Viral dynamics of the Respiratory Syncytial Virus during human experimental challenge: insights for transmission and treatment

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[2]hVIVO, London
[3]IMRB INSERM U955, Team « Viruses, Cancer », Hepatology, Créteil, France
[4]Department of Virology, Hôpitaux Universitaires Henri Mondor, Assistance Publique – Hôpitaux de Paris, Créteil,INSERM U955 France
[5]Department of Medicine 5, Friedrich-Alexander-University Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany

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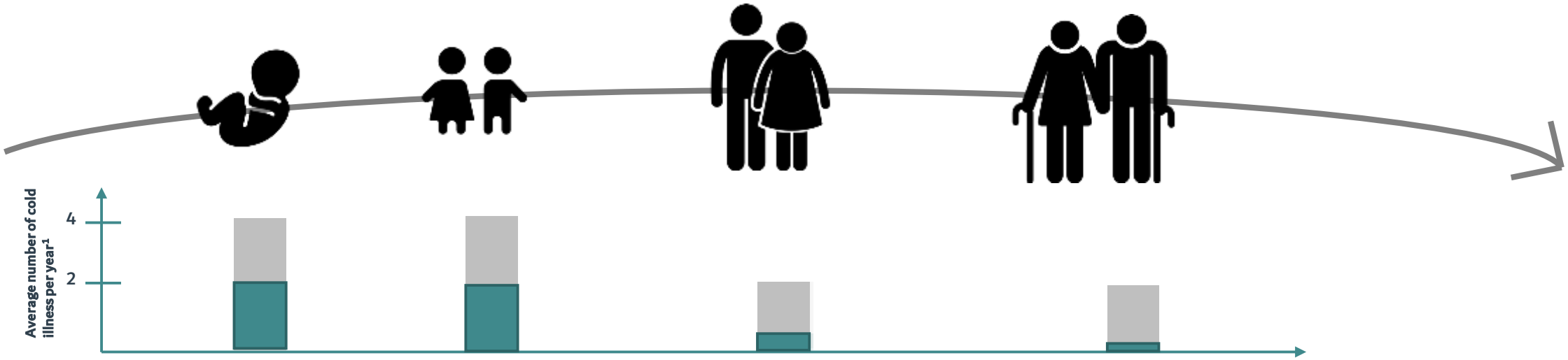
Inserm La science pour la santé From science to health

RSV: A common virus with large global impact



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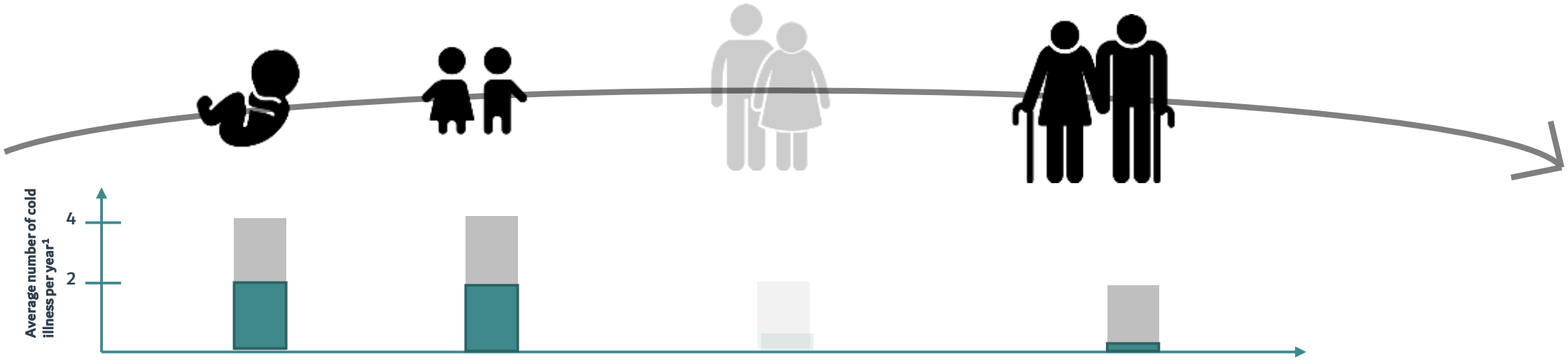

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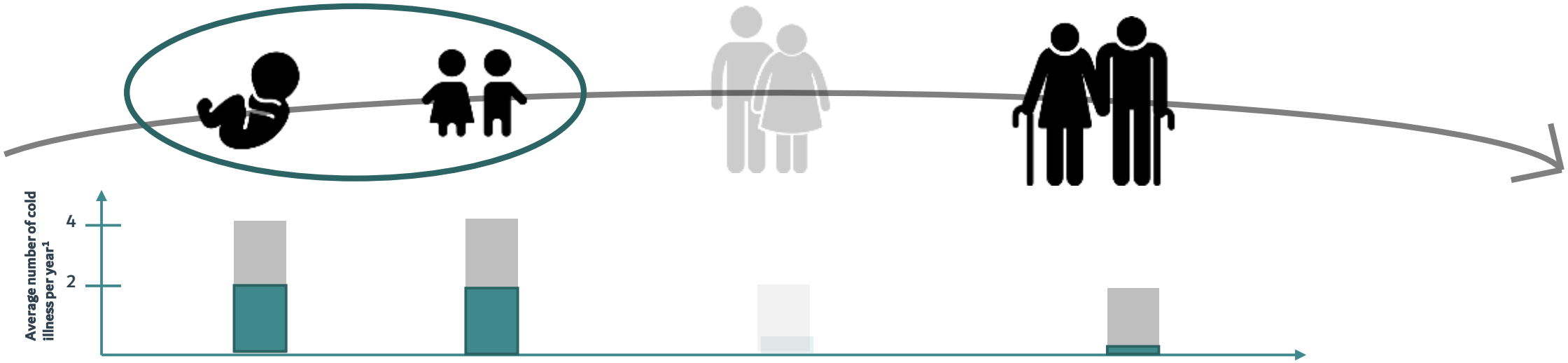

Pneumonia
Bronchiolitis

100,000 deaths each year[2]

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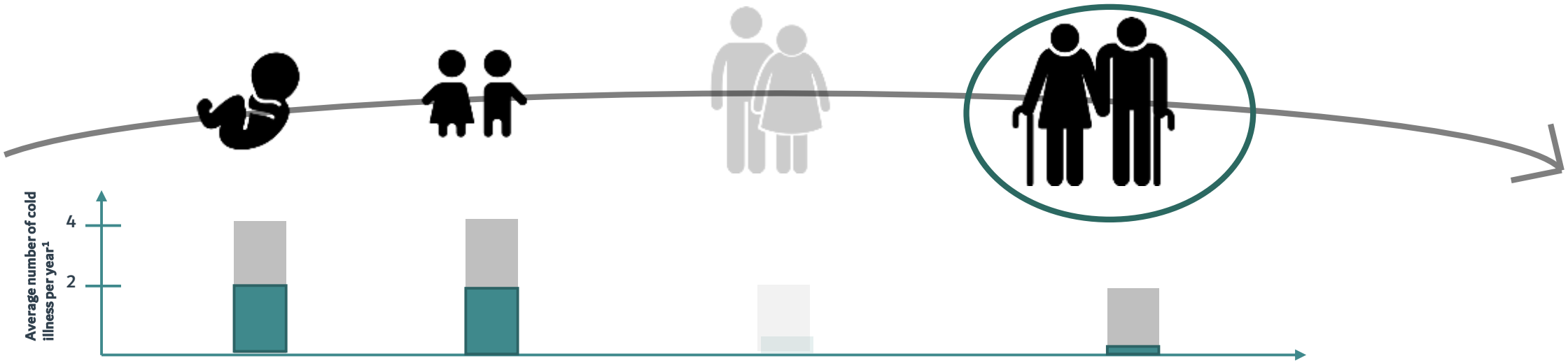

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Exacerbations of chronic disease

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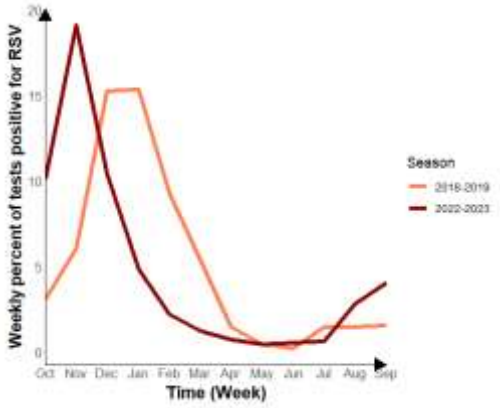
The changing landscape in RSV circulation and prophylaxis

Increase in RSV incidence[4]

- **More detections in the general population**
- **More hospitalizations**

↑ **detections**



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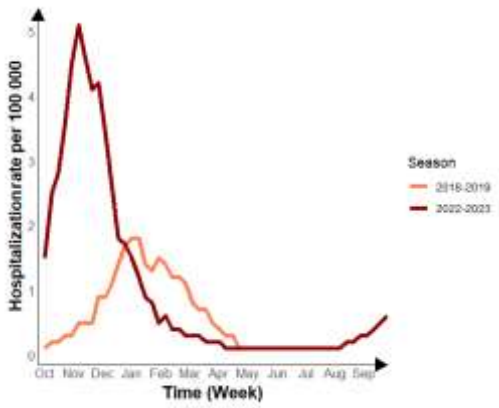

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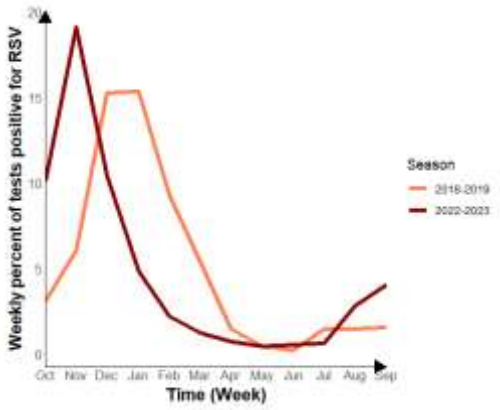

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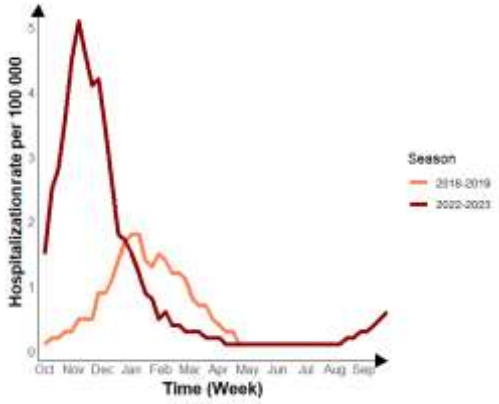

Evolving prevention strategies

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Arexvy (2023)[5]

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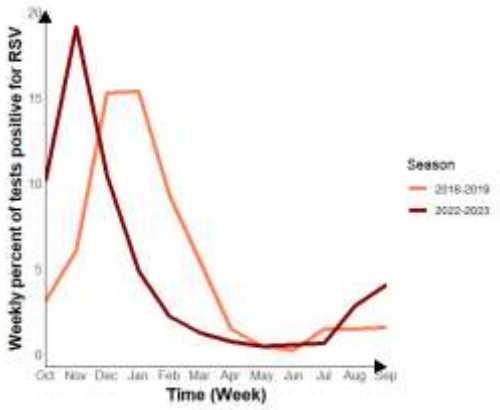

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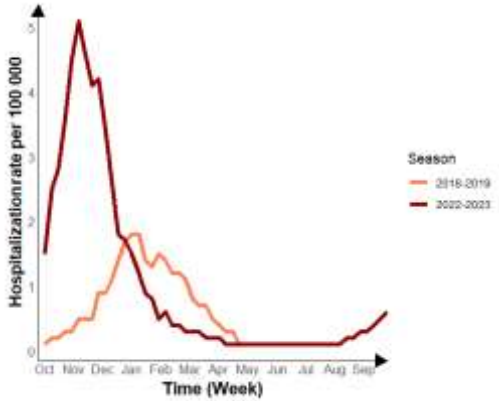

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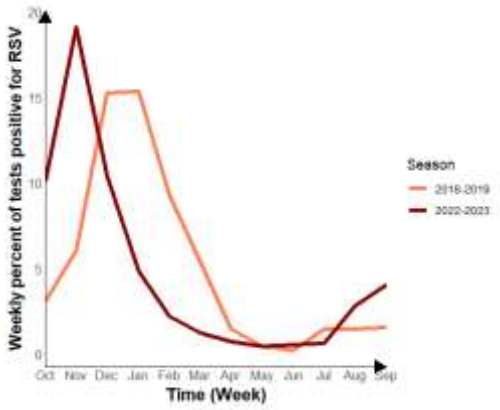

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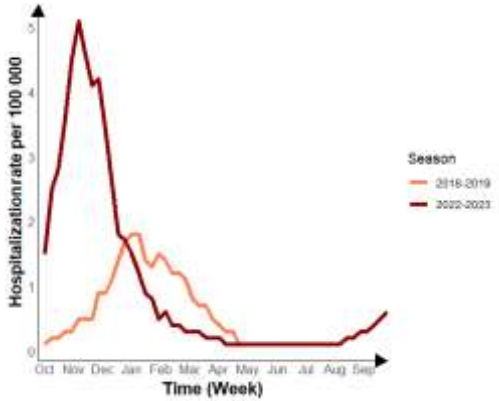

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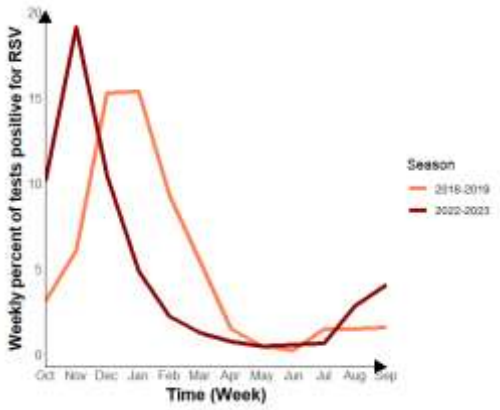

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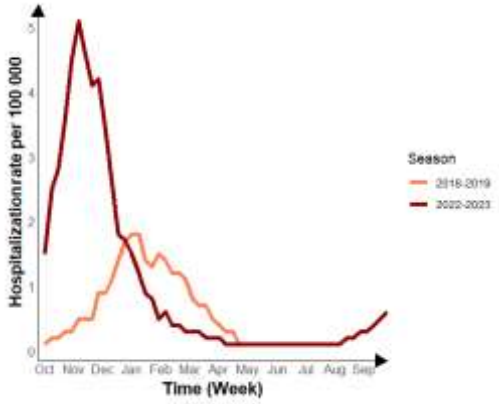

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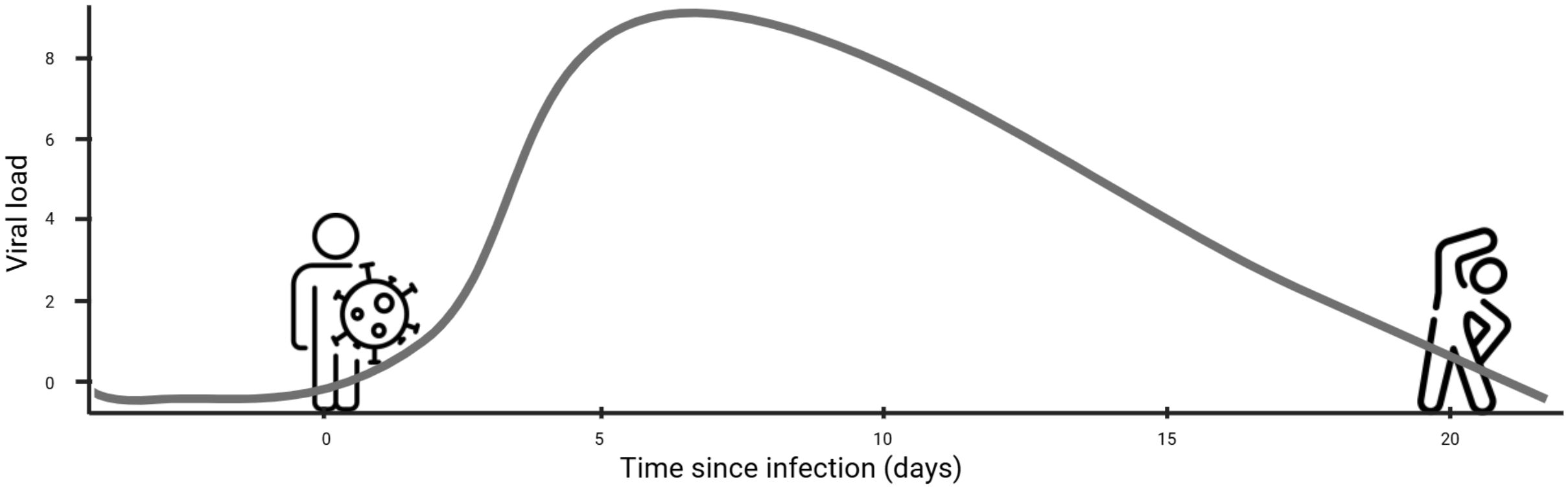
Viral kinetics to better understand RSV pathogenesis & transmission



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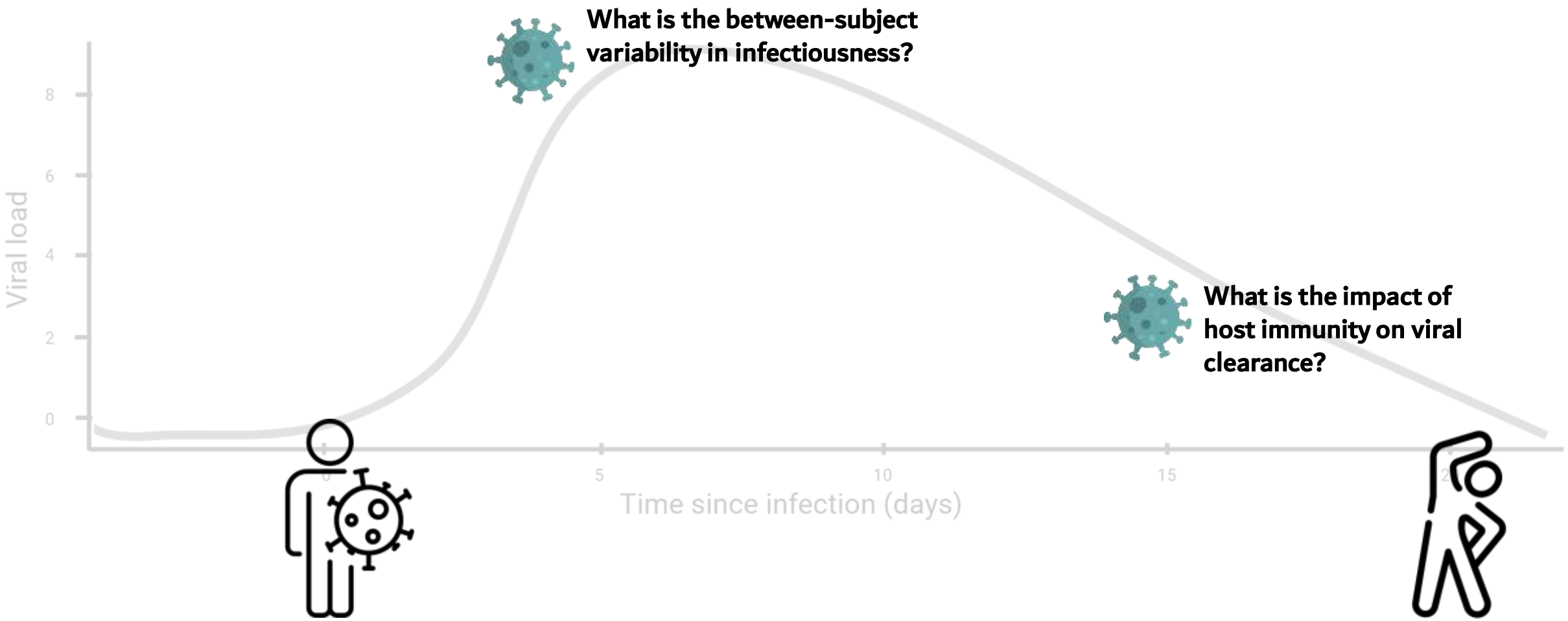

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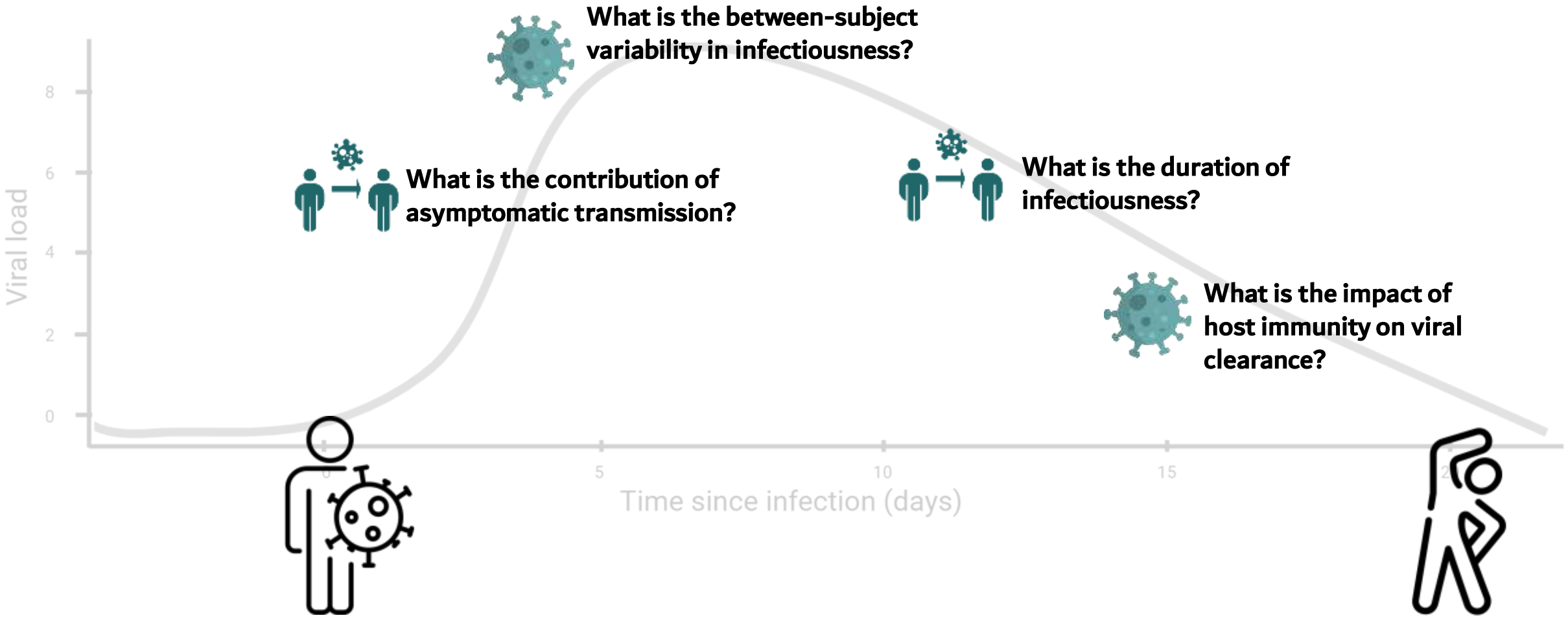

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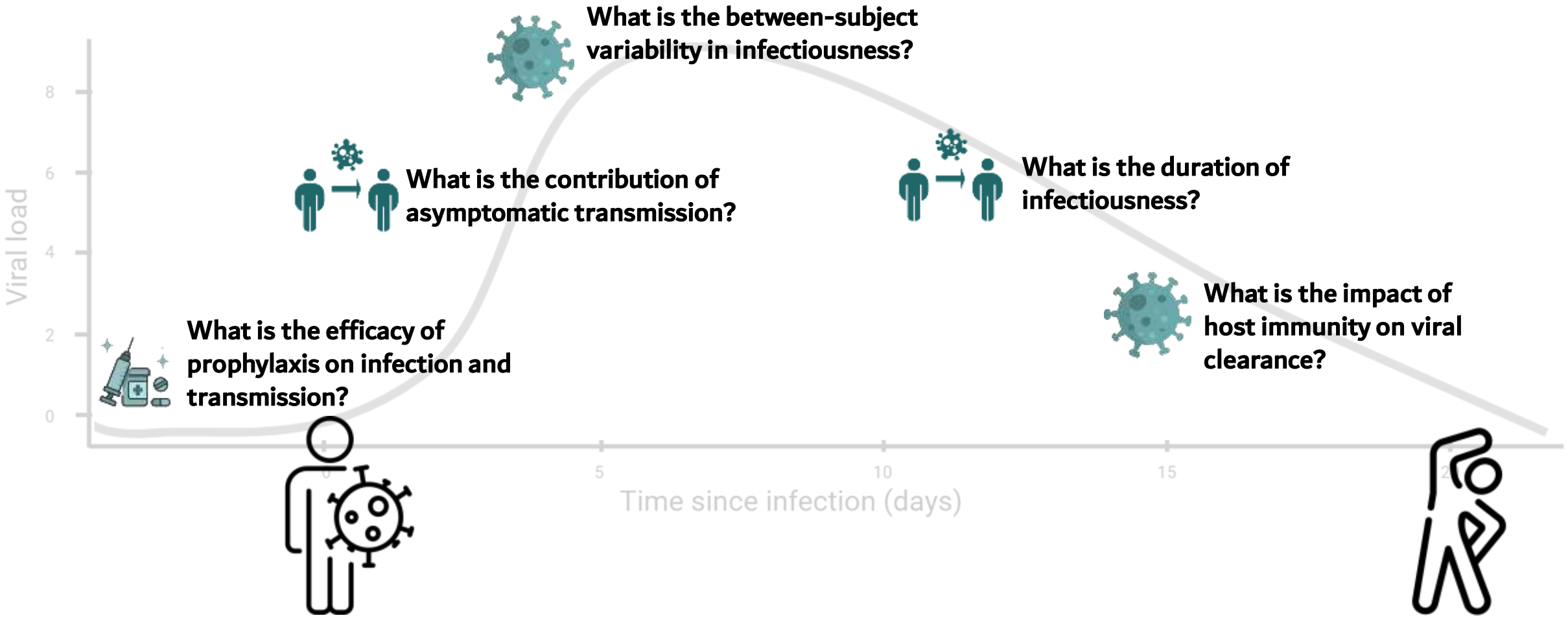
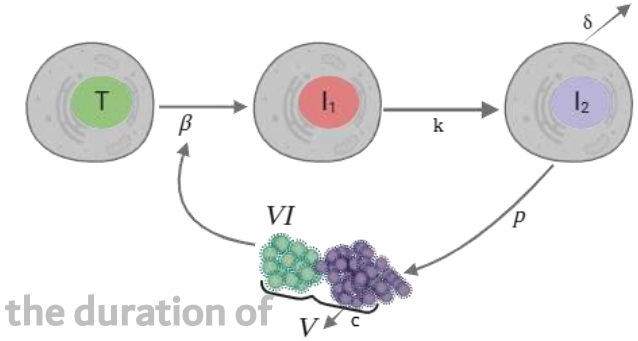


Viral kinetics to better understand RSV pathogenesis & transmission

Mechanistic model[10,11]



What is the between-subject variability in infectiousness?

What is the contribution of asymptomatic transmission?

What is the duration of infectiousness?

What is the efficacy of prophylaxis on infection and transmission?

What is the impact of host immunity on viral clearance?

10- Baccam et al., Journal of Virology, 2006
11- Néant et al., PNAS, 2021

Experimental challenges: A unique opportunity to track viral kinetics

- Experimental human challenge allows to have highly-detailed kinetics

hVIVO
Expert in human challenge

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- 252 healthy individuals aged 18-49, inoculated with RSV Memphis-37b

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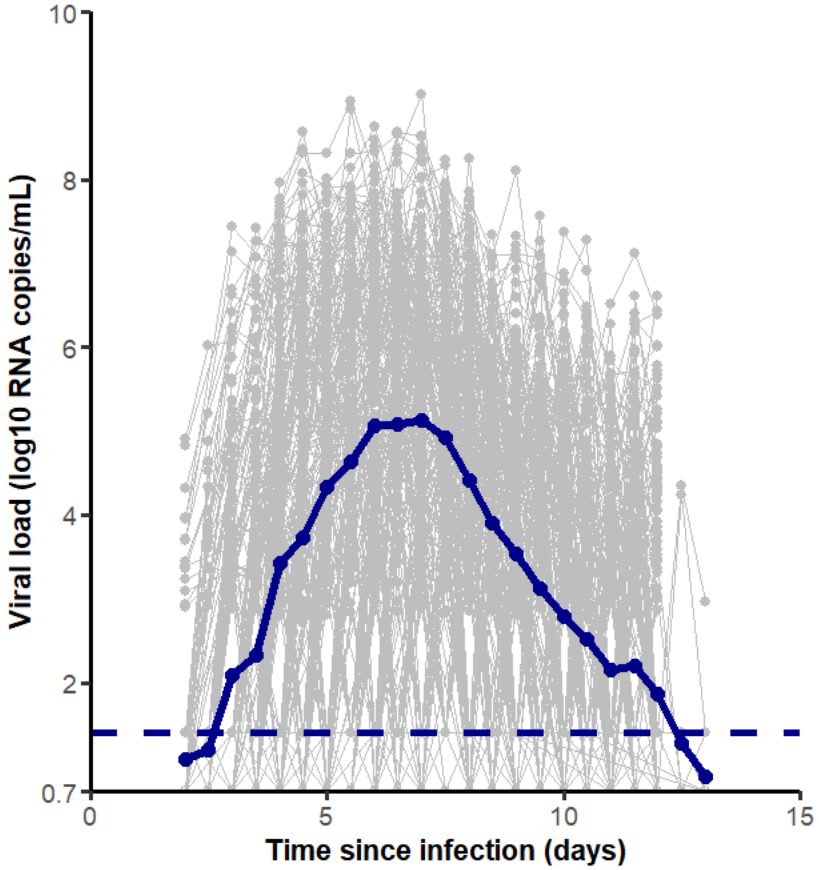
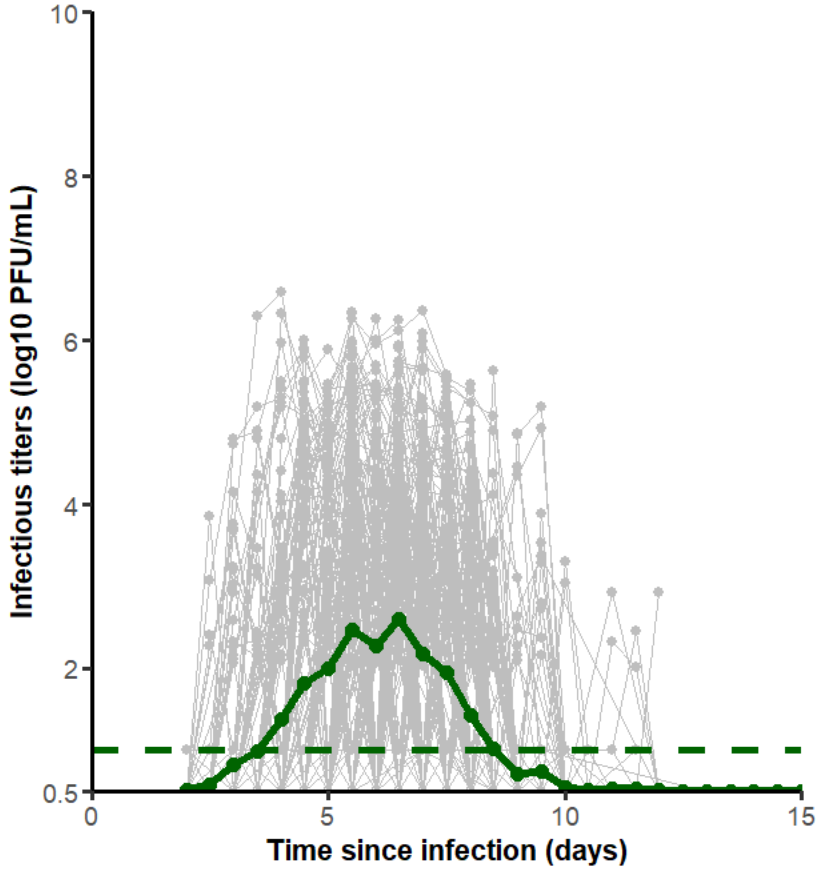
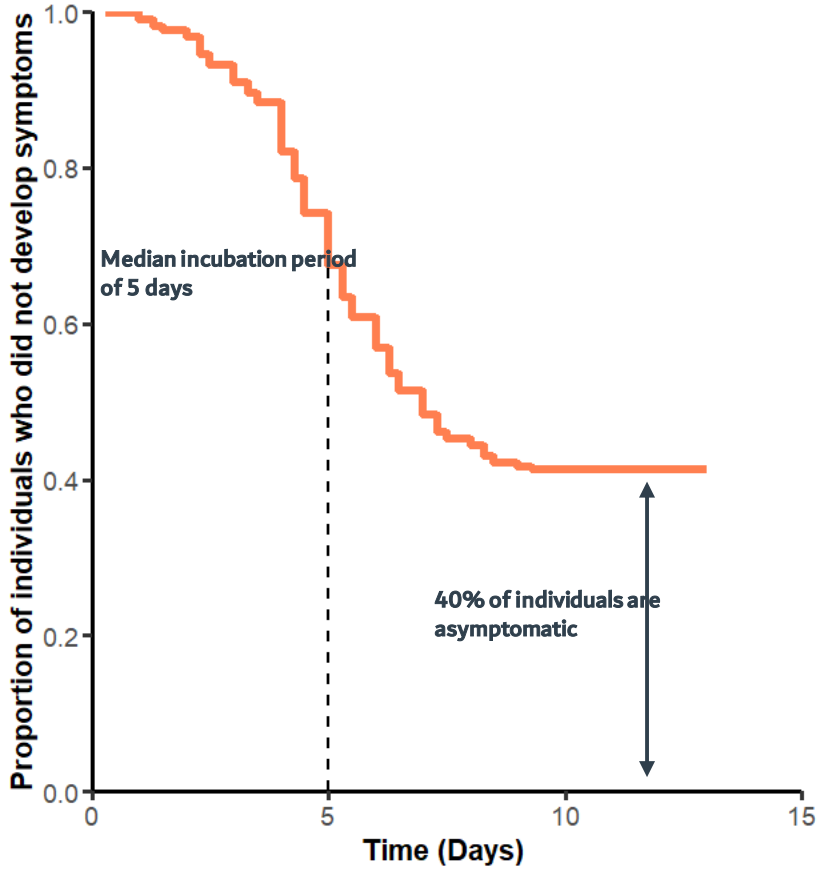
- Measurements:
  - Viral load
  - Infectious titers
  - Symptom score

Overview of data







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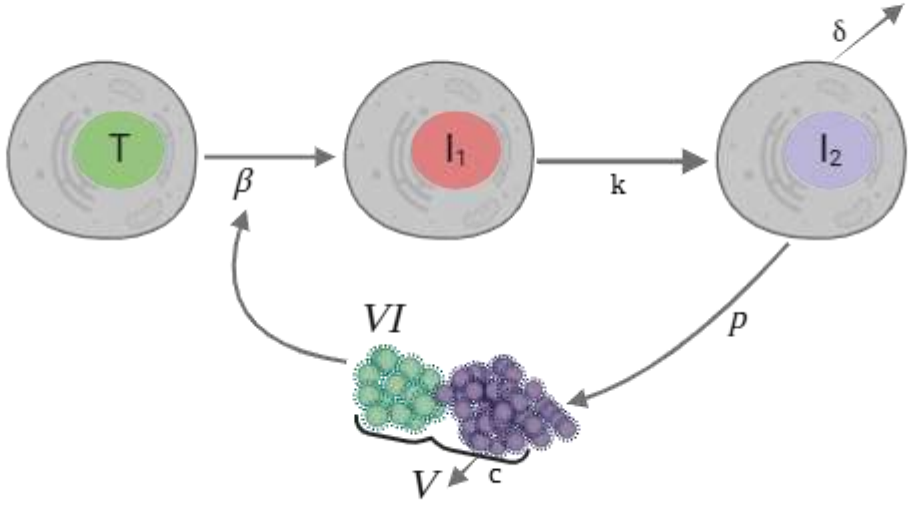

Parameters are estimated using SAEM algorithm

Model selection using Bayesian Information Criteria Corrected (BICc)

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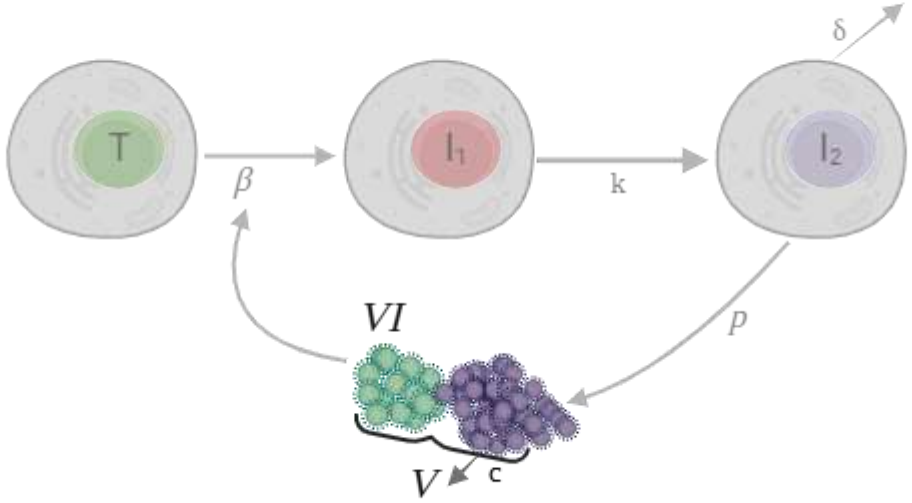

Step 1: Which model to describe interaction between viral load (V) and infectious titers (VI) ?

- **Linear relation**

$$VI = aV$$

- **Power relation**

$$VI = aV^b$$

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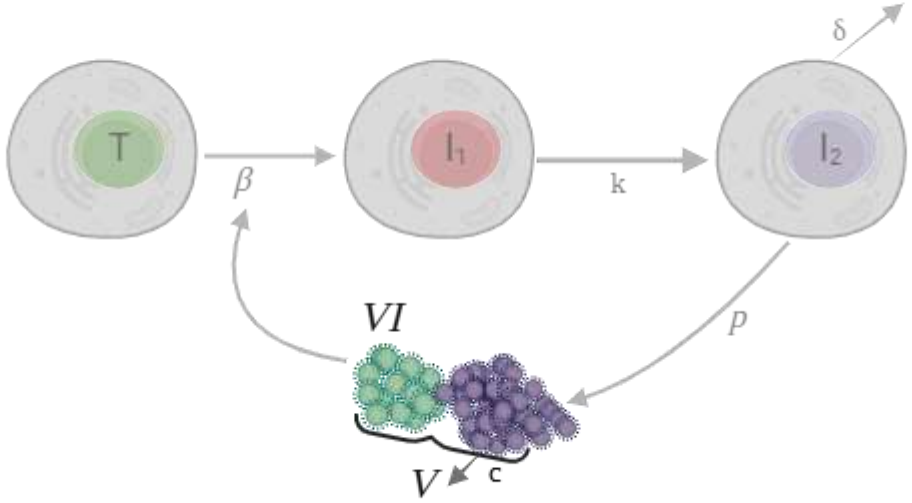

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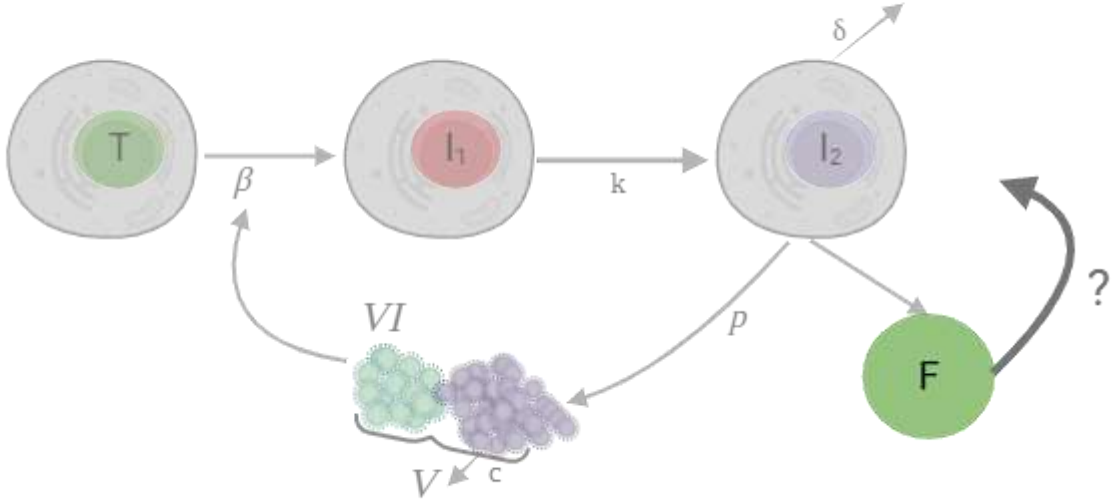

Step 1: Which model to describe interaction between viral load (V) and infectious titers (VI) ?

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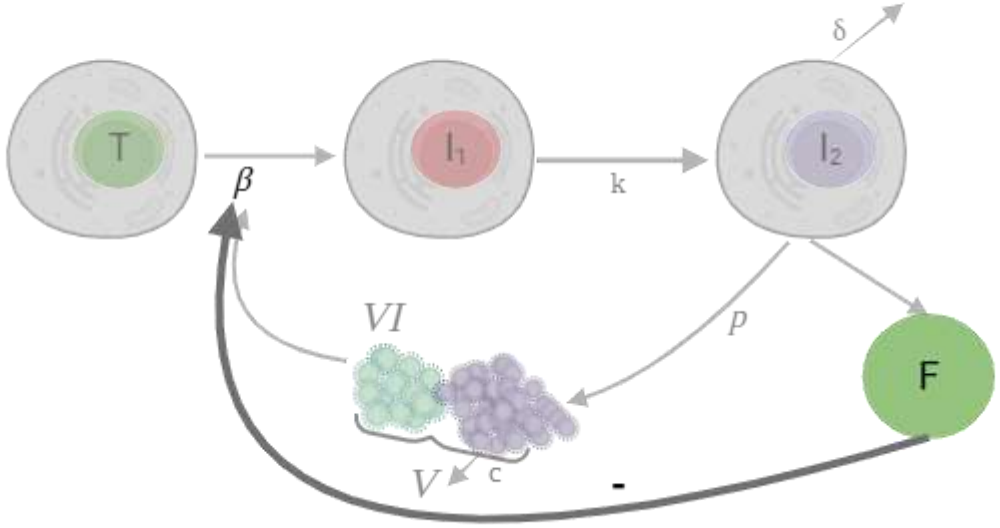

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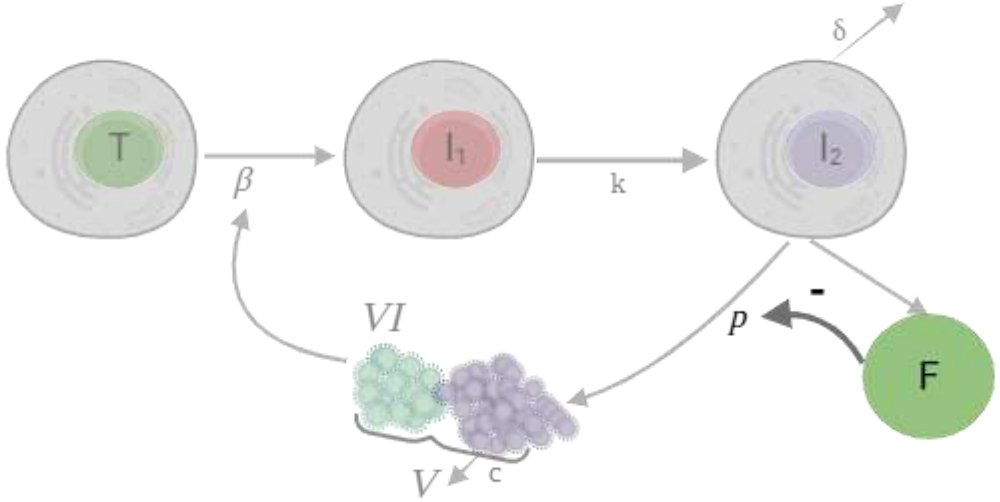

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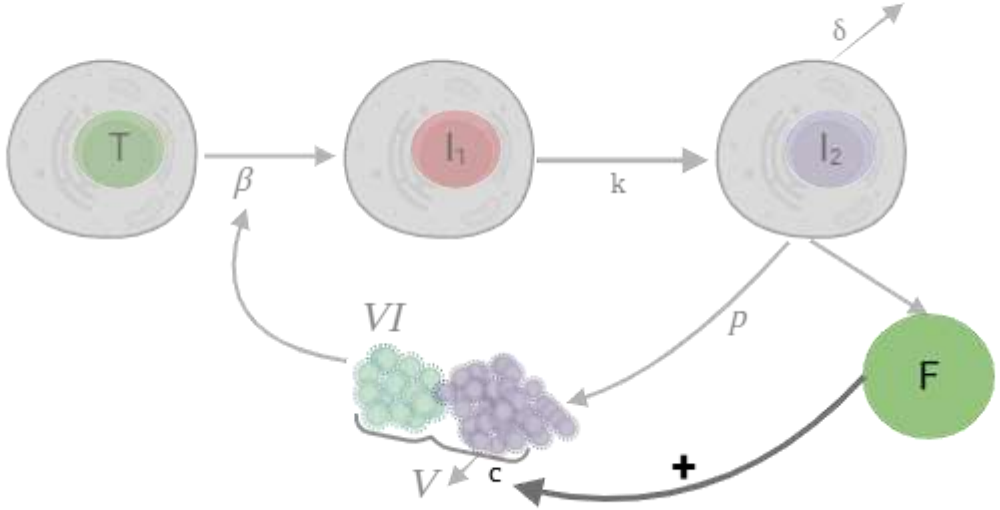

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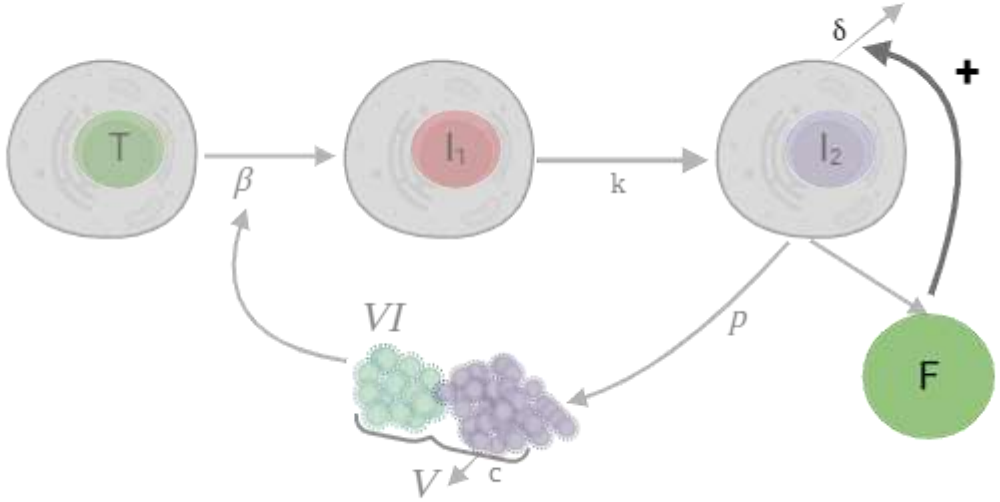

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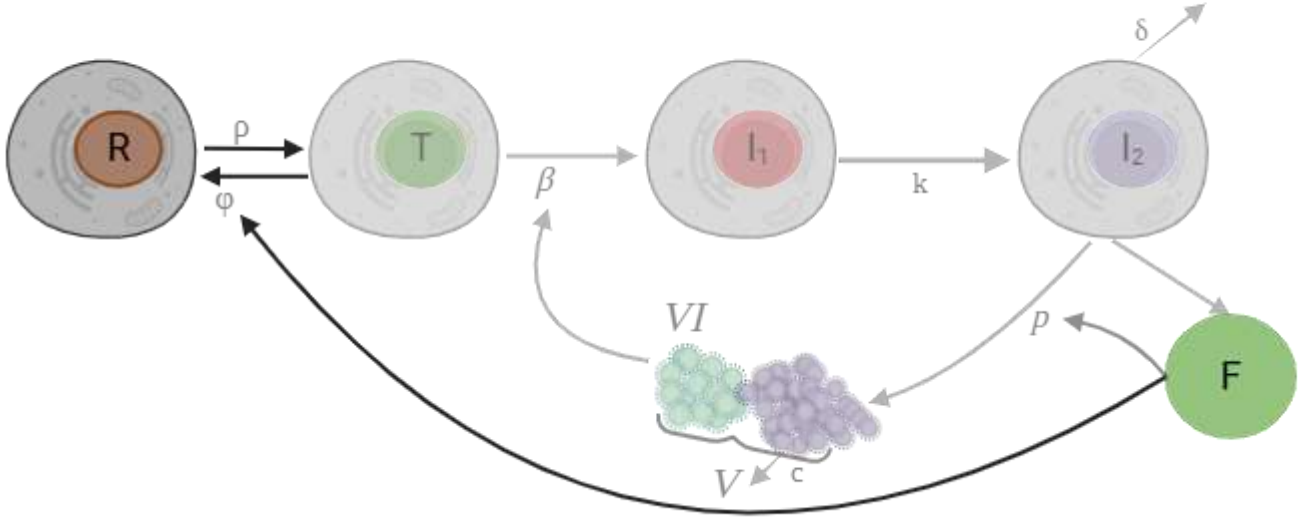

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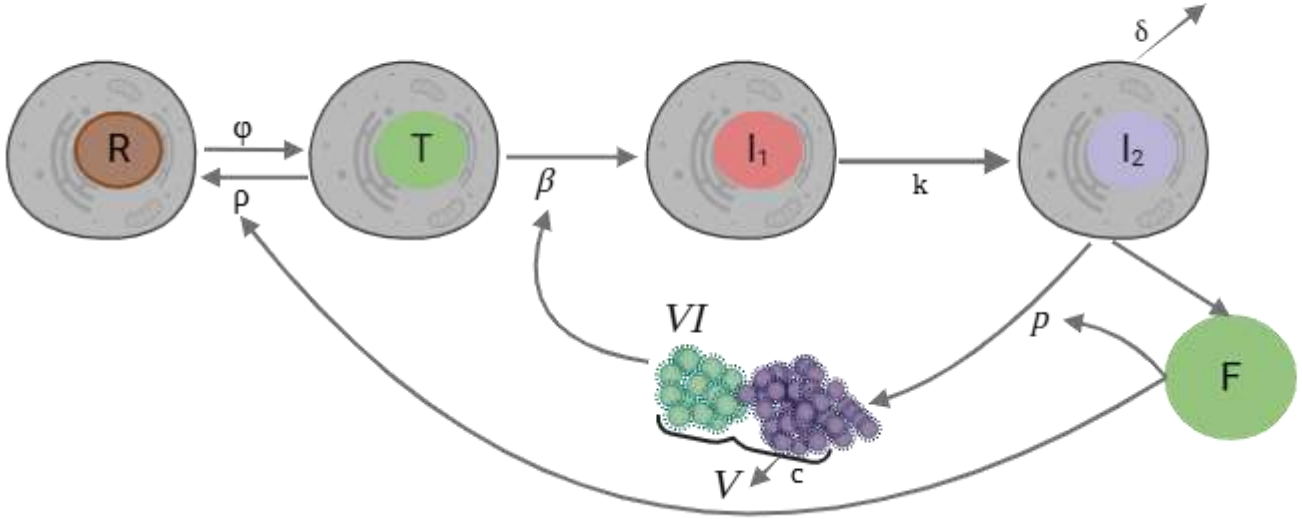

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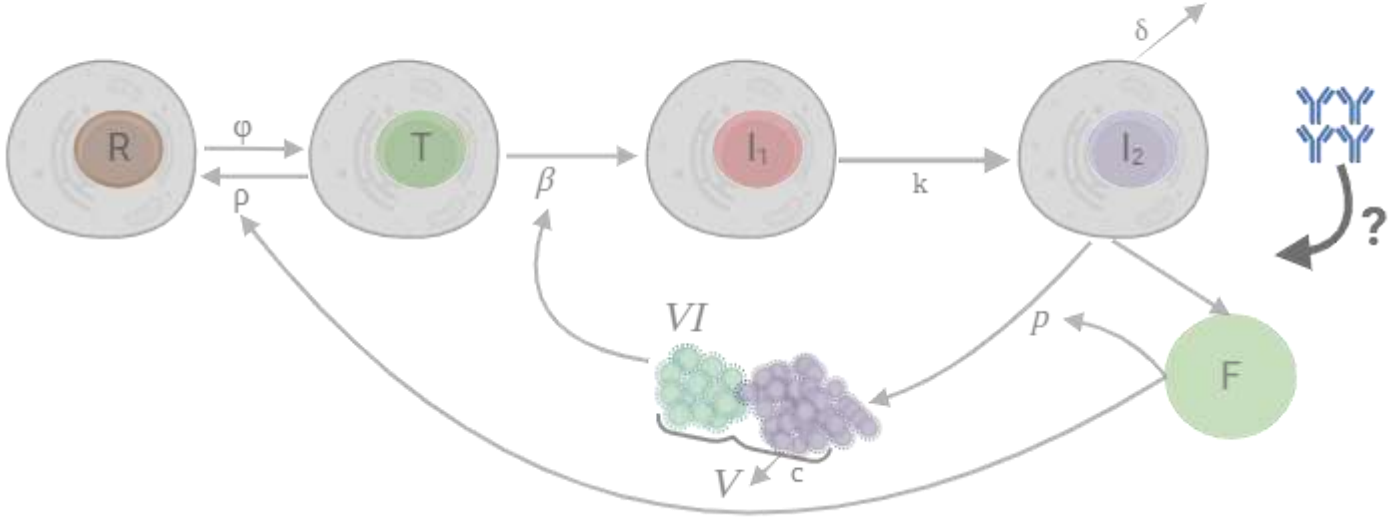

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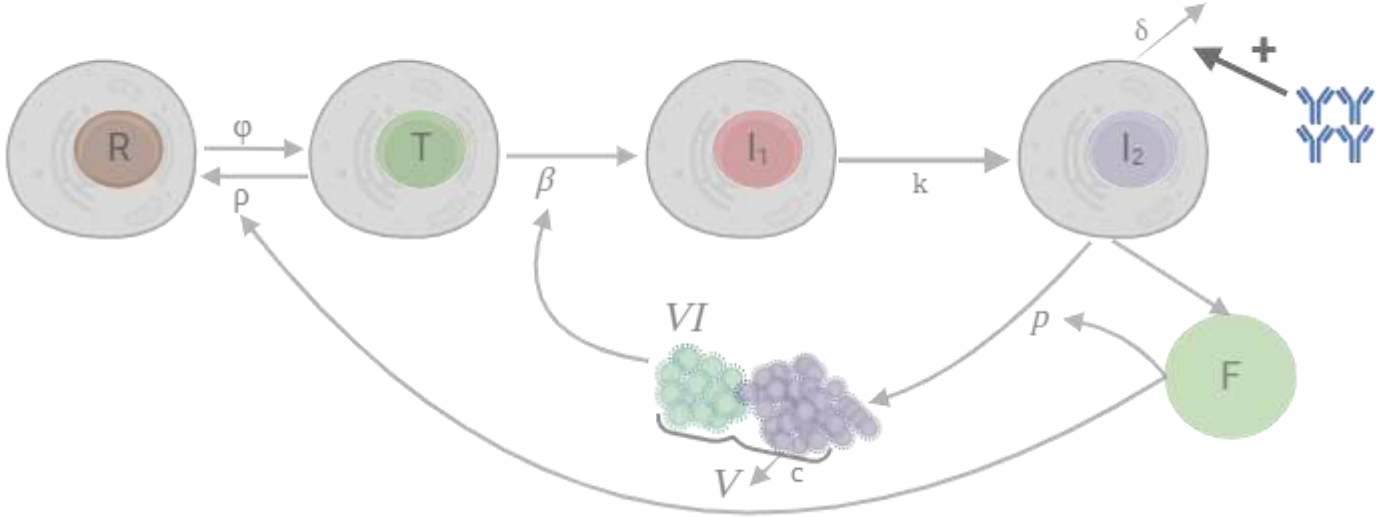

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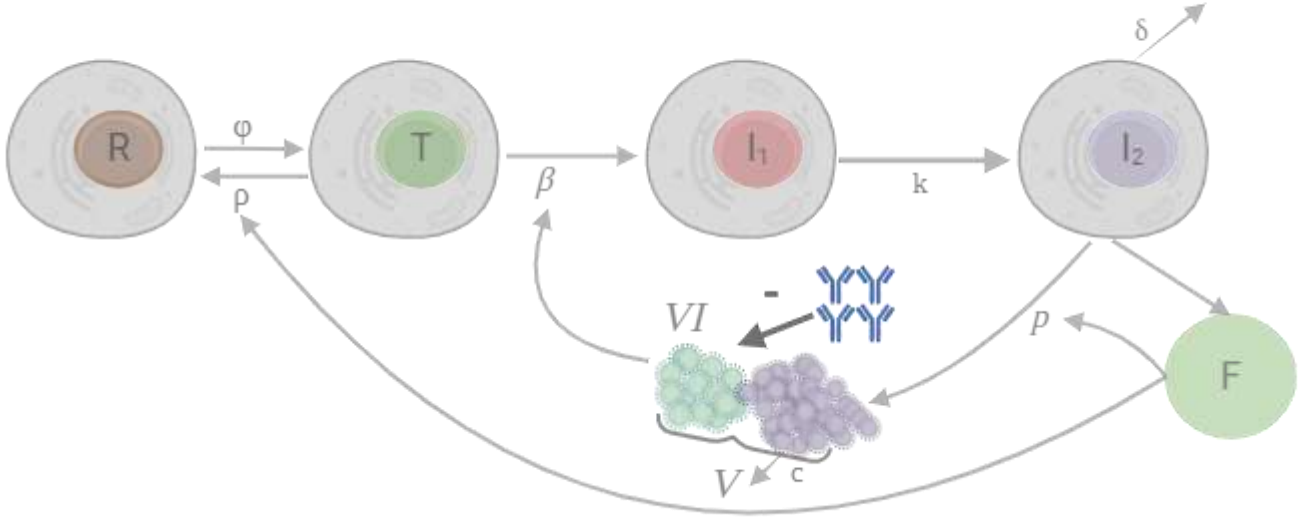

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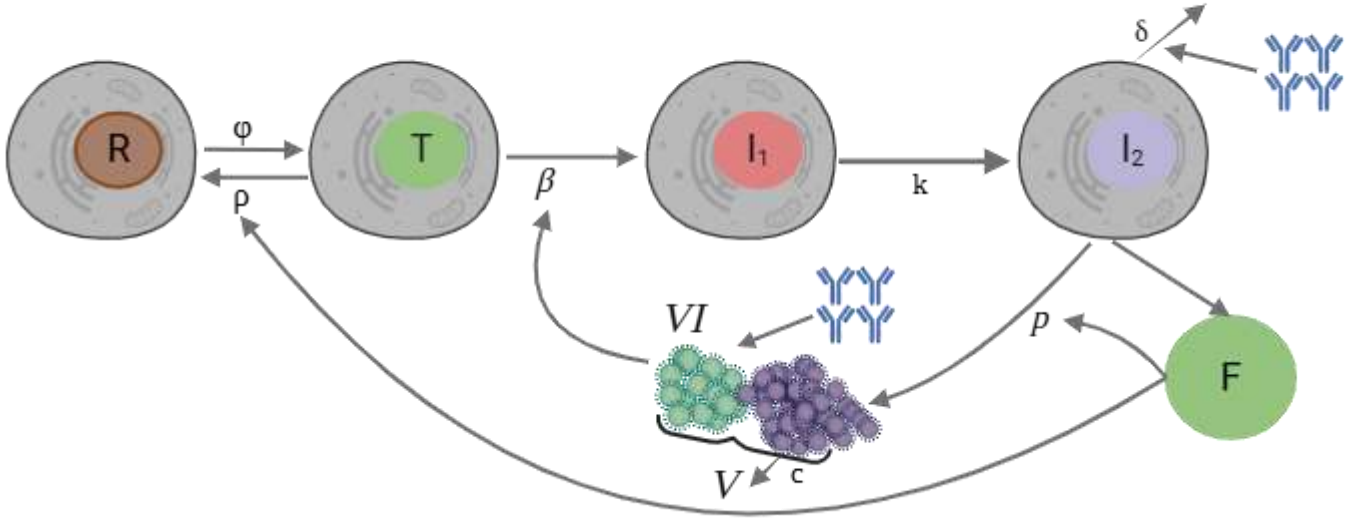
VI ↓ Infectivity

Parameters are estimated using SAEM algorithm

Model selection using Bayesian Information Criteria Corrected (BICc)

Building a within-host model



Step 1: Which model to describe interaction between viral load (V) and infectious titers (VI) ?

Power relation

$$VI = aV^b$$

Step 2: What are the effects of innate immunity?

p ↓ production rate

R Induce refractory status

Step 3: What are the effects of adaptive immunity?

δ ↑ cell death rate

VI ↓ Infectivity

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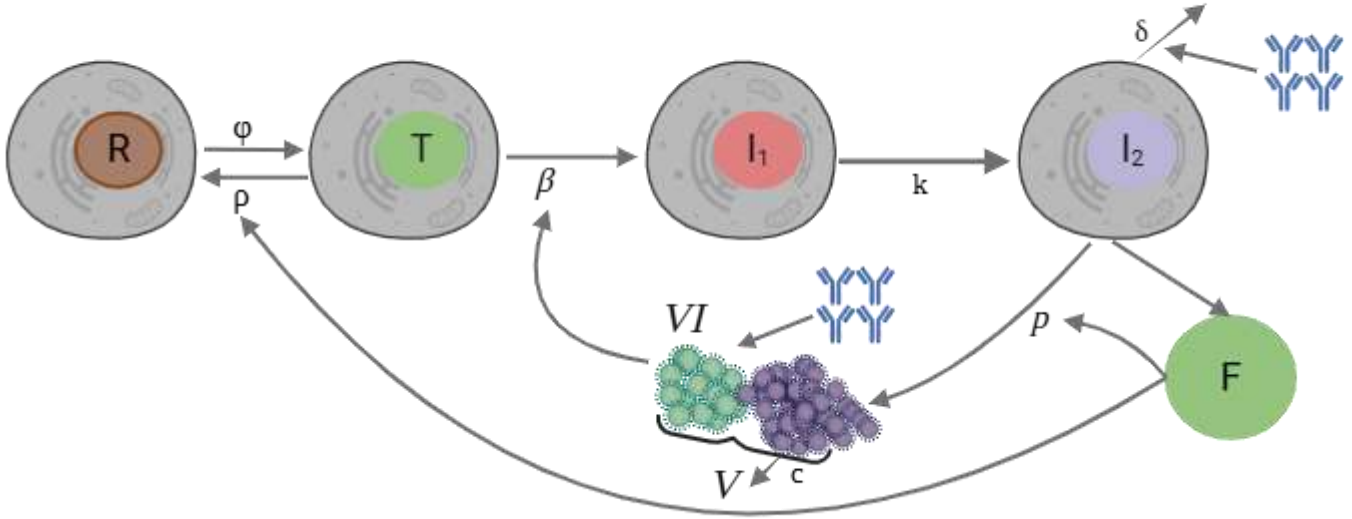

Final model

$$\frac{dT}{dt} - \beta VIT - \varphi FT + \rho R$$

$$\frac{dR}{dt} = \varphi FT - \rho R$$

$$\frac{dI1}{dt} = \beta VIT - kE$$

$$\frac{dI2}{dt} = kE - \delta(t)I2$$

$$\frac{dV}{dt} = pI2\left(1 - \frac{F}{F+\theta}\right) - cV$$

$$\frac{dF}{dt} = I - d_F F$$

$$\boldsymbol{VI = aV^{b(t)}}$$

At time of adaptive immune activation τ

$$b(t) = \begin{cases} b_0, & t < \tau \\ b_0 exp(-\sigma(t-\tau)), & t \geq \tau \end{cases}$$

$$\delta(t) = \begin{cases} \delta_0, & t < \boldsymbol{\tau} \\ \delta_1, & t \geq \boldsymbol{\tau} \end{cases}$$

12- Iyaniwura et al., PNAS, 2024

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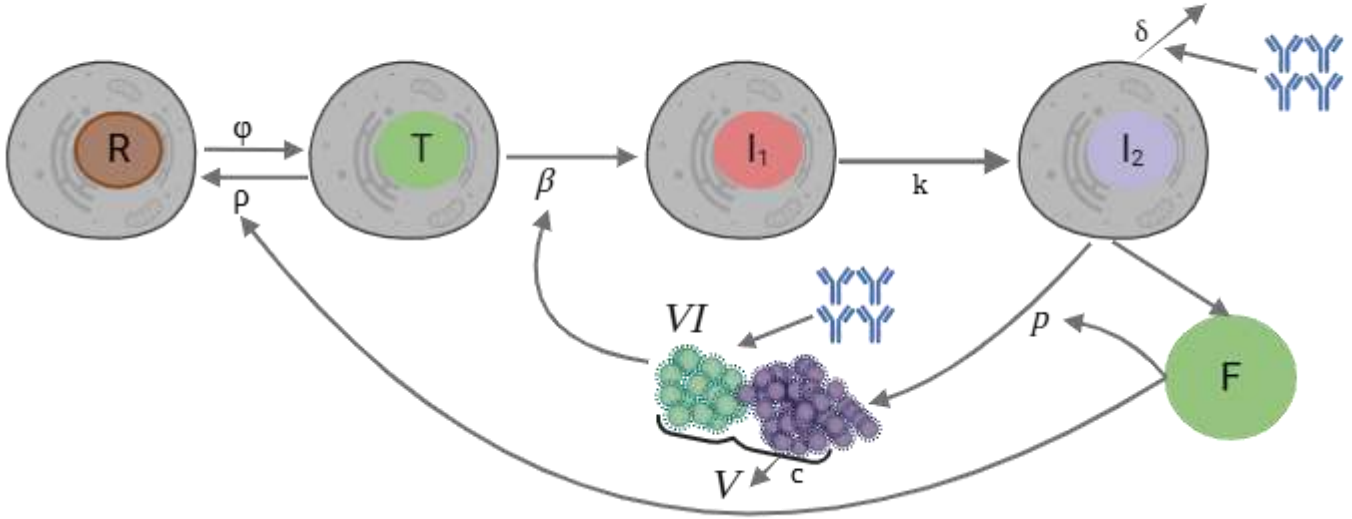

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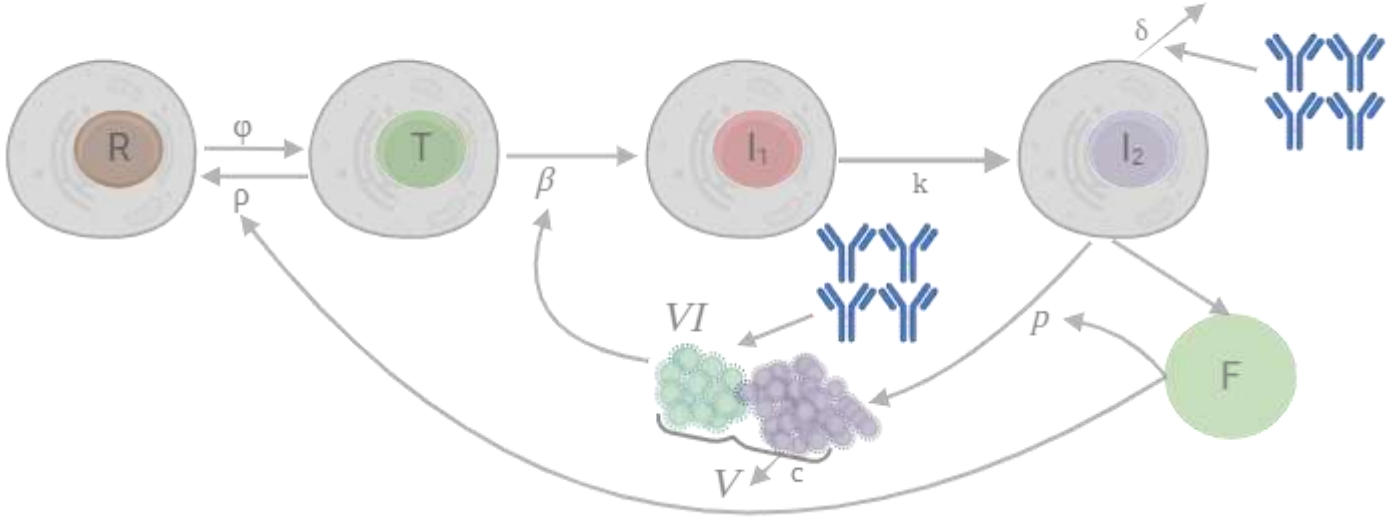

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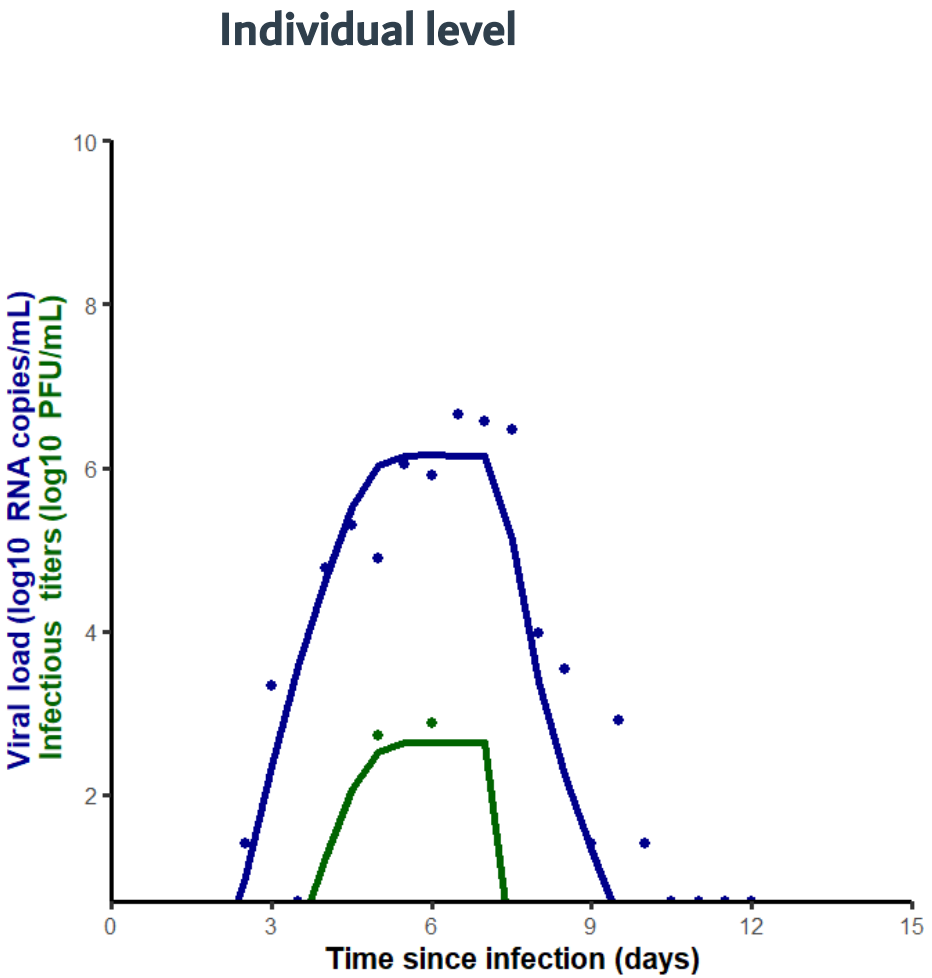
Prediction insights at the individual and population level



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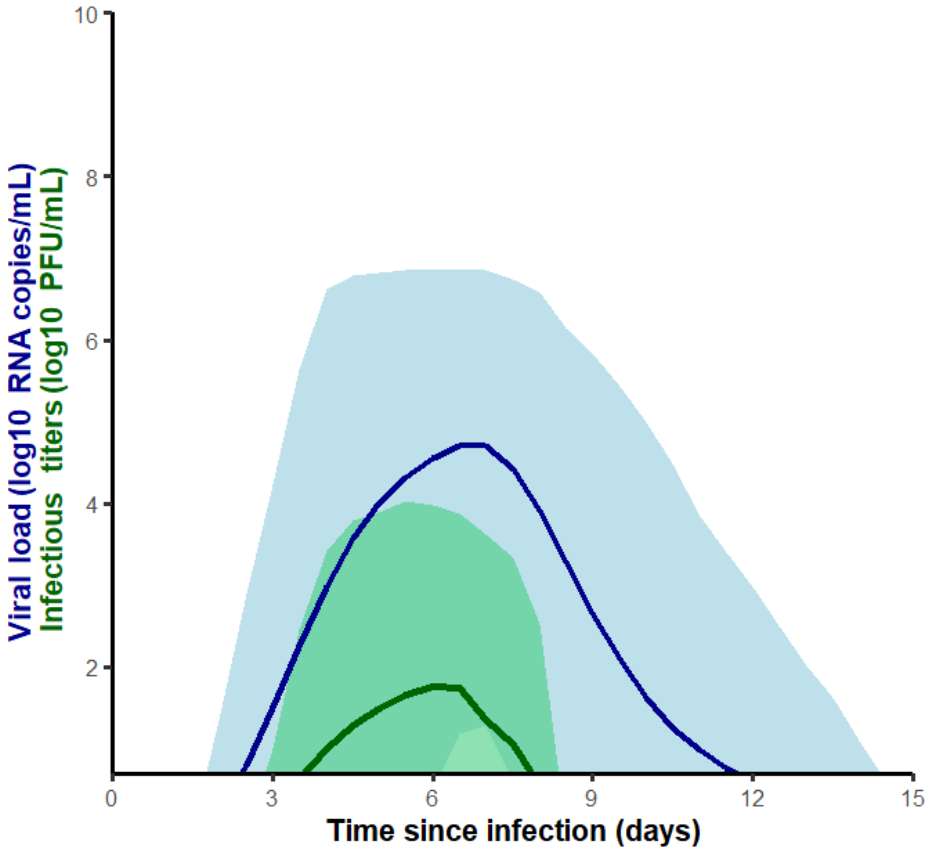
Population level



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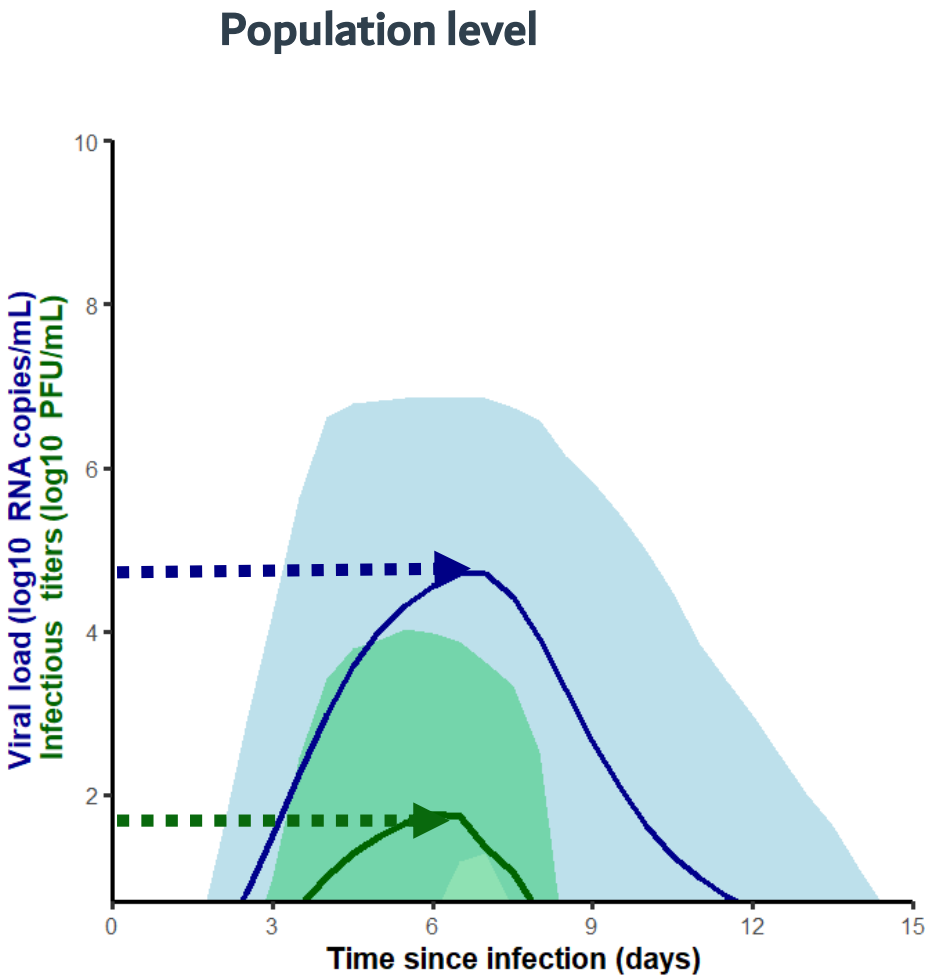

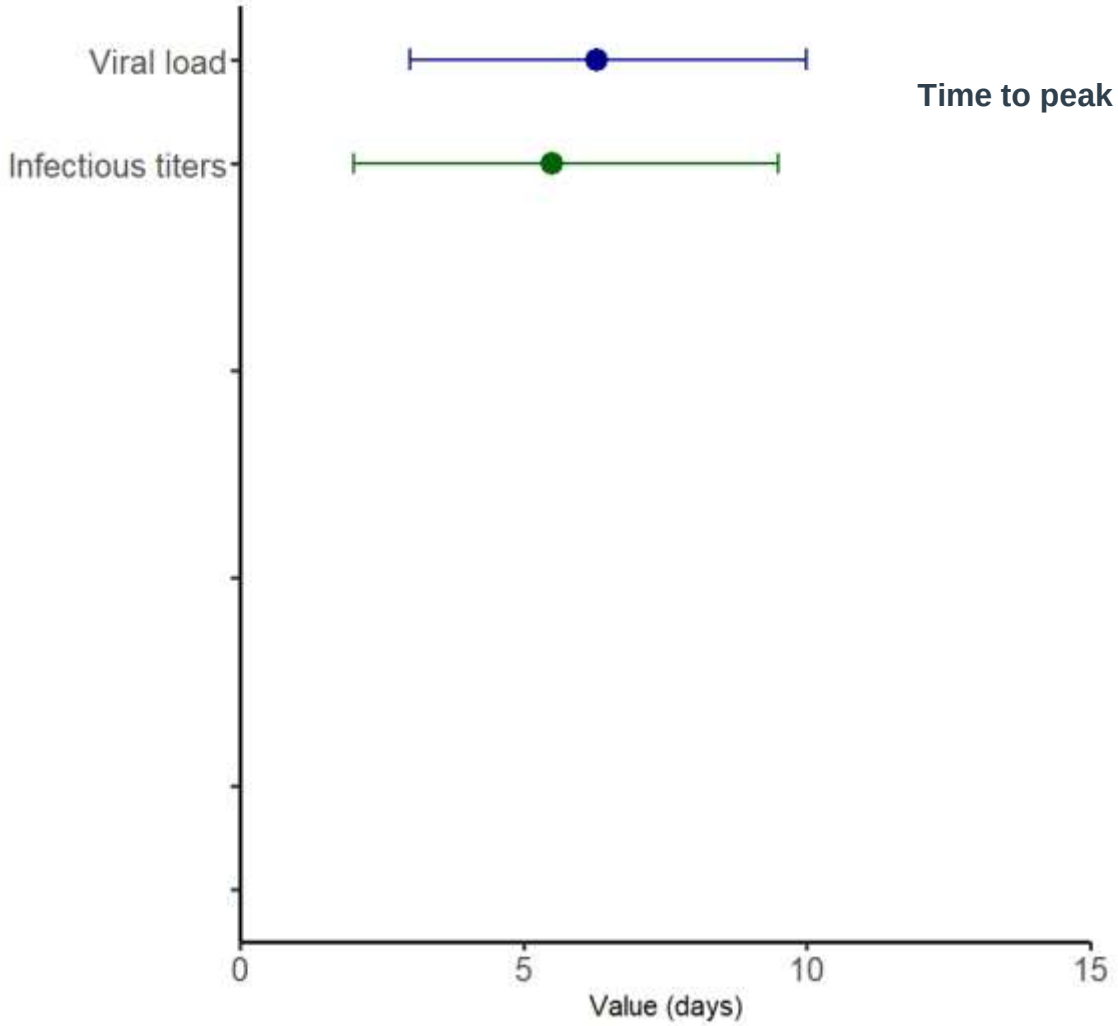

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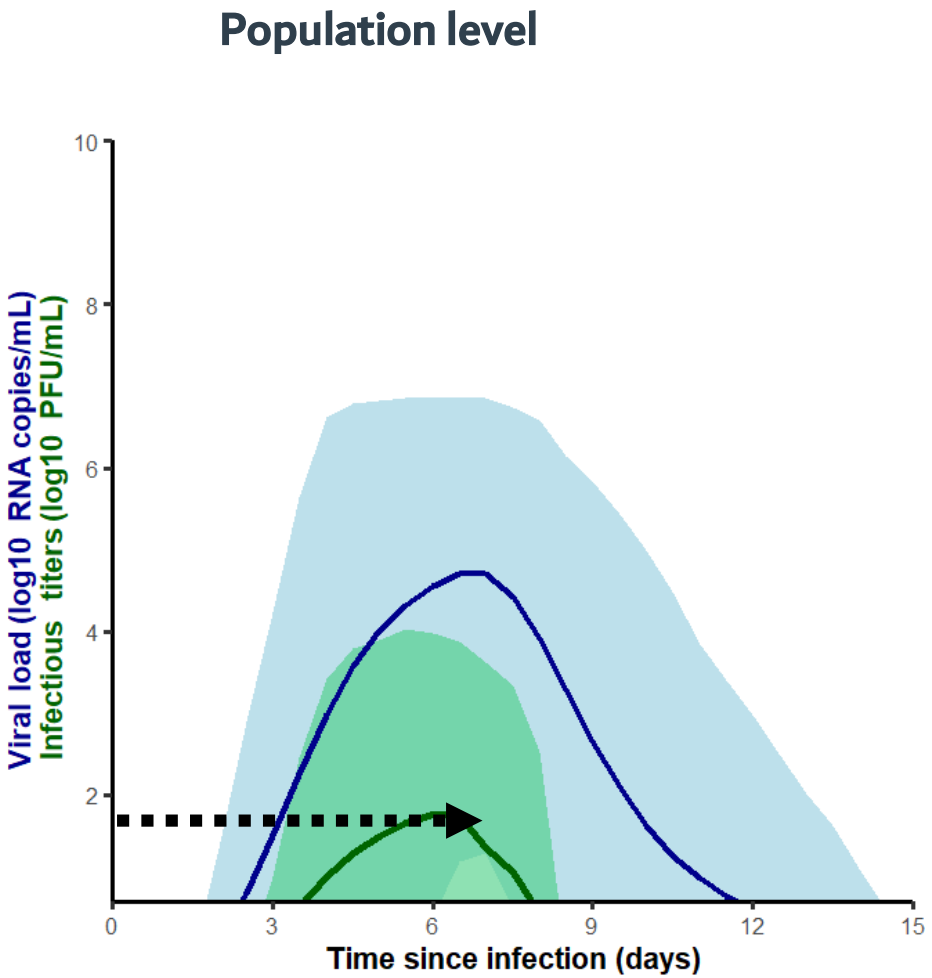

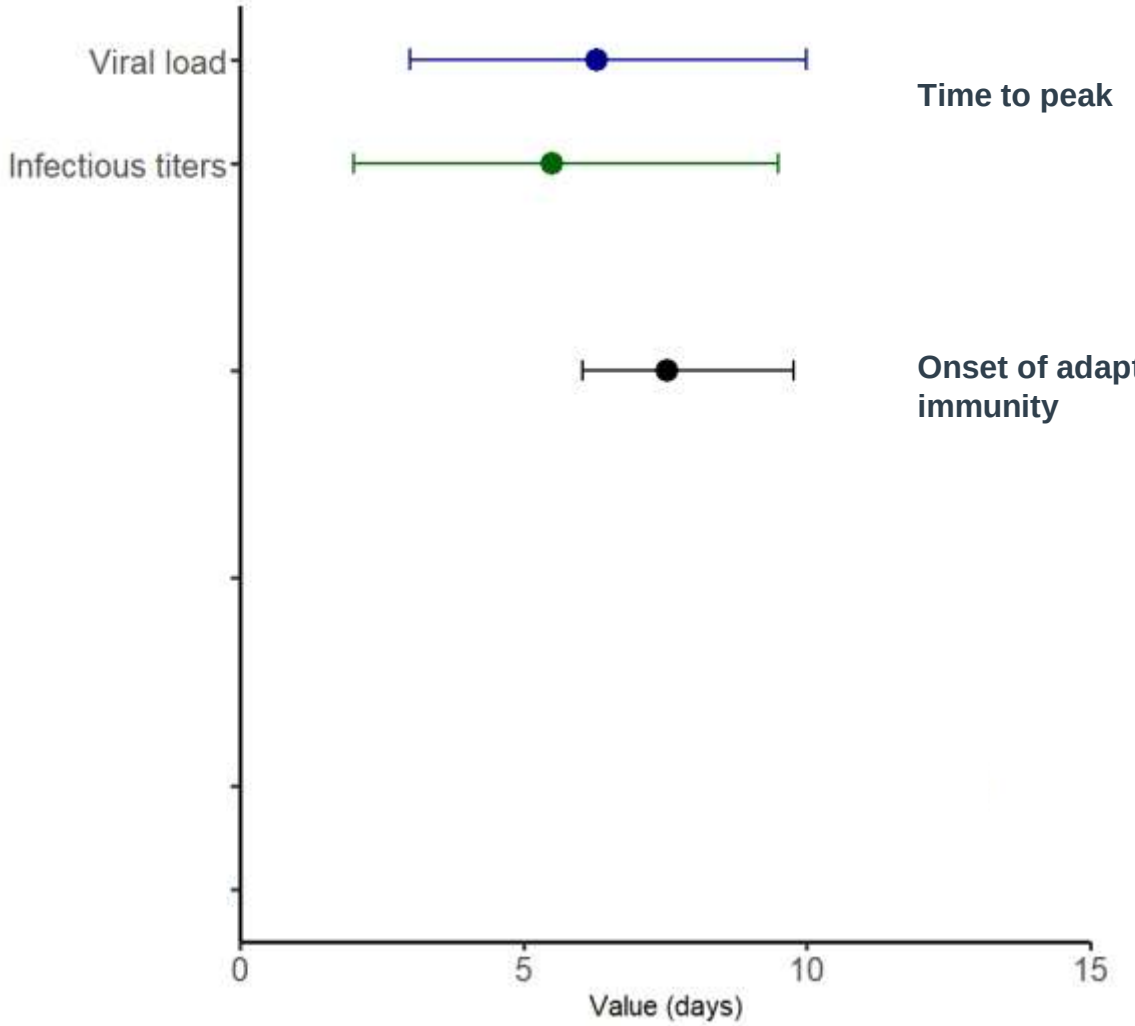

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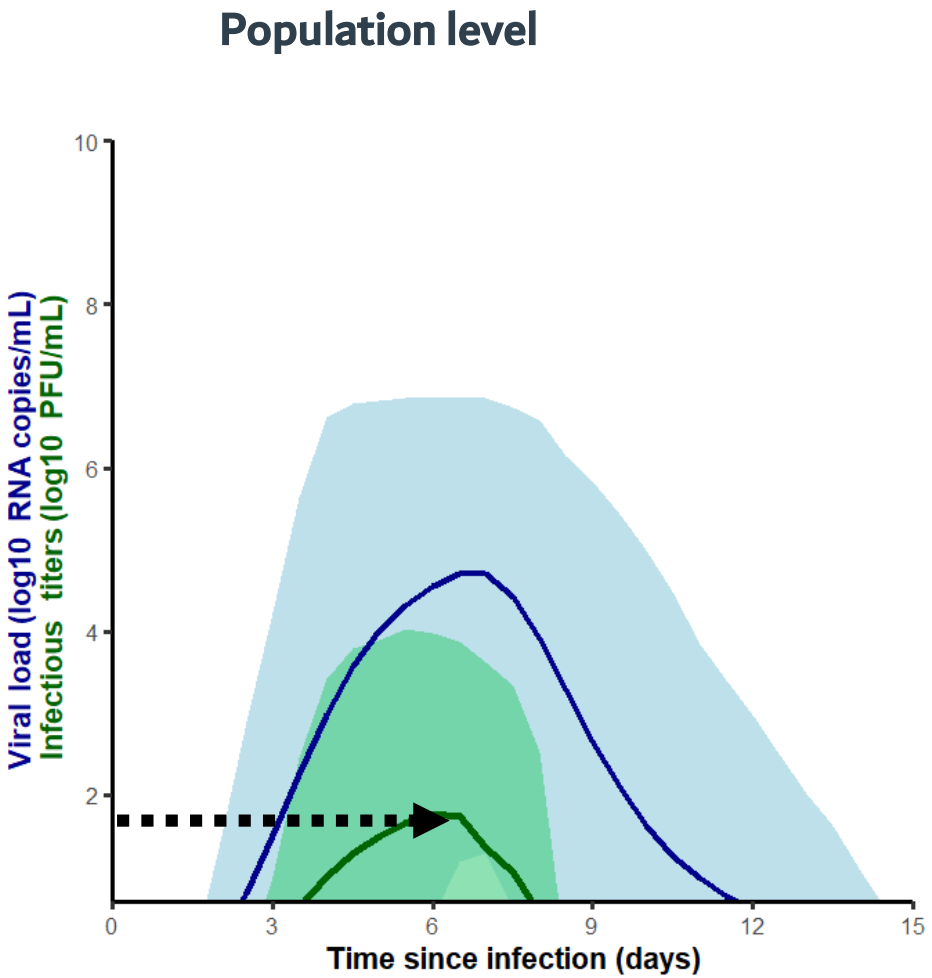

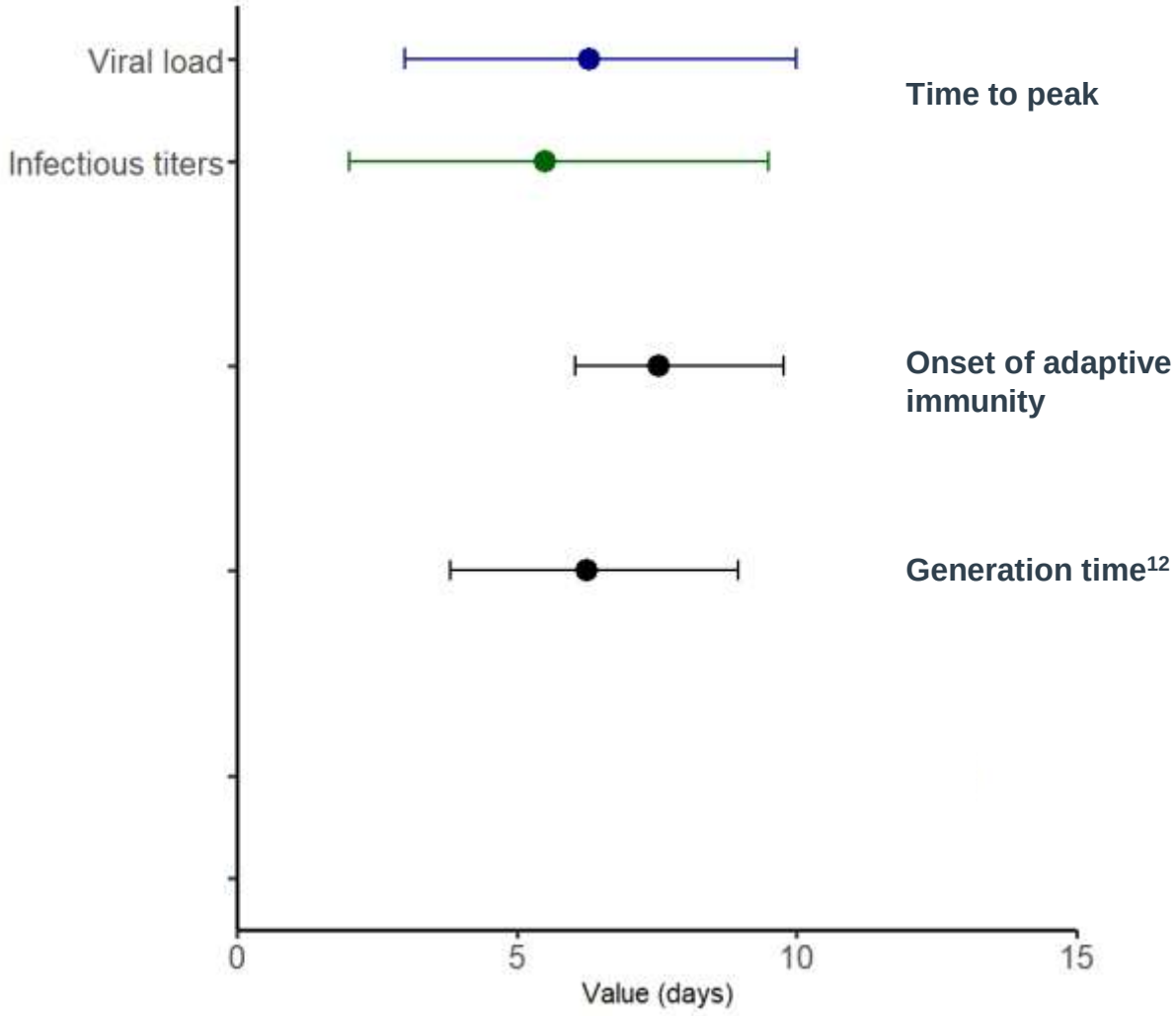

13- Canini et Carrat., Journal of virology, 2010

Prediction insights at the individual and population level

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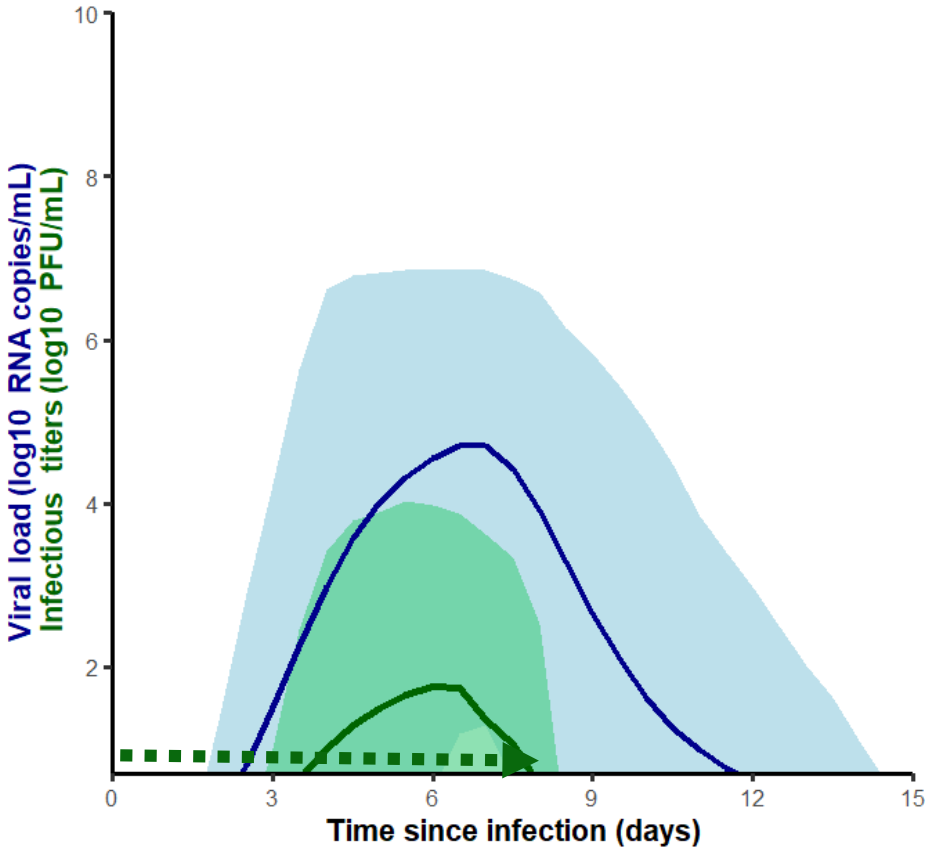

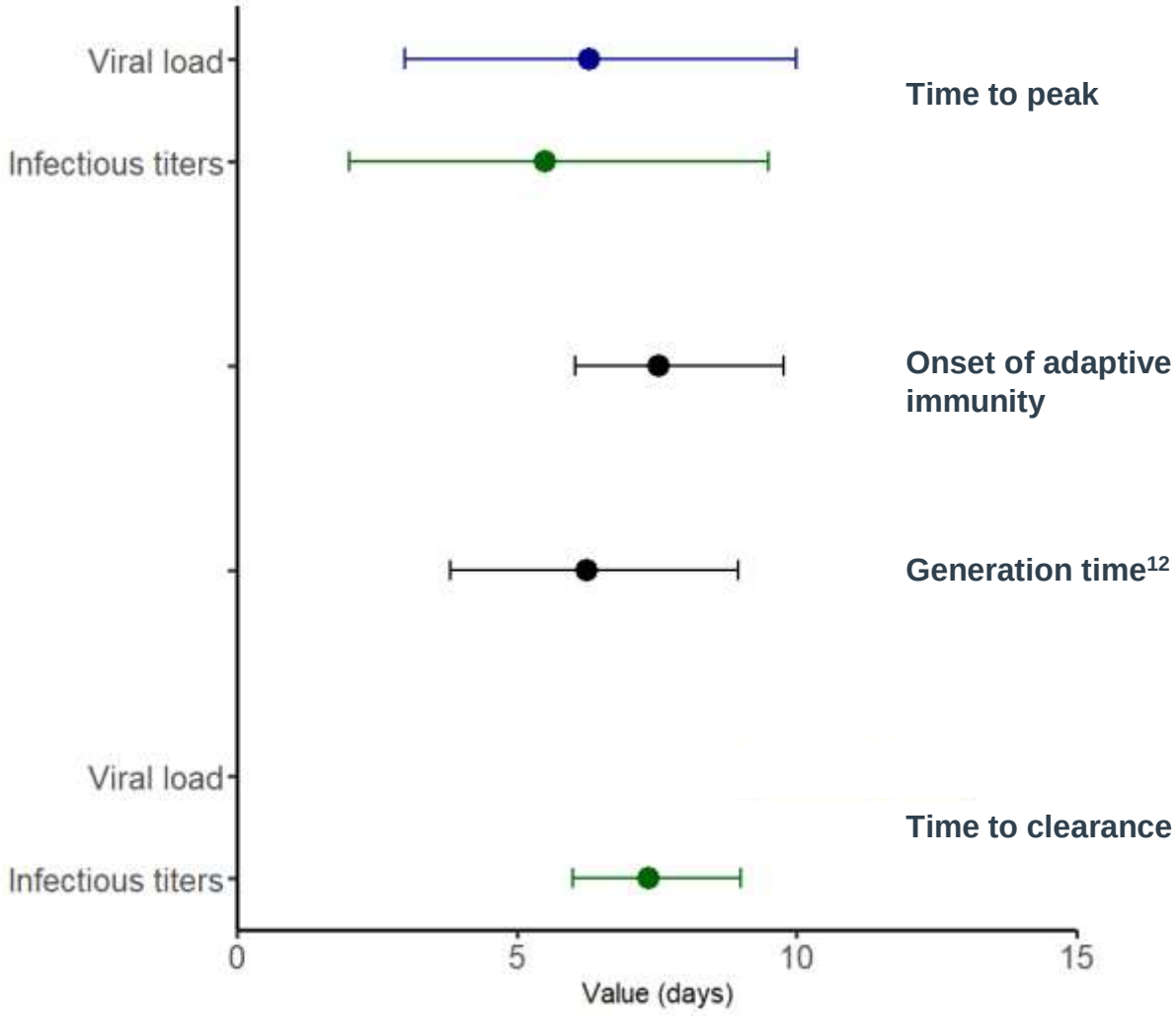

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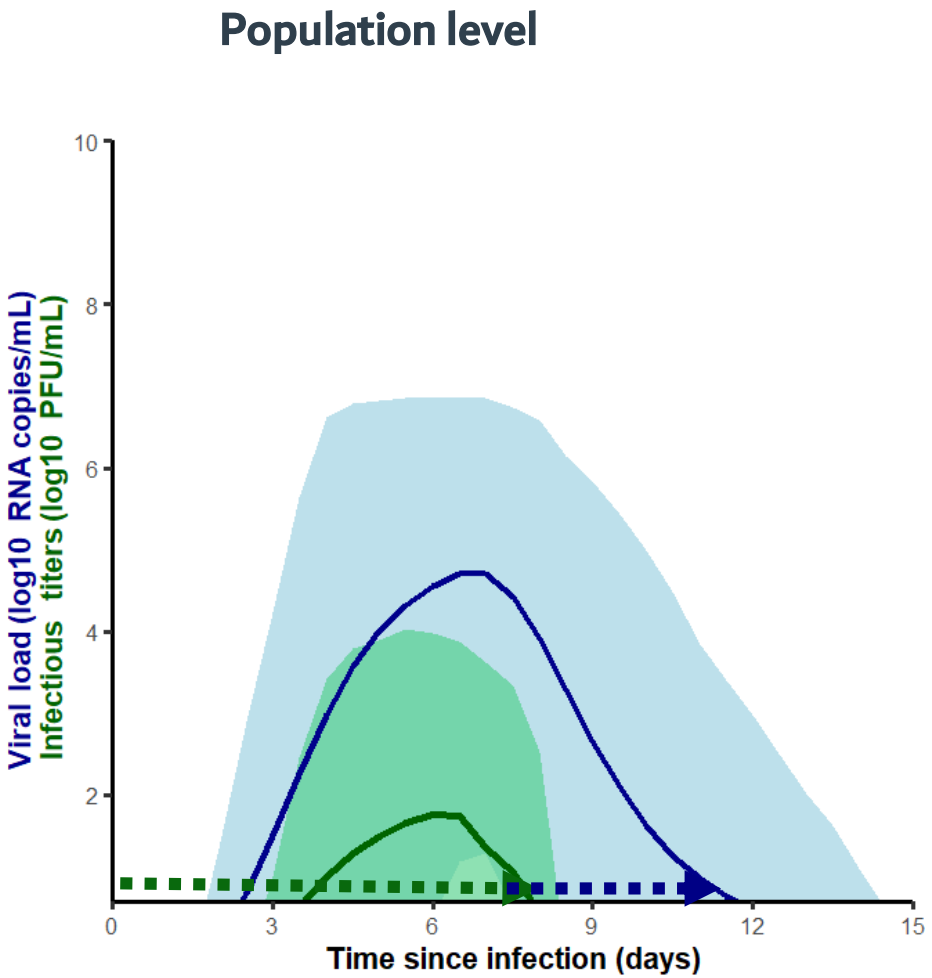

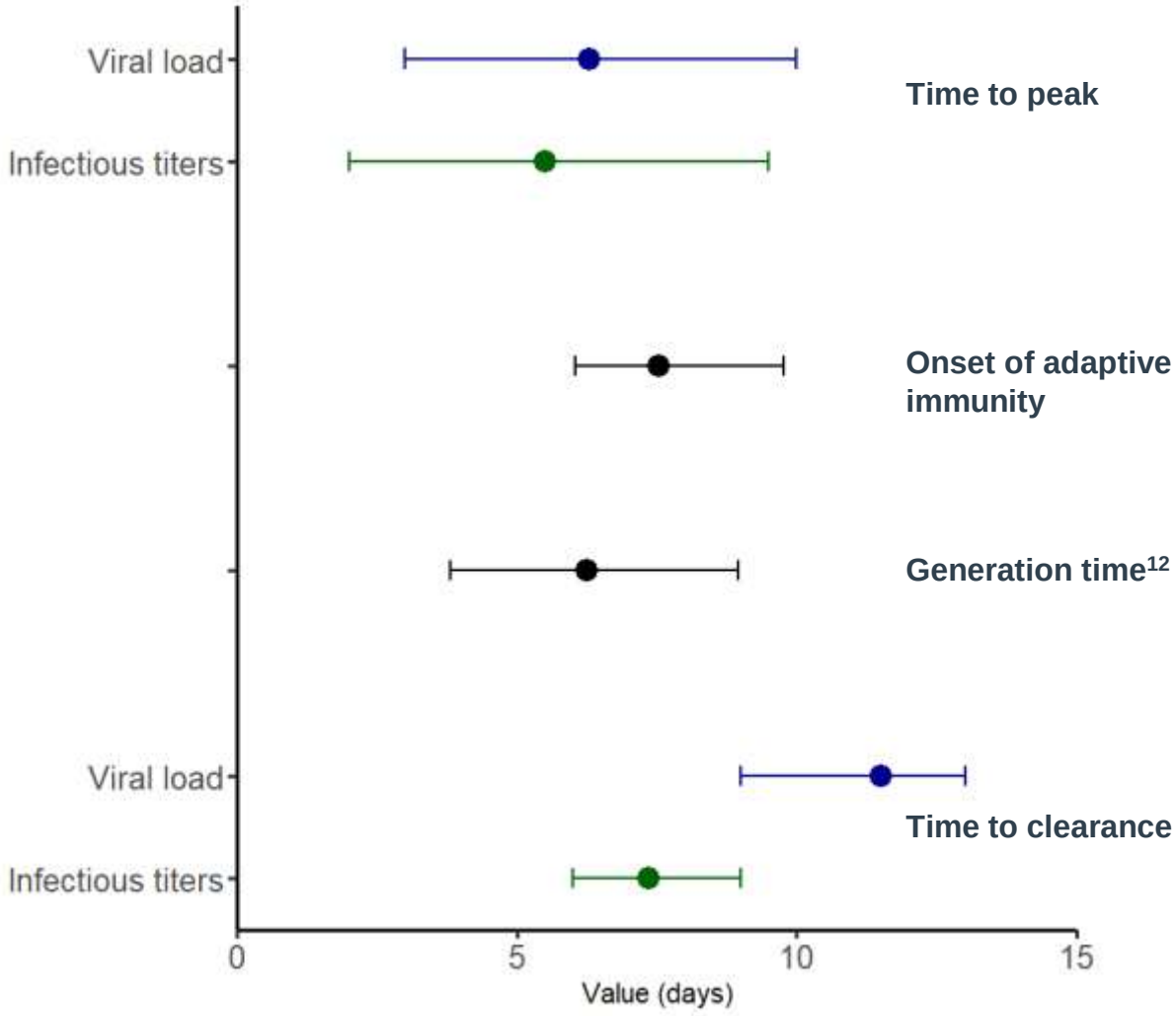

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Linking viral load to symptom onset timing

Step 4: Associate time to symptom onset to viral load

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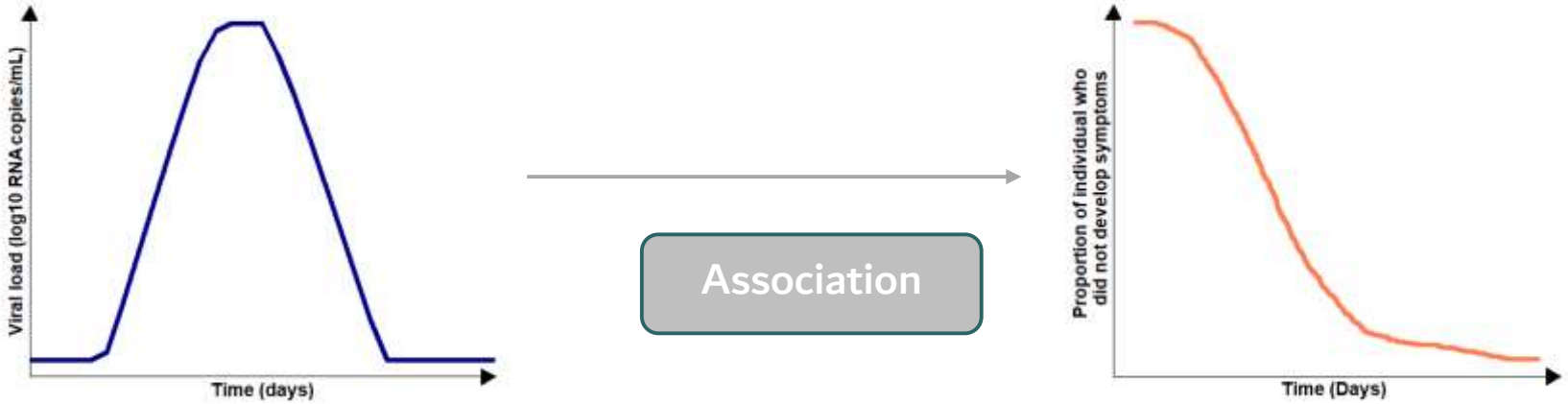
→ Joint model



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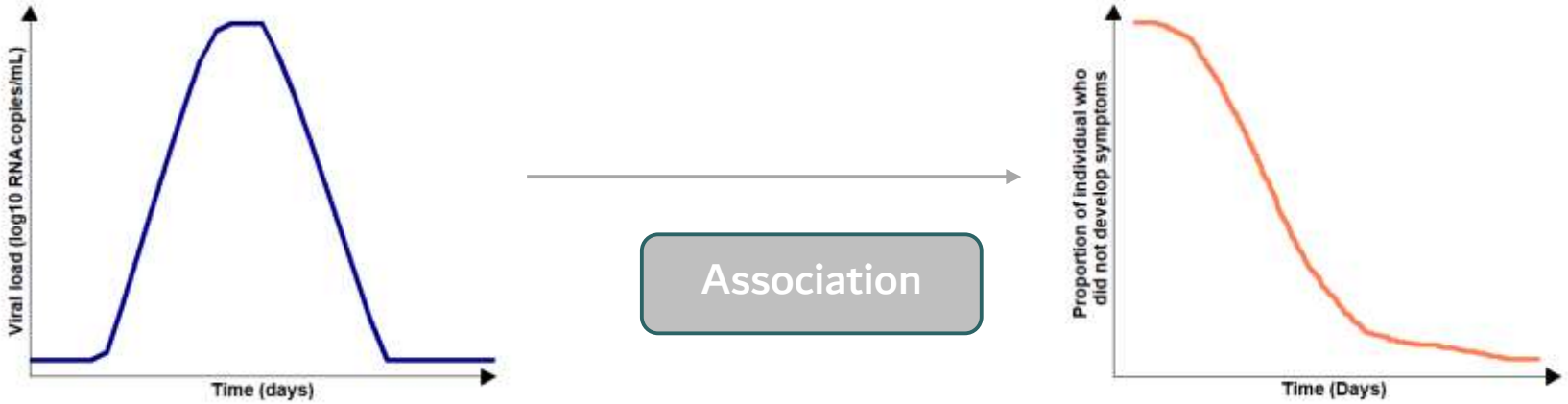

h(t): instantaneous risk of developing symptom at time t

Linking viral load to symptom onset timing

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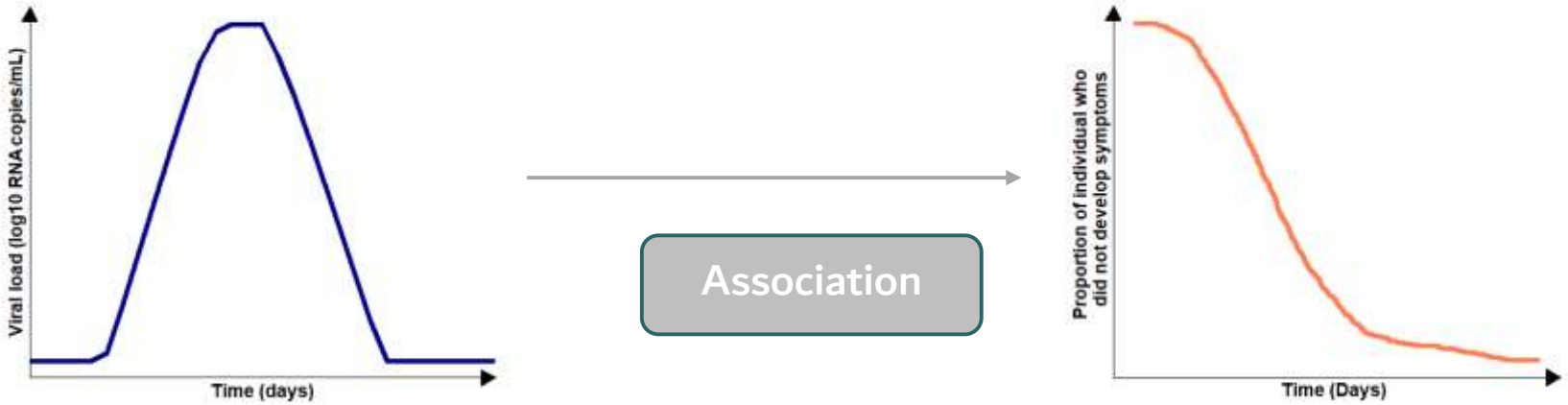


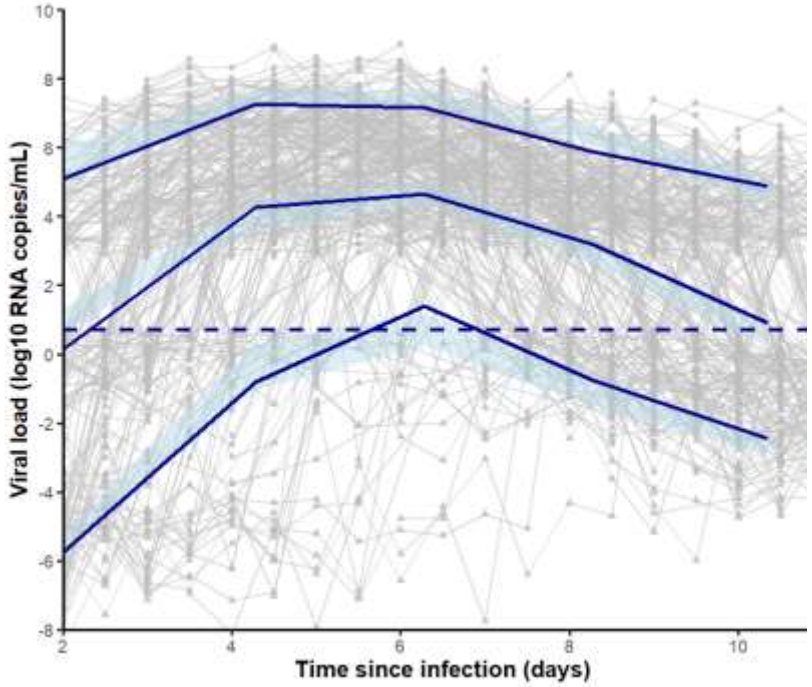
h(t): instantaneous risk of developing symptom at time t

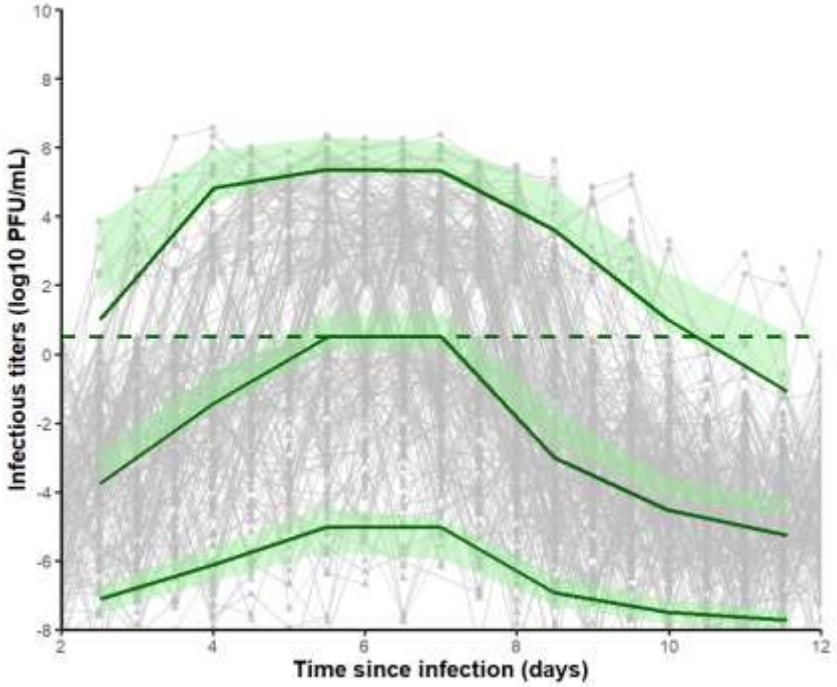
$$h(t) = h_0(t)\exp(\alpha \times \log(V(t)))$$

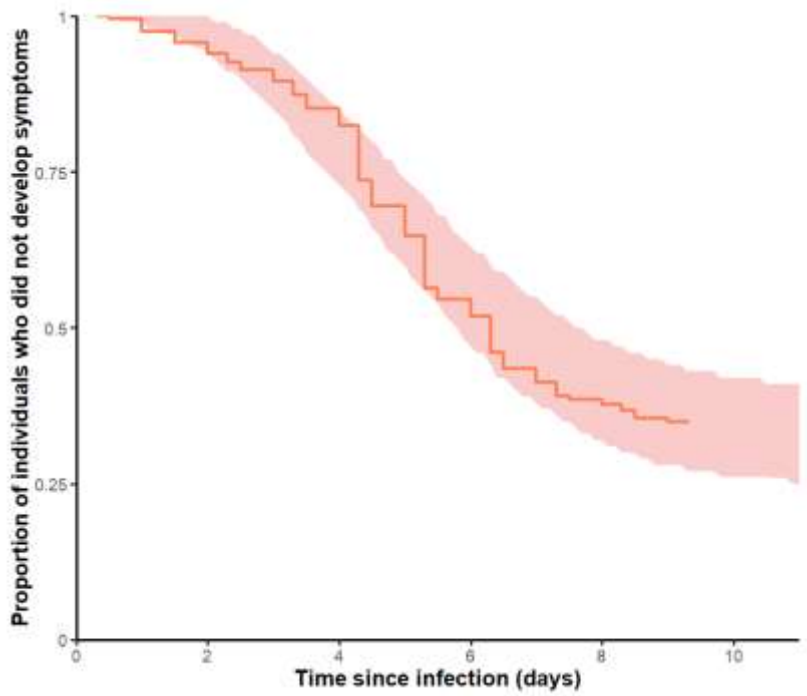
Weibull hazard:

$$h_0(t) = \frac{k}{\lambda}(\frac{t}{\lambda})^{k-1}$$

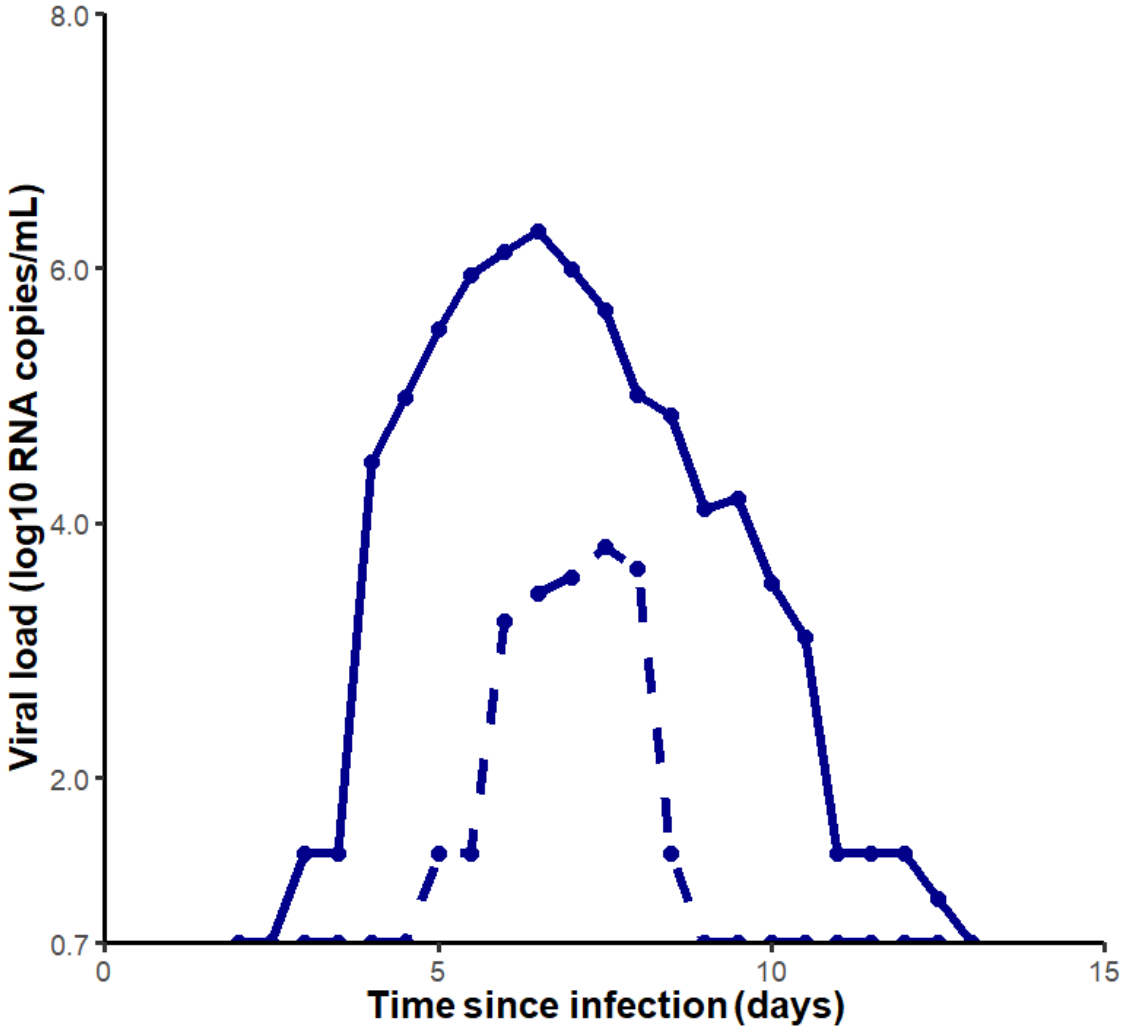
Model adequately describes observed kinetics

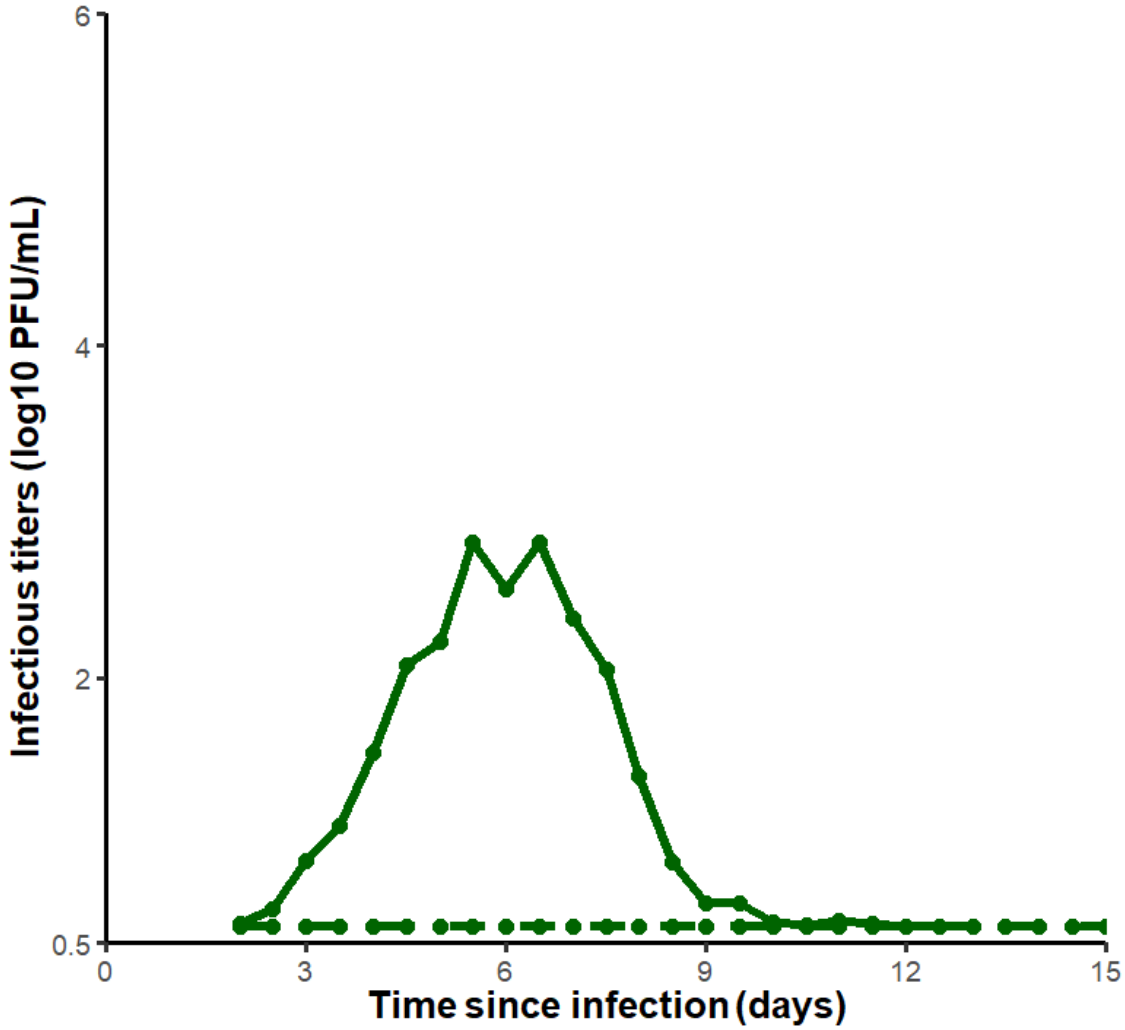




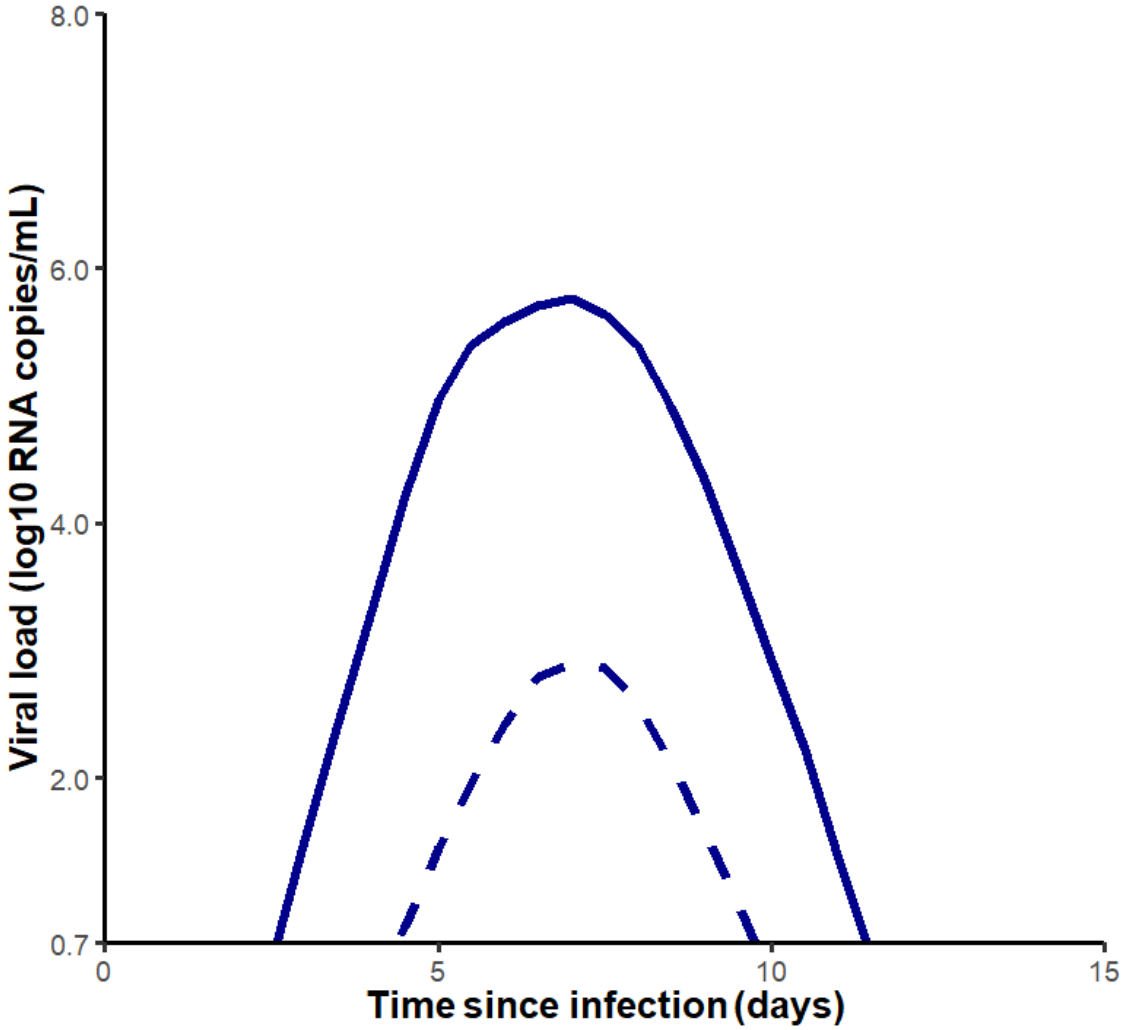


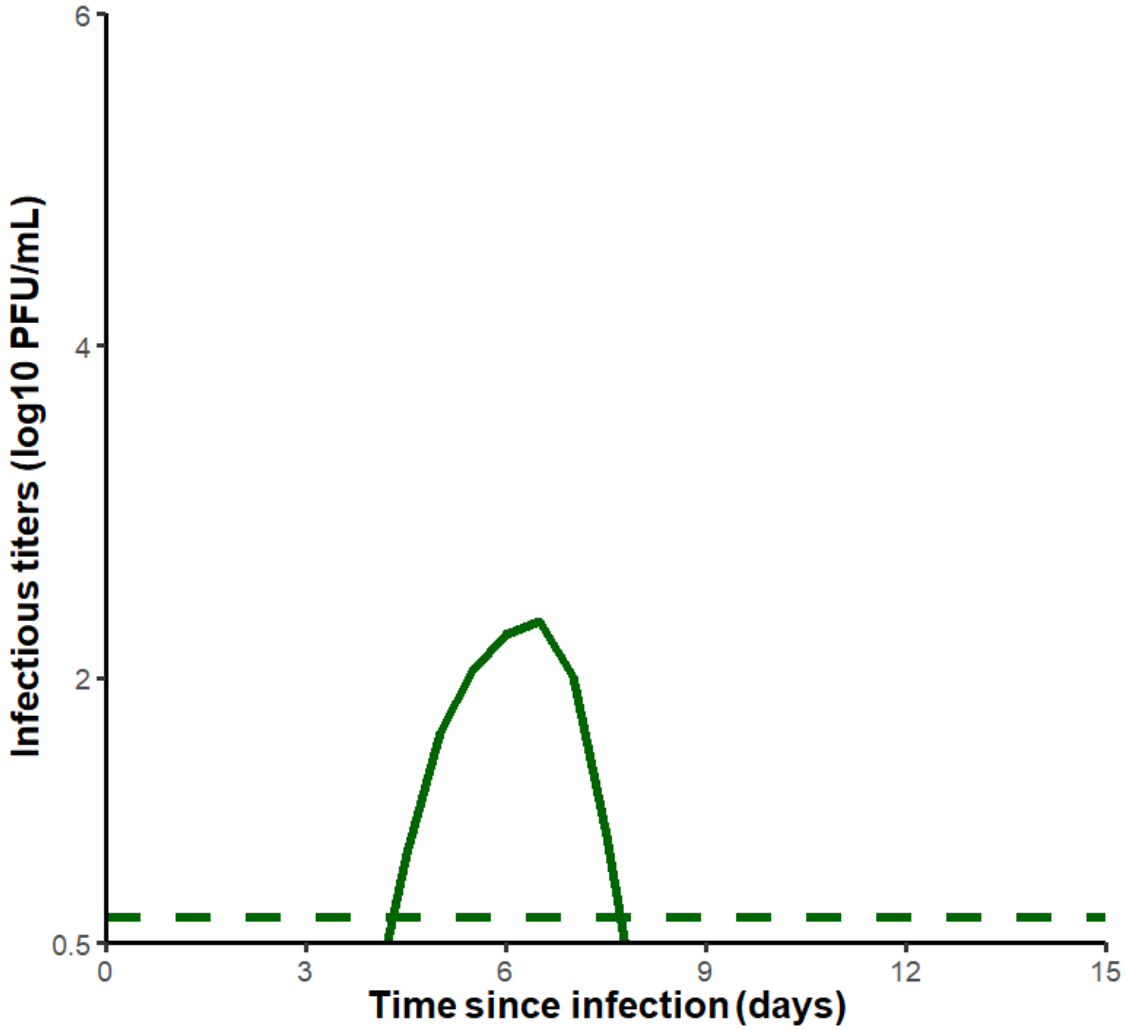
Observed data shows higher viral replication in symptomatic vs asymptomatic individuals





Model accurately captures kinetics in symptomatic and asymptomatic individuals





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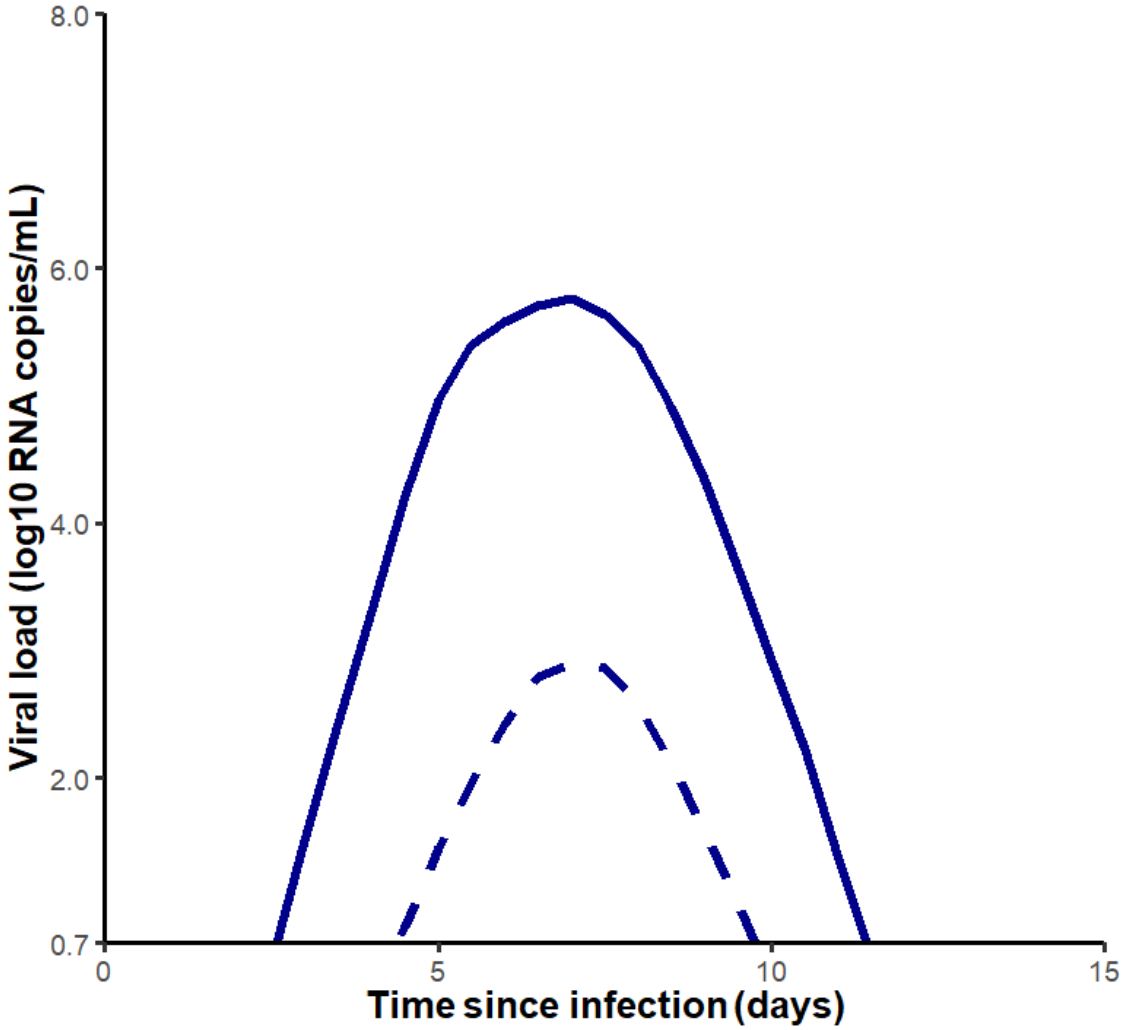
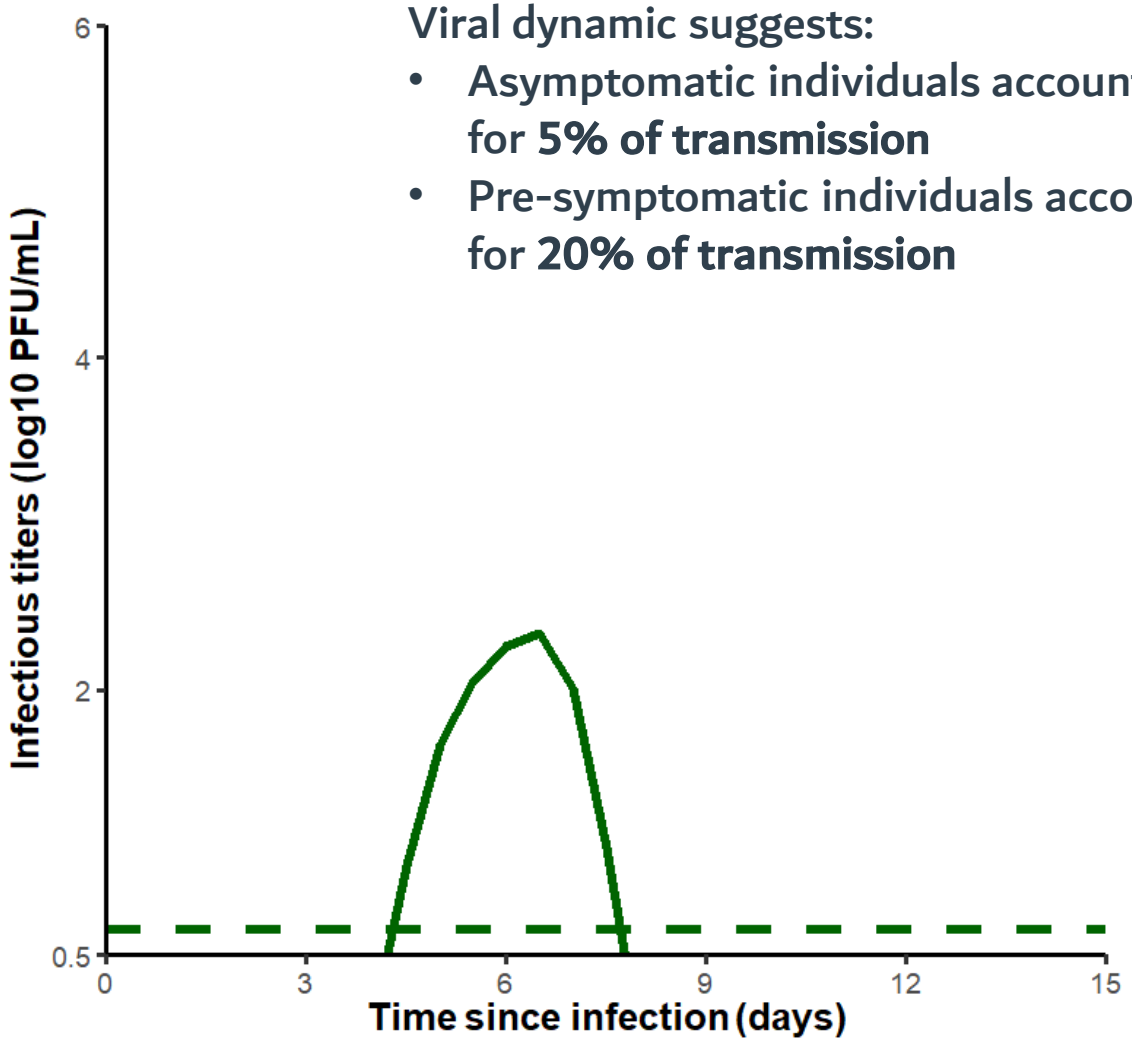




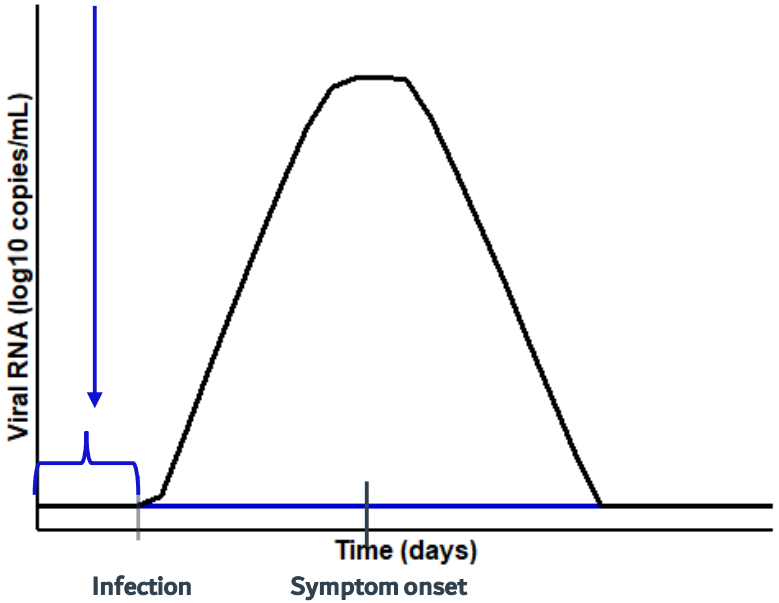
Viral dynamic suggests:

- Asymptomatic individuals account for **5% of transmission**
- Pre-symptomatic individuals account for **20% of transmission**

Evaluation of the protection given by monoclonal antibodies

Initiation of treatment

Pre-exposure prophylaxis



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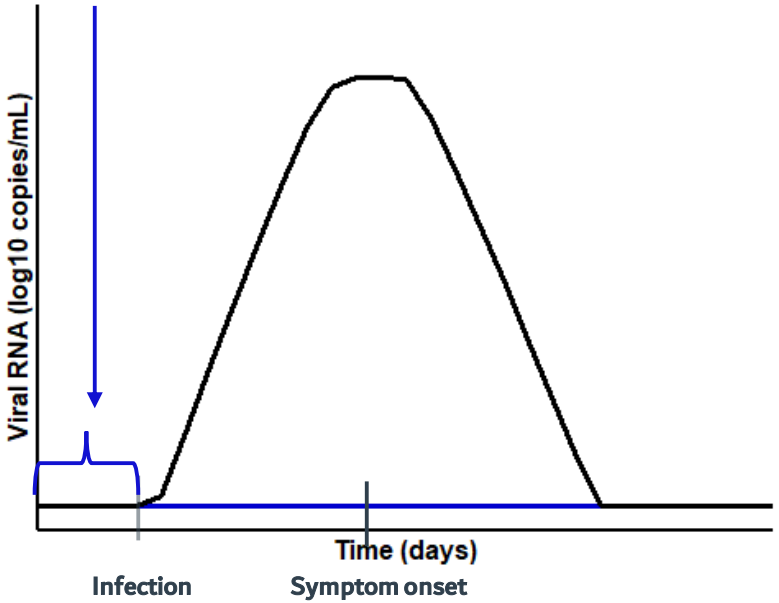
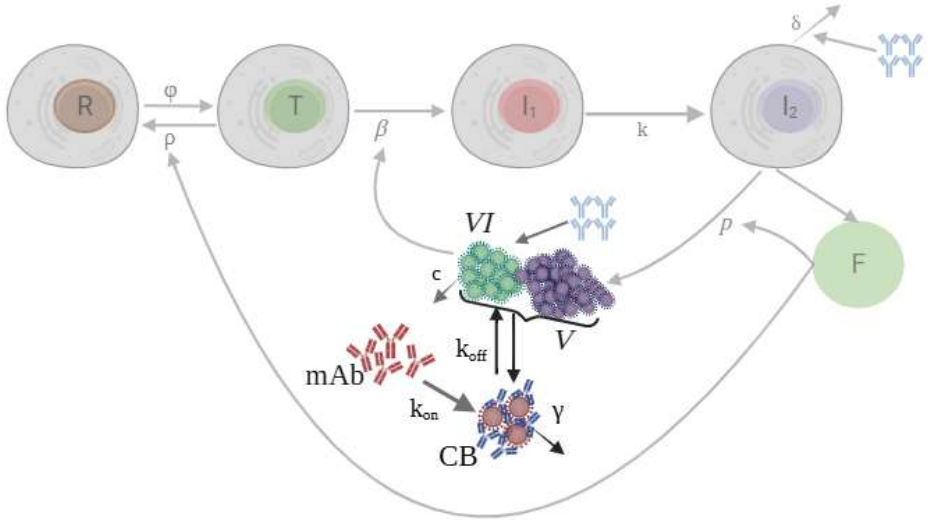


Simulation of protection

Modeling



14- Beaulieu et al., JAC, 2024

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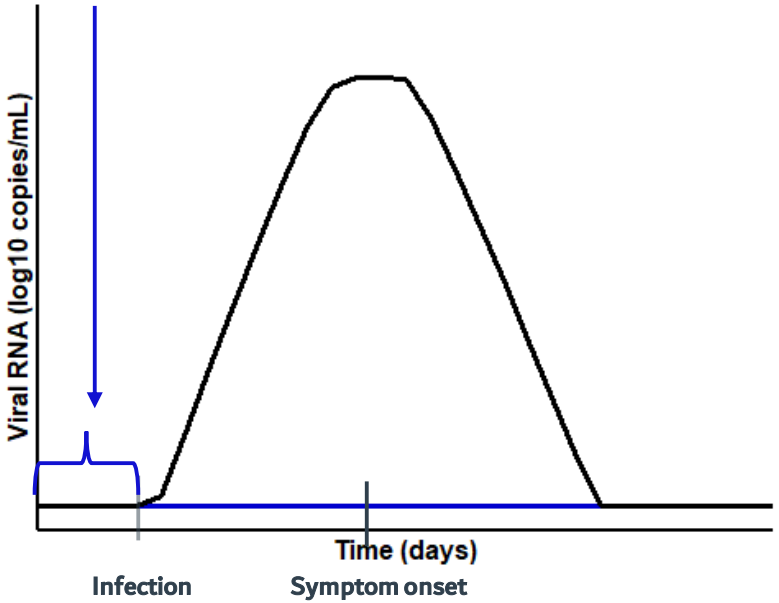

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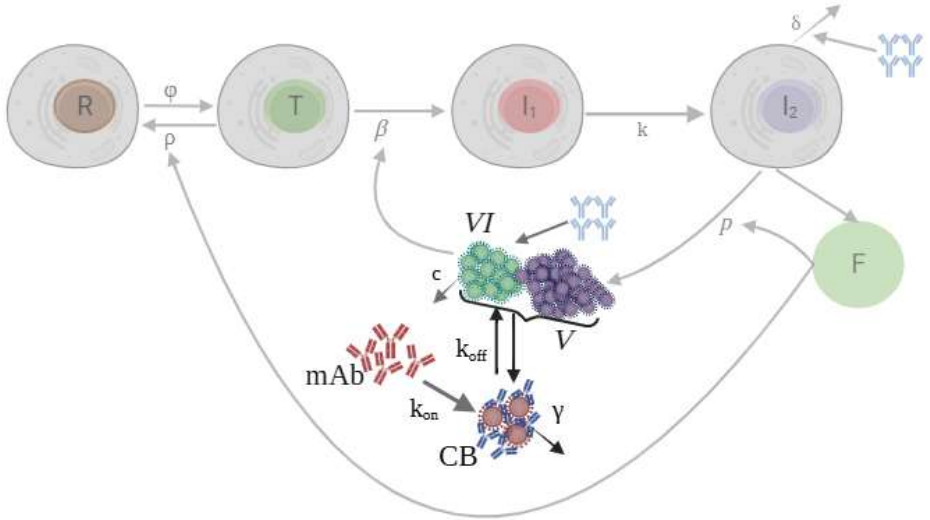

Binding parameters

mAb	K_{on} ($M^{-1}.S^{-1}$)	K_{off} (s^{-1})
Nirsevimab	$3.34*10^{5}$ [15]	$6.87*10^{-6}$ [15]
Palivizumab	$5.4*10^{4}$ [16]	$1.5*10^{-3}$ [16]
Clesrovimab	$7.35*10^{6}$ [18]	$1.64*10^{-4}$ [18]

14- Beaulieu et al., JAC, 2024
15- Griffin et al., Antimicrob Agents Chemother, 2017
16- Astra-Zeneca- Synagis Product Information, 2022
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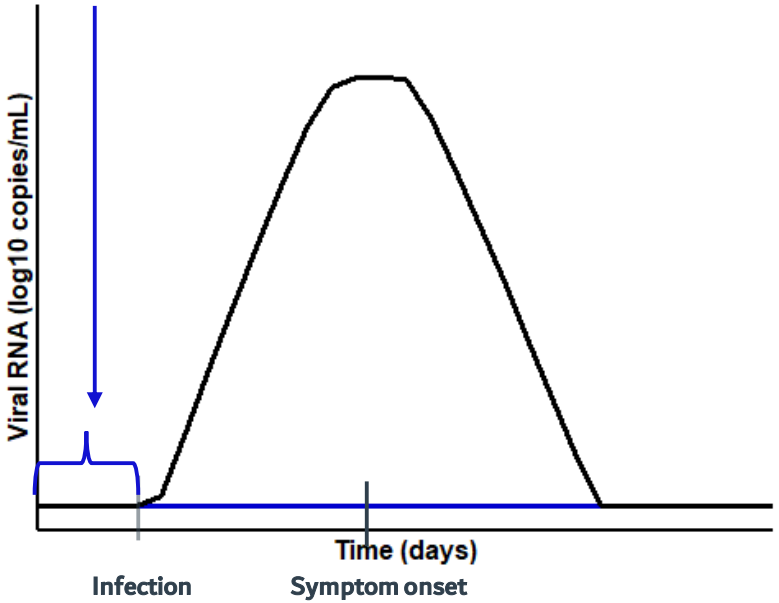

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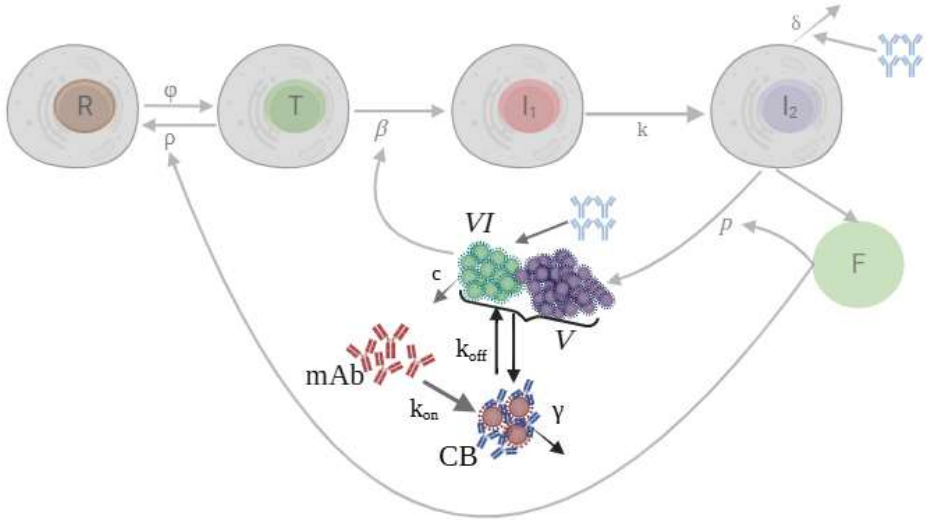

Binding and pharmaco-kinetic parameters

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Nirsevimab	$3.34*10^{5}$ [15]	$6.87*10^{-6}$ [15]	47.5 (12.5) [15]	74.3 (26.3) [15]
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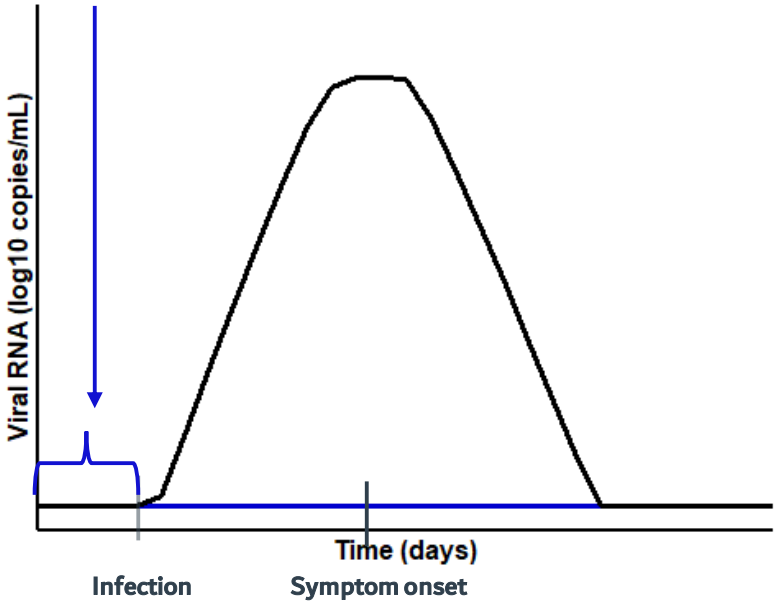

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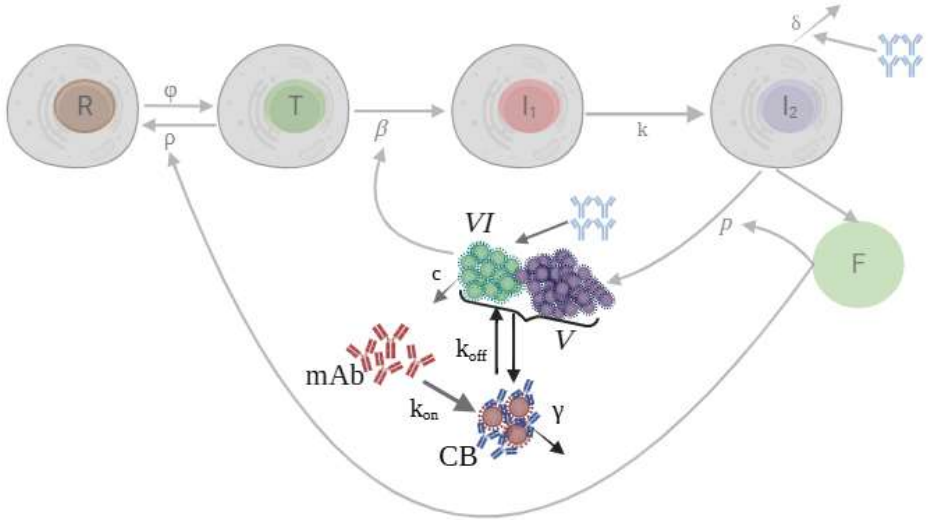

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Criteria of efficacy:

Symptom breakthrough prevention

Viral load breakthrough prevention

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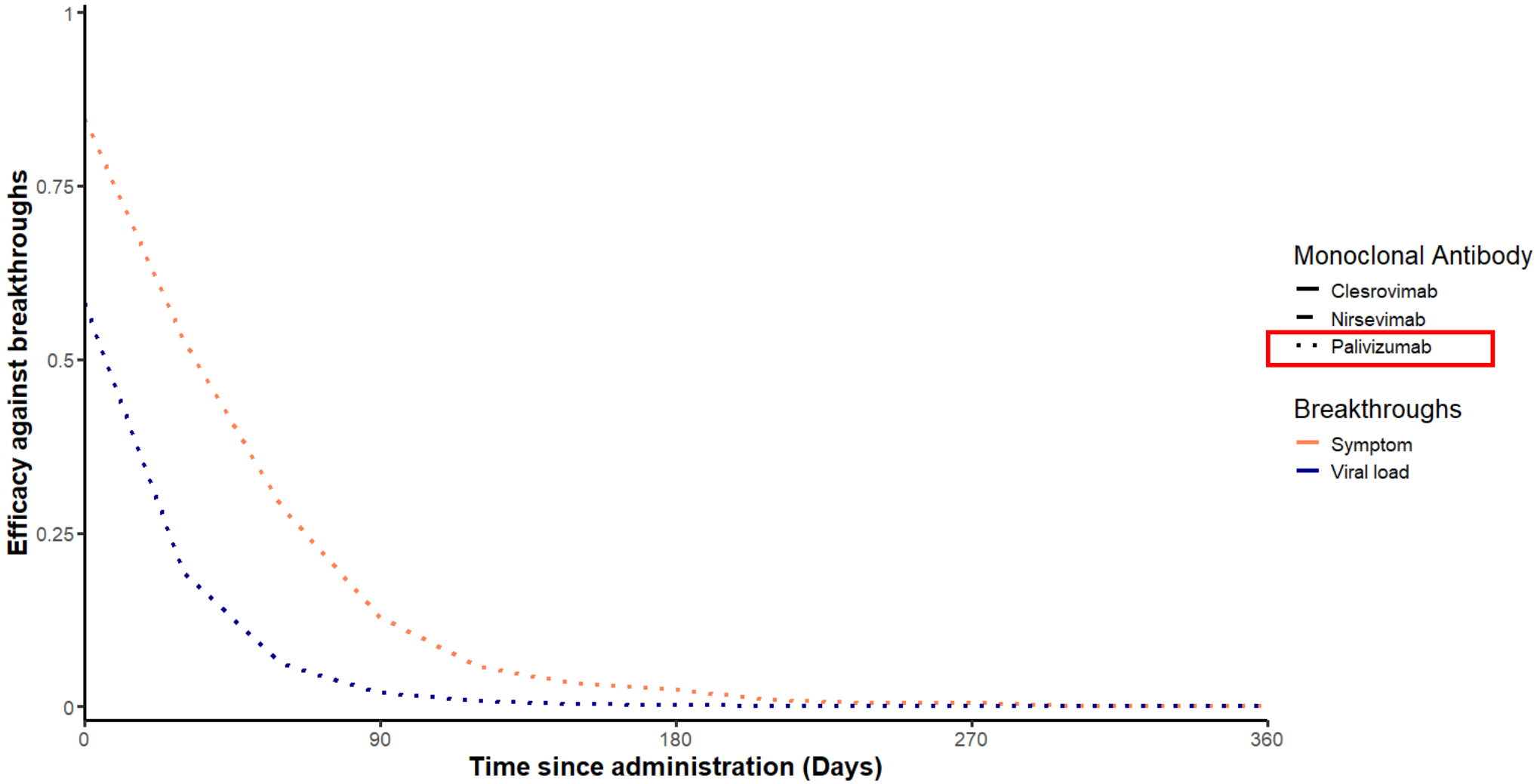
Palivizumab provides lower protection than Nirsevimab and Clesrovimab



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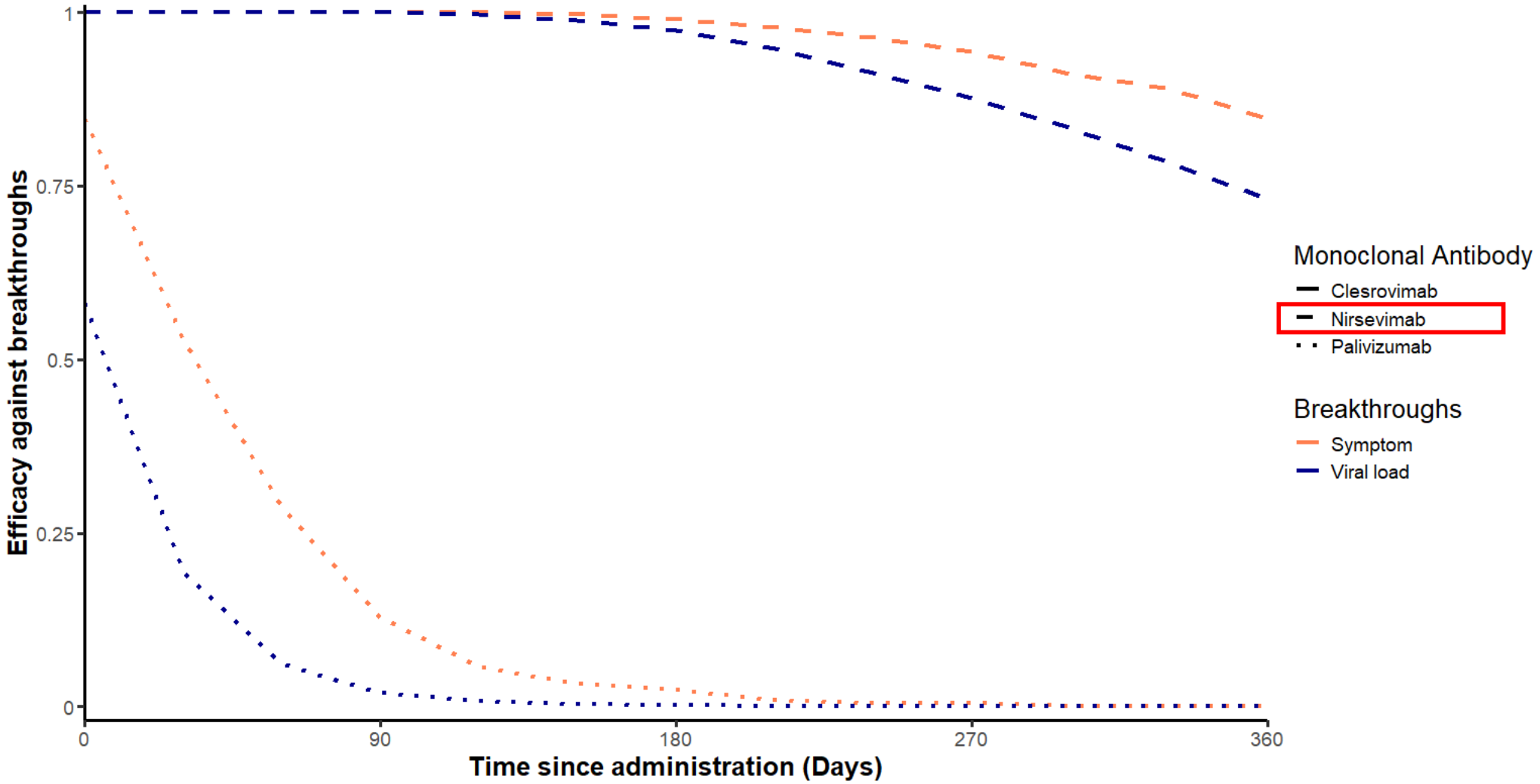
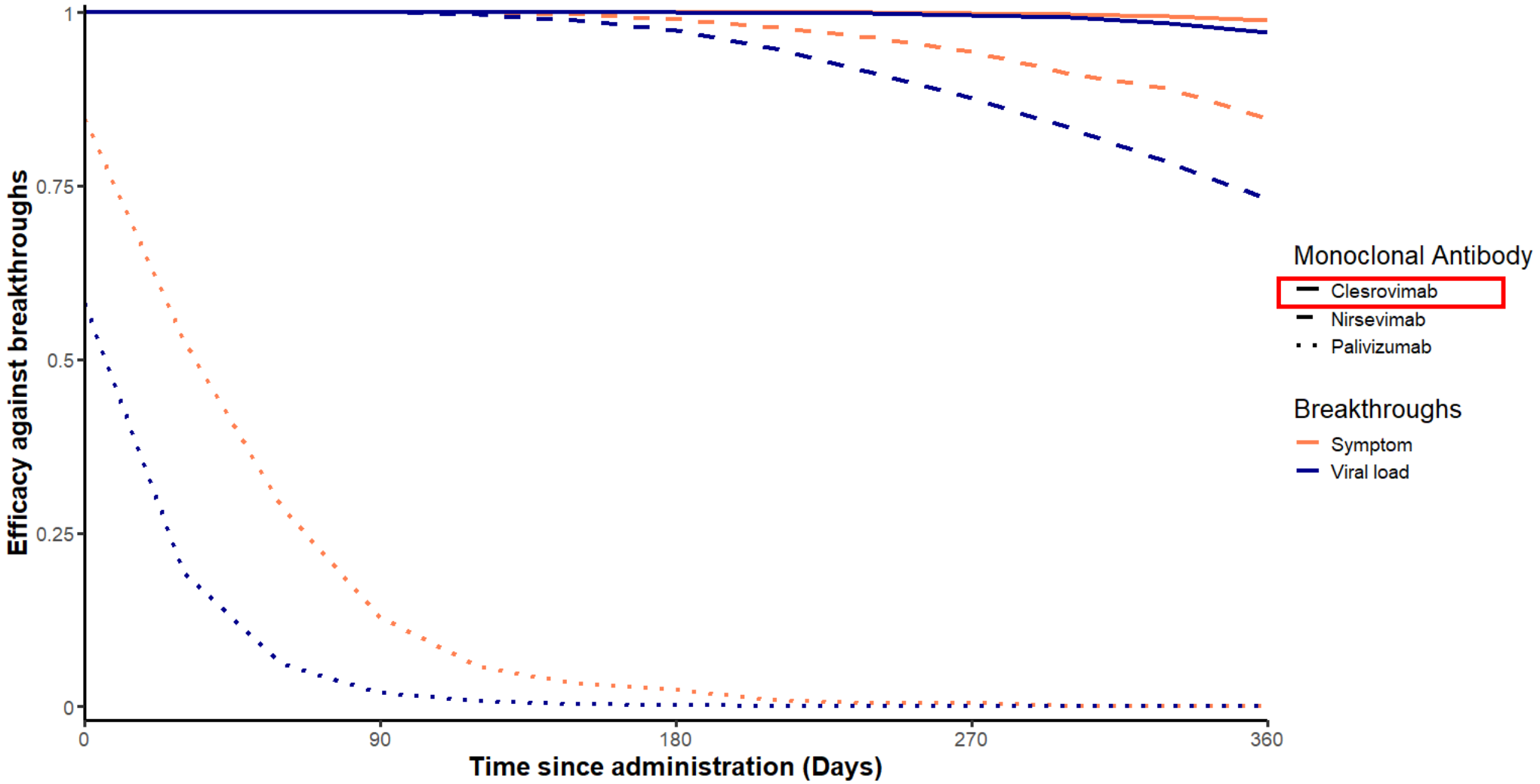
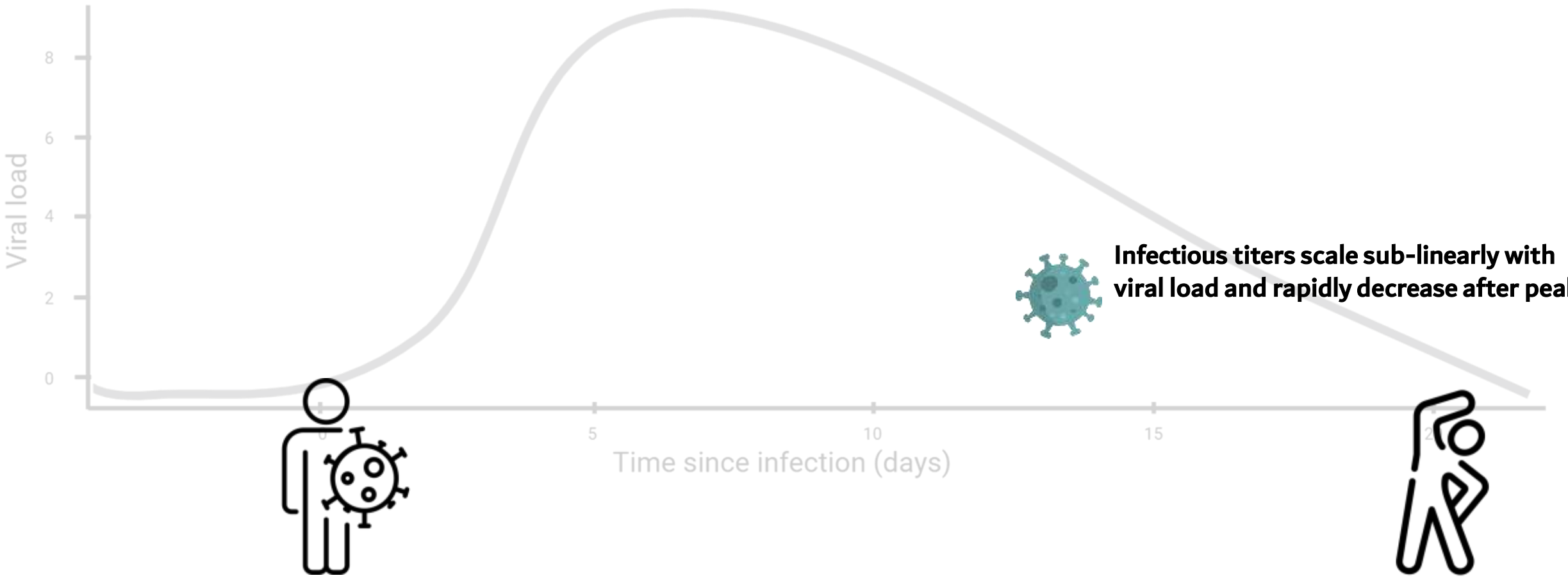


Palivizumab provides lower protection than Nirsevimab and Clesrovimab

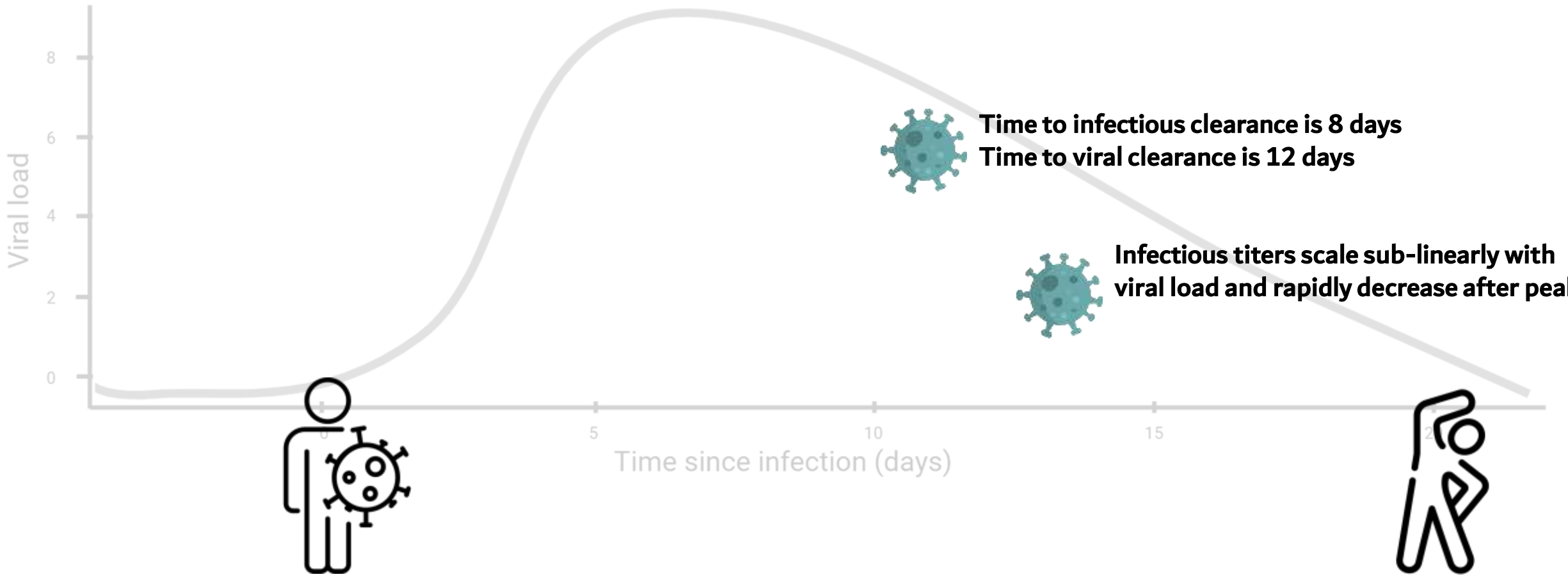


Conclusion



Infectious titers scale sub-linearly with viral load and rapidly decrease after peak

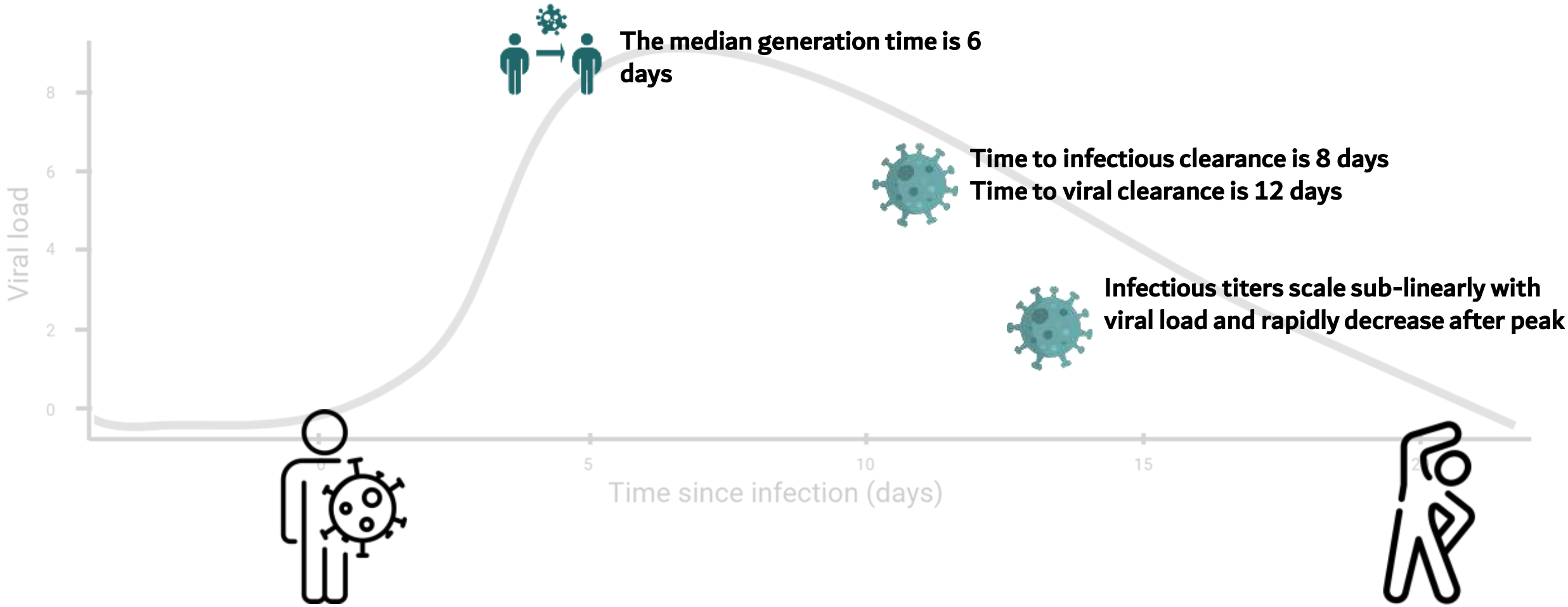
Conclusion



Time to infectious clearance is 8 days
Time to viral clearance is 12 days

Infectious titers scale sub-linearly with viral load and rapidly decrease after peak

Conclusion



The median generation time is 6 days

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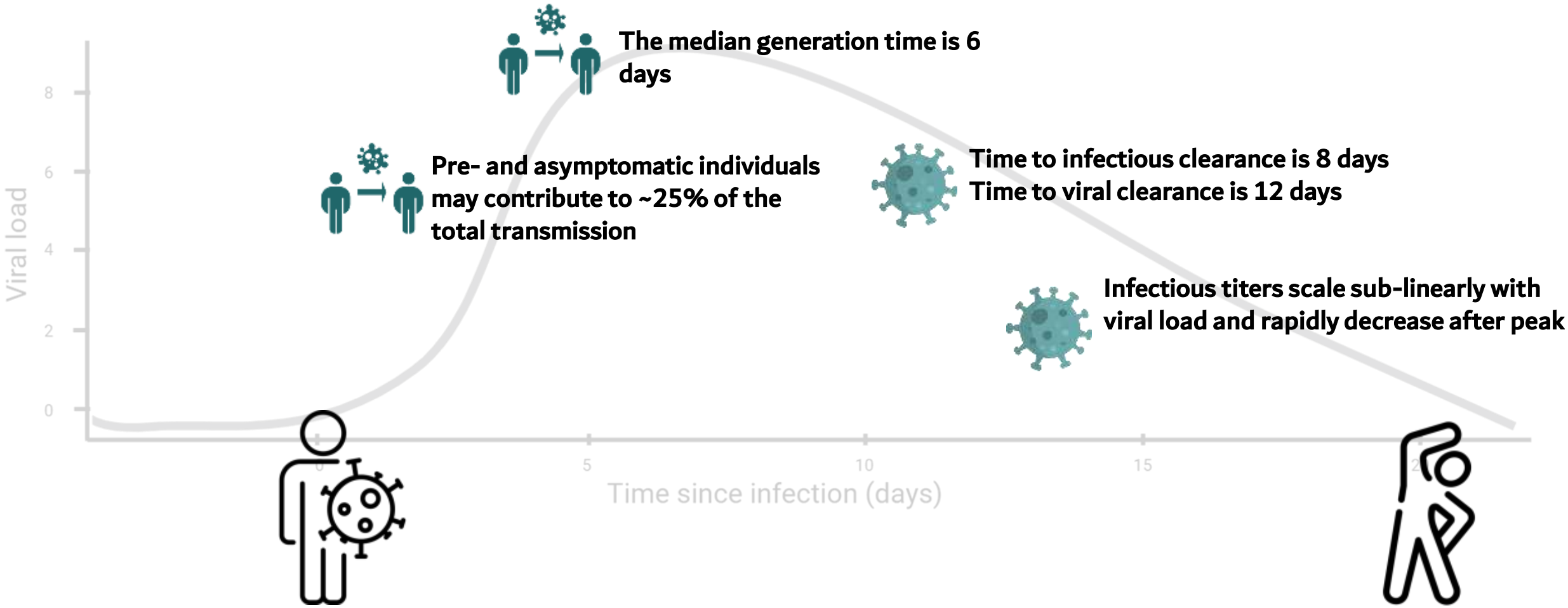
Infectious titers scale sub-linearly with viral load and rapidly decrease after peak

Conclusion



The median generation time is 6 days

Pre- and asymptomatic individuals may contribute to ~25% of the total transmission

Time to infectious clearance is 8 days
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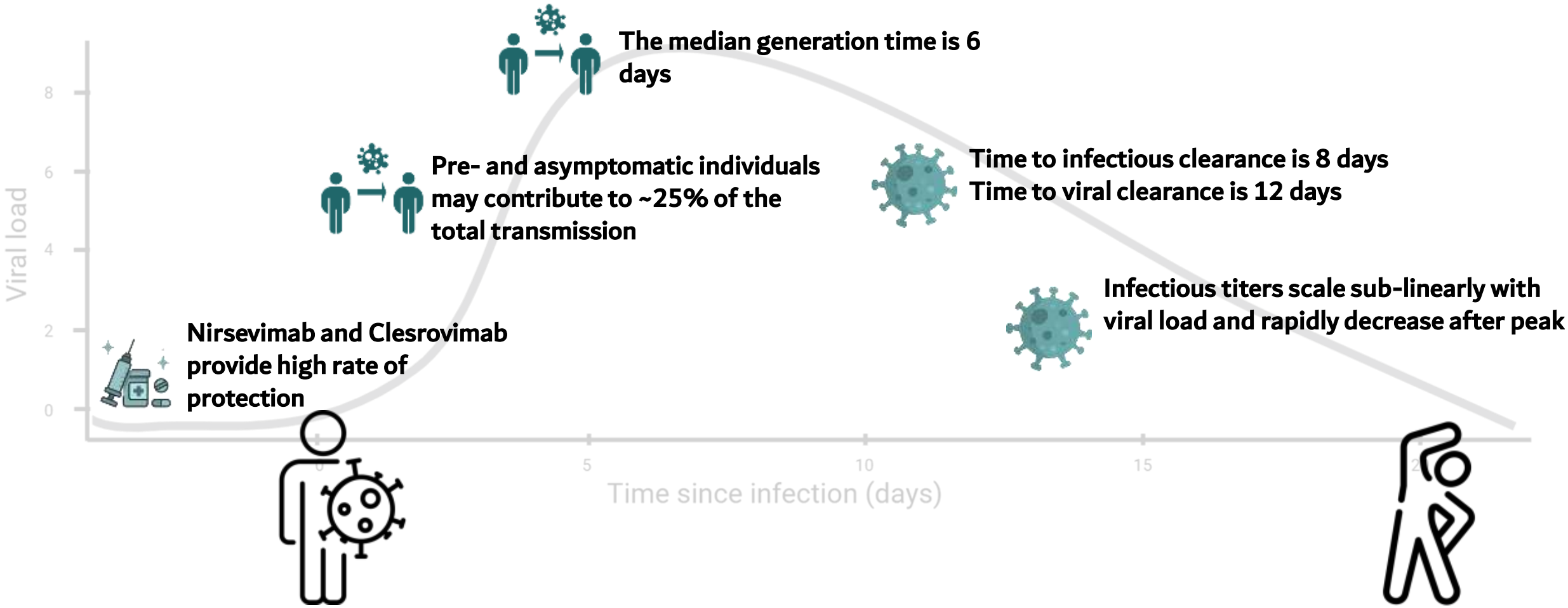
Infectious titers scale sub-linearly with viral load and rapidly decrease after peak

Conclusion



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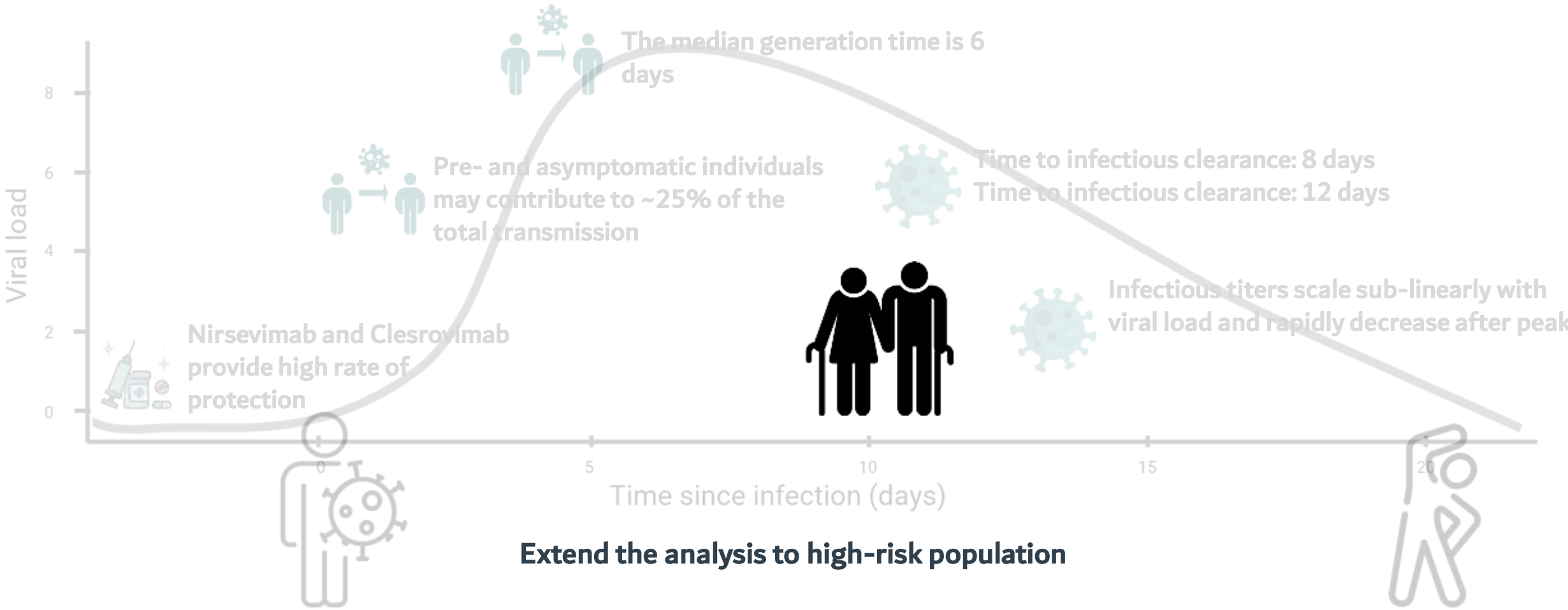
Nirsevimab and Clesrovimab provide high rate of protection

Perspectives



Extend the analysis to high-risk population

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