The epiMOX-SUIHTER model

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European COVID Forecast HUB
October 20th, 2021

Contribution of the epiMOX work group

- design and calibration of a new compartmental model for COVID-19
- analysis and visualization of epidemiological data (epiMOX dashboard)
- enable what-if and forecast scenarios

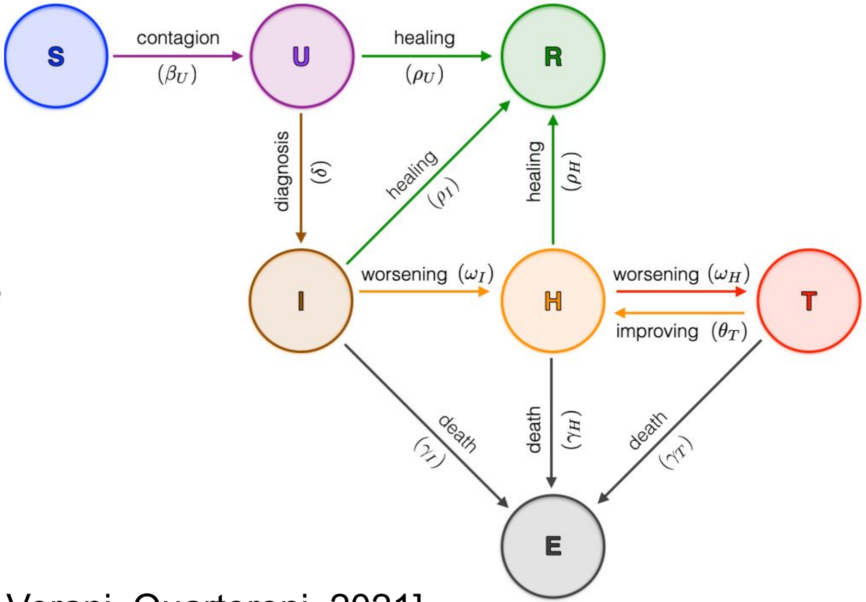
Wishlist for the new model:

- set of compartments matching the available data
- capability to account for the infected but undetected individuals
- parameters depending on different phases of the epidemic due to different NPI (Non-Pharmaceutical Interventions), improvement of therapies and vaccination
- possibility to describe different NPIs scenarios
- forecast capability for critical indicators

The SUIHTER epidemiological model

- a new compartmental model designed around the available epidemiological data daily supplied by DPC (Dipartimento della Protezione Civile)
- parameters: β_U (transmission rate), δ (detection rate), $\omega_{I,H}$ (worsening rates), θ_T (improving rate), $\rho_{U,I,H}$ (recovery rates), $\gamma_{I,H,T}$ (mortality rates)

SUSCEPTIBLES	$\dot{S}(t) = -S(t)\dfrac{\beta_U U(t)}{N},$
UNDETECTED	$\dot{U}(t) = S(t)\dfrac{\beta_U U(t)}{N} - (\delta + \rho_U) U(t),$
ISOLATED	$\dot{I}(t) = \delta U(t) - (\rho_I + \omega_I + \gamma_I) I(t),$
HOSPITALIZED	$\dot{H}(t) = \omega_I I(t) - (\rho_H + \omega_H + \gamma_H) H(t) + \theta_T T(t),$
THREATENED	$\dot{T}(t) = \omega_H H(t) - (\theta_T + \gamma_T) T(t),$
EXTINCT	$\dot{E}(t) = \gamma_I I(t) + \gamma_H H(t) + \gamma_T T(t),$
RECOVERED	$\dot{R}(t) = \rho_U U(t) + \rho_I I(t) + \rho_H H(t)$



[P., Dede', Antonietti, Ardenghi, Manzoni, Miglio, Pugliese, Verani, Quarteroni, 2021]
https://doi.org/10.1098/rspa.2021.0027

Model parameters

- Some parameters are assumed to be **constant in time**: the detection rate δ, the improving rate θ_T, the isolated mortality rate γ_I and the recovery rates ρ_U, ρ_I, ρ_H
- The others (β_U, ω_H, ω_T, γ_T) are piecewise constant on time, to better fit the phases corresponding to specific critical events.
- e.g., for the second epidemic wave (Fall 2020), starting on August 20, 2020, we considered 10 phases associated to introduction of NPIs.

Two-step calibration procedure based on:

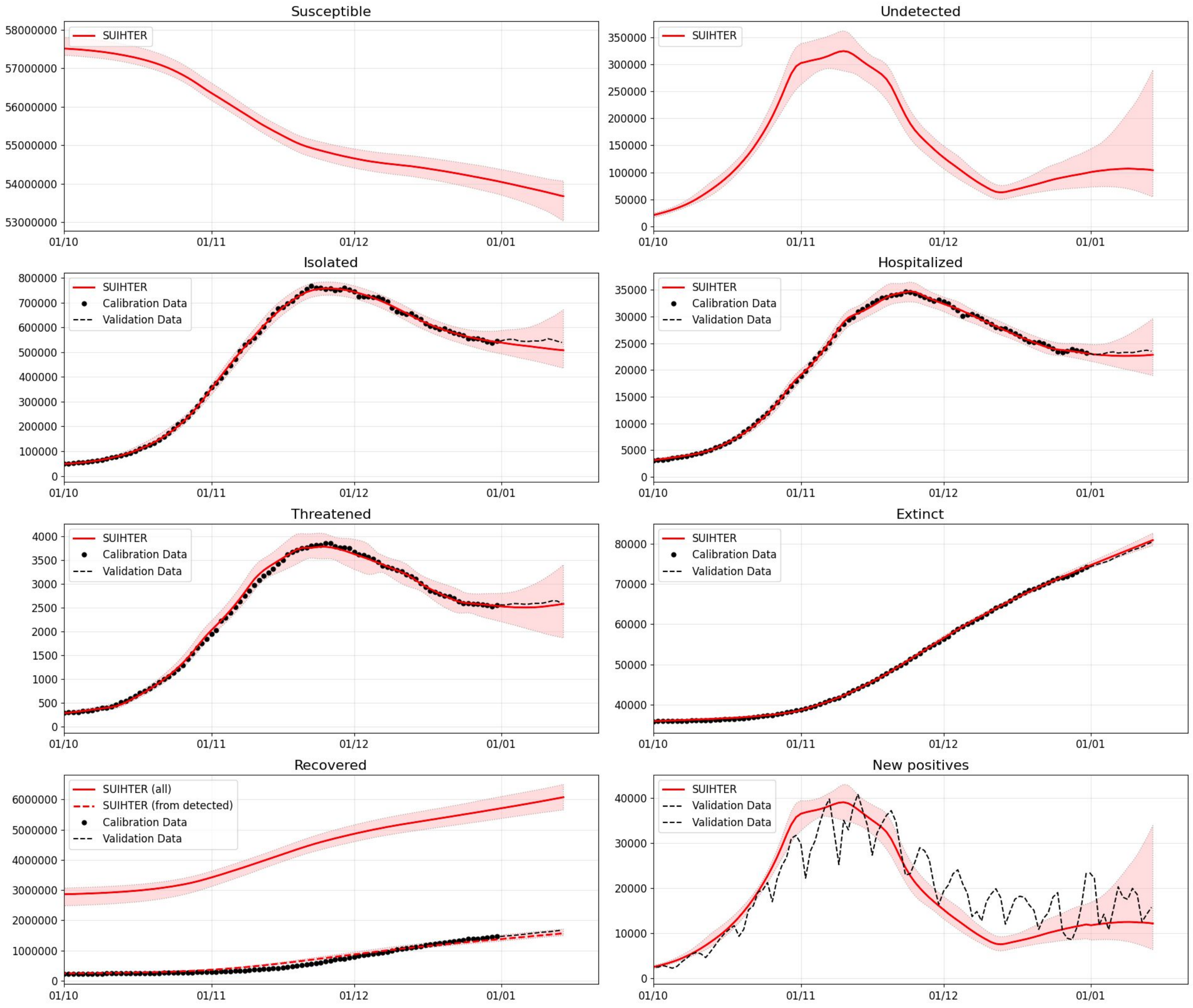
1. **least-square procedure** to evaluate the parameters, best fitting the measured time-series of the **Isolated ad home**, **Hospitalized**, **Threatened** and **Expired** compartments

$$\mathcal{J}(\mathbf{p}) := \sum_{j=1}^{n_{me}} \sum_{k=\{I,H,T,E,R_D\}} \alpha_k(t_j) \|\mathbf{Y}_k(t_j, \mathbf{p}) - \hat{\mathbf{Y}}_k(t_j)\|_2^2$$

2. **Monte-Carlo Markov Chain (MCMC)** procedure to compute the posterior probability distribution of the parameters starting from prior distributions centered on the least-square estimates

Simulation of the second outbreak in Italy

- good fitting with the data
- capability of the model to reconstruct non calibrated time series (e.g. *New positives* and *Recovered)*
- accurate short term forecast

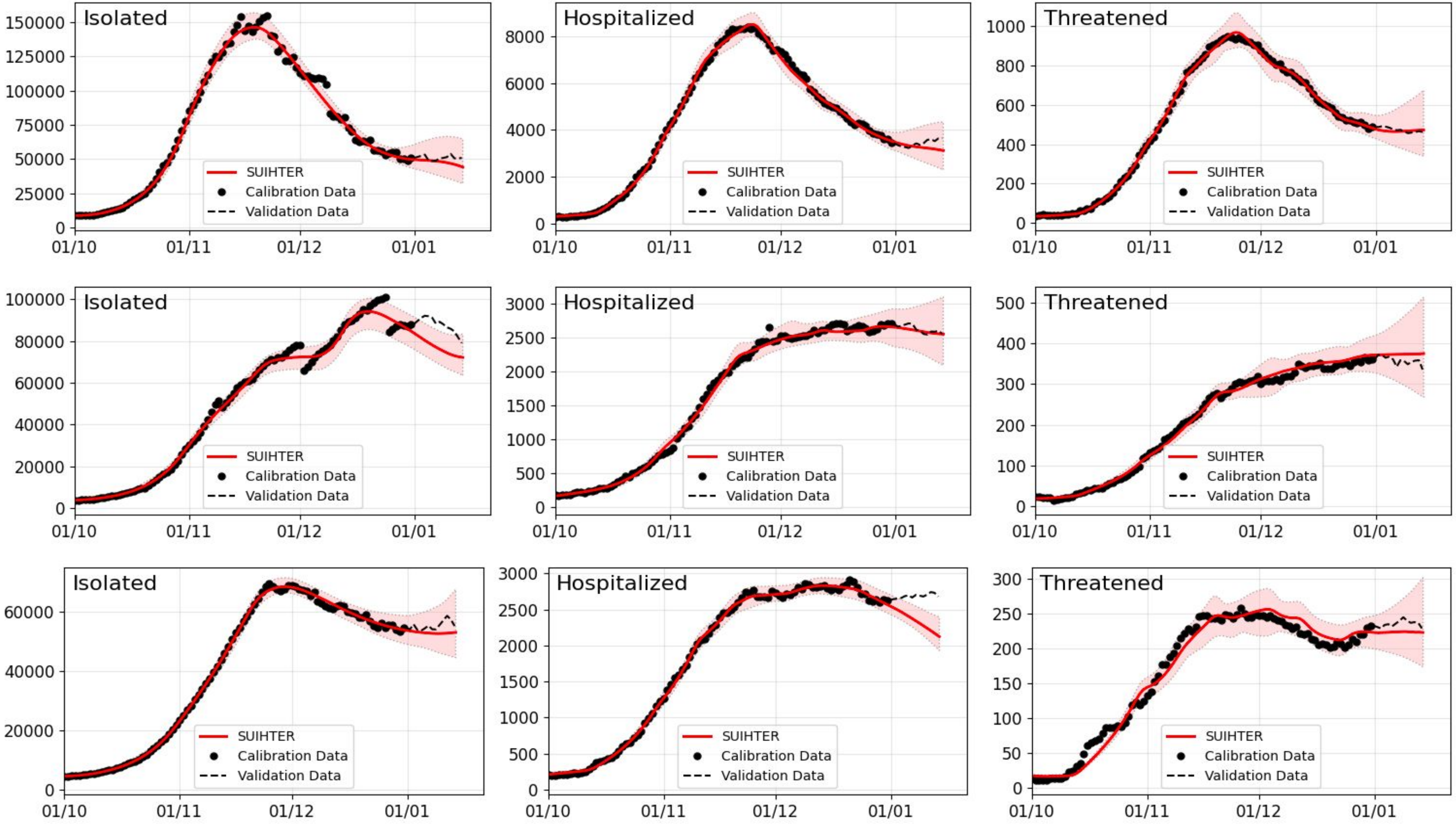


Simulation of the second outbreak - regional level

Lombardia

Veneto

Emilia-Romagna



Model initialization

- The model can be calibrated starting from an arbitrary time instant t_0
- Reinitialization strategy for compartments not covered by data is required, namely U and R (data on recovered only include recovered that were previously detected)
- The initialization is based on the Infection Fatality Ratio (IFR=1.2%, assumed constant) and a time-dependent Case Fatality Ratio CFR(t) over a moving time window [t-Δt/2, t+Δt/2] with Δt=28 days

$$\mathrm{IFR} = \frac{E}{R+E} \qquad \mathrm{CFR}(t) = \frac{\Delta E(t)}{\Delta R_D(t) + \Delta E(t)}$$

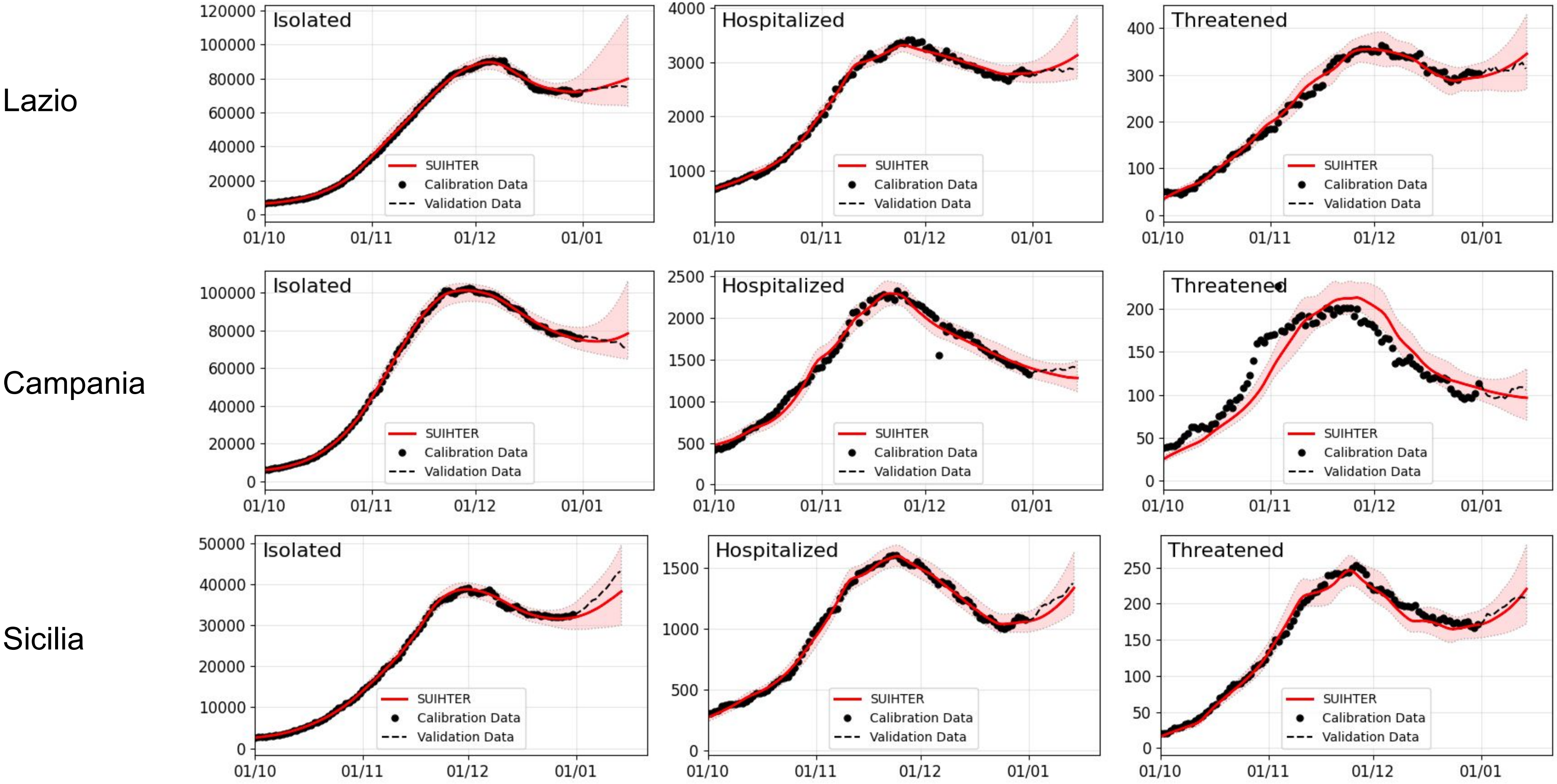
- The Undetected and Recovered compartments at a given time can be estimated as

$$R(t) = \left(\frac{1}{\mathrm{IFR}} - 1\right) E(t) \qquad U(t) = \left(\frac{\mathrm{CFR}(t+d)}{\mathrm{IFR}} - 1\right) (I(t) + H(t) + T(t))$$

- Total Recovered was estimated to around 4.8% of the population at August 20, 2020, in line with others estimates [1,2]

[1] Marziano et al. *Retrospective analysis of the Italian exit strategy from {COVID}-19 lockdown*, PNAS, 2021
[2] O'Driscoll et al, *Age-specific mortality and immunity patterns of SARS-CoV-2 infection in 45 countries*, Nature, 2021

Simulation of the second outbreak - regional level

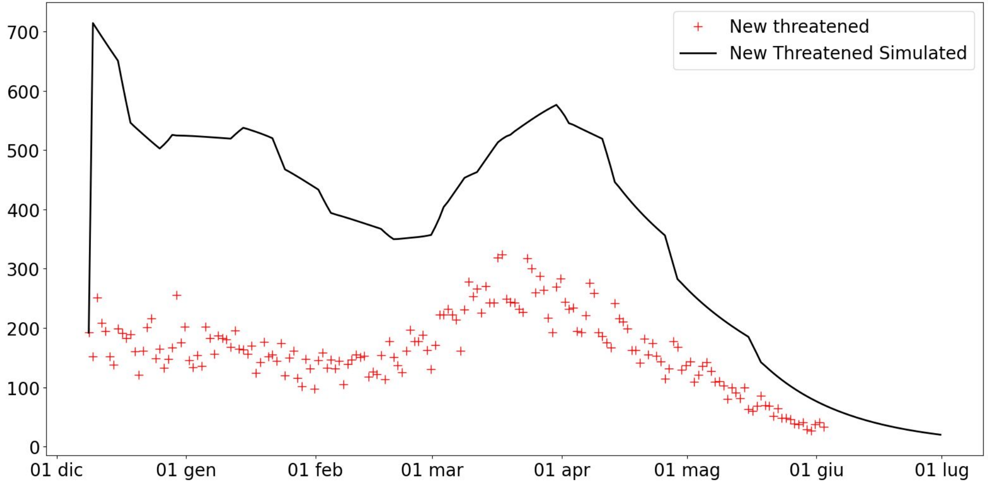


Model limitations

- Reducing the number of time dependent parameters would improve the efficiency and robustness of the calibration process

- When additional data became available (e.g. new admission in ICUs), we had the evidence that some fluxes were not accurately estimated by the model

- Not always easy to identify the temporal phases with changes of environmental conditions and NPIs



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New data improve the model\

- Reduction of free model parameters by exploiting new data that were made available

- Worsening rates ω_I and ω_H obtained from new DPC and ISS data

$$\omega_I(t) \approx \frac{nH_{ISS}(t)}{I(t)} \qquad \omega_H(t) \approx \frac{nT(t)}{H(t)}$$

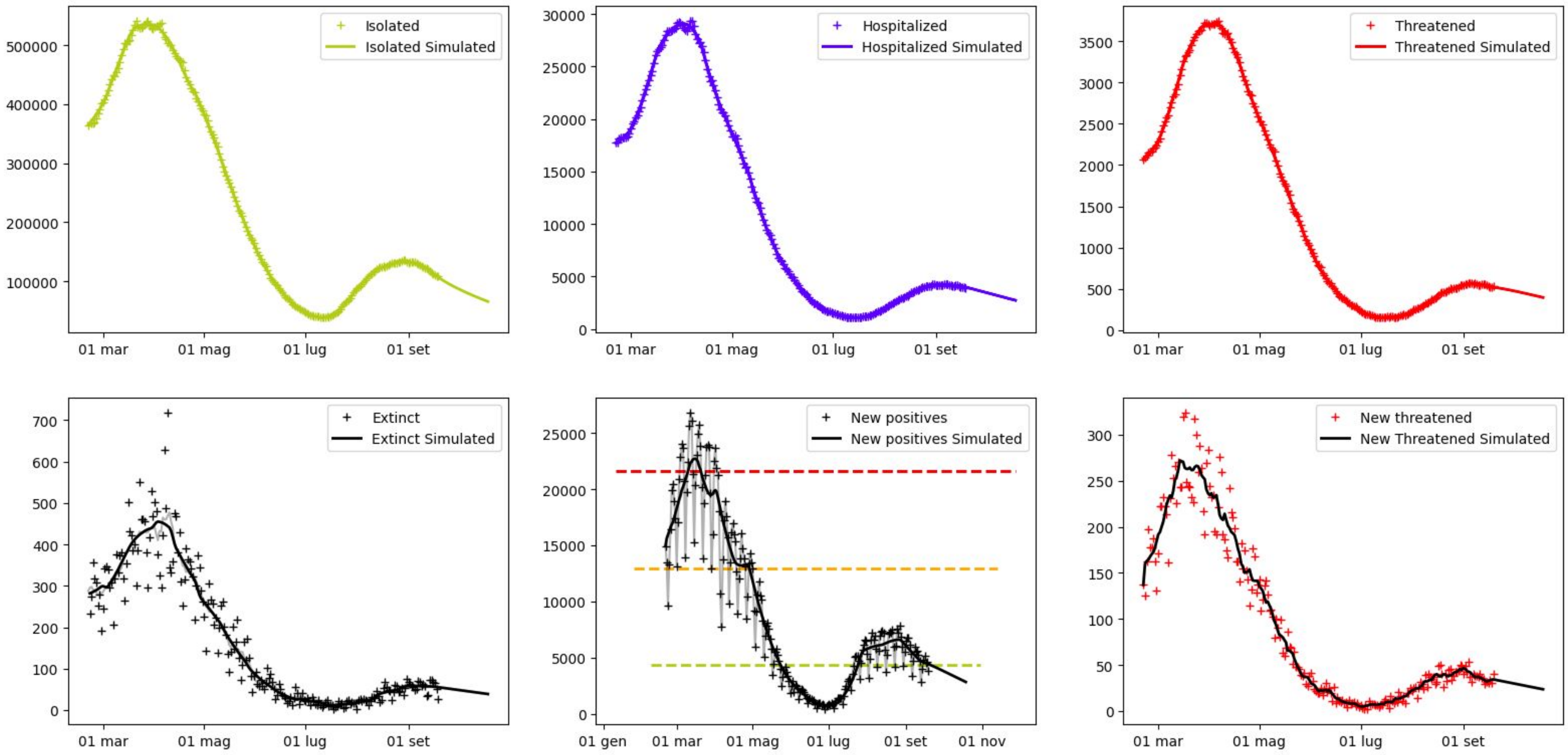
- Detection rate δ estimated from data based on IFR and time-dependent CFR(t)

$$\delta(t) = \frac{1}{t_d} p_d(t) = \frac{1}{t_d} \frac{IFR}{CFR(t+d)}$$

- Improved match on some compartment fluxes

- Temporal phases are now fixed a-priori with a uniform time duration (typically 2 weeks)

New data improve the model



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Accounting for virus variants

The SUIHTER model was extended to include the appearance of new variants and their increased prevalence (Alfa has 37% higher transmission rate than wild-type virus, Delta has 50% higher transmission rate than Alfa)

$$\dot{S}(t) = -S(t)\,\frac{\beta_U^b\,U^b(t)+\beta_U^v\,U^v(t)}{N},$$

$$\dot{U}^b(t) = S(t)\,\frac{\beta_U^b\,U^b(t)}{N} - (\delta+\rho_U)\,U^b(t),$$

$$\dot{U}^v(t) = S(t)\,\frac{\beta_U^v\,U^v(t)}{N} - (\delta+\rho_U)\,U^v(t),$$

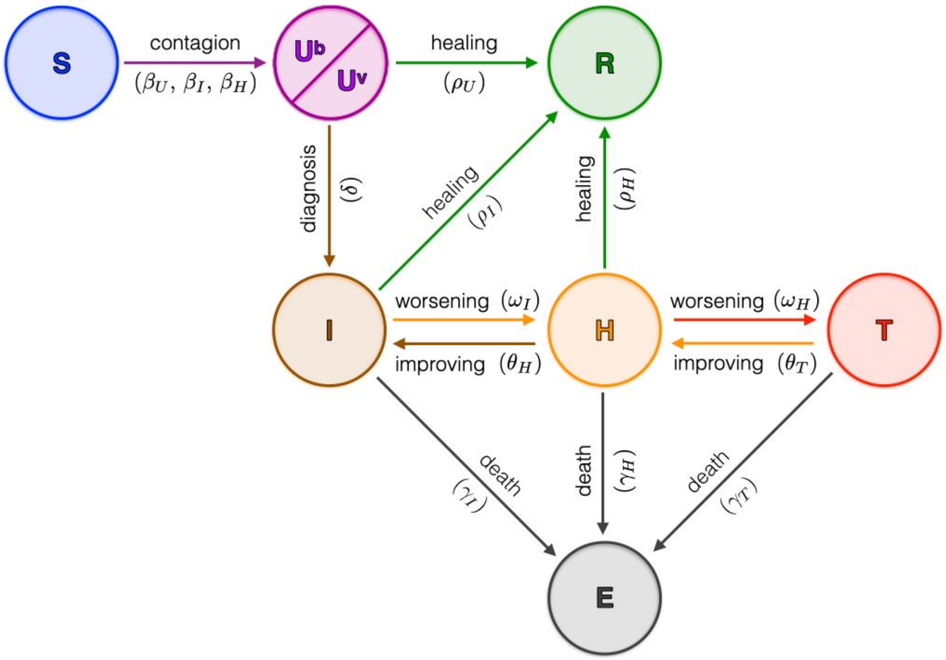
$$\dot{I}(t) = \delta\,\left(U^b(t)+U^v(t)\right) - (\rho_I+\omega_I+\gamma_I)\,I(t),$$

$$\dot{H}(t) = \omega_I\,I(t) - (\rho_H+\omega_H+\gamma_H)\,H(t) + \theta_T T(t),$$

$$\dot{T}(t) = \omega_H\,H(t) - (\theta_T+\gamma_T)\,T(t),$$

$$\dot{E}(t) = \gamma_I\,I(t) + \gamma_H\,H(t) + \gamma_T\,T(t),$$

$$\dot{R}(t) = \rho_U\,\left(U^b(t)+U^v(t)\right) + \rho_I\,I(t) + \rho_H\,H(t),$$



Accounting for virus variants

- Model adopted in February-March with Alfa variant and in May-June with Delta variant

- Variant model used for prediction from time t_0, with an initialization based on variant prevalence (p_v) data from ISS

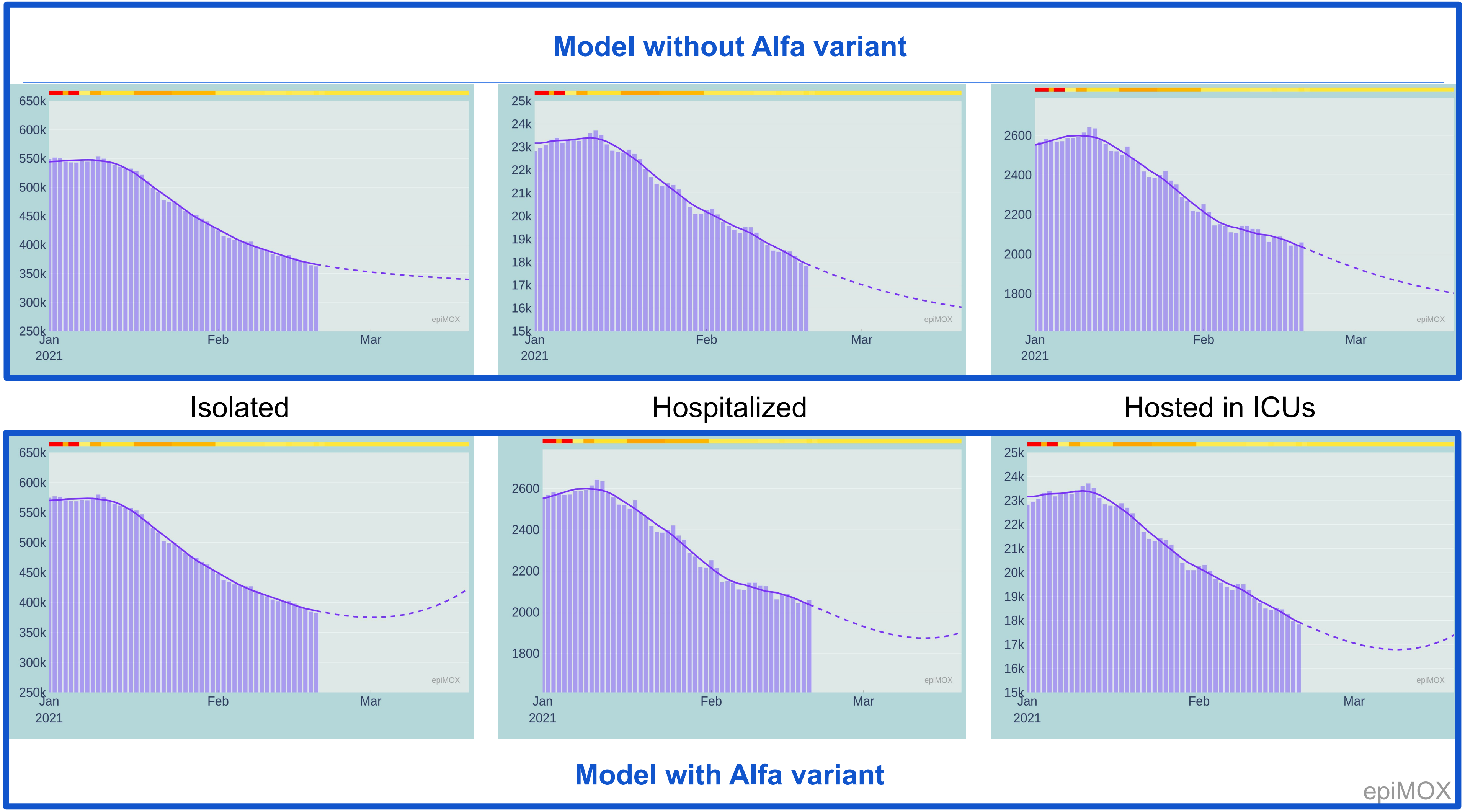
$$U^b(t_0) = (1 - p_v)U(t_0) \qquad U^v(t_0) = p_v U(t_0)$$

- Calibrated transmission rate β_U can be computed as a linear combination of the base transmission rate and the increased variant transmission rates (f_v = 1.37 for Alfa variant and f_v = 1.5 for Delta variant)

$$\beta_U(t_0) = \beta_U^b(1 - p_v(t_0)) + \beta_U^v p_v(t_0) = \beta_U^b(1 - p_v(t_0)) + \beta_U^b f_v p_v(t_0)$$

- Base and variant transmission rates can than be computed as:

$$\beta_U^b = \frac{\beta_U(t_0)}{1 + (f_v - 1)p_v(t_0)}, \qquad \beta_U^v = f_v \beta_U^b$$



Model without Alfa variant
650k
600k
550k
500k
450k
400k
350k
300k
250k
Jan
2021
Feb
Mar
epiMOX
25k
24k
23k
22k
21k
20k
19k
18k
17k
16k
15k
2600
2400
2200
2000
1800
Isolated
Hospitalized
Hosted in ICUs
Model with Alfa variant
epiMOX

Forecast scenarios

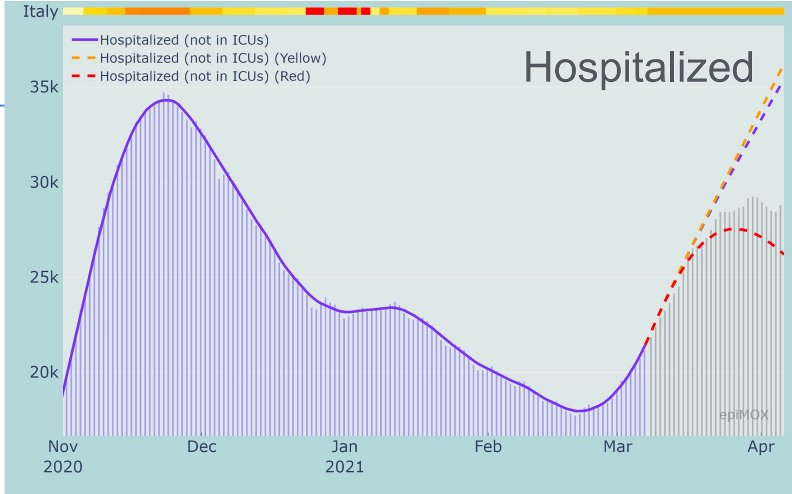
- different forecast scenarios can be explored accounting for different level of restrictions

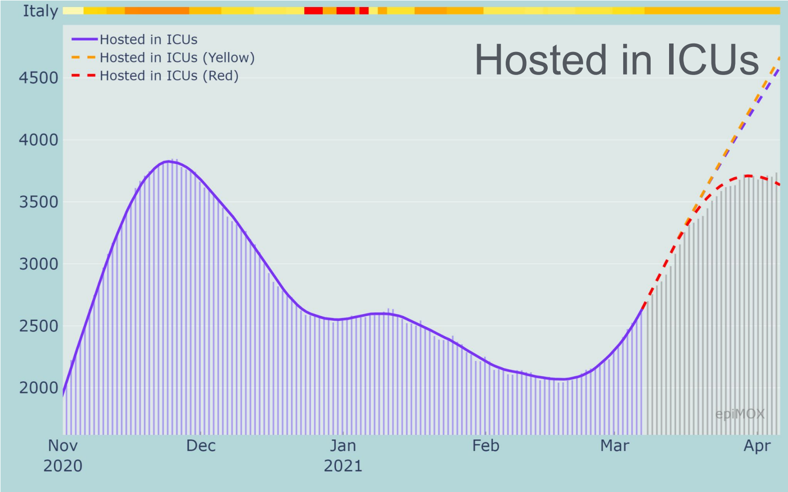
- the different restriction regimes can be associated to a restriction coefficient τ, used to model the transmission rate

$$\beta(t) = \beta(\text{today}) \frac{\tau(t)}{\tau(\text{today})}$$

- restriction coefficient τ can be estimated based on the change on contacts matrices associated to different NPIs

- **Forecast performed on March 7th**: without strict NPIs (actually adopted on March 14th), the epidemic curve would not have been controlled





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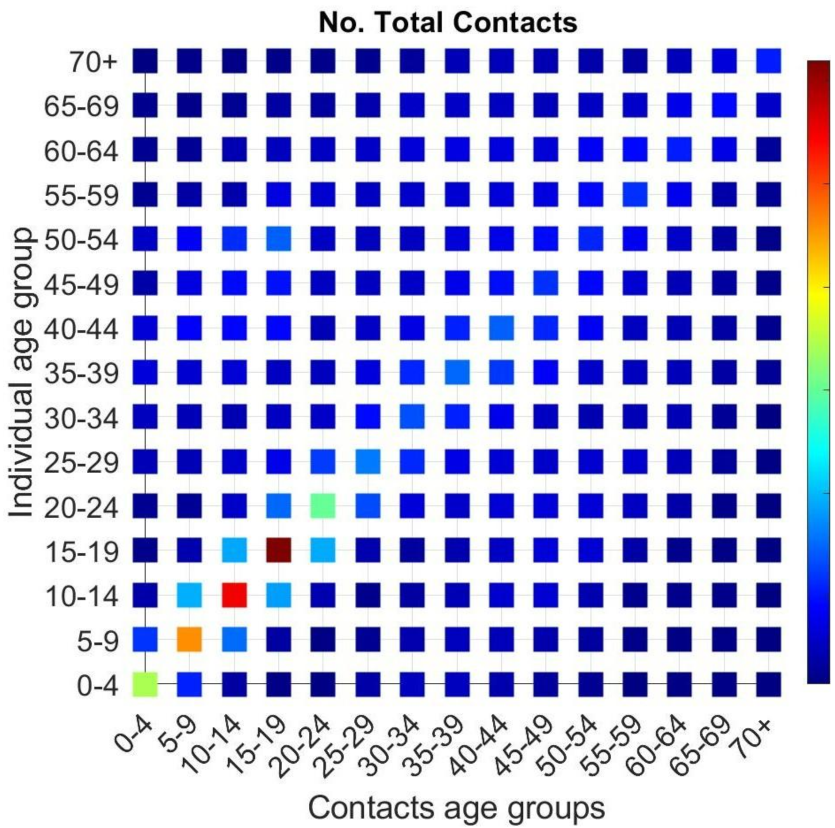
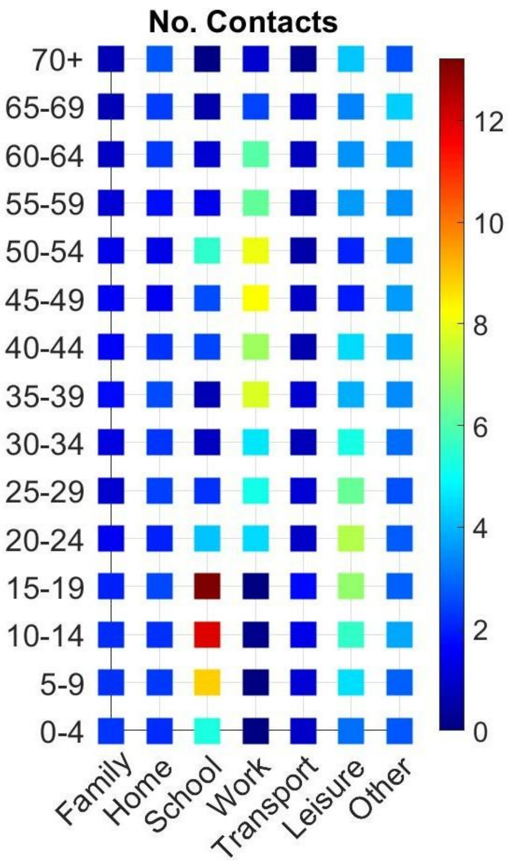
Contact matrices (POLYMOD + ISTAT)





Mossong et al, *Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases*, Plos Medicine, 2008

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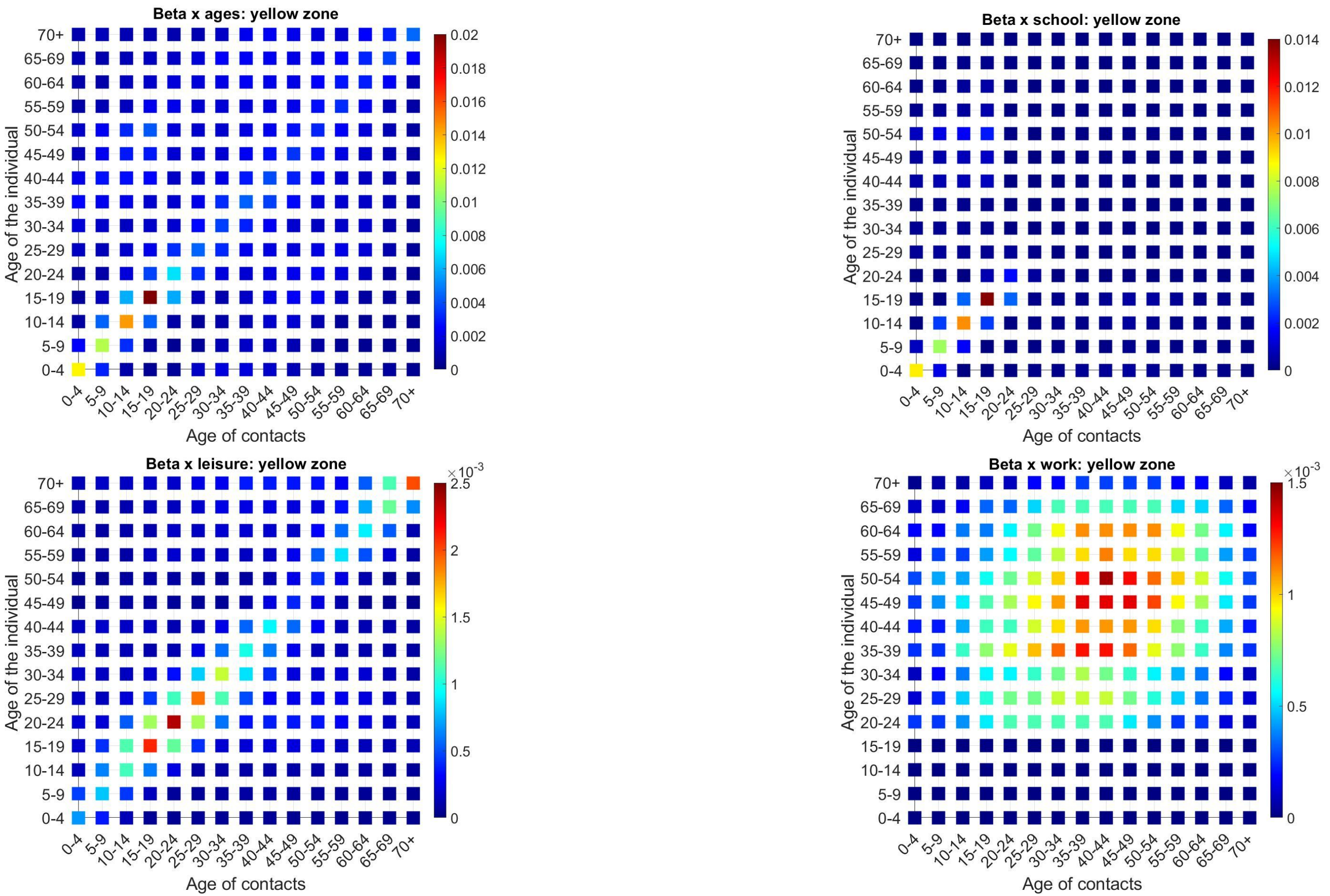
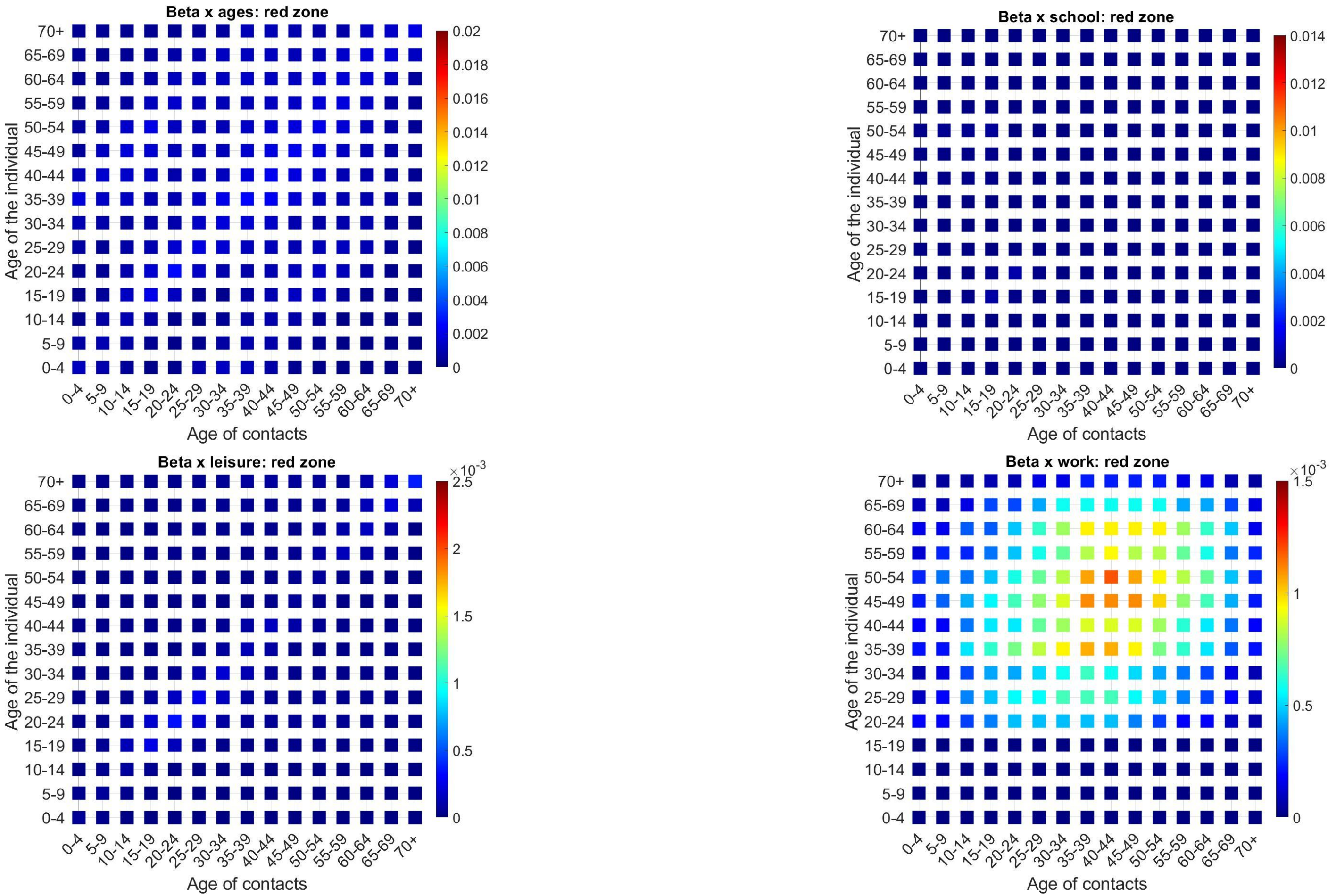
Effect of NPIs - yellow regions



Effect of NPIs - red regions



Including the vaccination campaign

Vaccines act through a reduced transmissibility after first and second dose and reduced worsening rates

$$\dot{S}(t) = -S(t)\,\frac{\beta_U^b\,U^b(t)+\beta_U^v\,U^v(t)}{N} - dV_1\,\frac{S}{S+R_U},$$

$$\dot{U}^b(t) = \left(S(t) + \sigma_1^b\,V_1 + \sigma_2^b\,V_2\right)\,\frac{\beta_U^b\,U^b(t)}{N} - (\delta+\rho_U)\,U^b(t),$$

$$\dot{U}^v(t) = \left(S(t) + \sigma_1^v\,V_1 + \sigma_2^v\,V_2\right)\,\frac{\beta_U^v\,U^v(t)}{N} - (\delta+\rho_U)\,U^v(t),$$

$$\dot{I}(t) = \delta\,(U^b(t)+U^v(t)) - (\rho_I + \bar{\omega}_I + \bar{\gamma}_I)\,I(t),$$

$$\dot{H}(t) = \bar{\omega}_I\,I(t) - (\rho_H + \bar{\omega}_H + \gamma_H)\,H(t),$$

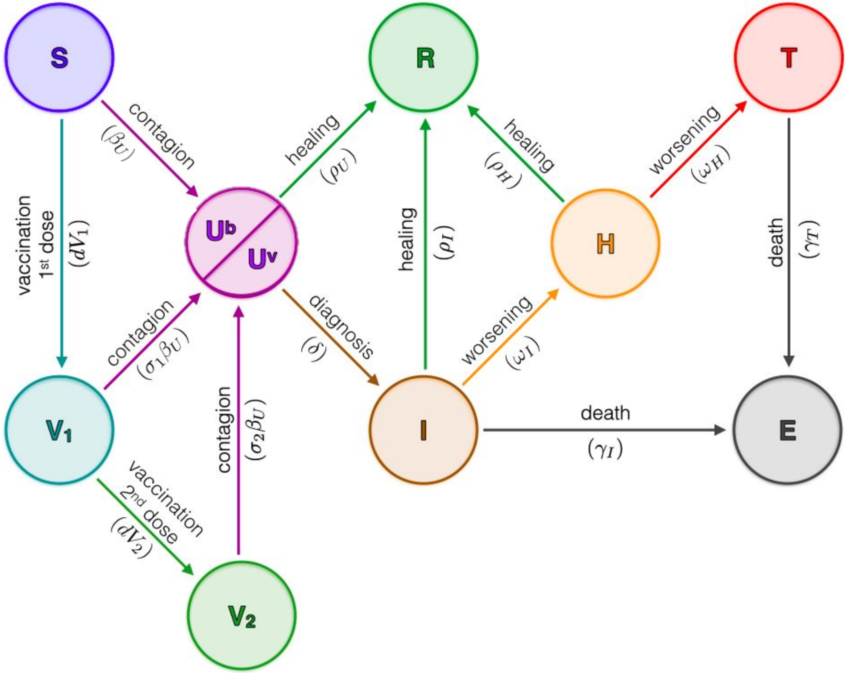
$$\dot{T}(t) = \bar{\omega}_H\,H(t) - (\theta_T + \gamma_T)\,T(t),$$

$$\dot{E}(t) = \bar{\gamma}_I\,I(t) + \gamma_H\,H(t) + \gamma_T\,T(t),$$

$$\dot{R}(t) = \rho_U\,(U^b(t)+U^v(t)) + \rho_I\,I(t) + \rho_H\,H(t),$$

$$\dot{V}_1(t) = dV_1\,\frac{S}{S+R_U} - dV_2\,\frac{S}{S+R_U} - \sigma_1^b\,V_1\,\frac{\beta_U^b\,U^b(t)}{N} - \sigma_1^v\,V_1\,\frac{\beta_U^v\,U^v(t)}{N},$$

$$\dot{V}_2(t) = dV_2\,\frac{S}{S+R_U} - \sigma_2^b\,V_2\,\frac{\beta_U^b\,U^b(t)}{N} - \sigma_2^v\,V_2\,\frac{\beta_U^v\,U^v(t)}{N},$$



Accounting for vaccines effectiveness

- Vaccinated individuals are infected with a lower probability (-70% after first dose, -88% after second dose) ⟶ lower transmission rates (σ_1=0.3, σ_2=0.12)
- Vaccines reduce probability of hospitalization, ICUs admission and mortality (from [ISS])
  - hospitalization reduction due to first and second dose: h_1, h_2
  - ICUs admission reduction due to first and second dose: t_1, t_2
  - mortality reduction due to first and second dose: m_1, m_2
- Parameters in forecast are rescaled based on the percentages of new cases that were susceptible (S) and vaccinated (V_1 or V_2) and normalized at the end of the calibration

$$u_S(t) = \frac{S}{S + \sigma_1 V_1 + \sigma_2 V_2}$$

$$u_1(t) = \frac{\sigma_1 V_1}{S + \sigma_1 V_1 + \sigma_2 V_2}$$

$$u_2(t) = \frac{\sigma_2 V_2}{S + \sigma_1 V_1 + \sigma_2 V_2}$$

⟶

$$\bar{\omega}_I(t) = \omega_I(t_0) \frac{u_S(t) + h_1 u_1(t) + h_2 u_2(t)}{u_S(t_0) + h_1 u_1(t_0) + h_2 u_2(t_0)}$$

$$\bar{\omega}_H(t) = \omega_H(t_0) \frac{u_S(t) + t_1 u_1(t) + t_2 u_2(t)}{u_S(t_0) + t_1 u_1(t_0) + t_2 u_2(t_0)}$$

$$\bar{\gamma}_I(t) = \gamma_I(t_0) \frac{u_S(t) + m_1 u_1(t) + m_2 u_2(t)}{u_S(t_0) + m_1 u_1(t_0) + m_2 u_2(t_0)}$$

[ISS] https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_8-settembre-2021.pdf

Monitoring the vaccination campaign

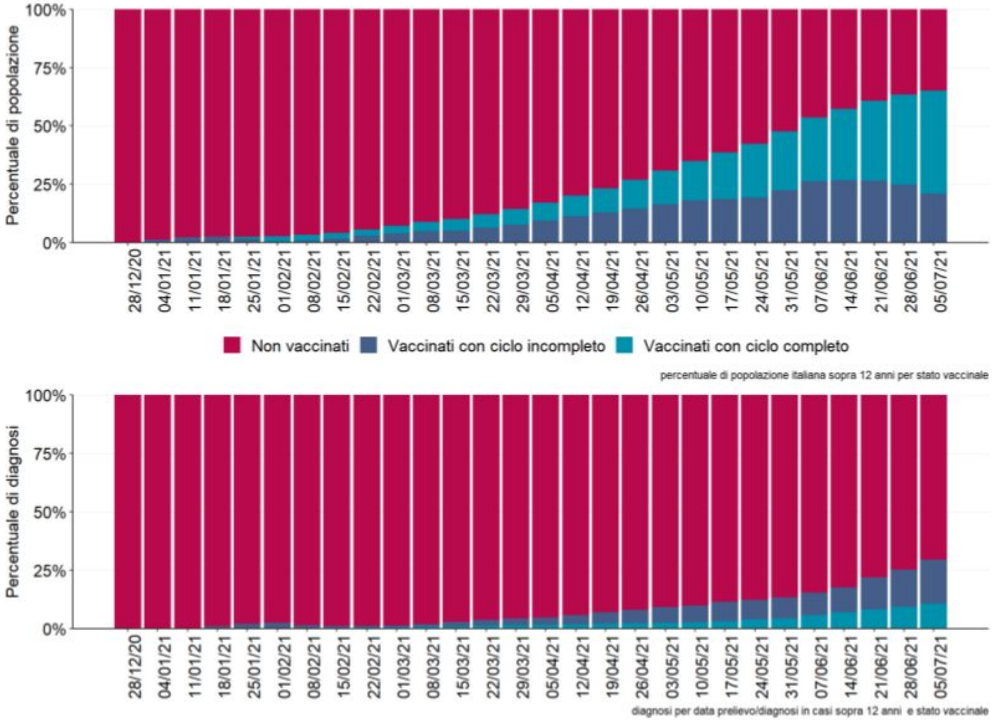


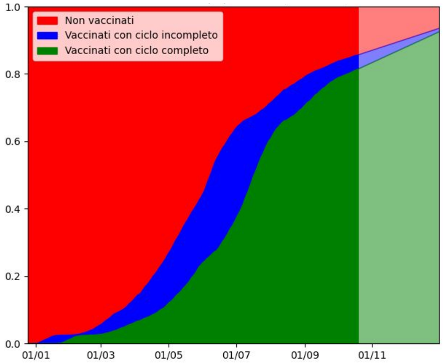
FIGURA 22 – PERCENTUALE DI POPOLAZIONE (IN ALTO) E DI CASI (IN BASSO) DI ETÀ > 12 ANNI PER STATO VACCINALE E SETTIMANA IN ITALIA, 27 DICEMBRE 2020 – 11 LUGLIO 2021

Nota: Ogni barra indica la percentuale di casi in ciascuna settimana (lunedì-domenica). La data riportata si riferisce all'inizio della settimana

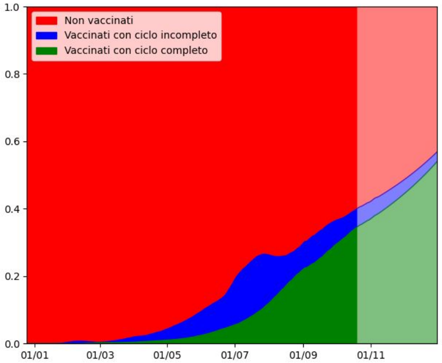
Monitoring the vaccination campaign

No vaccine
First dose
Second dose

Population

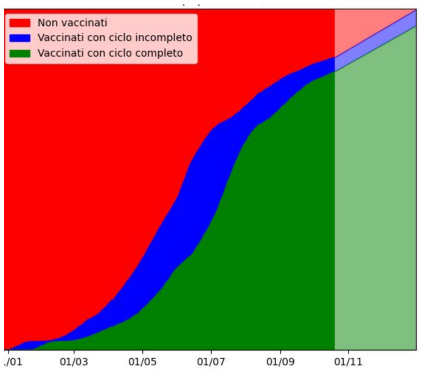


New cases

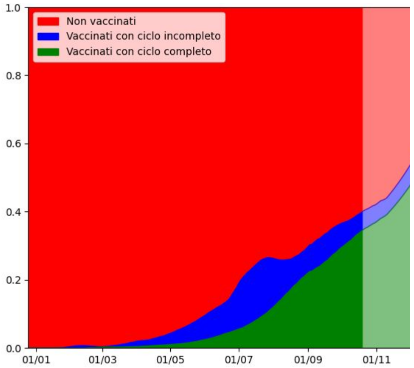


Current vaccination rate (~ 140k doses/day)

Population



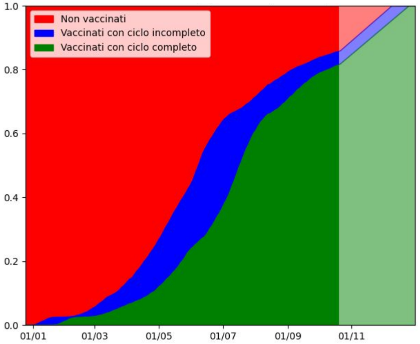
New cases



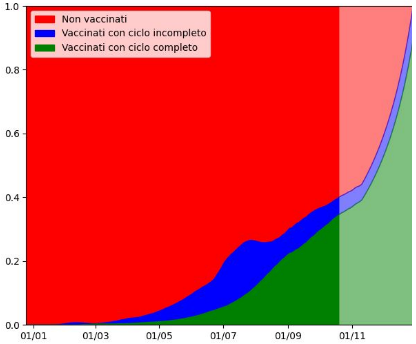
200k doses/day

- 20% of the population over 12 is still not fully vaccinated
- With current vaccination rate at the end of 2021, 50% of new cases will still be unvaccinated
- Unvaccinated are more susceptible to severe symptoms
- Current model is able to study different possible vaccination scenarios with different infected distributions

Population



New cases



300k doses/day

Model calibration

Two-step calibration procedure based on:

1. **least-square procedure** to evaluate the parameters, best fitting the measured time-series of the **Isolated ad home**, **Hospitalized**, **Threatened** and **Expired** compartments

$$\mathcal{J}(\mathbf{p}) := \sum_{j=1}^{n_{me}} \sum_{k=\{I,H,T,E,R_D\}} \alpha_k(t_j) \| \mathbf{Y}_k(t_j, \mathbf{p}) - \hat{\mathbf{Y}}_k(t_j) \|_2^2$$

2. **Monte-Carlo Markov Chain (MCMC)** procedure to compute the posterior probability distribution of the parameters starting from prior distributions centered on the least-square estimates

	Median	95% CI
δ	0.12041	[0.10739, 0.12841]
γ_I	3.78e-5	[3.43e-5, 4.15e-5]
ρ_U	0.12320	[0.11303, 0.13593]
ρ_I	0.02408	[0.02197, 0.02658]
ρ_H	0.06677	[0.06171, 0.07212]
θ_T	0.05026	[0.04517, 0.05456]
$U(t_I)$	12 571	[9 346,15 775]
$R(t_I)$	2 551 280	[2 270 830,2 832 576]

Constant parameters

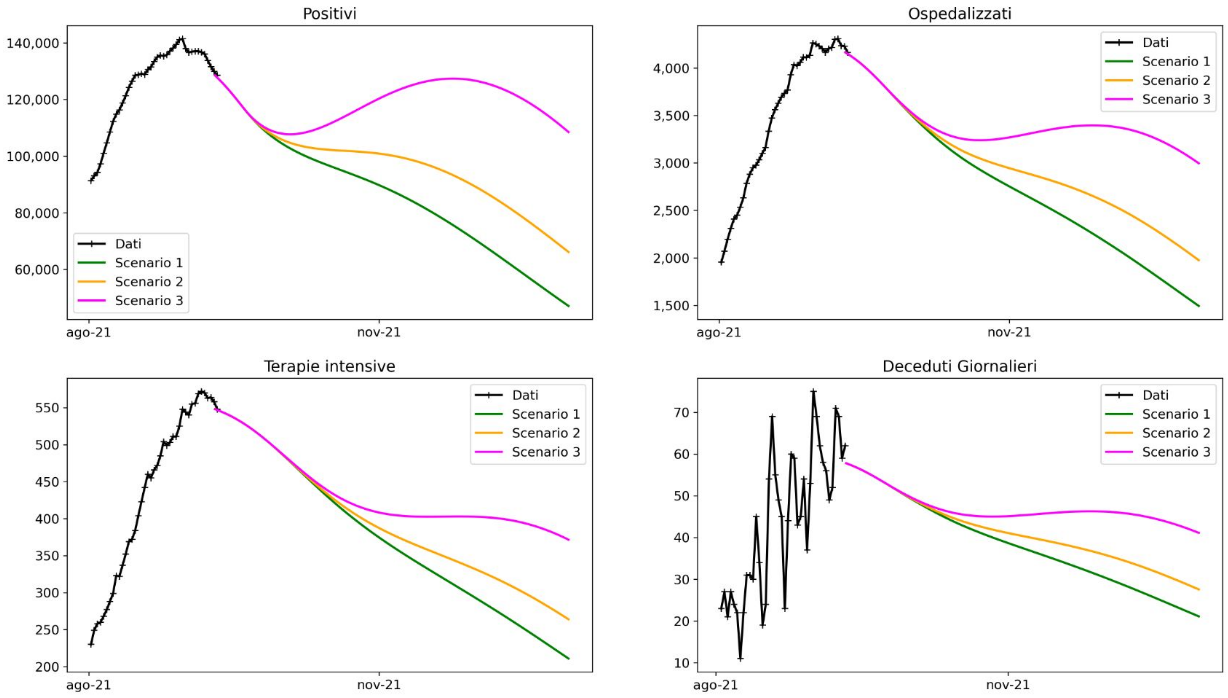
Phase	β_U		ω_I		ω_H		γ_T	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
1	0.2640	[0.2475, 0.2825]	0.0059	[0.00537, 0.00648]	0.0132	[0.0121, 0.0146]	0.0760	[0.0691, 0.0837]
2	0.3658	[0.3329, 0.3936]	0.00771	[0.00701, 0.00847]	0.0192	[0.0173, 0.0210]	0.1252	[0.1133, 0.1372]
3	0.3449	[0.3223, 0.3685]	0.00933	[0.00849, 0.01018]	0.0223	[0.0202, 0.0243]	0.0886	[0.0793, 0.0958]
4	0.2756	[0.2485, 0.2972]	0.00691	[0.00629, 0.00755]	0.0264	[0.0238, 0.0286]	0.1561	[0.1400, 0.1689]
5	0.2421	[0.2202, 0.2658]	0.00496	[0.00445, 0.00537]	0.0259	[0.0233, 0.0281]	0.1673	[0.1517, 0.1830]
6	0.1779	[0.1615, 0.1952]	0.00422	[0.00383, 0.00464]	0.0269	[0.0243, 0.0293]	0.1909	[0.1741, 0.2103]
7	0.2093	[0.1906, 0.2307]	0.00340	[0.00309, 0.00373]	0.0263	[0.0238, 0.0286]	0.1900	[0.1726, 0.2079]
8	0.1924	[0.1743, 0.2109]	0.00313	[0.00283, 0.00342]	0.0251	[0.0226, 0.0272]	0.1872	[0.1708, 0.2055]
9	0.3052	[0.2780, 0.3354]	0.00309	[0.00281, 0.00339]	0.0244	[0.0223, 0.0269]	0.1924	[0.1729, 0.2086]
10	0.2949	[0.2686, 0.3251]	0.00351	[0.00319, 0.00385]	0.0249	[0.0226, 0.0272]	0.1867	[0.1700, 0.2053]

Time-varying parameters

Vaccine model in action - 1

Scenario analysis on the effect of the school reopening combined with the application of GreenPass in schools and universities:

- Scenario 1: with GreenPass applied 100%
- Scenario 2: with GreenPass applied 50%
- Scenario 3: without GreenPass

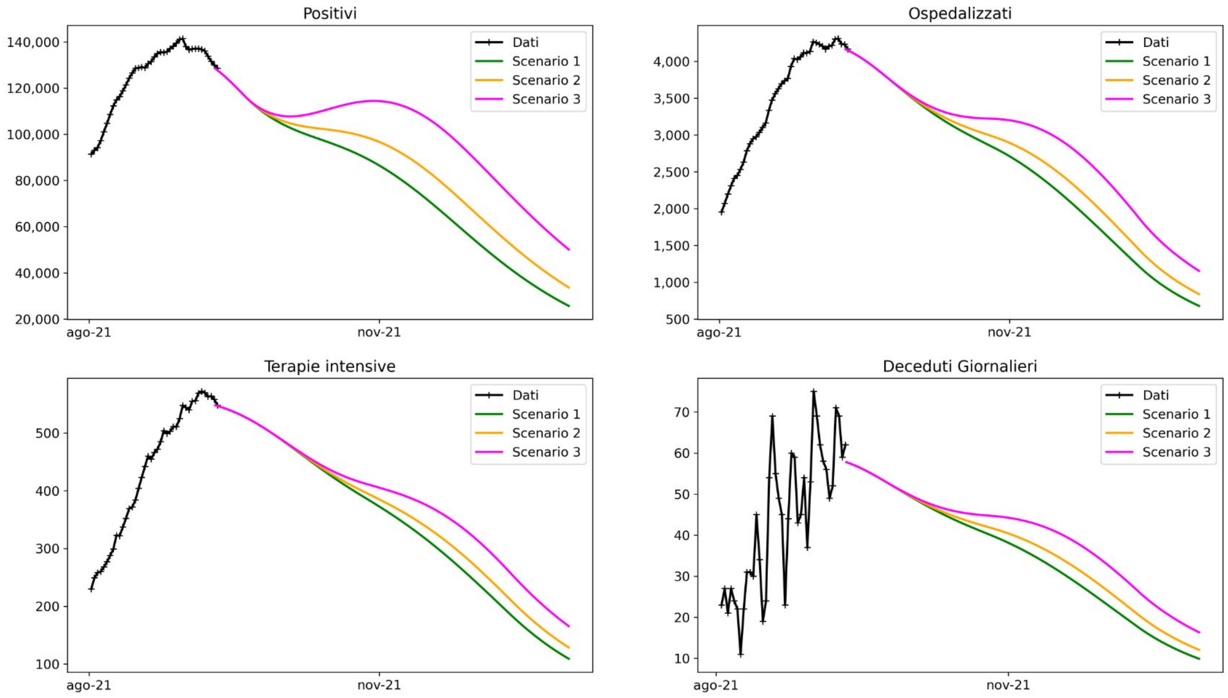


Current vaccination rate

Vaccine model in action - 2

Scenario analysis on the effect of the school reopening combined with the application of GreenPass in schools and universities:

- Scenario 1: with GreenPass applied 100%
- Scenario 2: with GreenPass applied 50%
- Scenario 3: without GreenPass

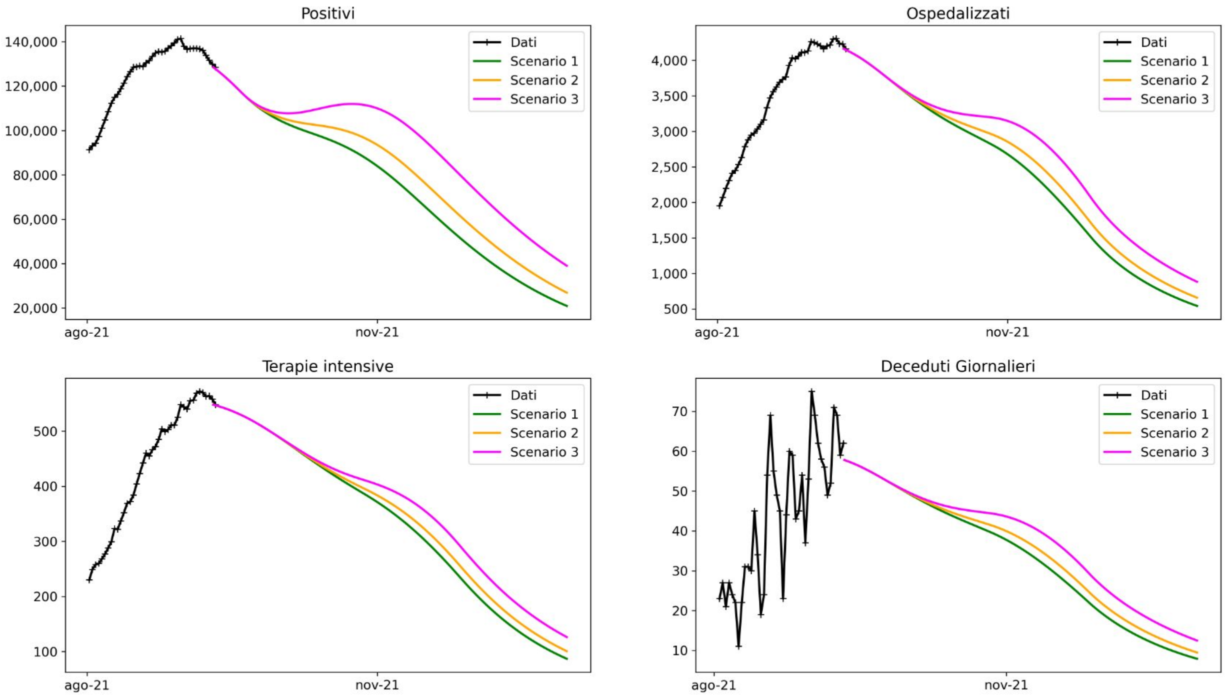


200k first doses/day - 200k second doses/day

Vaccine model in action - 3

Scenario analysis on the effect of the school reopening combined with the application of GreenPass in schools and universities:

- Scenario 1: with GreenPass applied 100%
- Scenario 2: with GreenPass applied 50%
- Scenario 3: without GreenPass



300k first doses/day - 300k second doses/day

epiMOX

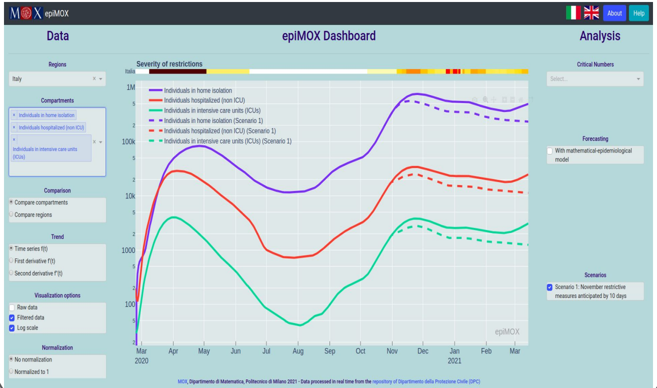
Integration in the **epiMOX Dashboard** (epimox.polimi.it)

epidemiological data

	data	stato	ricoverati_con_sintomi	terapia_intensiva	totale_ospedalizzati
1	data	stato	ricoverati_con_sintomi	terapia_intensiva	totale_ospedalizzati
2	2020-02-24T18:00:00	ITA	101	26	127
3	2020-02-25T18:00:00	ITA	114	35	150
4	2020-02-26T18:00:00	ITA	128	36	164
5	2020-02-27T18:00:00	ITA	248	56	304
6	2020-02-28T18:00:00	ITA	345	64	409
7	2020-02-29T18:00:00	ITA	401	105	506

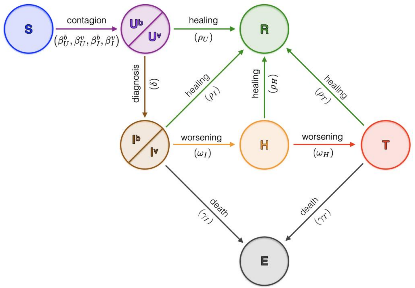
analysis
processing
visualization

epiMOX dashboard



model
calibration

SUIHTER model



what-if and
forecast
scenarios

[P., Ardenghi, Dede', Quarteroni, 2021]
https://onlinelibrary.wiley.com/doi/full/10.1002/cnm.3513

Ongoing developments and next challenges

Model extension: the age-structure has been already included in the SUIHTER model. Further work is required to make the age-based calibration satisfactory

Model calibration: investigation of alternative strategies for parameter prior distributions [1]

Vaccination: addition of immunity duration for recovered and vaccinate and possible adoption of the third dose

Control: definition an optimal control strategy for the identification of optimal strategies in the vaccination campaign [2]

[1] Bartolucci, Pennoni, Mira, *A multivariate statistical approach to predict COVID-19 count data with epidemiological interpretation and uncertainty quantification*, SIM, 2021

[2] Ziarielli, *Numerical modelling of optimal vaccination strategies for SARS-CoV-2*, Master Thesis, Politecnico di Milano, 2021

Thank you for your attention!

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Acknowledgements: Paola F. Antonietti, Andrea Manzoni, Edie Miglio, Andrea Pugliese, Marco Verani