 standard deviation of 100). The factors for test (or lab) were included as random effects with mean zero
153 and a gamma distributed prior for the standard deviation. Markov Chain Monte Carlo (MCMC) sampling
154 was performed using the R package *nimble*. We used three MCMC chains with 10,000 iterations each
155 and a burn-in of 4,000 iterations to perform posterior inference, while convergence of the different chains
156 was checked using the Gelman-Rubin statistic.

157 **3.2. LABORATORY DATA**

158 Reporting of laboratory results to a centralized database was mandatory during the COVID-19 pandemic
159 in Belgium. While SARS-CoV-2 IgG testing was not required in any situation, a large number of IgG

160 tests was performed. Within the centralized databases available through the LinkVacc project, test
161 results could be linked with data on vaccination, contact tracing and hospital surveillance using
162 pseudologized unique identifiers. We grouped test results by severity, age, test/laboratory and number
163 of weeks since PCR-confirmed infection. The number of positive samples out of all samples is fitted to
164 the previously defined binomial likelihood.

165

166 We considered three age groups: 18 to 49 years, 50 to 64 years and 65 to 74 years and three different
167 categories of clinical severity: self-reported asymptomatic, self-reported symptomatic or notified
168 hospitalized. Symptoms could be reported either before diagnosis (e.g., during the consultation) or
169 during contact tracing (when cases were interviewed about their contacts). If the case reported
170 symptoms at any point, the case was classified as symptomatic. If, upon investigation, the case reported
171 no symptoms, it was classified as asymptomatic. If this information was missing, the records were
172 excluded. Additionally, if a hospitalization for COVID-19 was reported in a period of 7 days before to 60
173 days after the first positive PCR test through the clinical hospital survey, the case was classified as
174 hospitalized [27]. Unfortunately, the specific serological test and cut-offs used were not reported by the
175 laboratory. The reporting laboratory was therefore used as a substitute for test and included as a random
176 variable in the model formulated in Section 3.1.

177

178 We only included information on subjects with positive PCR tests conducted in 2020, given the
179 documented changes in epidemiology and immunological responses after infection with new variants
180 (as compared to the wild-type SARS-CoV-2 strain) emerging from 2021 onwards. We excluded all IgG
181 tests that followed any subsequent PCR test after the first positive test as PCR-testing could be
182 indicative for additional exposure to SARS-CoV-2. IgG test results after vaccination were also excluded
183 from the analysis. We included no IgG test results obtained after June 2021.

184

185 **3.3. LITERATURE DATA**

186 We included two tests, chosen because of their use in two repeated cross-sectional seroprevalence
187 studies in Belgium, a semi-quantitative test (EuroImmun), targeting the S1 protein and a semi-
188 quantitative test (Wantai) targeting the RBD. We included all studies listed in the systematic review by
189 Owusu-Boaitey et al. [3] in our statistical analysis. For the Wantai test, we also included the findings

190 from the study by Hønge et al. [28], originally excluded by Owusu-Boaitey et al. because the study
191 cohort, consisting exclusively of healthy blood donors, was not considered representative. Since our
192 model allowed us to differentiate by disease severity (including asymptomatic presentation), we did
193 include the study.

194

195 The data from scientific literature is included in the model in a similar way to the data obtained from
196 Belgian laboratories. As opposed to the data from the Belgian laboratories, the specific test is known
197 and included in the model as level for the random effect u_{test/lab_i} . For each included paper, we obtained
198 the test, the number of (positive) samples by weeks since infection, the proportions of asymptomatic,
199 symptomatic and hospitalized persons in the cohort and the proportions within the age groups 18-49,
200 50-64 and 65-74 years. Whenever specifics on severity and age were not available, we included the
201 following default distributions. For clinical severity: 50% asymptomatic, 45% symptomatic and 5%
202 hospitalized (severe) as this was reported by Takahashi et al. [29] to be the average over serosurveys.
203 For age: we either included the default for Germany, if the study was performed in Germany: 18-49
204 (45%), 50-64 (35%) and 65-74 (20%) based on Neuhauser et al. [30] or the default for Denmark: 18-49
205 (64%), 50-64 (26%) and 65-74 (10%) based on Pires et al. [31]. For studies and regions outside of
206 Denmark and Germany for which we could not obtain a specific age distribution, we used as default a
207 distribution in between the German and Danish distributions: 18-49 (55%), 50-64 (30%) and 65-74
208 (15%). Details by study and weeks since infection are provided in S1 Table.

209

4. Results

4.1. NUMBERS INCLUDED

210
211 In the centralized database there were 472 223 persons with a positive PCR test in 2020 in Belgium in
212 the age group from 18 years to 74 years. Of these persons 15% (N = 70 951) had IgG tests (N = 93
213 127) before July 2021. We had to exclude (in order of exclusion criterion) 6 856 IgG tests because they
214 followed vaccination, 39 622 tests because they either preceded the first positive PCR test or followed
215 any PCR test after the first positive PCR test. For 13 251 IgG tests, data on the severity of infection was
216 missing. Therefore, we could include 33 398 IgG tests from 30 002 persons reported by 84 laboratories.
217 The laboratory with the most records accounted for 14% of all IgG tests.

218

219 Of these tests 28% were taken from individuals with asymptomatic infection, 67% from individuals with
 220 symptomatic infection and 5% from hospitalized individuals. The division by age group was 51% (18-49
 221 years), 35% (50-64 years) and 14% (65-74 years). 16% of tests were collected in the first 4 weeks, 42%
 222 in weeks 4-11, 40% in weeks 12-35 and 1% later. The numbers by weeks since first positive PCR test,
 223 clinical severity and age group are presented in Table 1.

224

225 **Table 1: Number (and percentage) of included IgG tests following a positive SARS-CoV-2 PCR**
 226 **test in 2020, by weeks since positive PCR test, clinical severity and age group, Belgian laboratory**
 227 **data.**

228

Severity	Weeks since positive PCR test	18-49 years	50-64 years	65-74 years
Asymptomatic	0-3	1247 (3.7)	687 (2.1)	285 (0.9)
	4-11	1854 (5.6)	1139 (3.4)	506 (1.5)
	12-35	1917 (5.7)	1083 (3.2)	400 (1.2)
	36+	145 (0.4)	50 (0.1)	8 (0)
Symptomatic	0-3	1430 (4.3)	965 (2.9)	421 (1.3)
	4-11	5125 (15.3)	3520 (10.5)	1430 (4.3)
	12-35	5063 (15.2)	3357 (10.1)	1082 (3.2)
	36+	64 (0.2)	33 (0.1)	4 (0)
Hospitalized	0-3	102 (0.3)	135 (0.4)	162 (0.5)
	4-11	129 (0.4)	288 (0.9)	198 (0.6)
	12-35	121 (0.4)	266 (0.8)	167 (0.5)
	36+	5 (0)	4 (0)	6 (0)

229

230

231 4.2. HIERARCHICAL BAYESIAN MODEL

232 4.2.1. Group specific effects

233 The proportion that eventually undergoes seroconversion was associated with test, disease severity and
234 age. More specifically, the odds ratio of seroconversion when individuals were eventually hospitalized
235 as compared to self-reported asymptomatic was 6.98 (95%CrI: 4.85-11.37). Higher seroconversion was
236 associated with older age (OR 1.67 95%CrI 1.43-1.92) compared to the youngest age group (18-49-
237 years-old) (Table 2). Faster waning was associated with the youngest age group and symptomatic
238 infection as compared to the older age groups and asymptomatic infection (Table 3). The effect of the
239 different tests/laboratories is presented in the supporting information.

240

241 **Table 2: Odds Ratios (OR) derived from the posterior distributions of the regression coefficients**
242 **for the proportion that eventually undergoes seroconversion after a positive PCR-test in 2020**
243 **(asymptomatic = self-reported asymptomatic, symptomatic = self-reported symptomatic,**
244 **hospitalized = notified hospitalized, SD = standard deviation), Belgian laboratory data and data**
245 **from published research.**

246

Variable	OR	95% CrI:	
		Lower	Upper
Age			
18-49 (ref)	1		
50-64	1.31	1.16	1.47
65-74	1.67	1.43	1.92
Severity			
Asymptomatic (ref)	1		
Symptomatic	2.21	1.95	2.55

Variable	OR	95% CrI:	
		Lower	Upper
Hospitalized	6.98	4.85	11.37
Random intercept	SD		
test/lab	1.71	1.51	1.97

247

248

249 **Table 3: Odds Ratios (OR) derived from the posterior distributions of the regression coefficients**
 250 **for the proportion associated with faster waning (asymptomatic = self-reported asymptomatic,**
 251 **symptomatic = self-reported symptomatic, hospitalized = notified hospitalized, SD = standard**
 252 **deviation), Belgian laboratory data and data from published research.**

253

Variable	OR	95% CrI:	
		Lower	Upper
Age			
18-49 (ref)	1		
50-64	0.12	0.02	0.29
65-74	0.03	0	0.14
Severity			
Asymptomatic (ref)	1		
Symptomatic	2.58	1.23	6.91
Hospitalized	0	0	0.62

Variable	OR	95% CrI:	
		Lower	Upper
Random intercept	SD		
test/lab	2.41	1.58	3.69

254

255

256 **4.2.2. SeroConversion and SeroReversion**

257 We present the posterior distributions for seroconversion and seroreversion separately by clinical
 258 severity and age group for the EuroImmun and Wantai test in Fig 1. The process of seroconversion was
 259 set equal over groups. By week 5, over 95% of those that will seroconvert had seroconverted. The
 260 seroreversion occurred faster in younger age groups and in those with less severe infections not
 261 requiring hospitalization. The EuroImmun test was associated with more and faster seroreversion
 262 compared to the Wantai test. The combined effects of proportion, conversion and reversion over time
 263 since PCR-confirmed infection are presented in Fig 2.

264

265 **Fig 1: Plots of the posterior Weibull distributions for seroconversion (upper) and seroreversion**
 266 **(lower) by weeks since positive PCR test, clinical severity and age group for the EuroImmun (left)**
 267 **and the Wantai (right) test, Belgian laboratory data and data from published research.**

268

269 **Fig 2: Plots of the posterior scaled Weibull-Bi-exponential distribution for time-varying**
 270 **seropositivity for the EuroImmun (upper) and Wantai (lower) test by weeks since positive PCR**
 271 **test, clinical severity and age group, Belgian laboratory data and data from published research.**

272

273 **4.2.3. Goodness of fit**

274 We present the model fit to both Belgium's laboratory data (Fig 3) and the data obtained from literature
 275 (Fig 4). Considerable variation was linked to the test used or reporting laboratory. We presented the
 276 distributions of the random effects (scale reversion and proportion converted) in S1 Fig.

277

278

279 **Fig 3: Plots of the posterior scaled Weibull-Wi-exponential distribution for the time-varying**
280 **seropositivity averaged over all laboratories (unweighted average) by weeks since positive PCR**
281 **test, clinical severity and age group, Belgian laboratory data, IgG tests after a positive PCR test**
282 **in 2020.**

283

284 **Fig 4: Posterior Predictive Checks: The proportion positive reported (dot) and the posterior**
285 **binomial confidence interval (error bars) by study (color) and weeks since positive PCR test for**
286 **the EuroImmune (upper) and Wantai (lower) test, data from published research.**

287

288

5. Discussion

289 This study provides a comprehensive analysis of factors influencing SARS-CoV-2 IgG test sensitivity
290 using a hierarchical Bayesian approach including data from published studies and Belgian laboratories.
291 Our key findings demonstrate that seropositivity following SARS-CoV-2 infection is significantly
292 influenced by three primary factors: the specific serological test used, the age of the individual, and the
293 severity of the initial infection.

294

295 Adjusting qualitative seroprevalence results for test-specific sensitivity and specificity to estimate past
296 exposure has become more common, but remains relatively rare. In a 2020 systematic review of global
297 SARS-CoV-2 antibody seroprevalence, Bobrovitz et al. reported that only 24% of studies provided
298 sensitivity and specificity estimates, with an even smaller proportion adjusting their seroprevalence
299 estimates accordingly [32]. The importance of these adjustments has been demonstrated. Studies using
300 the same seroprevalence data, but different sensitivity estimates have reported considerably different
301 infection fatality rates [33,34]. The limited use may be attributed to the complexity of these metrics.
302 Sensitivity depend not only on the test itself but also on the study cohort and time since infection. For
303 example, for the EuroImmun serological test sensitivity estimates have been reported ranging from 94%
304 to 53%: the manufacturer reported a sensitivity ≥ 10 days post symptom onset of 94.4%. Researchers
305 in South Africa estimated sensitivity at 64.1% [6], Public Health England at 72%, 74.5% [35], 77.2% [36]
306 and a study on Antarctic cruise passengers at 81% declining to 76% at 3 months and 53% at 1 year
307 [37]. In this work, we propose a framework to harmonize these estimates and quantify test-specific
308 sensitivity by time since infection and given cohort characteristics: age and severity of the infection.
309 Previous meta-analysis with a comparable aim have disregarded these cohort characteristics and
310 limited their included studies to those with cohorts considered representative for the general population.
311 Given the high risk of patient selection bias associated with these studies [4,8], this is a considerable
312 limitation. The systematic review by Owusu-Boaitey et al. [3], for example, quantified test-specific
313 sensitivity over time but could only include one study [12] to estimate the sensitivity of the Wantai test
314 beyond 5 months after symptom-onset. This study by Scheiblauer et al. included PCR-confirmed cases
315 (N=390) of which none were asymptomatic and a large proportion (15.8%) were hospitalized. Other
316 studies on the Wantai test could not be included because the cohort was not considered representative.
317 For example, a study on blood donors [28] was excluded. We could include this population by accounting

318 for the severity of the infection. In addition, we could include studies too recent to be included by Owusu-
319 Boaitey et al. [28,38]. We could not include the study by Perez-Saez et al. [39] since their cohort (N=354)
320 was established out of persons with an initial positive EuroImmuno test. Not all persons within the cohort
321 had a PCR-confirmed infection and dates of infection had to be estimated. Given initial seroconversion,
322 they estimated 40% seroreversion after 9 months. Likewise in our study we observed a decrease in the
323 sensitivity of the EuroImmuno test over time, albeit one less rapid. We observed a drop of around 20%
324 points for 18-49 year-olds with an initial symptomatic infection. This translates to seroreversion of around
325 25% of those that seroconverted over a 50 week period. For the Wantai serological test we observed
326 both higher initial and more durable seropositivity. The assay used has previously been established as
327 a major factor for seropositivity [40]. The Wantai serological test, the most sensitive and durable
328 serological test in this study, remains associated with a proportion non-responders. Non-response, non-
329 conversion or also sero-silence, is the absence of detectable antibodies at any time after infection. The
330 proportion of sero-silence after a PCR-confirmed infection is estimated at 5.2-7.8% [41–43]. As with the
331 previous findings this proportion also depends on the test used and the cohort characteristics.

332
333 Our other findings also largely agree with previously published longitudinal studies and reviews. The
334 severity of infection has been associated with high and persistent antibody levels by several studies
335 [44–49]. In addition, research reports lower sensitivity in young adults (ages younger than 40-50 years)
336 [50–52], but the association in older age groups seems less clear with contradictory findings. Higher age
337 has been mostly associated with slower waning [11,39,46,47,53,54] of the humoral immune response,
338 with some studies reporting faster waning [21,48]. We found higher seropositivity in those aged over 50
339 as compared to those below, but the effect of age was smaller than the effect of severity of infection.
340 We could not include persons beyond the age of 75 years. An age beyond which frailty and
341 immunosenescence might impact sensitivity [55].

342
343 This study has several limitations. The process of seroreversion was included using a bi-exponential
344 distribution. Some studies have opted for a Weibull distribution [26,56], others for a single exponential
345 [57,58] or splines on the logit scale [59]. We did not extrapolate beyond the periods available within the
346 data, but most of our data concerns the first weeks after PCR confirmation. As many other studies we
347 set a positive PCR-test as reference. Laboratory confirmation by PCR however has its own time-varying
348 sensitivity and specificity [60]. As no data were available on the test used by the reporting laboratory,

349 we used the reported laboratory as level for a random effect. We opted not to explore sex because initial
350 analysis did not associated sex with large differences in seropositivity after infection. Studies have
351 claimed to find no strong evidence of heterogeneity in antibody persistence by sex [61]. With some
352 claiming a more durable response in females [48]. The age groups in this analysis as well as the specific
353 tests were chosen in preparation of future work on two cross-sectional seroprevalence studies.

354

355 In conclusion, our study provided a comprehensive framework for estimating time-varying, test-specific
356 sensitivity in serological testing for SARS-CoV-2, accounting for the critical factors of disease severity,
357 age, and time since infection. The results demonstrate that seropositivity is significantly influenced by
358 test selection, with the Wantai test showing superior performance compared to the EuroImmun test in
359 both initial detection and long-term durability. Our findings reveal that older age (50-74 year) and more
360 severe infection lead to higher and more durable seropositivity.

361

362

6. Supporting Information Captions

363 **S1 Fig: Discrete approximation of the distribution of the random effects associated with test/lab**
364 **for the random effect in proportion seroconverted (upper) and the scale of the Weibull**
365 **representing seroreversion (lower). The values associated with the EuroImmun and Wantai tests**
366 **are annotated.**

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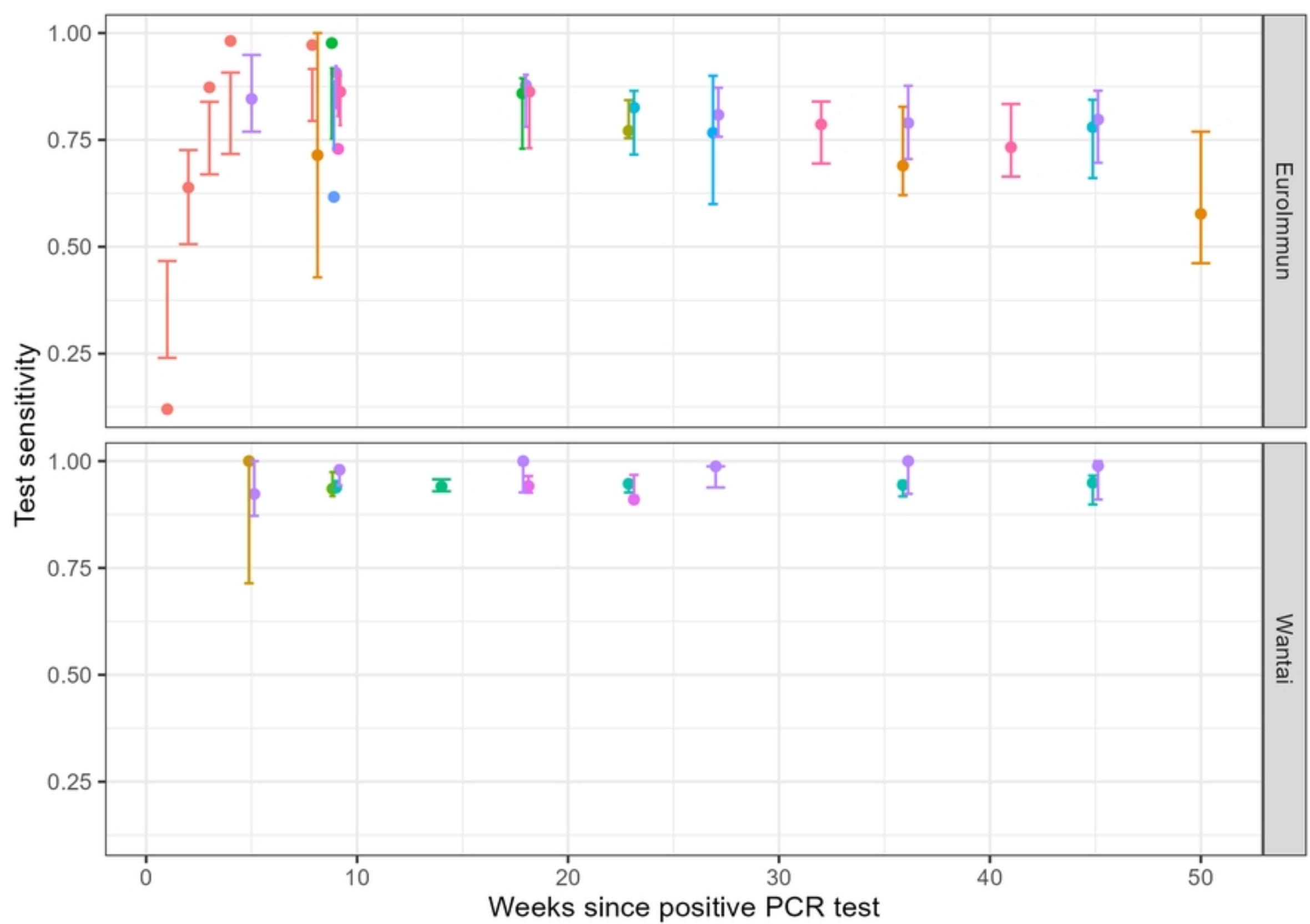
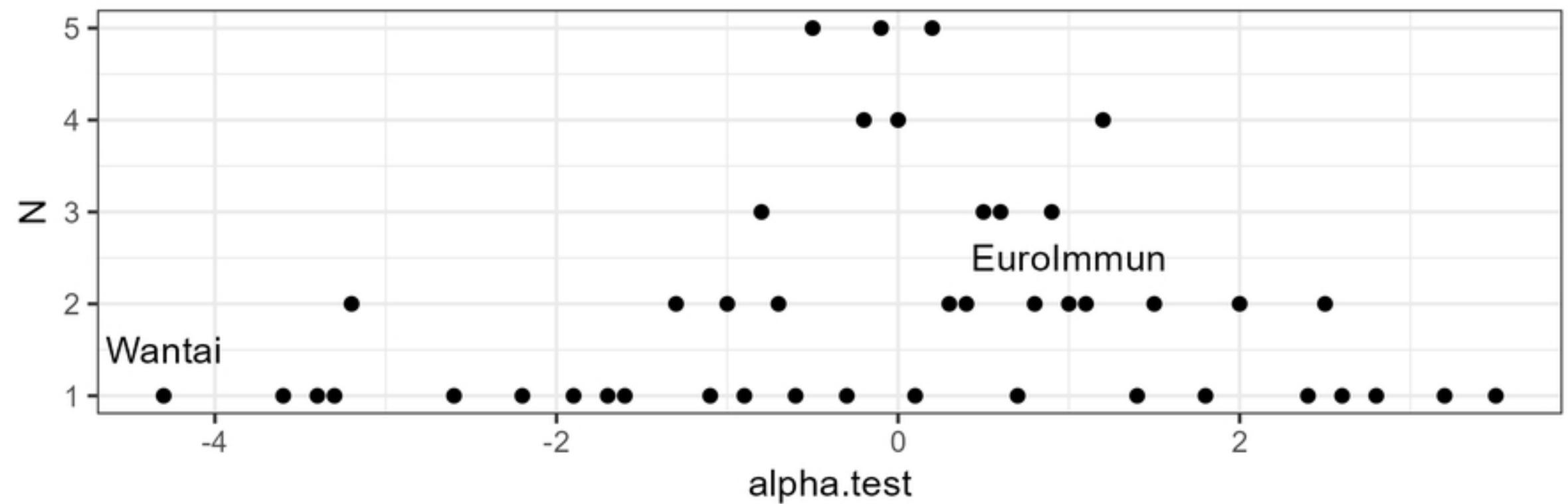
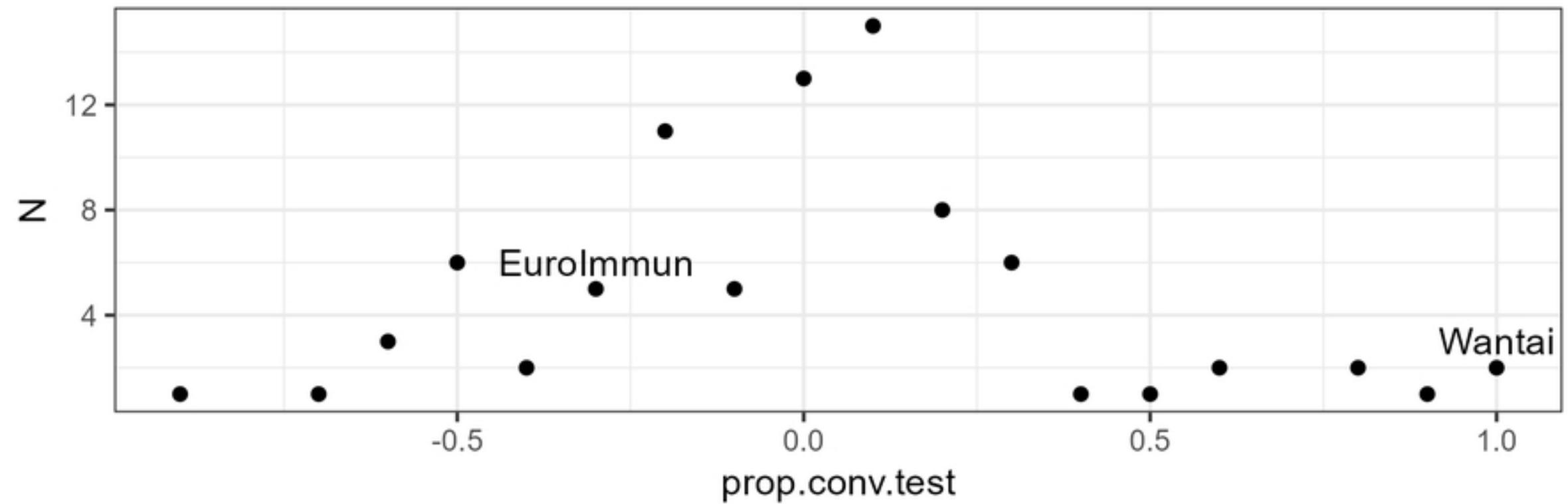
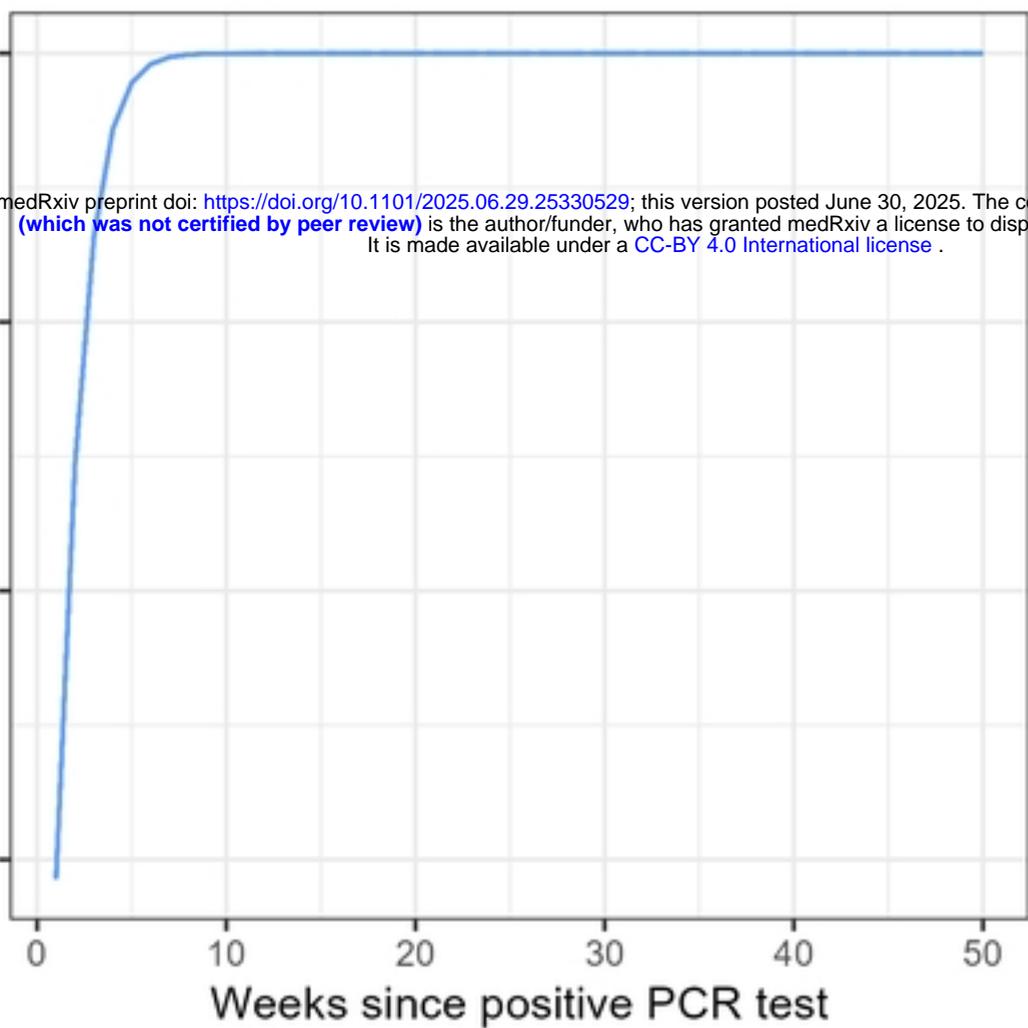


Fig4

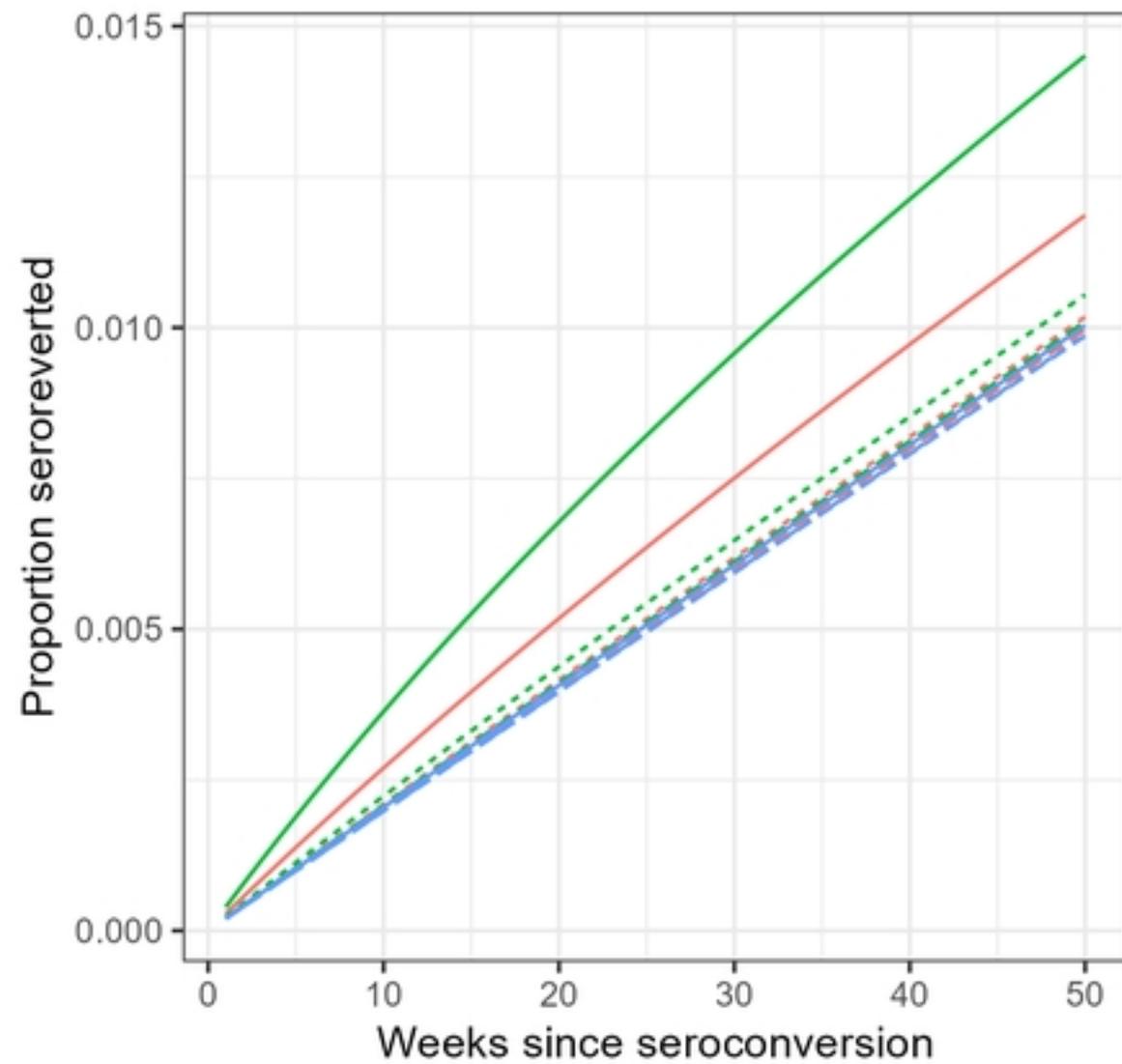
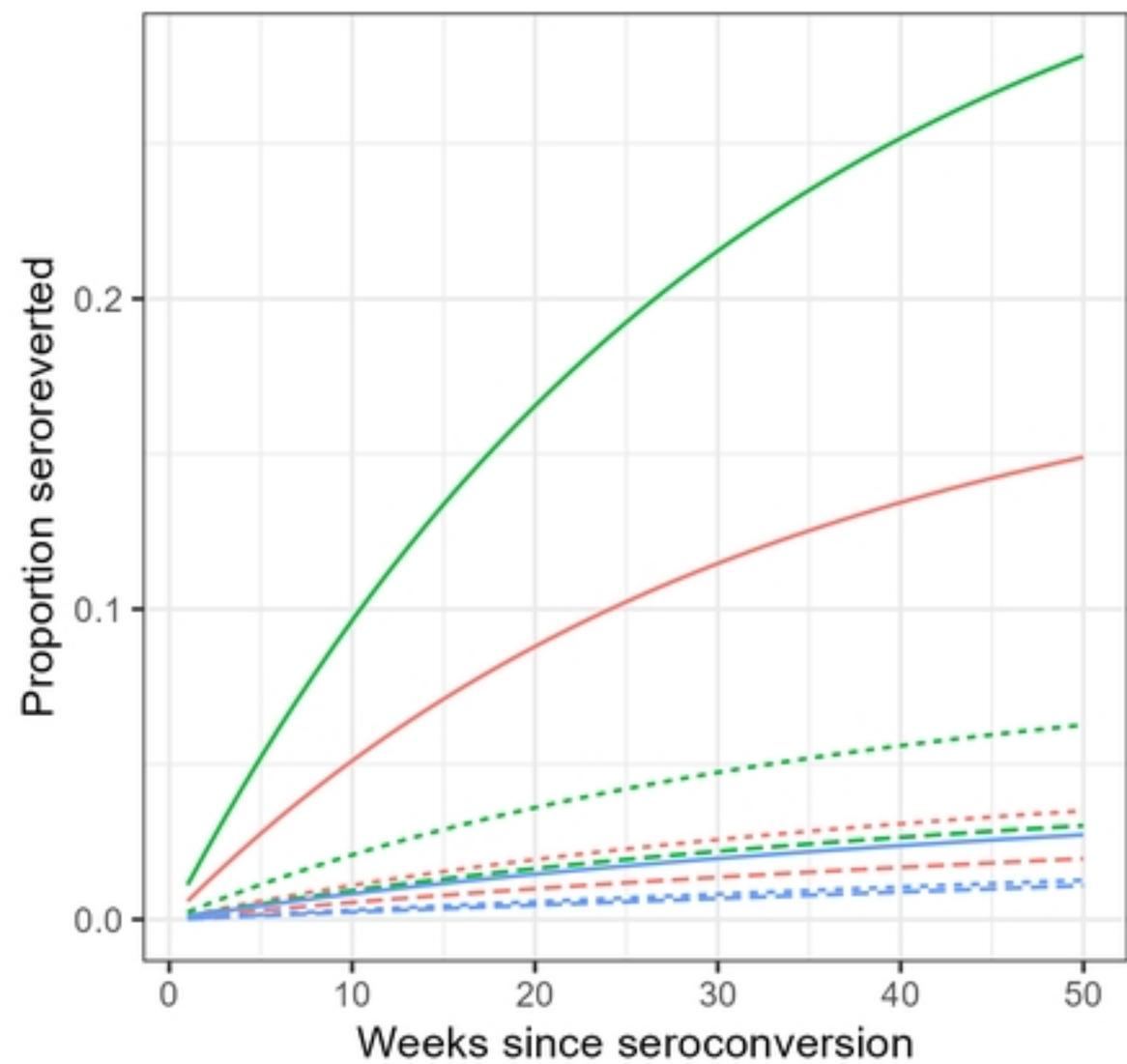
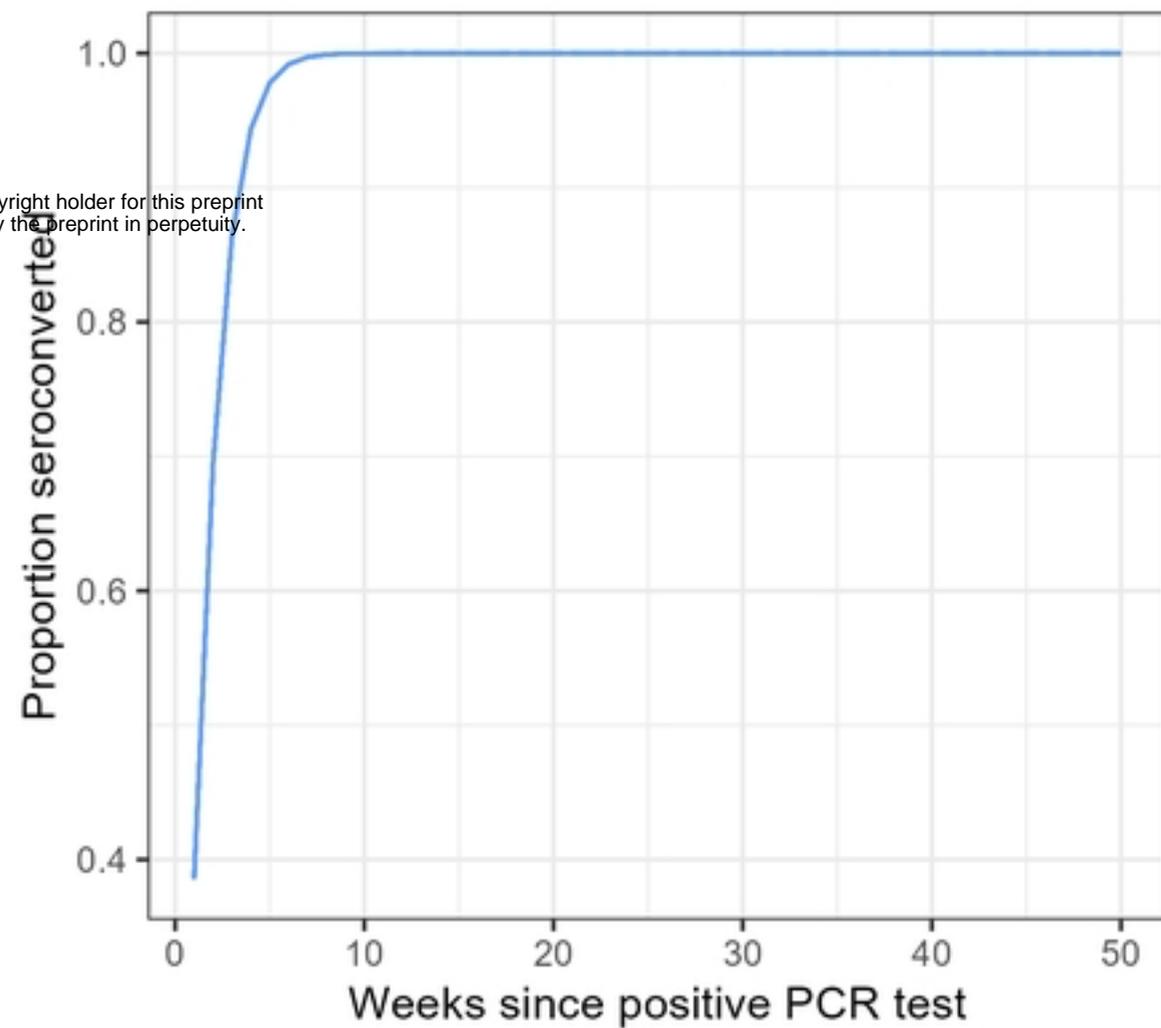


Supporting Information Fig1

EuroImmun



Wantai

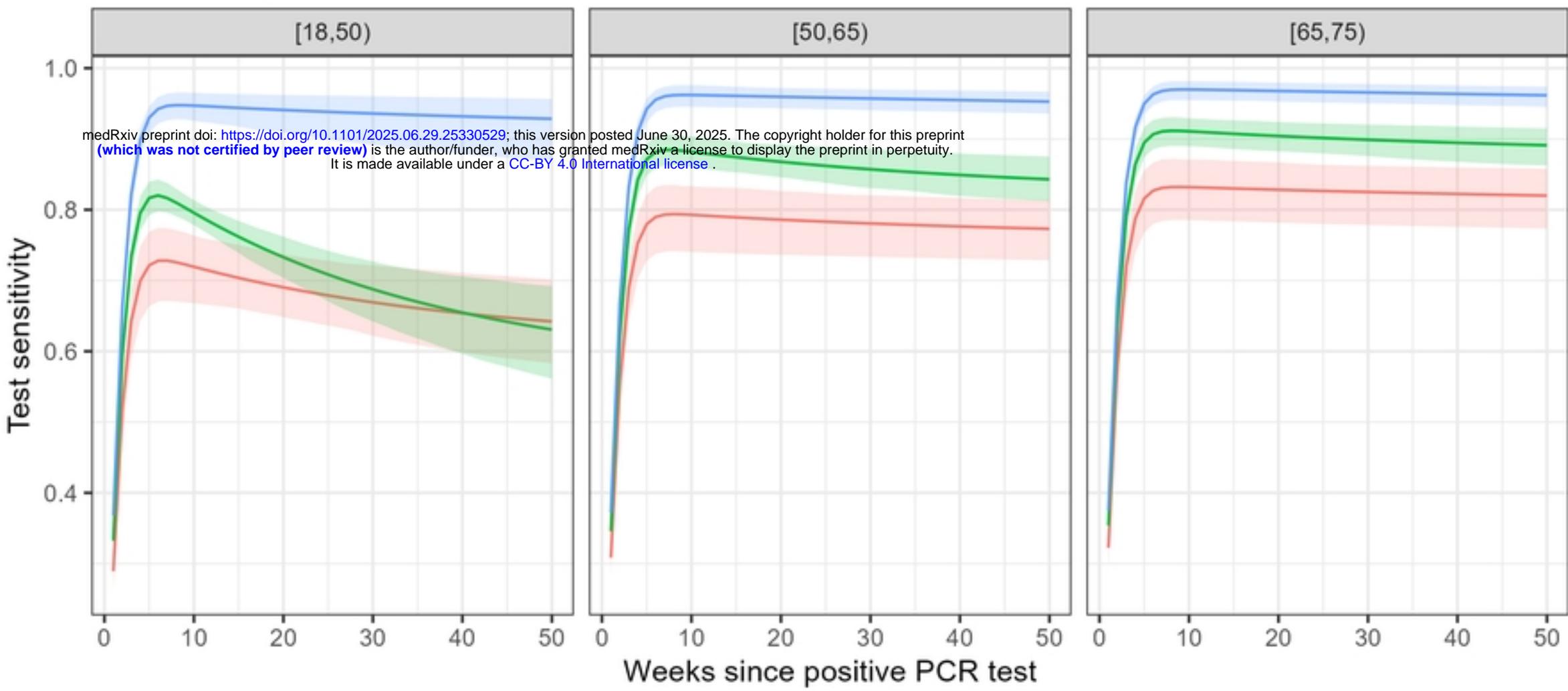


Age Group — [18,50) - - - [50,65) - - - [65,75)

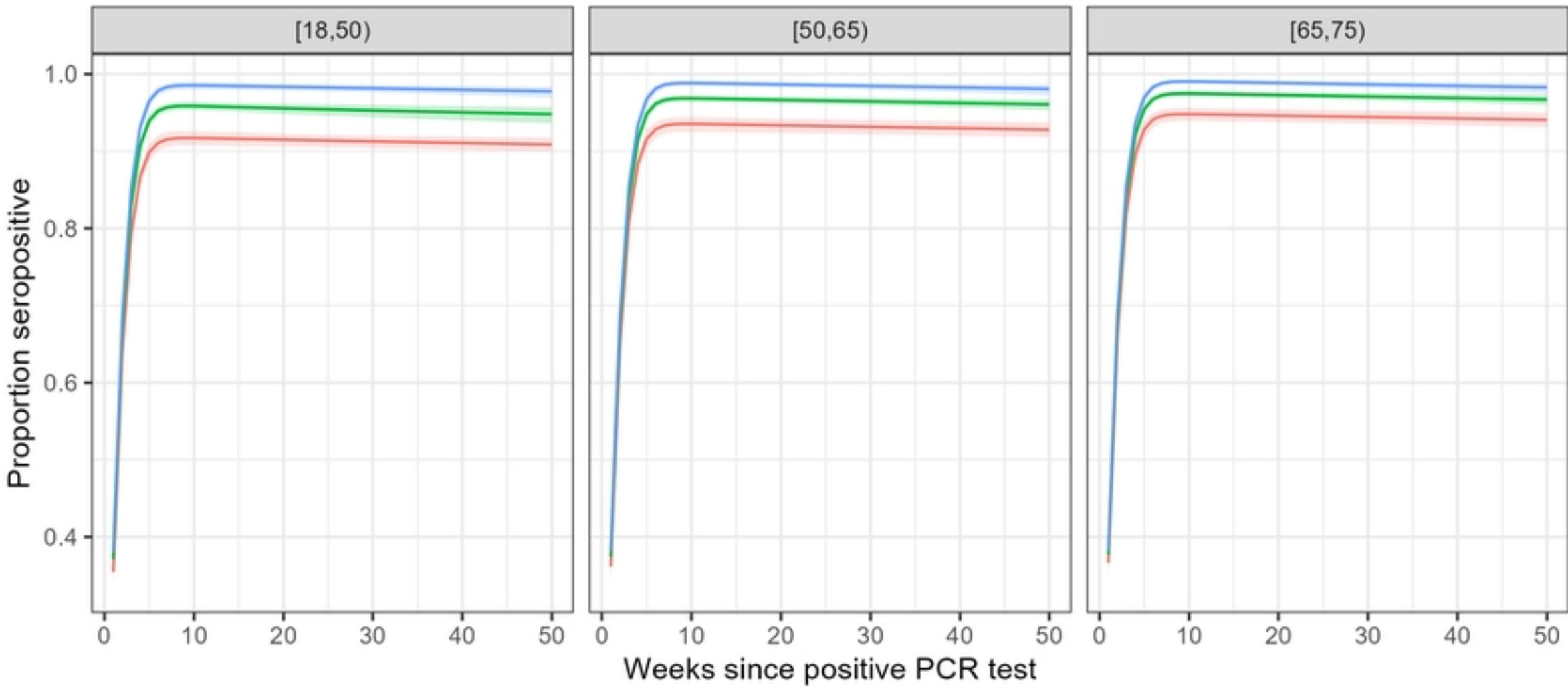
Severity — asymp — symp — hosp

Fig1

EuroImmune



Wantai



Severity — asymp — symp — hosp

Fig2

Weibull-Two-exponential Model Fit

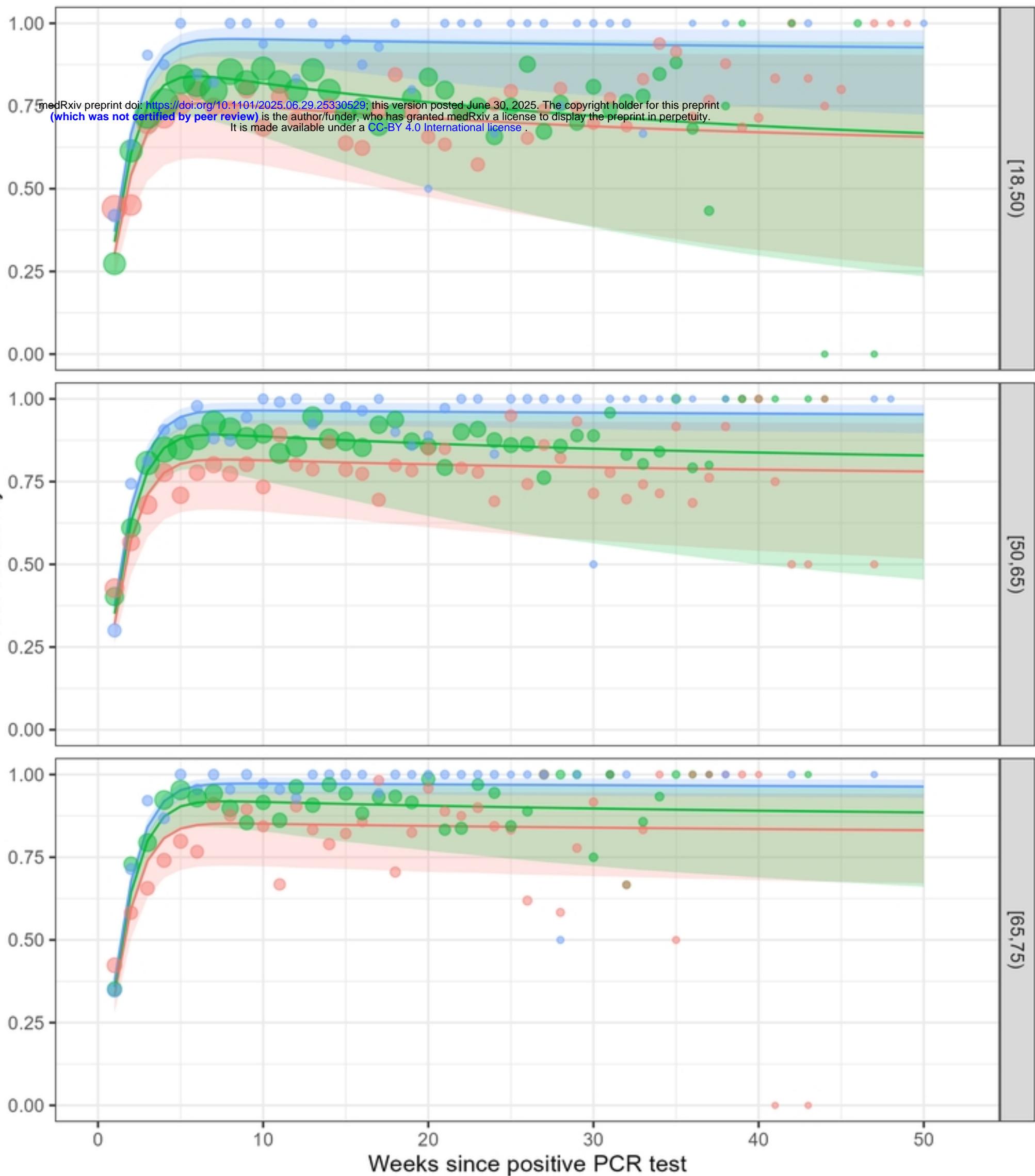


Fig3