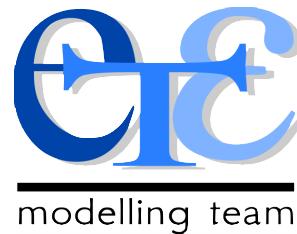


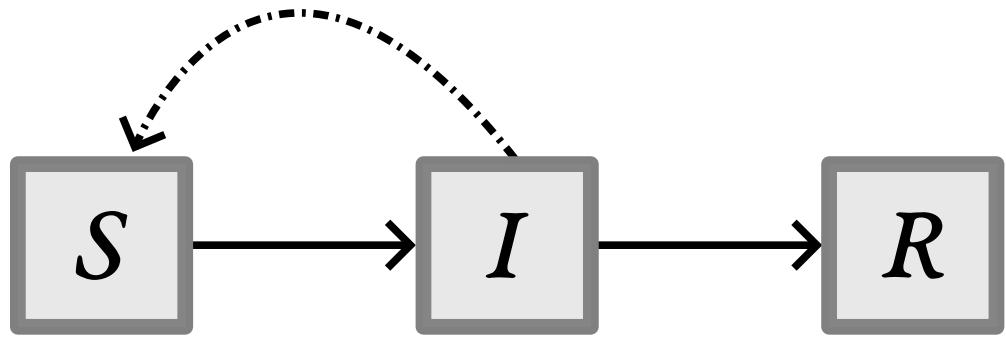
Interests and application of non-Markovian formalism: example of COVID-19

Bastien Reyné

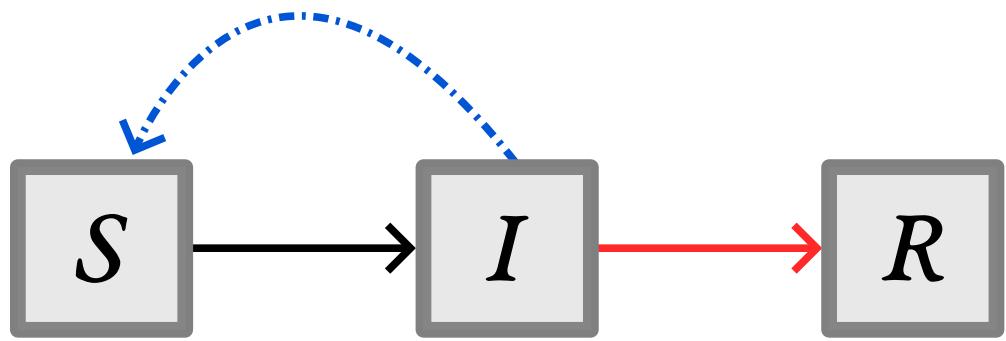
June 2023



Context



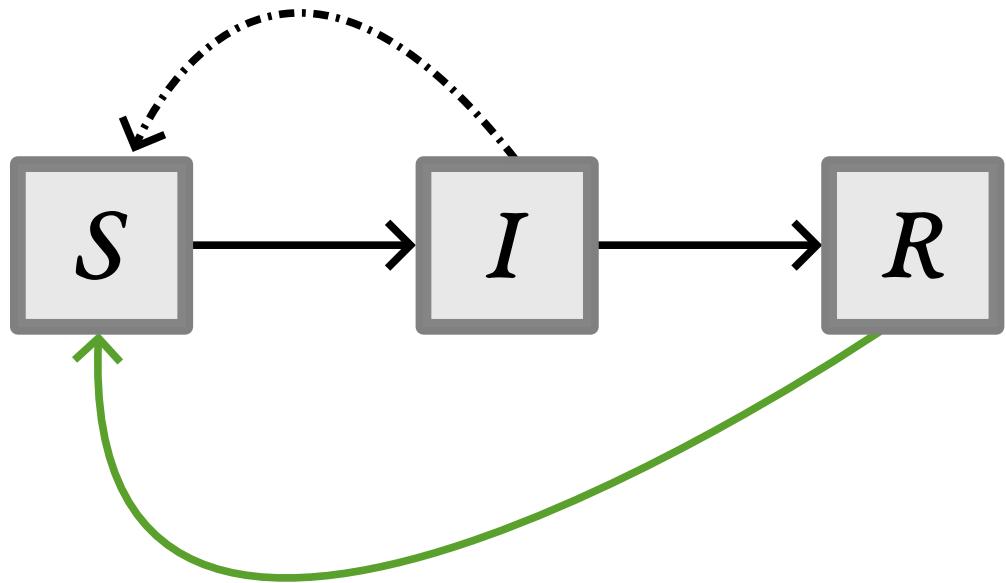
$$\left\{ \begin{array}{l} \frac{dS}{dt} = -\beta S I, \\ \frac{dI}{dt} = \beta S I - \gamma I, \\ \frac{dR}{dt} = \gamma I \end{array} \right.$$



constant over the
infectious period

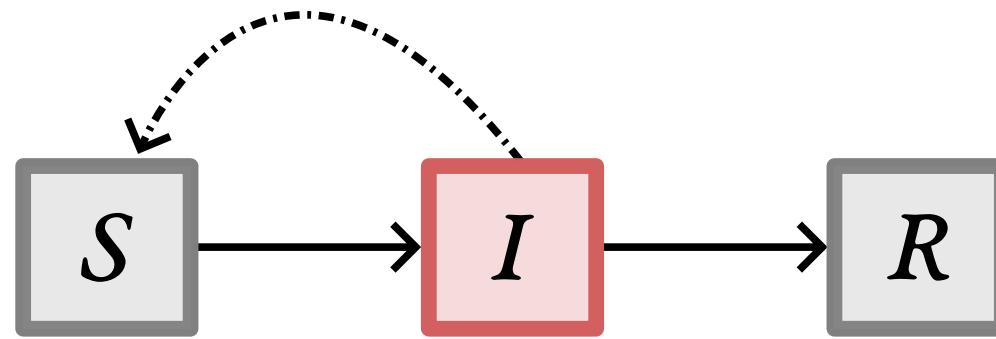
$$\left\{ \begin{array}{l} \frac{dS}{dt} = -\beta S I, \\ \frac{dI}{dt} = \beta S I - \gamma I, \\ \frac{dR}{dt} = \gamma I \end{array} \right.$$

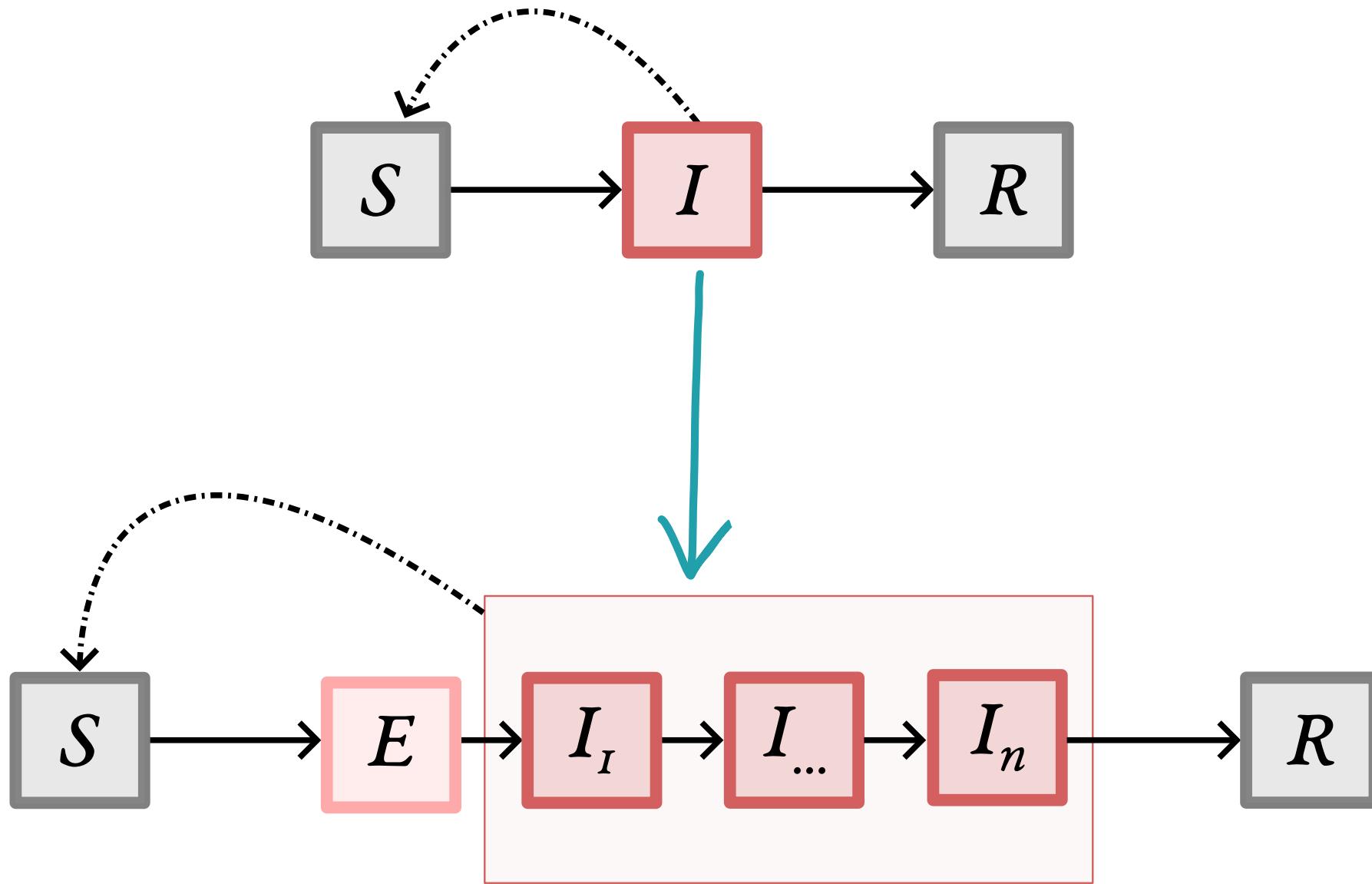
The equation set describes the differential rates of change for each state. The term $\beta S I$ is circled in blue, and the term γI is circled in red. An arrow points from the text "constant over the infectious period" to the β coefficient in the first equation.

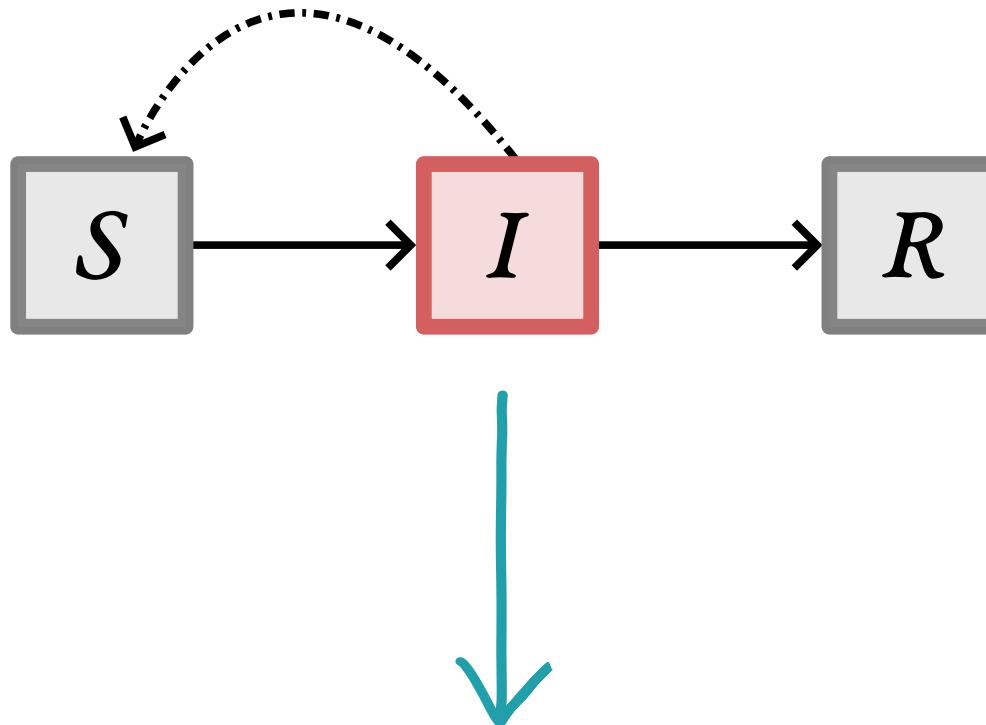


constant over the recovered period

$$\left\{ \begin{array}{l} \frac{dS}{dt} = -\beta S I + \sigma R, \\ \frac{dI}{dt} = \beta S I - \gamma I, \\ \frac{dR}{dt} = \gamma I - \sigma R \end{array} \right.$$



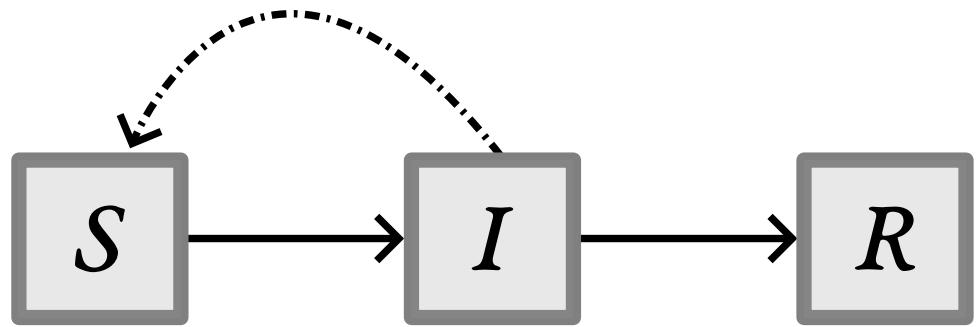




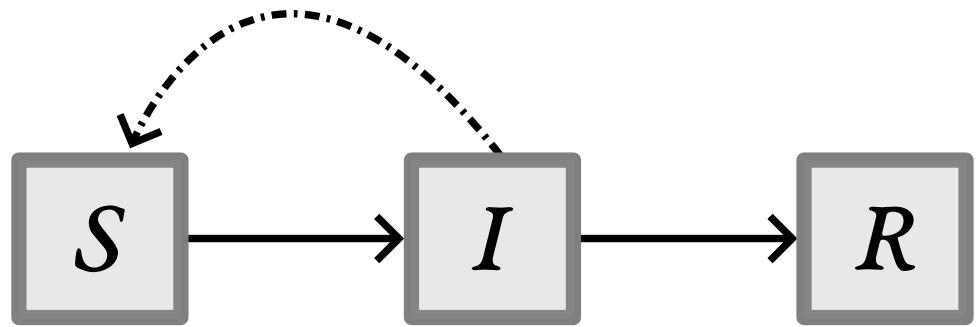
Non-Markovian properties

Take into account the time spent in each compartment

Method



$$\left\{ \begin{array}{l} \frac{dS}{dt} = -\beta S I, \\ \frac{dI}{dt} = \beta S I - \gamma I, \\ \frac{dR}{dt} = \gamma I \end{array} \right.$$



$$\left\{ \begin{array}{l} \frac{dS}{dt} = -\beta S I, \\ \frac{dI}{dt} = \beta S I - \gamma I, \\ \frac{dR}{dt} = \gamma I \end{array} \right.$$

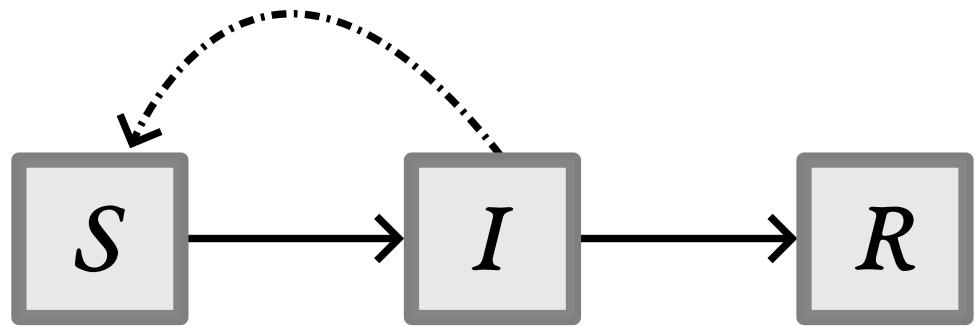
Step 1

Remember when individuals enter the compartment

Step 2

Make a function of the time spent in the compartment the biological processes

ODE-based models



$$\left\{ \begin{array}{l} \frac{dS}{dt} = -\beta S I, \\ \frac{dI}{dt} = \beta S I - \gamma I, \\ \frac{dR}{dt} = \gamma I \end{array} \right.$$

PDE-based models (non-Markovian)

$$\frac{\partial S(t)}{\partial t} = -\underline{\lambda}(t) S(t),$$

Step 1 $I(t, 0) = \underline{\lambda}(t) S(t),$

Step 2 $\left(\frac{\partial I(t, k)}{\partial t} + \frac{\partial I(t, k)}{\partial k} \right) = -\gamma(k) I(t, k),$

$$\frac{\partial R(t)}{\partial t} = \int_0^\infty \gamma(k) I(t, k) dk$$

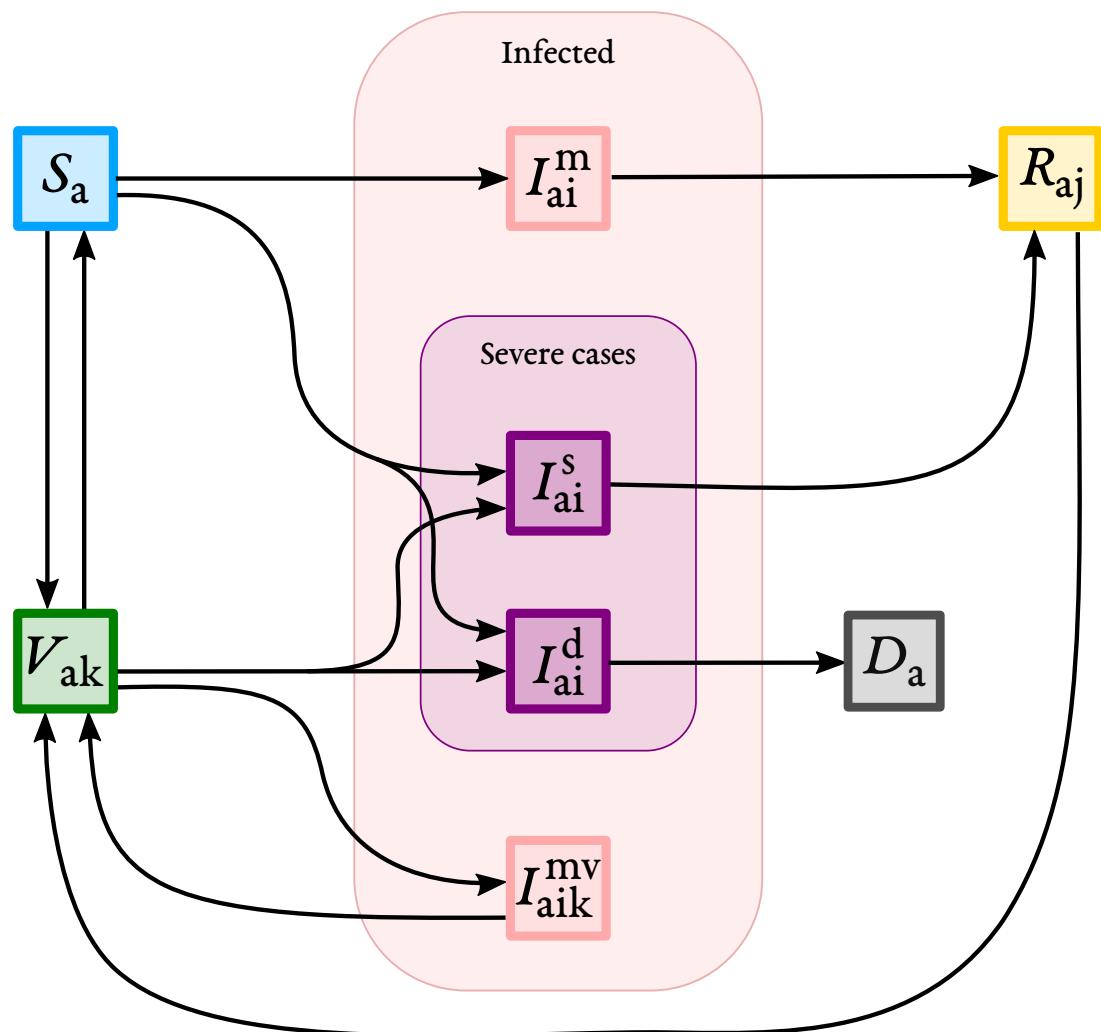
PDE-based models (non-Markovian)

$$\frac{\partial v_{t\theta}}{\partial t} + \frac{\partial v_{t\theta}}{\partial \theta} = - (l_\theta + d_\theta) v_{t\theta}$$

— Kermack & McKendrick, 1932

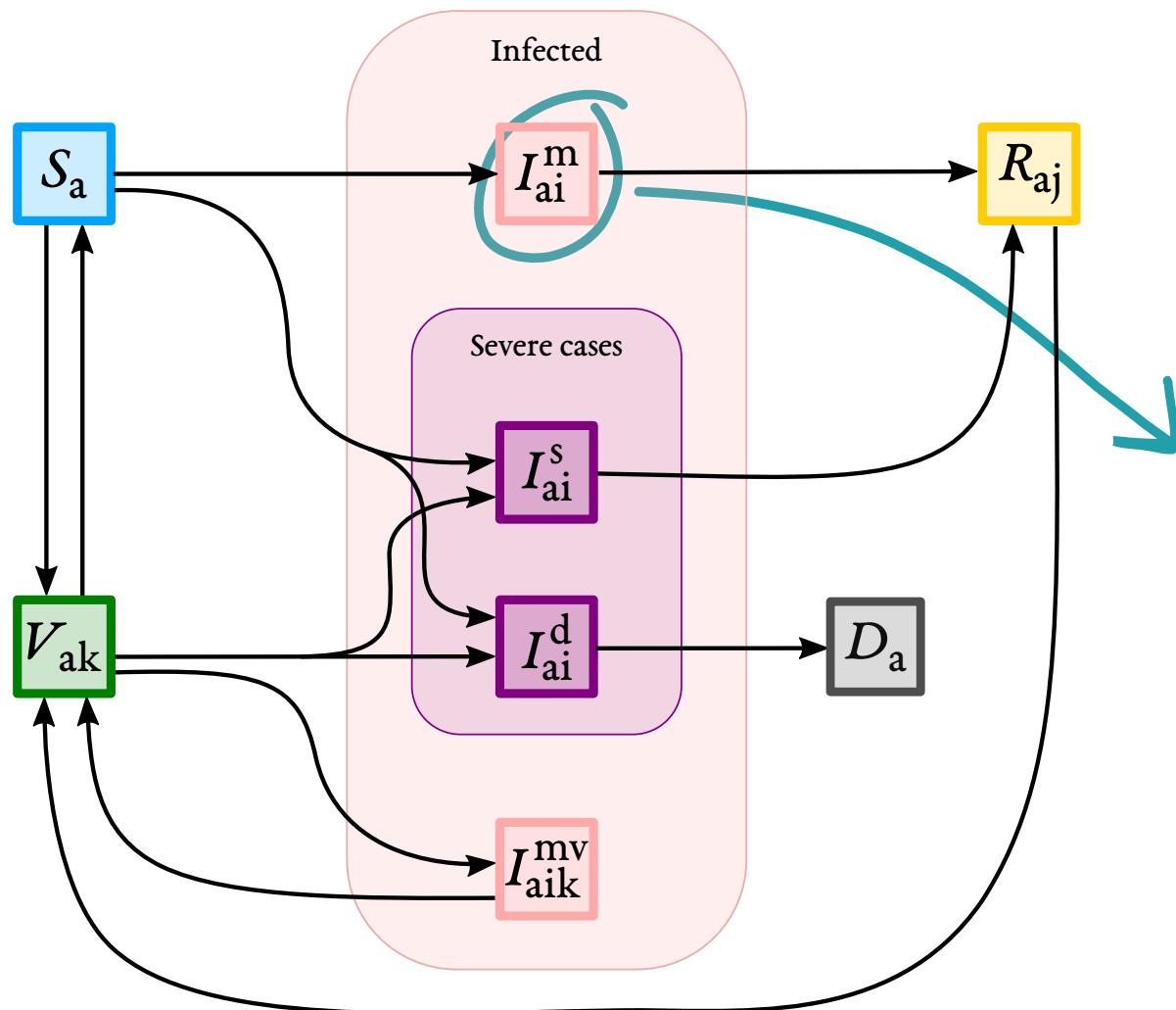
COVID-19 modelling project

Model (early 2021)



a host age
 i time since infection
 j time since clearance
 k time since vaccination

Model (early 2021)



a host age
 i time since infection
 j time since clearance
 k time since vaccination

Step 1: Entrance

$$I^m(t, a, 0) = (1 - p_a) \Lambda(t, a) S(t, a)$$

Step 2: Departure

$$\left(\frac{\partial I^m(t, a, i)}{\partial t} + \frac{\partial I^m(t, a, i)}{\partial i} \right) = -\gamma^m(a, i) I^m(t, a, i)$$

Model equations

$$\frac{\partial S(t, a)}{\partial t} = -\lambda(t, a)S(t, a) - \rho(a)S(t, a) + \int_0^{j_{\max}} \sigma(j)R(t, a, j) dj$$

$$+ \int_0^{k_{\max}} w(a, k)V(t, a, k) dk$$

$$I^m(t, a, 0) = (1 - p_a) \lambda(t, a) S(t, a) \leftarrow \left(\frac{\partial I^m(t, a, i)}{\partial t} + \frac{\partial I^m(t, a, i)}{\partial i} \right) = -\gamma^m(a, i)I^m(t, a, i)$$

$$\dots \leftarrow \left(\frac{\partial I^s(t, a, i)}{\partial t} + \frac{\partial I^s(t, a, i)}{\partial i} \right) = -\gamma^s(a, i)I^s(t, a, i)$$

$$\dots \leftarrow \left(\frac{\partial I^d(t, a, i)}{\partial t} + \frac{\partial I^d(t, a, i)}{\partial i} \right) = -\mu(a, i)I^d(t, a, i)$$

$$\dots \leftarrow \left(\frac{\partial R(t, a, j)}{\partial t} + \frac{\partial R(t, a, j)}{\partial j} \right) = -\rho(a)R(t, a, j) - \sigma(j)R(t, a, j)$$

$$\dots \leftarrow \left(\frac{\partial V(t, a, k)}{\partial t} + \frac{\partial V(t, a, k)}{\partial k} \right) = -w(a, k)V(t, a, k)$$

$$- (1 - \varepsilon(a, k))(1 - \nu(a, k))p_a \lambda(t, a)V(t, a, k)$$

$$- (1 - \varepsilon(a, k)) [1 - (1 - \nu(a, k))p_a] \lambda(t, a)V(t, a, k)$$

$$+ \int_0^{i_{\max}} \gamma^{m,v}(a, i)I^{m,v}(t, a, i, k) di$$

$$\dots \leftarrow \left(\frac{\partial I^{m,v}(t, a, i, k)}{\partial t} + \frac{\partial I^{m,v}(t, a, i, k)}{\partial i} + \frac{\partial I^{m,v}(t, a, i, k)}{\partial k} \right) = -\gamma^{m,v}(a, i)I^{m,v}(t, a, i, k)$$

Parameters and uncertainty

- ▶ Contact rate and vaccination rate fitted on French data
- ▶ Others parameters retrieved from the literature
- ▶ 9 parameters were drawn in their CIs using LHS
- ▶ Dynamics CIs constructed with the 2.5 and 97.5 quantiles

Variant switch

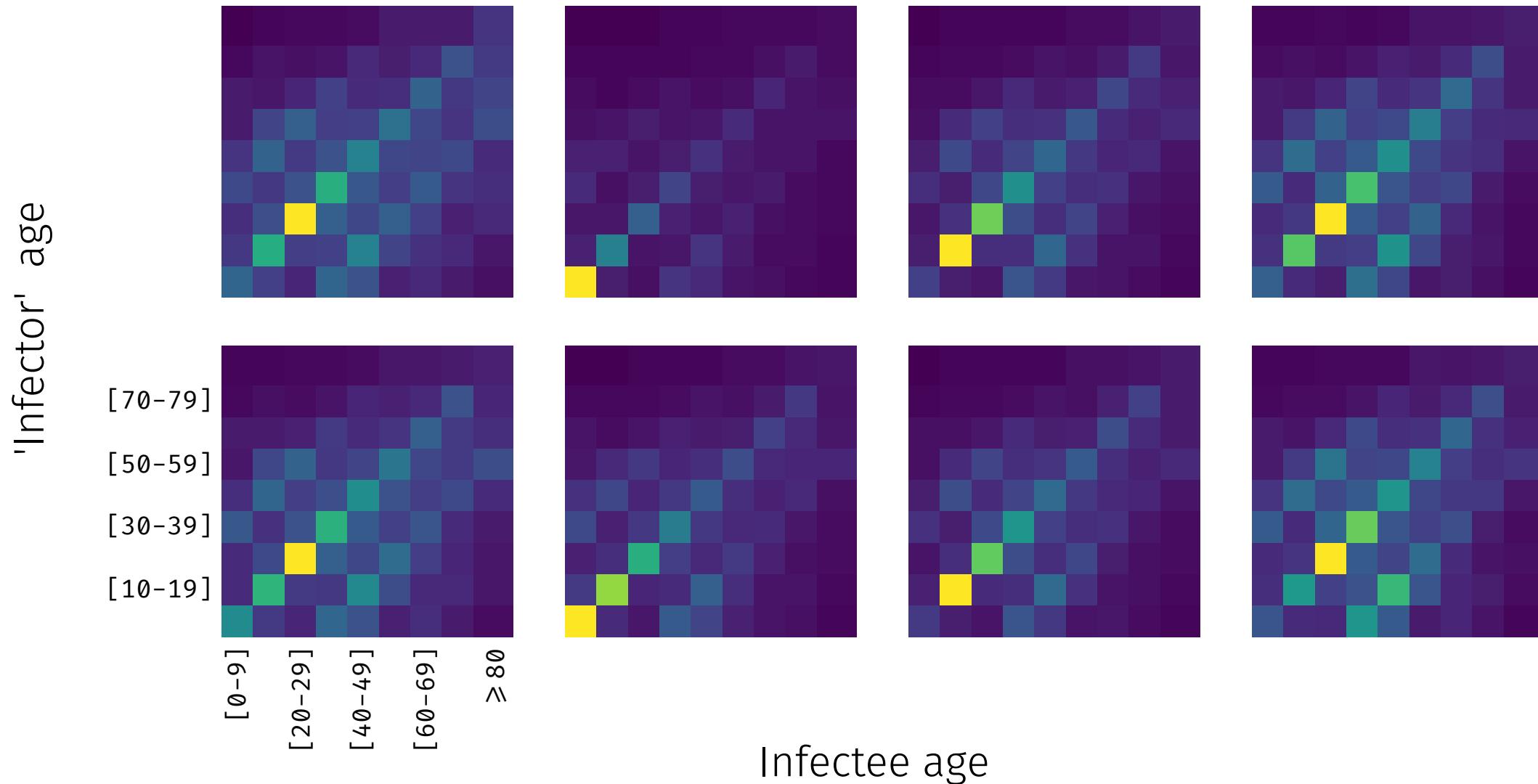
- ▶ A new variant arrival is modelled by a switch in the model's parameters

Parameters

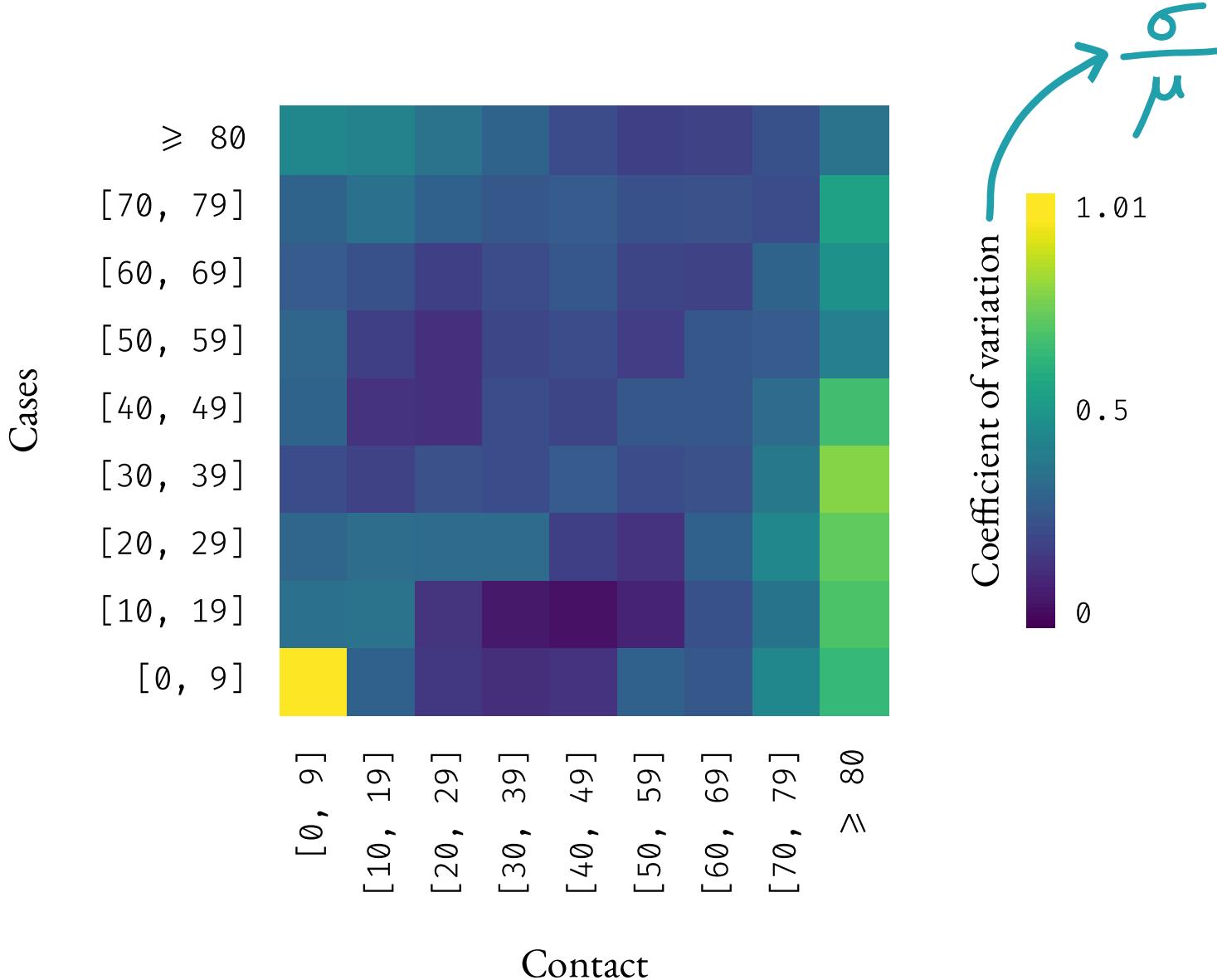
- ▶ Generation time
 - Feretti *et alii*, 2020
- ▶ Proportion of severe cases, IFR
 - Verity *et alii*, 2020
- ▶ Alpha VOC increase in virulence
 - Challen *et alii*, 2020
- ▶ Clearance rate
 - Salje, Kiem *et alii*, 2020
- ▶ Initial proportion of recovered
 - Hozé *et alii*, 2021
- ▶ Alpha \mathcal{R}_0 , Delta \mathcal{R}_0
 - Haim-Boukobza *et alii* 2021, Alizon *et alii*, 2021
- ▶ Vaccine effectiveness
 - Public Health England, 2021

38 contact matrixes

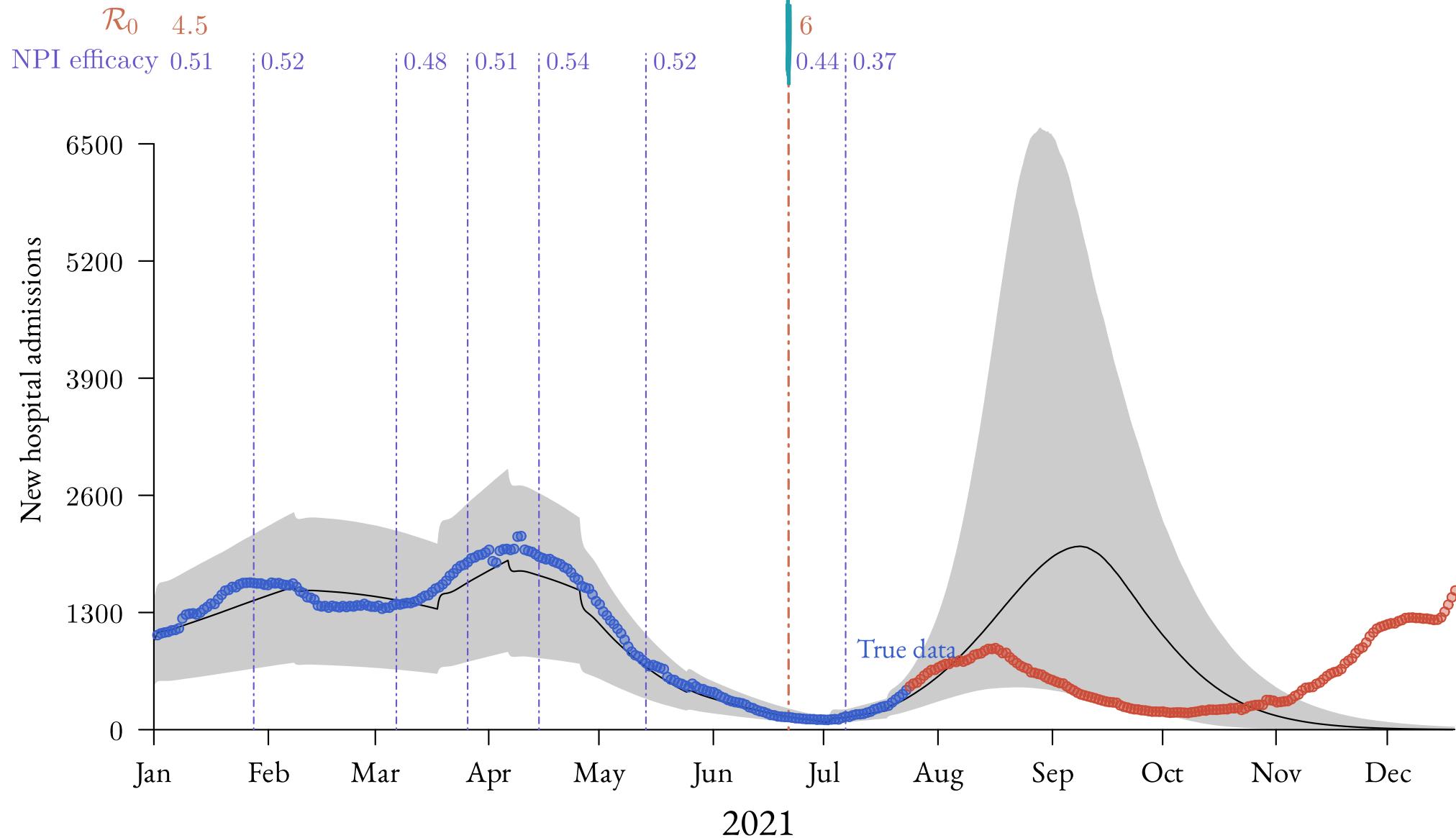
- Weekly basis, from August '20 to April '21
- Provided by the French National Health Insurance



Matrixes coefficient of variation



Dynamics

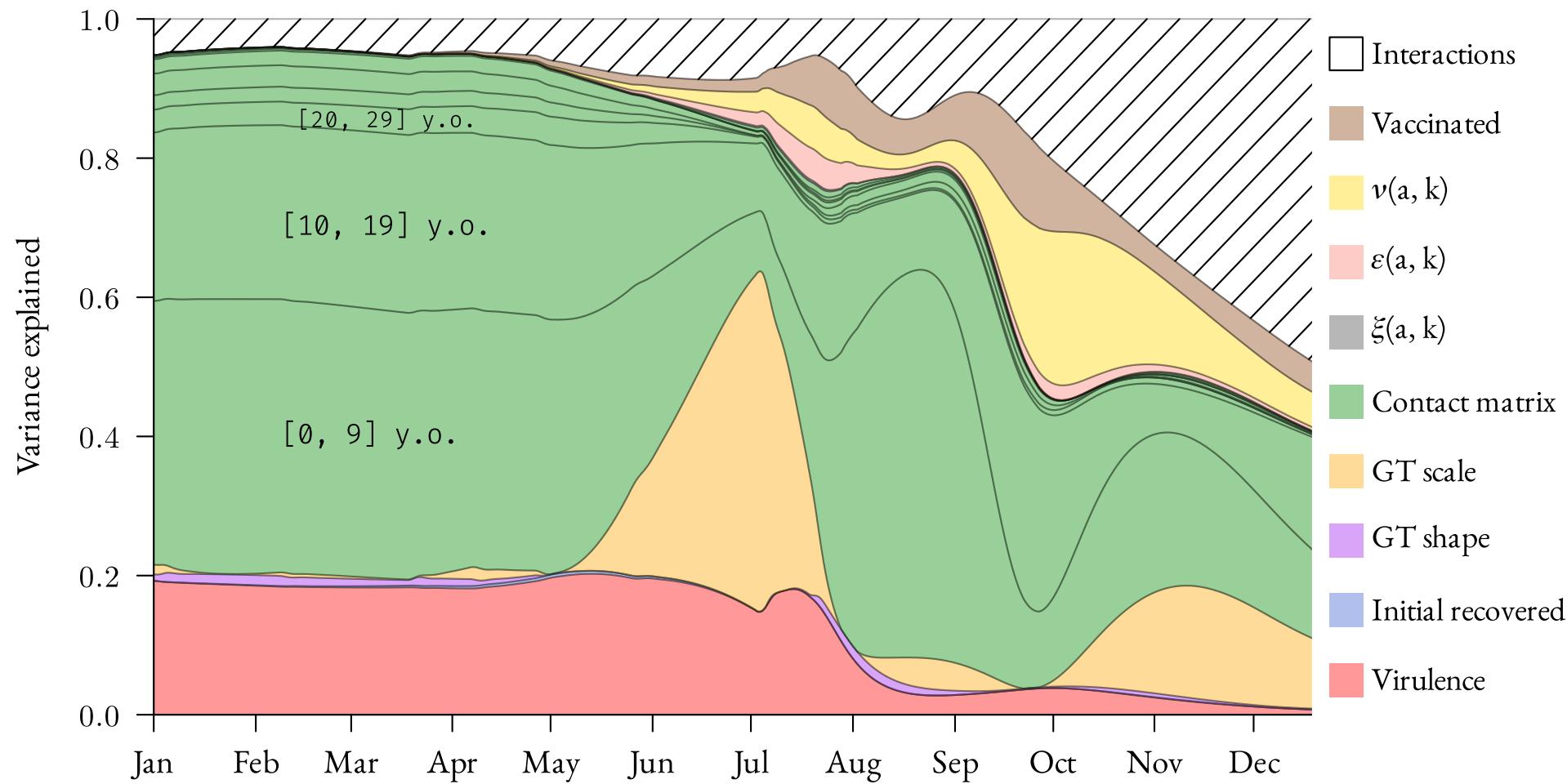


Sensitivity analysis

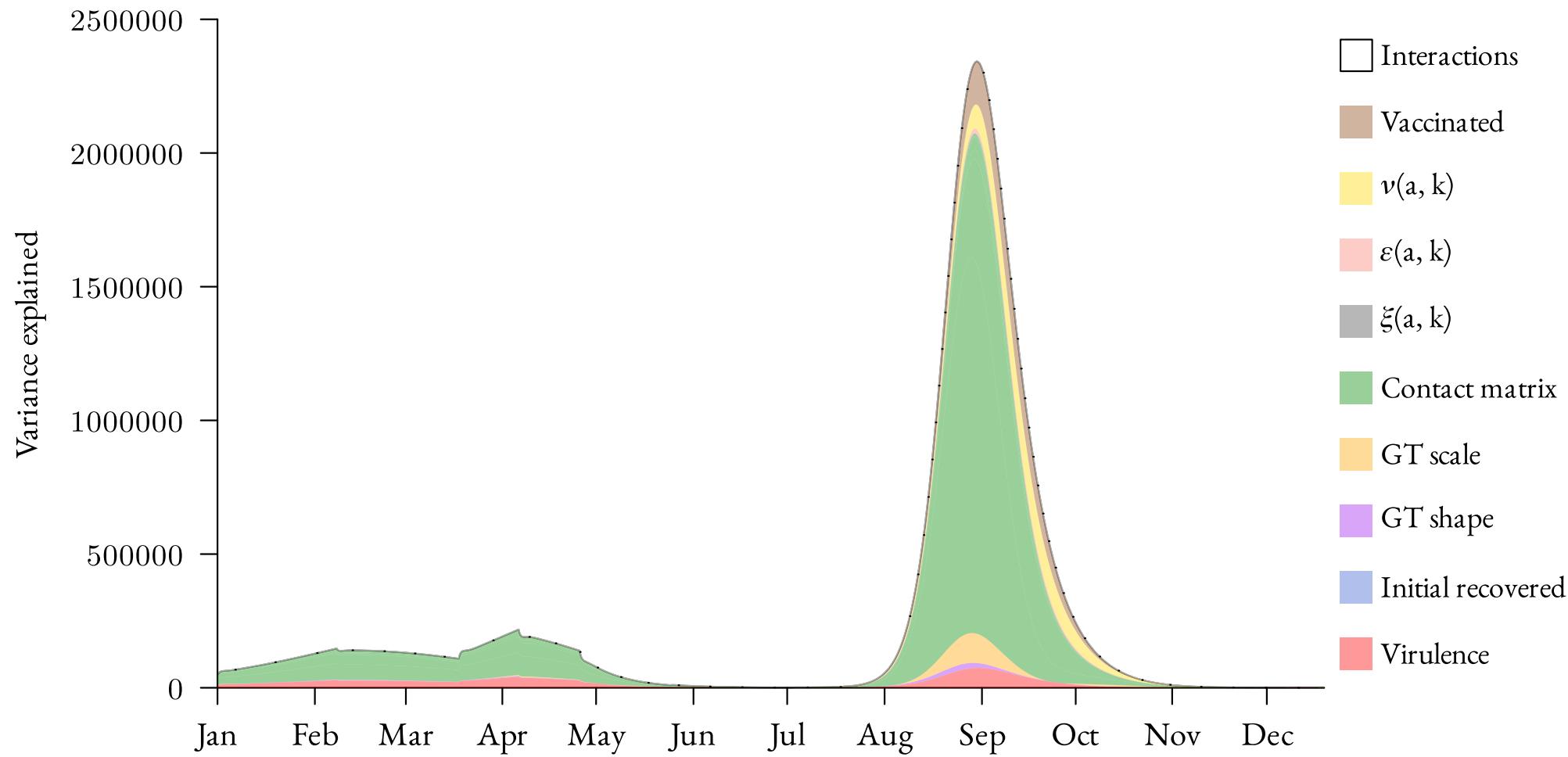
- ▶ Decompose the variance of the output between the different parameters
- ▶ For each parameter X_i , compute the **Sobol main indice**:

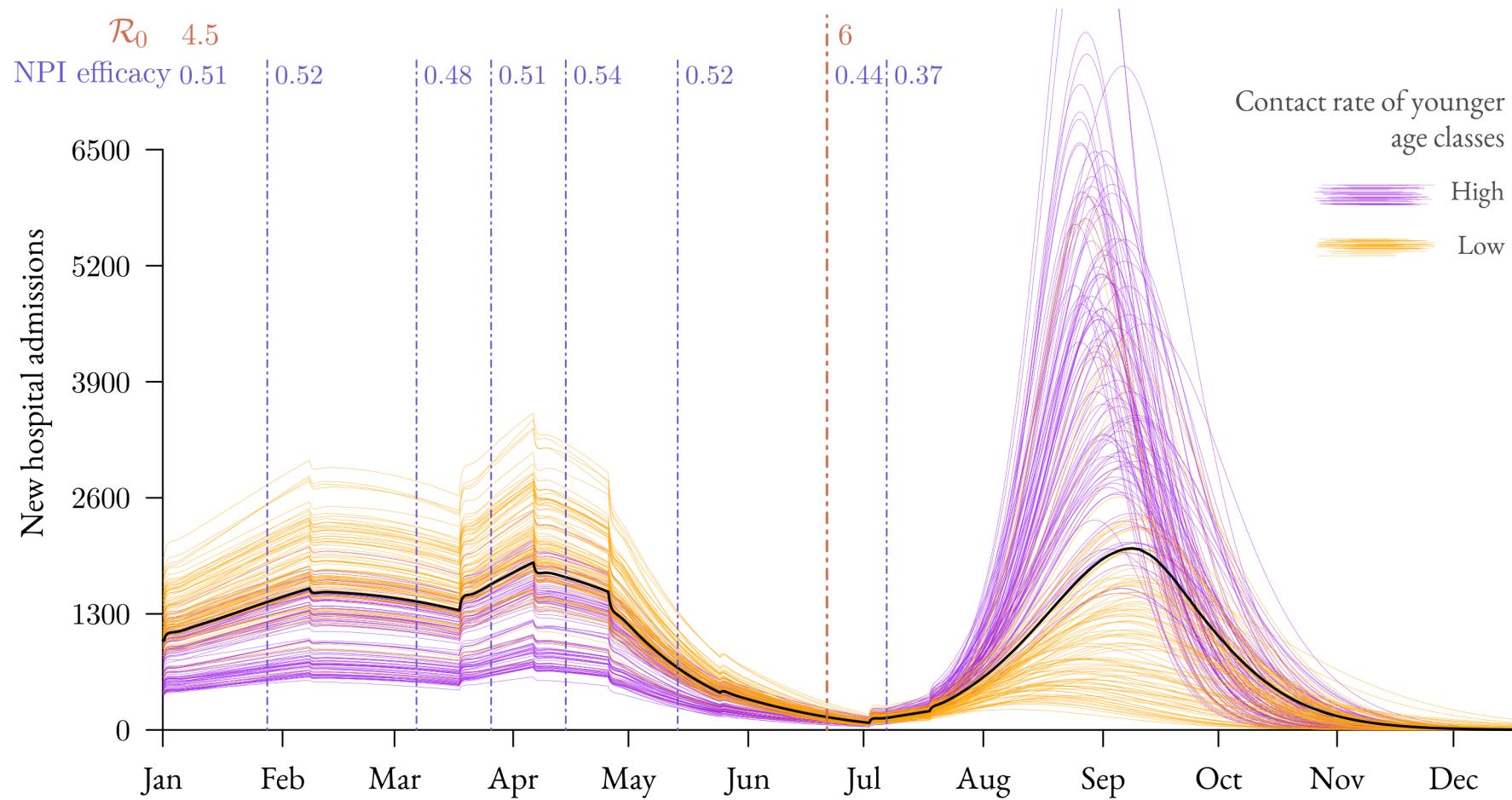
$$S_i = \frac{\mathbf{Var}(\mathbf{E}[Y | X_i])}{\mathbf{Var}(Y)}$$

Sensitivity analysis



Sensitivity analysis



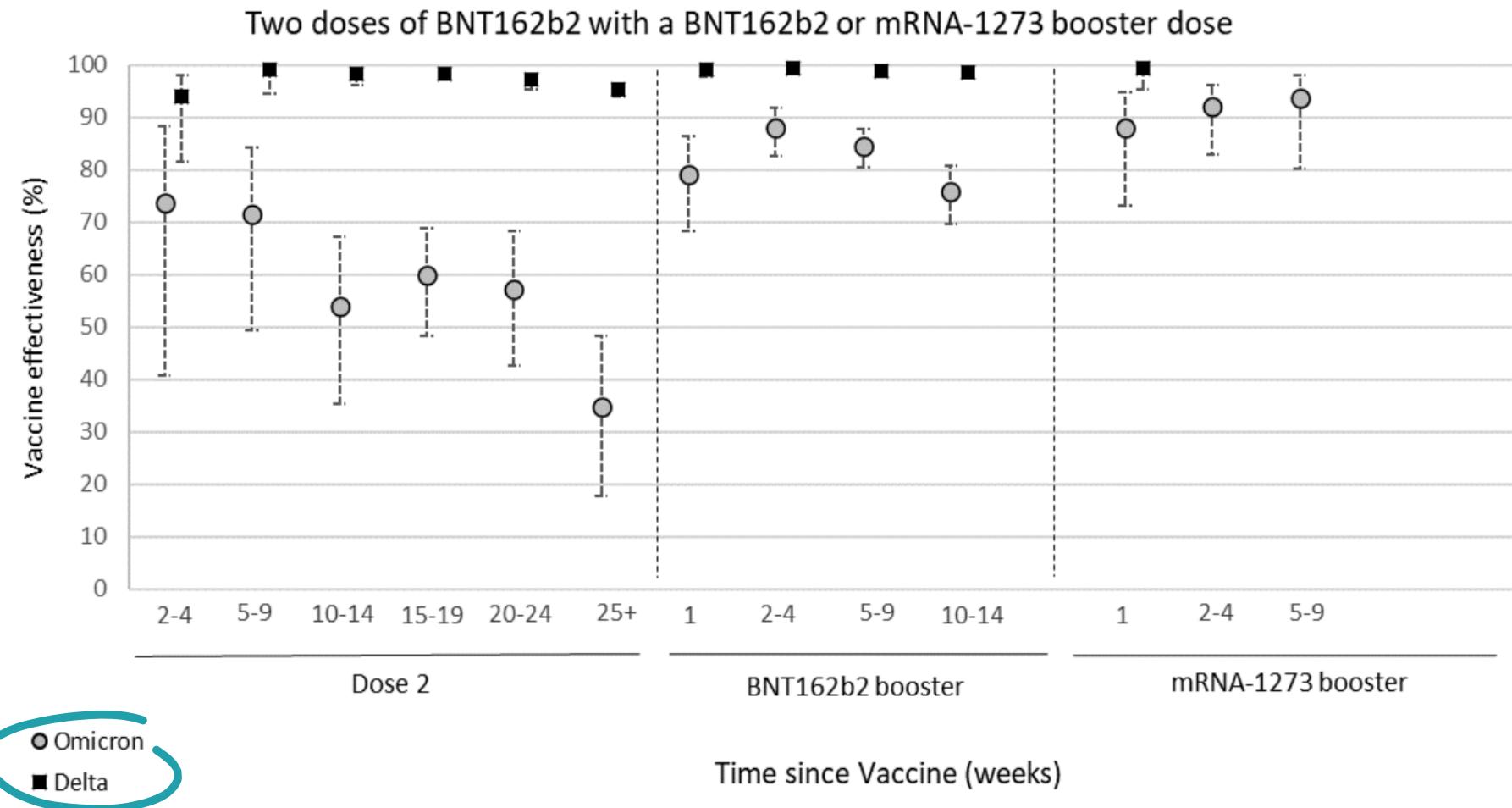


Discussion

- ▶ In our model, matrix did not change over time
- ▶ Contact matrixes brought a lot of variance in a model output
- ▶ Probably not a problem for small time scale
- ▶ Contact matrixes are not known

Long-term and immunity waning

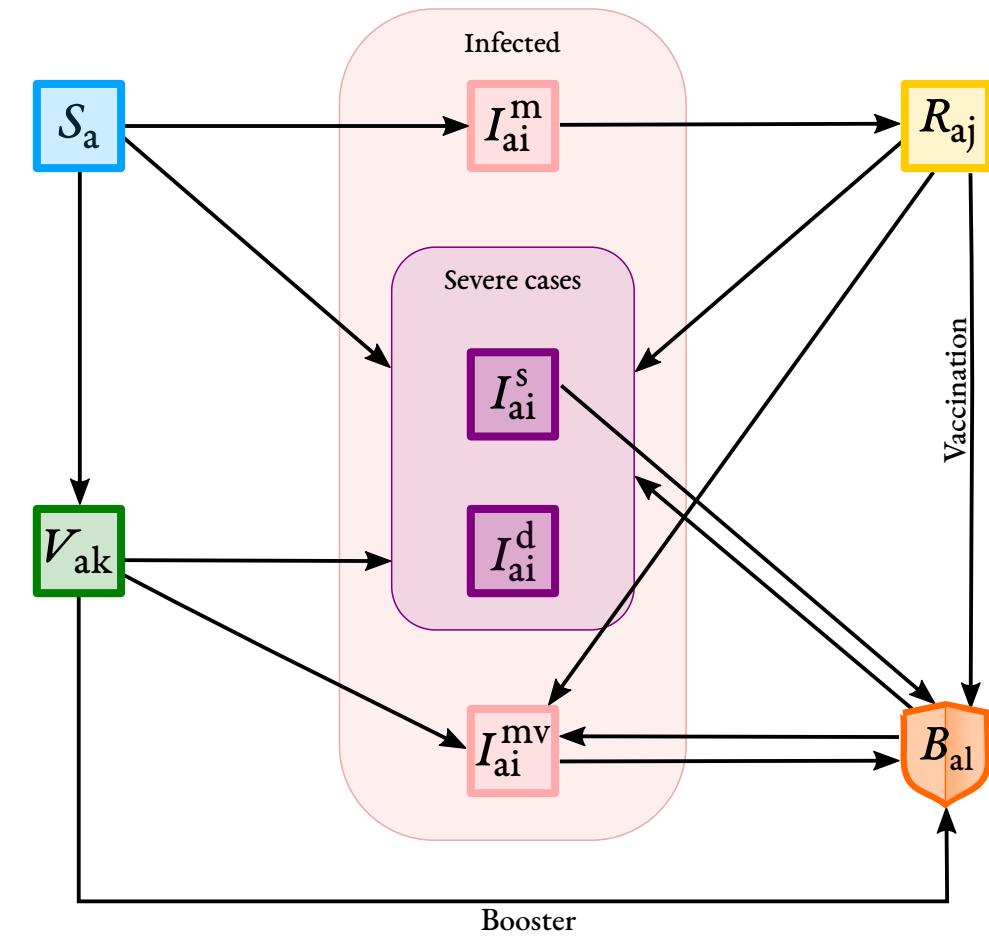
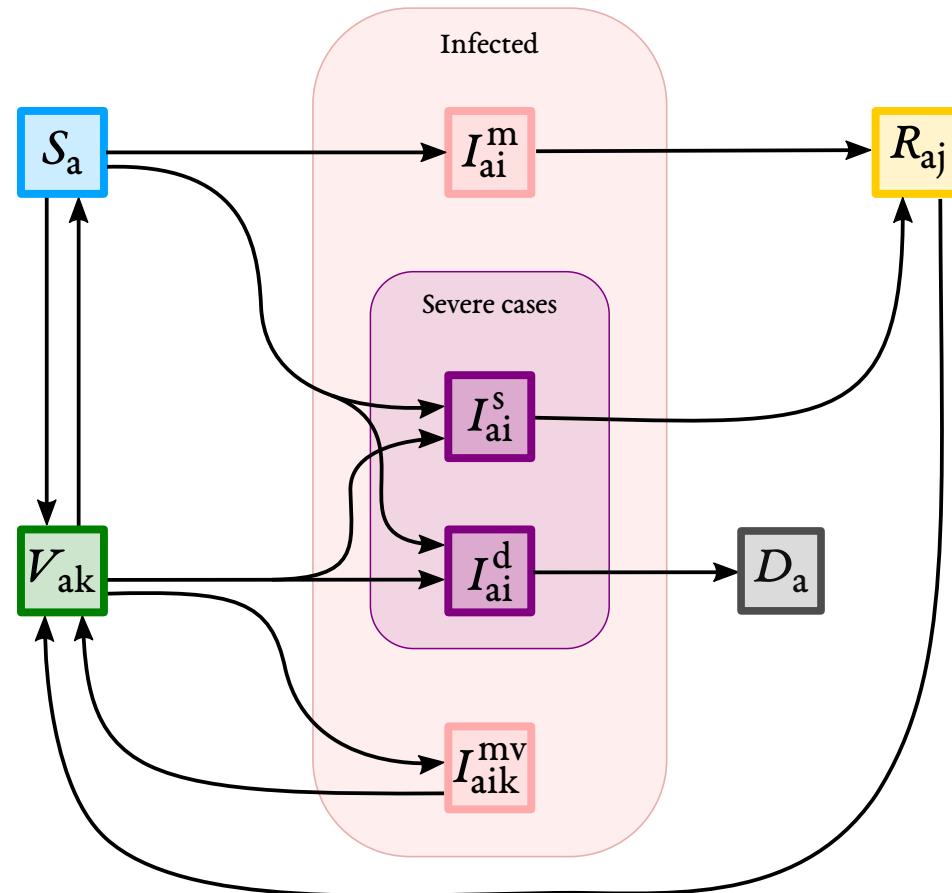
Vaccine efficacy over time



Infection
Hospitalisation

— UKHSA Vaccine surveillance reports, 2021 – 2022

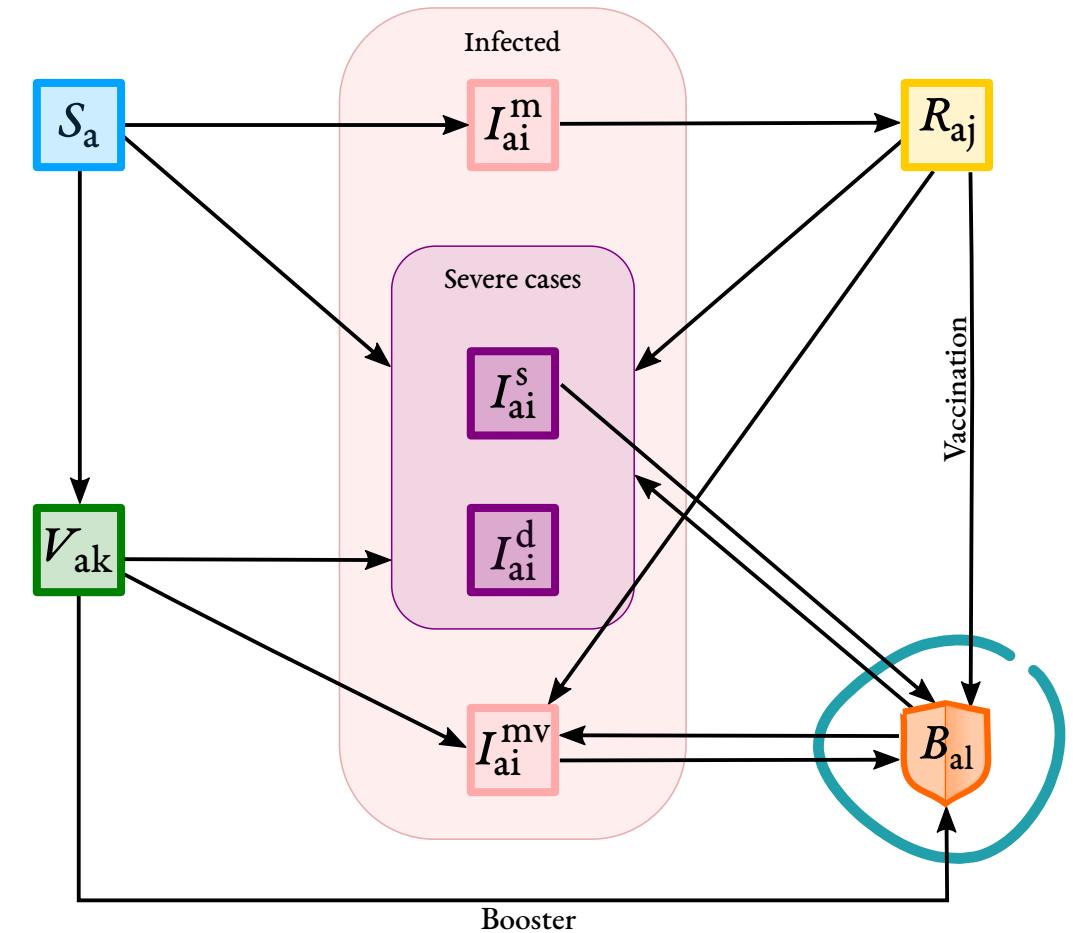
Model updated



Model updated

B_{al} boosted individuals
vaccination + infection
two infections

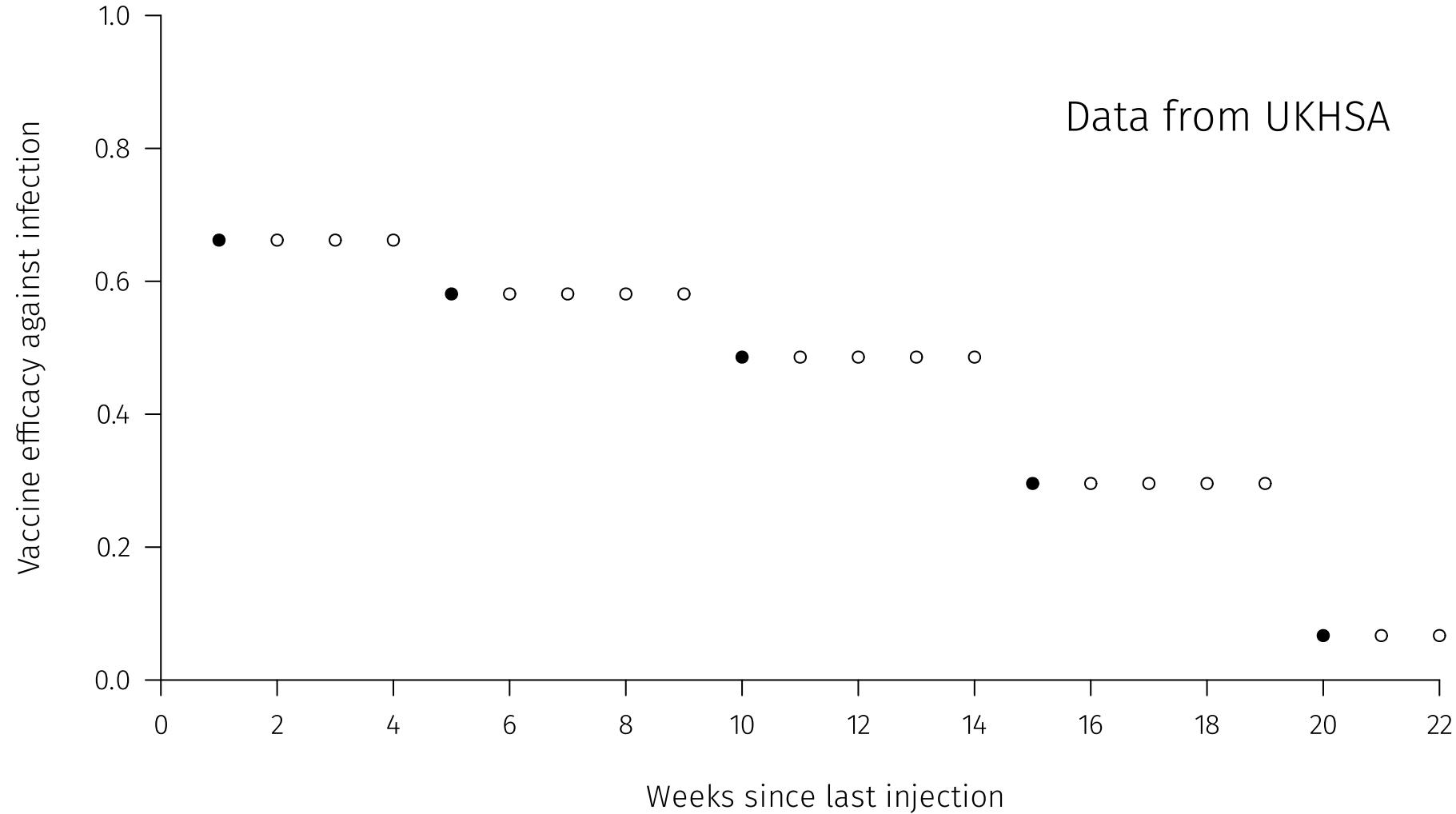
Immunity efficacy
Recovered \leftarrow Vaccine protection



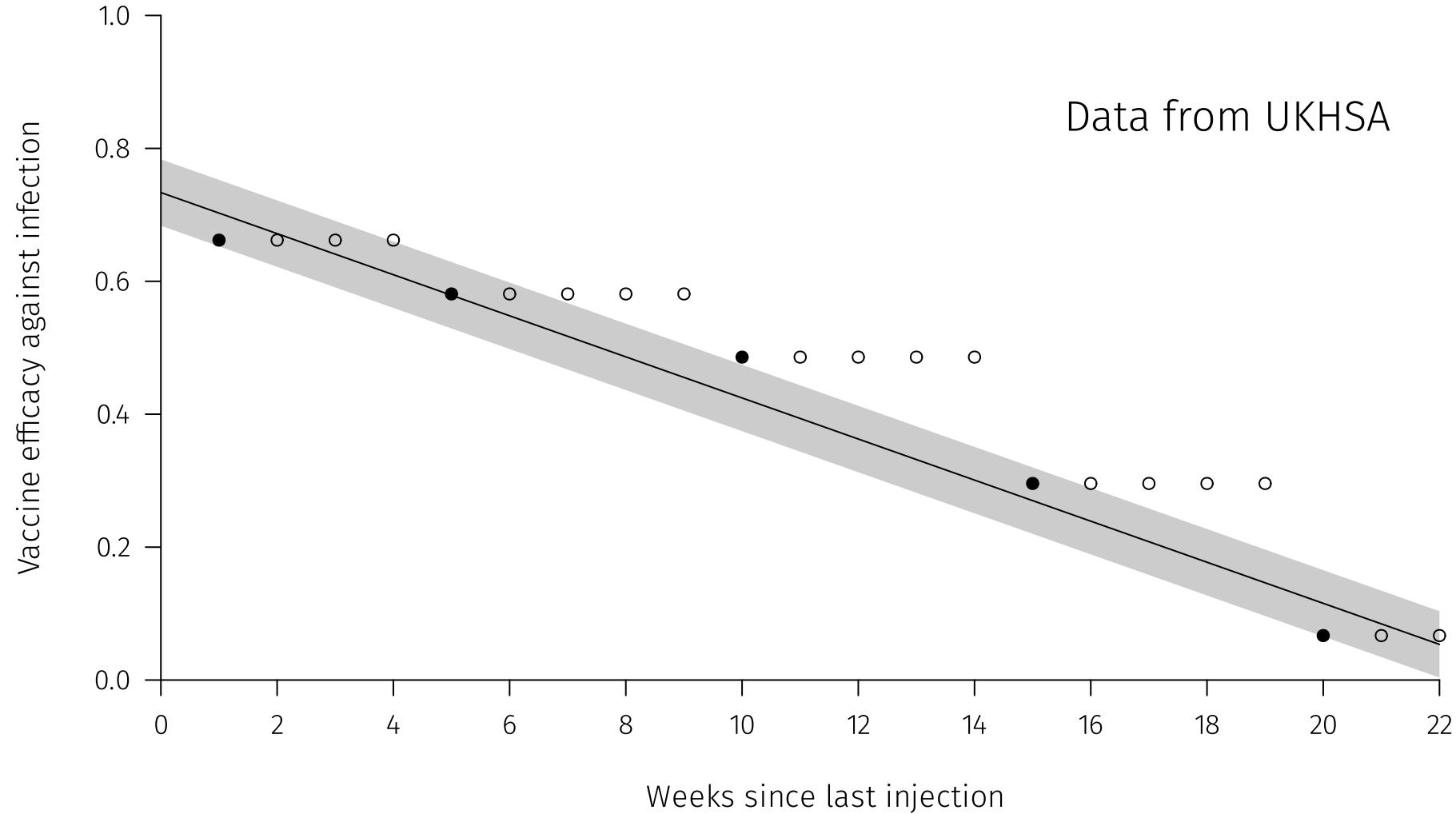
Parameters

- ▶ Omicron generation time — UKSHA report
- ▶ Contact rate seasonality — Ma *et alii*, 2020
- ▶ Reduction of transmission — Bosetti *et alii*, 2020
- ▶ Reduction of virulence compared to Delta — Nyberg *et alii*, 2020

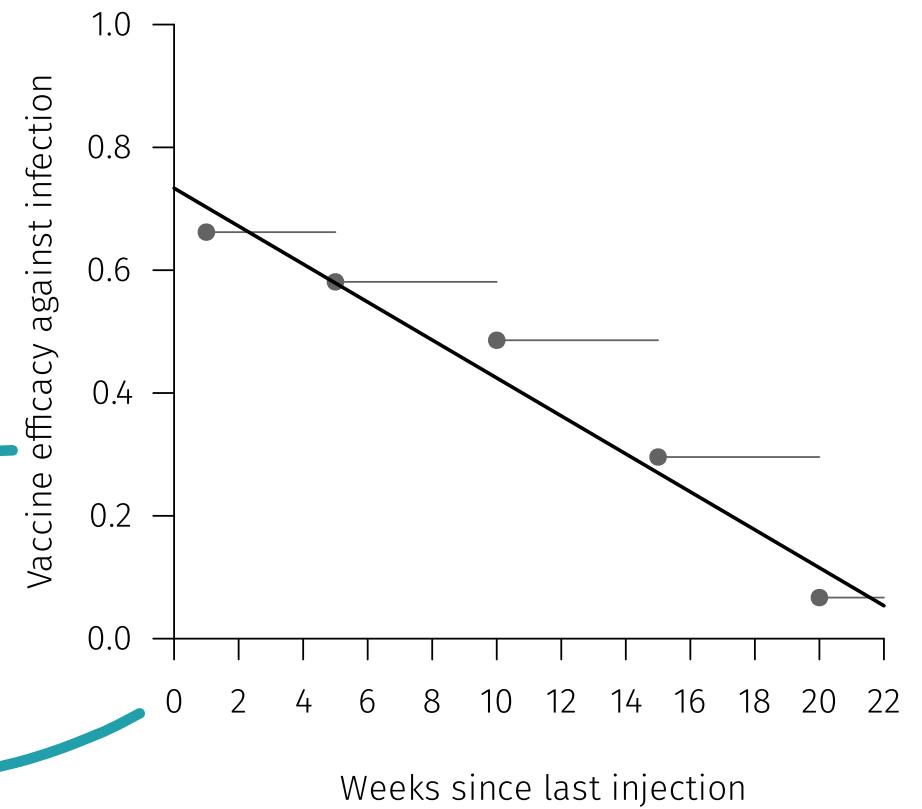
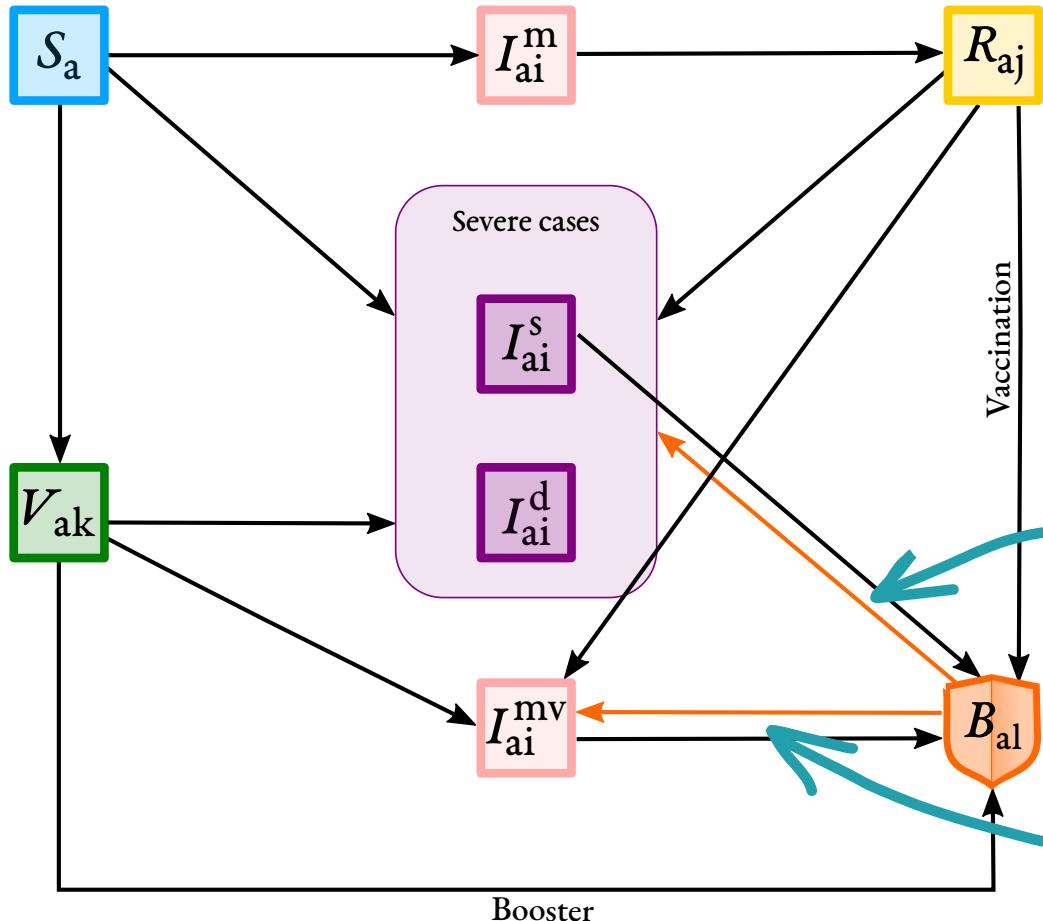
Immunity waning



Immunity waning



Immunity waning



Assumptions

- ▶ Everyone received a third dose 6 months after the second
- ▶ We added a seasonnality to the contact rate (higher in winter)
- ▶ The last contact rate fitted value is our baseline

Scenarios

Scenario A

No further vaccination campaign

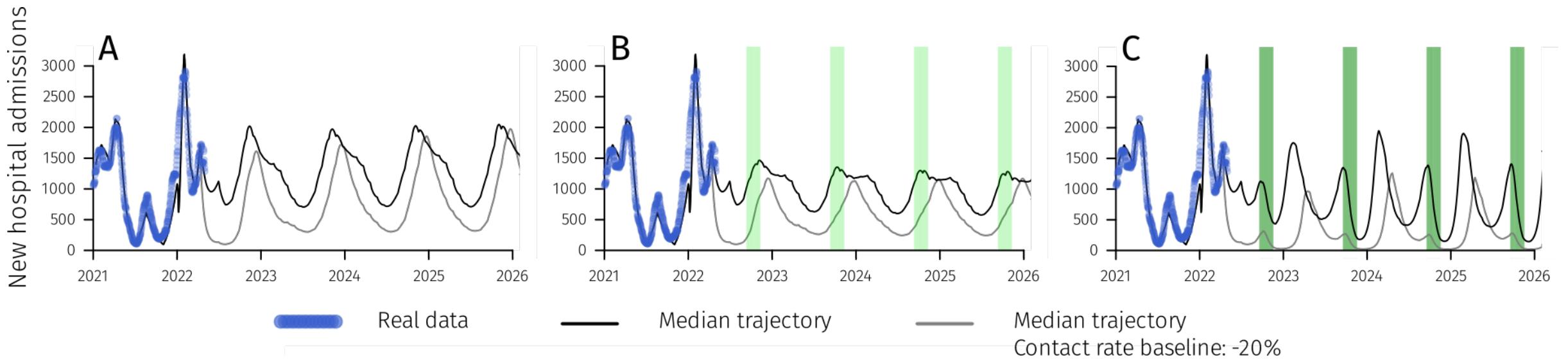
Scenario B

+60 y.o. are boosted once a year (sept. – oct.)

Scenario C

Everyone is boosted once a year (sept. – oct.)

Scenarios dynamics



Scenario A

No further vaccination campaign

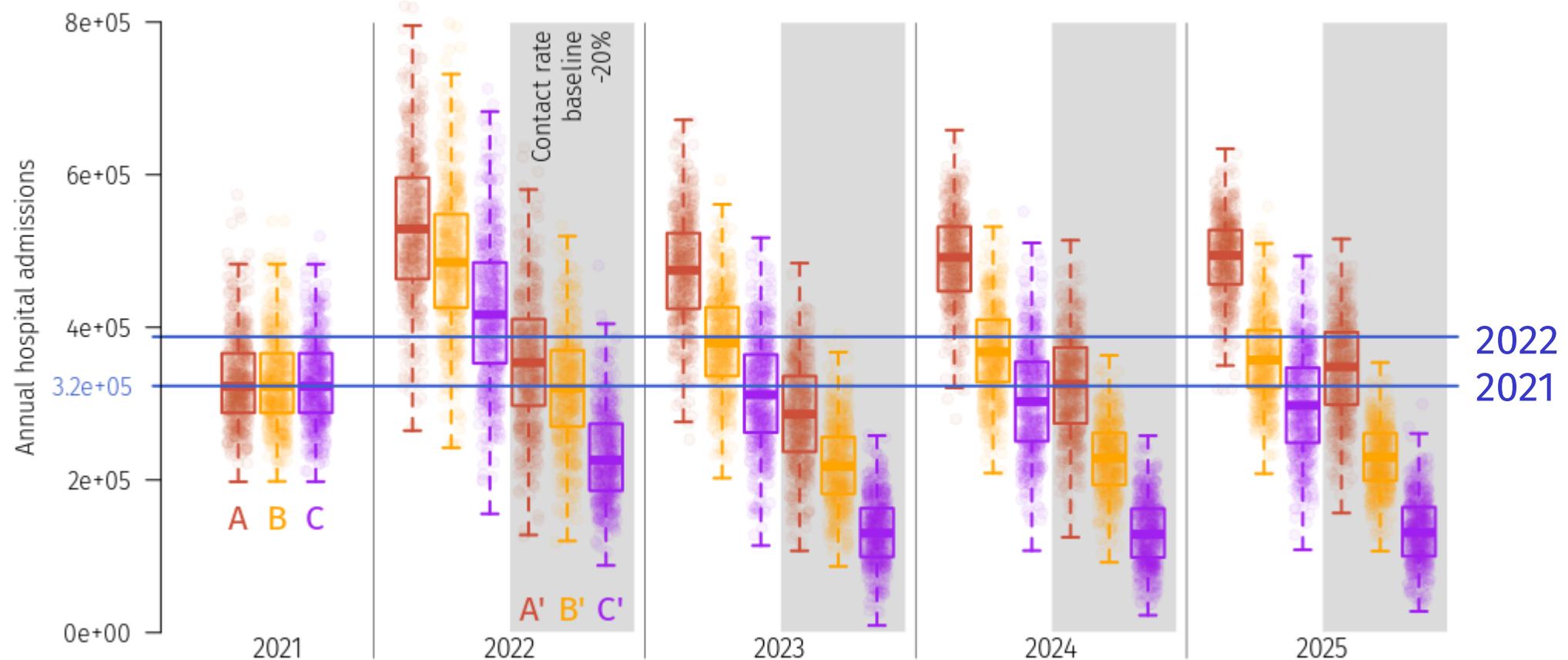
Scenario B

+60 y.o. are boosted once a year (sept. – oct.)

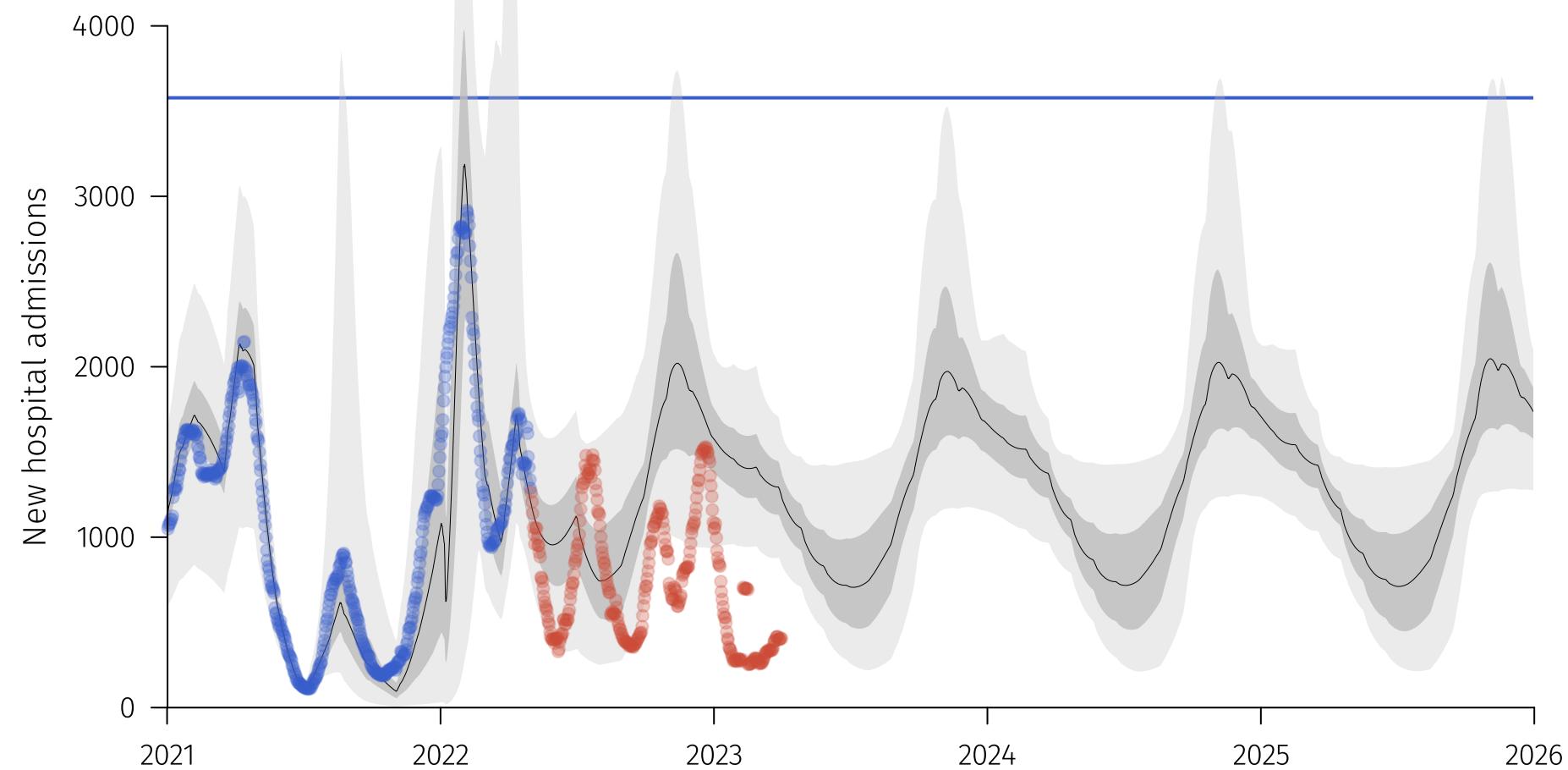
Scenario C

Everyone is boosted once a year (sept. – oct.)

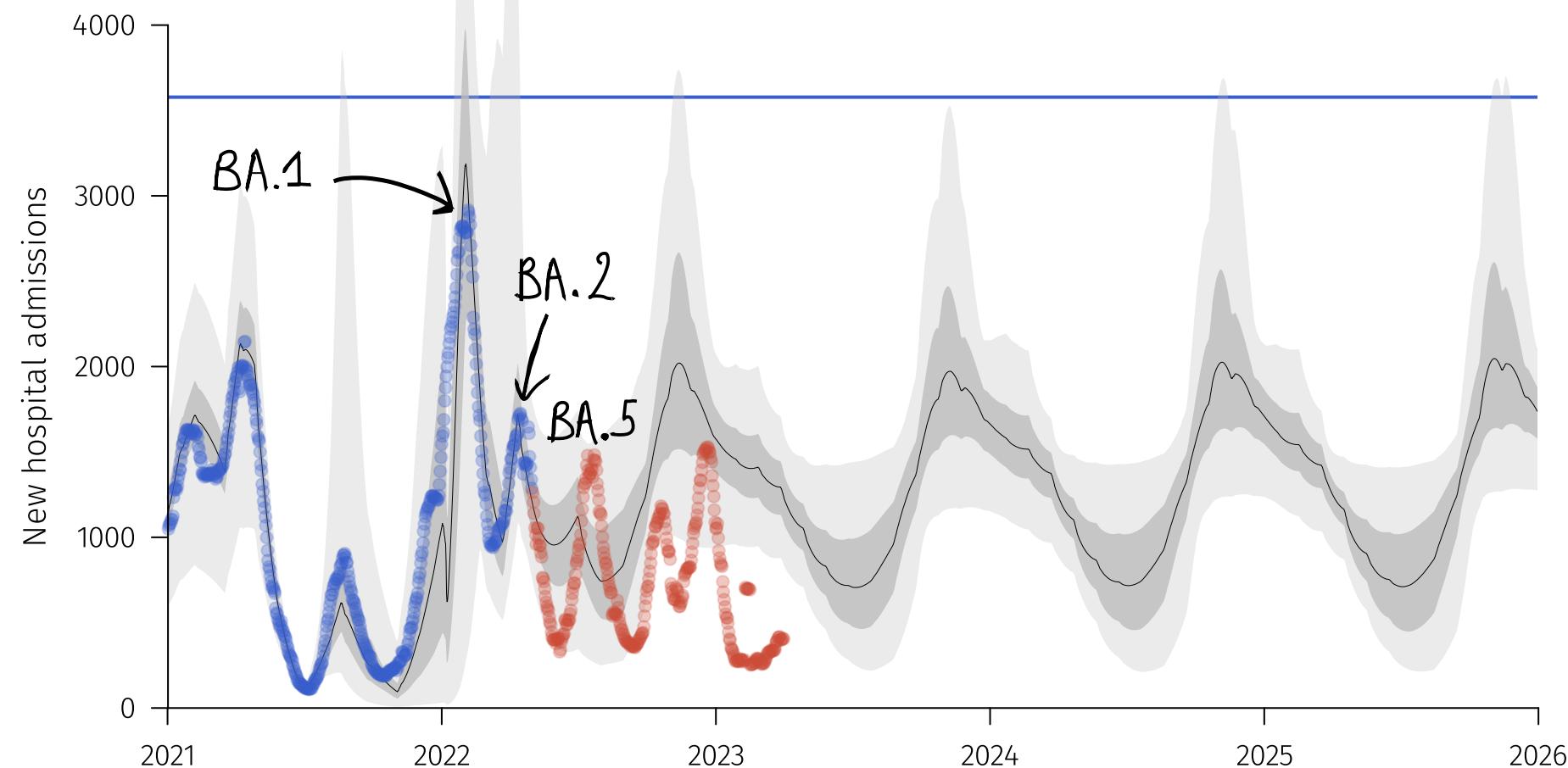
Annual hospital admissions comparisons



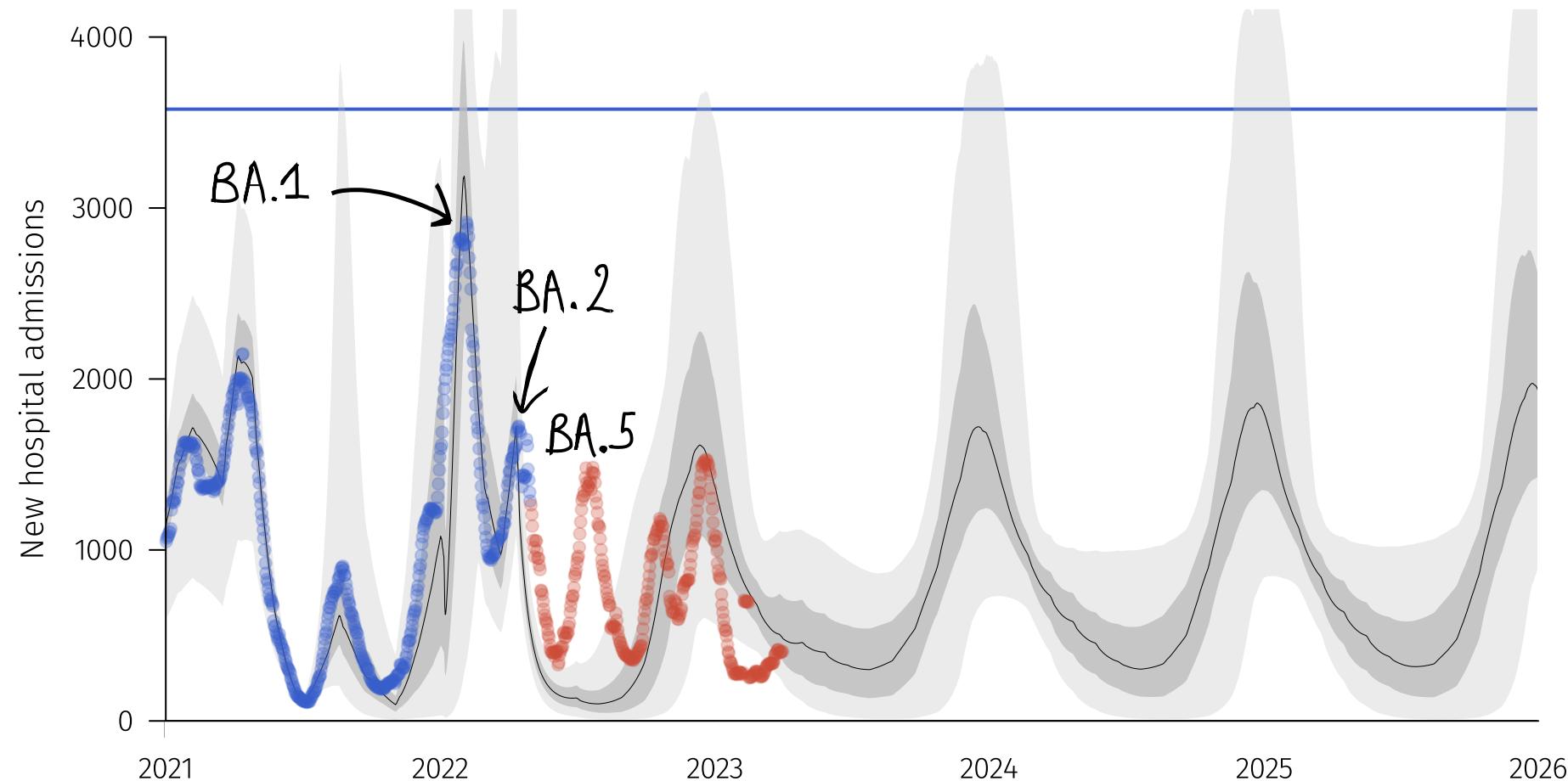
No further vaccination scenario & new data



No further vaccination scenario & new data



No further vaccination scenario & -20% contact rate & new data



Discussion

- ▶ Highly uncertain
- ▶ Any scenario where the epidemics ends
- ▶ Useful to compare scenarios with each other
- ▶ Neglects virus evolution

COVID-19 invasion analysis

(work in progress)

Motivation

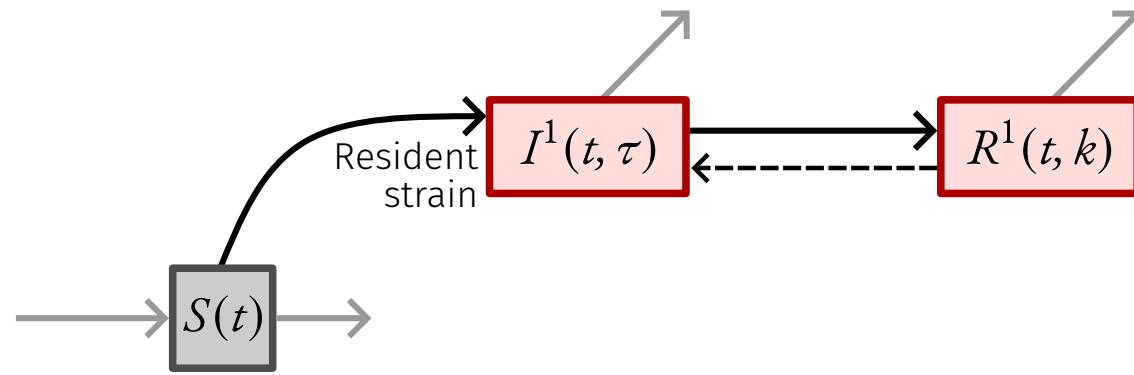
- ▶ Determine which phenotypic trait allows a mutant to invade
- ▶ Include some parameters including the \mathcal{R}_0 , the generation time, immune escape and immunity waning

Motivation

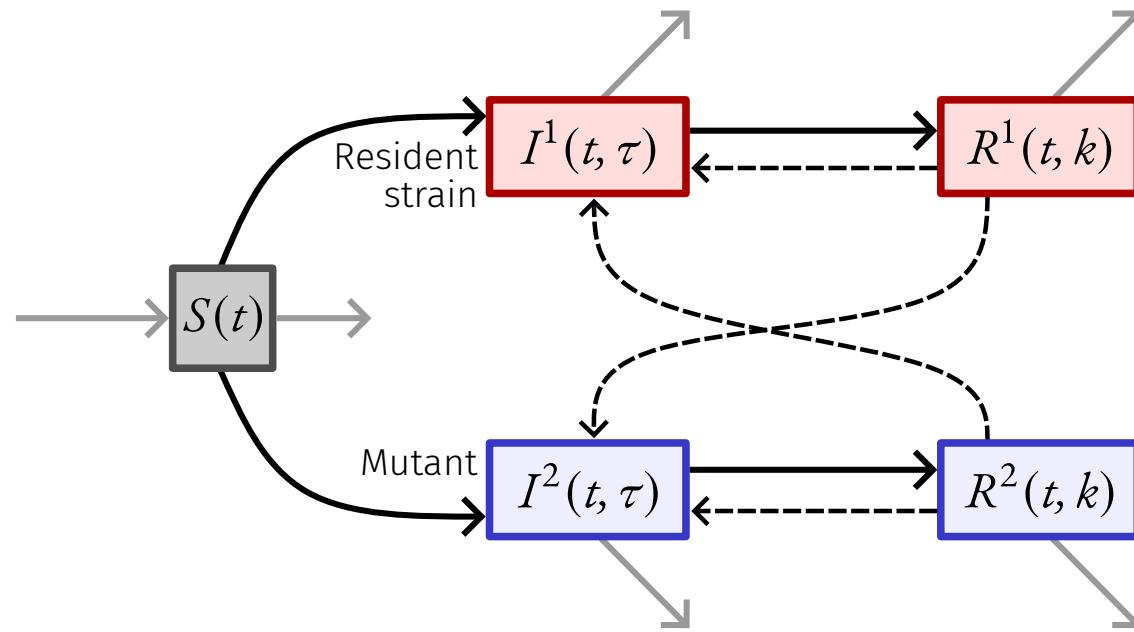
- ▶ Determine which phenotypic trait allows a mutant to invade
- ▶ Include some parameters including the \mathcal{R}_0 , the generation time, immune escape and immunity waning

Invasion is defined as the ability for a mutant to reach a non-null endemic equilibrium

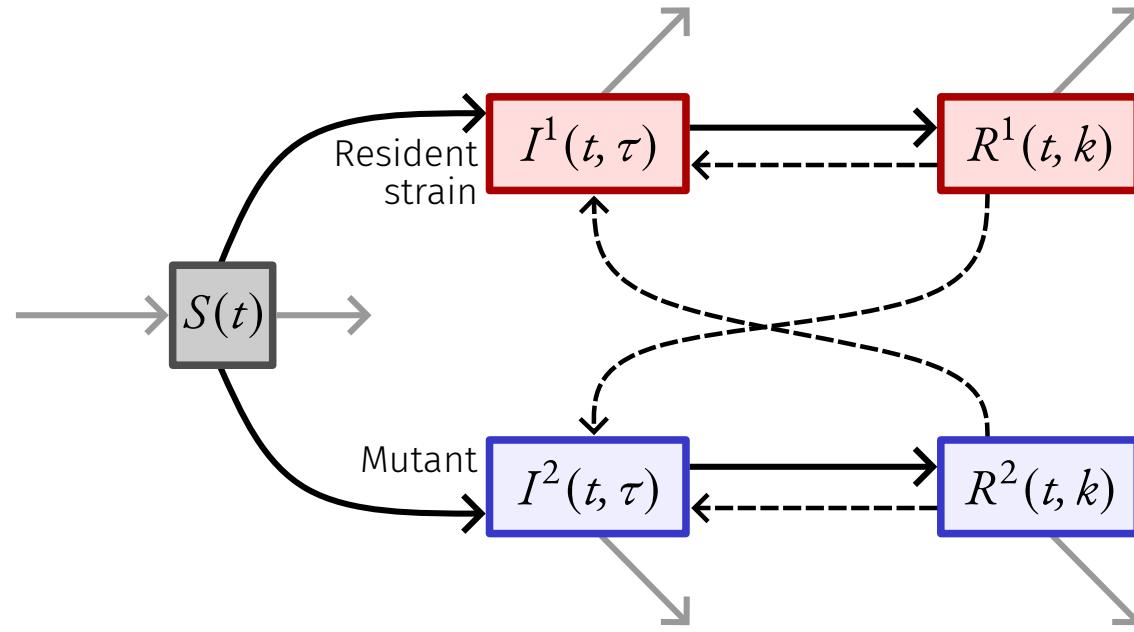
Model



Model



Model



SARS-CoV-2 specific

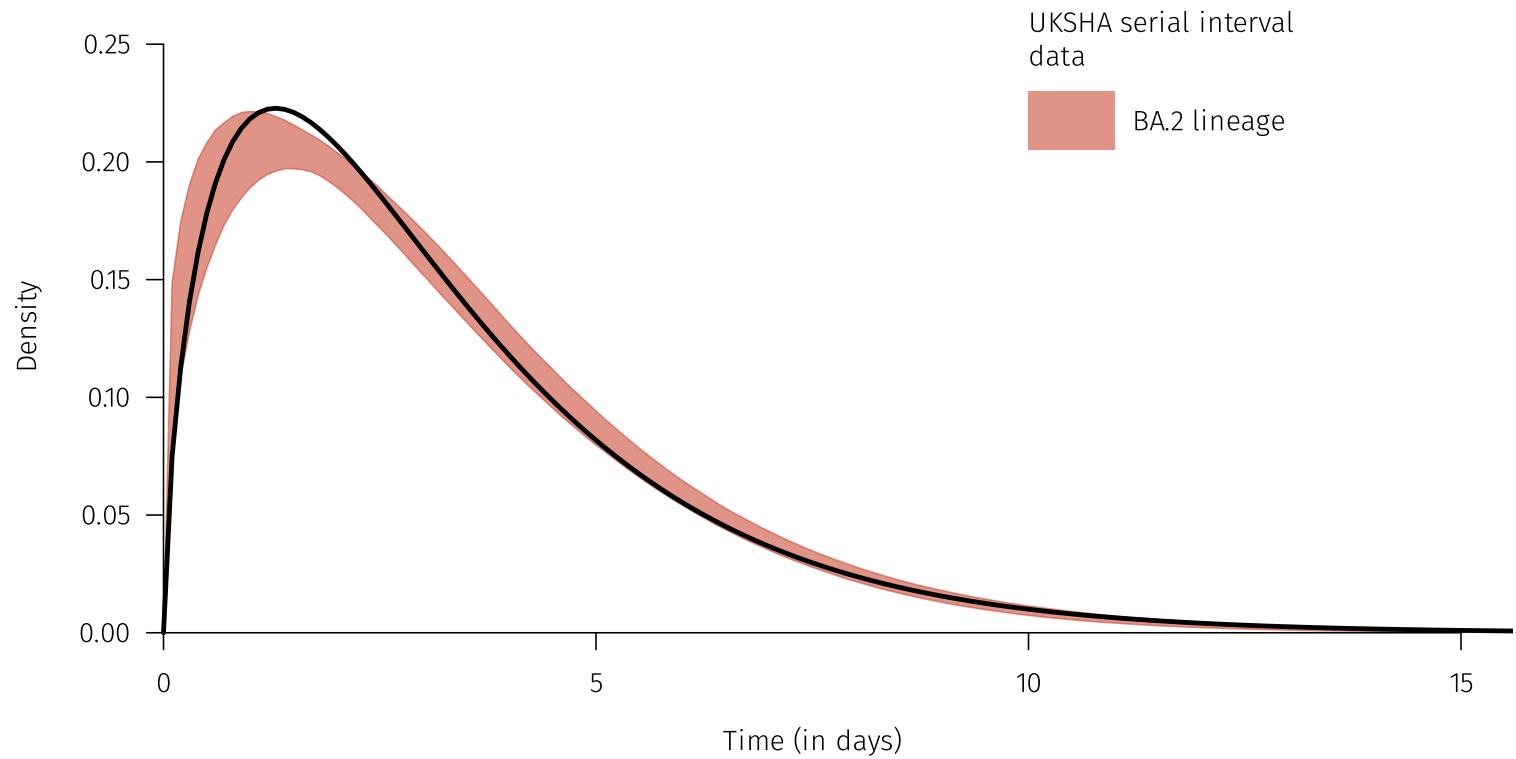
- Resident strain = Omicron BA.2

Resident strain parametrization

$$\mathcal{R}_0 = 8$$

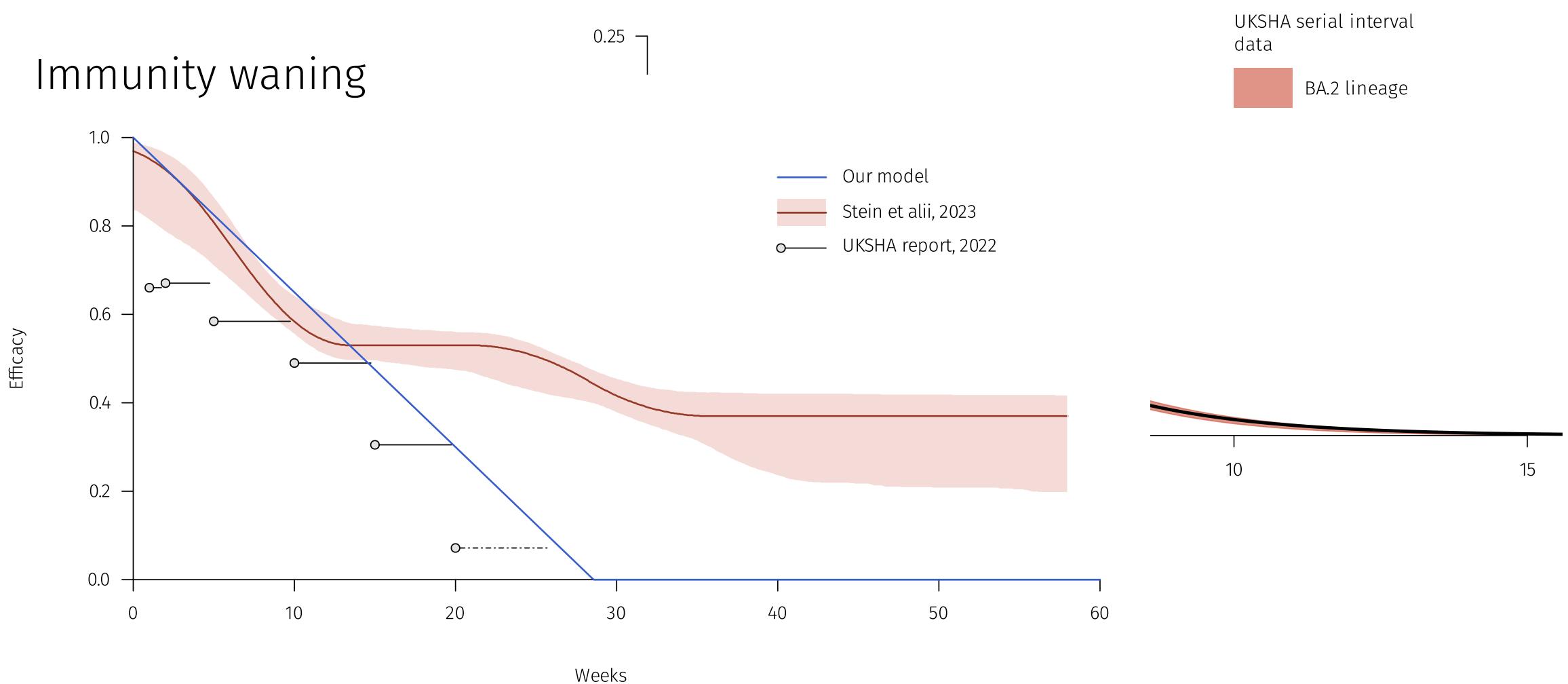
Resident strain parametrization

$$\mathcal{R}_0 = 8$$



Generation time

Resident strain parametrization



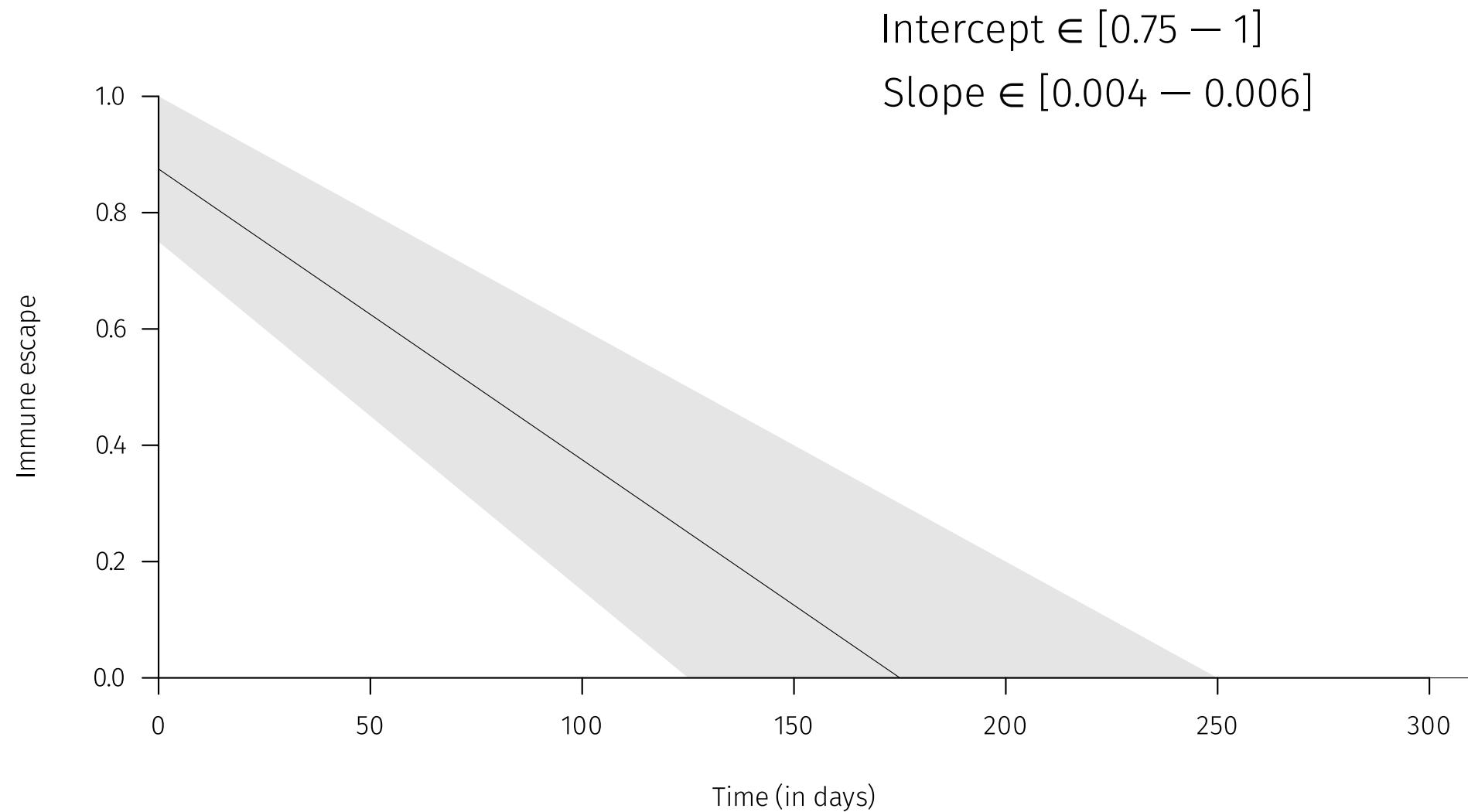
Mutant strain parametrization

$$\mathcal{R}_0 \in [3-10]$$

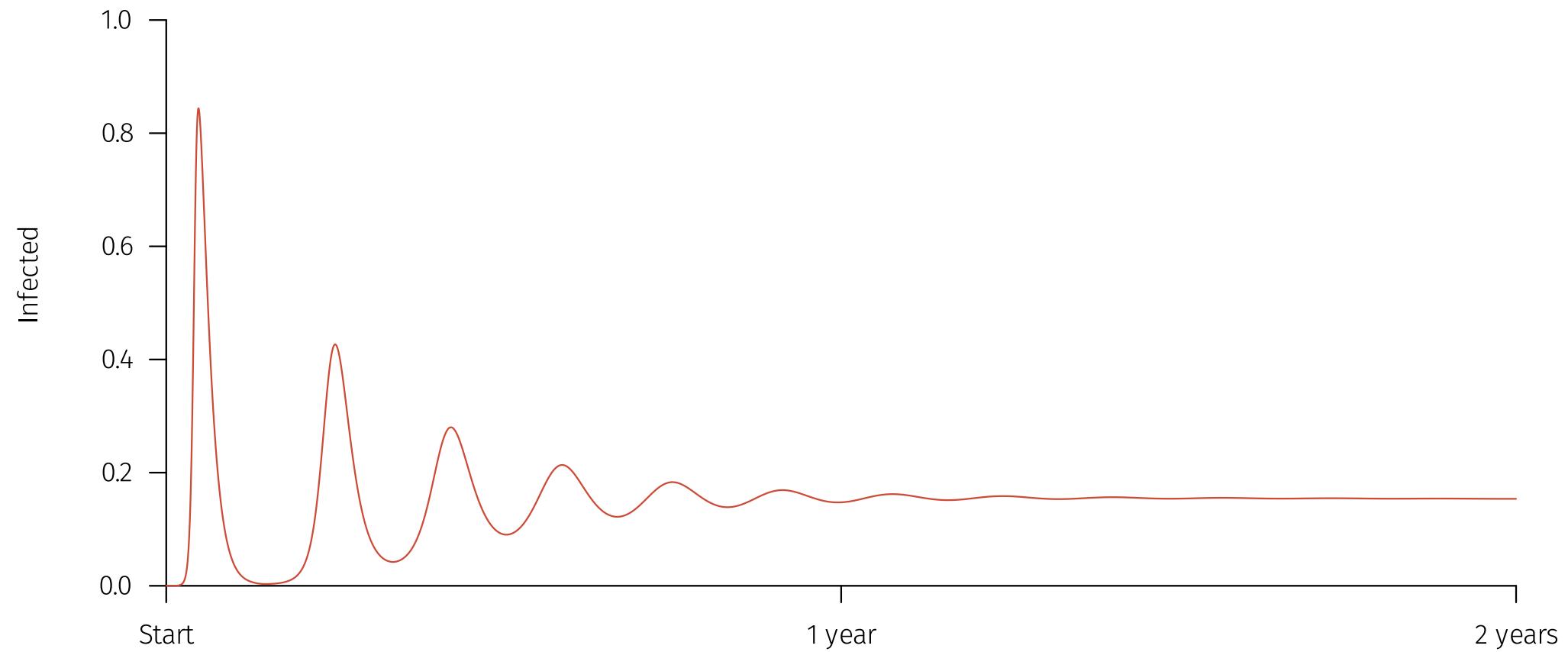
Generation time Shape = +/- 50%
Scale = +/- 50%

Immunity waning slope : +/- 20%

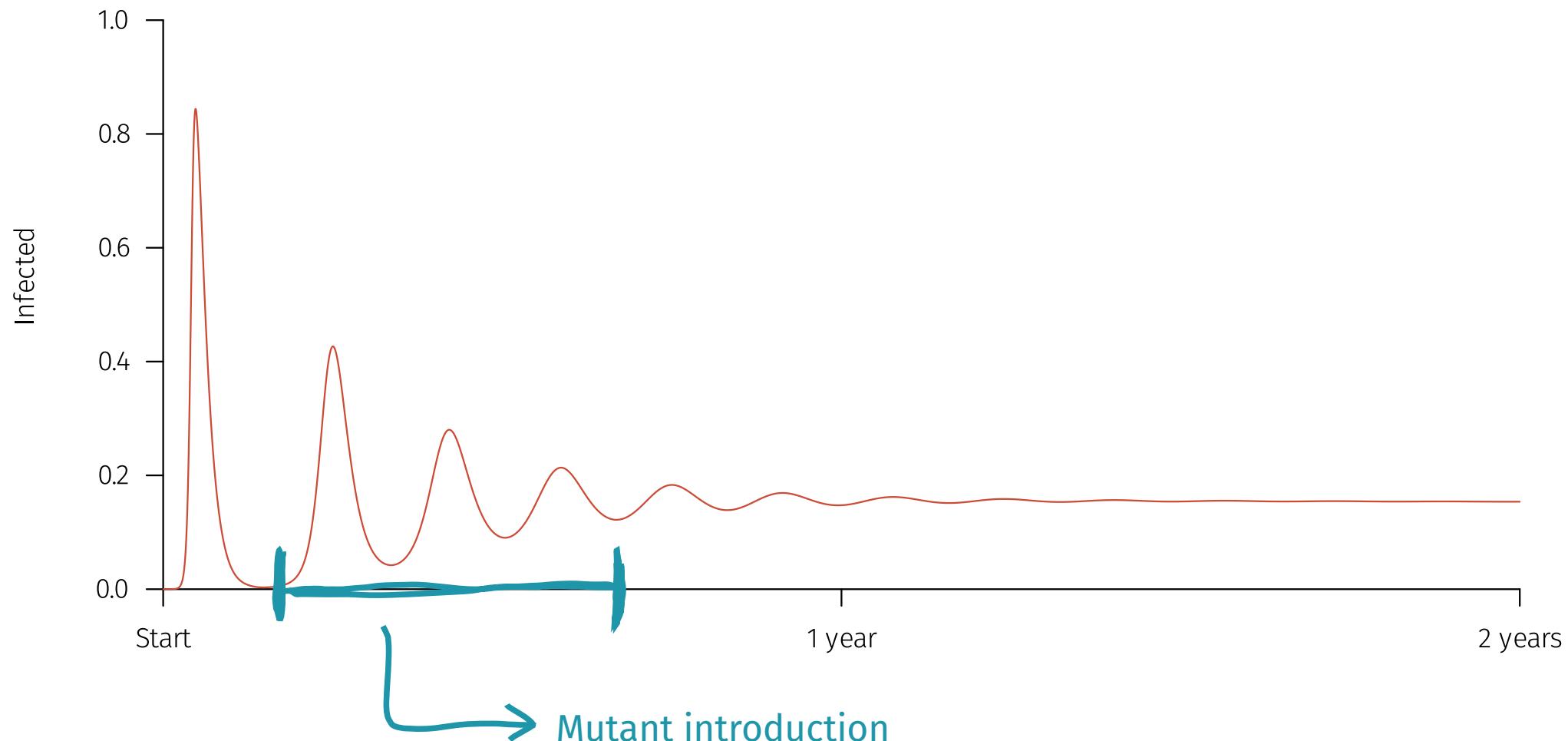
Immune escape



Resident strain dynamics



Resident strain dynamics

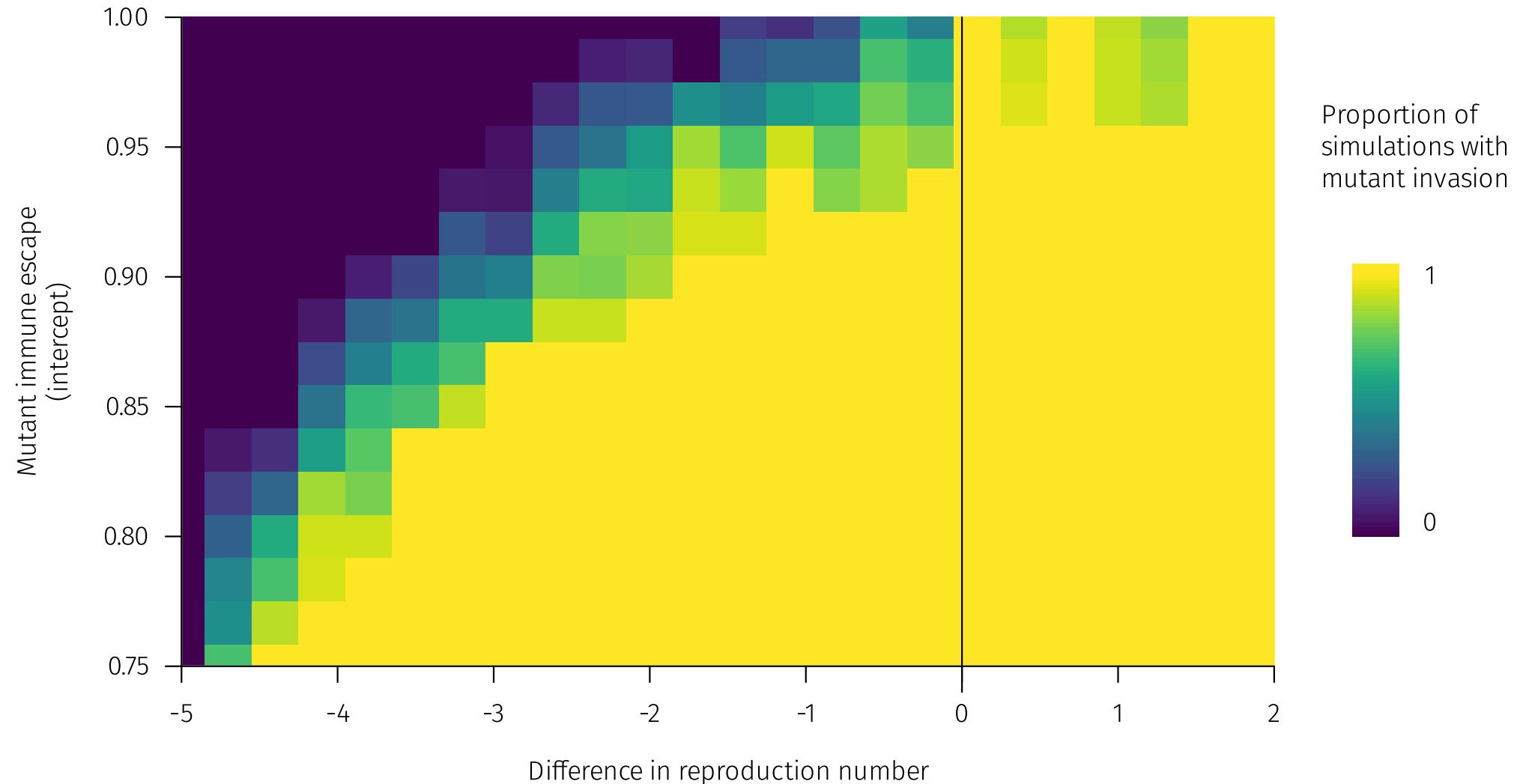


Latin hypercube sampling

	Mutant \mathcal{R}_0
	Invasion date
Generation time	Scale
	Shape
Immunity waning	Slope
Immune escape	Intercept
	Slope

1000 runs

Results



Results

- ▶ Interaction between **immune escape** and \mathcal{R}_0
- ▶ Low impact of the others parameters
- ▶ Similar results when both strains are introduced at $t = 0$
- ▶ Immunity waning had very low impact
- ▶ A higher growth rate did not matter
- ▶ A fixed point is not always reached (limit cycle)

Fitness

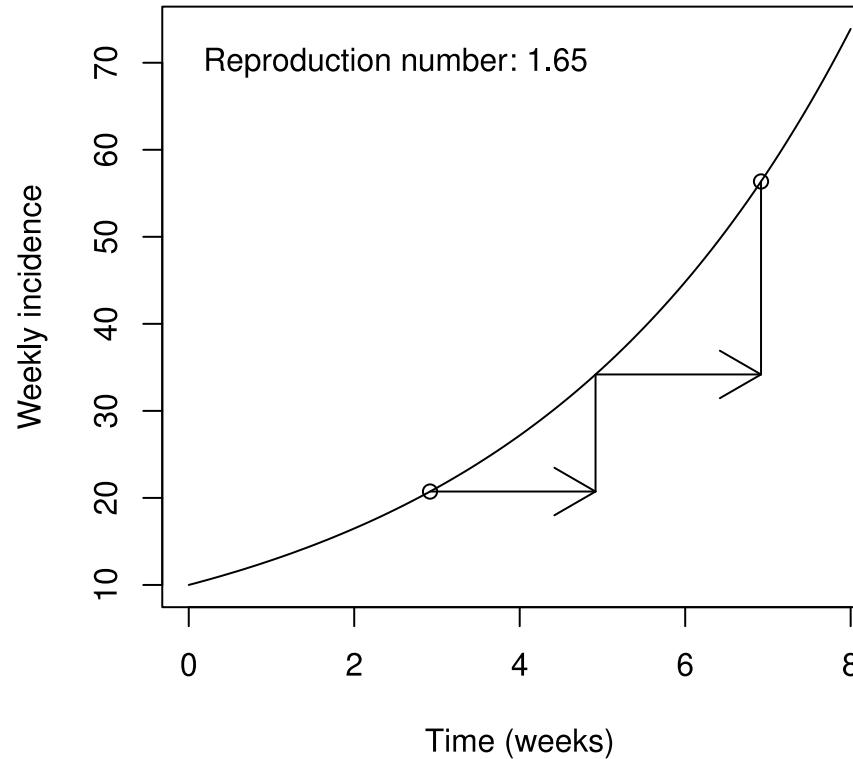
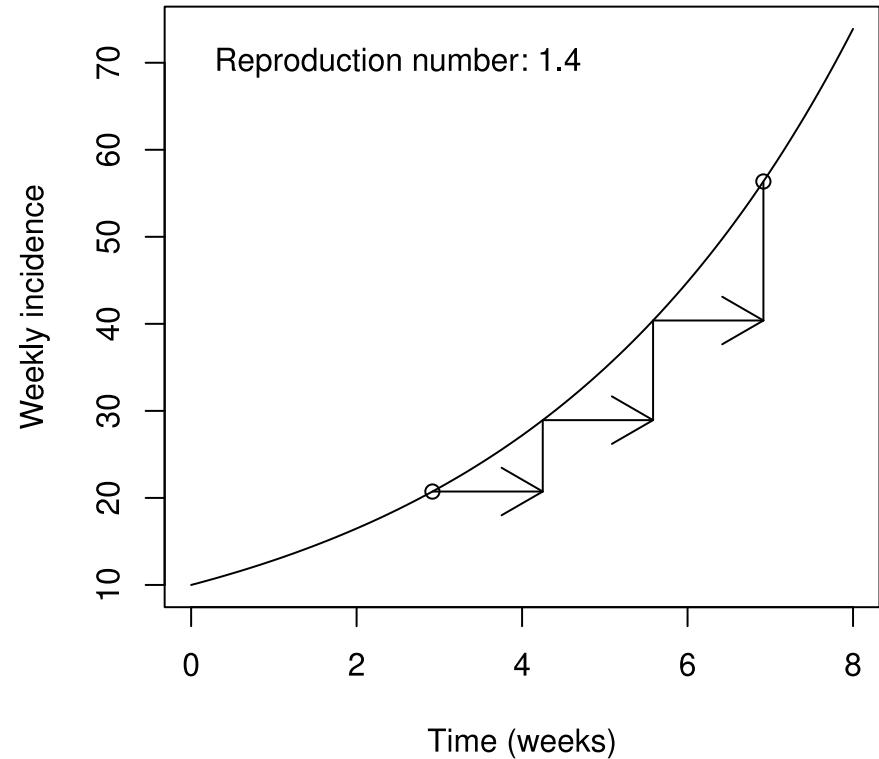
When competing strains provide complete protection for each other, the strain with the largest \mathcal{R}_0 will force the other strain to extinction. [...] Although \mathcal{R}_0 determines the eventual competitive outcome, pathogens with a more rapid life cycle may be favored in the short term.

— Keeling & Rohani, 2008

The evolutionary fate of an emerging variant is ultimately determined by its exponential growth rate relative to that of the circulating strains.

— Blanquart et alii, 2022

Link between \mathcal{R}_0 and the growth rate



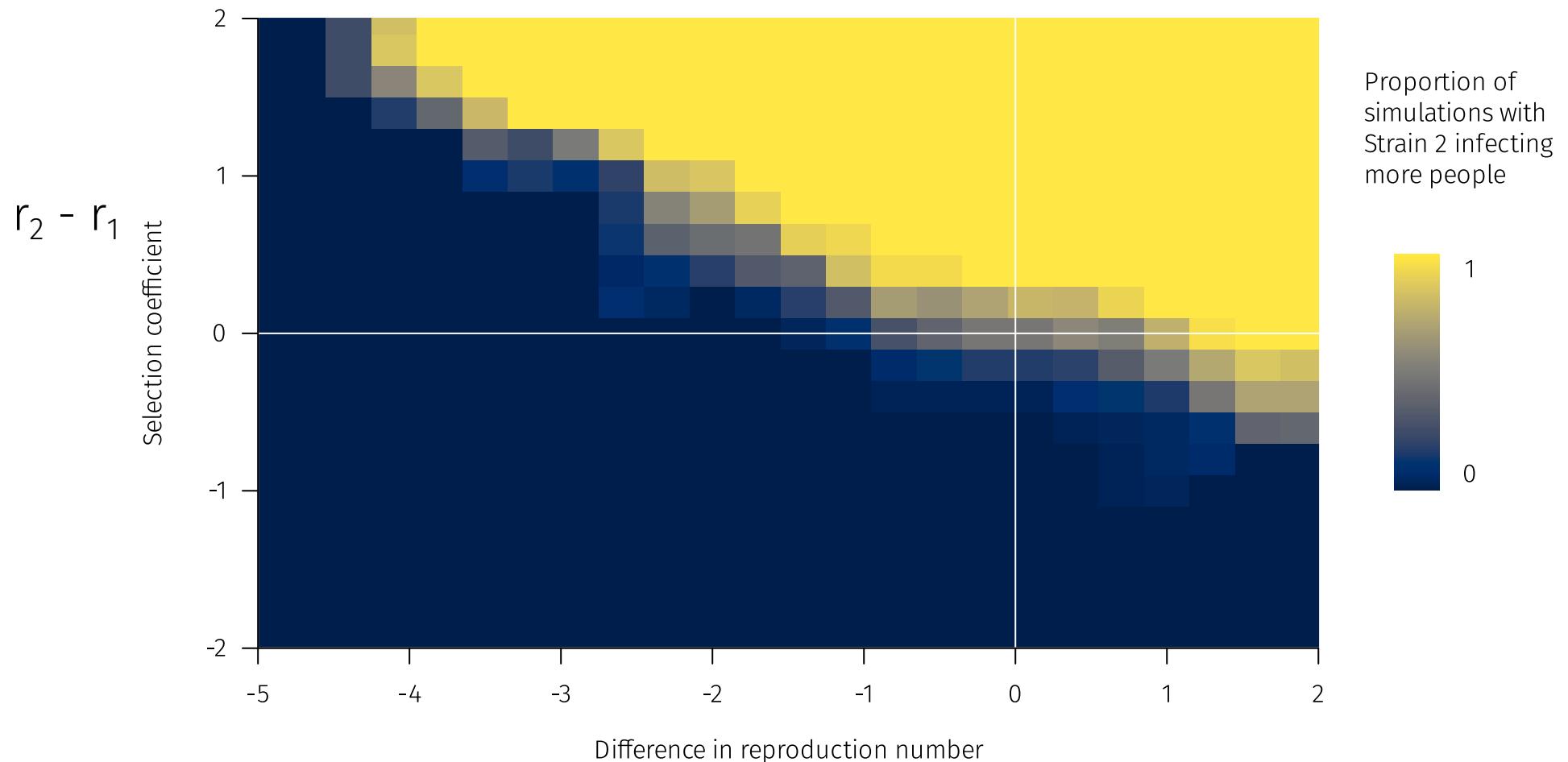
— Park et alii, 2019

Competing strains providing perfect cross-immunity

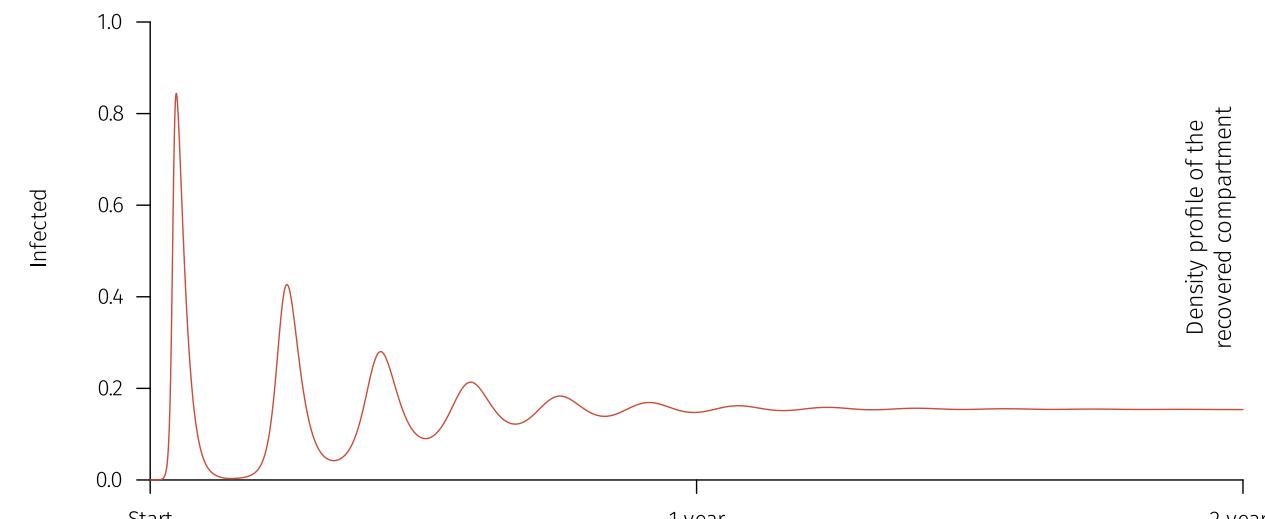
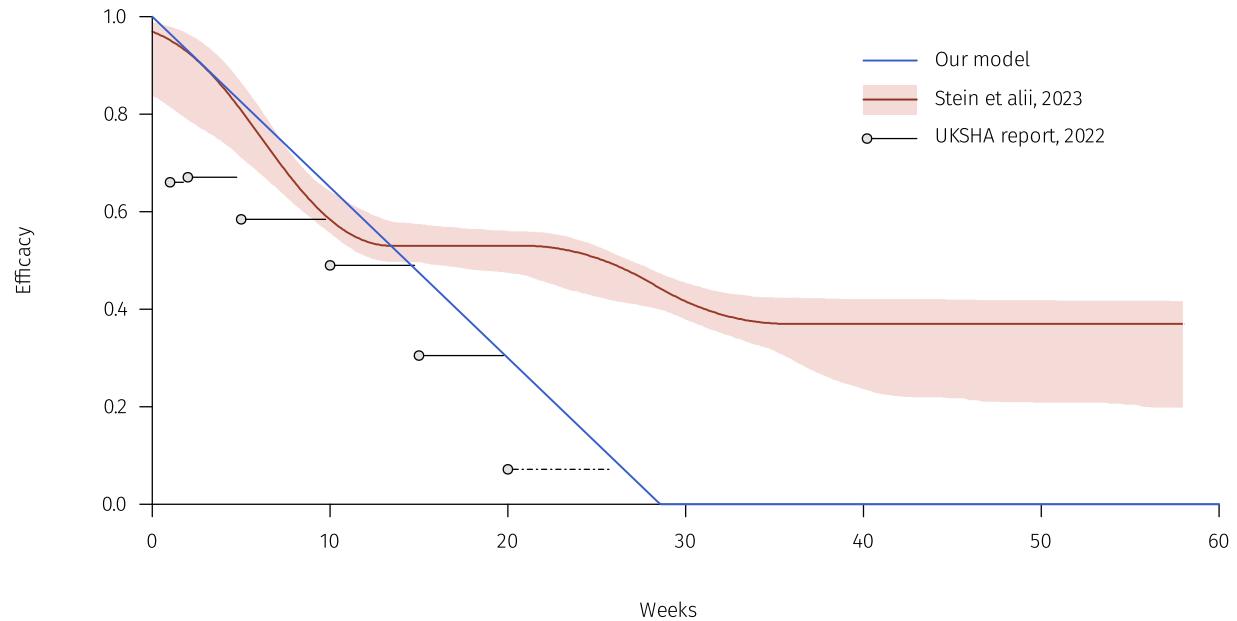
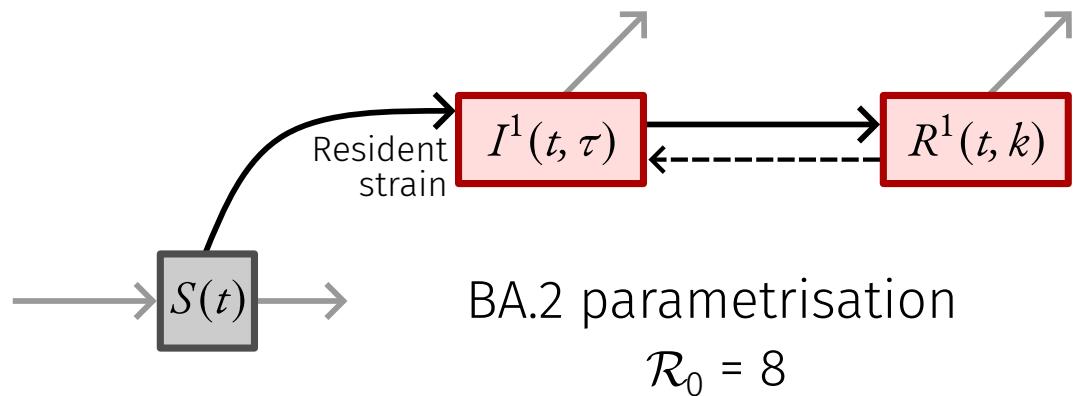
- ▶ Both strains are introduced at $t = 0$
- ▶ Winning strain is the one that infects most people

Competing strains providing perfect cross-immunity

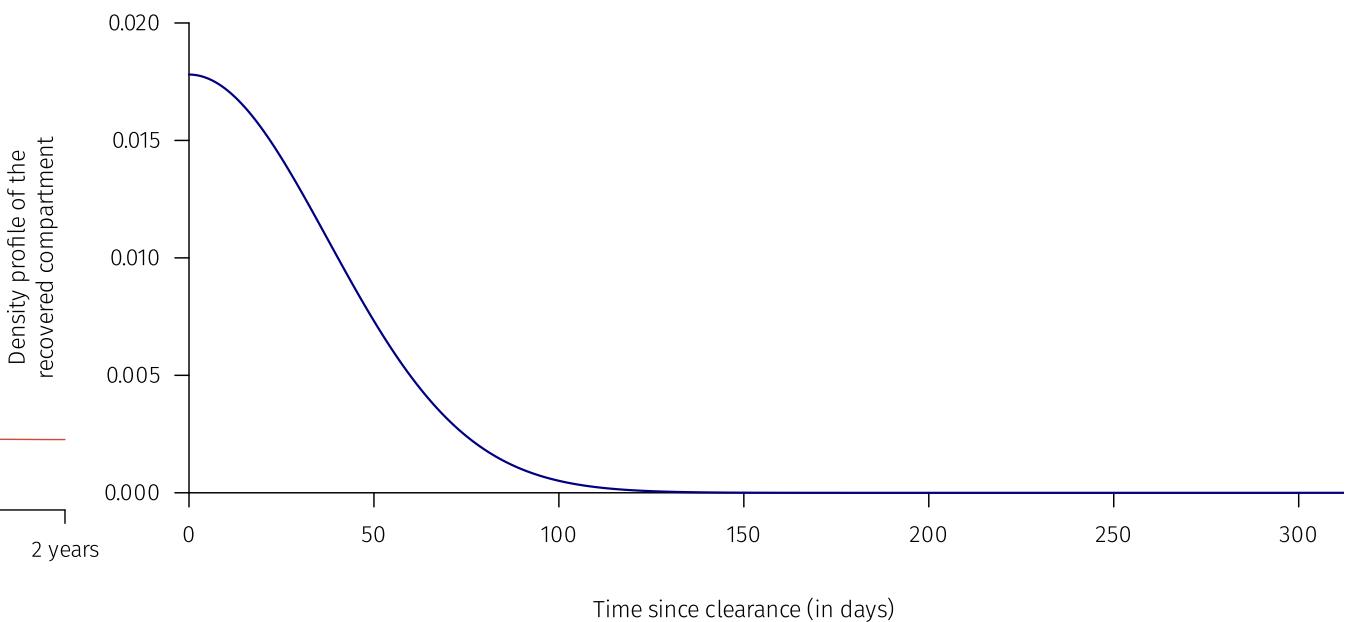
- Both strains are introduced at $t = 0$
- Winning strain is the one that infects most people



SARS-CoV-2 considerations

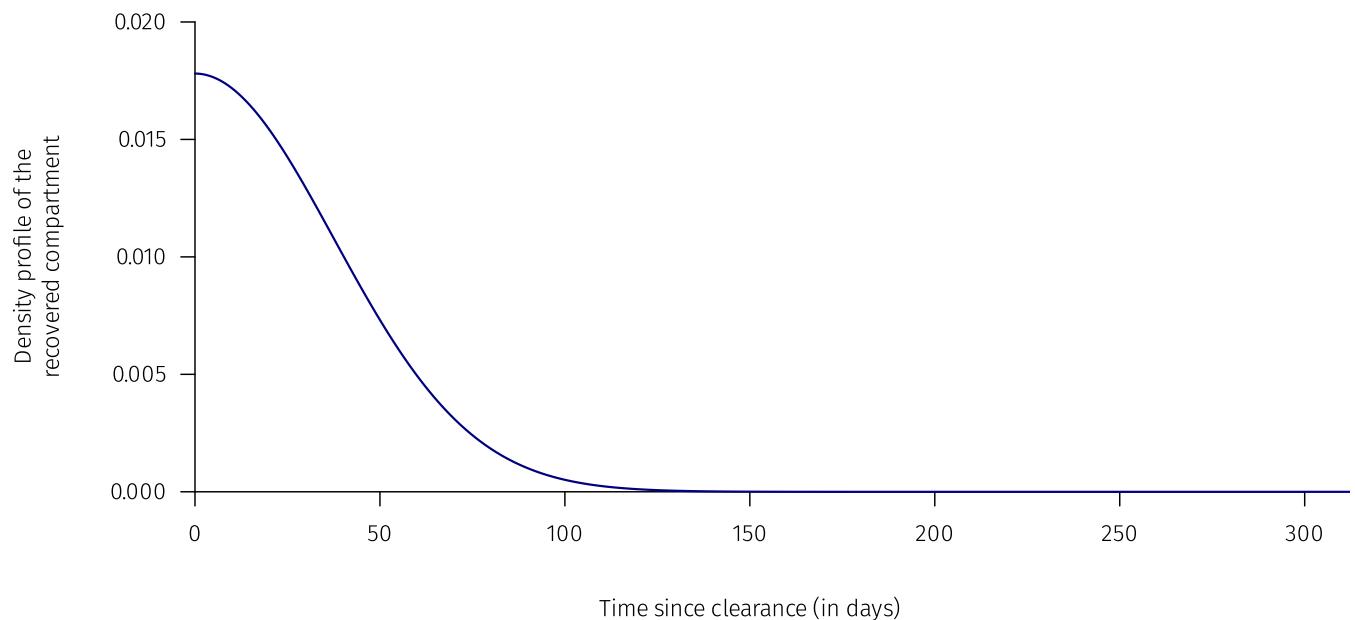


Density profile of the recovered compartment



SARS-CoV-2 considerations

- ▶ Either the $\mathcal{R}_0 = 8$ is overestimated
- ▶ Either the immunity efficacy is underestimated
- ▶ Either previously recovered individuals transmit less
- ▶ Either there is way more asymptotic than detected



Discussion & conclusion

Benefits and limitations of PDE-based formalism

- ▶ Implementation not out-of-the box
- ▶ Useless just to implement simple processes (e.g. generation time)
- ▶ Useful for non-standard biological shapes
- ▶ Useful for non-linear leaky (not all-or-nothing) processes (e.g. immunity efficacy)
- ▶ Note that other sources of uncertainty (e.g. contact matrixes) might discard usefulness of precision brought by non-Markovian processes

Thank you

Supervision

Samuel Alizon
Mircea T. Sofonea
Ramsès Djidjou-Demasse
Christian Selinger

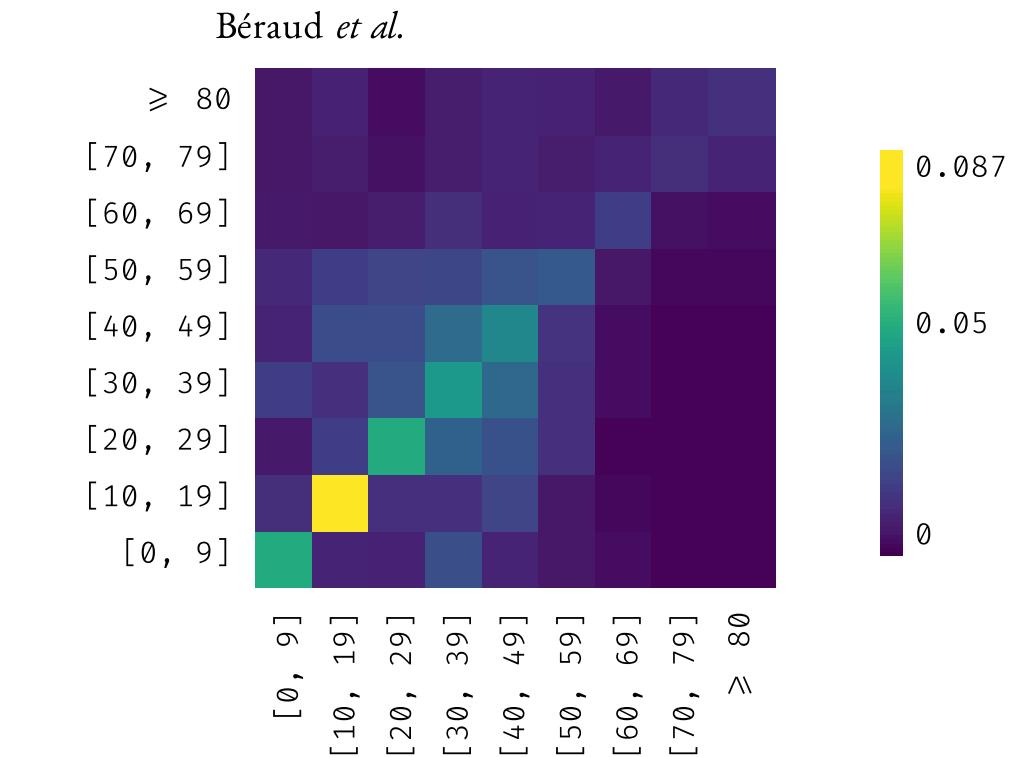
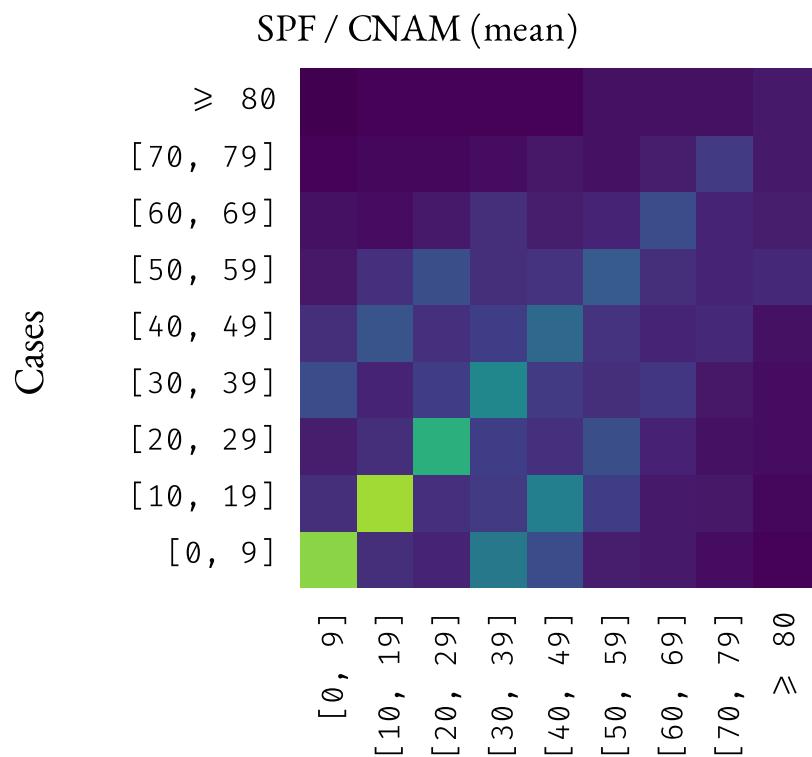
Team

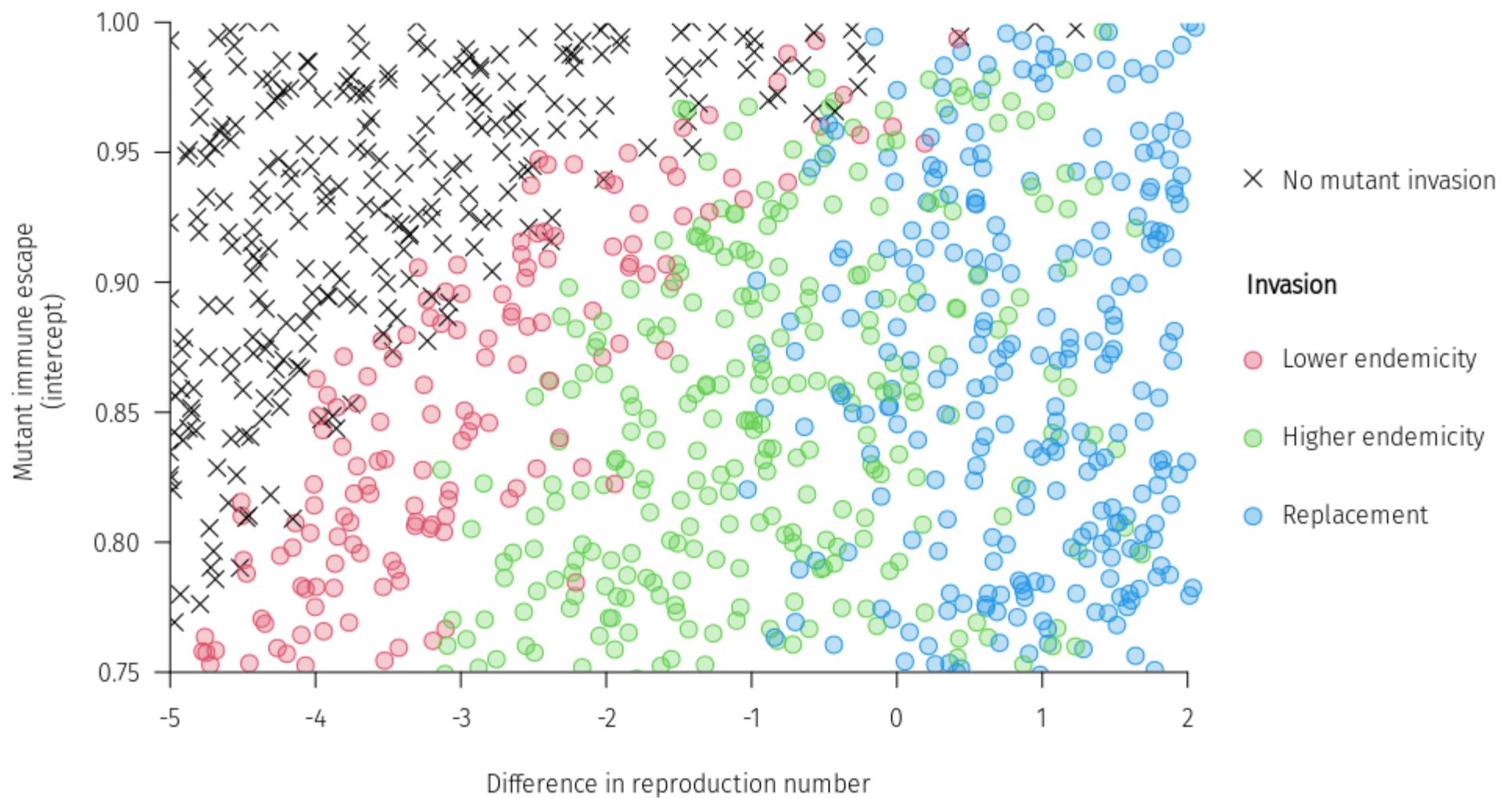
Thomas Bénéteau
Vanina Boué
Gonché Danesh
Baptiste Elie
Tsukushi Kamiya
Yannis Michalakis
Quentin Richard
Olivier Supplisson
Nicolas Tessandier

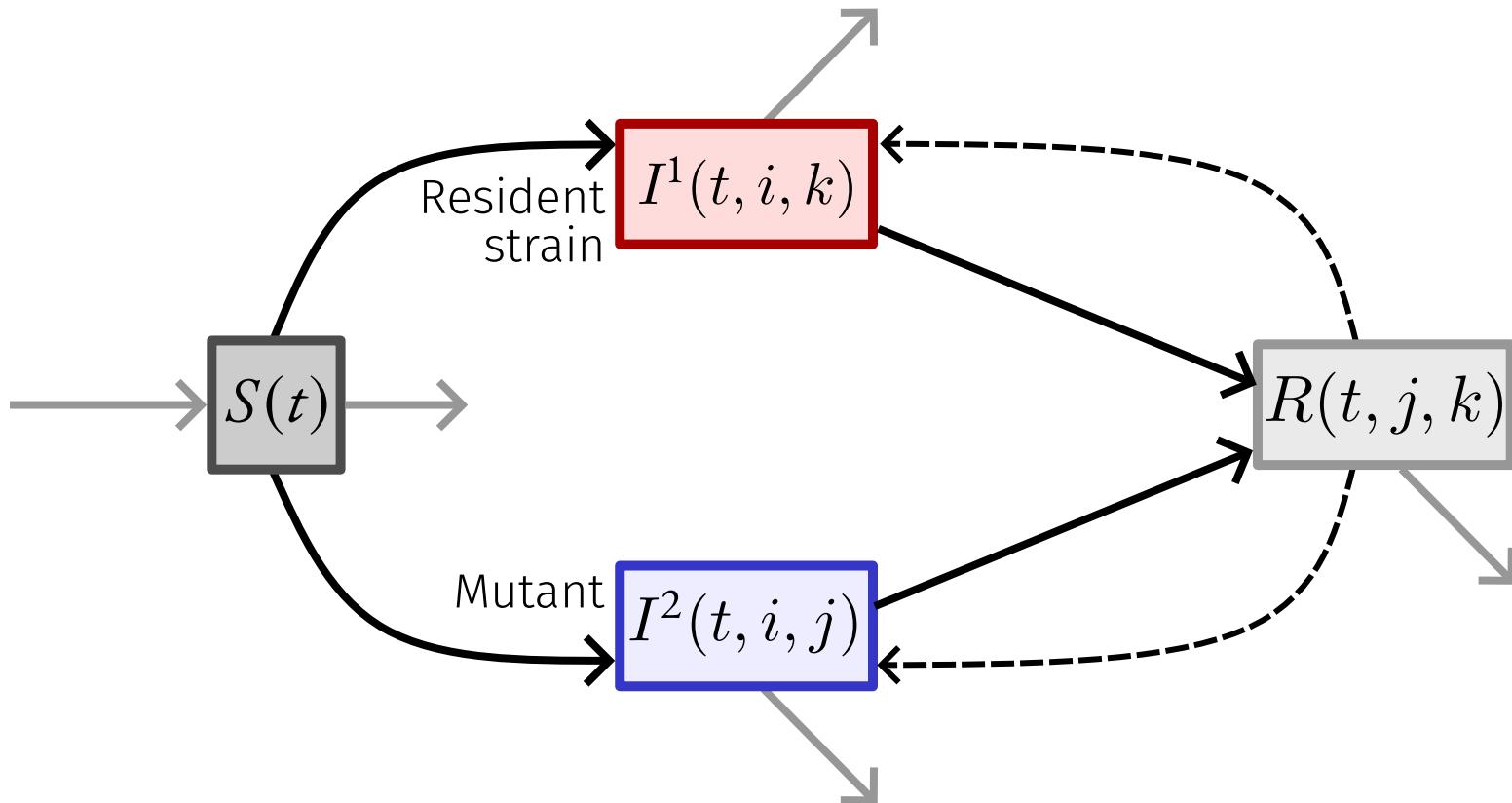
Funding



Appendix







i age infection
 j age immunité 1
 k age immunité 2