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1 **Impact of variants of concern on SARS-CoV-2 viral dynamics in non-human** 2 **primates**

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16

17 **Abstract**

18 The impact of variants of concern (VoC) on SARS-CoV-2 viral dynamics remains poorly understood
19 and essentially relies on observational studies subject to various sorts of biases. In contrast, experimental
20 models of infection constitute a powerful model to perform controlled comparisons of the viral dynamics
21 observed with VoC and better quantify how VoC escape from the immune response.

22 Here we used molecular and infectious viral load of 78 cynomolgus macaques to characterize in detail
23 the effects of VoC on viral dynamics. We first developed a mathematical model that recapitulate the
24 observed dynamics, and we found that the best model describing the data assumed a rapid antigen-
25 dependent stimulation of the immune response leading to a rapid reduction of viral infectivity. When
26 compared with the historical variant, all VoC except beta were associated with an escape from this
27 immune response, and this effect was particularly sensitive for delta and omicron variant ($p < 10^{-6}$ for
28 both). Interestingly, delta variant was associated with a 1.8-fold increased viral production rate
29 ($p = 0.046$), while conversely omicron variant was associated with a 14-fold reduction in viral production
30 rate ($p < 10^{-6}$). During a natural infection, our models predict that delta variant is associated with a higher
31 peak viral RNA than omicron variant ($7.6 \log_{10}$ copies/mL 95% CI 6.8 – 8 for delta; $5.6 \log_{10}$ copies/mL

32 95% CI 4.8 – 6.3 for omicron) while having similar peak infectious titers ($3.7 \log_{10}$ PFU/mL 95% CI
33 2.4 – 4.6 for delta; $2.8 \log_{10}$ PFU/mL 95% CI 1.9 – 3.8 for omicron). These results provide a detailed
34 picture of the effects of VoC on total and infectious viral load and may help understand some differences
35 observed in the patterns of viral transmission of these viruses.

36 **Introduction**

37 The severe acute respiratory coronavirus 2 (SARS-CoV-2) is the causative agent of the Coronavirus-
38 induced disease 2019 (COVID-19) cumulating more than 500 million cases and over 18 million death
39 as measured by excess mortality as the end of 2022 (1,2). Repeatedly, several variants have emerged
40 and although most of them vanished quickly, some of them, called Variants of Concern (VoC), in
41 particular alpha, beta, gamma, delta and omicron have caused dramatic epidemic rebounds (3–5). These
42 variants have acquired specific mutations enhancing their infectious capacities and escaping the immune
43 response, leading to a dramatic loss of efficacy of monoclonal antibodies (6). They have also caused a
44 large drop in vaccine efficacy against disease acquisition even though until now vaccine remain largely
45 effective against severe disease (7–9).

46 While several millions of individuals have been infected by these VoC, we still do not have a precise
47 understanding on the effects of VoC on viral load. Even though some effects on larger levels of viral
48 excretion have been reported (10–13), these studies often lack of robustness, and may be biased by many
49 confounding factors that complicate comparisons, in particular reporting biases, heterogeneity in the
50 incubation period and vaccination coverage.

51 In that context where human clinical data are difficult to interpret, the non-human primate (NHP)
52 experimental model offers a unique opportunity to describe infection with SARS-CoV-2 in detail in a
53 fully controlled environment. Since 2020, our group has conducted many studies to evaluate the effects
54 of antiviral drugs or vaccines in this model (14,15), and showed its large predictive value (16). Here,
55 we analysed retrospectively viral load data obtained in 78 animals that were included as control arms of
56 these studies and that were infected with different strains of SARS-CoV-2 (historical, beta, gamma,
57 delta and omicron (BA.1)). In addition, we performed longitudinal measures of viral culture to evaluate

58 a potential effect of VoC on viral infectivity. Using the techniques of mathematical modelling, we
59 characterize the viral kinetics in these animals and we discuss their biological insights.

60

61 **Results**

62 **Variant of concern viral kinetics**

63 Several biomarkers were measured, both genomic RNA and subgenomic RNA were quantified at regular
64 interval over all the study period and infectious titers at 2 times points. All macaques developed a rapid
65 infection with genomic viral load peaking between 2- and 3-day post-infection (dpi) for the historical
66 and beta variant, 3.5 dpi for variant delta and 4 dpi for variants gamma and omicron (BA.1). Genomic
67 viral load was cleared at 8 dpi for the historical variant, 10 dpi for the beta variant, at 12 dpi for variants
68 delta and omicron (BA.1) and at 14 dpi for variant gamma (Fig 1 and S1 Table). In addition to viral
69 RNA, infectious titers were measured for 41 animals. Infectious titers were measured by Tissue Culture
70 Infectious Dose (TCID₅₀) from nasopharyngeal swab sampled at 2 time points per animal (day 2, 3 or 4
71 plus at day 5 or 7 post-infection). As we included several control animals from different studies, infected
72 with either TCID₅₀ or Plaque Forming Units (PFU), all TCID₅₀ were converted to PFU assuming 1 PFU
73 = 0.7 TCID₅₀ (17). All infectious titers quickly dropped to undetectable levels for the historical variant
74 at 5 dpi, where for the other variants the infectious titers remained consistent over the course of the
75 infection (Fig 1).

76 **Fig 1. Longitudinal measurements of genomic RNA, subgenomic RNA and infectious titers in 78**
77 **infected cynomolgus macaques.** Both limit of quantification and detection are depicted as empty dots,
78 the latter being lower. Upper limit of detection is depicted as filled squares.

79

80 **Viral dynamic model**

81 To account for the quick drop in infectious titers observed in the historical variant, (Fig 1 and S1 Fig)
82 several models incorporating an action of an antigen-mediated immune response were tested (Fig 2).
83 All models, except a model targeting the viral production parameter, provided an improvement of BIC

84 compared to a target cell limited model (Table 1). We found that a model targeting the infectious ratio
85 best described our data. In the following, we discuss the parameter values of the final constructed model
86 accounting for both an effect of the immune effector and variant specific effect on the parameters (see
87 below). For the historical variant, we estimated the infectivity rate parameter β at 1.86×10^{-5} copies $^{-1}$.d $^{-1}$
88 (95% confidence interval (CI) $1 \times 10^{-5} - 3.39 \times 10^{-5}$) and the loss rate of infected cells δ at 1.38 d $^{-1}$ (95%
89 CI 1.22 – 1.55), corresponding to a half-life of 12 hours. We estimated the viral load production
90 parameter p at 9.44×10^5 copies.cells $^{-1}$.day $^{-1}$ (95% CI $2.1 \times 10^5 - 1.68 \times 10^6$). This corresponds to a within-
91 host basic reproductive number R_0 (i.e., the number of newly infected cells by one infected cell at the
92 beginning of the infection) of 3.1 (95% CI 2 – 4.3) and a burst size (i.e the total number of infectious
93 virus produced by one cell over its lifespan at the beginning of the infection) of 136 (95% CI 121 – 153
94).

95 **Table 1: Alternative immune response models.**

Models	Description	Δ BIC
Reference model	Absence of immune response	–
Model 1	Reduction of the infectious ratio	–42.8
Model 2	Increase in infected cell clearance	–14.8
Model 3	Reduction of viral infection rate	–36.1
Model 4	Reduction of the viral production	+9

96

97 **Fig1. Schematic model of SARS-CoV-2 infection and action of the immune system.** The basic
98 model is a target cell limited model without any immune response. The parameters are : β the
99 infectivity rate, k the transfer rate between non-productive and productive infected cells, δ the loss
100 rate of productive infected cells, p the viral production rate, μ the ratio of infectious virus, g the
101 transfer rate between the compartments of the immune response and c the loss rate of both infectious
102 and non-infectious virus

103 **VoC specific effect on viral dynamic parameters**

104 Once an effect of the immune response was selected, a covariate search algorithm was used to find the
105 most likely VoC associated effects (see methods) and considered the historical variant as the reference.
106 Several variant-specific covariates were found on viral kinetics parameters that we detail below (Fig 3
107 and S2 Table). First, beta variant was characterized with a reduced infected cells death rate (δ) by a
108 factor of 0.7 (95% CI 0.6 – 0.9) compared with the historical variant (p-value < 0.01). This led to an

109 infected cell half-life of 17 hours and resulted in a longer period of viral load shedding as infected cells
110 produced viruses for longer period of time. Gamma variant had an effect on the parameter θ (p-value <
111 0.001), the amount of immune effector F_{20} required to reduce by half the infectious ratio, increasing it
112 by a factor of 9508 (95% CI 387 – 50 041) resulting in higher peak viral load and a longer duration of
113 infectious virus shedding (Fig 4). Variant delta is characterized by an effect on both θ (p-value < 0.001)
114 and the viral production parameter p (p-value < 0.05), increasing those parameters by factors 336 (95%
115 CI 49 – 1191) and 1.78 (95% CI 1 – 3) respectively. Finally, omicron variant (BA.1) affected the
116 parameters of the immune system θ (p-value < 0.001), the viral production rate parameter p (p-value <
117 0.001) and the infectious ratio μ (p-value < 0.001) modifying them by factors 229 (95% CI 27 – 884),
118 0.07 (95% CI 0.02 – 0.2) and 18 (95% CI 4 – 51) respectively (Fig 4). The model well reproduced the
119 viral load of all animals in the individuals fits (S2 Fig). Additionally, we performed a sensitivity analysis
120 on our best model (i.e. Model 1 including an effect on the infectious ratio μ). We tested several delays
121 of the immune effector (from 1 to 6 days post infection) and several numbers of transfer compartments
122 (from 5 to 30) and performed the covariate search on all models. We found that a delay of 3 days yielded
123 the best results (S3 Table) and very similar covariate were selected across all models (S3 and S4 Fig).

124 **Fig 3. Estimated population parameters for each variant.** We represent the mean value and 95%
125 confidence interval of populations parameters for each variant. We represent only parameters having at
126 least one variant-specific effect. Full table for population parameters is in S2 Table. The dashed black
127 line represents the historical value.

128 **Fig 4. Simulation of variant of concern impact on viral load.** Using simulations, we sampled
129 parameters considering both the uncertainty in the estimation and the inter-individual variability (see
130 methods) . We represent the mean viral load of all variants and its 95% confidence interval. Dotted lines
131 are the limits of detections

132

133 **Predicted impact of variants in a natural infection setting**

134 The main limitation of translating these results to humans is the fact that infection in animals is done
135 with a large inoculum dose (10^5 - 10^6 PFU), while human infections are presumably initiated with much
136 lower virus dose (18). Human experimental infections were performed with 10 TCID₅₀ (19) in the nose,
137 i.e., 10,000-100,000 times less virus than in the animal model. Using simulations with lower inoculum,

138 considering both uncertainty in the estimation and inter-individual variability (see methods), we are able
139 to derive metrics of interest for each variant.

140 The historical variant is characterized by a mean time to peak of 4.3 dpi (95% CI 3.7 – 4.8) and of 3.5
141 dpi (95% CI 3 – 3.9) for genomic RNA and infectious titers respectively. We found a mean peak viral
142 load of 6.3 log₁₀ copies/mL (95% CI 5.5 – 7) and of 2.1 PFU/mL (95% CI 1.2 – 2.9) for genomic RNA
143 and infectious titers, respectively.

144 The reduced infected cell clearance rate of the beta variant resulted in a longer period of viral load
145 shedding. The duration of the acute infection stage was consequently increased from 10.9 days (95% CI
146 9.5 – 13.1) for the historical variant to 13.4 days (95% CI 11.1 – 15.7) for the beta variant.

147 All variants except beta have shown an effect on the antigen-mediated response, greatly reducing its
148 impact on viral kinetics. As the effect of the antigen-mediated response was reduced, the infectious ratio
149 was increased leading to more infectious particles produced over longer periods of time. This led to the
150 increase of the infectious titers clearance stage duration from 1.5 days for the historical variant (95% CI
151 0.6 – 1.9) to 6 days (95% CI 4.4 – 7.5), 3.8 days (95% CI 3.1 - 4.6) and 3.7 days (95% CI 2.8 – 4.5) for
152 the gamma, delta and omicron variants respectively (Fig 5). This is in line with numbers of studies
153 showing the immune escape capabilities of those variants (20–22).

154 An effect increasing the viral production parameter (p), as observed for the delta variant, results in
155 largely higher peak viral load of 7.6 log₁₀ copies/mL (95% CI 6.8 – 8.2) and peak infectious titers of 3.7
156 PFU/mL (95% CI 2.4 – 4.6). Conversely, an effect reducing the viral production parameter, as observed
157 for the omicron variant, results in lower peak viral load compared to the historical variant of 5.6 log₁₀
158 copies/mL (4.8 – 6.3) but very similar peak infectious titers at 2.8 PFU/mL (95% CI 1.9 – 3.8). This is
159 due to an effect of omicron on the infectious ratio, increasing the proportion of infectious virus produced.

160 **Fig 5. Impact of VoC on viral load metrics in the context of an infection with a low inoculum.** We
161 represent the mean and 95% confidence interval for each variant. The dashed black line represents the
162 historical mean value.

163 Discussion

164 Here, we used mechanistic models to characterize in detail the viral dynamics of the main variants of
165 concern in an experimental model of non-human primates. We evaluated the impact of an antigen-
166 mediated immune response on the viral dynamics and found that an effect reducing the infectious ratio
167 best described our data. Some of the variants of concern, gamma, delta and omicron (BA.1) showed a
168 strong ability to escape this response greatly increasing the number of infectious viruses produced over
169 the course of the infection compared to the historical variant. Interestingly, the delta variant was
170 associated with an increased viral production rate, whereas the omicron variant was associated with a
171 lower viral production rate but a higher infectious ratio.

172 Using simulations in a natural infection scenario, we found that omicron infections, relative to delta
173 infections, are associated with lower peak viral RNA and reduced duration of viral RNA clearance while
174 having similar peak infectious titers and duration of infectious titers clearance.

175 These results suggest that omicron's infectiousness cannot be attributed to an increased viral RNA
176 production but maybe due to an immune escape coupled with an increased infectious ratio, greatly
177 increasing the number of infectious particles produced.

178 Although many other factors are at play to explain the increased transmissibility of certain variants of
179 concern, differences in viral dynamics can provides insights into the biology of those variants. As such,
180 delta infections featuring increased peak viral load and infectious titers can increase the risk of
181 "superspreading" events and infections outside of close-contact settings (23). Omicron infections, on
182 the other hand, featuring lower peak viral load concentration (24) but similar infectious titers respective
183 to other variants, may result in transmission events that would not occur with other variants because
184 insufficient infectious titers would be produced. These results are coherent with reports showing lower
185 pathogenicity of omicron infection (25), as they are associated with lower viral burden.

186 The combination of immune escape abilities, increased infectious ratio and longer duration of infectious
187 virus shedding could be a possible mechanism to explain the enhanced transmissibility of omicron
188 variant. As such, the quantification of infectious titers over time is crucial to inform further public health
189 policies and adjust the isolation period accordingly.

190

191 Our study has some important limitations. First, although we can characterise in detail the viral dynamics
192 of SARS-CoV-2 in nonhuman primates in a controlled environment, the inoculated dose is extremely
193 high (10 000 to 100 000 times higher (19)) compared with human infection. This leads to rapid saturation
194 of target cells and makes it difficult to accurately estimate the early phase of infection. In the future,
195 studies evaluating lower inoculum in NHP can greatly improve the precision in the estimation of the
196 early phase of infection. Second, we developed an extension of the target cell limited model considering
197 the effect of an antigen-mediated immune response decreasing the infectious ratio μ . We here attribute
198 this effect to the immune system but we have no information to which immune effectors (antibodies,
199 cytokines, cytotoxic cells, natural killers, intracellular processes etc...) this could be linked if even
200 attributable to one. This type of antigen-mediated response allows us to incorporate the effect of time
201 on a parameter but the underlying biological mechanisms are unclear and may be due to inherent
202 differences between variants not captured by any covariates.

203 Third, we assumed a 3-days delay in the establishment of this antigen-mediated reduction of the
204 infectious ratio and verified that it performed best in a sensitivity analysis (S4 Fig). Although there is
205 some variability, the covariates search is overall consistent.

206 Fourth, the infectious titers are only a measure of *in vitro* infectivity, and to what extent they translate
207 into infectiousness is unknown. In addition, both the upper and lower limit of quantification makes it
208 difficult to precisely estimate the infectious ratio parameter μ . Finally, in a context where more than
209 half of the world population has received at least one dose of COVID-19 vaccine (26), there is very little
210 information on the natural infection with different variants. Additional data with vaccinated animals
211 could help differentiate certain aspects of the abilities of the new variants to escape the immune system.

212

213 **Materials and methods**

214 **Experimental procedure**

215 Data comes from studies performed on cynomolgus macaques to evaluate the viral dynamics of SARS-
216 CoV-2 variants. Our study includes 78 cynomolgus macaques (*Macaca fascicularis*) coming from

217 control arms of several studies and have received no pharmacological interventions besides placebo. All
218 animals were infected with doses ranging from 7×10^4 to 10^6 PFU of different SARS-CoV-2 strains.
219 Animals are infected via both nasopharyngeal and intratracheal route with 10% of the initial volume
220 administered in the nose and 90% in the trachea. The study is composed of 5 groups, each infected with
221 a different SARS-CoV-2 strains: 44 Historical (hCoV-19/France/IDF0372/2020 strain; GISAID
222 EpiCoV platform under accession number EPI_ISL_406596), 9 Bêta (B.1.351 - hCoV-19/USA/MD-
223 HP01542/2021, BEI NR-55283), 5 Gamma (P.1 - hCoV-19/Japan/TY7-503/2021, BEI NR-54984), 11
224 Delta (B.1.617.2 - hCoV-19/USA/MD-HP05647/2021, BEI NR-55674) and 9 Omicron (B.1.1.529 –
225 hCoV-19/USA/MD-HP20874/2021, BEI NR-56462). For each group both genomic RNA and
226 subgenomic RNA swab samples were quantified using real time PCR in both the nasopharynx and in
227 the trachea. For 41 animals (13 Historical, 3 Beta, 5 Gamma, 11 Delta and 7 Omicron (BA.1)) infectious
228 titers were measured at 2 time points, early (2, 3 or 4 days post infection) and late (5 or 7 days post
229 infection) using Tissue Culture Infectious Dose (TCID₅₀) from nasopharyngeal swab samples (16). As
230 we included animals from different studies that were inoculated with different methods (PFU or
231 TCID₅₀), we normalized all measures of infectious titers by converting all TCID₅₀ measurements to
232 Plaque Forming Units (PFU) using the formula $1 \text{ PFU} = 0.7 \text{ TCID}_{50}$ (17). As no infectious titers were
233 measured in the trachea samples, we focused the main analysis on the nasopharyngeal compartment.
234 The results mainly focus on the genomic viral load as the subgenomic is a directly proportional to the
235 latter.

236 **Basic viral dynamic model**

237 We used a previously described model of SARS-COV-2 viral dynamics to reconstruct the
238 nasopharyngeal viral load of infected animals. In this model, target cells (T) become infected cells (I_1)
239 at a rate β . Infected cells transition into productive infected cells (I_2) at a rate k and produce infectious
240 virus (V_I) at a rate $p\mu$ and non-infectious virus (V_{NI}) at a rate $p(1 - \mu)$. Productive infected cells are
241 cleared at a rate δ and both infectious and non-infectious virus are cleared at a rate c . The basic within-
242 host reproductive number, representing the number of newly infected cells by one infected cell, is $R_0 =$

243 $\frac{\beta p T_0 \mu}{c \delta}$ and the burst-size, representing the number of infectious virus produced by on infected cells over
244 its lifespan, is $N = \frac{p \mu}{\delta}$. The model is described with the following set of ordinary differential equations:

$$245 \quad \frac{dT}{dt} = -\beta V_I T \quad (1)$$

$$246 \quad \frac{dI_1}{dt} = \beta V_I T - k I_1 \quad (2)$$

$$247 \quad \frac{dI_2}{dt} = k I_1 - \delta I_2 \quad (3)$$

$$248 \quad \frac{dV_I}{dt} = p \mu I_2 - c V_I \quad (4)$$

$$249 \quad \frac{dV_{NI}}{dt} = p(1 - \mu) I_2 - c V_{NI} \quad (5)$$

250 **Assumption on parameter values**

251 Some parameters of the model were fixed to ensure identifiability. The transfer rate parameter between
252 infected cells and productive infected cells was fixed to $k = 4 \text{ day}^{-1}$ (corresponding to a mean duration
253 of the eclipse phase, i.e. the time for infected cells to start producing viruses, of $\frac{1}{k} = 6 \text{ hours}$) (27). The
254 viral clearance c was set to 10 day^{-1} based on previous work (14,16,28). As only the product $p T_0$ is
255 identifiable, we choose to fix the initial number of target cell to $T_0 = 12\,500$ cells following the same
256 assumptions as in (16). As the nasal cavity of the animals is small, a substantial fraction of the inoculum
257 does not penetrate the upper respiratory tract. To account for this, we introduced a parameter h
258 representing the proportion of the inoculum that arrive on the site of infection. We fixed this parameter
259 at 20% with a standard deviation of 20% to allow for individual variability. As both the initial infectious
260 inoculum and the number of RNA copies were known we used that information as our initial condition
261 for the infectious virus and non-infectious virus compartment. Therefore, our initial conditions were set
262 to :

$$263 \quad T_0(t = 0) = 1.25 \times 10^4 \quad (6)$$

264 $I_1(t = 0) = 0$ (7)

265 $I_2(t = 0) = 0$ (8)

266 $V_I(t = 0) = V_I(0)_i \times h_i \times 0.1$ (9)

267 $V_{NI}(t = 0) = (V_{NI}(0)_i - V_I(0)_i) \times h_i \times 0.1$ (10)

268 Where $V_I(0)_i$ is the administered dose in PFU of subject i , $V_{NI}(0)_i$ is the total number of RNA copies
269 in the initial inoculum of subject i and h_i is the proportion of the inoculum actively initiating the
270 infection.

271 **Models incorporating antigen-mediated immune response**

272 To account for the quick drop in infectious titers observed for the historical variant (Fig 1 and S2 Fig),
273 we tested several models incorporating an action of an antigen-mediated immune response. We assumed
274 a delay of 3 days for the immune response to take place to account for the differentiation and
275 proliferation of the immune response (29). We modelled this delayed immune effector compartment
276 using the Linear Chain Trick (LCT) assuming an Erlang distribution with $j = 20$ transition compartment
277 and a mean time spent in those compartment of $\tau = 3 \text{ d}^{-1}$ (30). This number of compartments allowed us
278 to shift the distribution of the time spent in the transition's states from an exponential to a normal
279 distribution. The equations for the transfer compartments are written as follows:

280 $\frac{dF_1}{dt} = I_2 - gF_1$ (11)

281 $\frac{dF_2}{dt} = gF_1 - gF_2$ (12)

282 \vdots

283 $\frac{dF_{20}}{dt} = gF_{19} - d_F F_{20}$ (30)

284 In the following only the compartment F_{20} will serve as the effector for the action of the immune system.

285 The transfer rate parameter g is then written as $\frac{j}{\tau}$ and fixed to 6.67 d^{-1} and the loss rate of the final

286 effector d_F is fixed to 0.4 d^{-1} (28). Several modes of action of the response system were tested:

287 Model 1 : Immune effector decreases the infectious ratio μ

288 In this model, the immune effector directly decreases the infectious ratio parameter μ using an Emax

289 function type expression :

290
$$\frac{dV_I}{dt} = p\mu\left(1 - \frac{F_{20}}{F_{20} + \theta}\right)I_2 - cV_I \quad (31)$$

291
$$\frac{dV_{NI}}{dt} = p\left(1 - \mu\left(1 - \frac{F_{20}}{F_{20} + \theta}\right)\right)I_2 - cV_{NI} \quad (32)$$

292 With θ being the amount of immune effector F_{20} needed to reduce by half the infectious ratio.

293 Model 2 : Immune effector increases infected productive cells death rate δ

294 The death rate of infected cells is increased in proportion to the amount of immune effector F_{20} .

295
$$\frac{dI_2}{dt} = kI_1 - \delta(1 + \varphi F_{20})I_2 \quad (33)$$

296 Where φ is the strength of the immune system.

297 Model 3 : Immune effector reduces the infectivity rate β

298 In this model, the immune effector blocks virus entry in the cells by reducing the infectivity parameter

299 β .

300
$$\frac{dT}{dt} = -\beta(1 - \varphi F_{20})V_I T \quad (34)$$

301
$$\frac{dI_1}{dt} = \beta(1 - \varphi F_{20})V_I T - kI_1 \quad (35)$$

302 Model 4 : Immune effector reduces the production rate p

303 In the same way as model 1, the viral load production parameter is reduced by the immune effector with
304 an Emax type function:

$$305 \quad \frac{dV_I}{dt} = p \left(1 - \frac{F_{20}}{F_{20} + \theta} \right) \mu I_2 - cV_I \quad (36)$$

$$306 \quad \frac{dV_{NI}}{dt} = p \left(1 - \frac{F_{20}}{F_{20} + \theta} \right) (1 - \mu) I_2 - cV_{NI} \quad (37)$$

307 All models were compared based on the Bayesian Information Criterion (BIC). We selected the model
308 that yielded the lowest BIC and the best individual fits.

309 **Statistical model**

310 Parameter estimation was performed using non-linear mixed effect modelling. The statistical models
311 describing the genomic RNA, subgenomic RNA and the infectious titers are:

$$312 \quad y_{ij}^1 = \log_{10} V(t_{ij}, \Psi_i) + e_{ij}^1 \quad (38)$$

$$313 \quad y_{ij}^2 = \log_{10} f \times I_2(t_{ij}, \Psi_i) + e_{ij}^2 \quad (39)$$

$$314 \quad y_{ij}^3 = \log_{10} V_I(t_{ij}, \Psi_i) + e_{ij}^3 \quad (40)$$

315 Where the superscript 1, 2 and 3 refers to the genomic RNA, subgenomic RNA and infectious titers,
316 respectively. We denote y_{ij} is the j^{th} observation of subject i at time t_{ij} , with $i \in 1, \dots, N$ and $j \in 1, \dots, n_i$
317 with N the number of subject and n_i the number of observations for subject i . The function describing
318 the total viral load kinetics $V(t_{ij}, \Psi_i)$ predicted by the model at time t_{ij} defined as: $V_I(t_{ij}, \Psi_i) + V_{NI}(t_{ij},$
319 $\Psi_i)$ predicted by the model at time t_{ij} . The The vector of individual parameters of subject i is noted Ψ_i
320 and e_{ij} is the additive residual Gaussian error of constant standard deviation σ . The vector of individual
321 parameters depends on a fixed effects vector and on an individual random effects vector, which follows
322 a normal centered distribution with diagonal variance-covariance matrix Ω . All parameters follow a log-
323 normal distribution to ensure positivity except both parameters μ and h which follows logit-normal
324 distribution and are bounded between 0 and 1. We assumed random effect on all parameters and removed

325 them using backward procedure, if they were < 0.1 or their RSE $> 50\%$. All biomarkers (i.e. genomic
326 RNA, subgenomic RNA and infectious titers) were fitted simultaneously.

327 **Selection of variant-specific effect on the viral dynamic parameters**

328 Using the best model selected at the previous step, we sought to identify VoC-specific effect on the
329 parameters of the model (β , δ , p, μ and θ). We first performed a backward selection of the random effects
330 removing non-significant ones (i.e. relative standard error $> 50\%$) if the BIC wasn't degraded by more
331 than 2 points. We then used the Conditional Sampling use for Stepwise Approach on Correlation tests
332 (COSSAC) to identify variant specific effect (31). Then a backward procedure was used to remove any
333 non-significant covariate effect with a Wald test (i.e. the covariate was removed if its coefficient effect
334 relative standard error was $> 50\%$). This procedure was repeated until all nonsignificant covariate effects
335 had been eliminated. Additionally, we performed a sensitivity analysis on our best structural model. We
336 tested for several delays in the establishment of the antigen-mediated effector (from 1 to 6 days) and on
337 the number of transitions compartments (from 5 to 30) and then performed the covariate search on all
338 model combinations .

339 **Simulation of natural human infection**

340 Finally, we used our final model to assess the impact of variants of concern on viral load and viral
341 infectivity in a natural infection setting. We used a starting inoculum of 10 infectious virus, as described
342 in an experimental challenge conducted in England (19) to simulate a human infection. The initial
343 conditions are then written as:

$$344 \quad V_I(t = 0) = 10$$

$$345 \quad V_{NI}(t = 0) = 0$$

346 We provided confidence interval on the mean predicted viral load, considering both the uncertainty in
347 the estimation and the inter-individual variability. We first sampled $M = 100$ population parameters in
348 their estimation distribution and then, for each variant, sampled $N = 30$ individual parameters from each
349 sets of population parameters (leading to 3000 individual parameters per variant). We calculated the

350 predicted viral load of all individuals and derived the mean viral load over the simulated individuals at
351 all times with its 95% inter quantile range. Additionally, we provided the distribution of several viral
352 dynamic metrics, namely:

- 353 - the area under viral load curve,
- 354 - the peak and time to peak viral load
- 355 - the duration of the clearance stage, calculated as the time interval between the peak
356 viral load and the time to undetectable viral load
- 357 - the duration of the acute phase, calculated as the time between the first and the last
358 detectable viral load (32).

359 **Parameter estimation**

360 All parameters were estimated by computing the maximum-likelihood estimator using the stochastic
361 approximation expectation-maximization (SAEM) algorithm implemented in Monolix Software
362 2020R1 (33,34). Standard errors and the likelihood were computed by importance sampling.

363

364 **Acknowledgement**

365 We would like to thank everyone in the CEA and at Pasteur Institute that have helped for data
366 collection. We thank Alan Perelson for helpful discussions.

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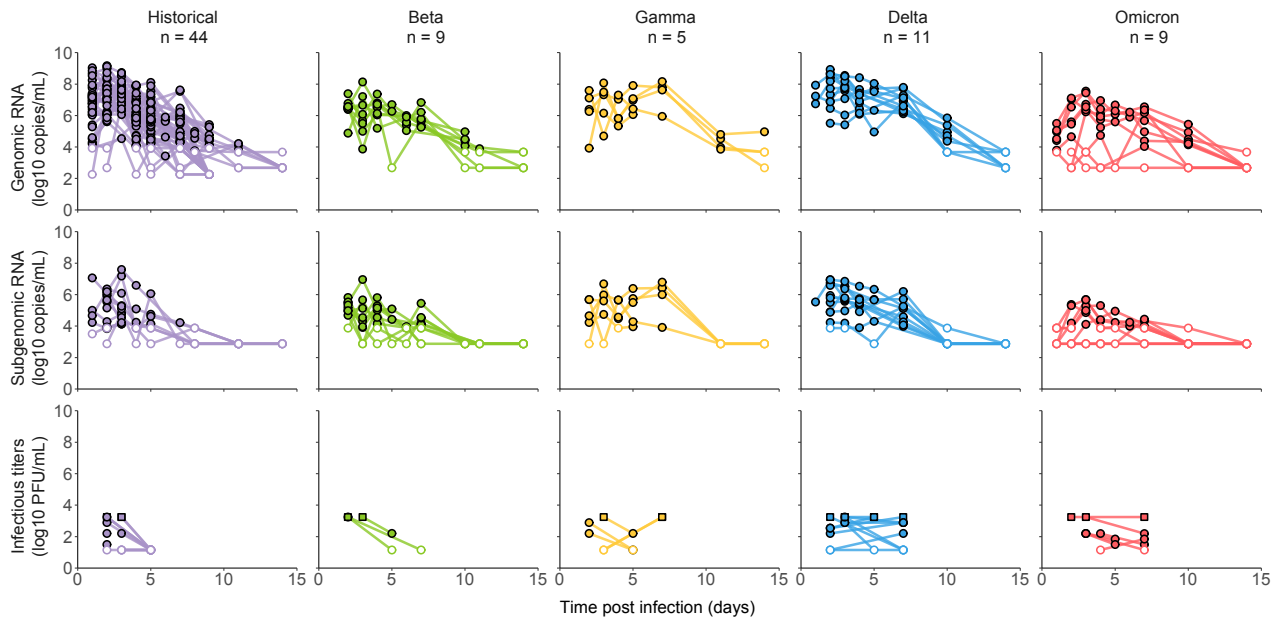
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373 Figures

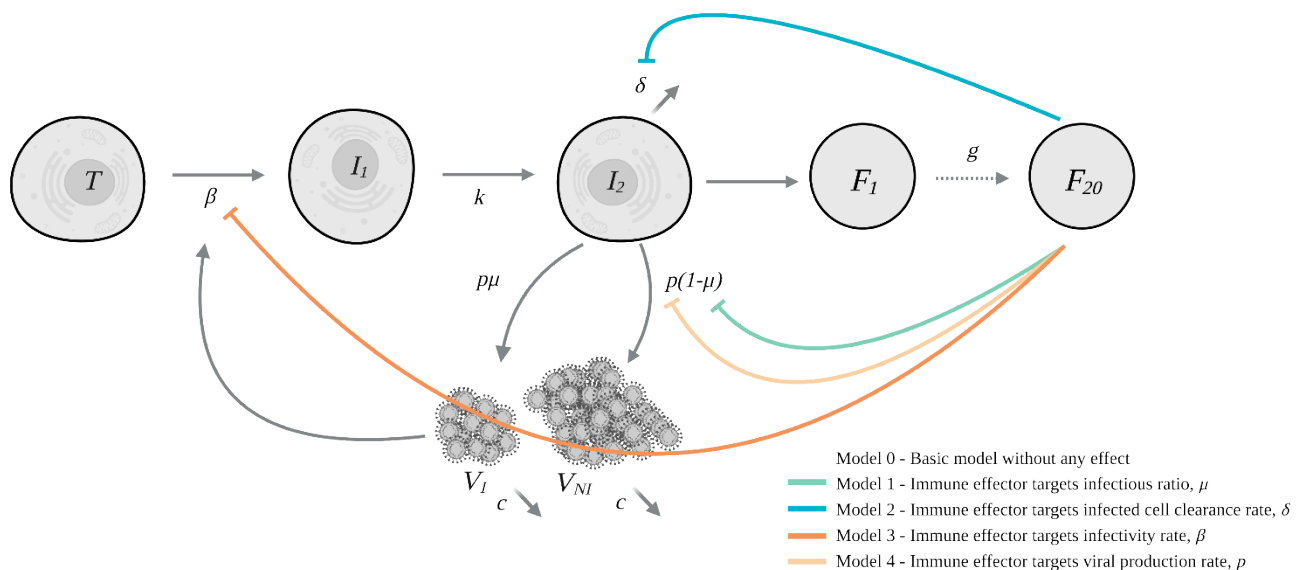
374 **Fig 1. Longitudinal measurements of genomic RNA, subgenomic RNA and infectious titers in 78**
 375 **infected cynomolgus macaques.** Both limit of quantification and detection are depicted as empty dots,
 376 the latter being lower. Upper limit of detection is depicted as filled squares (present only un infectious
 377 titers).



378

379 **Fig2. Schematic model of SARS-CoV-2 infection and action of the immune system.** The basic model is a target
 380 cell limited model without any immune response. The parameters are : β the infectivity rate, k the transfer rate
 381 between non-productive and productive infected cells, δ the loss rate of productive infected cells, p the viral
 382 production rate, μ the ratio of infectious virus, g the transfer rate between the compartments of the immune
 383 response and c the loss rate of both infectious and non-infectious virus.

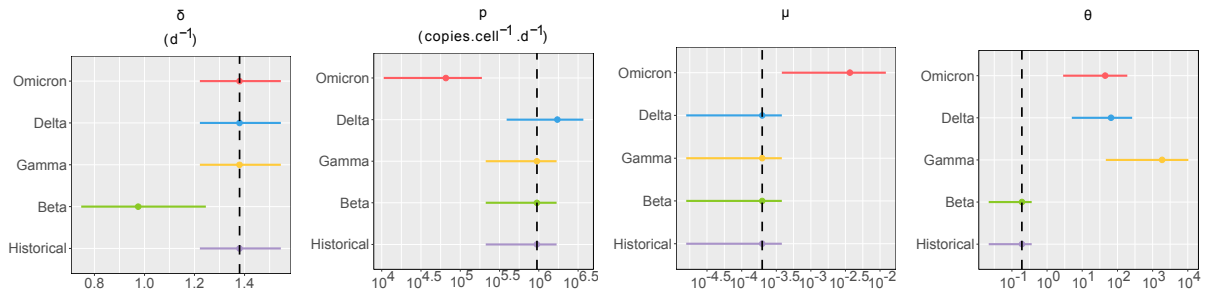
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386 **Fig 3. Estimated population parameters for each variant.** We represent the mean value and 95%
 387 confidence interval of populations parameters for each variant. We represent only parameters having at
 388 least one variant-specific effect. Full table for population parameters is in S2 Table. The dashed black
 389 line represents the historical value.

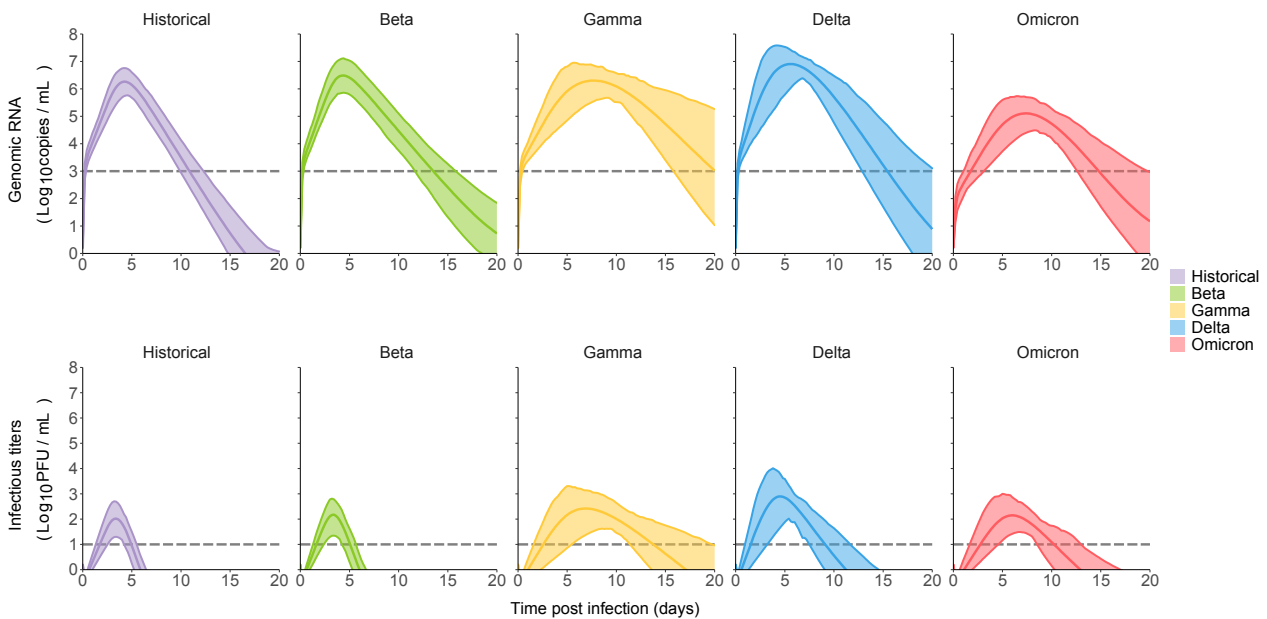
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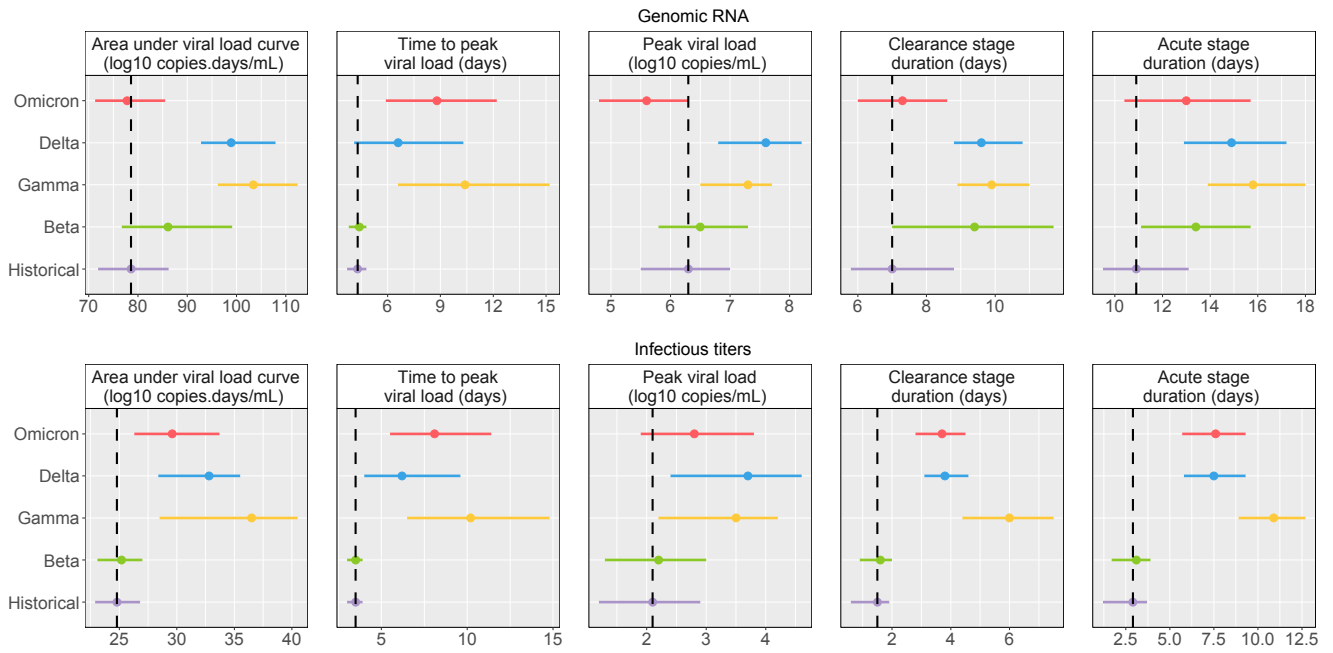
393 **Fig 4. Simulation of variant of concern impact on viral load.** Using simulations, we sampled
 394 parameters considering both the uncertainty in the estimation and the inter-individual variability (see
 395 methods). We represent the mean viral load of all variants and its 95% confidence interval. Dotted lines
 396 are the limits of detections.



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398

399 **Fig 5. Impact of VoC on viral load metrics in the context of an infection with a low inoculum.** We
400 represent the mean and 95% confidence interval for each variant. The dashed black line represents the
401 historical mean value.



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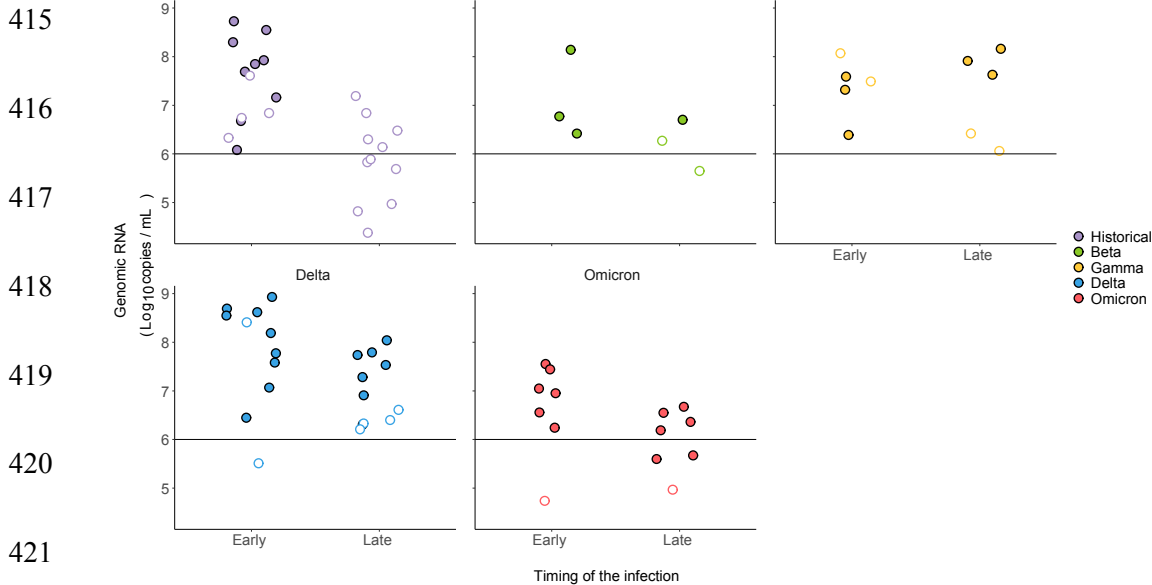
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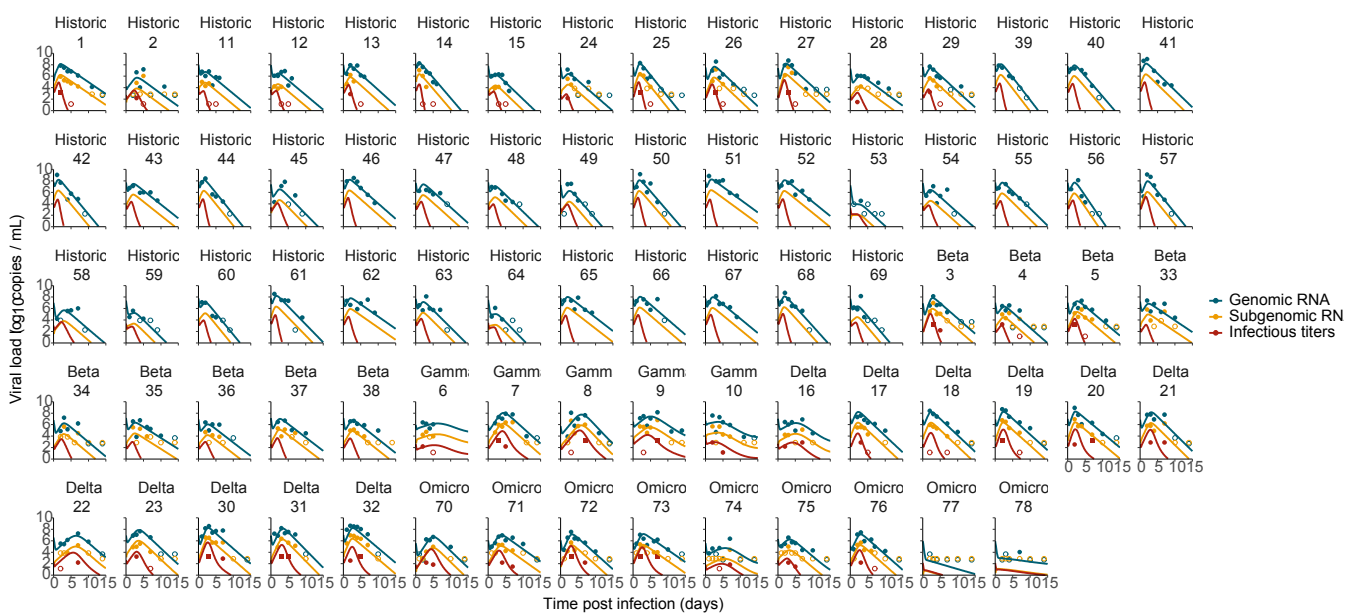
410 Supplementary material

411 **S1 Fig. Relationship between genomic RNA and infectious titers.** Undetectable infectious titers are
412 depicted as empty circles. The timings early and late correspond to swab sampled at 2, 3 or 4 days post
413 infection and 5 or 7 days post infection respectively.

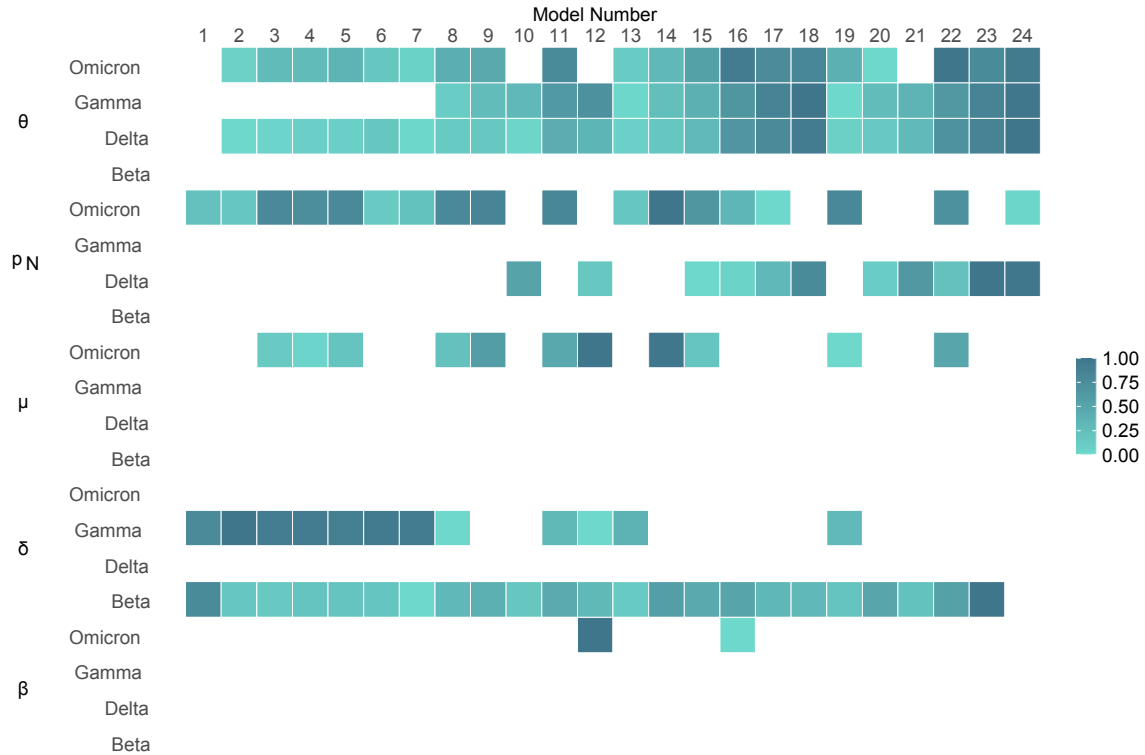
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424 **S2 Fig. Individual fit of genomic RNA, subgenomic RNA and infectious titers in all animals.**
425 Undetectable values are represented as empty dots. Values above the upper limit of quantification are
426 represented as squares.



427 **S3 Fig. Sensitivity analysis on the covariate selection algorithm.** We performed a sensitivity analysis
 428 on our best model. The model IDs are represented on top, as described in S3 Table. The scale represents
 429 the magnitude of the covariate effect rescaled for each row with 0 being the minimum value and 1 the
 430 maximum. Empty tiles indicate that no covariates were selected for this variant-parameter relationship.



431
 432 **S4 Fig. Consistency of the covariate selection algorithm.** We represent the number of times a
 433 covariate was found on a variant-parameter relationship across all 24 models. Empty tiles indicate that
 434 no covariates were found for this variant-parameter relationship.



447

448 **S1 Table. Characteristics of the 78 animals analysed.** Descriptive statistics of the animals calculated
 449 on the raw data.

450

Strains	Number of animals	Mean weight (kg)	Mean peak viral load (log ₁₀ copies/mL)	Mean peak PFU (log ₁₀ PFU/mL)	Mean time to first undetectable viral load	Mean time to first undetectable PFU
Historical	44	3.7	7.6	2.3	8	4
Beta	9	4.9	7.1	3.2	10	6
Gamma	5	4.2	7.8	3	14	5
Delta	11	3.6	8.1	2.9	12	5
Omicron	9	4.6	6.4	2.4	12	7

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454 **S2 Table. Estimates of the population parameter and covariate effects for the best model.** **The
 455 standard error for the R_0 parameters were calculated using the delta method.

<i>Population parameters (unit)</i>	Fixed effect (RSE%)	SD of random effect (RSE%)
β (copie.d ⁻¹)	1.85×10^{-5} (33)	-
p (copies.cell ⁻¹ .d ⁻¹)	9.44×10^5 (40)	0.61 (17)
δ (d ⁻¹)	1.38 (6)	0.2 (20)
f (unitless)	1.36×10^{-3} (19)	-
μ (unitless)	1.98×10^{-4} (47)	-
θ (unitless)	0.19 (45)	0.32 (103)
<i>Covariate model</i>	Covariate effect (RSE%)	p-value
Beta on δ	-0.357 (32)	0.00201
Gamma on θ	8.39 (15)	< 10^{-6}
Delta on p	0.554 (50)	0.047
Delta on θ	5.49 (15)	< 10^{-6}
Omicron on p	-2.82 (19)	< 10^{-6}
Omicron on μ	2.7 (23)	1.98×10^{-5}
Omicron on θ	5.04 (18)	< 10^{-6}
<i>Basic reproductive number</i>	Value (RSE%)**	
R_0	3.1 (19)	
$R_{0\beta}$	4.5 (20)	
$R_{0\gamma}$	3.1 (19)	
$R_{0\delta}$	5.4 (34)	
$R_{0\omicron}$	2.8 (28)	
<i>Residual errors</i>	Value (RSE%)	
$\sigma_{Genomic\ RNA}$ (log ₁₀ copies/mL)	0.98 (4)	
$\sigma_{Subgenomic\ RNA}$ (log ₁₀ copies/mL)	0.89 (6)	
$\sigma_{Infectious\ titers}$ (log ₁₀ PFU/mL)	1.79 (14)	

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462 **S3 Table. Sensitivity analysis on the delayed immune response.** Using the best structural model (i.e.
 463 Model 1 including an effect on the infectious ratio) we tested several delays for the immune response to
 464 take place and performed the covariate search algorithm on all models.

Model ID	Number of transfer compartments F	Delay (days)	Transfer rate parameter g (d^{-1})	BIC before COSSAC	BIC after COSSAC (Δ BIC)
1	5	1	5	2451	2429 (-22)
2	5	2	2.5	2409	2384 (-25)
3	5	3	1.666666667	2405	2374 (-31)
4	5	4	1.25	2408	2373 (-35)
5	5	5	1	2408	2375 (-33)
6	5	6	0.833333333	2409	2379 (-30)
7	10	1	10	2432	2409 (-23)
8	10	2	5	2409	2373 (-36)
9	10	3	3.333333333	2410	2361 (-49)
10	10	4	2.5	2411	2381 (-30)
11	10	5	2	2413	2366 (-47)
12	10	6	1.666666667	2414	2367 (-47)
13	20	1	20	2426	2402 (-24)
14	20	2	10	2409	2363 (-46)
15	20	3	6.666666667	2411	2360 (-51)
16	20	4	5	2414	2377 (-37)
17	20	5	4	2416	2379 (-37)
18	20	6	3.333333333	2417	2381 (-36)
19	30	1	30	2424	2397 (-27)
20	30	2	15	2408	2377 (-31)
21	30	3	10	2413	2385 (-28)
22	30	4	7.5	2417	2363 (-54)
23	30	5	6	2419	2380 (-39)
24	30	6	5	2420	2393 (-27)

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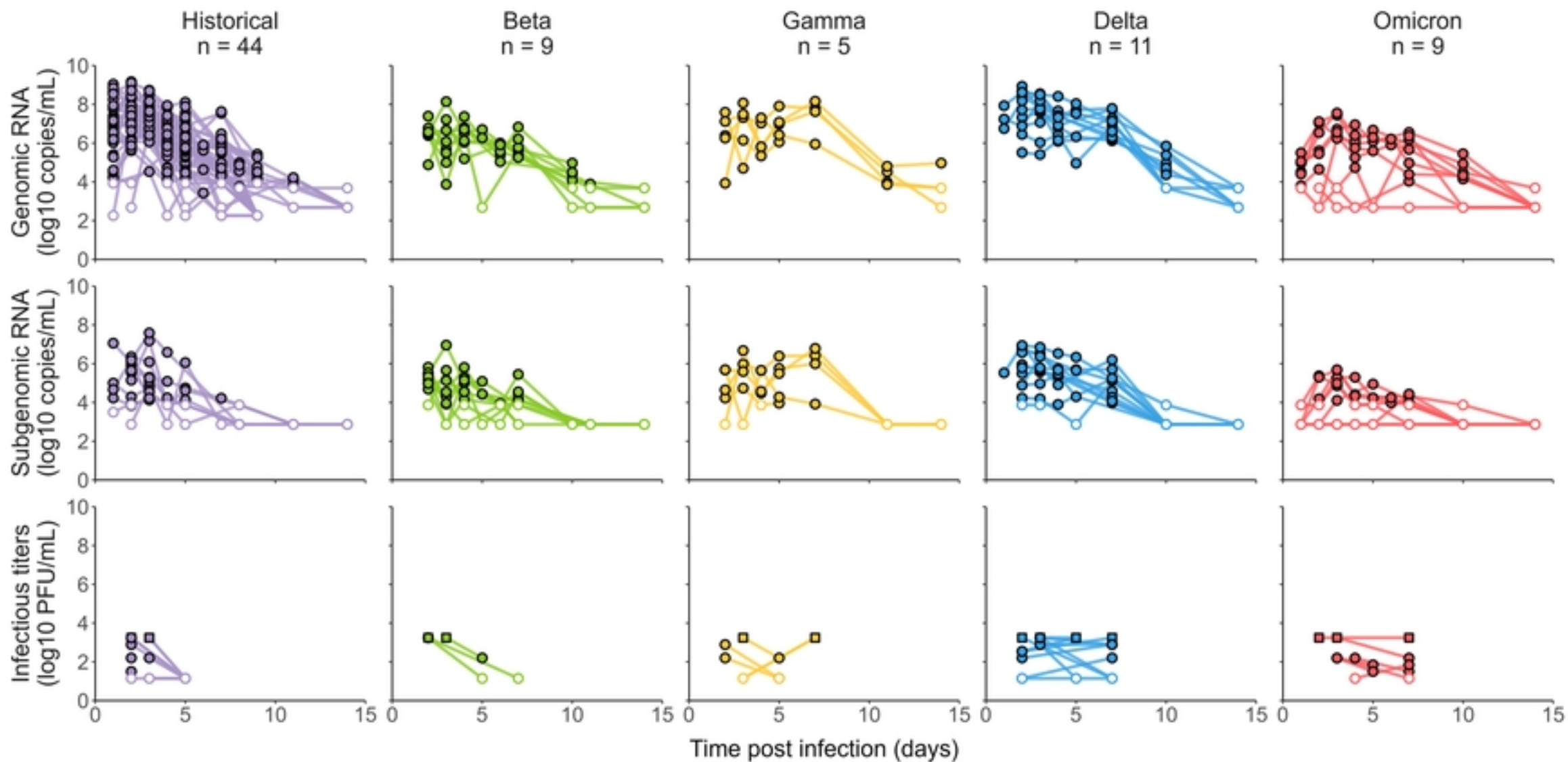
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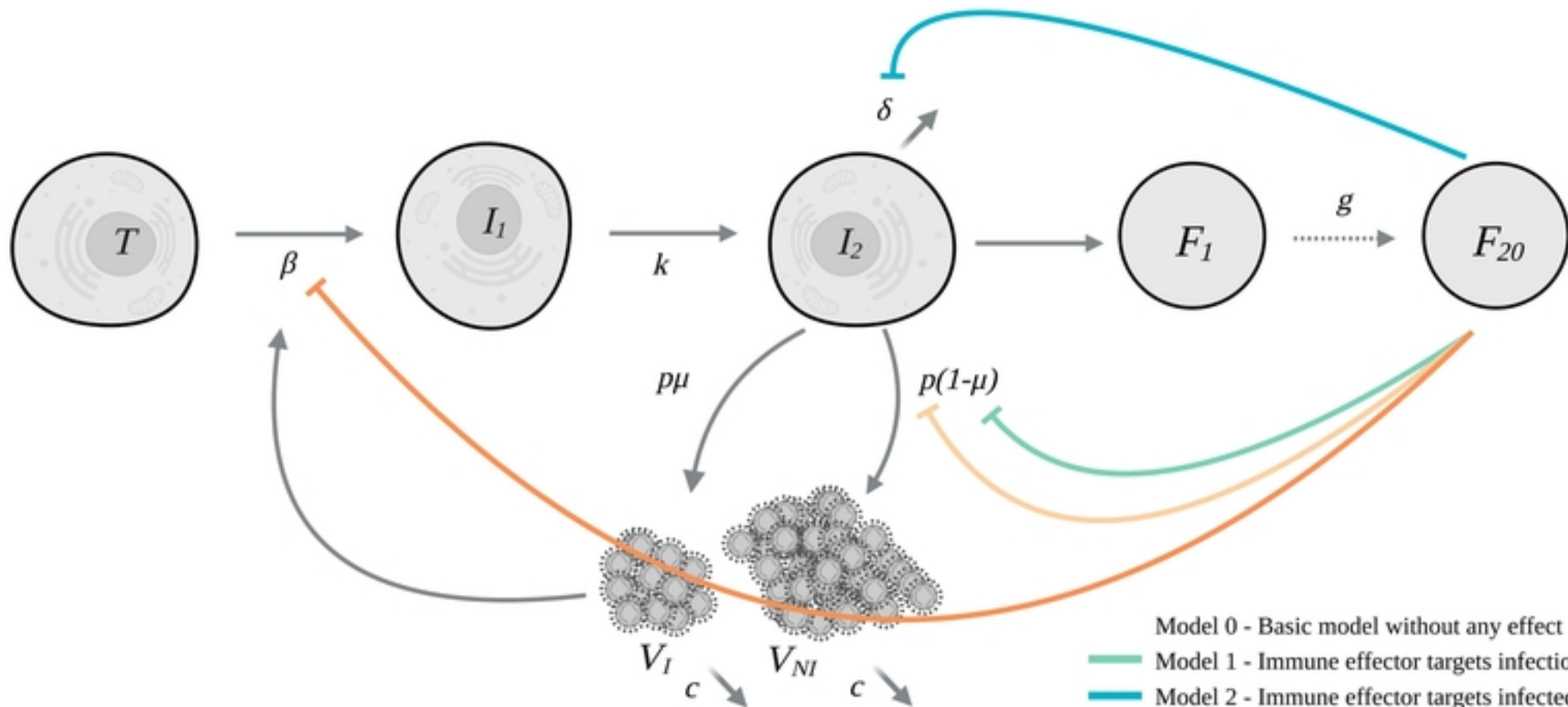
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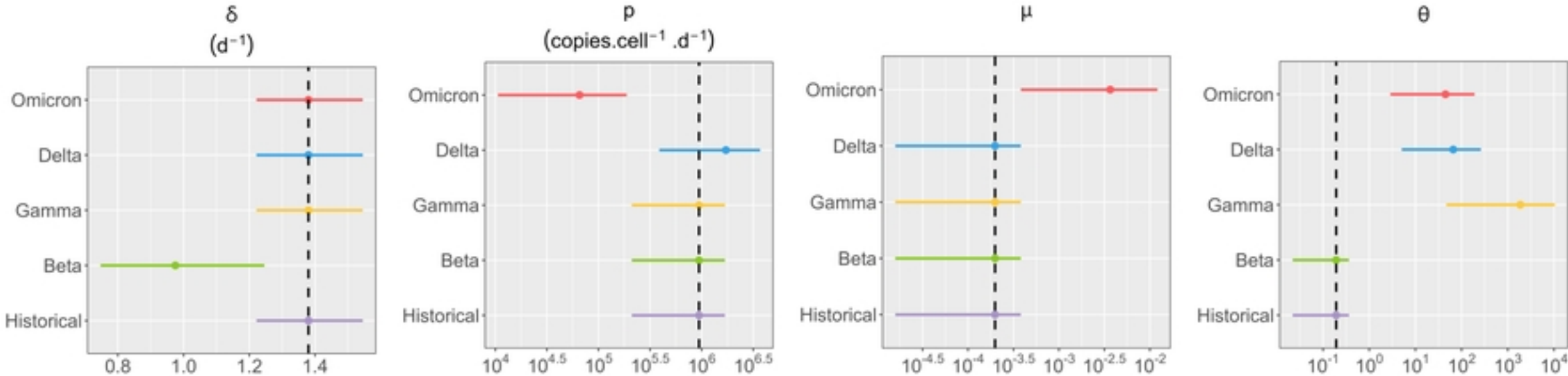


Longitudinal measurements of genomic RNA, subgenomic RNA and infectious titers

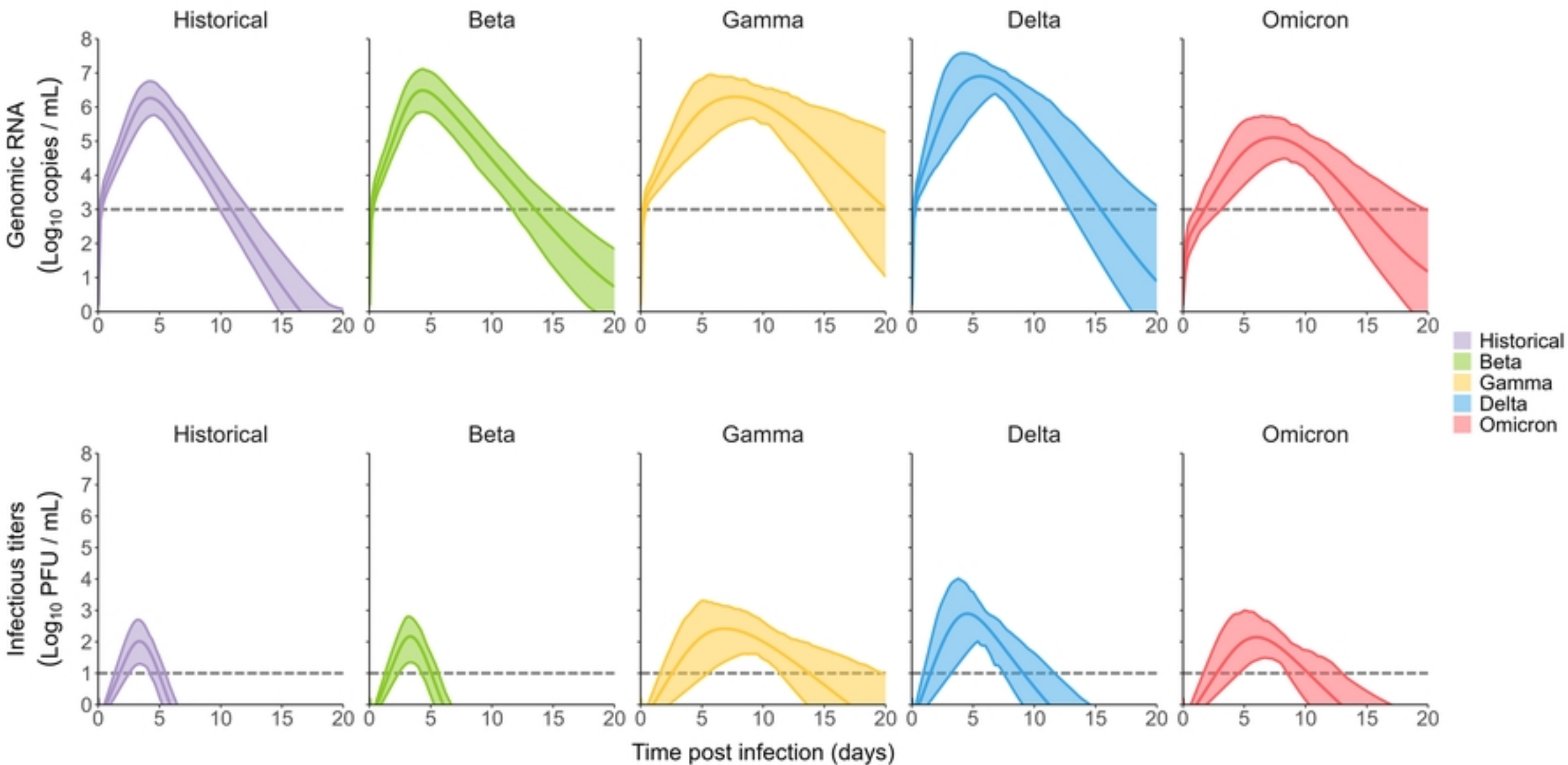


- Model 0 - Basic model without any effect
- Model 1 - Immune effector targets infectious ratio, μ
- Model 2 - Immune effector targets infected cell clearance rate, δ
- Model 3 - Immune effector targets infectivity rate, β
- Model 4 - Immune effector targets viral production rate, p

Schematic model of SARS-CoV-2 infection and action of the imm

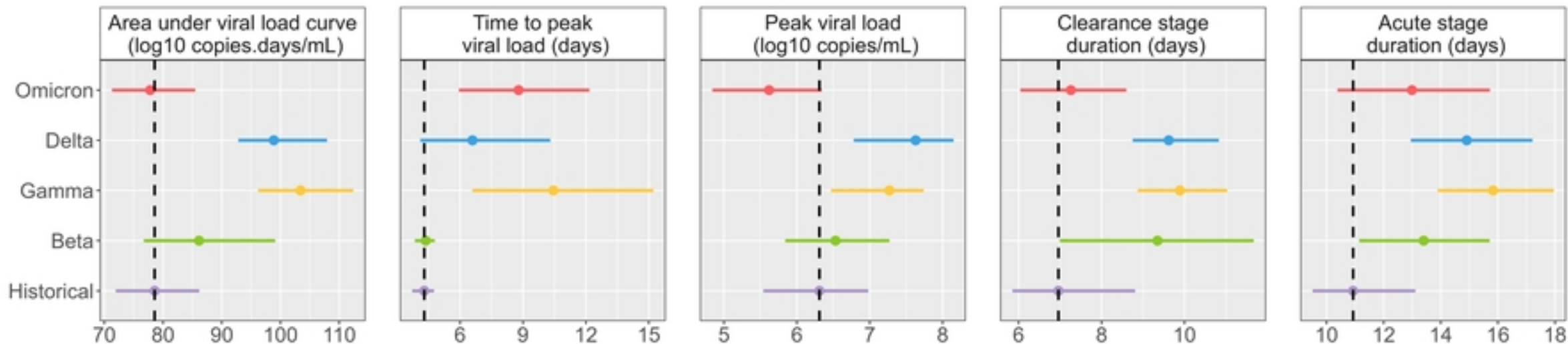


Estimated population parameters for each variant

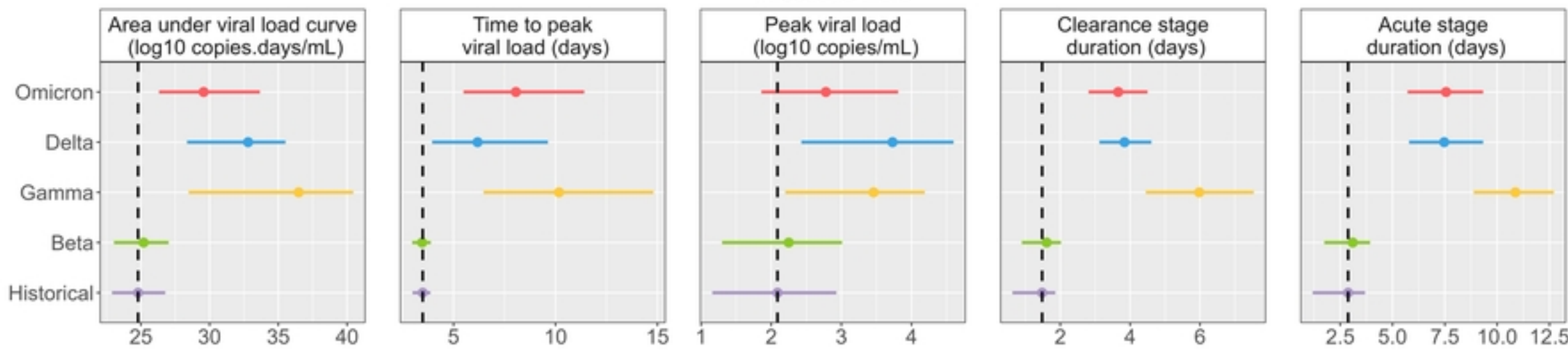


Simulation of variant of concern impact on viral load

Genomic RNA



Infectious titers



Impact of VoC on viral load metrics in the context of an infection