Modelling the efficacy of antiviral strategies of SARS-CoV-2 in a context of emerging variants: from hospitalized patients to general community

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RESEARCH CENTER
ON INFECTIOUS DISEASES

Inserm
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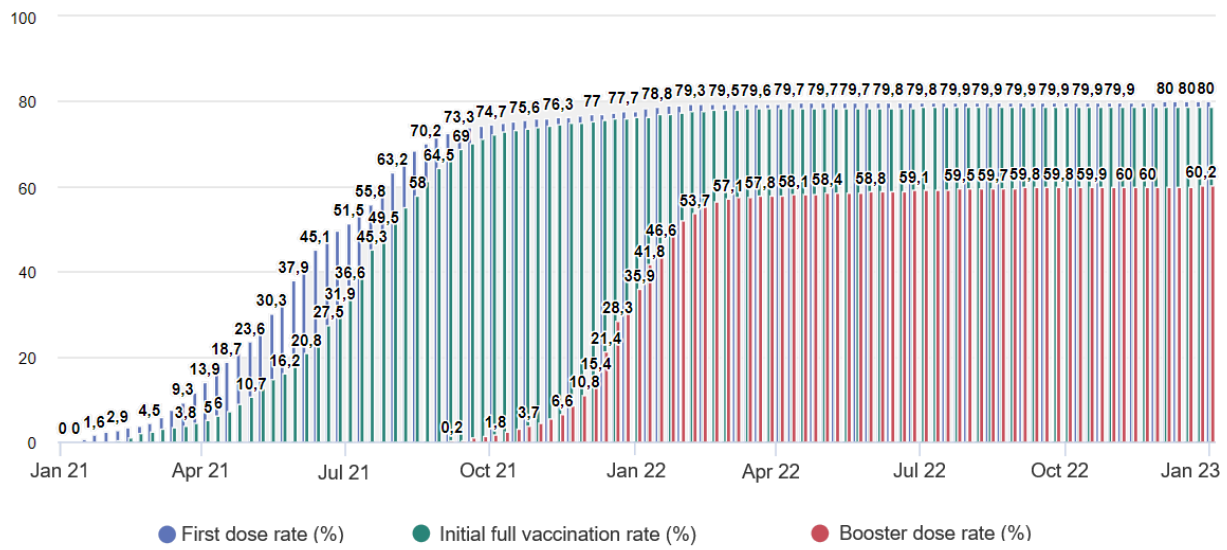
The COVID-19 pandemic – a changing landscape

From early 2021, the epidemic as been affected by:

- a strong **vaccination** campaign,
- and the **emergence of variants of concerns** (VoCs)



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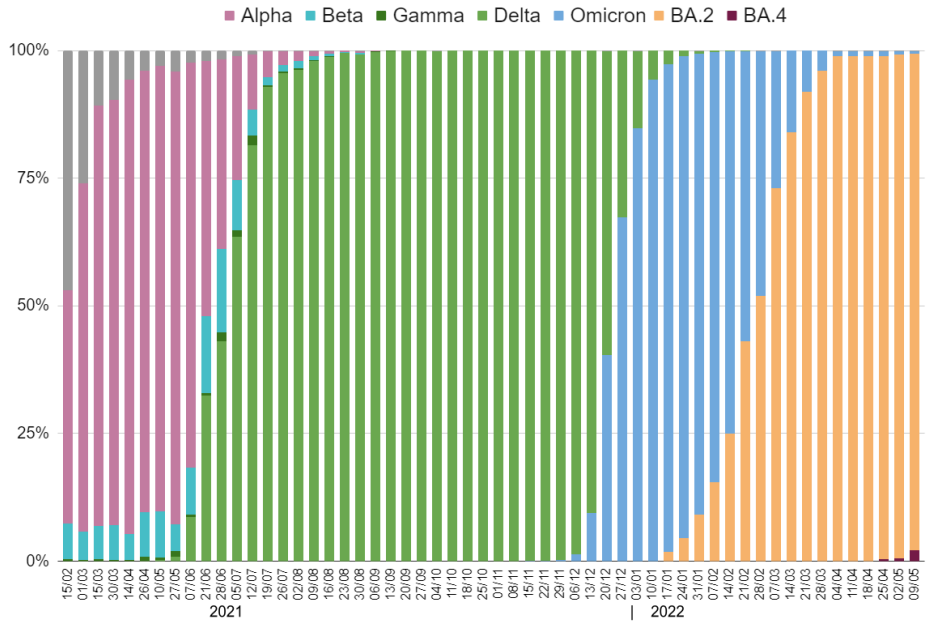

Successive waves of VoCs in France since 2021 [2]

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The COVID-19 pandemic – a changing landscape

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- a strong **vaccination** campaign,
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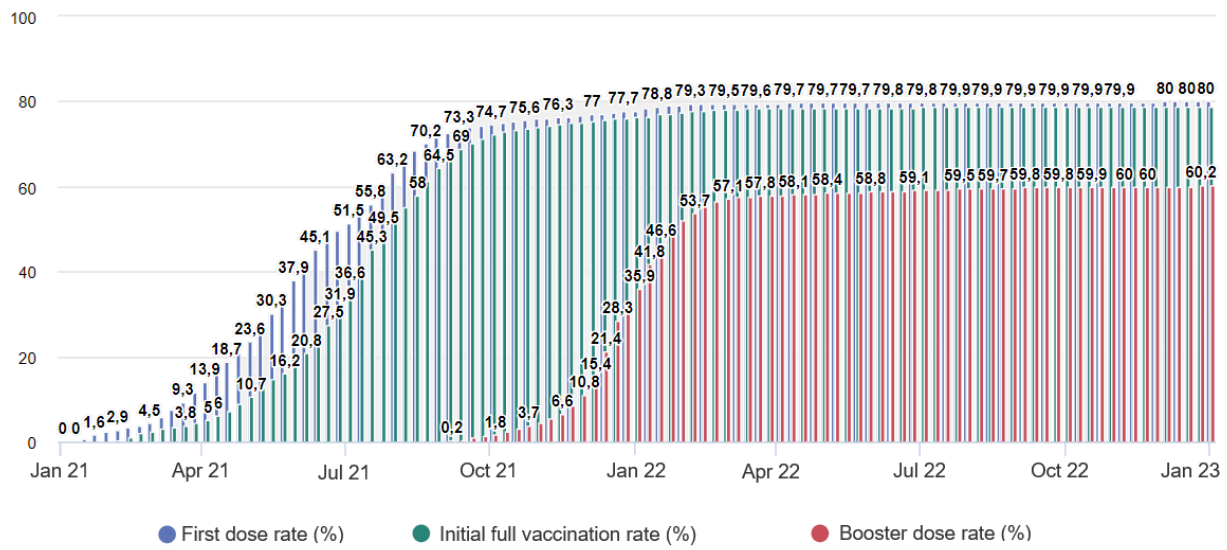
→ Modified the **severity** and **transmission** of the virus



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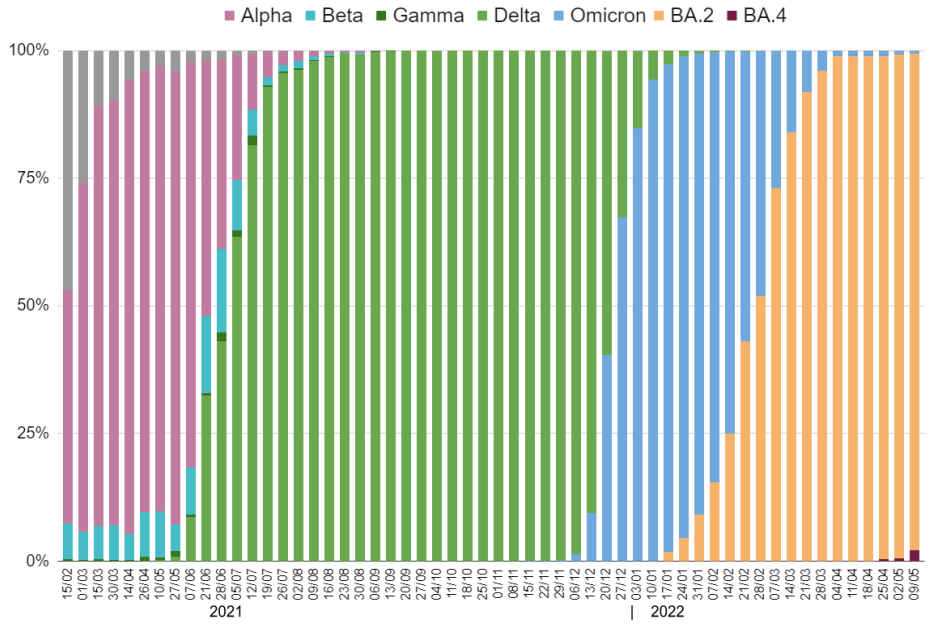

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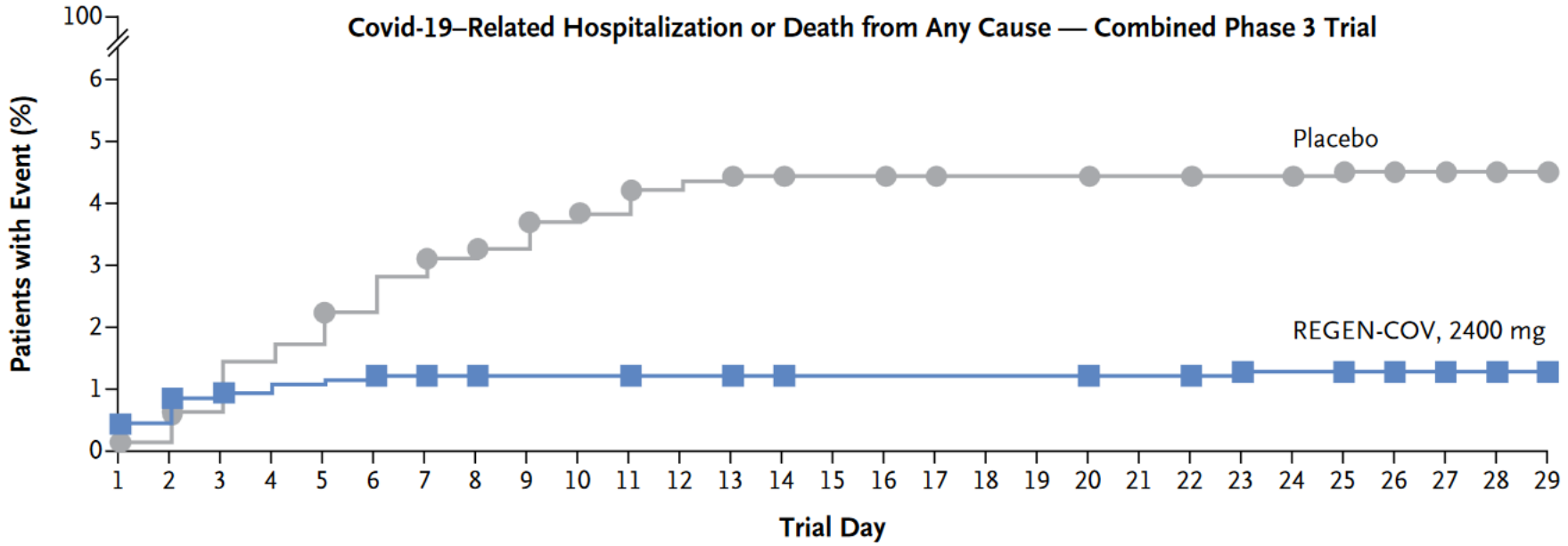
Antiviral treatments impacted by the changing landscape

- Variant of concerns could also modify the treatments efficacy
- Particularly the neutralizing monoclonal antibodies (mAbs) → sensitive to the variant of infection
- Reduce the risk of severe disease if administred early after symptom onset [3,4,5]



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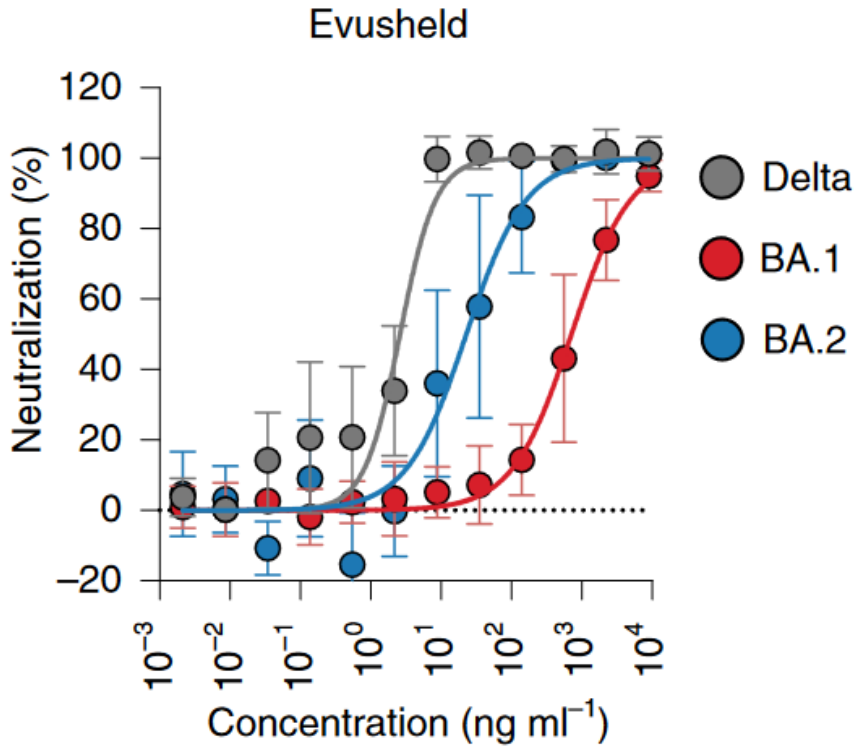
Evusheld (AZD7442)

- Combination of **Tixagevimab** (AZD8895) and **Cilgavimab** (AZD1061) [6]
- **FDA approved in pre-exposure prophylaxis** in fragile population
- *In vitro* loss of efficacy against Omicron [7]
- Use was progressively suspended [8]



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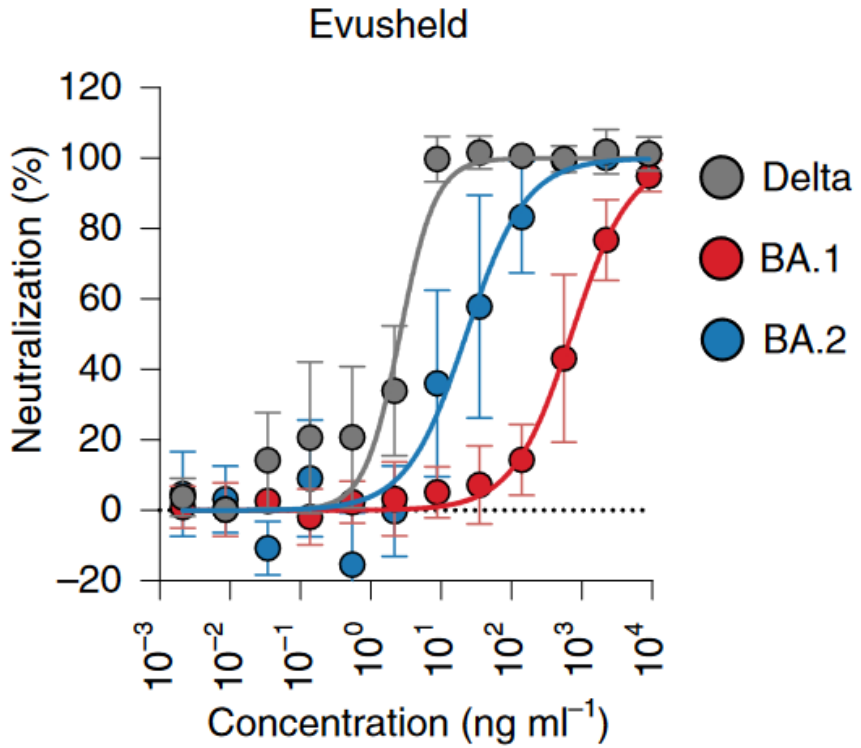
What is the impact of the variants on the efficacy of these mAbs *in vivo*?



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Evaluation of antiviral efficacy of mAbs in a context of changing landscape

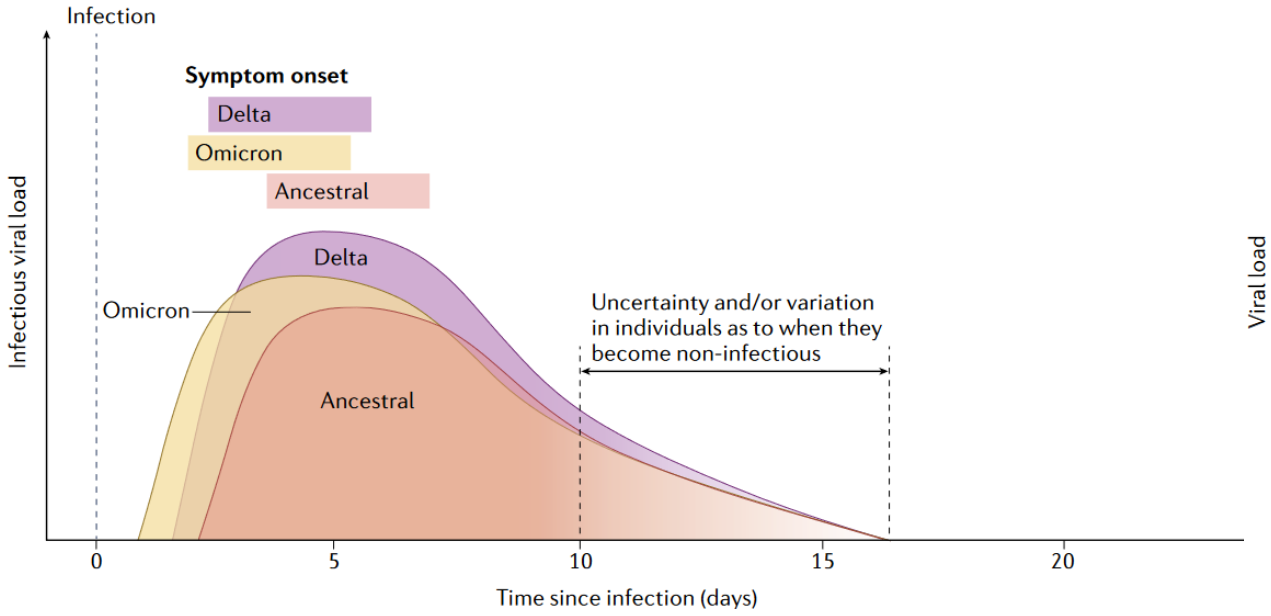
- Analyze ***in vivo*** data from **hospitalized patients**
  - **Heterogeneous population** [9,10] :
    - Different immune status (vaccination, prior infection, immunocompromised…)
    - Patients are treated at different stages of the disease
  - Patients arrive at **late stage of the disease** (lower viral load)

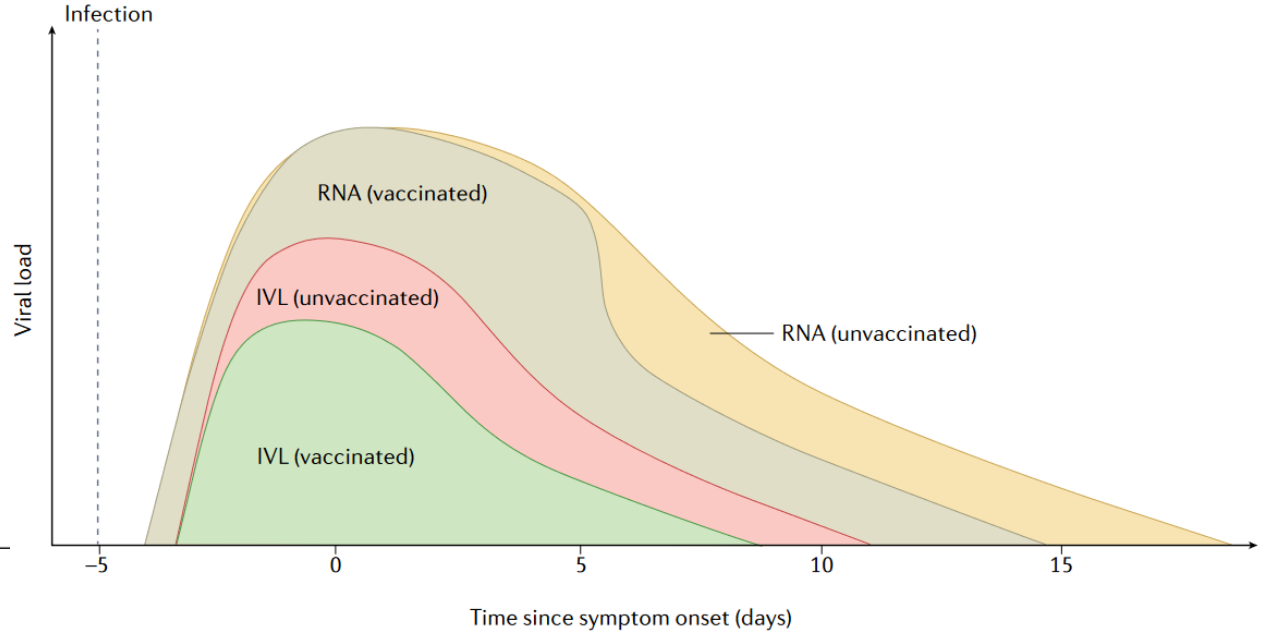
➔ The **relevance of modeling** by integrating:
- **virological**,
- **immunological**,
- and **pharmacological** data

[9] Lingas et al, *J Antimicrob Chemother.* (2022)
[10] Néant et al, *PNAS* (2021)

Study the impact of this changing landscape on viral dynamics in the population

- **Variant of infection** and **patient characteristics** may also **shape the viral dynamics** [11,12]
  - Studies often conducted on small specific cohorts (symptomatic, commorbidities…) → Potential selection bias





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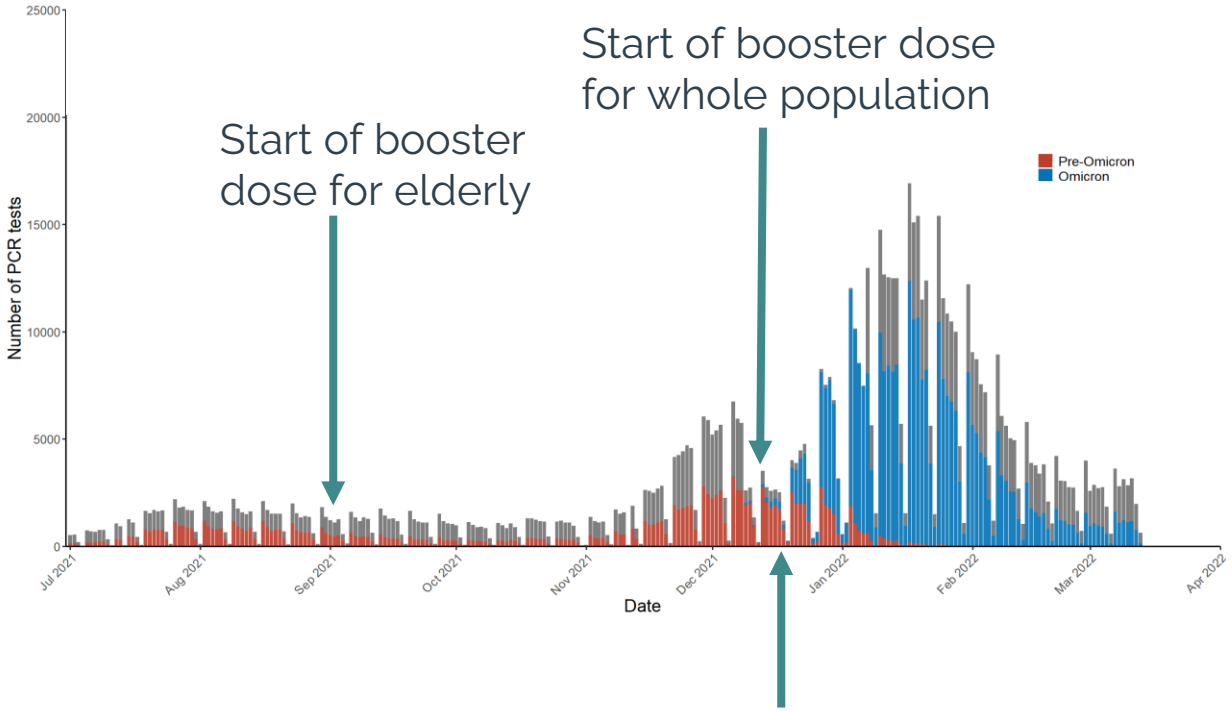

324,428 individuals (**407,375** obs) with:

- Date of **symptom onset**,
- **Vaccination status,**
- **Variant** of infection

BIOGROUP
biologie médicale

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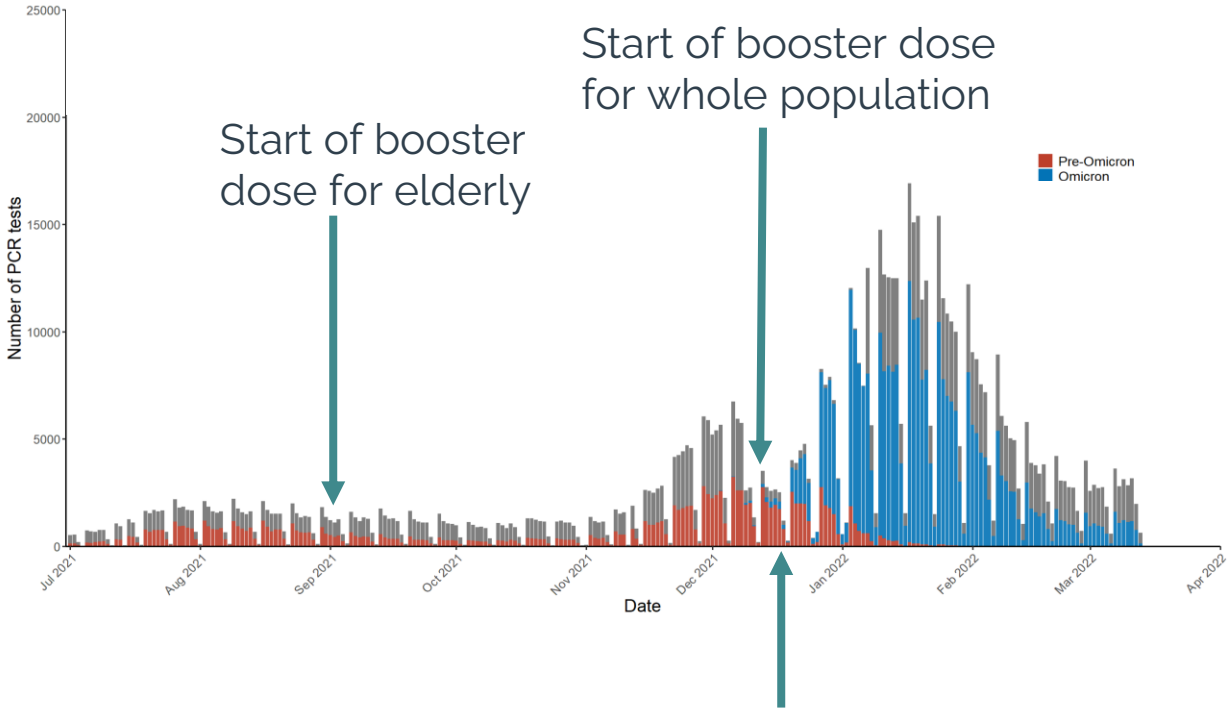

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Can we model the community labs tests to identify patterns in viral load ?

[11] Puhach et al, *Nat. Rev. Microbiol* (2023)
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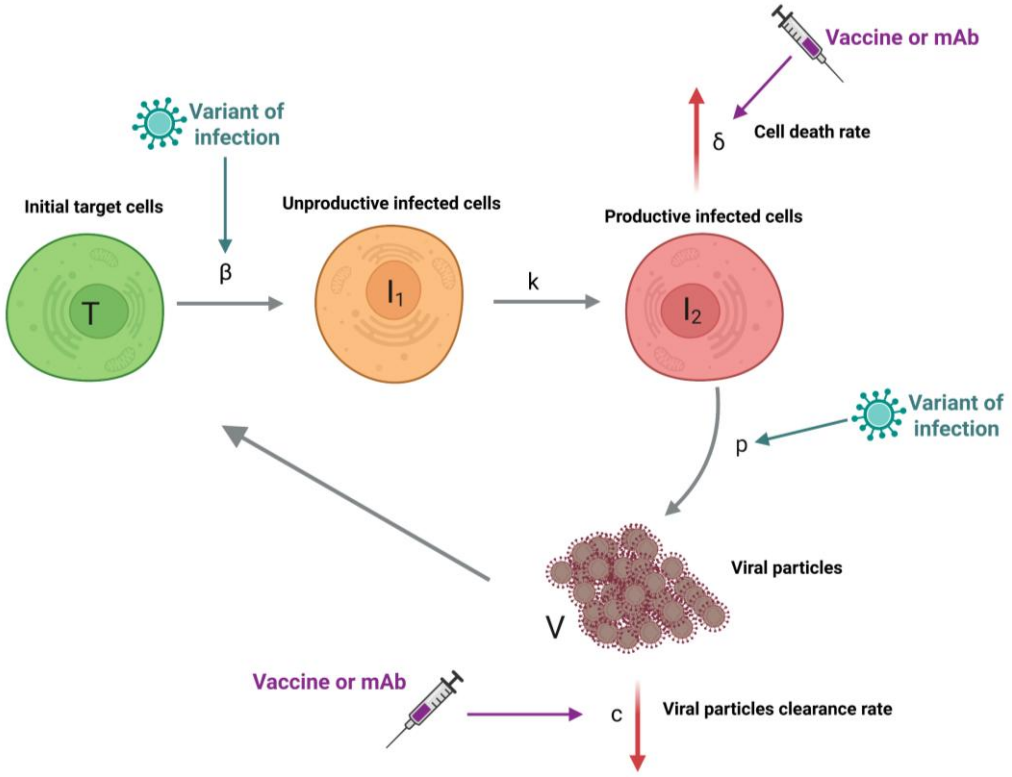
Various viral load dynamics models for use in different contexts

Semi-mechanistic models

➔ Identify how biological parameters are impacted by variants and vaccination



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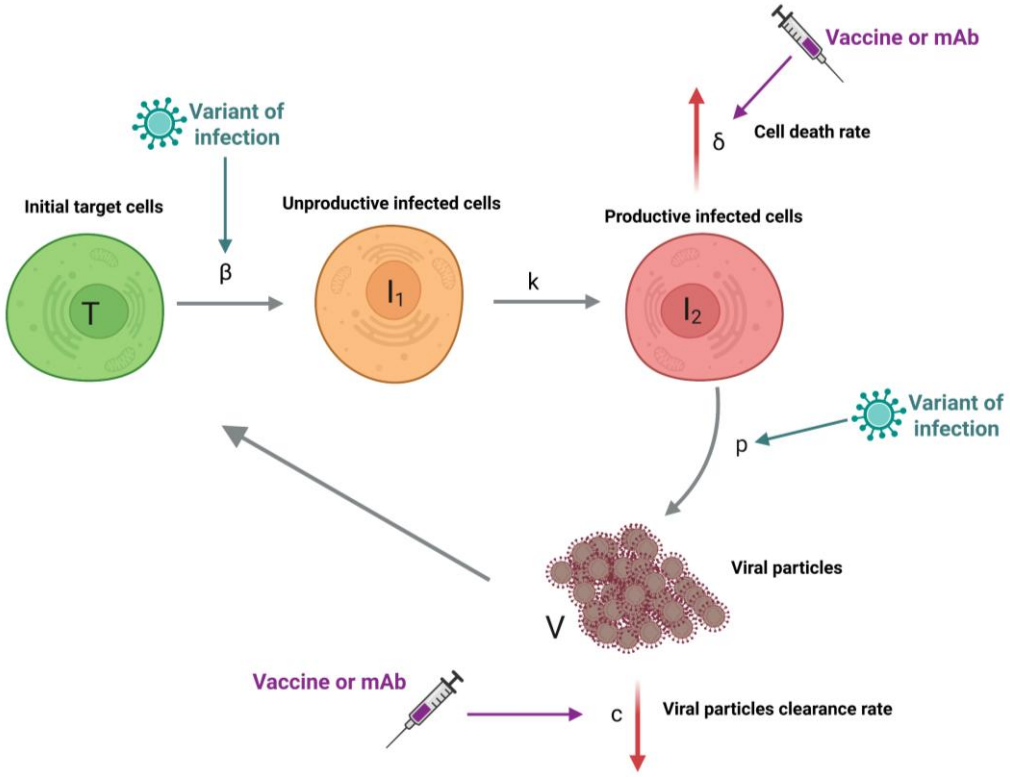
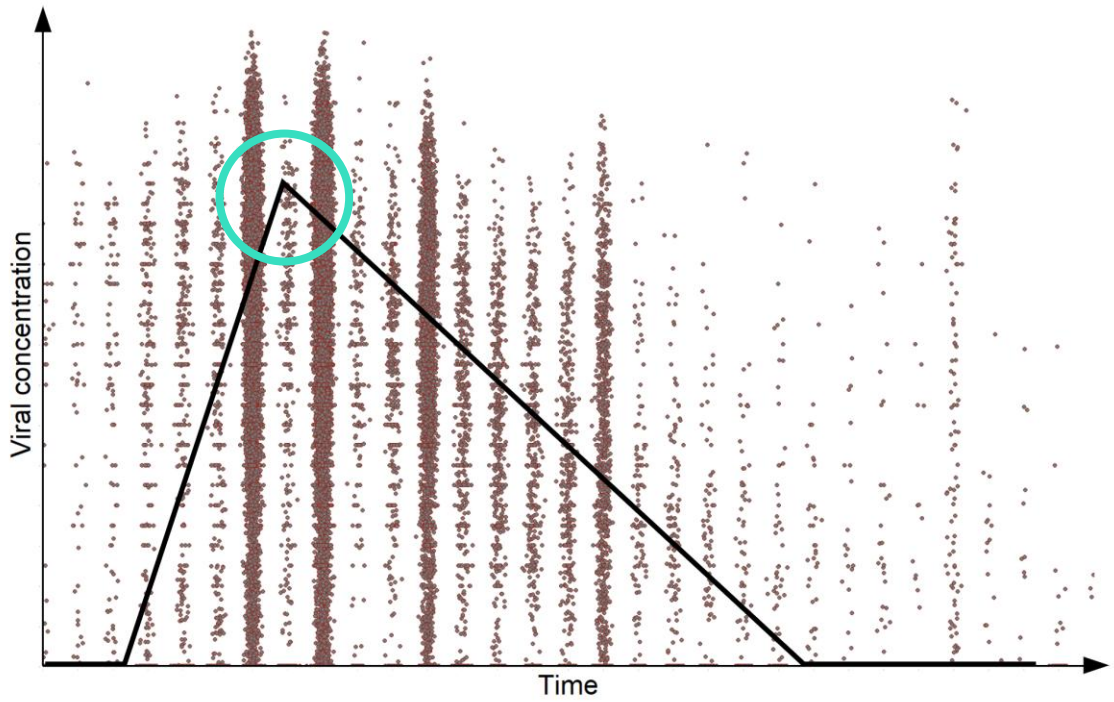


Empirical models

➔ Identify how viral dynamics patterns are impacted by variants and vaccination



Objectives of the studies

Objective 1

Using a semi-mechanistic model to reconstruct viral load dynamics, evaluate the virological effect of Evusheld on hospitalized patients in the DisCoVeRy clinical trial.

Objective 2

Using simulations inspired by data collected in community labs, study the feasibility of an empirical model for identifying patterns in viral load.

Evaluating Evusheld in hospitalized patients

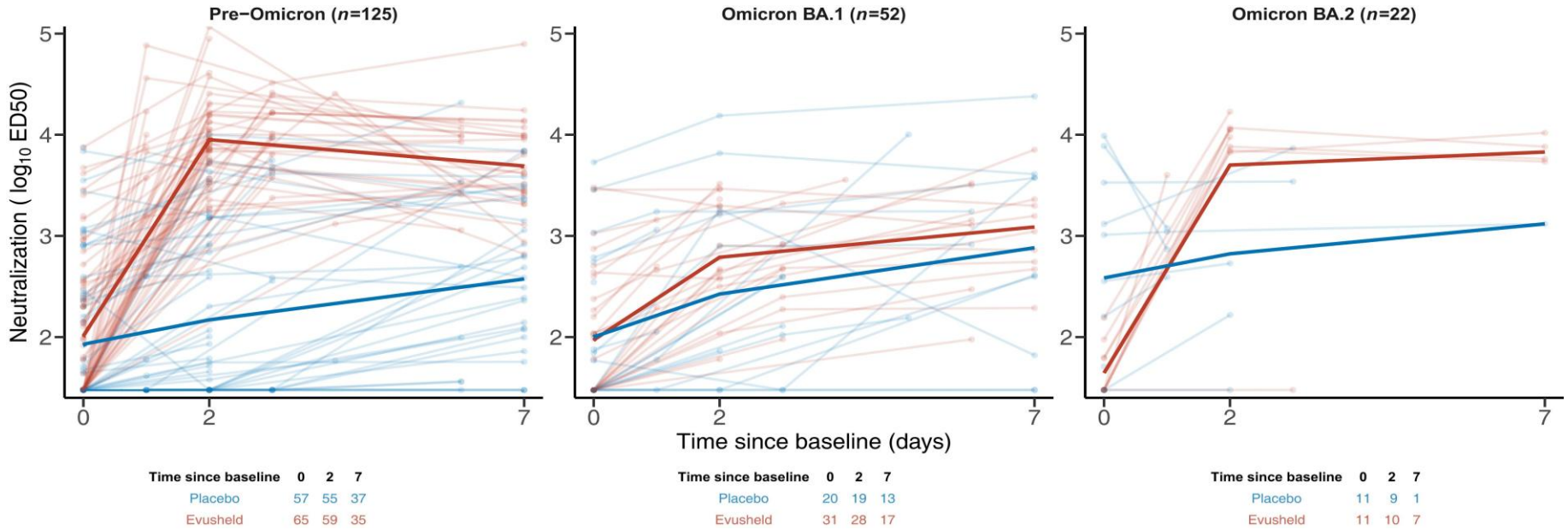
DISCOVERY

- European **phase III randomized clinical trial** (PI : F. Ader – methodologist : F. Mentré) [13]
- **> 200 patients** (2021-2022) in Evusheld or Placebo arms
- **Underpowered** due to **premature interruption of inclusions**

→ What is the *in vivo* virological effect of Evusheld ?

[13] Hites et al, *J. Infect.* (2024)

Large heterogeneity in neutralization activity and viral load



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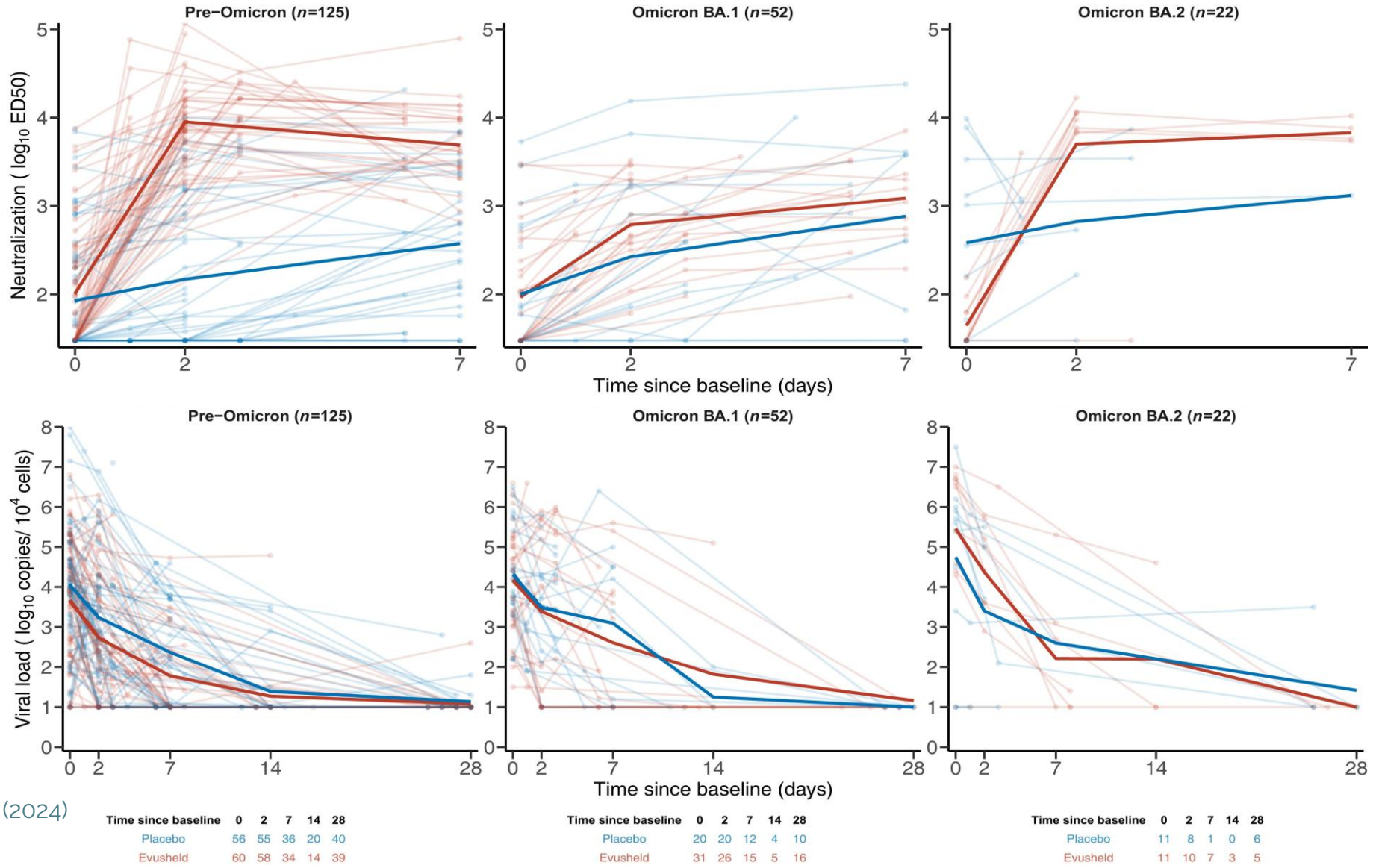

Time since baseline	0	2	7	14	28
Placebo	56	55	36	20	40
Evusheld	60	58	34	14	39

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Placebo	20	20	12	4	10
Evusheld	31	26	15	5	16

Time since baseline	0	2	7	14	28
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Evusheld	11	10	7	3	5

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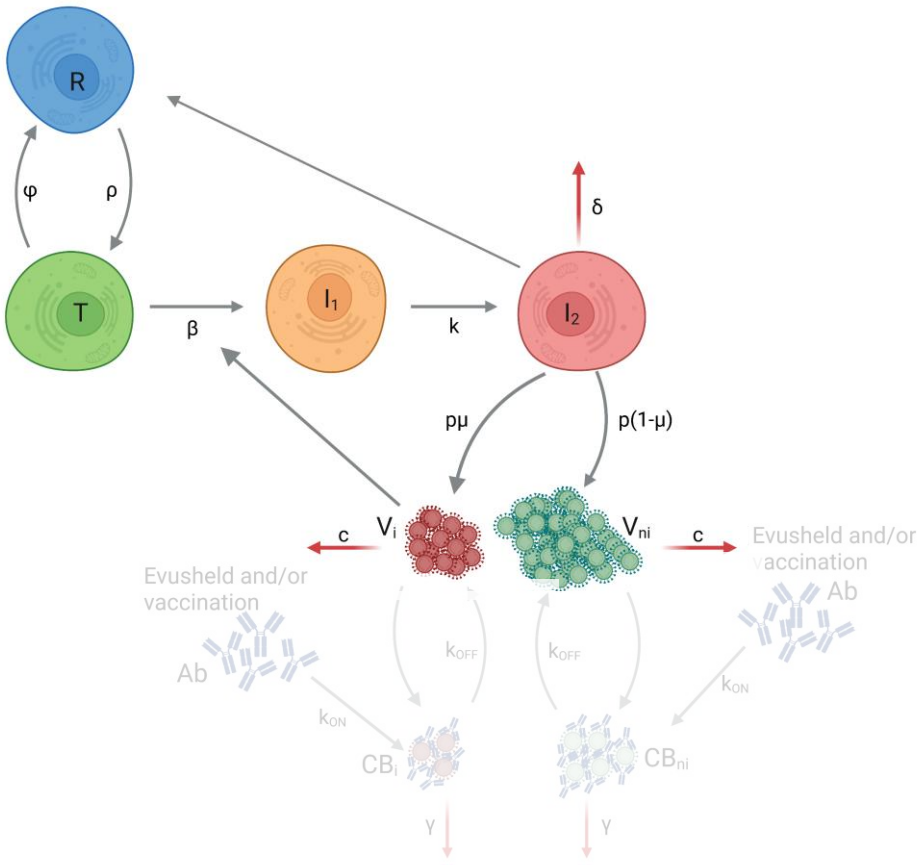
Simultaneously modeling neutralization activity and viral load dynamics

Target cell limited model [15]



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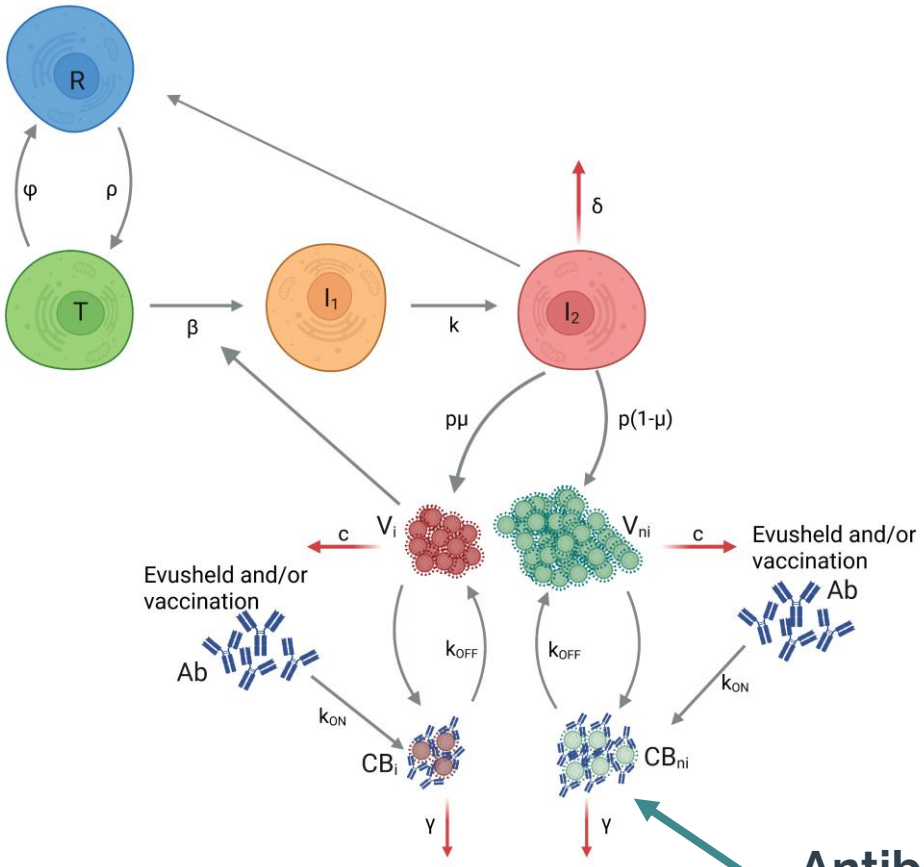

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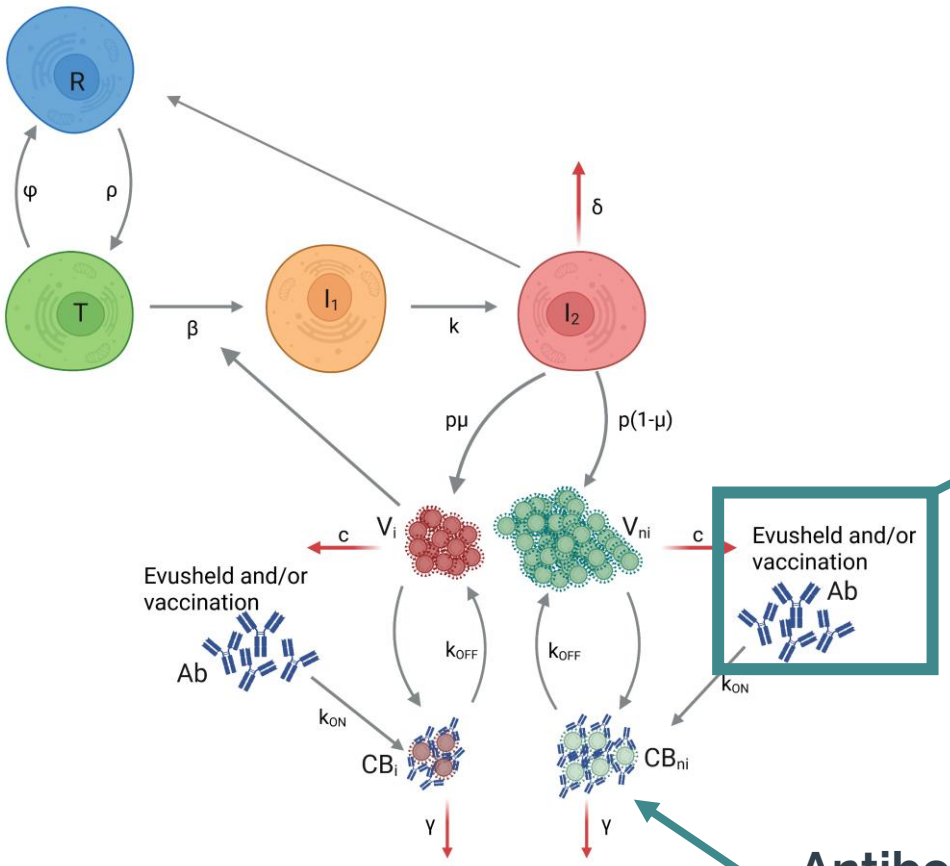
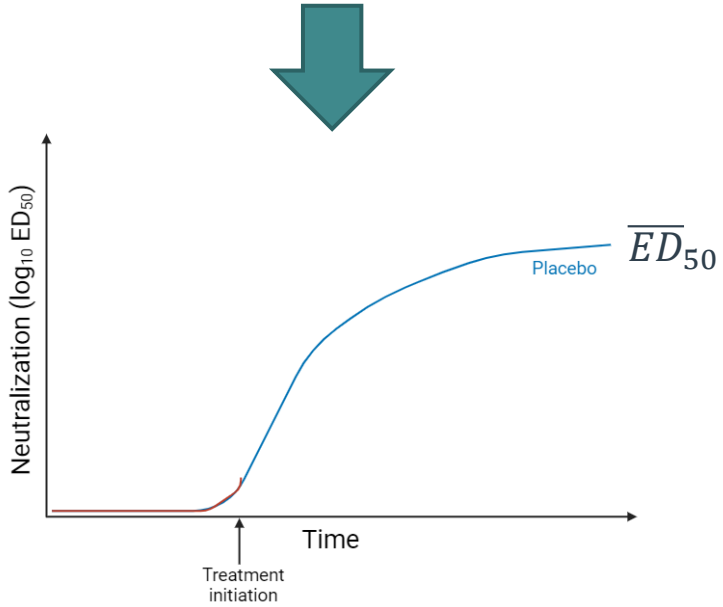


Antibody virus complex

Sigmoid **Gompertz function** to model the **neutralization activity** [16,17]

$$ED_{50}(t) = \begin{cases} \overline{ED}_{50} \times e^{e^{-g\times(t-\tau)}}, & t \leq t_x \end{cases}$$

With t_x the Evusheld treatment initialization



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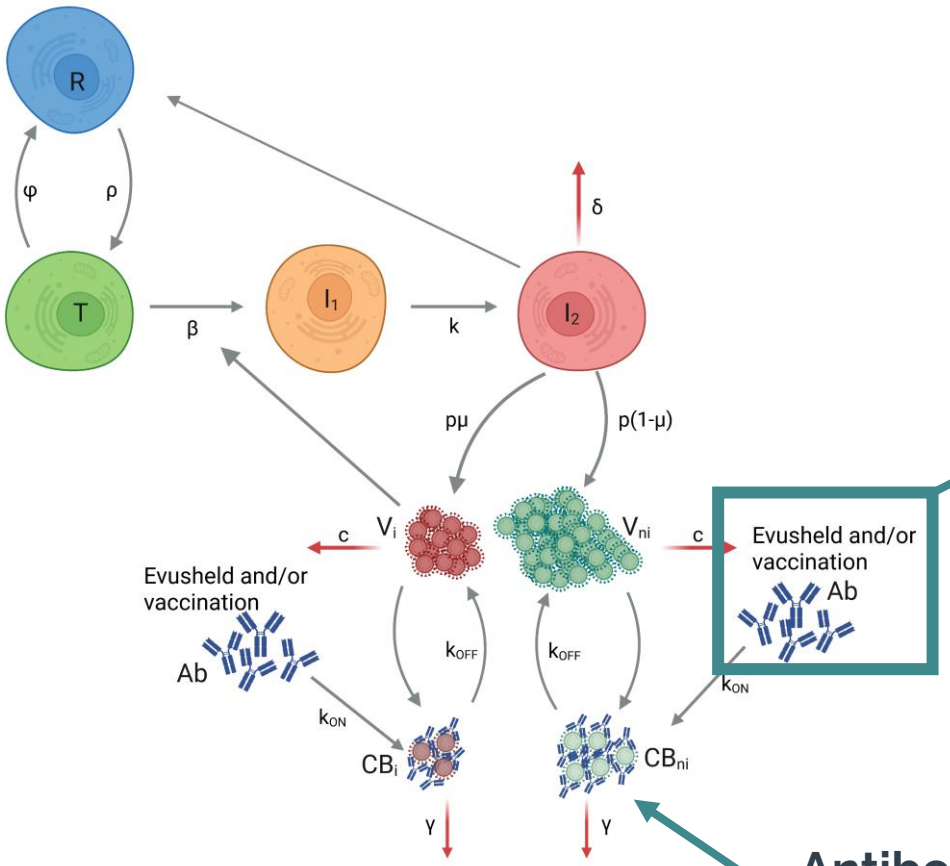

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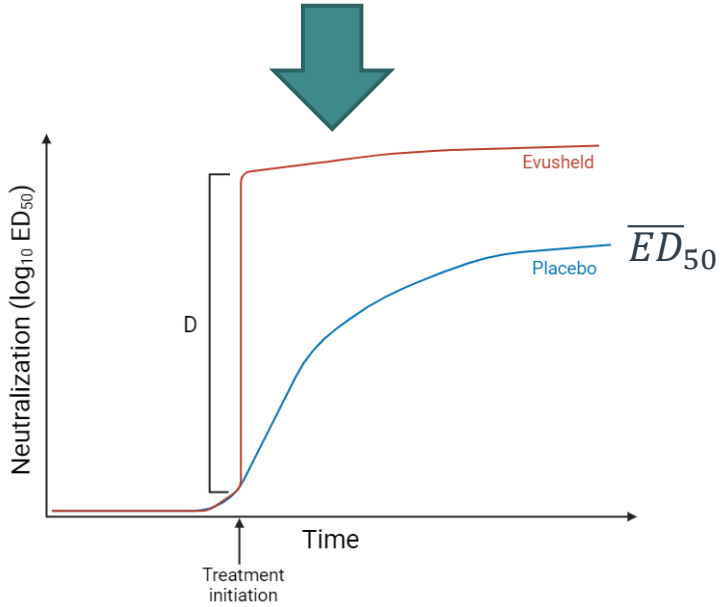

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Parameters estimation

Covariates association

- Using COSSAC algorithm
- Baseline characteristics (**Wald test, P < 0.05**)
  - Sex
  - Age
  - Clinical status at inclusion (score)
  - **Vaccination status**
  - **Variant of infection**

Parameter	Estimate (RSE in %)	SD of the random effect ω (RSE in %)
$\overline{ED}_{50\{Unvaccinated\}}$ (ED_{50})	**1501 (46)**	**1.74 (8)**
$\overline{ED}_{50\{Fully\ vaccinated\}}$ (ED_{50})	**6272 (23)**	**1.74 (8)**
g	0.14 (16)	0.24 (20)
τ (days)	22.26 (9)	0.10 (fixed)
$D_{\{Pre-Omicron\}}$ (ED_{50})	**5956 (12)**	**0.68 (18)**
$D_{\{Omicron\ BA.1\}}$ (ED_{50})	**263 (36)**	**0.68 (18)**
$D_{\{Omicron\ BA.2\}}$ (ED_{50})	**4325 (17)**	**0.68 (18)**
R_0	4.51 (21)	0.73 (6)
p (10^7virus cells $^{-1}$ day $^{-1}$)	2.86 (47)	-
δ (day $^{-1}$)	2.37 (53)	-
φ (10^{-6}cells day $^{-1}$)	2.02 (82)	-
ρ (day $^{-1}$)	1.01 (28)	-
k_{ON} (day $^{-1}$ ED_{50}^{-1})	0.0018 (52)	-
σ_1 $(log_{10}ED_{50})$	0.43 (5)	-
σ_2 (log_{10}RNA copies/10^4 cells)	1.17 (4)	-

Using the SAEM algorithm in Monolix Software

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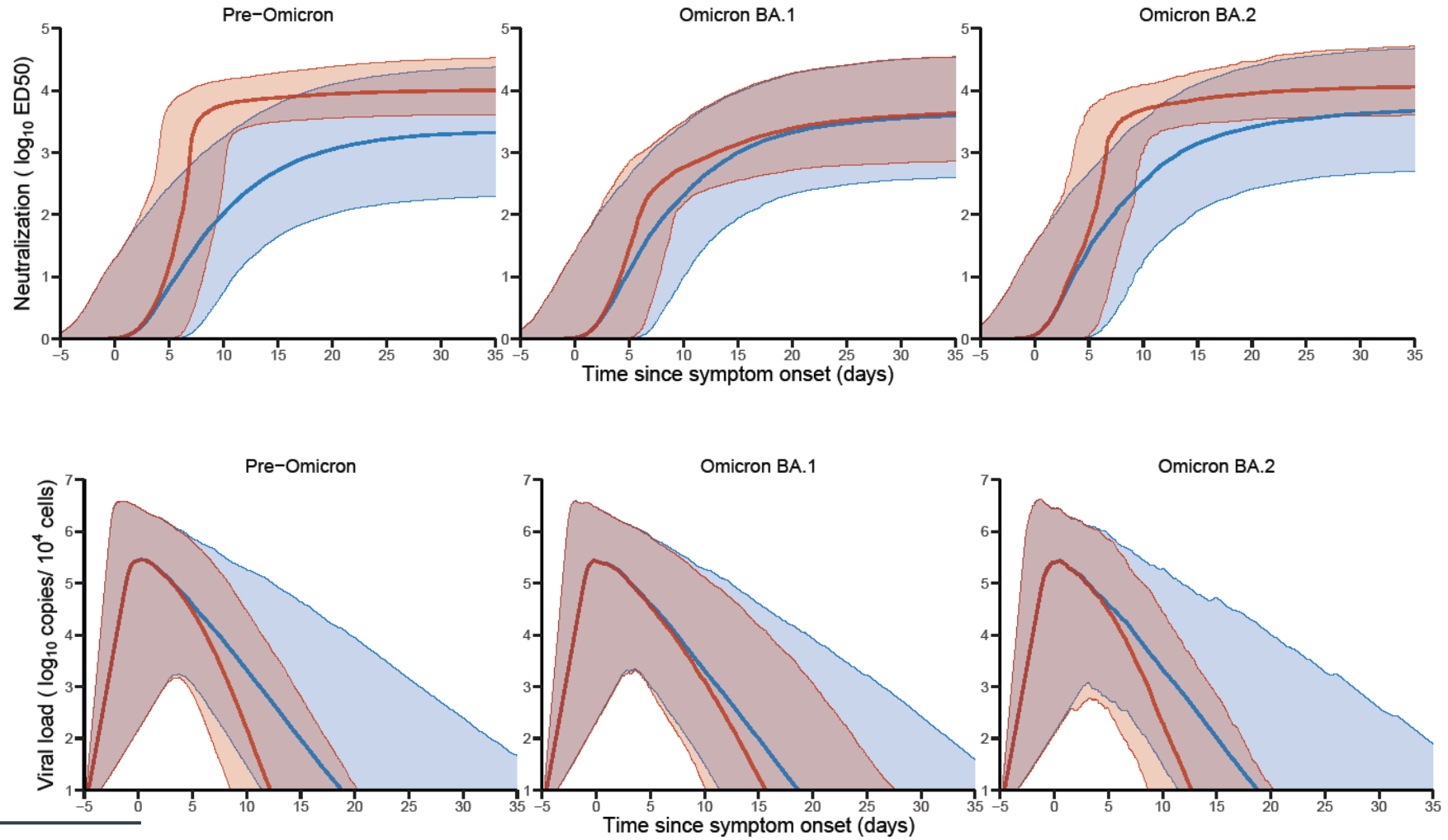
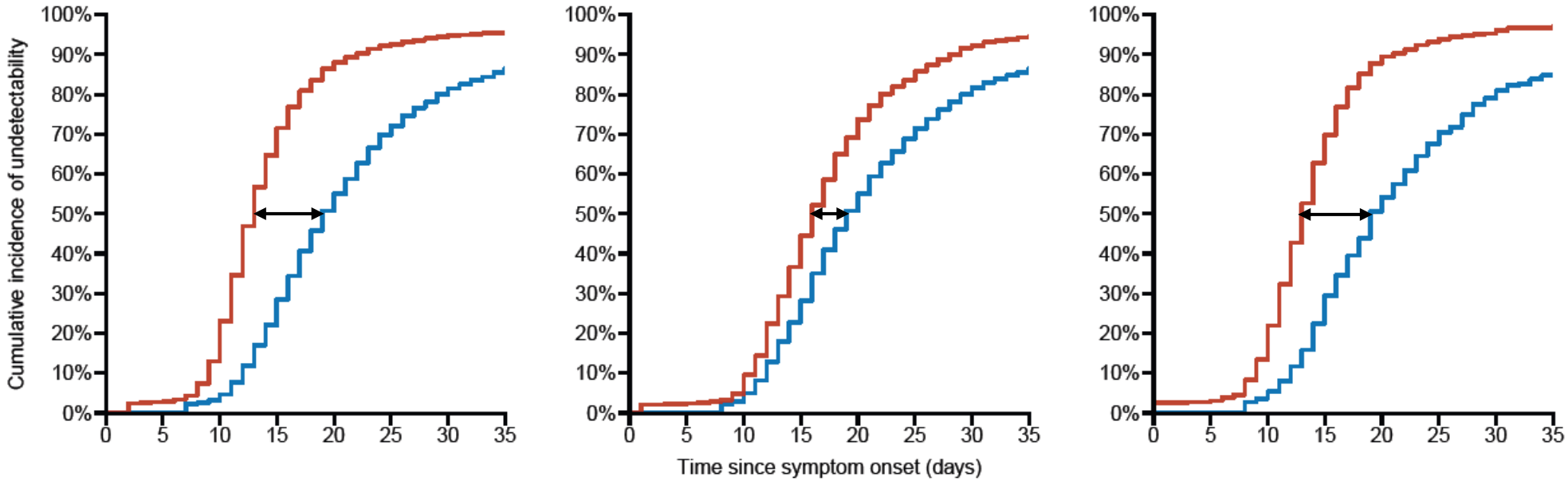
Using the SAEM algorithm in Monolix Software

Simulated neutralization and viral load trajectories



[14] Beaulieu et al, *J Antimicrob Chemother* (2024)

Gain in time to reach viral undetectability

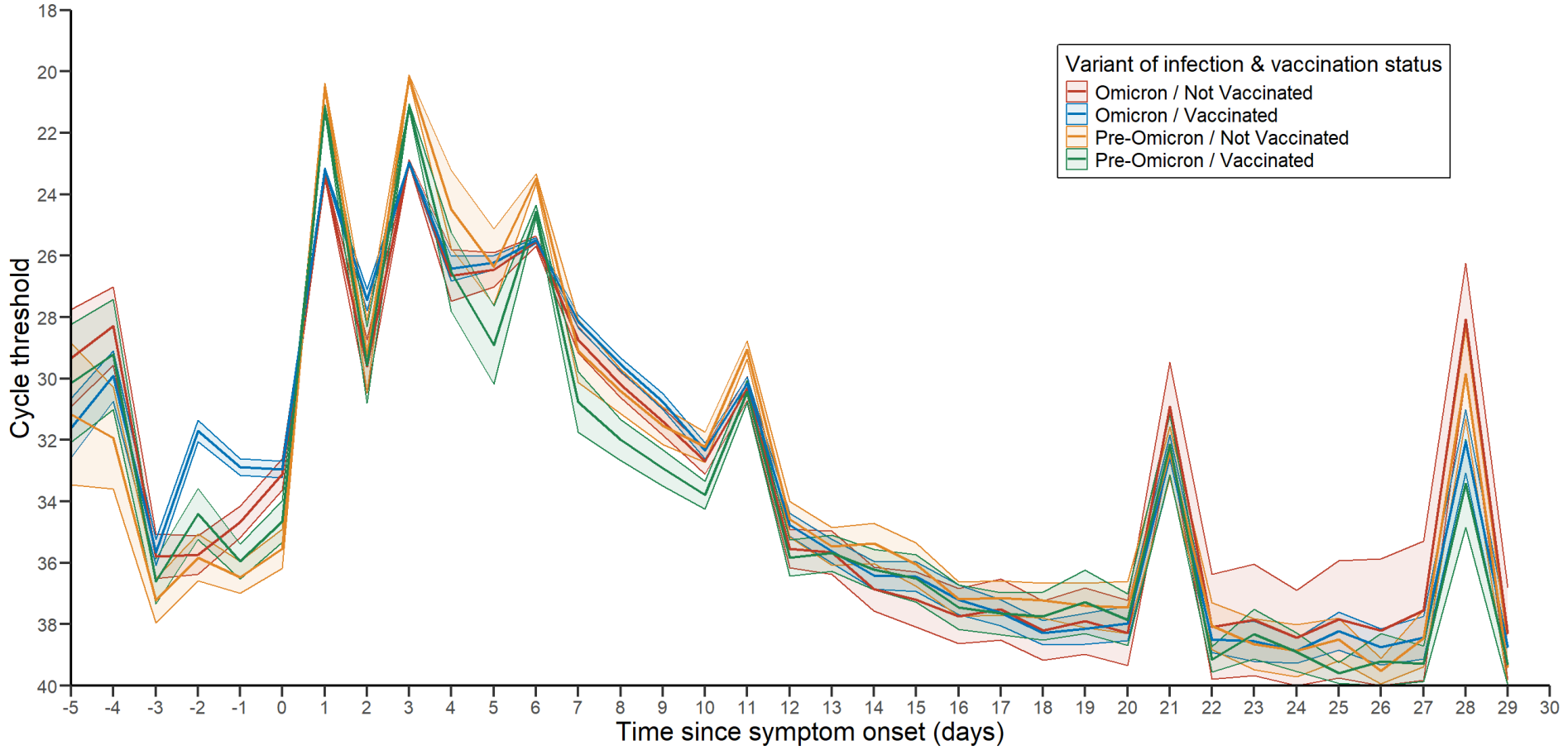


Pre Omicron	Omicron BA.1	Omicron BA.2
5.9 (2.1-13.6)	2.2 (0.4-8.9)	5.4 (2.0-12.4)

Median (80% PI) difference in days to reach undetectability between in silico treated patients and their own control

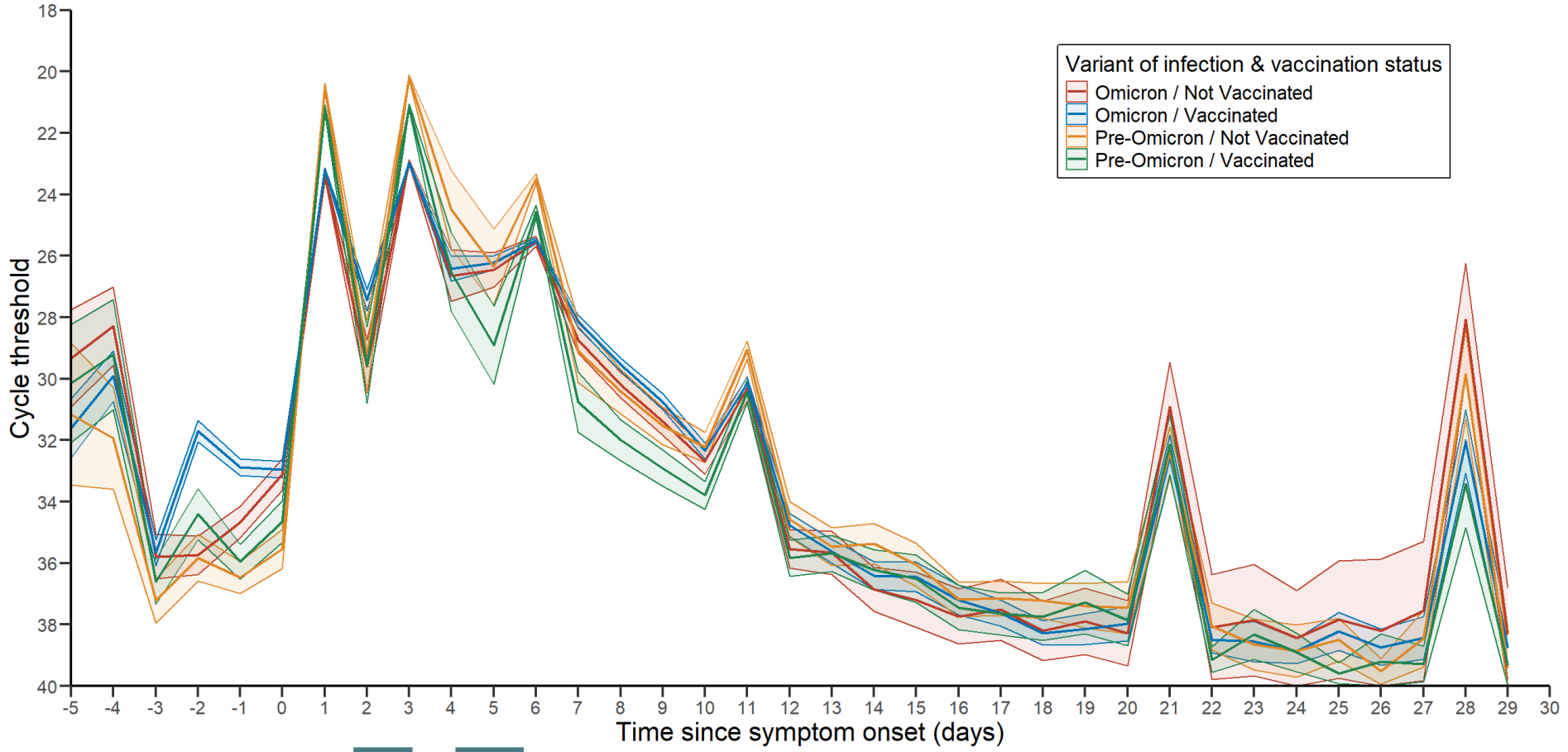
[14] Beaulieu et al, *J Antimicrob Chemother* (2024)

Description of the data from community labs



	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Omicron / Not Vaccinated	108	152	413	540	997	1125	24016	373	26776	269	553	5574	942	1010	808	890	1217	301	238	161	119	88	89	72	55	52	131	30	43	35	31	26	18	78	34
Omicron / Vaccinated	306	425	1192	2453	4153	3972	62326	2205	110467	1166	2987	19890	3772	3460	2546	2525	4127	919	804	579	485	417	445	338	260	246	538	219	161	217	174	151	182	292	128
Pre-Omicron / Not Vaccinated	63	128	306	410	775	650	13439	295	26501	188	196	6072	247	342	450	693	2093	344	294	256	218	213	230	192	145	104	367	90	69	74	63	56	52	168	53
Pre-Omicron / Vaccinated	81	107	348	434	725	604	11100	249	24604	170	180	4841	253	389	475	708	1705	322	312	239	188	175	178	132	102	113	286	69	86	98	70	56	59	142	48

Description of the data from community labs



	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Omicron / Not Vaccinated	108	152	413	540	997	1125	24016	373	26776	269	553	5574	942	1010	808	890	1217	301	238	161	119	88	89	72	55	52	131	30	43	35	31	26	18	78	34
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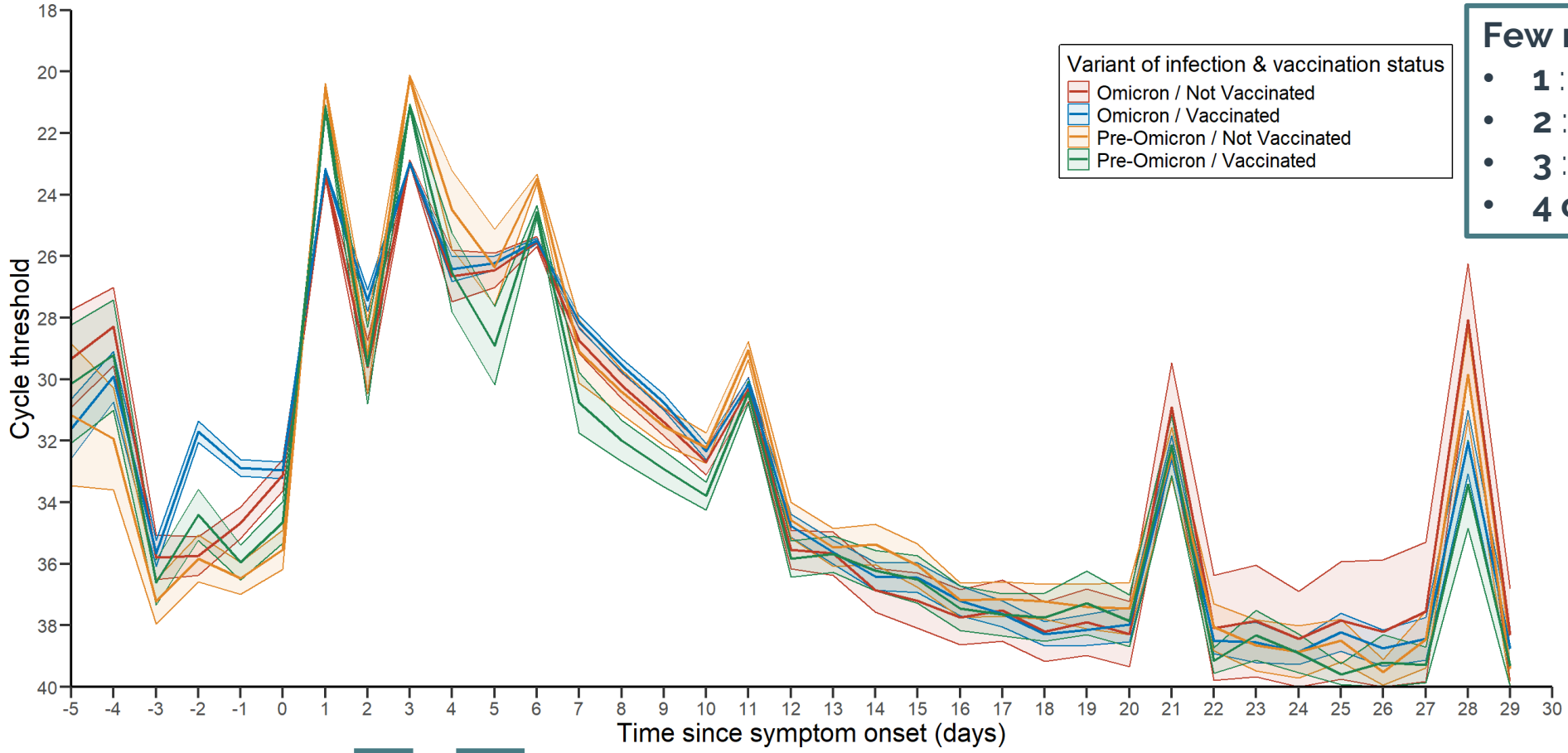

Few repeated tests :

- **1** : 79% (N = 256,650)
- **2** : 17% (N = 55,560)
- **3** : 3 % (N = 9,957)
- **4 or more** : 1% (N = 2,261)

	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
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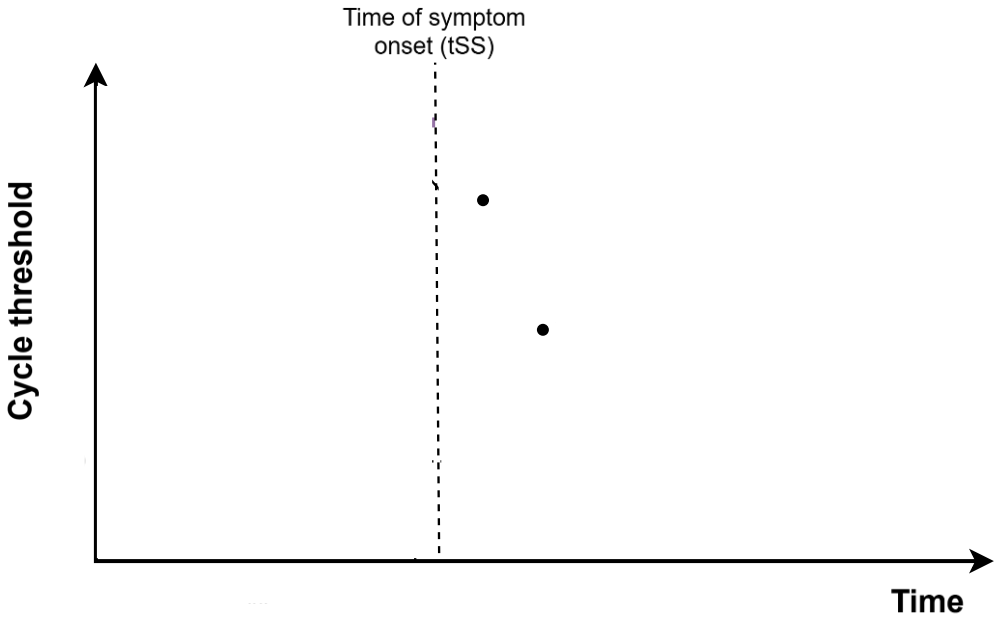
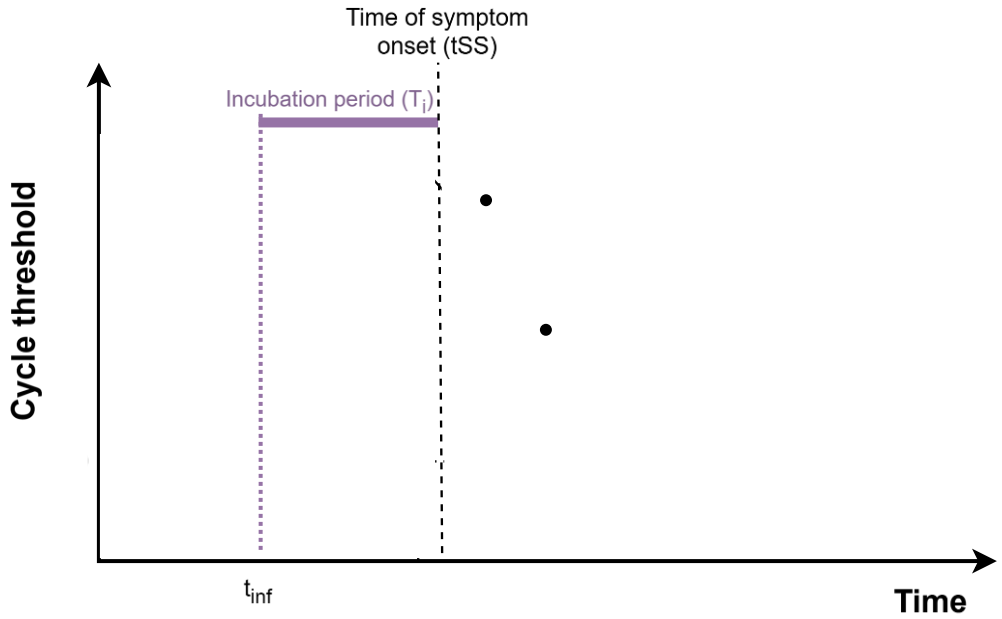
Piecewise linear model to capture the viral load dynamics



Piecewise linear model to capture the viral load dynamics



We estimate 4 parameters:

- Incubation period (days), $\boldsymbol{T_i}$

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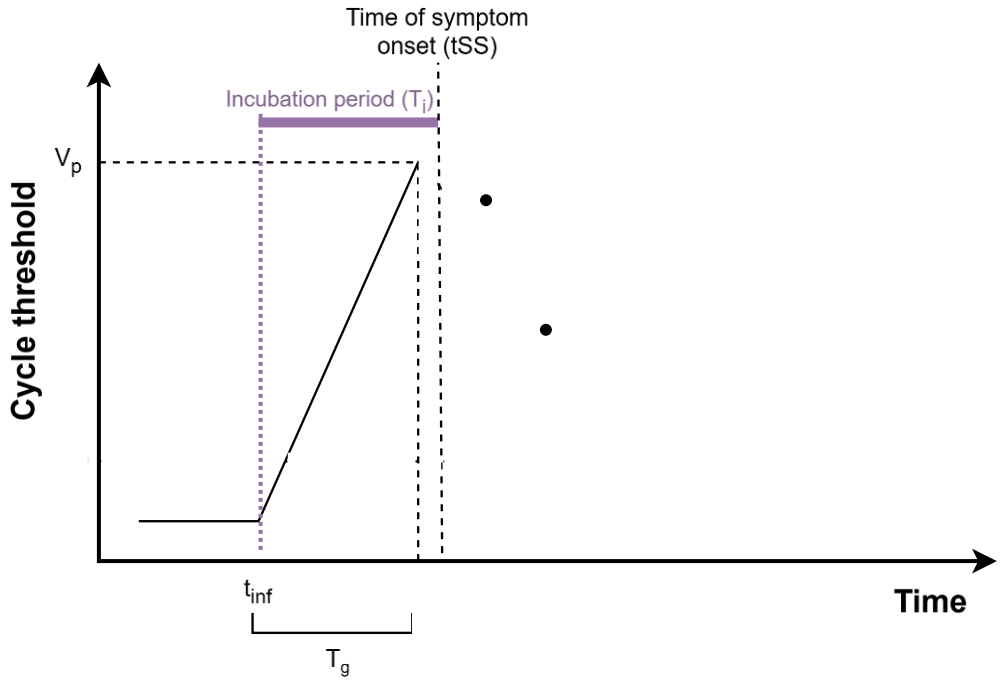

We estimate 4 parameters:

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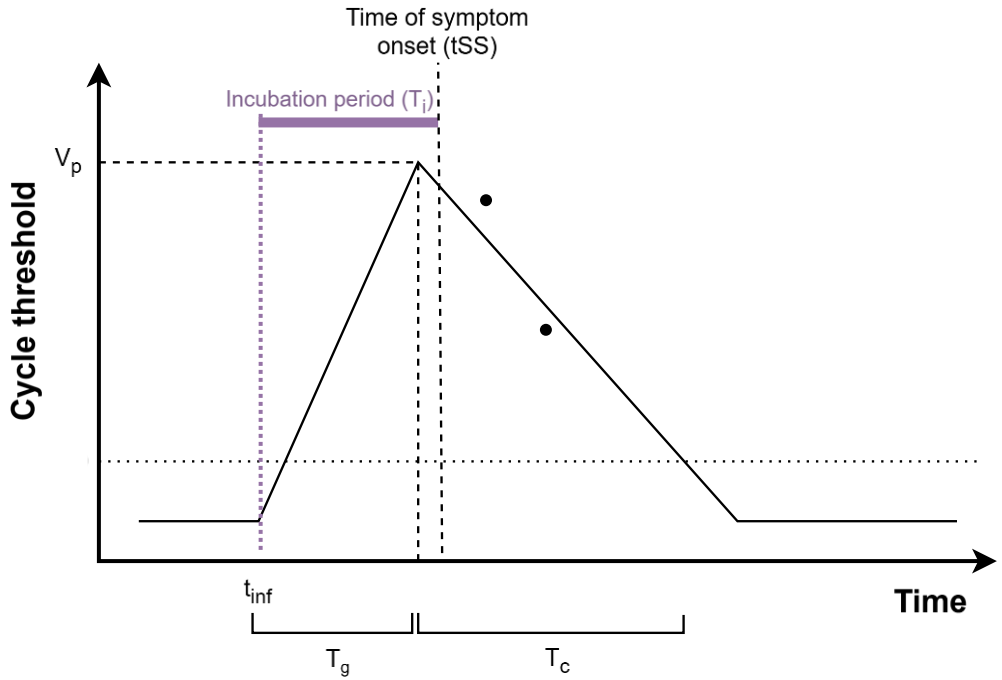

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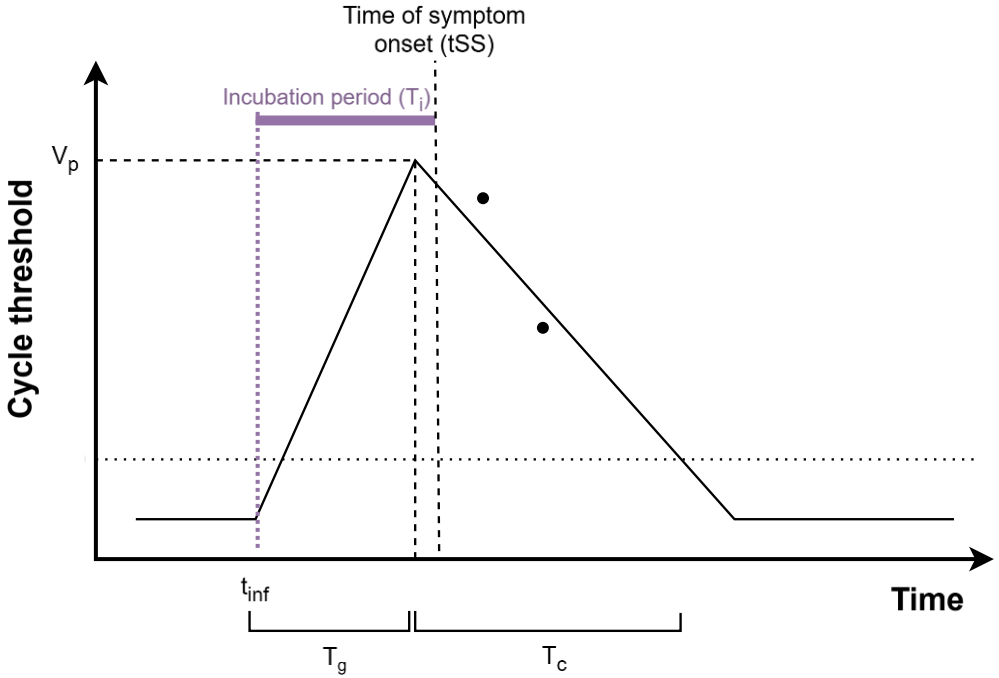

Bayesian inference framework, HMC NUTS algorithm in Stan

Add information with prior distributions

We estimate 4 parameters:

- Incubation period (days), $\boldsymbol{T_i \sim N^+(5,1)}$
- Proliferation phase (days), $\boldsymbol{T_g \sim N^+(6,1)}$
- Viral load at peak (Ct), $\boldsymbol{V_p \sim N^+(25,2)}$
- Clearance phase (days), $\boldsymbol{T_c \sim N^+(15,2)}$

Weakly informative prior distributions

Simulation study

- 50 simulated datasets of 1000 individuals
- 50% of the population is infected

- Few repetead tests

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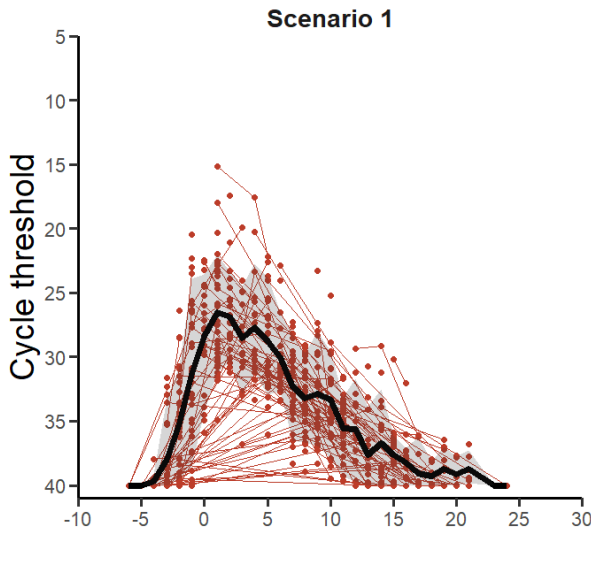
	Inclusion criteria	Percentage of infected individuals (P_{inf})	Timing of testing
Scenario 1	≥ 1 positive PCR	100%	Uniform from infection to clearance



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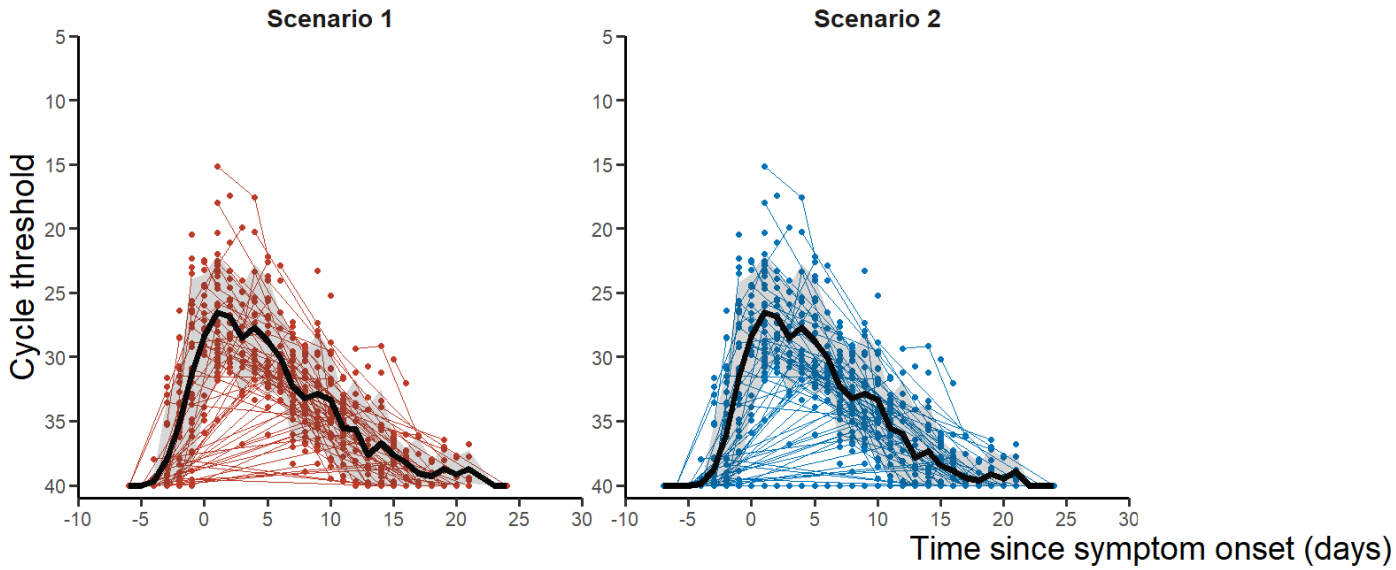

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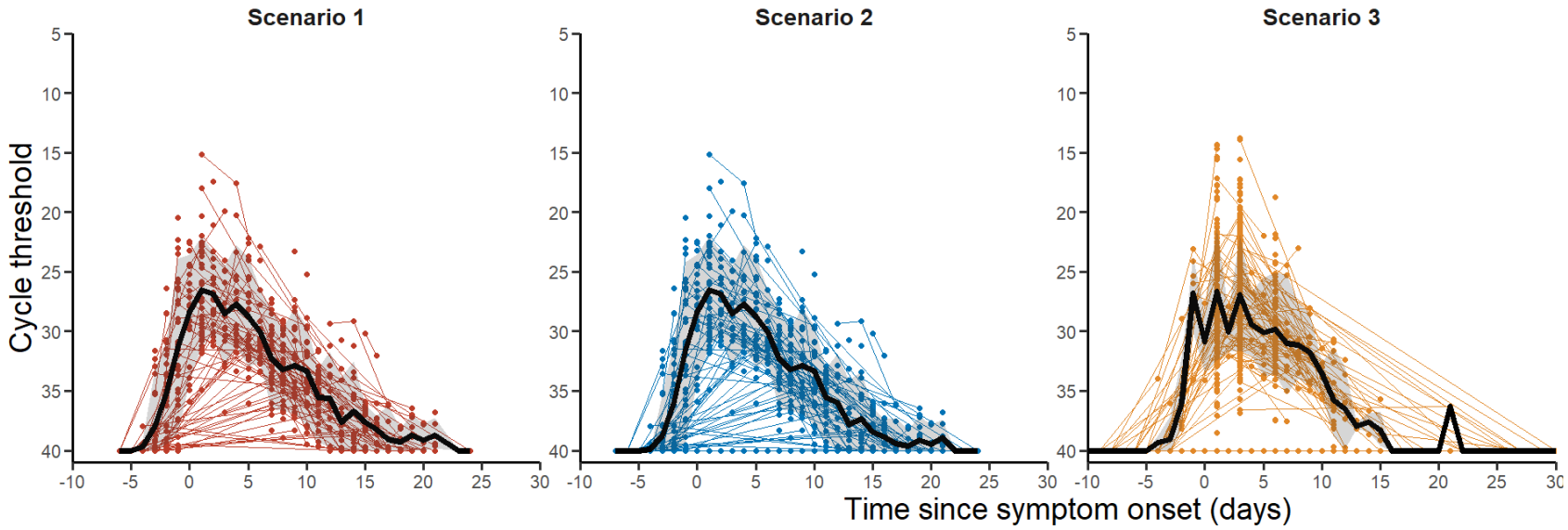

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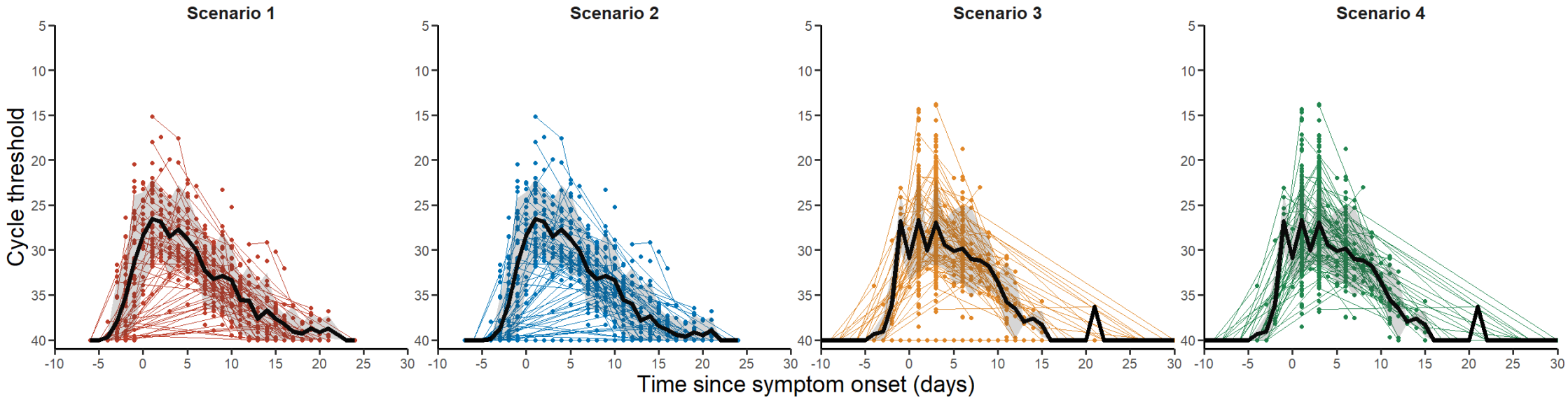
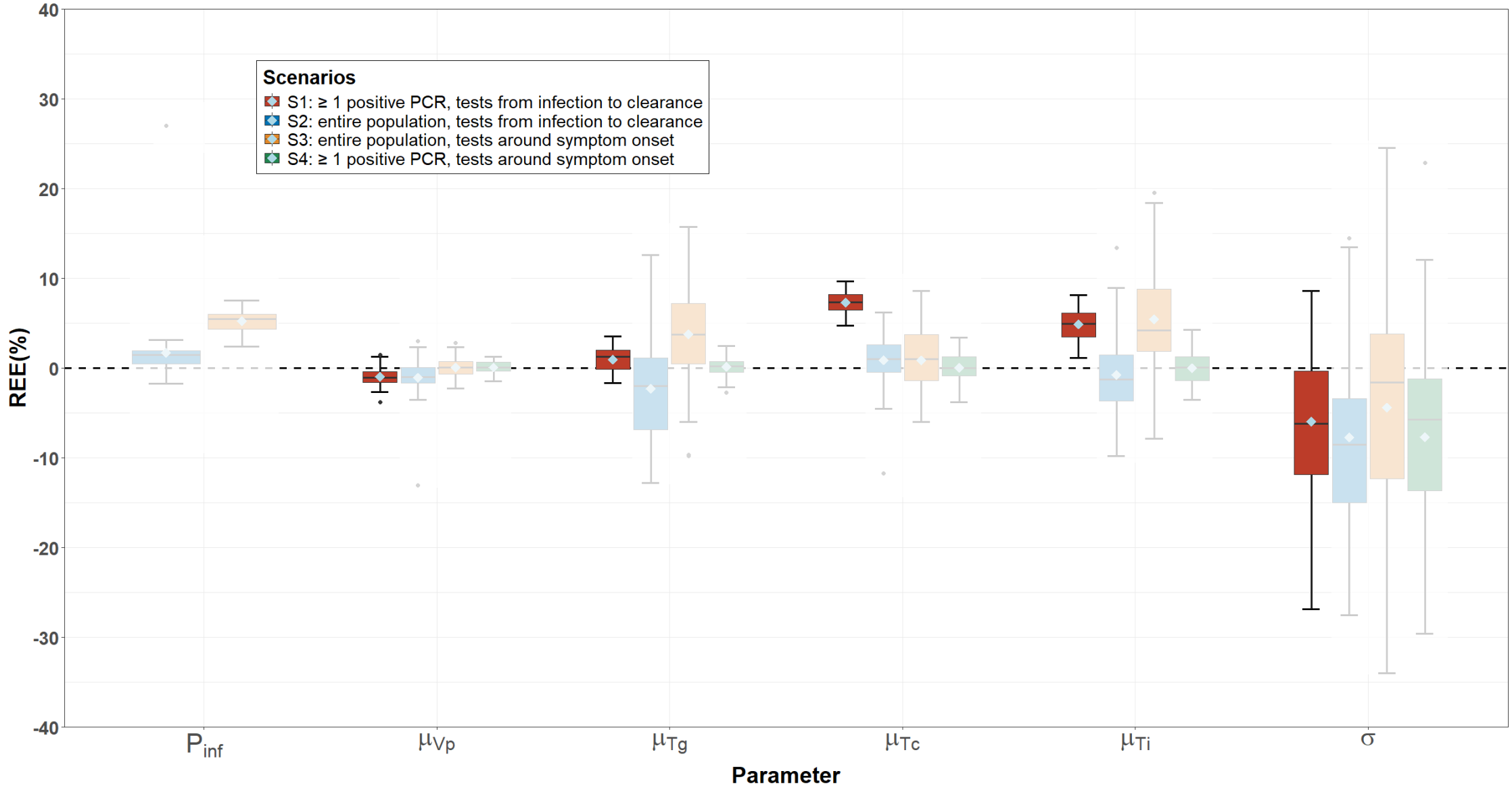
Scenario 4	≥ 1 positive PCR	100%	Mostly at symptom onset



Relative Estimates Errors (REEs)



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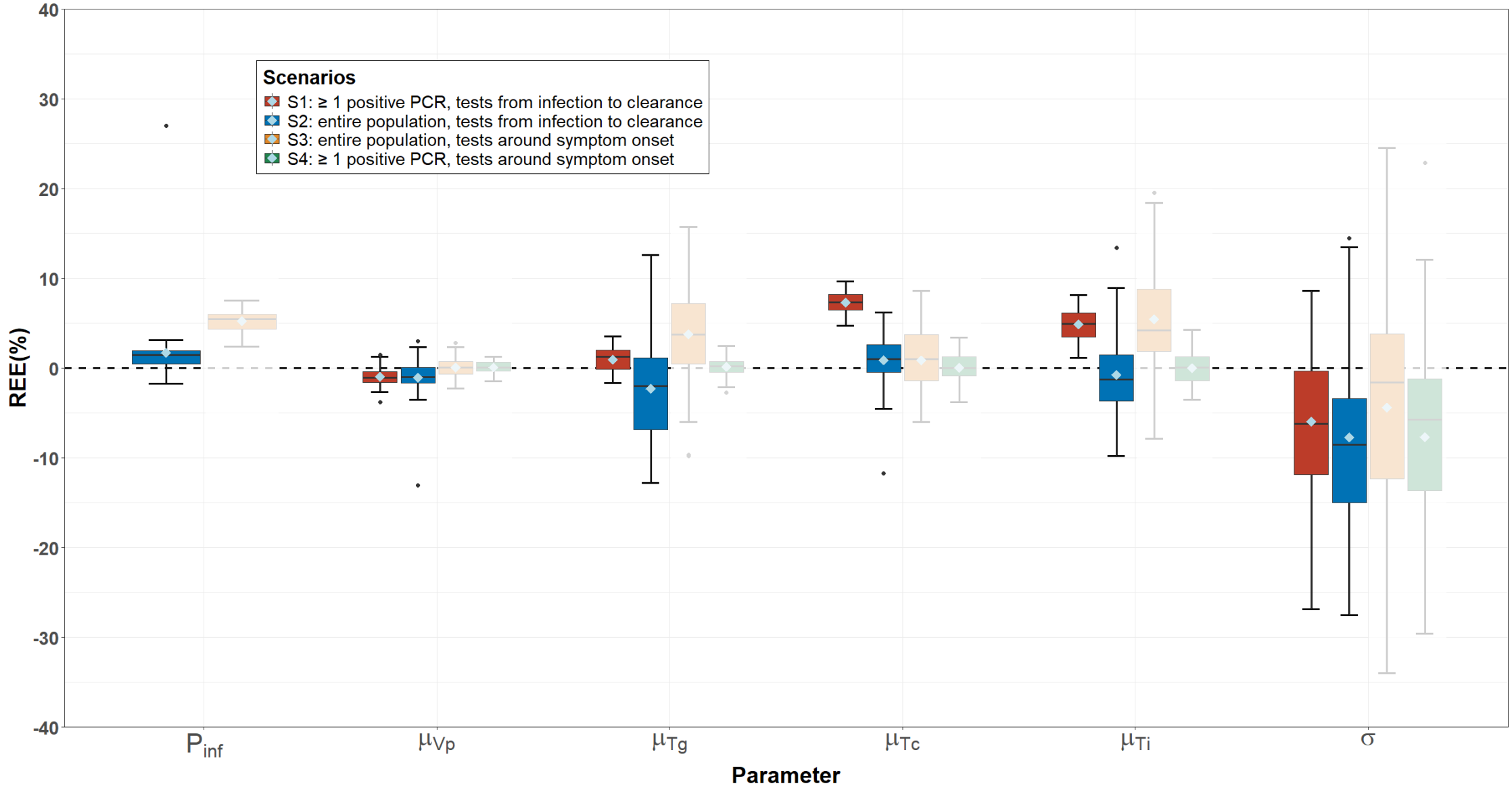

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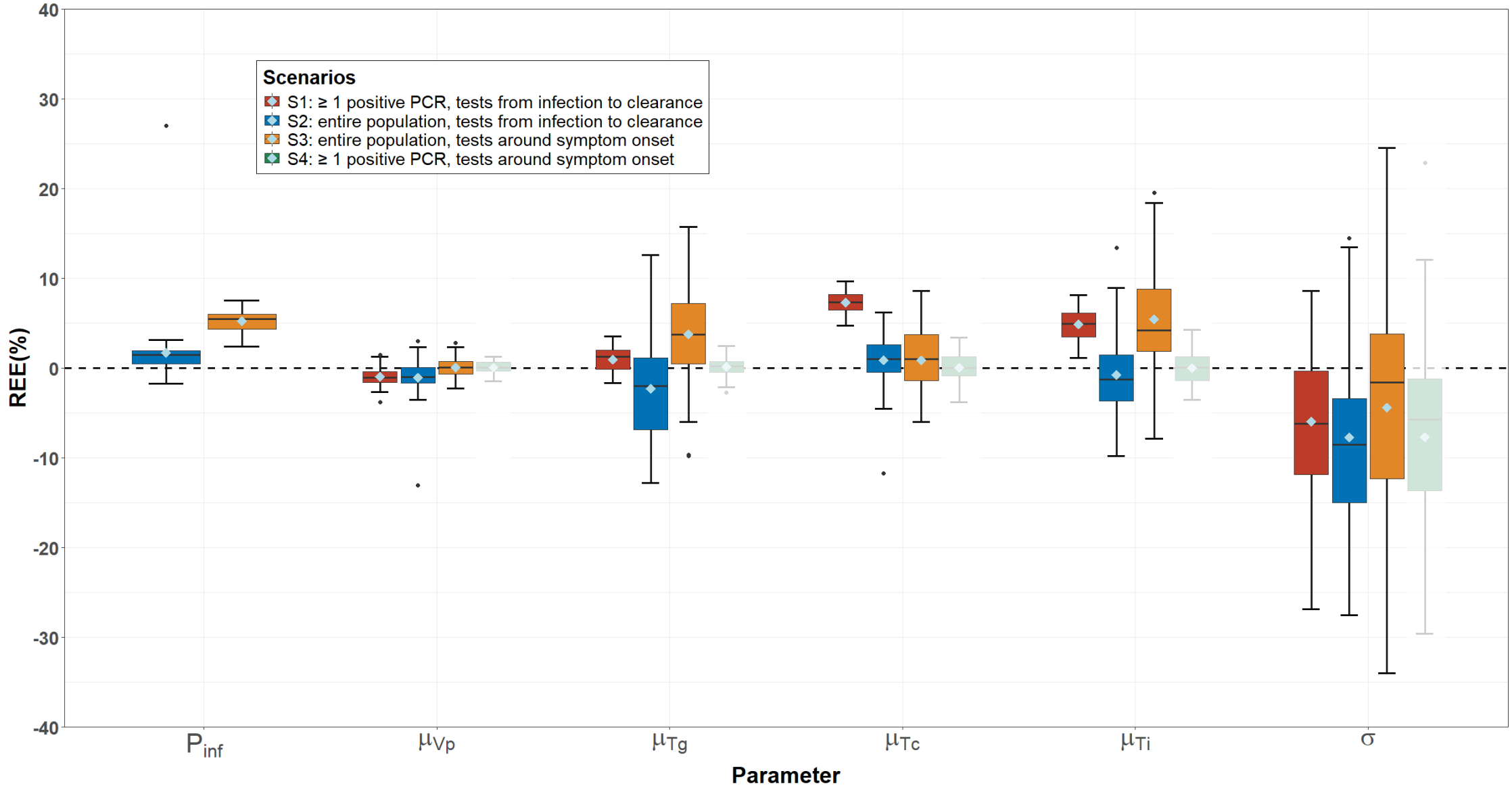

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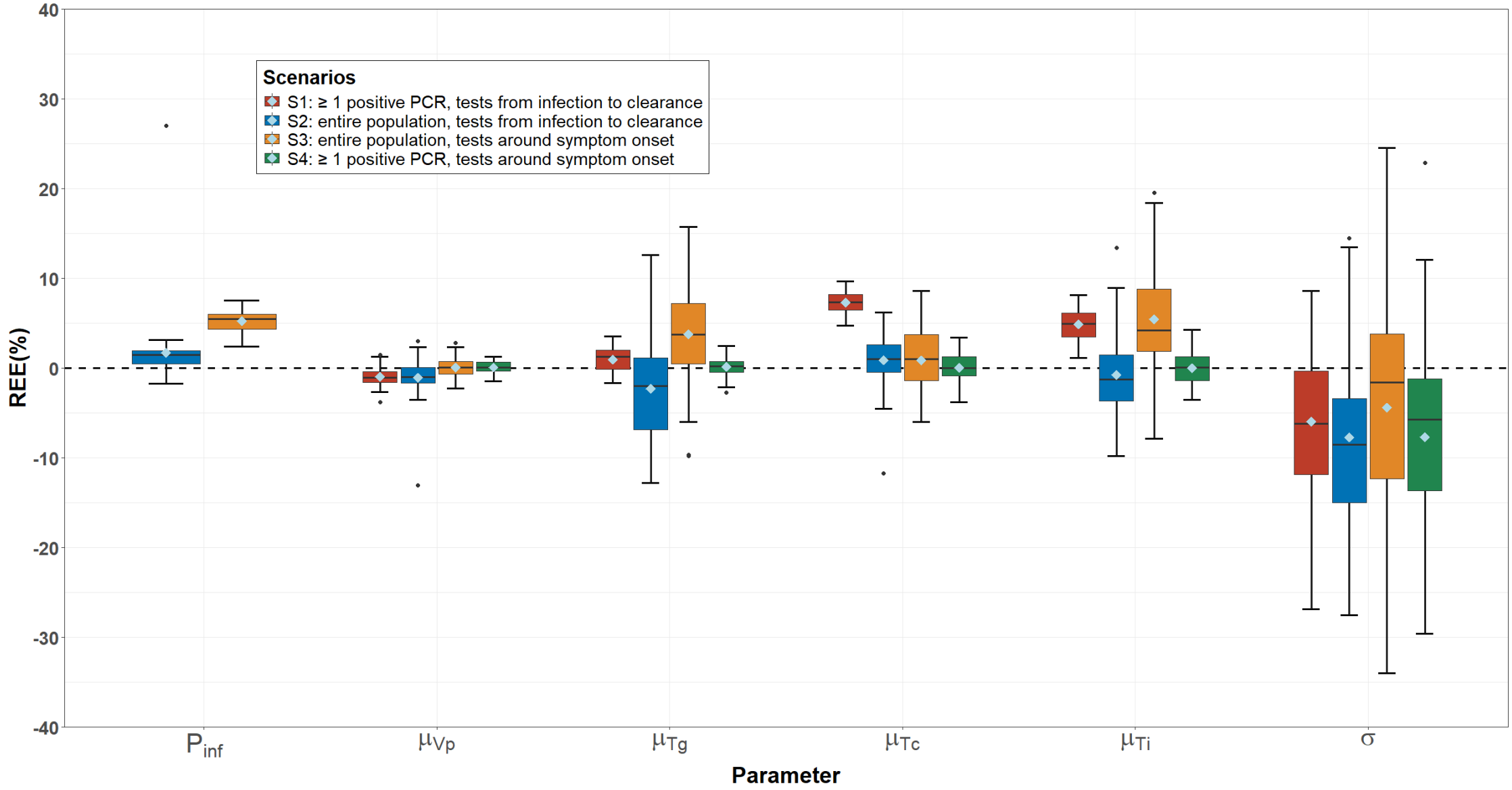

Discussion

Findings

- We identified an antiviral activity of a mAb on hospitalized patients by integrating neutralization activity into a viral dynamics model
- Pre-Omicron and Omicron BA.2 hospitalized patients had higher neutralization activity leading to faster viral clearance

Limitations

- Evusheld is no longer used due to lack of efficacy in patients

Perspectives

- Can we find a clinical efficacy of mAbs adapted to latest VoCs in hospitalized patients ?

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DISCOVERY

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BIOGROUP biologie médicale

Findings

- We can identify the main patterns of viral load with a piecewise linear model

Limitations

- High computation time due to Bayesian framework

Perspectives

- Impact of variant of infection and vaccination in patterns of viral load ?

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F. Ader, M. Hites, P. Poignard

Biogroup team

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