Modelling the viral dynamics of SARS-CoV-2 in the general community in a context of emerging variants

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Université Paris Cité

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Inserm La science pour la santé From science to health

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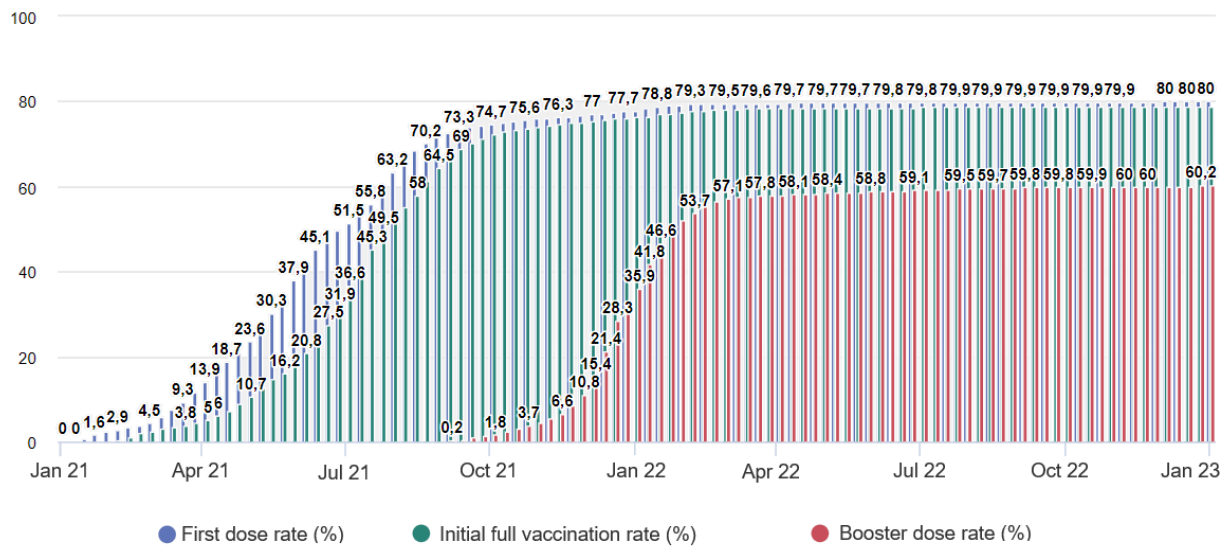
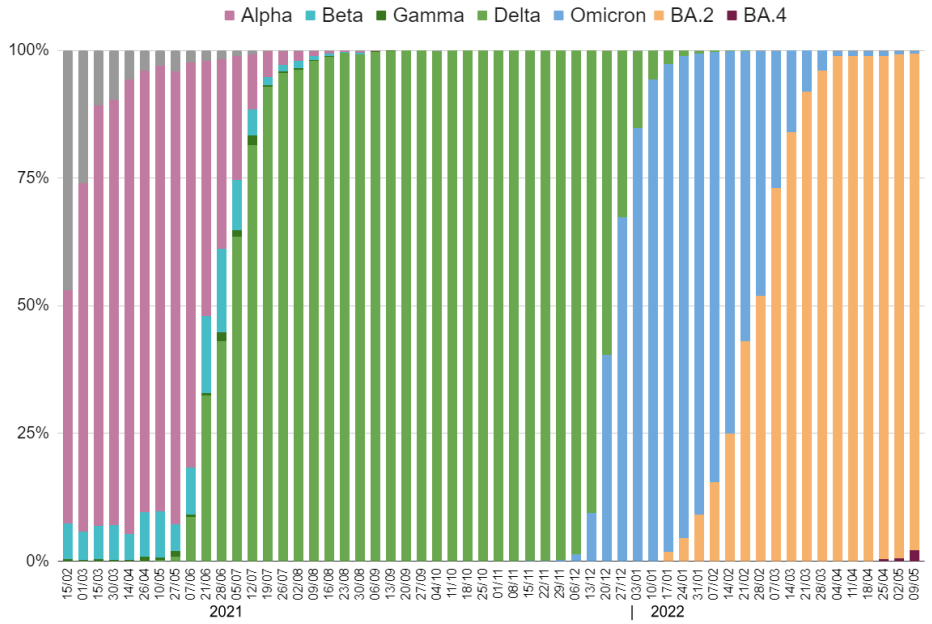
The COVID-19 pandemic – a changing landscape

From early 2021, the epidemic as been affected by:

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



Vaccination rate in France since 2021 [1]



Successive waves of VoCs in France since 2021 [2]

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The COVID-19 pandemic – a changing landscape

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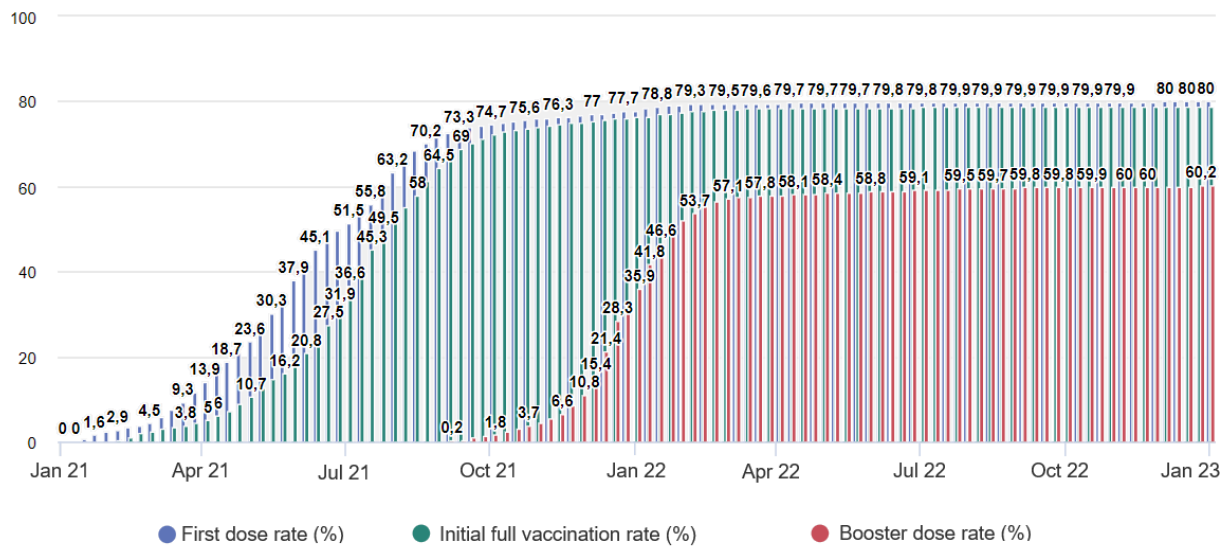
→ Modified the **severity** and **transmission** of the virus



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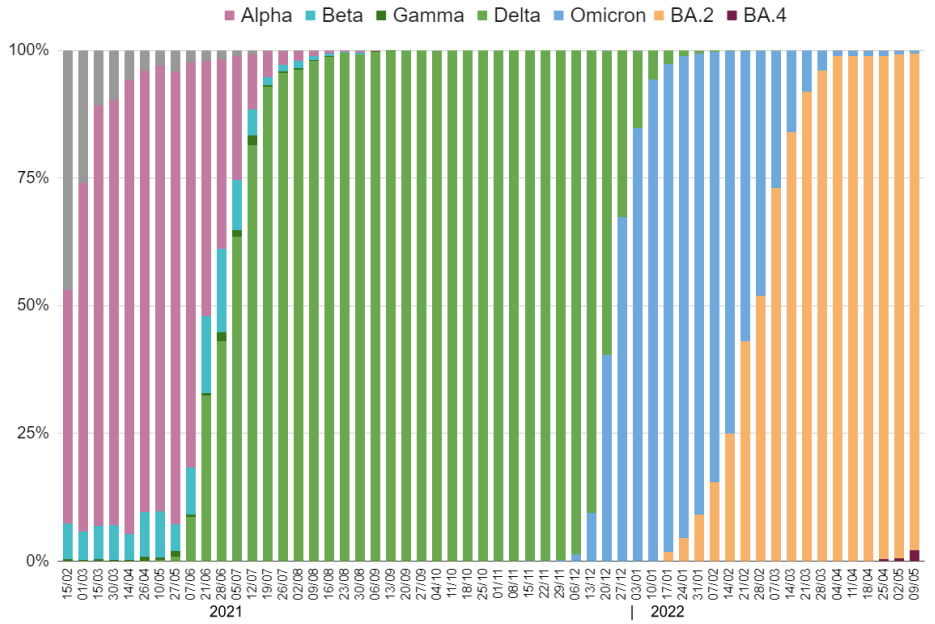

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Study the impact of this changing landscape on viral dynamics in the population

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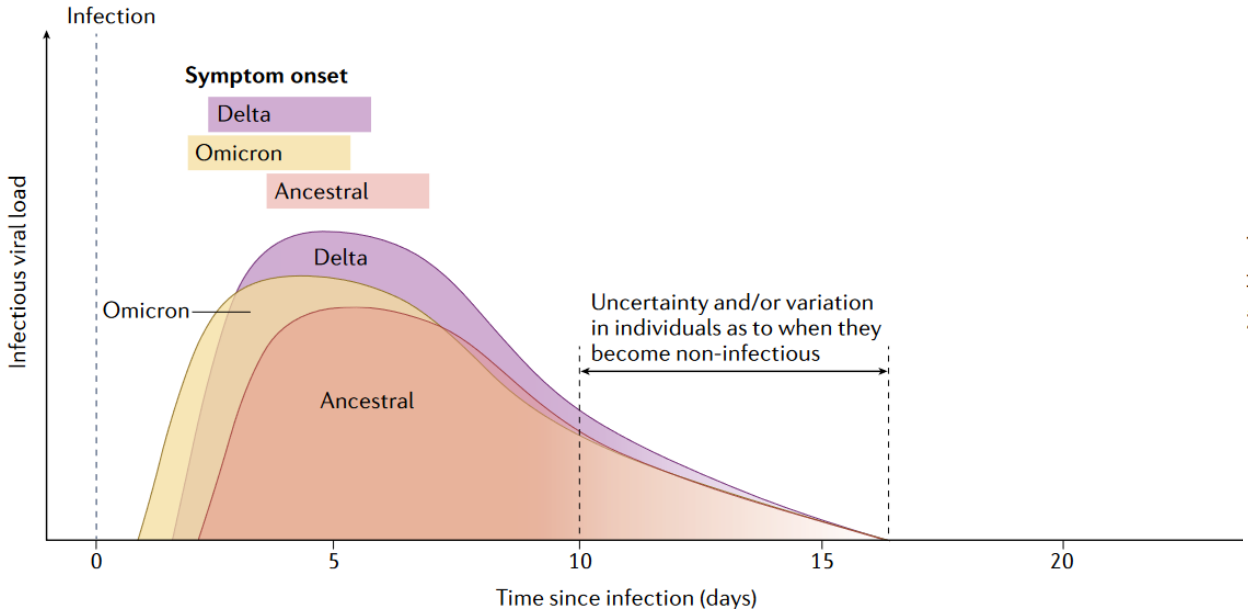
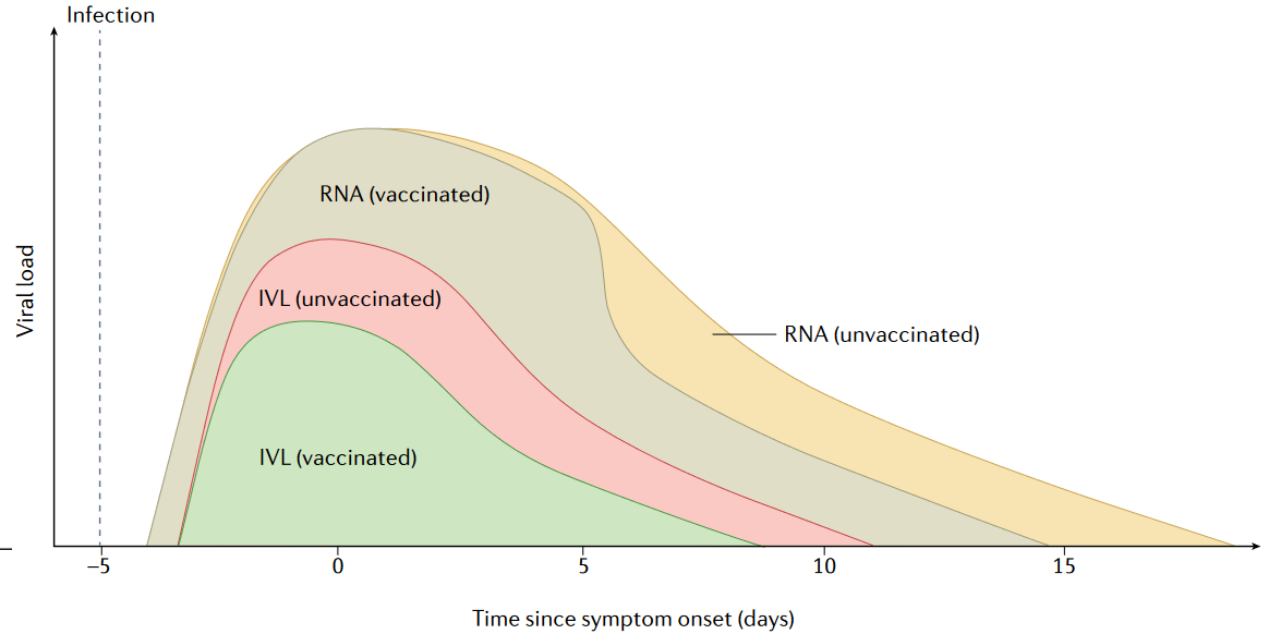
  - Studies often conducted on small specific cohorts (symptomatic, commorbidities…) → Potential selection bias





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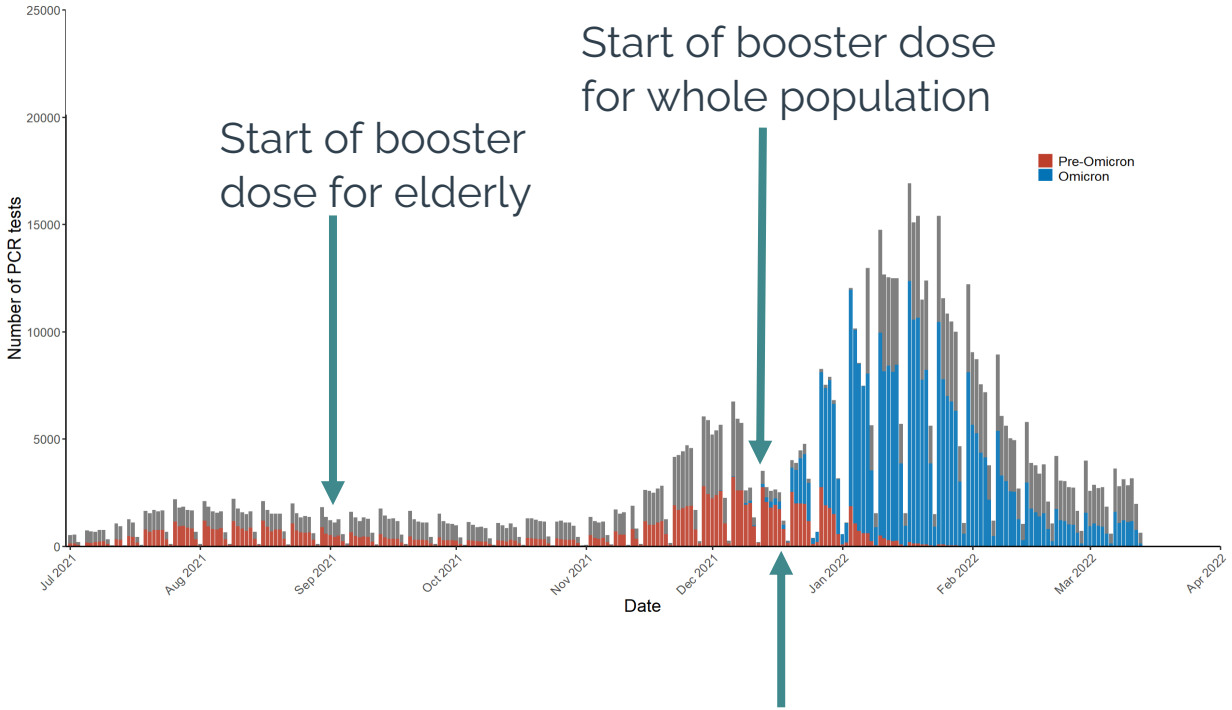
➔ Analyzing millions of PCR tests performed **in community labs**



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

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

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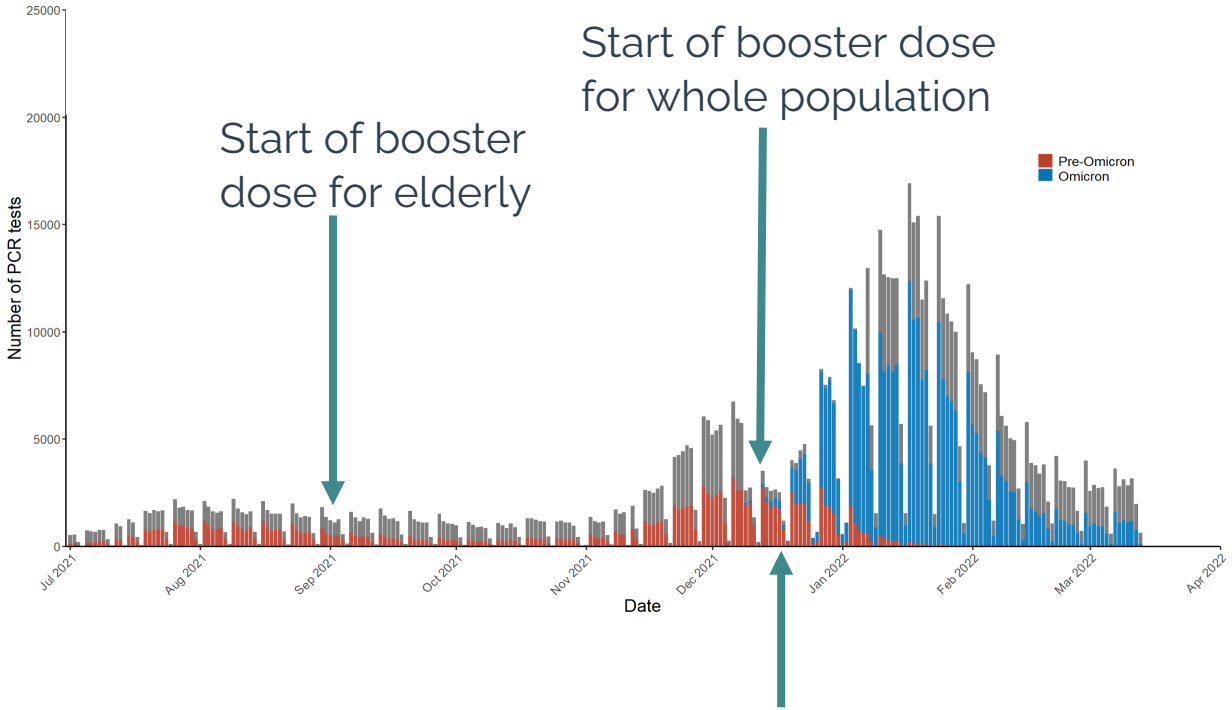

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Can we model the community labs tests to identify patterns in viral load ?

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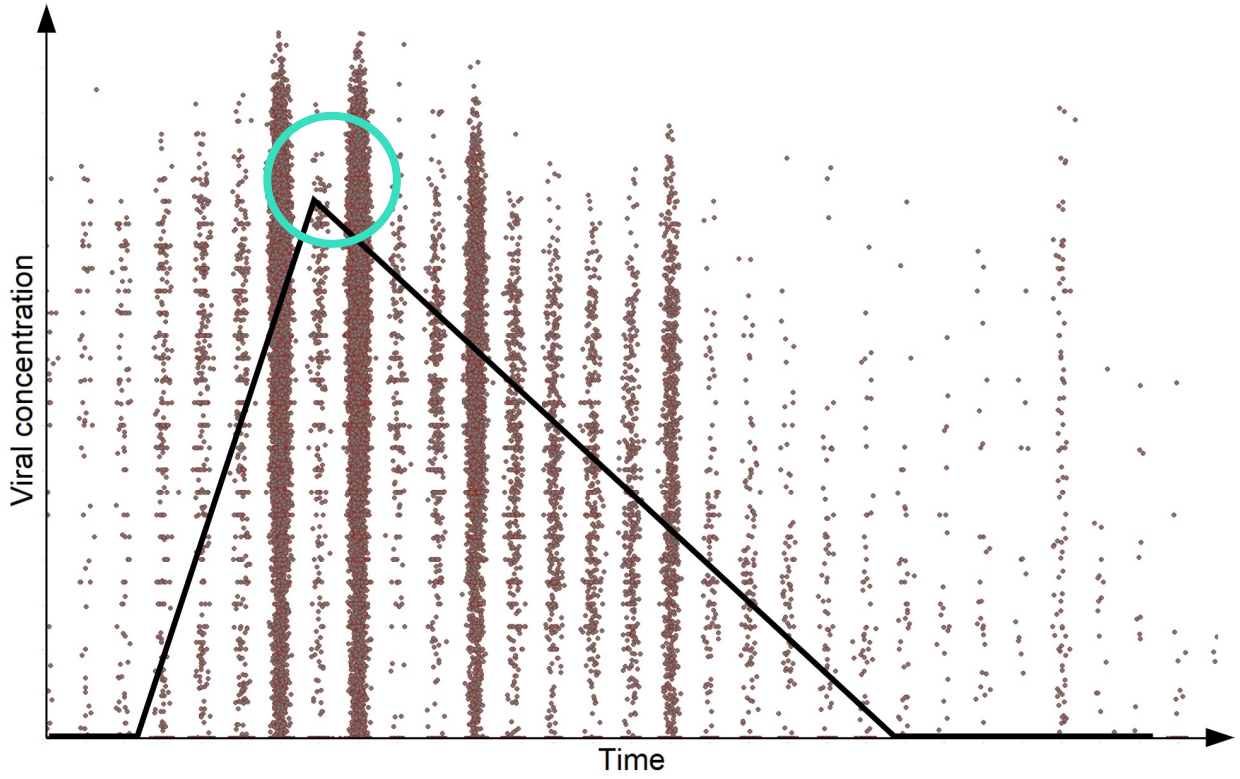
Simple viral load dynamics model to identify patterns

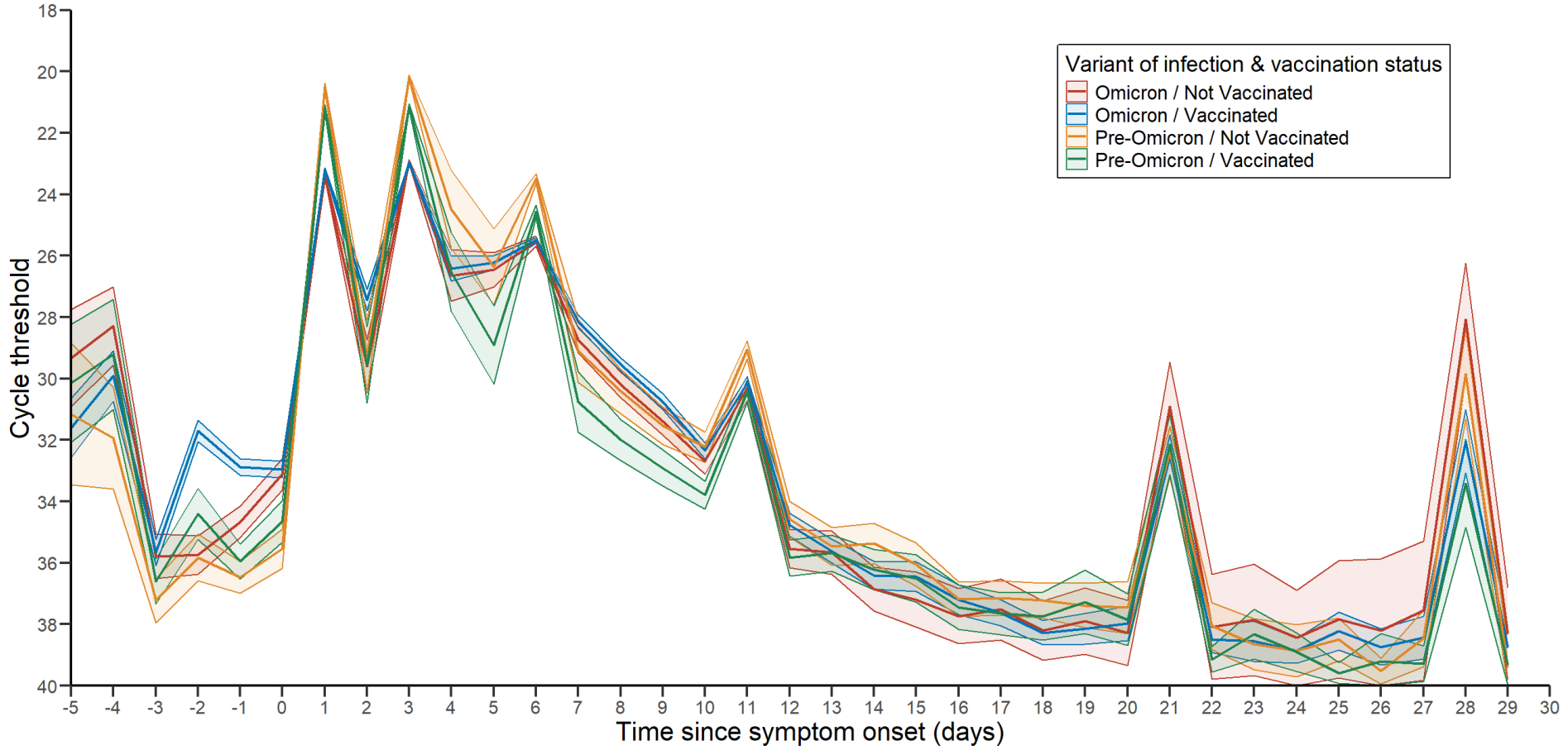
Modelling the viral load dynamics : reconstruct the individual viral load trajectories with mathematical models

Empirical models



- ➔ Identify how viral dynamics patterns are impacted by variants and vaccination
- ➔ Using simple mathematical models
- ➔ Estimate subset of key parameters related to viral dynamics
- ➔ Adapted to massive datasets

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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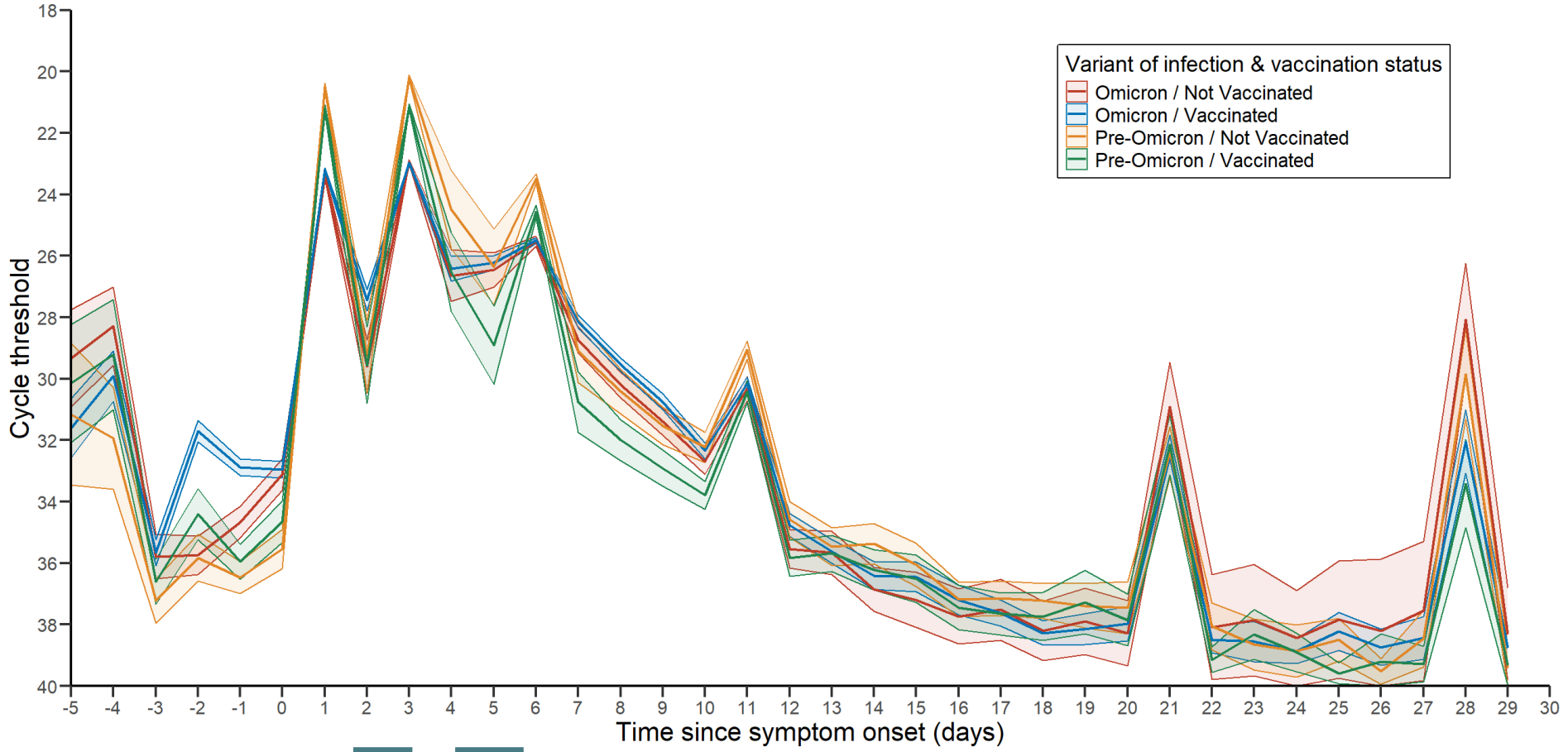

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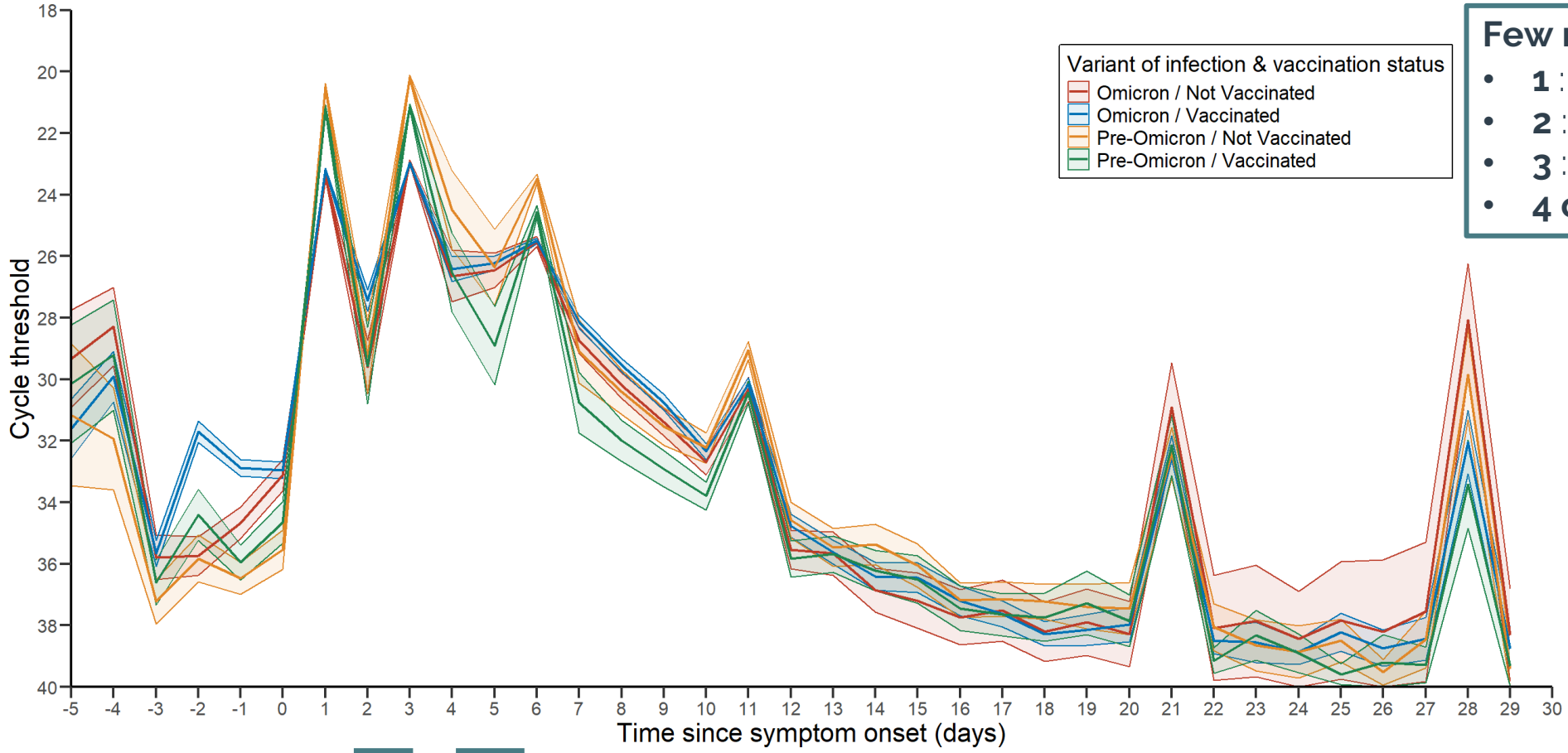

Few repeated tests :

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

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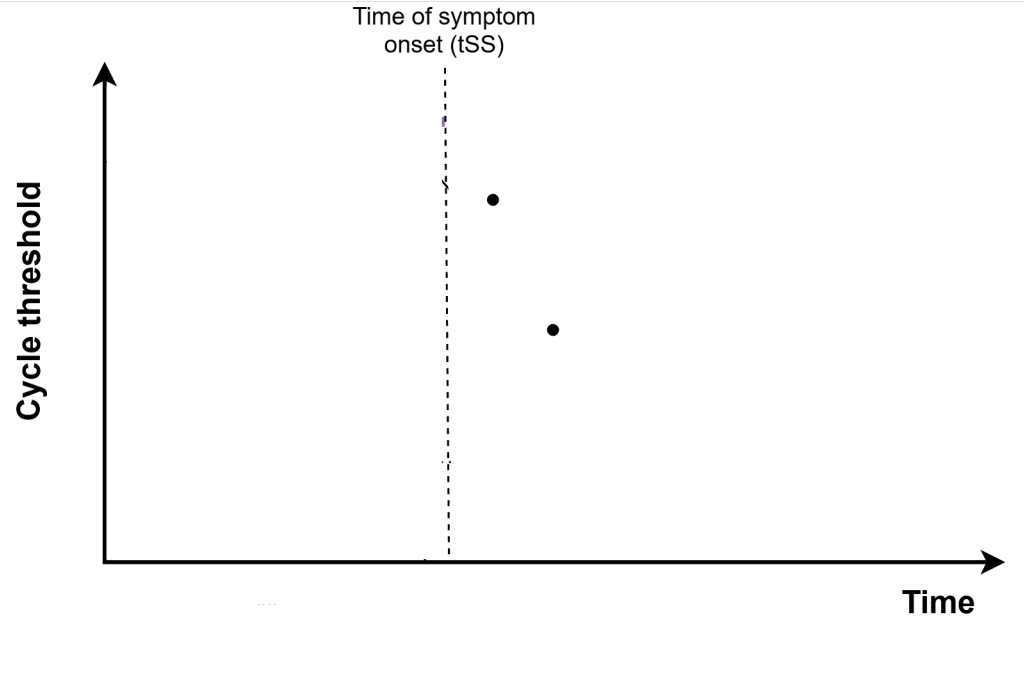
Piecewise linear mixed-effects model to capture the viral load dynamics



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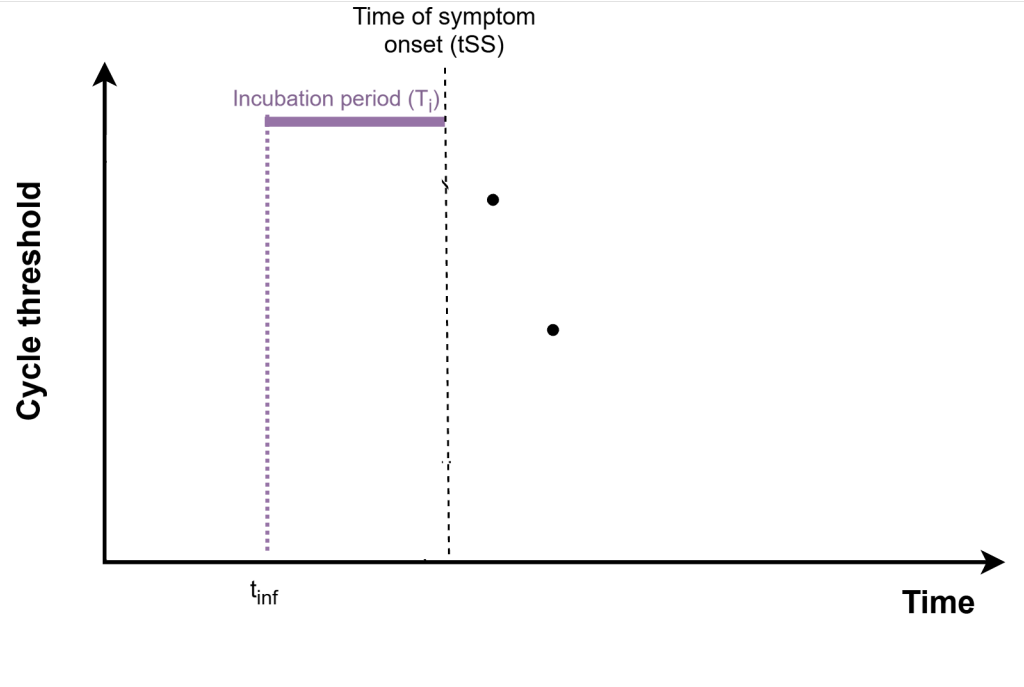

We estimate 4 parameters:

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

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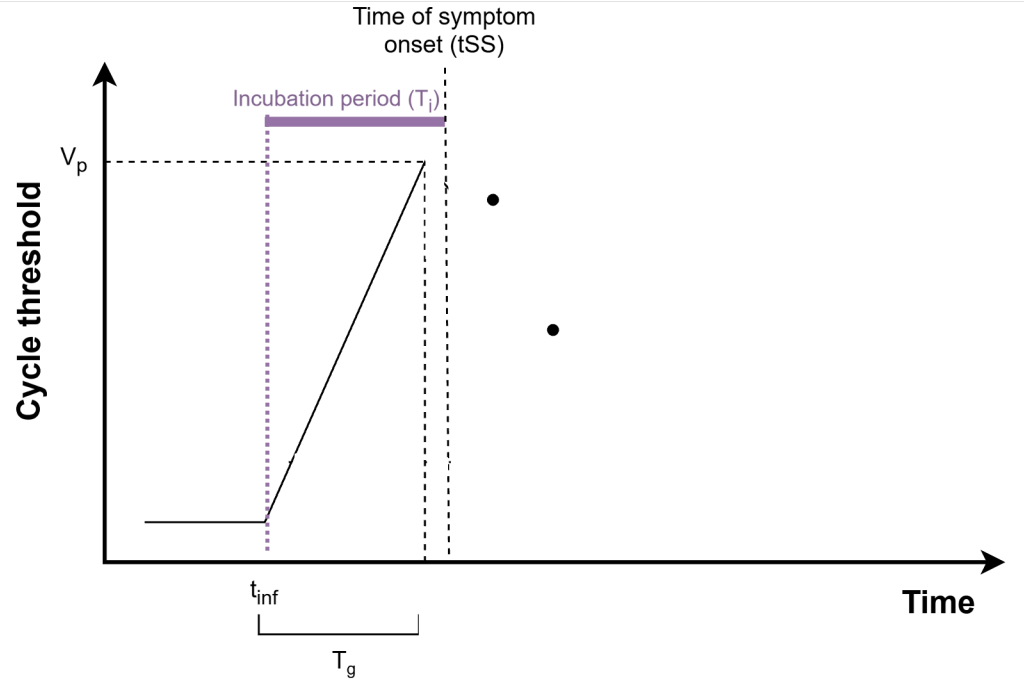

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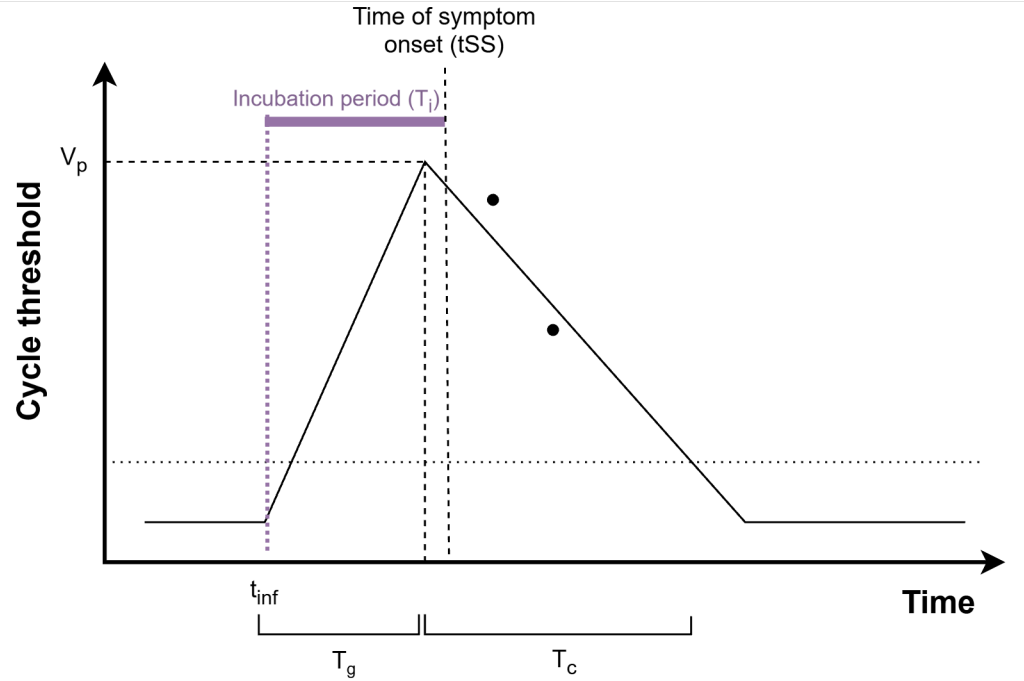

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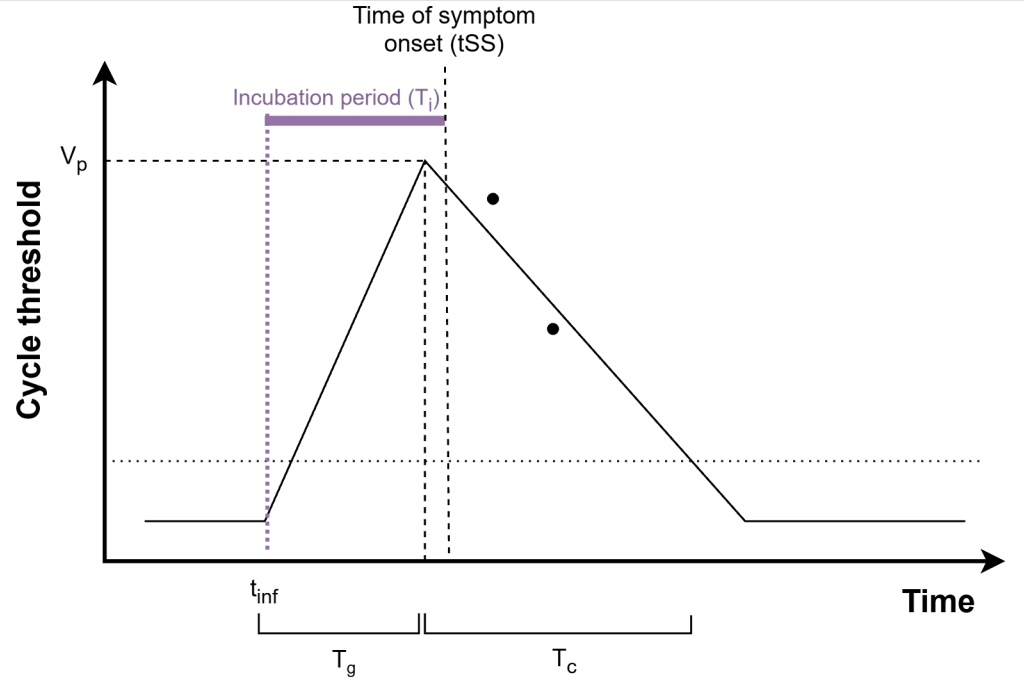

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$$t_{inf} = tSS - T_i$$

- We deduct the time to peak ($\boldsymbol{t_p}$) as followed:

$$t_p = t_{inf} + T_g$$

Proliferation phase

$$\text{E}[\Delta\text{Ct(t)}] = \begin{cases} 0 & t = t_{inf} \\ Vp \times \left(\frac{t - t_{inf}}{t_p - t_{inf}}\right) & t_{inf} < t < t_p \\ Vp & t = t_p \end{cases}$$

Clearance phase

$$\text{E}[\Delta\text{Ct(t)}] = \begin{cases} Vp & t = t_p \\ Vp + (V_{inf} - LOD - Vp) \times \left(\frac{t - t_p}{t_c - t_p}\right) & t_p < t < t_c \\ V_{inf} - LOD & t = t_c \end{cases}$$

with $\Delta\text{Ct(t)} = V_{inf} - Ct(t)$, $V_{inf} = 50$, and $LOD = 40$

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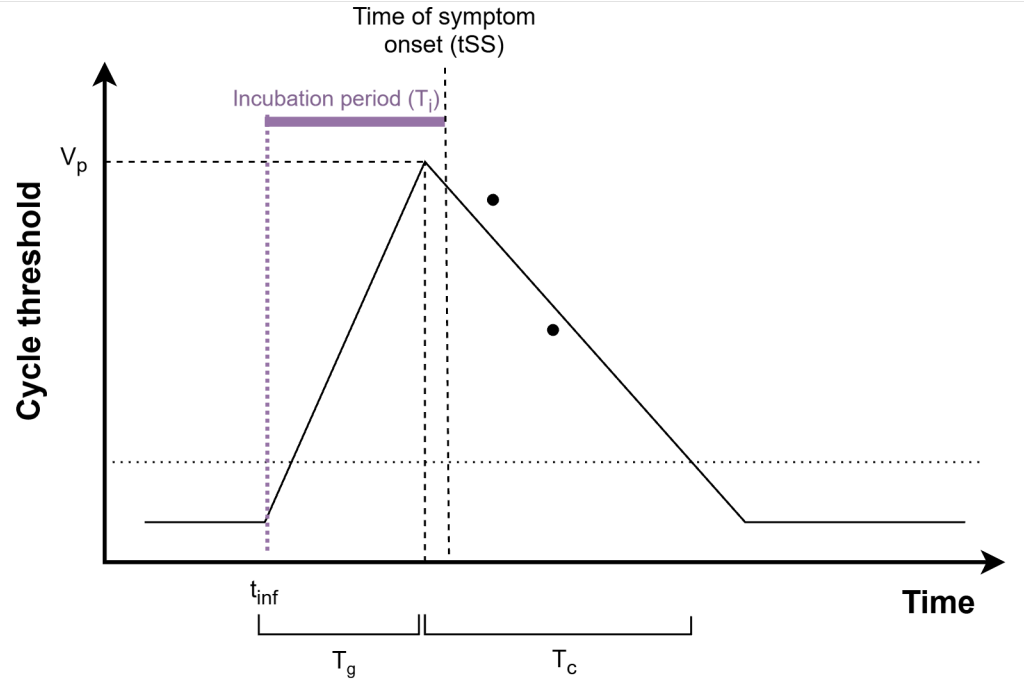

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- Vector of individual parameters $\boldsymbol{\theta}[i] = \{T_i[\mathrm{i}], T_g[\mathrm{i}], T_c[\mathrm{i}], V_p[\mathrm{i}]\}$ is defined as followed:

$$\log(\boldsymbol{\theta}[i]) = \boldsymbol{exp}(\log(\mu_{\boldsymbol{\theta}}) + \boldsymbol{\eta}_{\boldsymbol{\theta}[i]})$$

Fixed effects: $\mu_{\boldsymbol{\theta}} \sim \boldsymbol{N}^{+}(\bar{m}_{\boldsymbol{\theta}}, \boldsymbol{\sigma}_{\boldsymbol{\theta}})$

Random effects: $\boldsymbol{\eta}_{\boldsymbol{\theta}[i]} \sim \boldsymbol{N}(\mathbf{0}, \boldsymbol{\omega}^{\mathbf{2}})$

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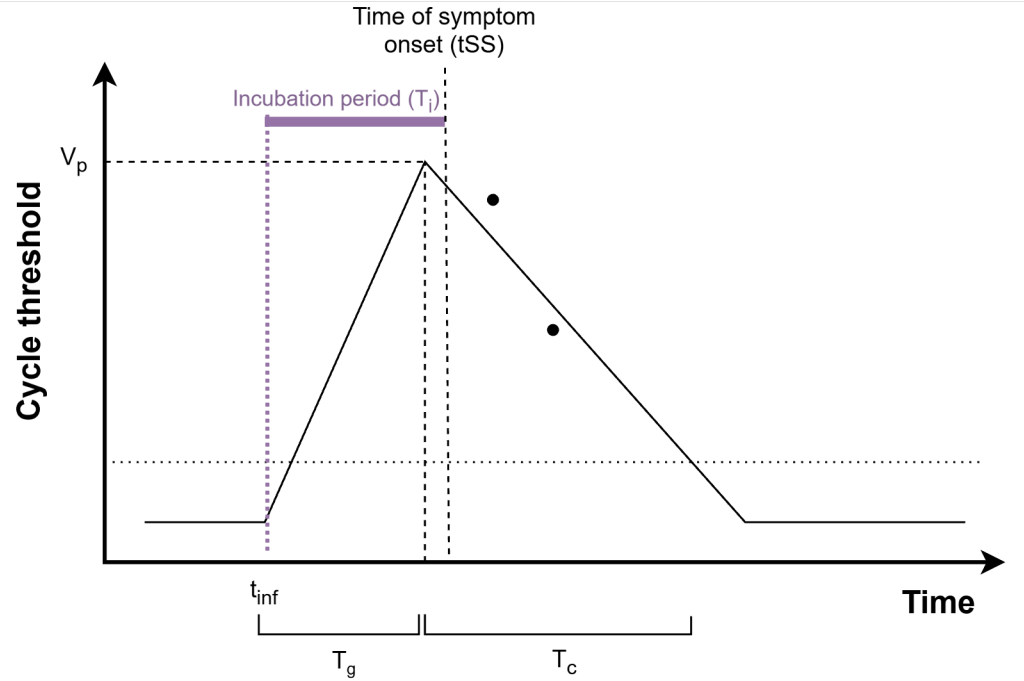

Bayesian inference framework, HMC NUTS algorithm in Stan

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 (centered on simulation value)

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

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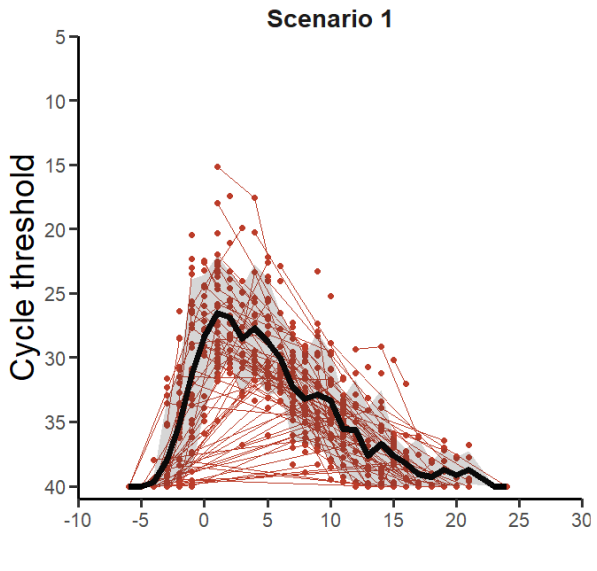

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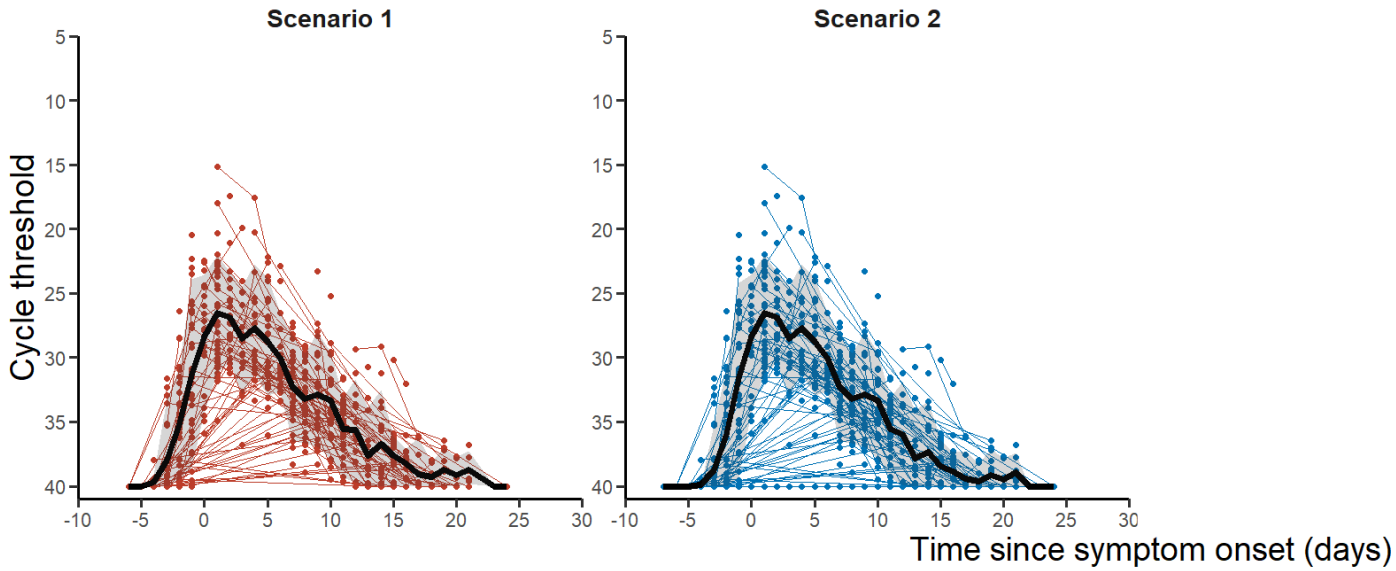

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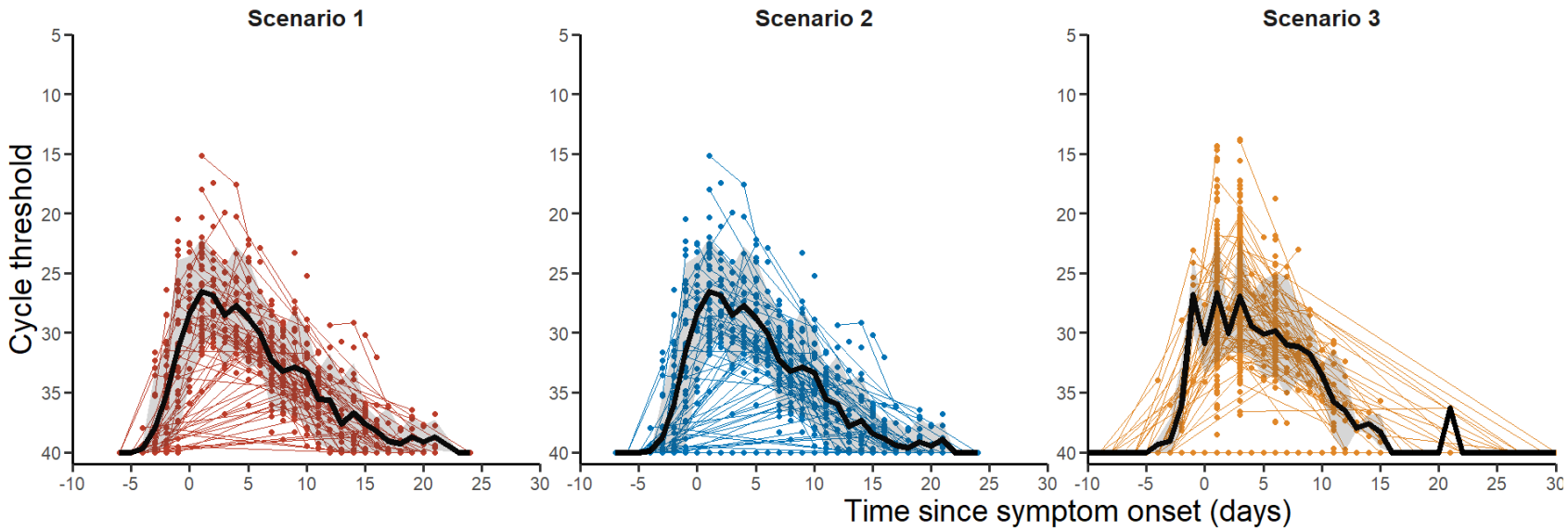
Scenario 3	Entire population	50%	Mostly at symptom onset



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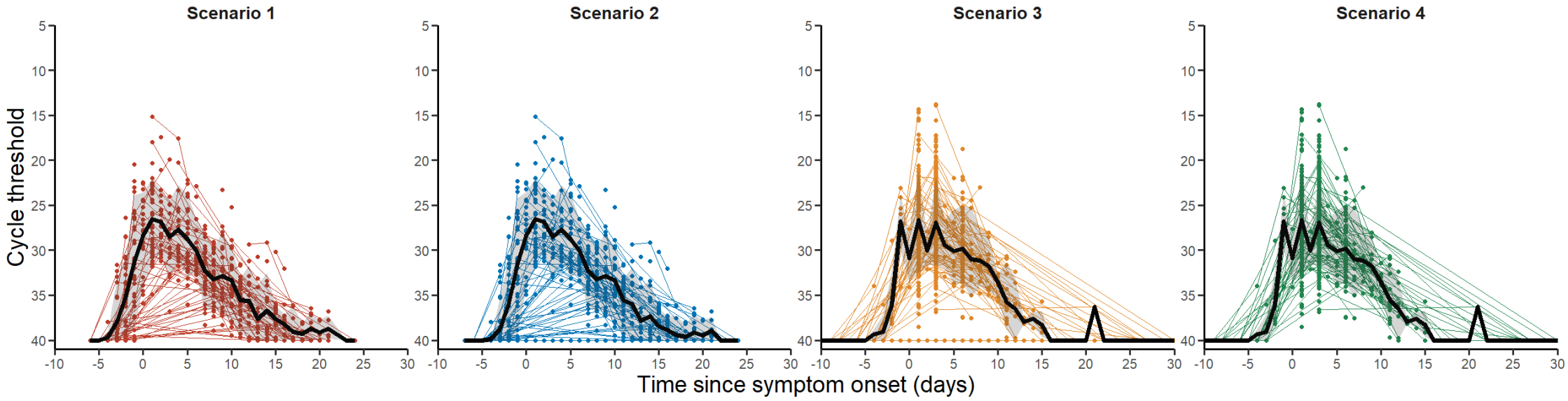
Scenario 4	≥ 1 positive PCR	100%	Mostly at symptom onset



Likelihood definition in each scenario

- Modelling the **viral dynamics of the infected individuals only** (**Scenario 1**, **4**)

$$L(y_{i,t}|\psi_i) = \mathbb{1}_{\{uncensored\}} f_N\left(x \middle| E[y_{i,t}|\psi_i], \sigma\right) + \mathbb{1}_{\{censored\}} F_N\left(LOD \middle| E[y_{i,t}|\psi_i], \sigma\right)$$

- f_N the Normal PDF, F_N the Normal CDF,
- *LOD* = Limit of detection

Contribution if infected

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- **Determining infectious status** and **modeling viral dynamics for all individuals** (**Scenario 2**, **3**)

$$L(y_{i,t}|\psi_i) = P_{inf}\left[\mathbb{1}_{\{uncensored\}} f_N\left(x|E[y_{i,t}|\psi_i], \sigma\right) + \mathbb{1}_{\{censored\}} F_N\left(LOD|E[y_{i,t}|\psi_i], \sigma\right)\right] + (1 - P_{inf})\left[\mathbb{1}_{\{uncensored\}} P(false\ positive) + \mathbb{1}_{\{censored\}} P(true\ negative)\right]$$

- f_N the Normal PDF, F_N the Normal CDF,
- LOD = Limit of detection
- $P(false\ positive)$ =0,0002, $P(true\ negative) = 0{,}9998$,
- P_{inf} the percentage of infected individuals in the dataset

Contribution if infected

Contribution if not infected

Evaluation of the model

- **Chains convergence**: R-hat [5]
  - Ratio of intra-chain to inter-chain variance
  - Must be less than 1.1 for each parameter

- **Error estimation**: (Relative Estimates Error, REE in %) [6]

$$REE\left(\hat{\theta}^k\right) = \frac{\hat{\theta}^k - \theta^*}{\theta^*} \times 100$$

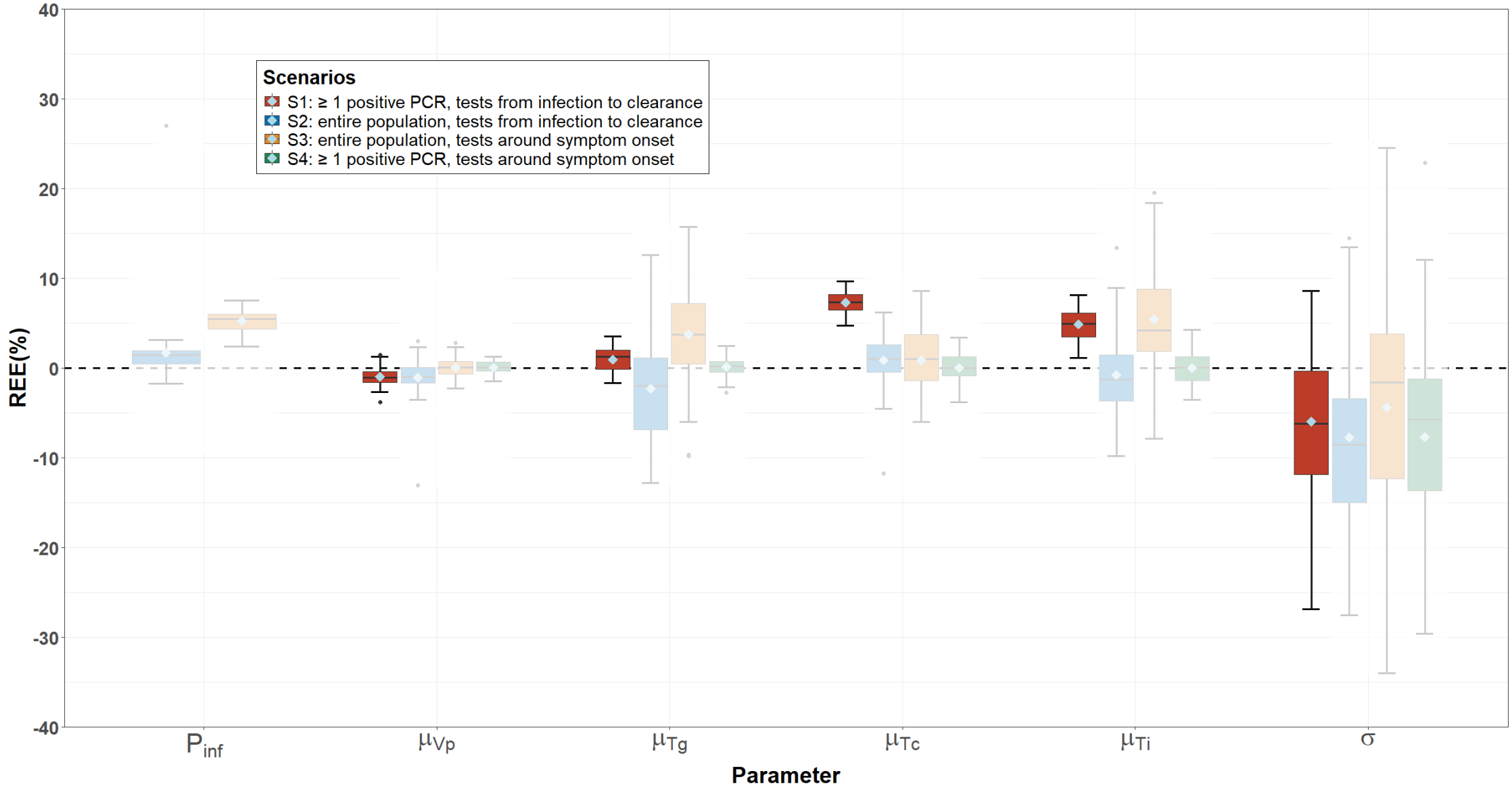
- **Estimation accuracy**: (Coverage rate, CR) [6]

$$CR_{(1-\alpha)}(\theta) = \frac{1}{K}\sum_{k=1}^{K} \mathbb{1}_{\{\theta^* \in \widehat{CI}^k_{(1-\alpha)}\}}$$

- **Goodness of fit**: (Posterior Predictive Check)

[5] Gelman et al, *Bayesian Data Analysis* (1995)
[6] Morris et al, *Statistics in Medicine* (2018)

Relative Estimates Errors (REEs)



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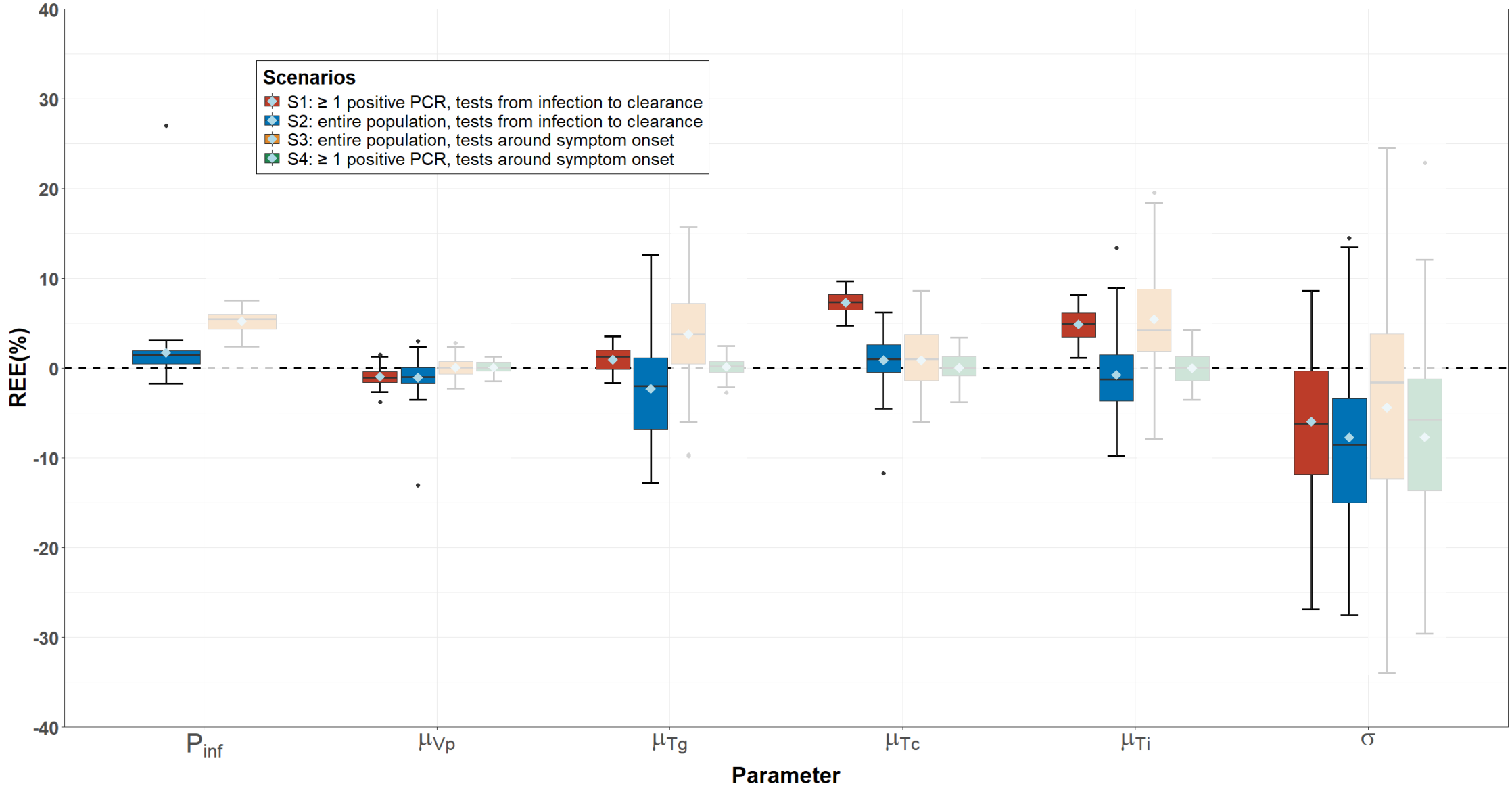

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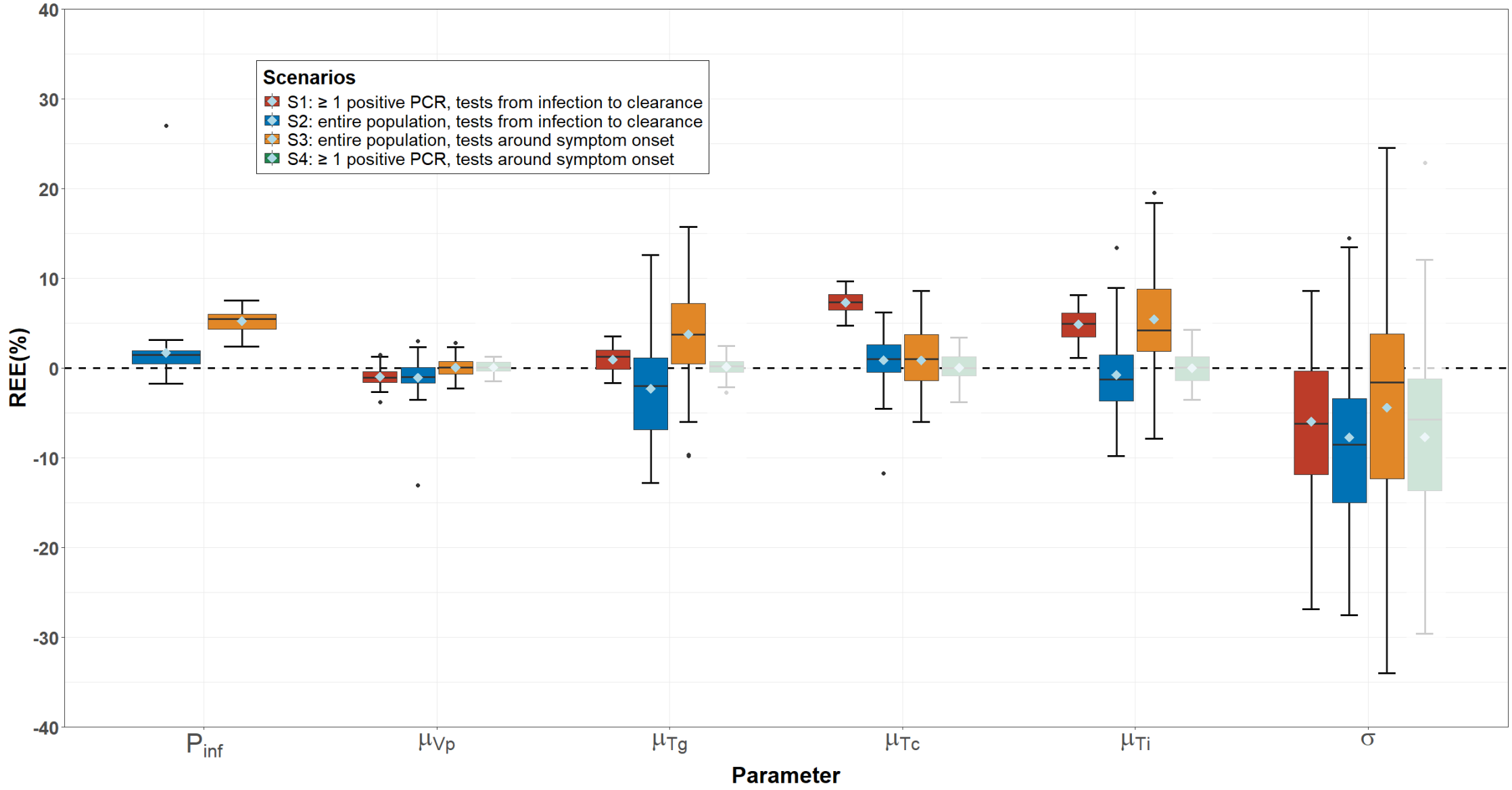

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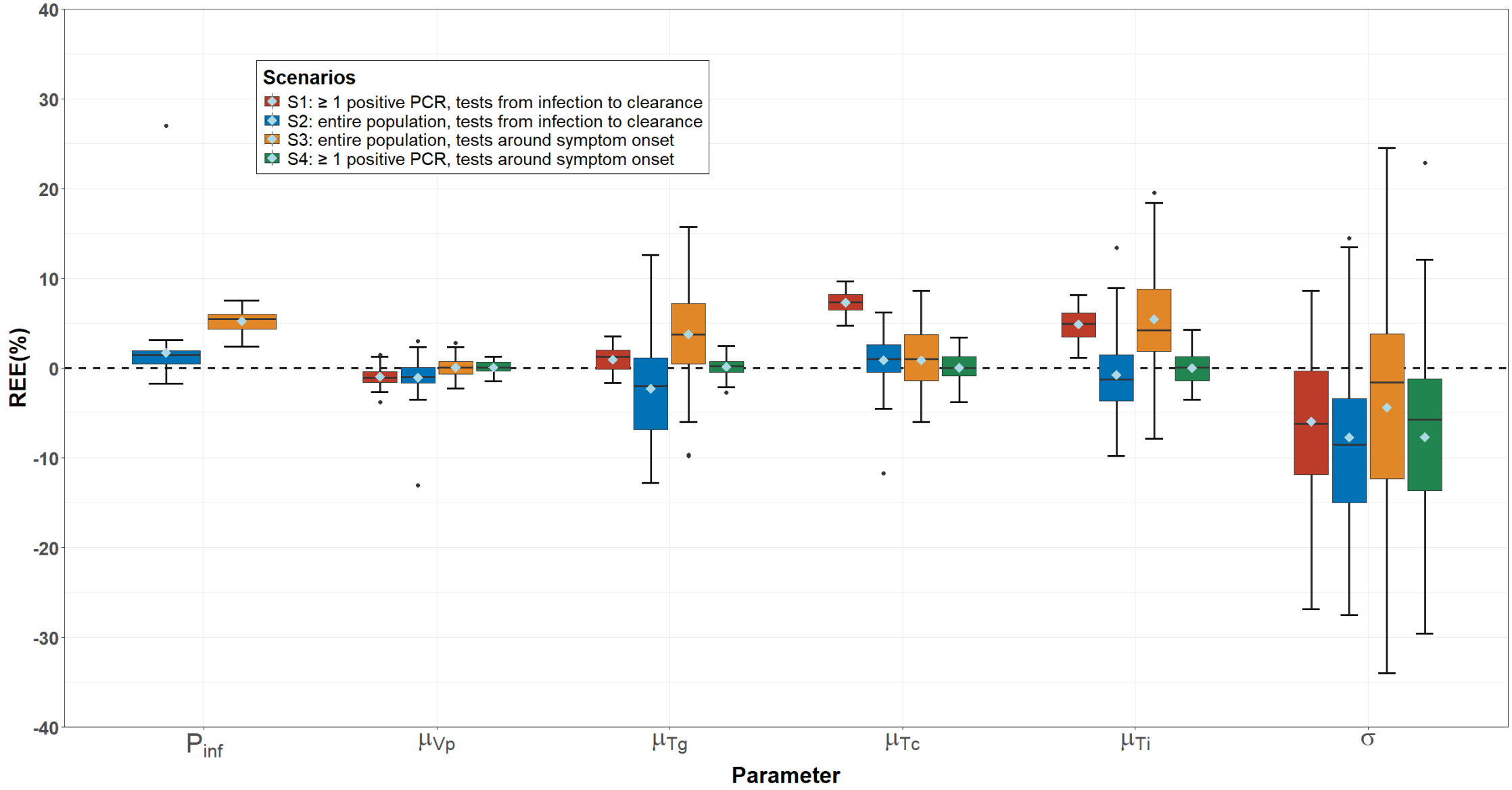
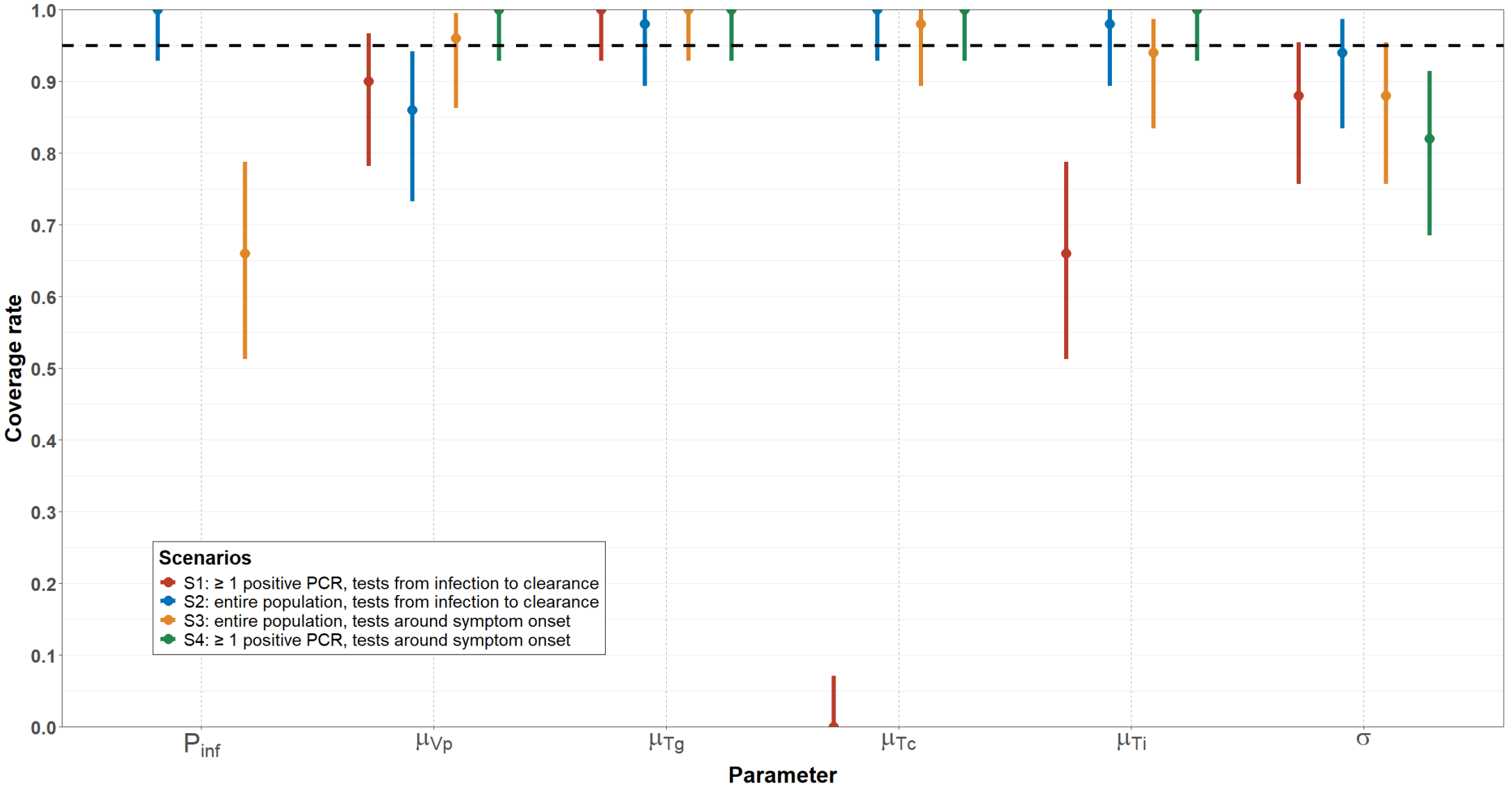
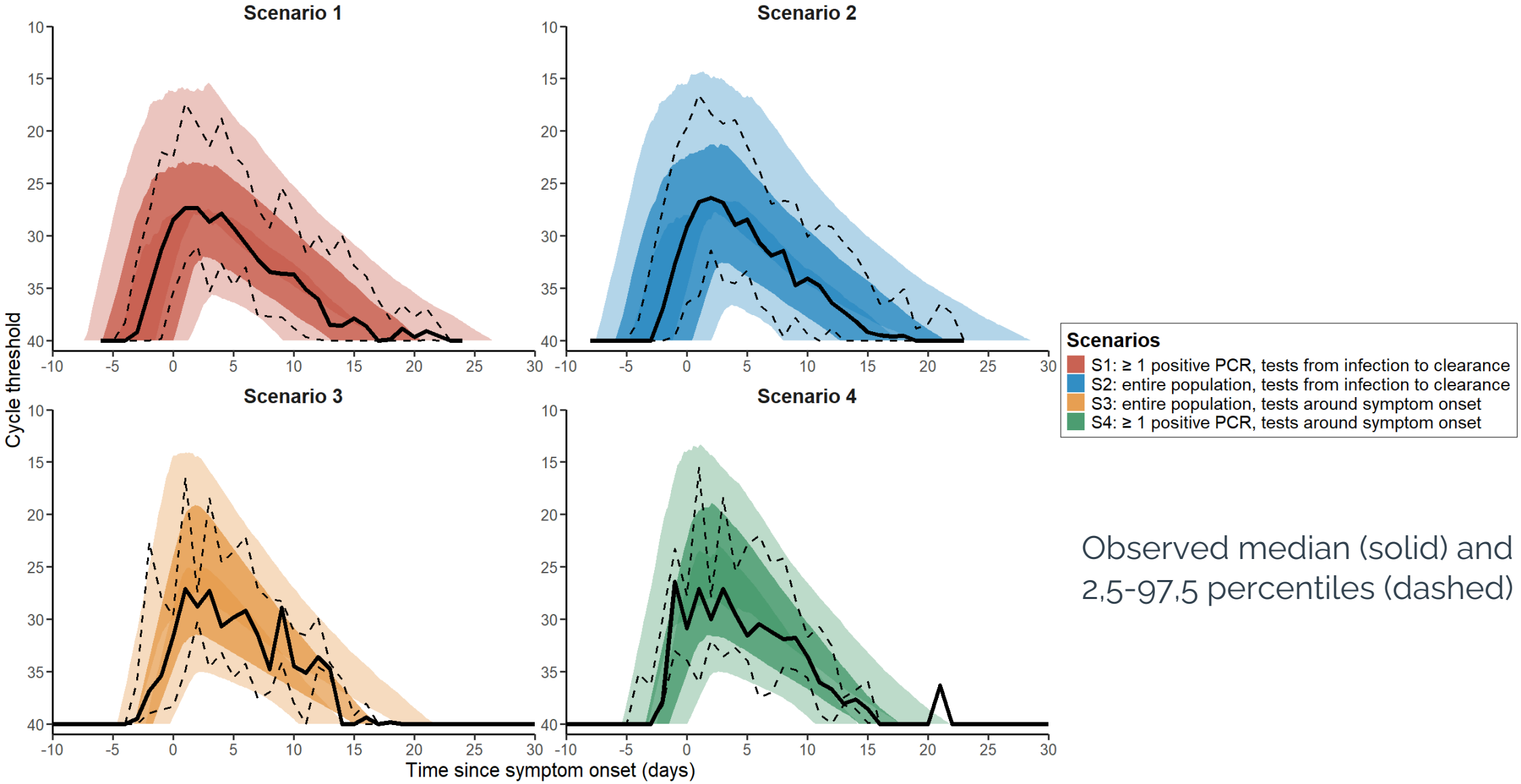


Coverage rate

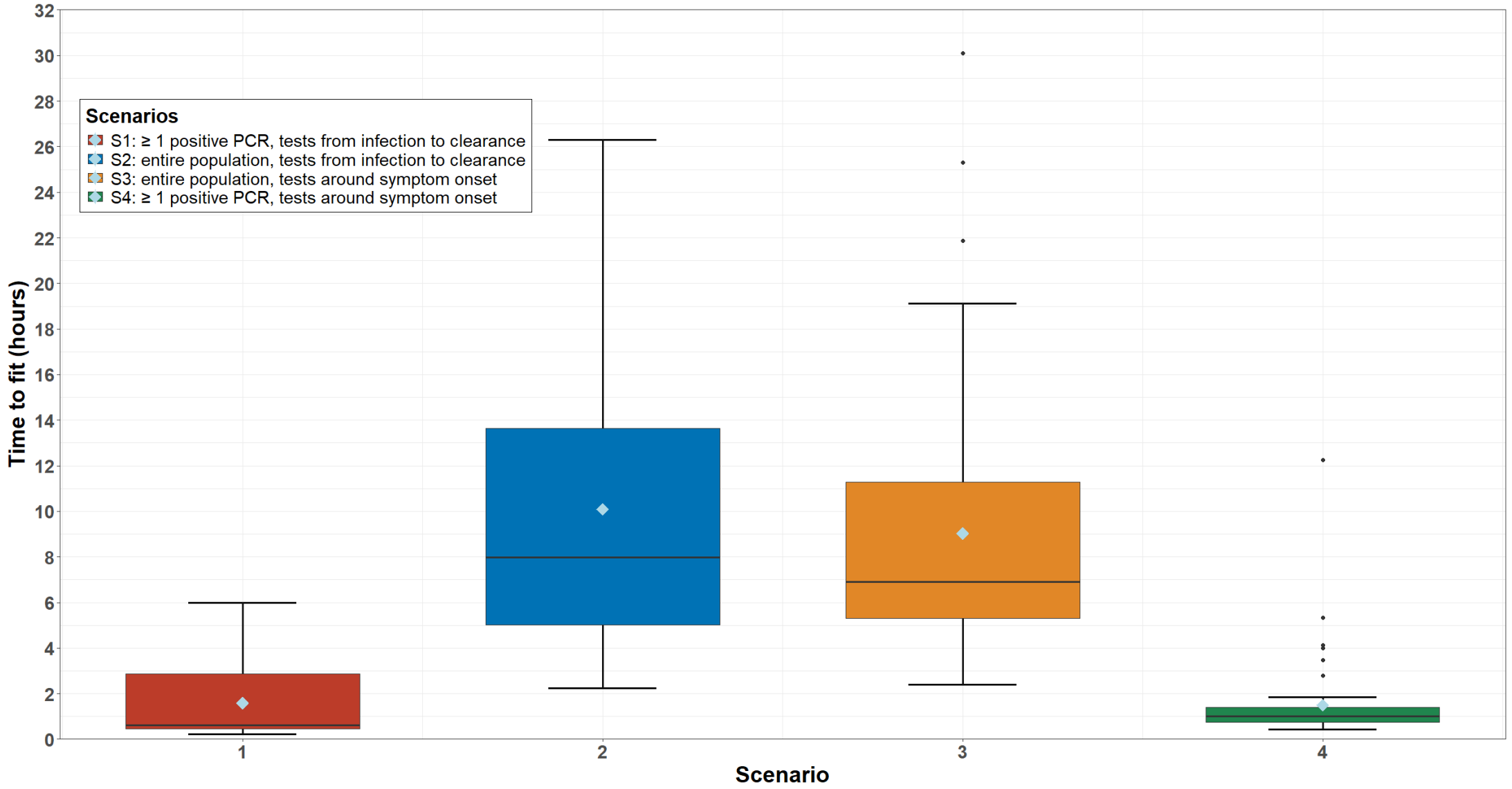


Posterior predictive checks

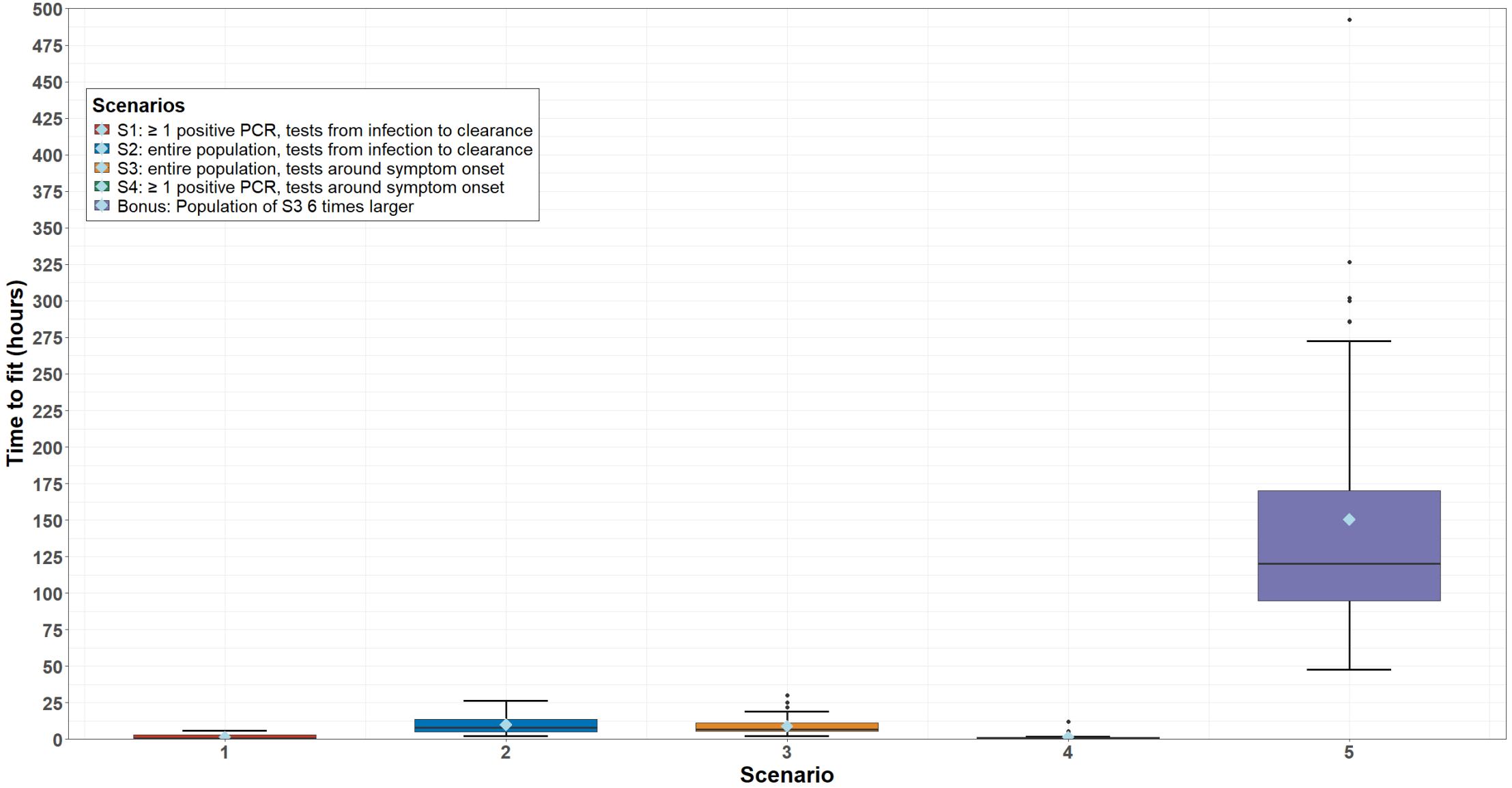


Observed median (solid) and 2,5-97,5 percentiles (dashed)

High computation time



High computation time



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Original dataset		Reduced dataset	
Number of individuals	Number of observations	Number of individuals	Number of observations
586,635	738,403	38,368	104,542

Divided by 15

We were unable to run ➔ The chains did not mix

Discussion

Findings

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

Limitations

- High computation time due to Bayesian framework
- Prior distributions are weakly informative but centred on the true value of the parameter

Perspectives

- Impact of variant of infection and vaccination in patterns of viral load ?
- Model other acute respiratory diseases (Influenza and RSV)

  M2 internship Laura MULAS (April-October 2025)

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Biogroup team

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