# Suivi épidémiologique et contrôle : applications d'une modélisation en temps discret de la dynamique hospitalière de COVID-19 en France

Mircea T. Sofonea, Corentin Boennec, Bastien Reyné, Baptiste Elie, Ramsès Djidjou-Demasse, Christian Selinger, Yannis Michalakis, Samuel Alizon

*ETE modelling team*,
MIVEGEC (Univ. Montpellier, CNRS, IRD)

**Congrès SMAI 2021,**
La Grande Motte 22.VI.2021

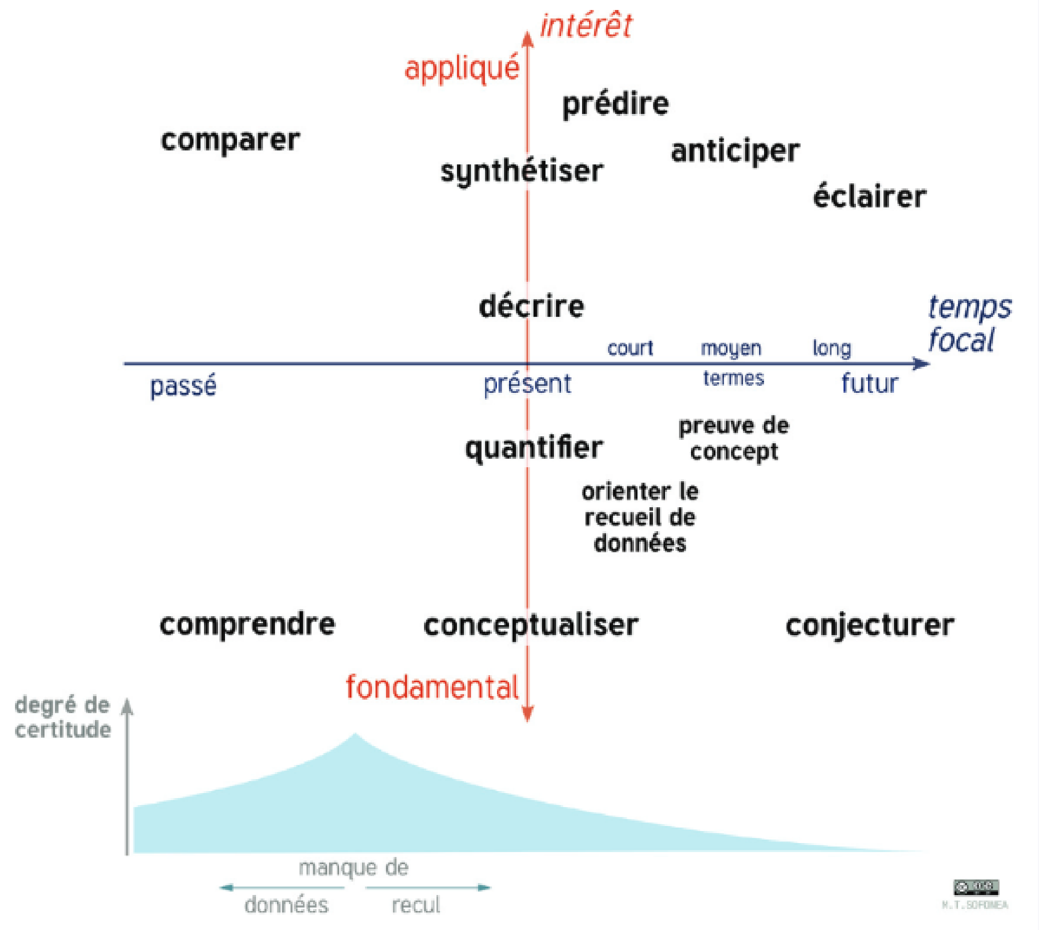
ETE modelling team

MIVEGEC
Maladies Infectieuses et Vecteurs
Écologie, Génétique, Évolution et Contrôle

Institut de Recherche pour le Développement FRANCE

# modelling: means and ends

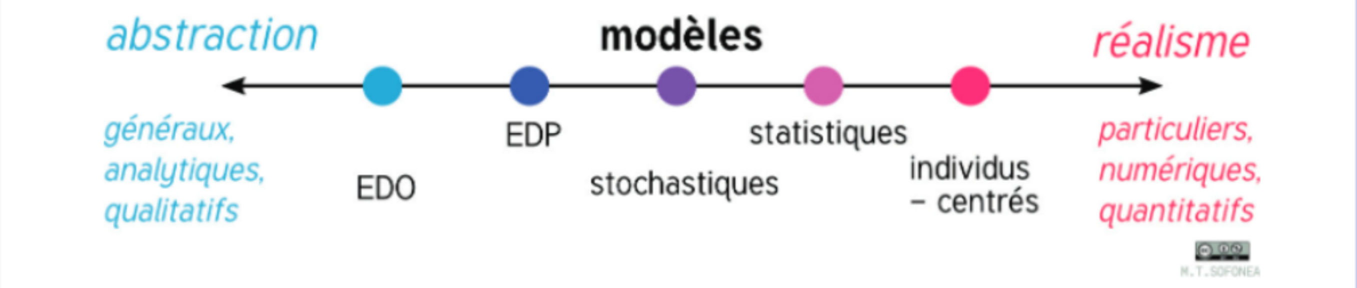
Figure 1. Typologie des questions abordées par les modèles.




La disposition absolue des objectifs dans le repère ainsi que la distribution du degré de certitude est arbitraire et n'a qu'une valeur indicative.



Figure 2. Principales catégories méthodologiques de modèles rencontrés en épidémiologie mathématiques.

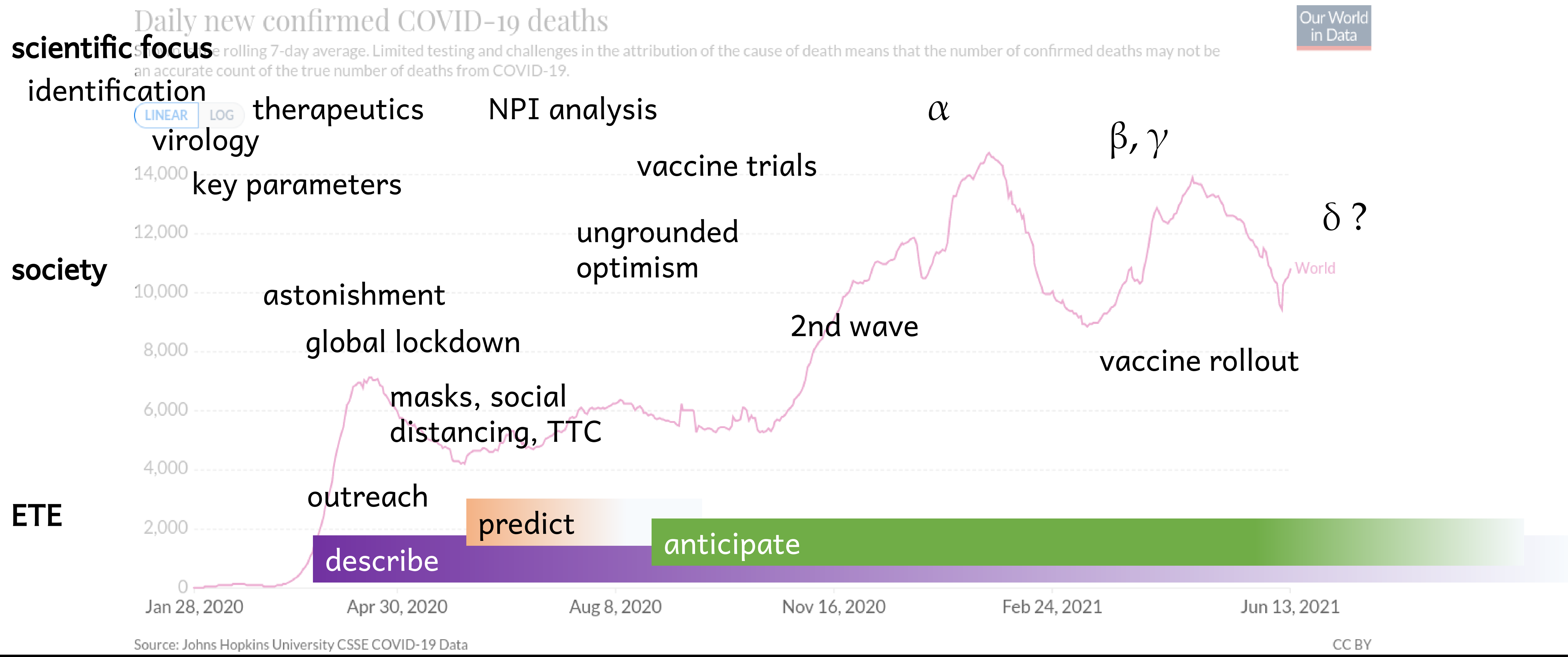



EDO : équations différentielles ordinaires. EDP : équations aux dérivées partielles.



**Djidjou-Demasse** ***R et al.*** (2020) Épidémiologie mathématique et modélisation de la pandémie de Covid-19 : enjeux et diversité. *Revue Francophone des Laboratoires*

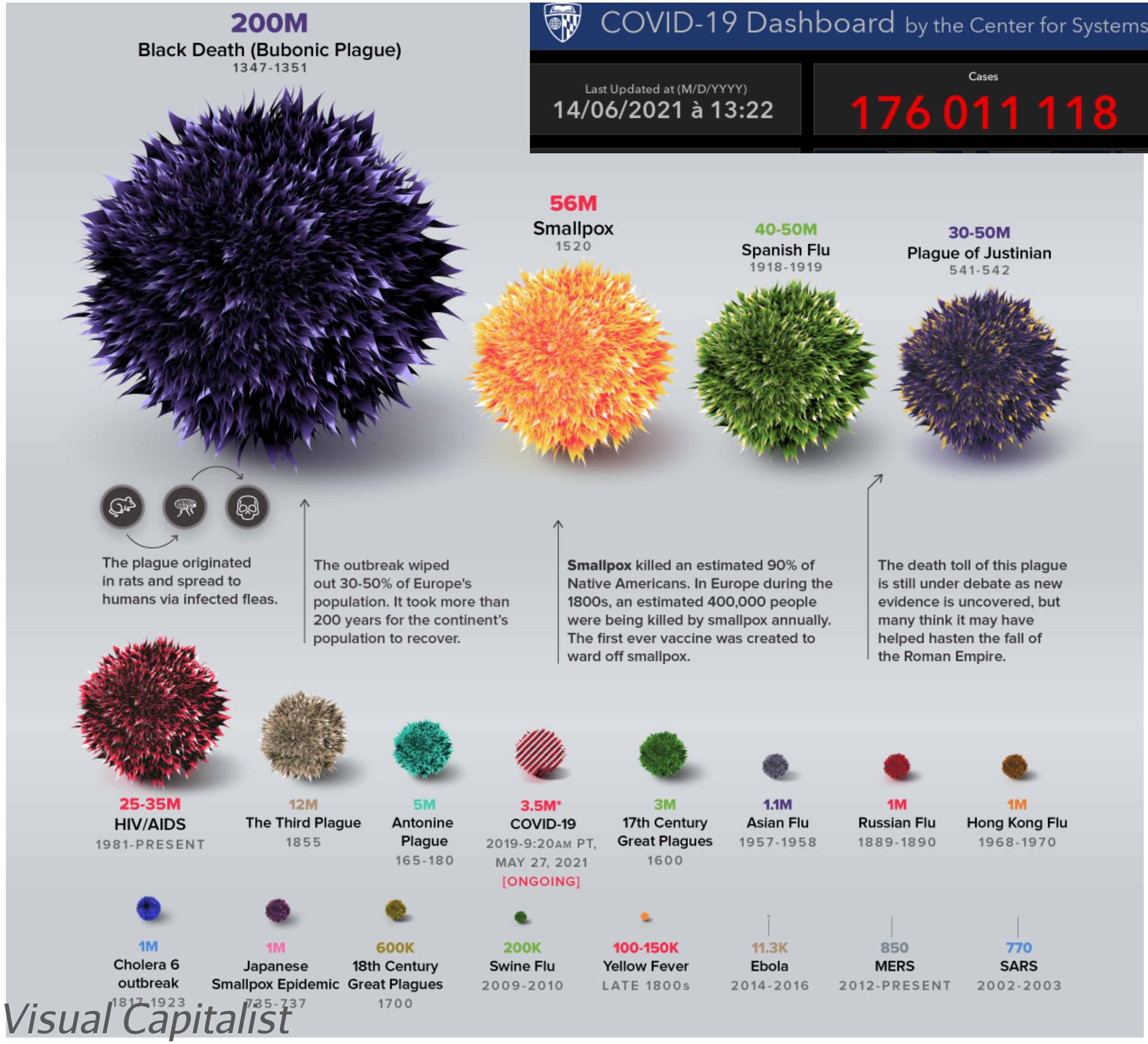
# ongoing research on an ongoing pandemic




**outline**

introductory elements — I. Structure — II. Counterfactuals — III. Projections

# provisional death toll





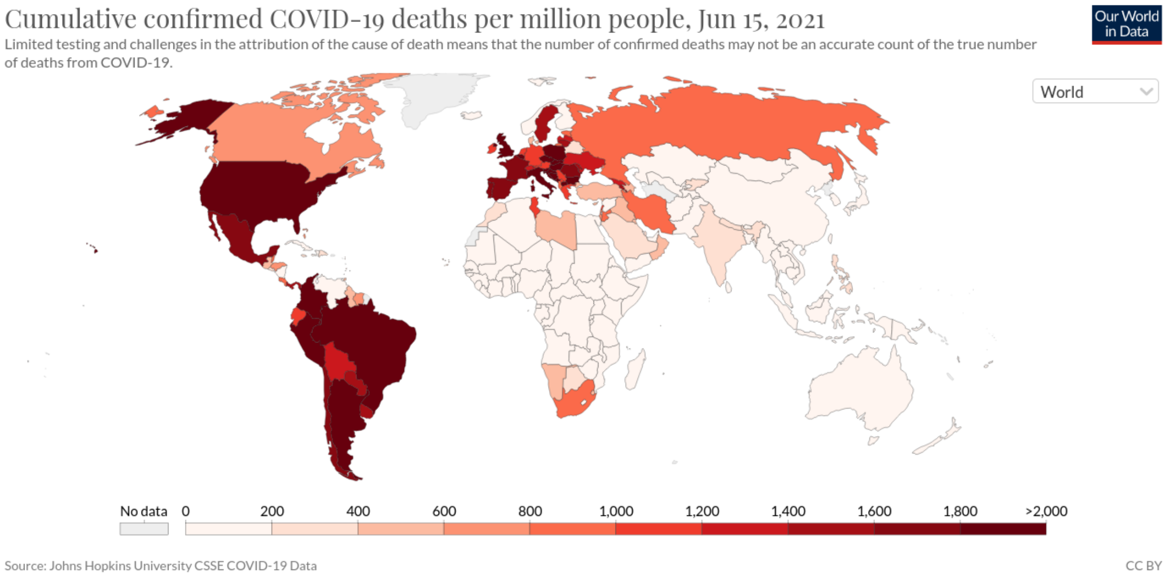
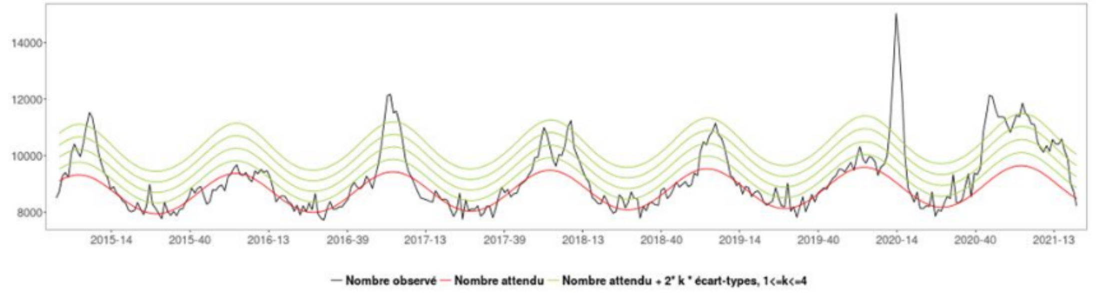



Figure 18. Mortalité toutes causes, tous âges confondus, de la semaine 36-2014 à la semaine 21-2021, France

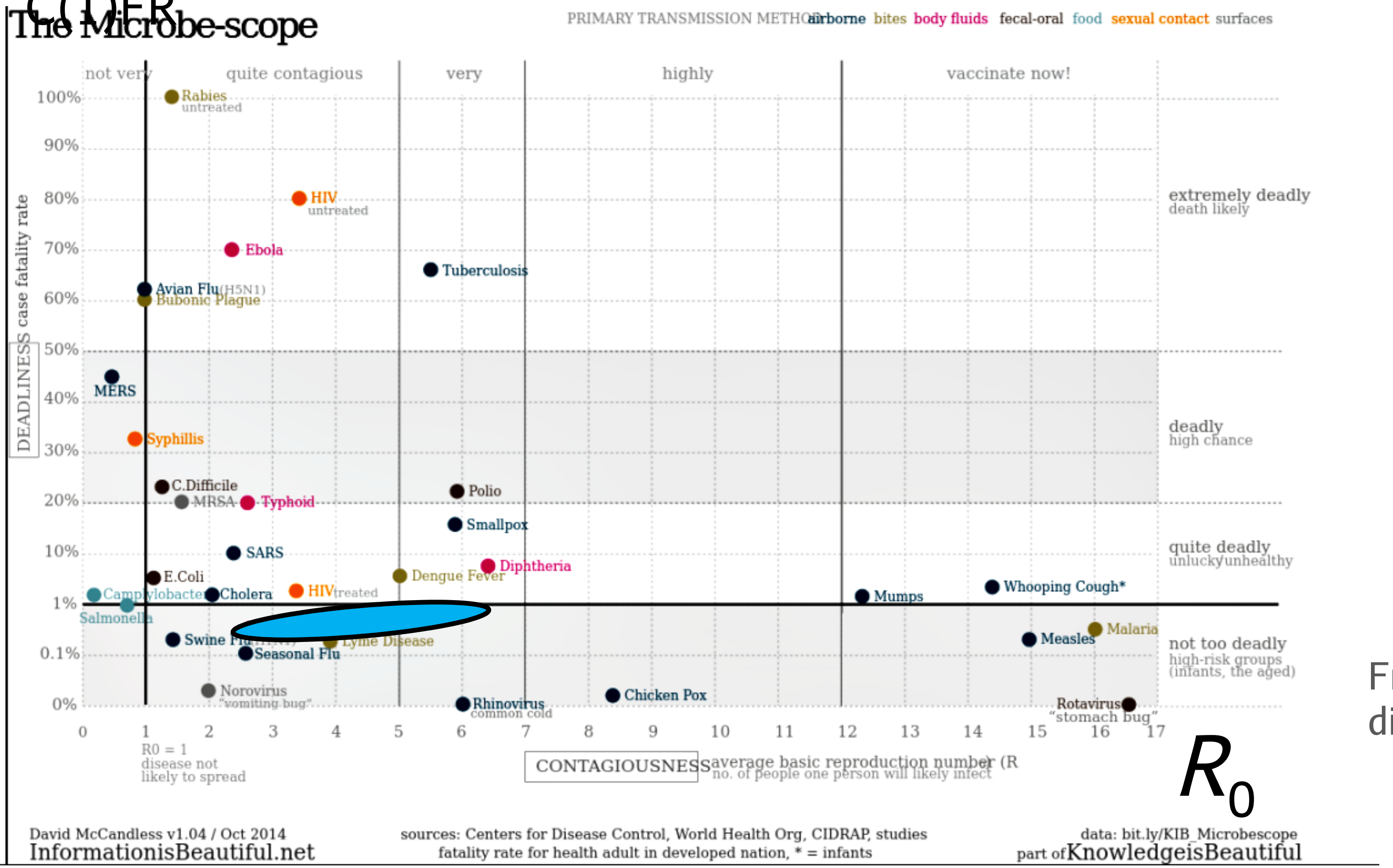



Sources : Santé publique France, Insee

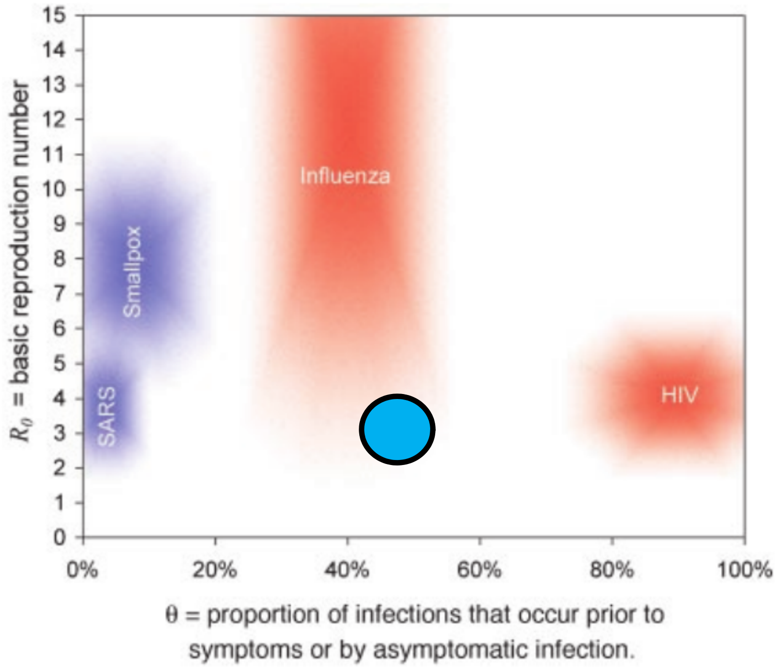
# why did COVID-19 become pandemic

COVID-19

C(I)FR

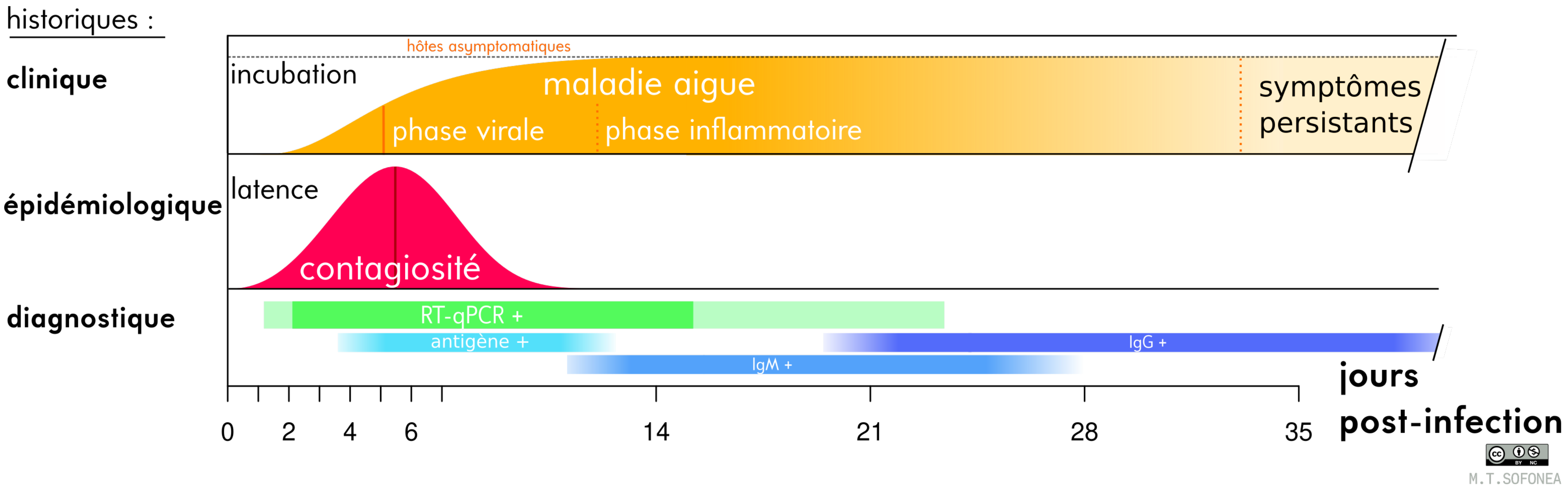



$R_0$

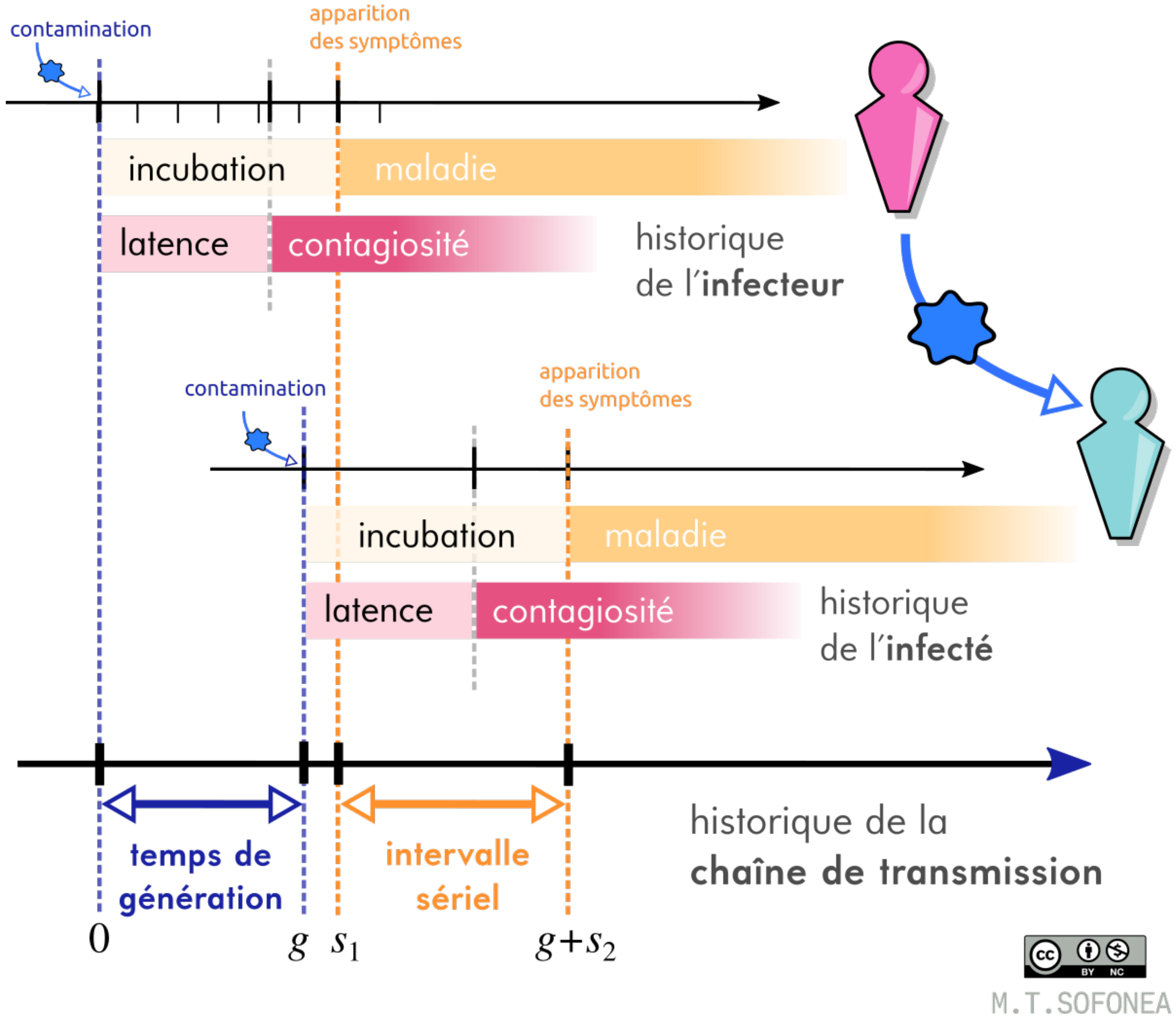



Fraser C *et al.* (2003) Factors that make an infectious disease outbreak controllable. *PNAS*

# the natural history of COVID-19



# generation time and serial interval



# computing the pace of the epidemic

$\beta_\tau$ is the number of contaminations caused an index case on her/his $\tau^{\text{th}}$ day of infection

$\beta_1 + \beta_2 + \ldots + \beta_\tau + \ldots = \sum_{\tau>0} \beta_\tau =: \mathscr{R}$ is the **reproduction number**

$w_\tau := \beta_\tau / \mathscr{R} \Longrightarrow \sum_{\tau>0} w_\tau = 1$ defines the **generation time distribution**

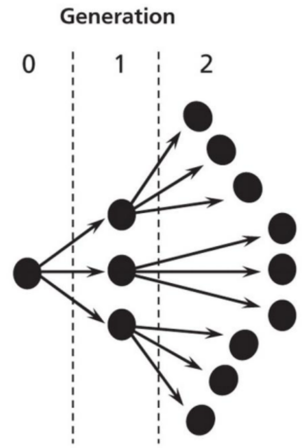
$y_t = \beta_1 y_{t-1} + \beta_2 y_{t-2} + \ldots + \beta_\tau y_{t-\tau} + \ldots = \mathscr{R} \sum_{\tau>0} w_\tau y_{t-\tau}$ links incidence $y_\cdot$ on day $t$ to those of previous days

$\widehat{\mathscr{R}_t} = y_t / \left( \sum_{\tau>0} y_{t-\tau} w_\tau \right)$ is the estimated reproduction number at time $t$ (as long as $y_t \propto y_t^{\text{true}}$)

An epidemic grows if and only if $\mathscr{R} > 1$ (**contagiosity**)

Assuming asymptotic behaviour, $y_t = \rho^t y_0 \Longrightarrow \mathscr{R} \sum_{\tau>0} \rho^{-\tau} w_\tau = 1$ (EULER-LOTKA equation)

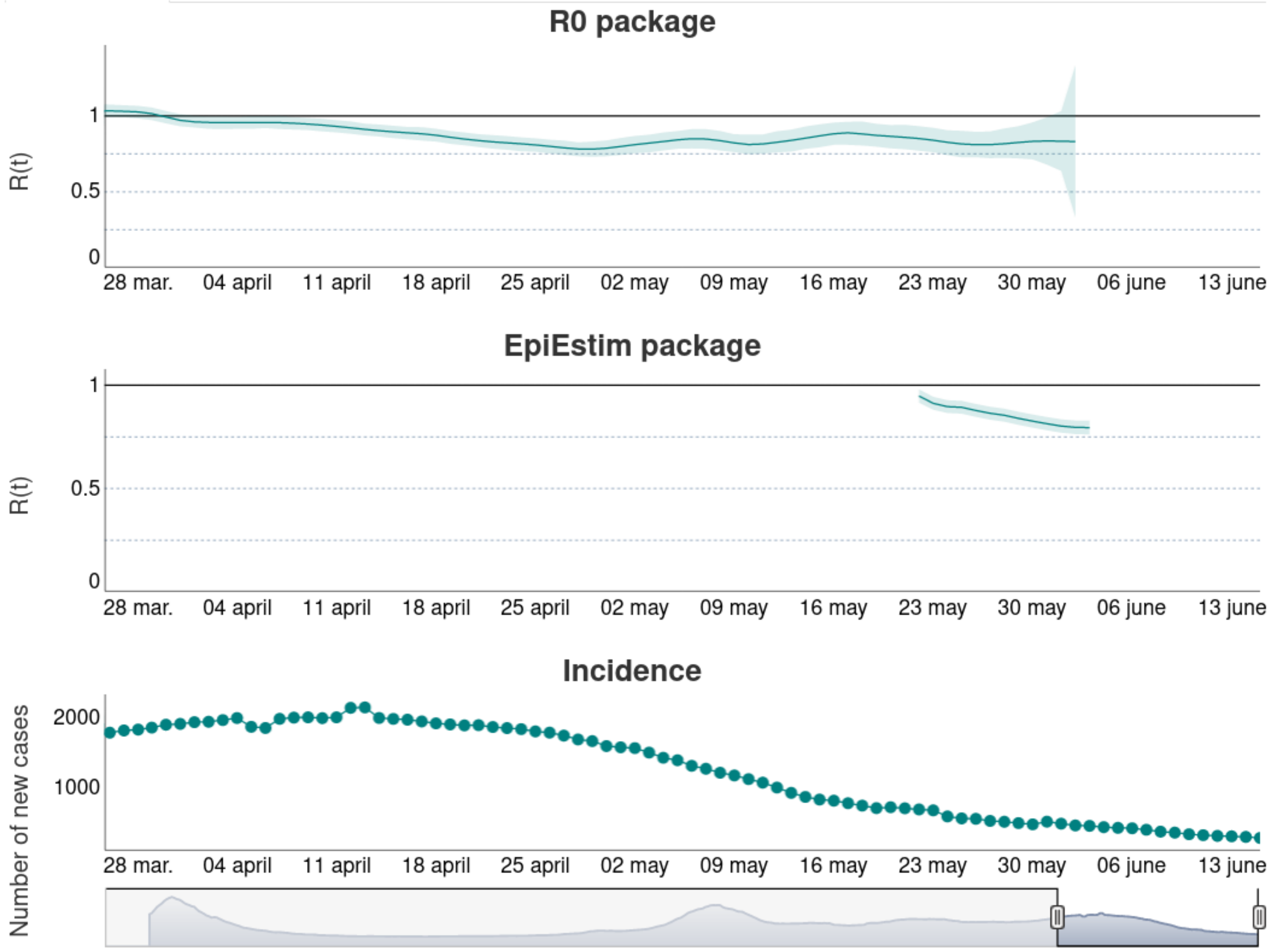
$\log 2 / \log \rho =: T_2$ is the doubling/halving time (**speed**)

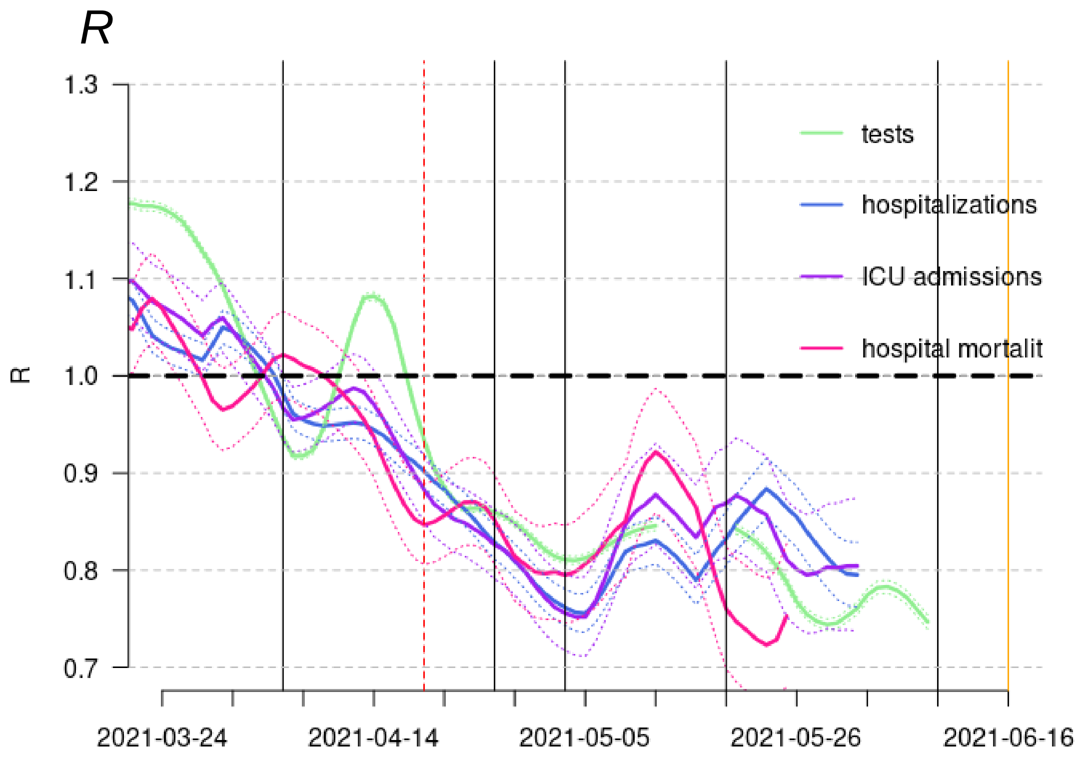



Initial phase of epidemic ($R_0 = 3$)

Pan-InfORM 2009 (CMAJ)

# estimating the reproduction number

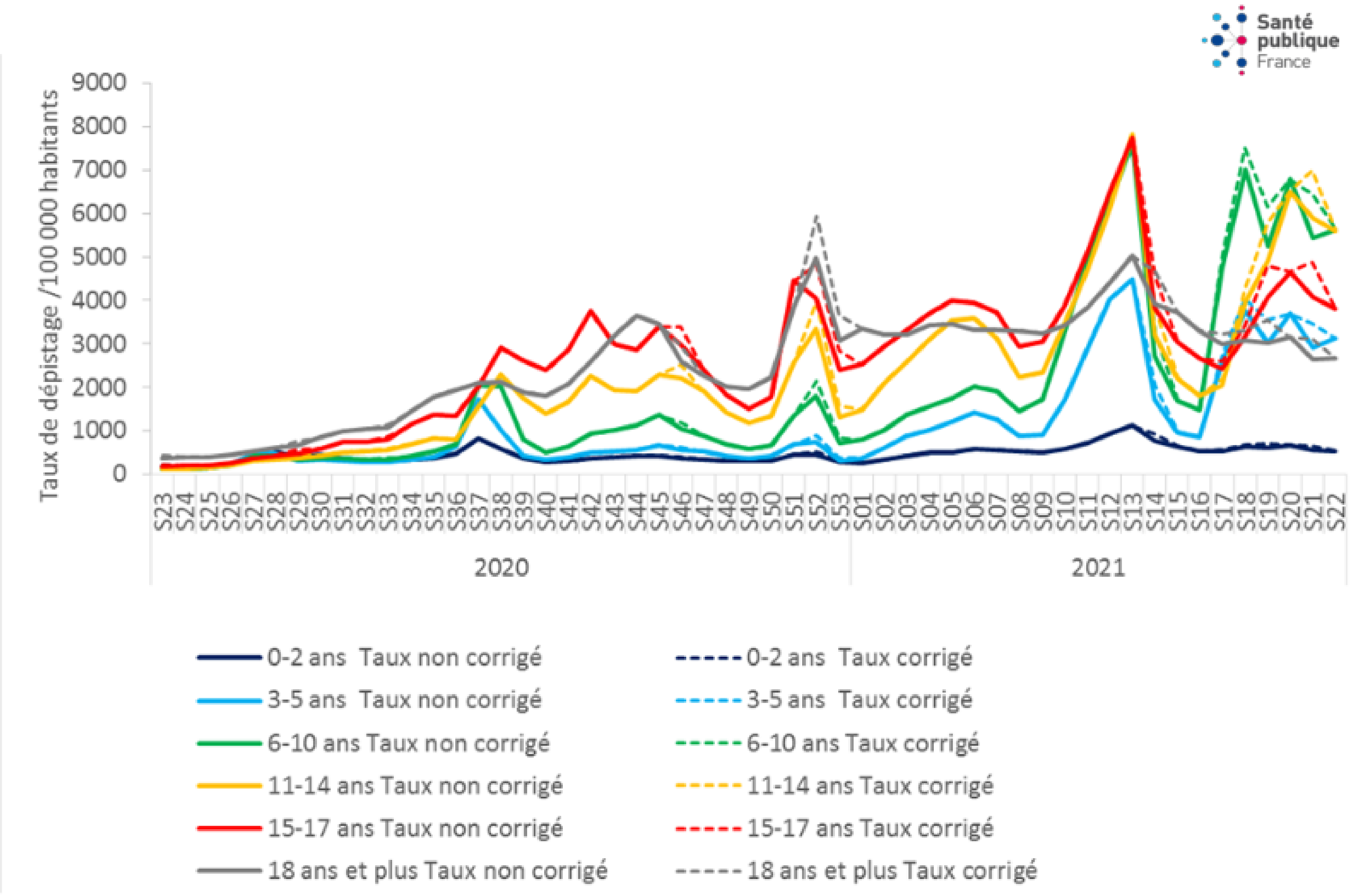



**Reyné B *et al.*** (2020) Rt2: https://cloudapps.france-bioinformatique.fr/covid19-rt2/

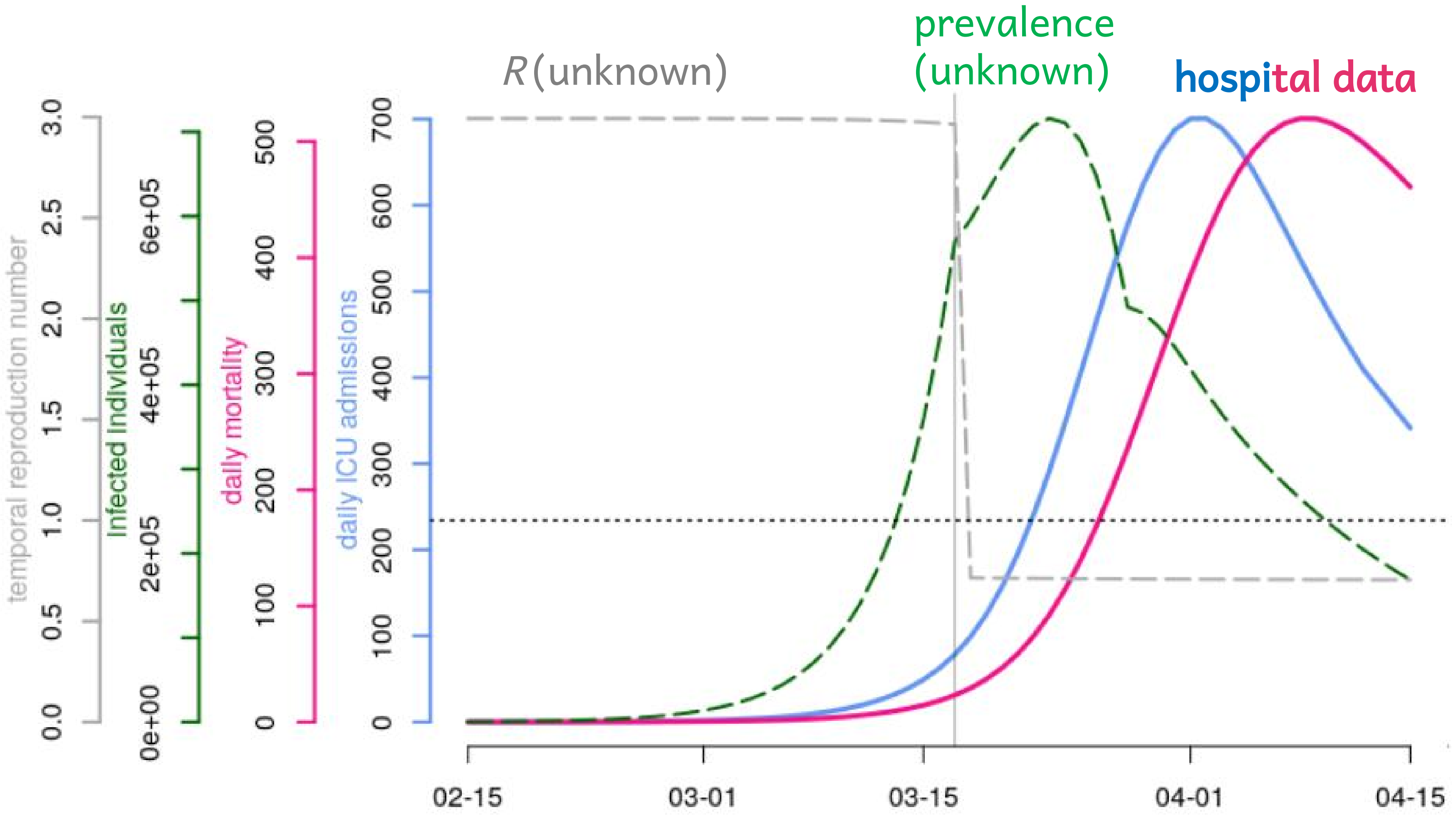
# the non homogeneous detection issue

**5b. Taux de dépistage**



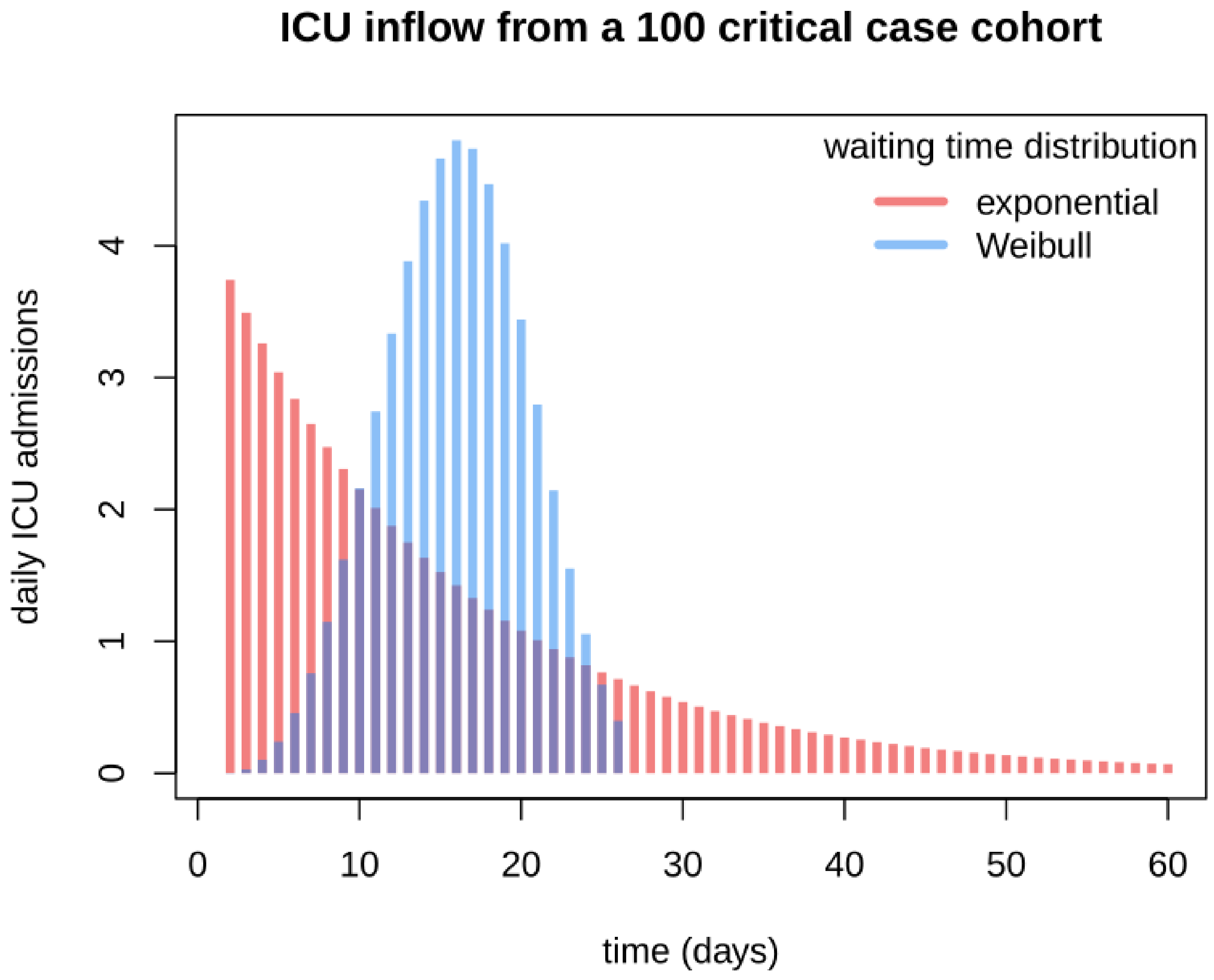
# infering the epidemic curve

- **date and height of hospital capacity strain peak?**
- **lockdown effect?**
- **herd immunity?**
- **alternative restrictions? (age-specific, periodic, adaptative)**

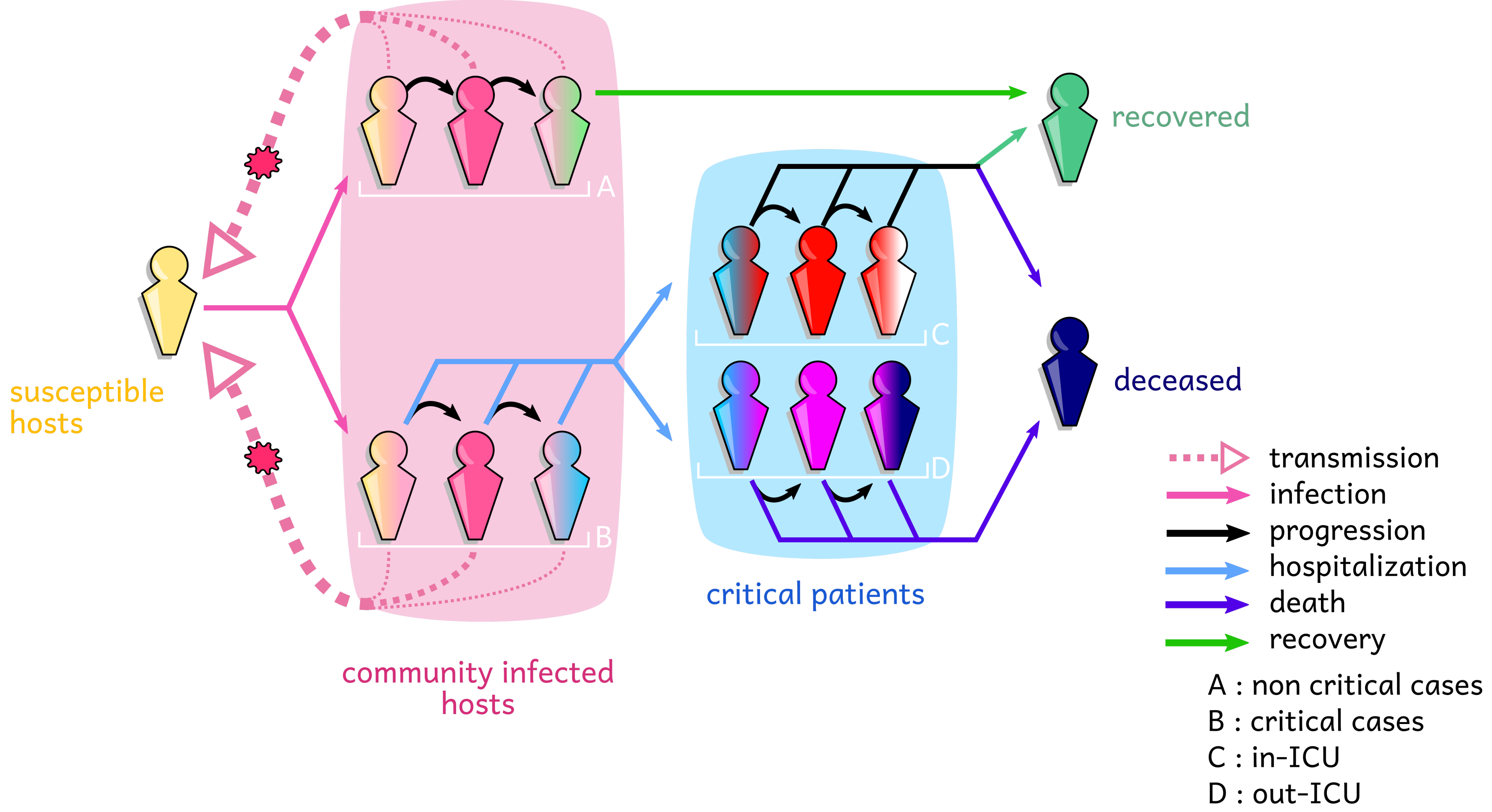



**Sofonea MT *et al.*** (2020) COVIDSIM: https://bioinfo-shiny.ird.fr/COVIDSIM2-fr/

# non-Markovian dynamics



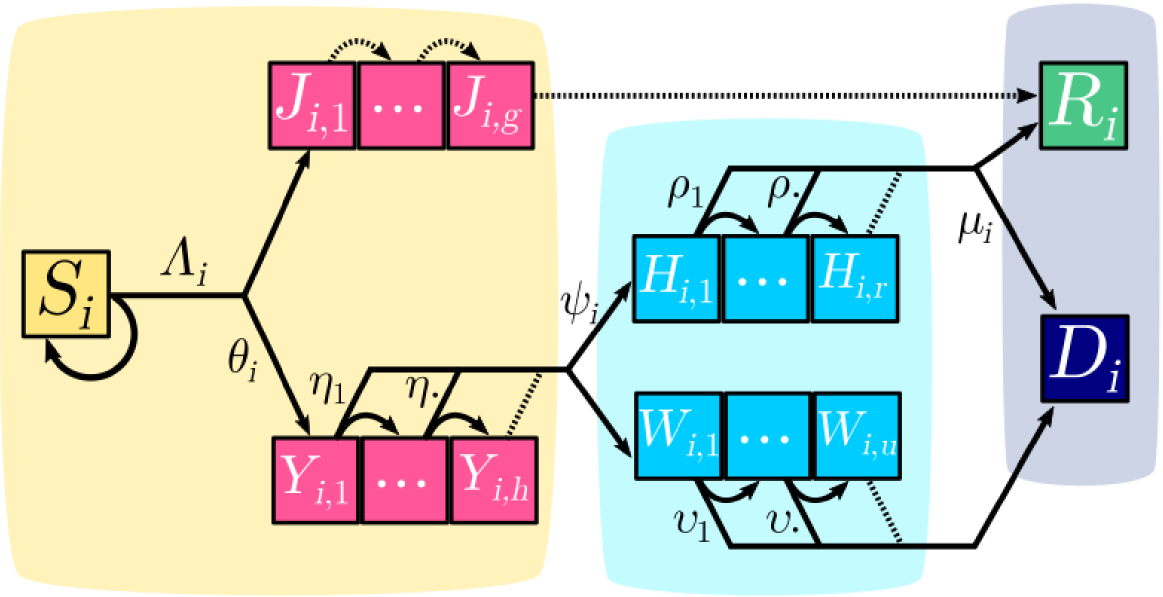
# discrete time modelling




MTS

# model structure

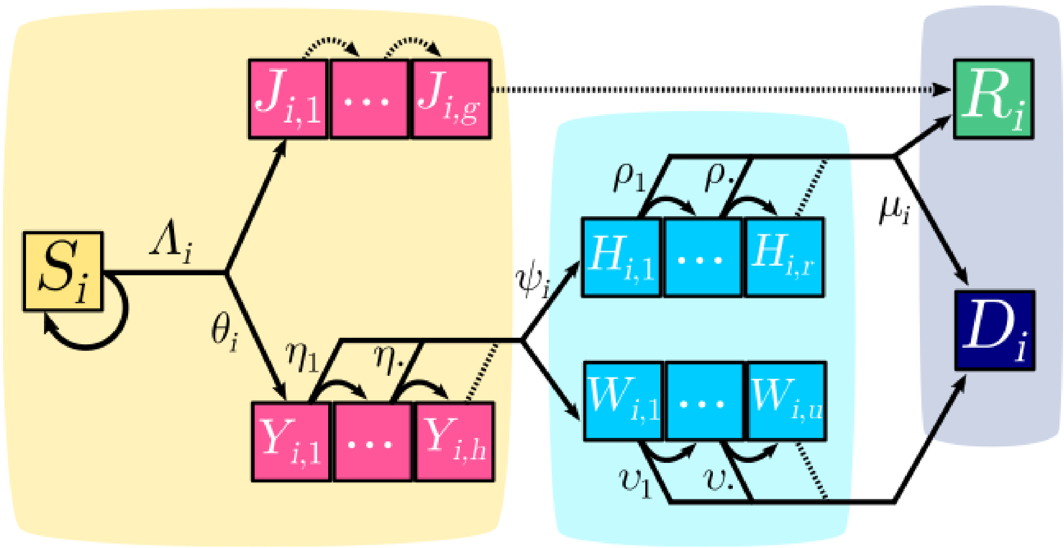
$S \equiv$ susceptible, $J \equiv$ non critical infectious, $Y \equiv$ critical inf.
$H \equiv$ hospitalized critical patient (HCP) group 1,
$W \equiv$ HCP2 (none or short ICU stay), $R \equiv$ recovered (immunized), $D \equiv$ dead




$i \equiv$ age group, $\Lambda \equiv$ force of infection, $\theta \equiv$ critical illness frequency
$\eta \equiv$ contamination to hospitalization interval distribution
$\psi \equiv$ long-stay ICU frequency among critical cases
$\rho \equiv$ (HCP1) ICU length distribution, $\mu \equiv$ (HCP1) fatality rate
$\upsilon \equiv$ (HCP2) hospitalization to death interval distribution

**Sofonea MT *et al.*** (2021) Memory is key in capturing COVID-19 epidemiological dynamics. *Epidemics*

# recurrence relation system

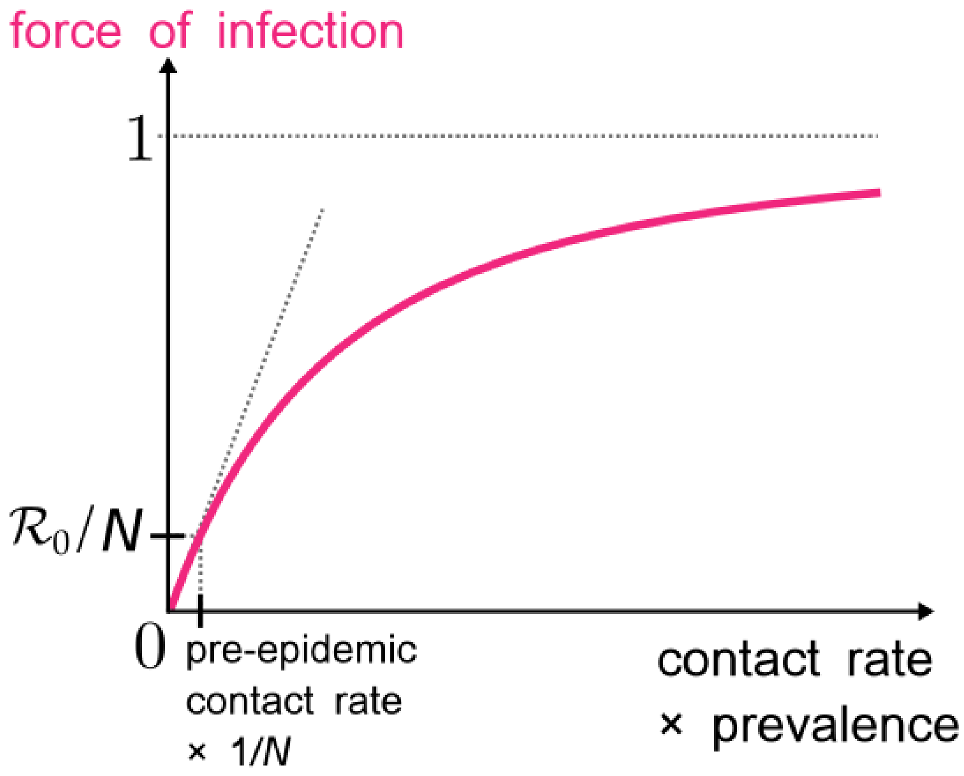



| | | | |
|---|---|---|---|
| susceptible | $S'_i = (1-\Lambda_i)\,S_i$ | | |
| non critical inf. | $J'_{i,1} = (1-\theta_i)\,\Lambda_i S_i$ | $J'_{i,k} = J_{i,k-1}$ | $(1 < k < g)$ |
| critical inf. | $Y'_{i,1} = \theta_i \Lambda_i S_i$ | $Y'_{i,k} = (1-\eta_{k-1})\,Y_{i,k-1}$ | $(1 < k < h)$ |
| HCP1 | $H'_{i,1} = \psi_i \sum_{k=1}^{h} \eta_k Y_{i,k}$ | $H'_{i,k} = (1-\rho_{k-1})\,H_{i,k-1}$ | $(1 < k < r)$ |
| HCP2 | $W'_{i,1} = (1-\psi_i) \sum_{k=1}^{h} \eta_k Y_{i,k}$ | $W'_{i,k} = (1-\upsilon_{k-1})\,W_{i,k-1}$ | $(1 < k < u)$ |
| recovered | $R'_i = R_i + J_{i,g} + (1-\mu_i) \sum_{k=1}^{r} \rho_k H_{i,k}$ | | |
| dead | $D'_i = D_i + \sum_{k=1}^{u} \upsilon_k W_{i,k} + \mu_i \sum_{k=1}^{r} \rho_k H_{i,k}$ | | |

# force of infection

$\pi_{j,\tau} \equiv$ prevalence of $j$-individuals infected since $\tau$ days
$k_j \equiv$ per capita contact rate ; $\zeta_\tau \equiv$ discretized serial interval distribution

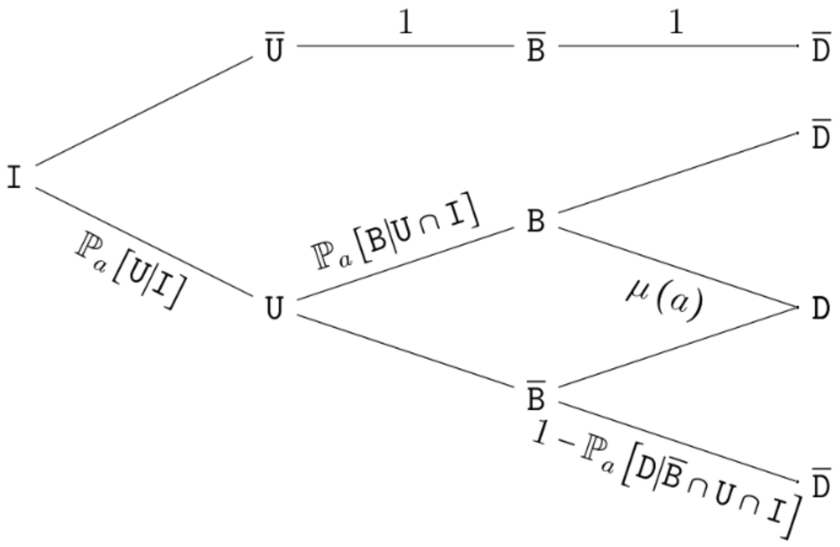
$$\Lambda_i(t) = 1 / \left( 1 + 1 / \left( \mathcal{R}_0 \frac{k_i(t)}{k_i(0)} \sum_j \frac{k_j(t)}{k_j(0)} \sum_\tau \zeta_\tau \pi_{j,\tau}(t) \right) \right)$$



# parametrisation

| **main input parameter** | **notation** |
|---|---|
| basic reproduction number | $\mathcal{R}_0$ |
| initiation day (YY-MM-DD) | $t_0$ |
| lock-down control (%) | $\kappa$ |
| critical case contamination to hospitalization interval expectation (days) | $\mathbb{E}[H]$ |
| critical case contamination to hospitalization interval variance (days$^2$) | $\mathbb{V}[H]$ |
| long ICU stay length expectation (days) | $\mathbb{E}[P]$ |
| critical case hospitalization to death interval expectation (non long-stay ICU patients (days) | $\mathbb{E}[\Upsilon]$ |
| infection fatality rate correction factor (%) | $\mathfrak{C}_F$ |
| long-stay ICU fatality rate correction factor | $\mathfrak{C}_M$ |
| long-stay ICU frequency correction factor | $\mathfrak{C}_\Psi$ |

I $\equiv$ being infected ; U $\equiv$ being hospitalized ; B $\equiv$ occupying an ICU bed for more than a day ; D $\equiv$ dying at the hospital from COVID-19.




$\hat{\mu}(a) = \mathfrak{C}_M \mu(a)$ ; $\hat{\psi}(a) = \mathfrak{C}_\psi / \left(1 - \hat{\mu}(a) + \frac{\mathbb{P}_a[D|U\cap I]}{\mathbb{P}_a[B|U\cap I]}\right)$ ;

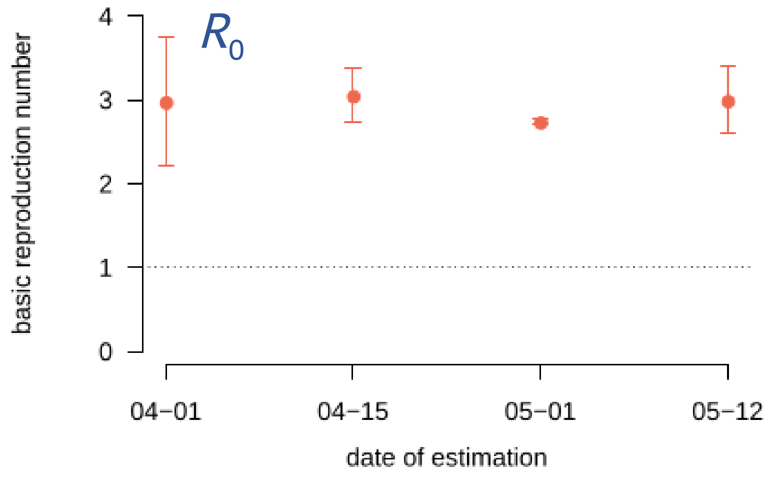
$\hat{\theta}(a) = \frac{\mathfrak{C}_F \mathrm{IFR}(a)}{1-(1-\hat{\mu}(a))\hat{\psi}(a)}$.

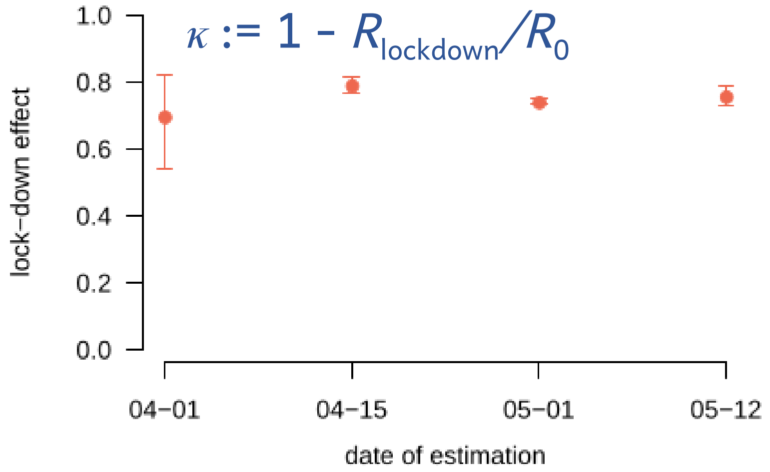
# fitting and early estimation of key parameters

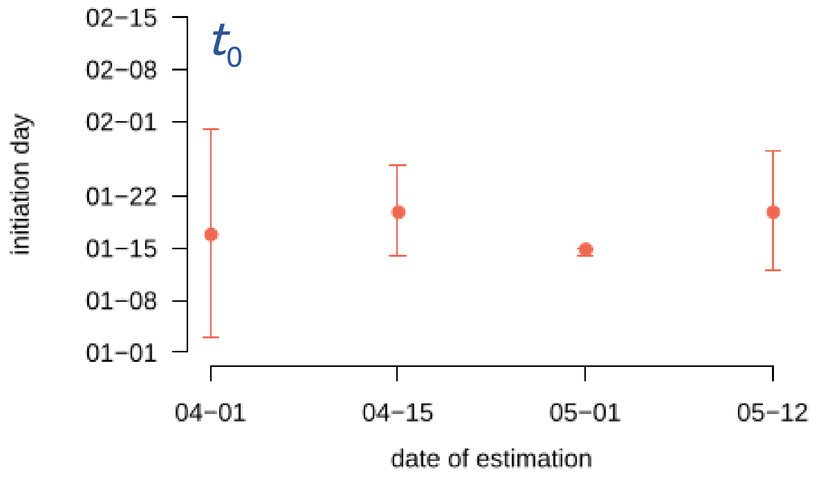
**Inference algorithm :** `R`, `mle2` (`bbmle` package).

Independent count process assumption : $X_{obs}(t) \sim \mathscr{P}(X_{sim}(t)) \longrightarrow$ MLE and likelihood intervals.

Random drawing around MLE $\xrightarrow{\text{Wilks}}$ $10^3$ parameter sets $\longrightarrow$ display 2.5, 50 and 97.5% output quantiles.



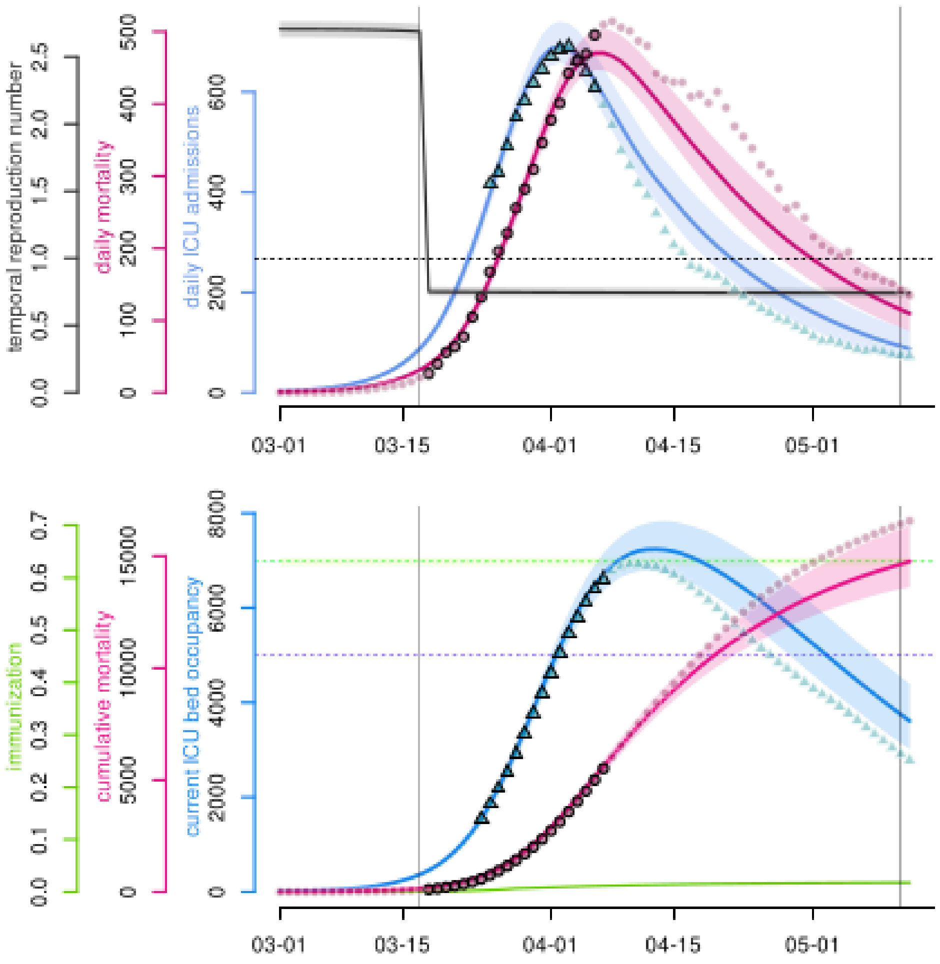




MLE [95%-likelihood interval]

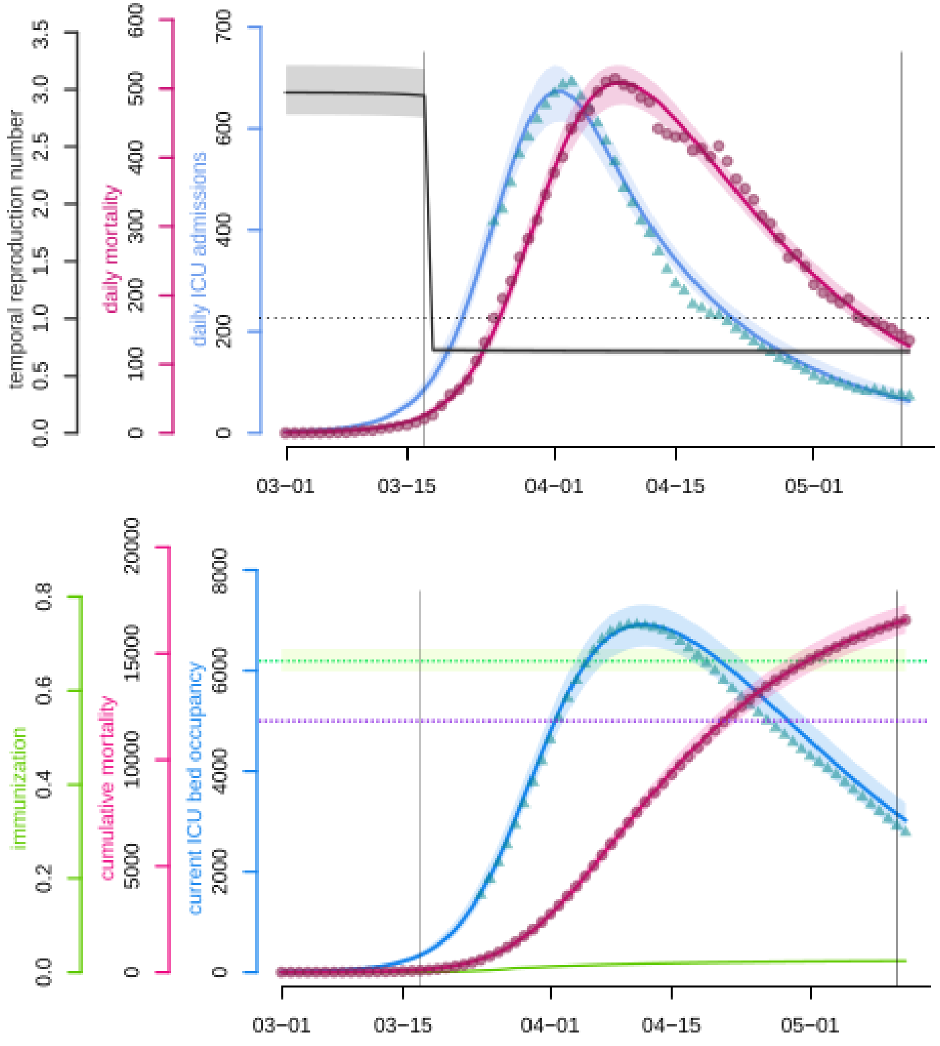
$\mathcal{R}_0 = 3.0\,[2.6, 3.4]$ ; $t_0 =$ Jan 20 [12, 28] ; $\kappa = 76\,[73, 79]\,\%$

# early estimation of key parameters

early forecasting
(data censored after Apr 7th 2020)




post-lockdown lifting (May 11th 2020)



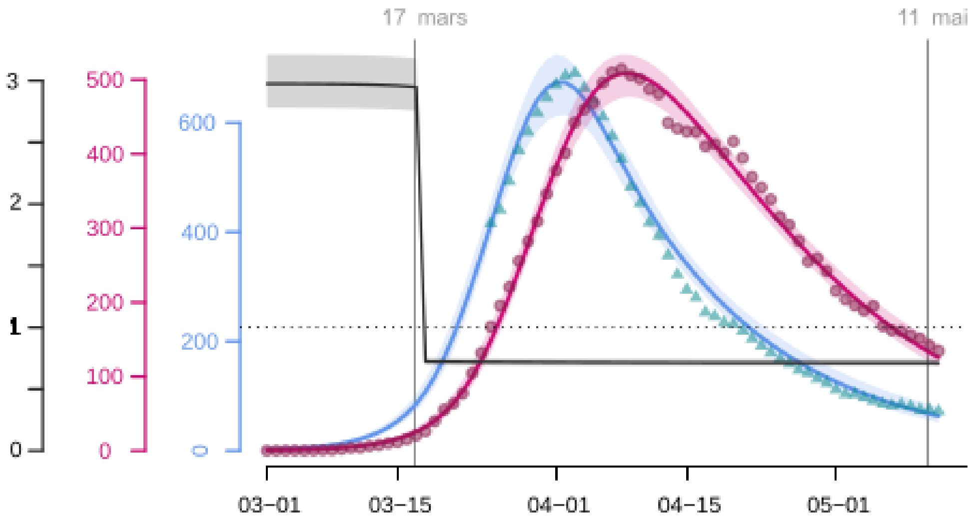

incidental

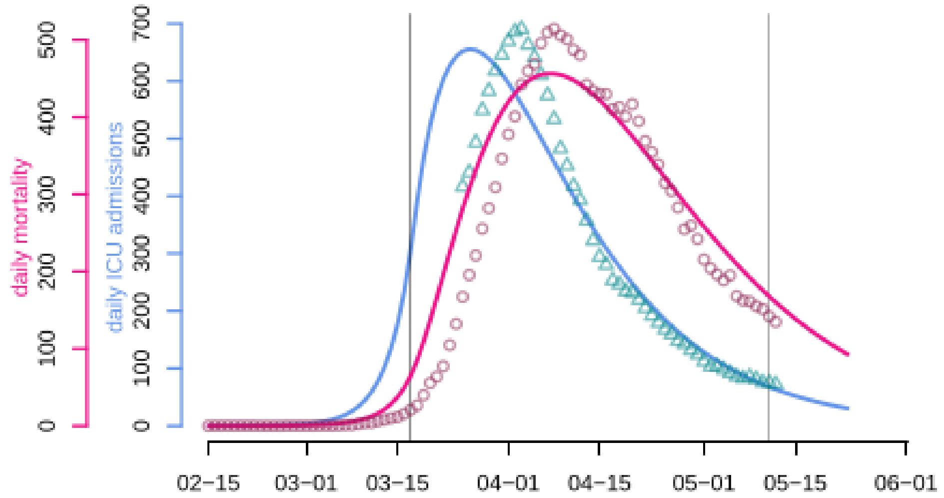
inertial

**Sofonea MT *et al.*** (2021) Memory is key in capturing COVID-19 epidemiological dynamics. *Epidemics*

# comparison with the Markovian approach

discrete time model vs SEAIR ODE

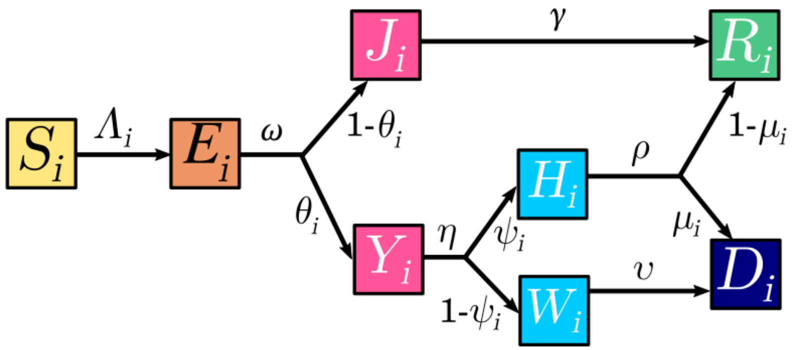


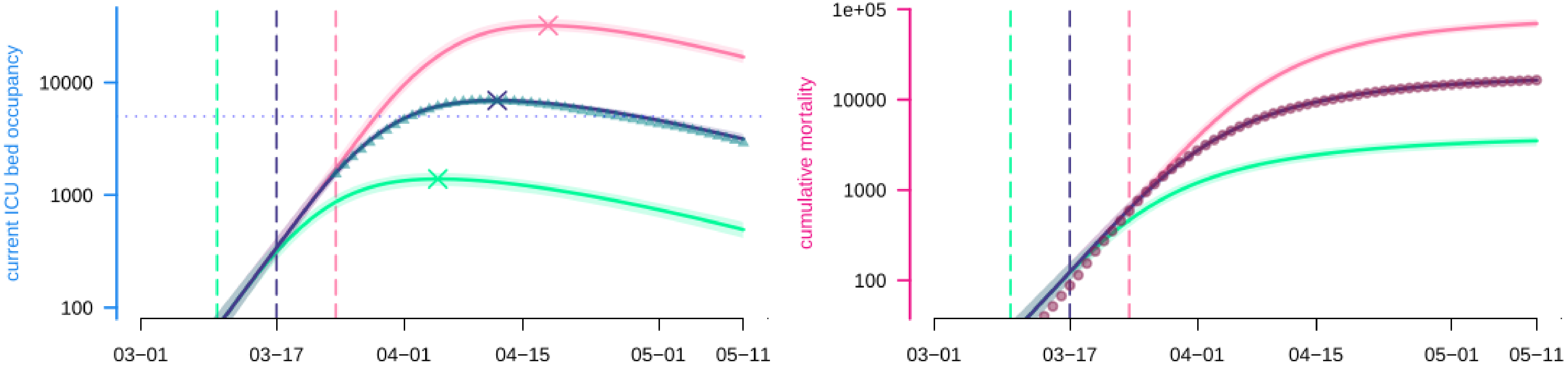

admissions en réanimation (nb/j)
médiane et $IC_{0,95}$ des simulations
données lissées sur la semaine

décès hospitaliers (nb/j)
médiane et $IC_{0,95}$ des simulations
données lissées sur la semaine

nombre de reproduction temporel
médiane et $IC_{0,95}$ des simulations

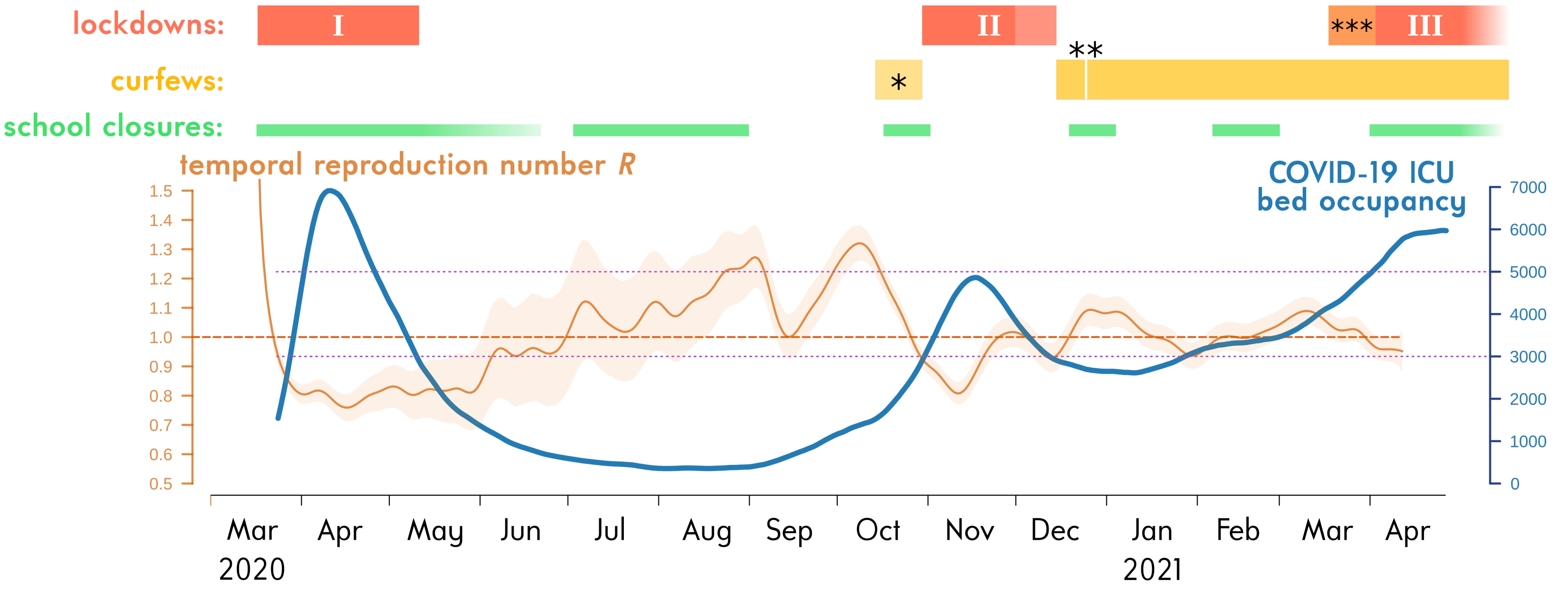


# counterfactuals: lock-down timing




one week before: -13,300 [12,900 - 13,700] deaths,
one week after: +52,800 [45,800 - 61,500] deaths.

# two waves and a high tide




**Sofonea MT *et al.*** (2021) Two waves and a high tide: the COVID-19 epidemic in France. *Anaesth Crit Care Pain Med*

# per capita contact ratio

PCCR $c_i(t) := k_i(t)/k_i(0)$, average potentially infectious contacts an individual has each day, relative to the pre-epidemic baseline.

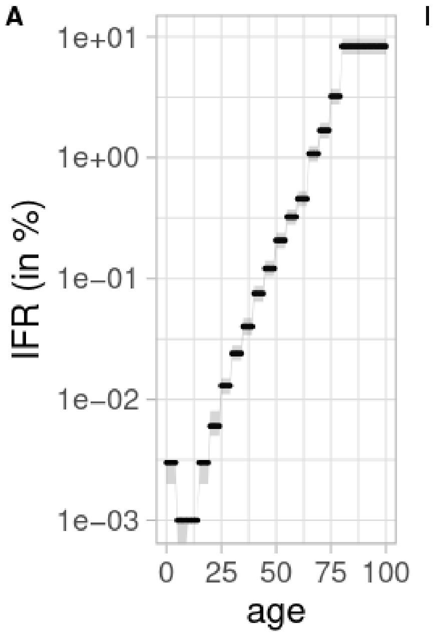
- proportionate mixing $\Rightarrow$ encounter rate at $t$ of an $i$- and a $j$-individuals $\propto c_i(t)\,c_j(t)$,
- $\overline{c_{\text{pre-lock}}} = 1$,
- $\overline{c_{\text{lock}}} = \sqrt{1-\kappa} = 50\%\ [48, 52]\,\%$,
- threshold PCCR value corresponding to $\mathcal{R} = 1$ is $c_{\text{t}} = \mathcal{R}_0^{-\frac{1}{2}} = 58\%\ [56, 60]\,\%$.

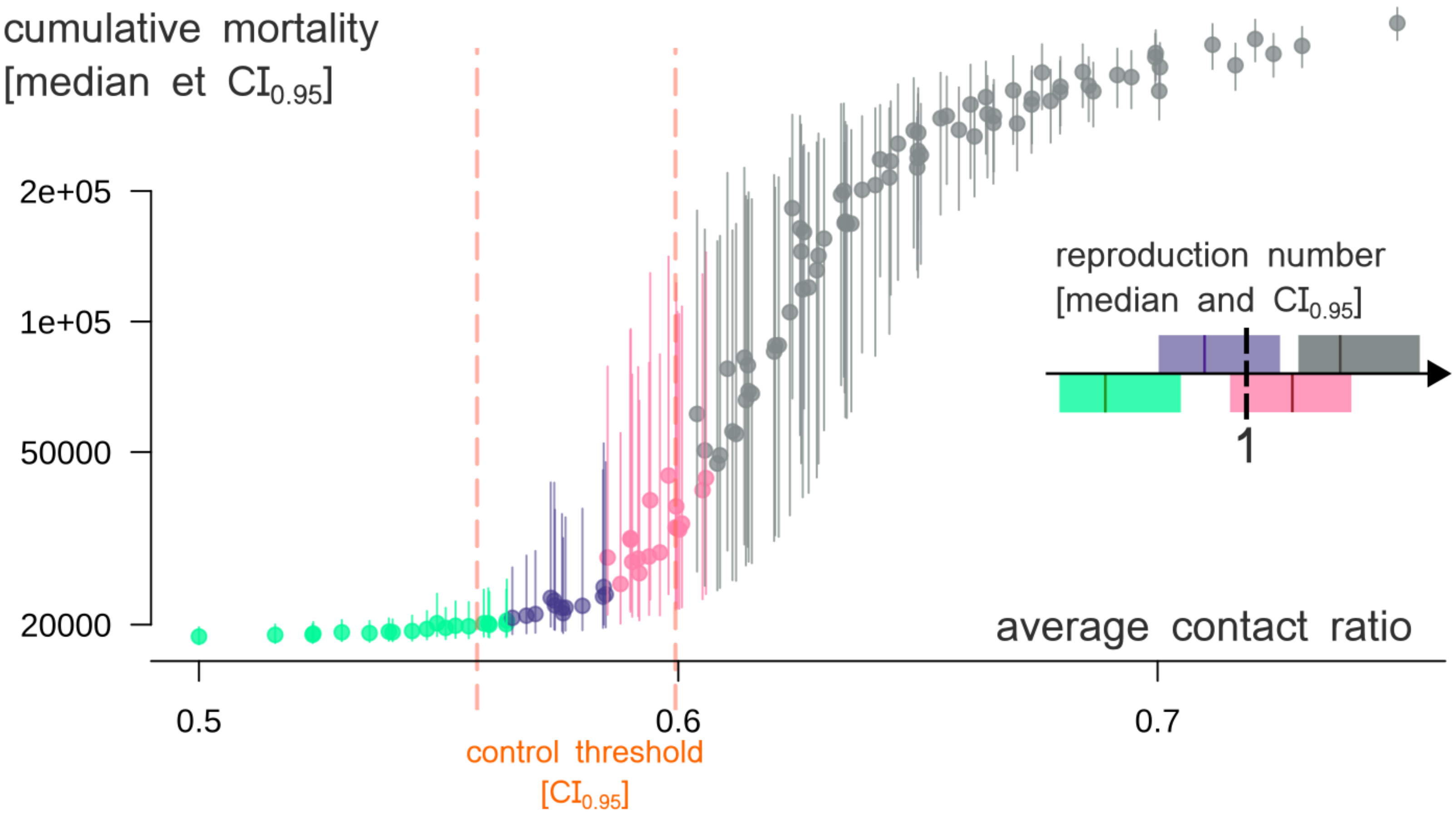
$$\overline{c_{\text{lock}}} < c_{\text{under ctrl}} < c_{\text{t}} < c_{\text{out of ctrl}} < 1.$$

**Sofonea MT** ***et al.*** (2020) Epidemiological monitoring and control perspectives: application of a parsimonious modelling framework to the COVID-19 dynamics in France. *medRxiv*

# limited leverage of *age*-differential control

- three age groups with cut-offs 25 and 65 years old
- all combinations of per capita contact ratio (PCCR) = 50, 58, 62, 65, 75%

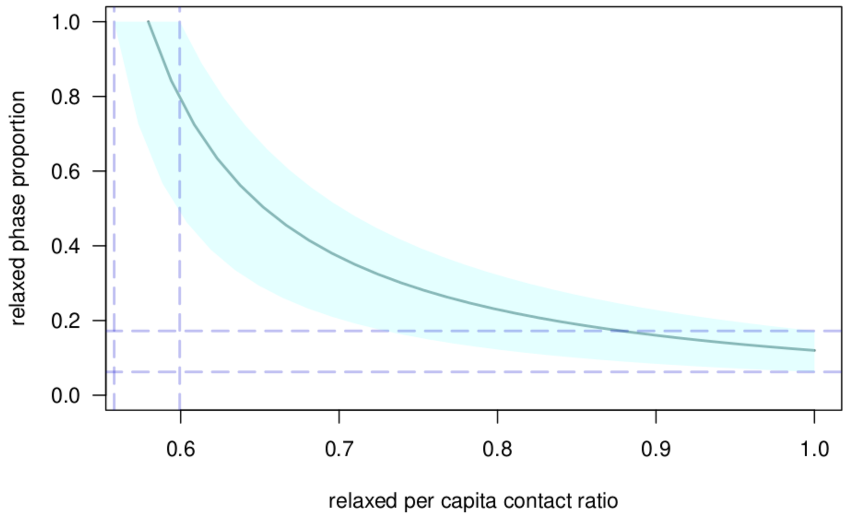


# the unexplored partial periodic lockdowns

$p_r \equiv$ time proportion of relaxed phase ; $c_r, c_h \equiv$ relaxed, restricted PCCR
**goal**: maximizing $p_r$ and $c_r$ while $\overline{\mathcal{R}} = \left(p_r c_r^2 + (1-p_r)\, c_h^2\right) \mathcal{R}_0 \leq 1$.

$$p_{r,\max} = \frac{\mathcal{R}_0^{-1} + \kappa - 1}{c_r^2 + \kappa - 1}.$$




the intensity-duration trade-off

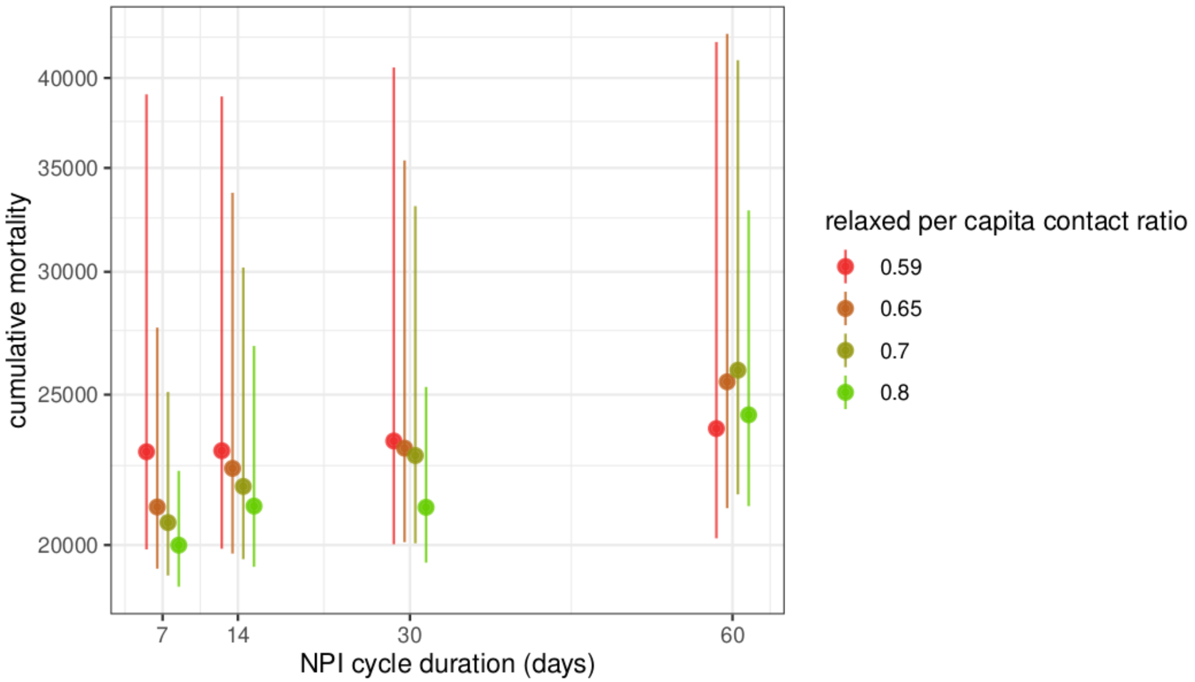
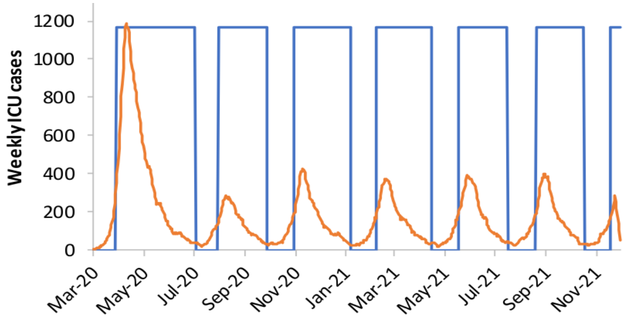
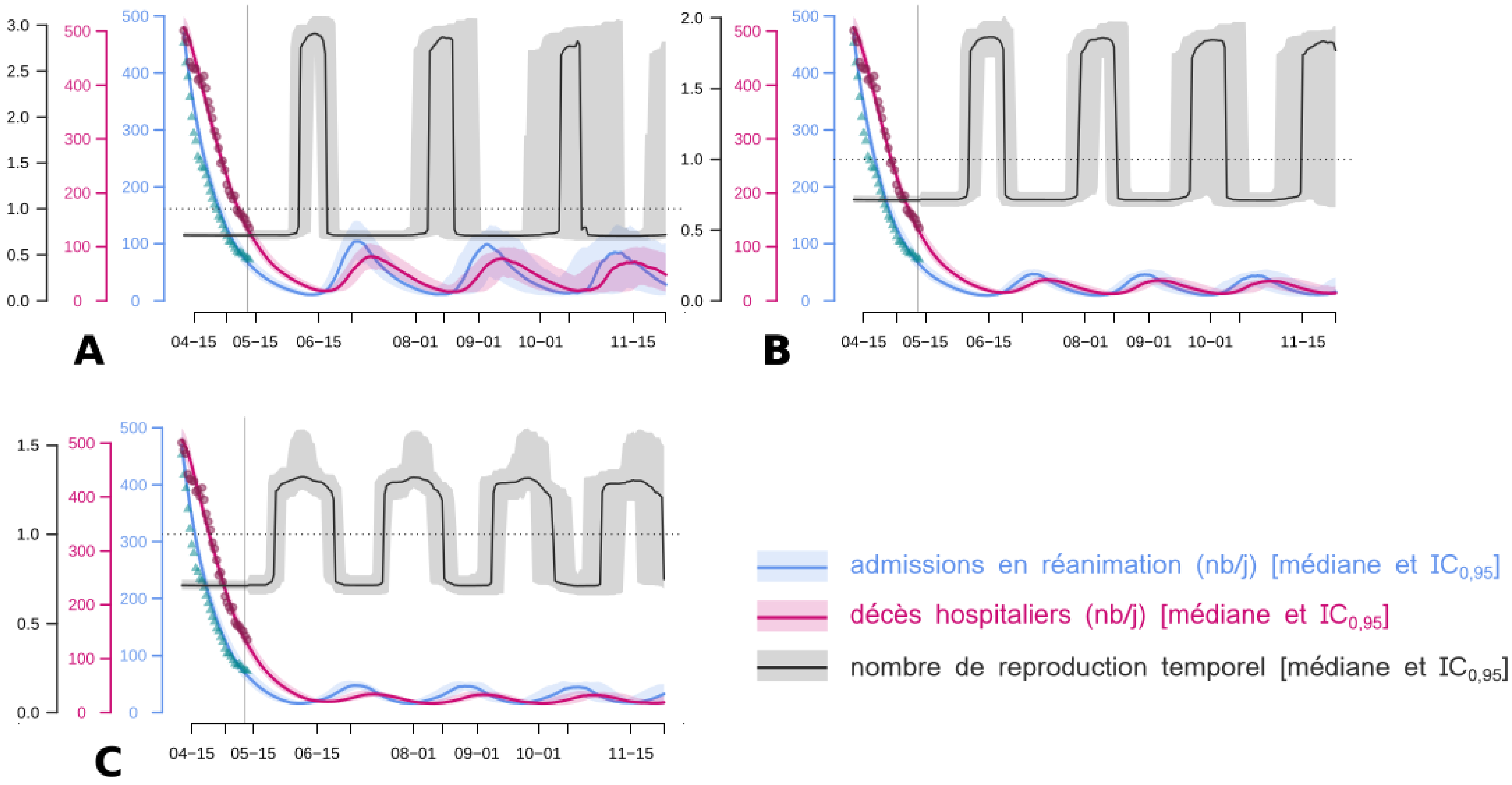



Figure 8: **Effect of NPI cycle duration on cumulative mortality.** We show the cumulative mortality by the end of the year 2020 if a periodic control is implemented from May 12. For each of the four NPI cycle durations, the model is run for four values for $c_r$ shown in different colors, with a proportion of time satisfying eq. 3 (truncated to an integer number of days). For example, in the red scenario, $p_{r,\max}(0.59) = 88\%$, so for the weekly cycle the relaxed phase was set to floor $(0.88 \cdot 7) = 6$ days.

# adaptive control: illustrative cases




Ferguson *et al*. 20-03-16 'Report 9'




DIAT = daily ICU admission threshold (nationwide)

**A**: DIAT = 15, $c_r = 1$ ; **B**: DIAT = 15, $c_r = .8$,

**C**: DIAT = 5 ($\geq$ 65 y.o.), 15 (< 25 y.o), 30 (others), $c_r = .8$.

# adaptive control: systematic analysis

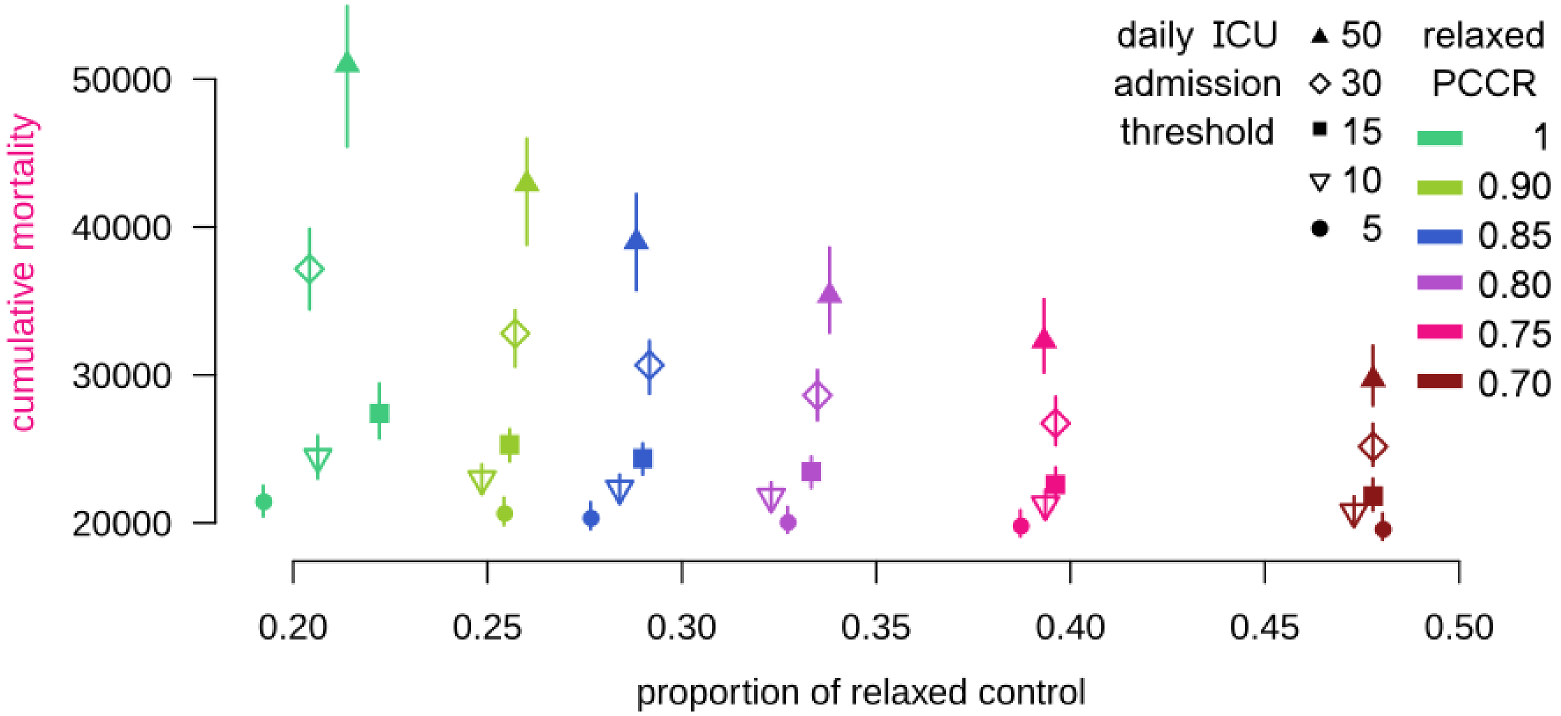


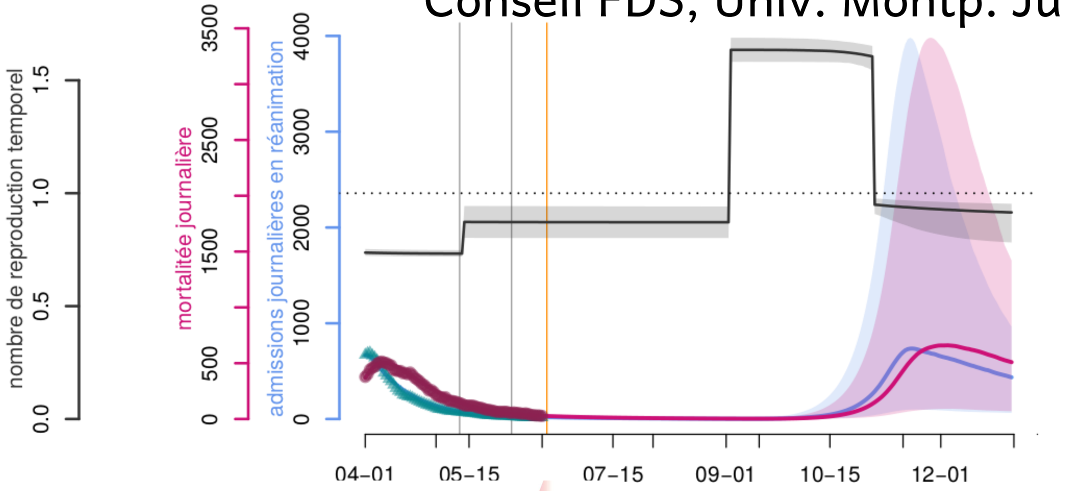

**Fig. 7. Adaptive lock-down analysis**

Each point represents a simulation of the model with adaptive lock-down implemented from May 12 given two input parameters: the lock-down triggering threshold in terms of daily ICU admissions nationwide and the PCCR during relaxed periods. The values of these parameters are respectively depicted by the shape and the color of the points, according to the legend. The abscissa show the median proportion of the time spent in the relaxed phase of each cycle. The ordinate represents the median final death toll by the end of the year, along with their 95%-confidence intervals (bars).

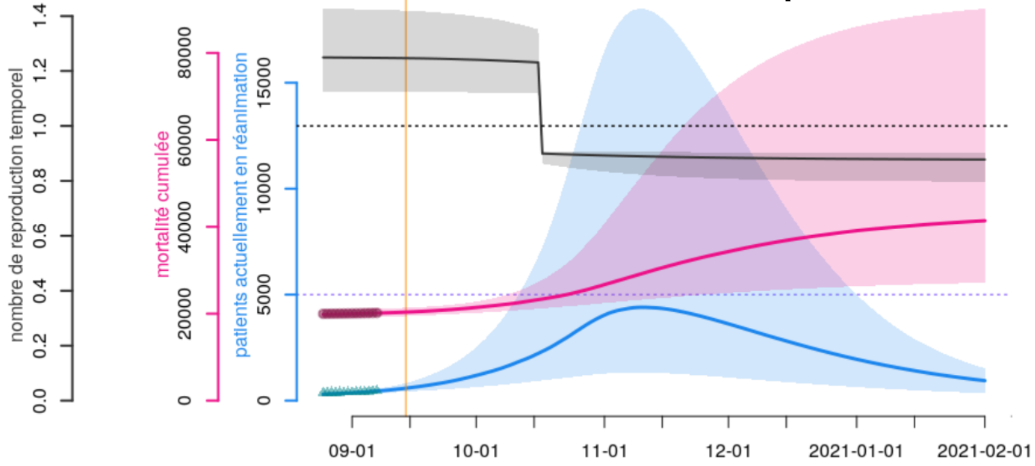
Sofonea MT (not published)

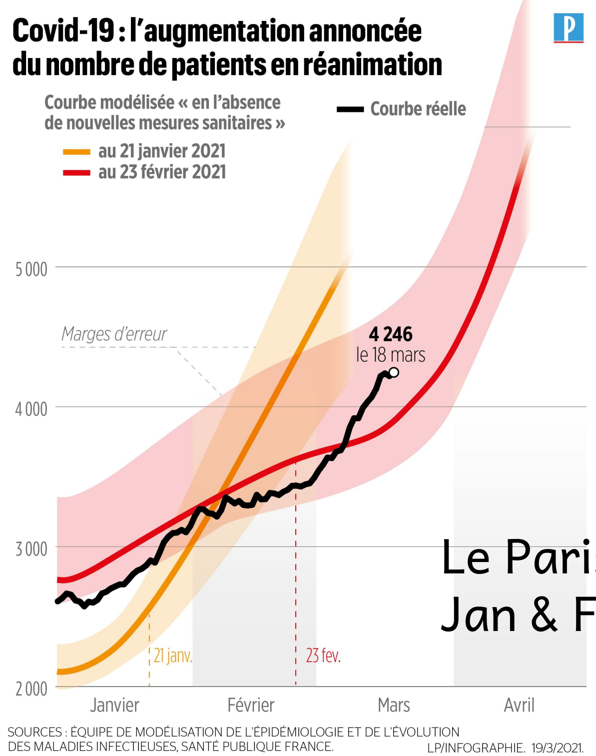
# past projections

Conseil FDS, Univ. Montp. Juin 20

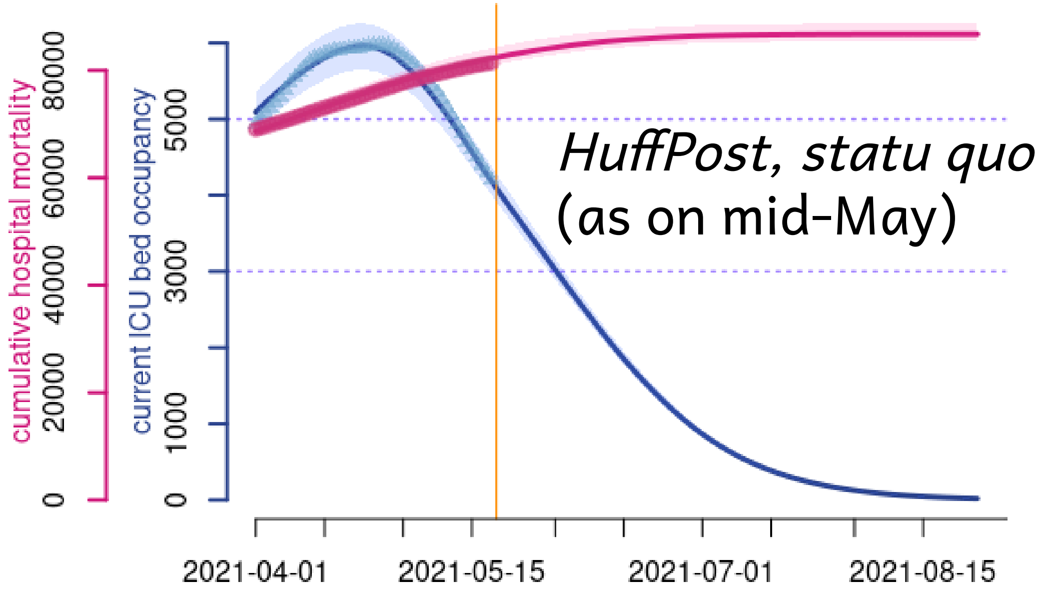



ESCMID Sept 20



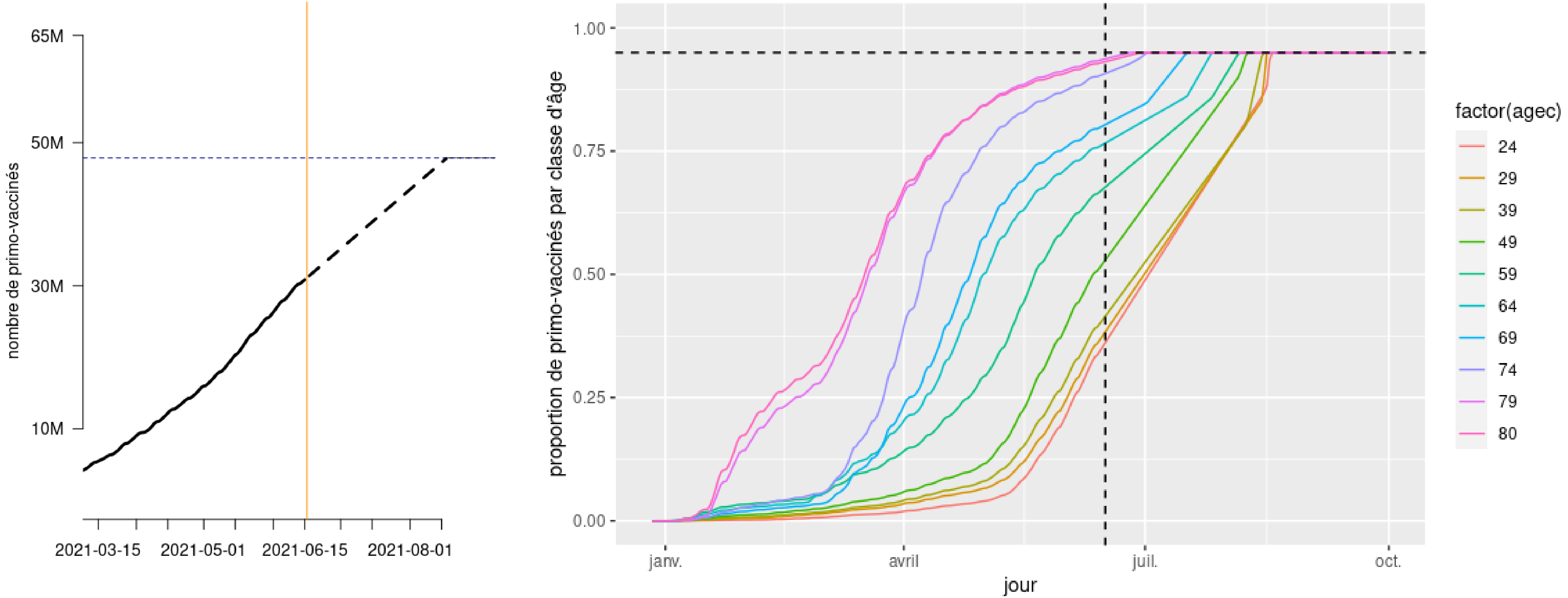

Le Parisien, Jan & Feb 21



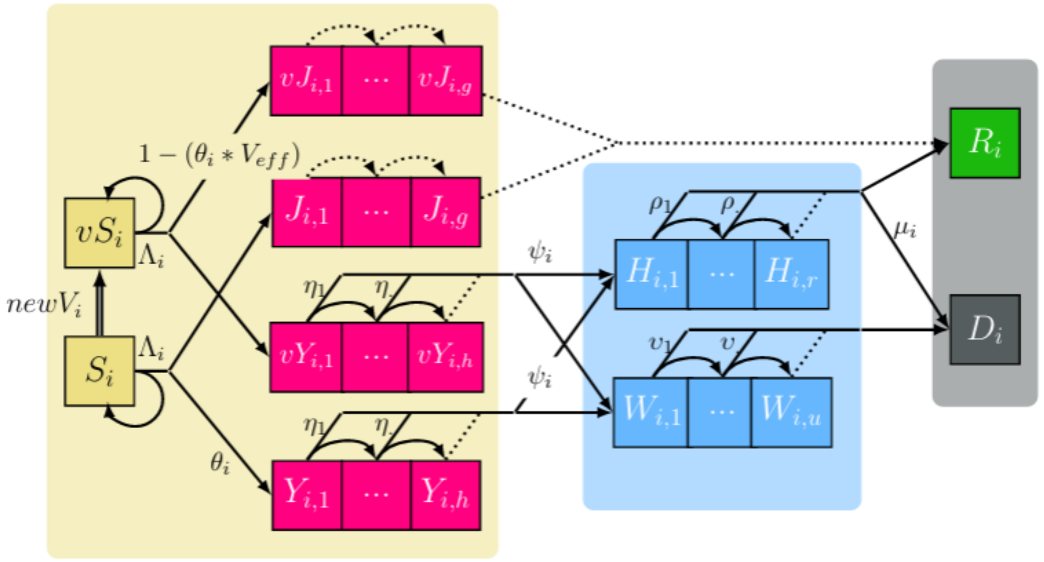

*HuffPost, statu quo (as on mid-May)*

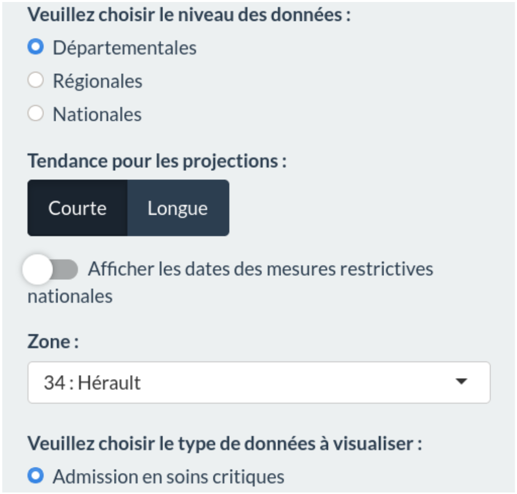
**Sofonea MT *et al.*** (2021) COVIDSIM

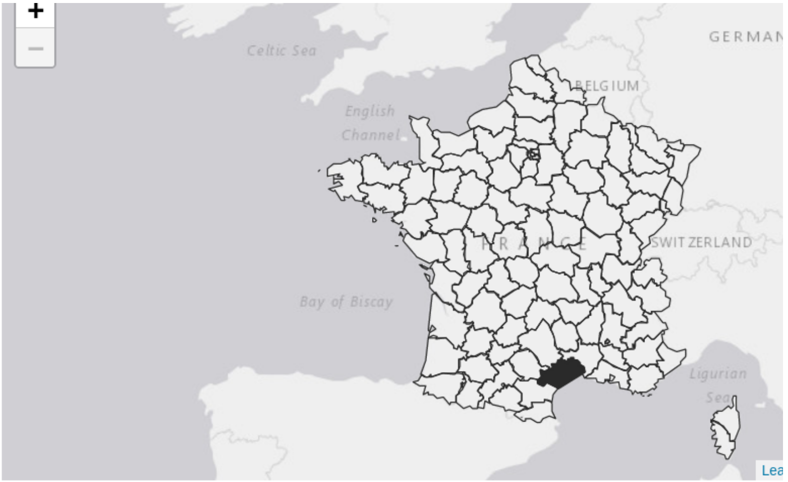
# vaccine rollout

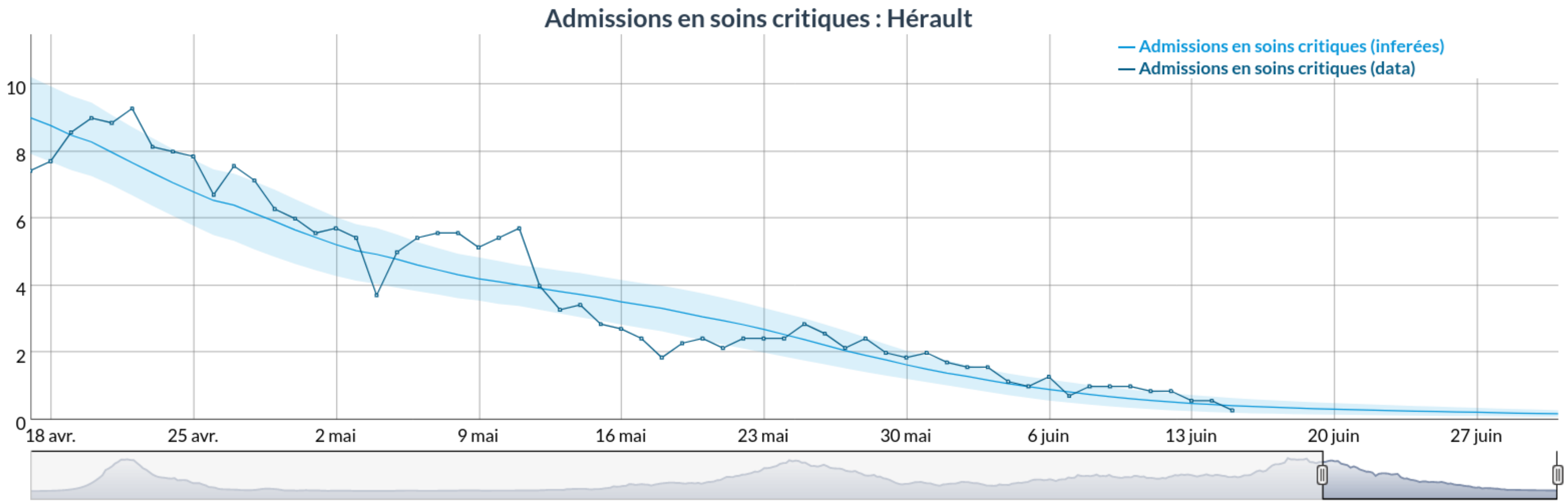


# COVIDici



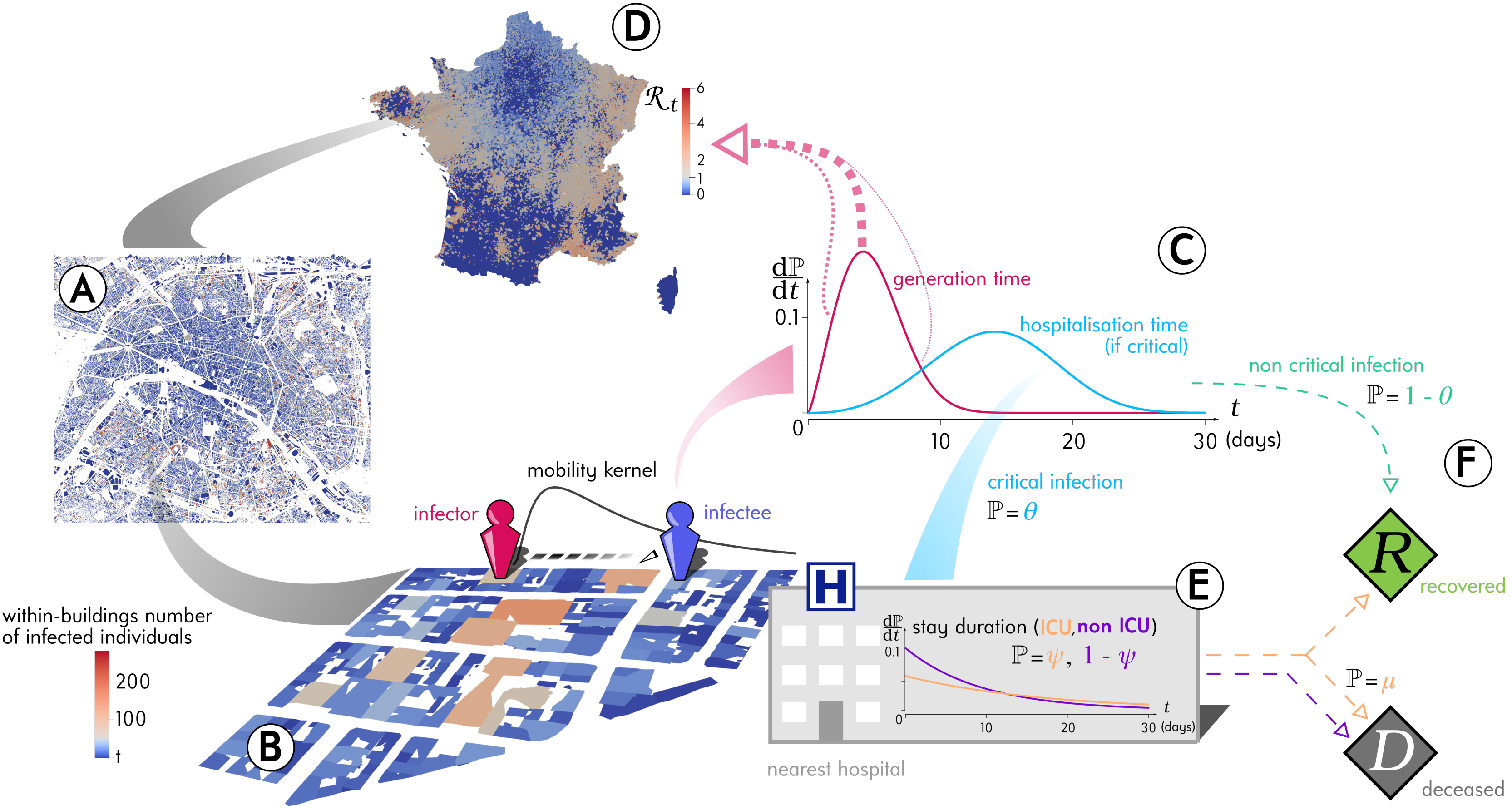


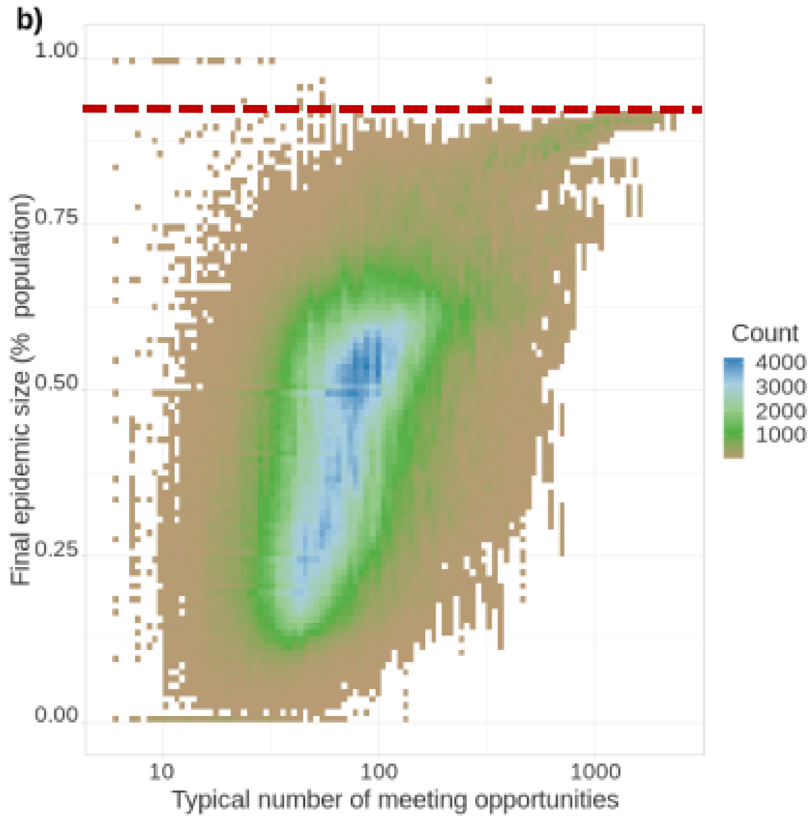






**Boennec C *et al.*** (2021) COVIDici: https://cloudapps.france-bioinformatique.fr/covidici/

# spatial considerations




Thomine O ***et al.*** (2021) Emerging dynamics from high-resolution spatial numerical epidemics. *Zenodo*

# perspectives and acknowledgments

**in brief**
- discrete time is useful for combining memory effects, parsimony & computability,
- accounting for the age of infection is crucial for short-term prediction,
- age-related control variance shows limited leverage,
- importance of early strong responses and permanent moderate restrictions

**future work**
- time-varying contact matrices
- incidence-dependent NPIs
- implicit spatialisation


ETE modelling team

**covid-ete.ouvaton.org**

@ete_fr

Samuel Alizon, Thomas Bénéteau, Corentin Boennec, Marc Choisy, Gonché Danesh, Ramsès Djidjou-Demasse Baptiste Elie, Yannis Michalakis, Bastien Reyné, Quentin Richard, Christian Selinger

CHU Montpellier Centre Hospitalier Universitaire: Hubert Blain, Jean Bousquet, Vincent Foulongne, Edouard Tuaillon

Cerba: Stéphanie Haim-Boukobza, Emmanuel Lecorche, Bénédicte Roquebert, Sabine Trombert, Laura Verdurme

Assistance Publique Hôpitaux de Paris: Sonia Burrel

Epidemap: Olivier Thomine

**funding** PHYEPI, La Région Occitanie Pyrénées · Méditerranée, Agence Nationale de la Recherche ANR

**logistical support** i-Trop bioinformatics, ifb

SFM Société Française de Microbiologie COVID-19 Study Group

# parameter estimates

| main input parameter | notation | maximum likelihood estimates | 95% - likelihood interval |
|---|---|---|---|
| basic reproduction number | $\mathcal{R}_0$ | 2.99 | $[2.59, 3.39]$ |
| initiation day (YY-MM-DD) | $t_0$ | 20-01-20 | [20-01-12, 20-01-28] |
| lock-down control (%) | $\kappa$ | 75.9 | $[72.9, 78.7]$ |
| critical case contamination to hospitalization interval expectation (days) | $\mathbb{E}[H]$ | 14.5 | $[13.6, 15.4]$ |
| critical case contamination to hospitalization interval variance (days$^2$) | $\mathbb{V}[H]$ | 20.0 | $[11.4, 30.9]$ |
| long ICU stay length expectation (days) | $\mathbb{E}[P]$ | 16.7 | $[14.9, 18.8]$ |
| critical case hospitalization to death interval expectation (non long-stay ICU patients (days) | $\mathbb{E}[\Upsilon]$ | 6.63 | $[6.19, 7.10]$ |
| infection fatality rate correction factor (%) | $\mathfrak{C}_{\mathrm{F}}$ | 87.2 | $[85.8, 88.5]$ |
| long-stay ICU fatality rate correction factor | $\mathfrak{C}_{\mathrm{M}}$ | 100.3 | $[100.2, 100.5]$ |
| long-stay ICU frequency correction factor | $\mathfrak{C}_{\Psi}$ | 93.8 | $[93.0, 94.5]$ |

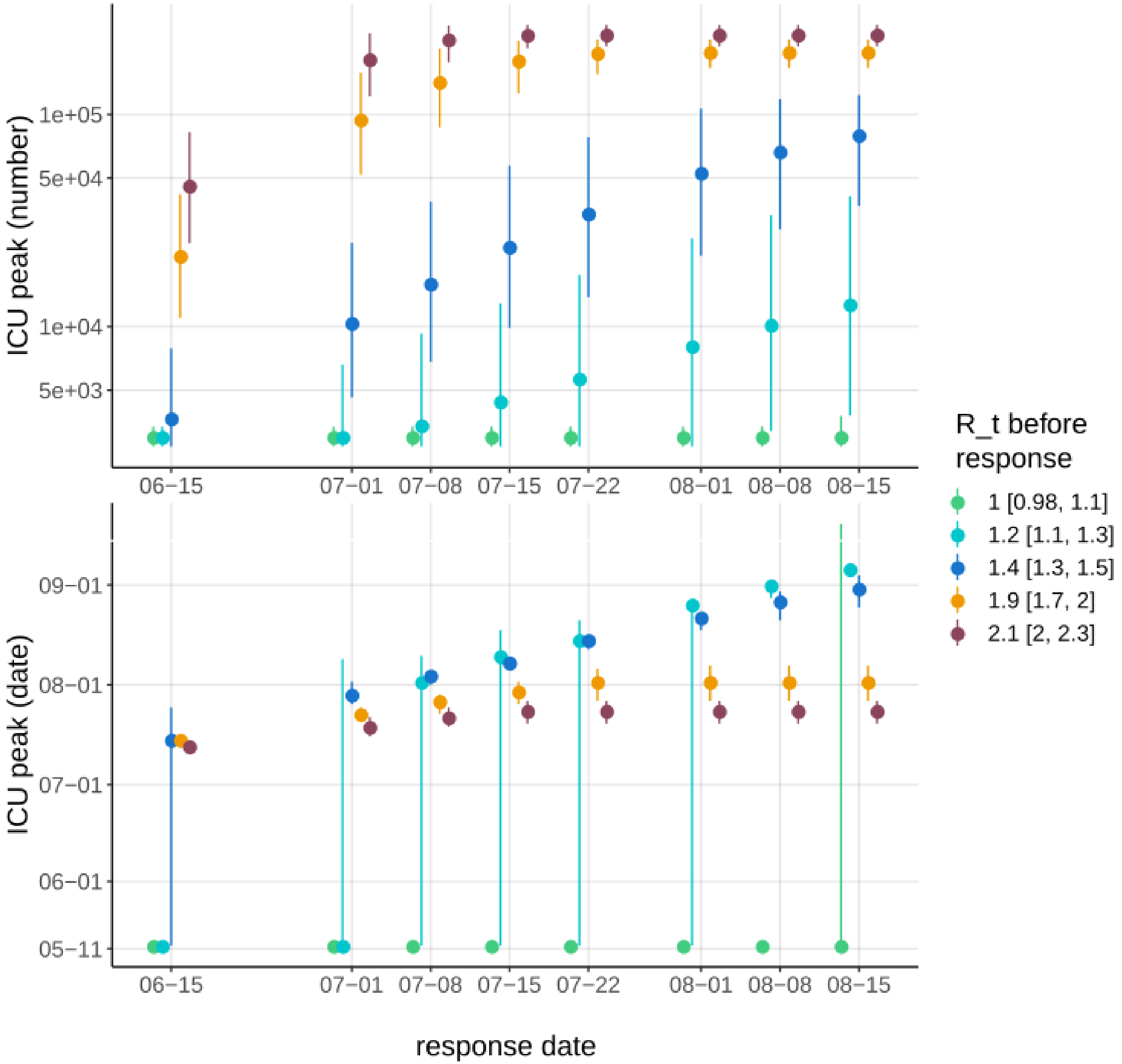
Table S-5: **Maximum likelihood estimates and associated 95% - likelihood intervals for the ten input parameters.** Details about the estimation procedure are provided in section S2.7.

# estimates with alternative IFR

| main input parameter | notation | maximum likelihood estimates | 95% - likelihood interval |
|---|---|---|---|
| basic reproduction number | $\mathcal{R}_0$ | 3.33 | $[3.16, 3.50]$ |
| initiation day (YY-MM-DD) | $t_0$ | 20-01-22 | [20-01-20, 20-01-25] |
| lock-down control (%) | $\kappa$ | 77.6 | $[76.4, 78.7]$ |
| critical case contamination to hospitalization interval expectation (days) | $\mathbb{E}[\mathrm{H}]$ | 14.0 | $[13.7, 14.3]$ |
| critical case contamination to hospitalization interval variance (days$^2$) | $\mathbb{V}[\mathrm{H}]$ | 19.4 | $[18.2, 20.6]$ |
| long ICU stay length expectation (days) | $\mathbb{E}[\mathrm{P}]$ | 19.2 | $[18.4, 19.9]$ |
| critical case hospitalization to death interval expectation (non long-stay ICU patients (days) | $\mathbb{E}[\Upsilon]$ | 9.43 | $[9.20, 9.66]$ |
| infection fatality rate correction factor (%) | $\mathfrak{C}_{\mathrm{F}}$ | 62.0 | $[61.0, 63.0]$ |
| long-stay ICU fatality rate correction factor | $\mathfrak{C}_{\mathrm{M}}$ | 110.0 | $[74.4, 146.0]$ |
| long-stay ICU frequency correction factor | $\mathfrak{C}_{\Psi}$ | 100.2 | $[100.1, 100.2]$ |

Table S-6: **Maximum likelihood estimates and associated 95% - likelihood intervals for the ten input parameters using alternative IFR values.** Details about the estimation procedure are provided in section S2.7.

# post-lock-down response delay



# adaptive control: threshold

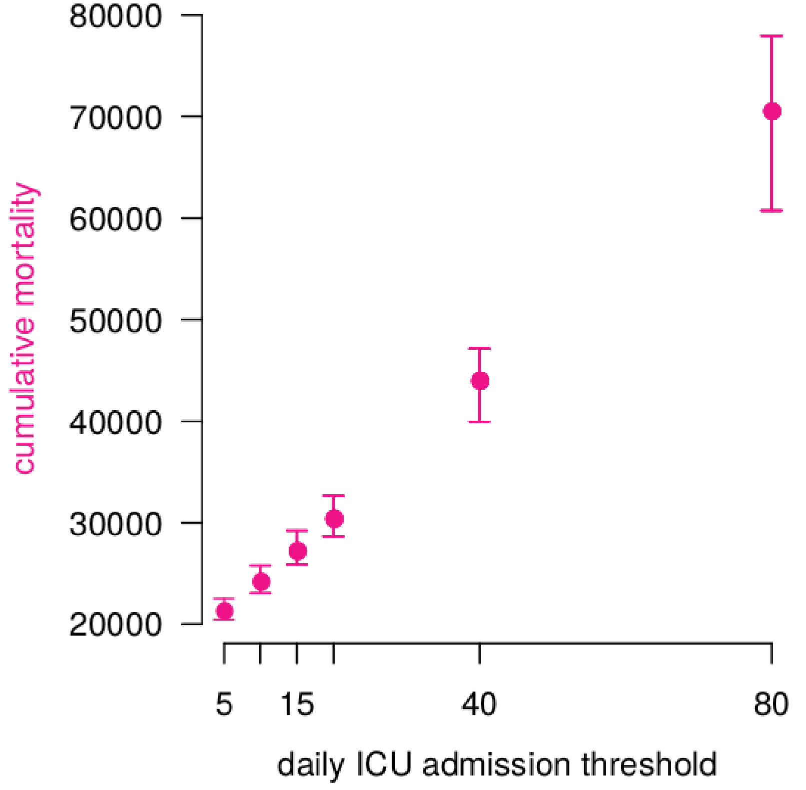



Figure S-8: **Adaptive lock-down threshold impact**
Each dot represents a simulation of the model with adaptive lock-down implemented from May 12. The abscissa show the lock-down triggering threshold in terms of daily ICU admissions nationwide. The ordinate represents the median final death toll by the end of the year, along with their 95%-confidence intervals. Lock-down lifting threshold variation has negligible impact on the results (not shown here).