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Model-based evaluation of the impact of school children on SARS-CoV-2 transmission during the pandemic

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About me

- Master in Applied Mathematics at University of Naples Federico II
- PhD student at the Faculty of Sciences, University of Lisbon
- Research Fellowship from the Portuguese Foundation for Science and Technology (FCT) project 2022.01448.PTDC

Fundação para a Ciência e a Tecnologia

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FCT Project

Targeted control of COVID-19 post mass vaccination

Aim

To evaluate vaccination strategies that increase vaccination effectiveness at the country-level while decreasing within-country COVID-19 disparities between different population groups (Netherlands and Portugal).

Objectives

1. Project transmission dynamics (done);
2. Investigate the dynamics in presence of variants of concern (done);
3. Evaluate post mass vaccination strategies (see aim);
4. Quantify disease burden under various strategies.

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My current Project

Aim

To evaluate retrospectively the impact of different pharmaceutical and non-pharmaceutical measures during the pandemic in the Netherlands.

Objectives

To evaluate the impact of

1. primary and secondary school closures and school holidays (ongoing work)

2. vaccination in children, adolescents and adults

3. other non-pharmaceutical measures (lockdowns and semilockdowns)

on SARS-CoV-2 infections and hospitalizations in children, adolescents and adults.

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Cornell University

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the Simons Foundation and member institutions.

arXiv > physics > arXiv:2212.13470

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COVID-19 e-print

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[Submitted on 27 Dec 2022]

Age-specific transmission dynamics of SARS-CoV-2 during the first two years of the pandemic

Otilia Boldea, Amir Alipoor, Sen Pei, Jeffrey Shaman, Ganna Rozhnova

During its first two years, the SARS-CoV-2 pandemic manifested as multiple waves shaped by complex interactions between variants of concern, non-pharmaceutical interventions, and the immunological landscape of the population. Understanding how the age-specific epidemiology of SARS-CoV-2 has evolved throughout the pandemic is crucial for informing policy decisions. We developed an inference-based modelling approach to reconstruct the burden of true infections and hospital admissions in children, adolescents and adults over the seven waves of four variants (wild-type, Alpha, Delta, Omicron BA.1) during the first two years of the pandemic, using the Netherlands as the motivating example. We find that reported cases are a considerable underestimate and a generally poor predictor of true infection burden, especially because case reporting differs by age. The contribution of children and adolescents to total infection and hospitalization burden increased with successive variants and was largest during the Omicron BA.1 period. Before the Delta period, almost all infections were primary infections occurring in naive individuals. During the Delta and Omicron BA.1 periods, primary infections were common in children but relatively rare in adults who experienced either re-infections or breakthrough infections. Our approach can be used to understand age-specific epidemiology through successive waves in other countries where random community surveys uncovering true SARS-CoV-2 dynamics are absent but basic surveillance and statistics data are available.

Comments: 23 pages, 5 figures, 1 table; supplementary materials to the main text available at this https URL
Subjects: **Physics and Society (physics.soc-ph)**; Populations and Evolution (q-bio.PE); Quantitative Methods (q-bio.QM)
Cite as: arXiv:2212.13470 **[physics.soc-ph]**
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Recap

This study

- Reconstructed the burden of true infections and hospital admissions in children, adolescents and adults over 7 waves of 4 variants (wild-type, Alpha, Delta and Omicron BA.1) during the first 2 years of the pandemic in the Netherlands

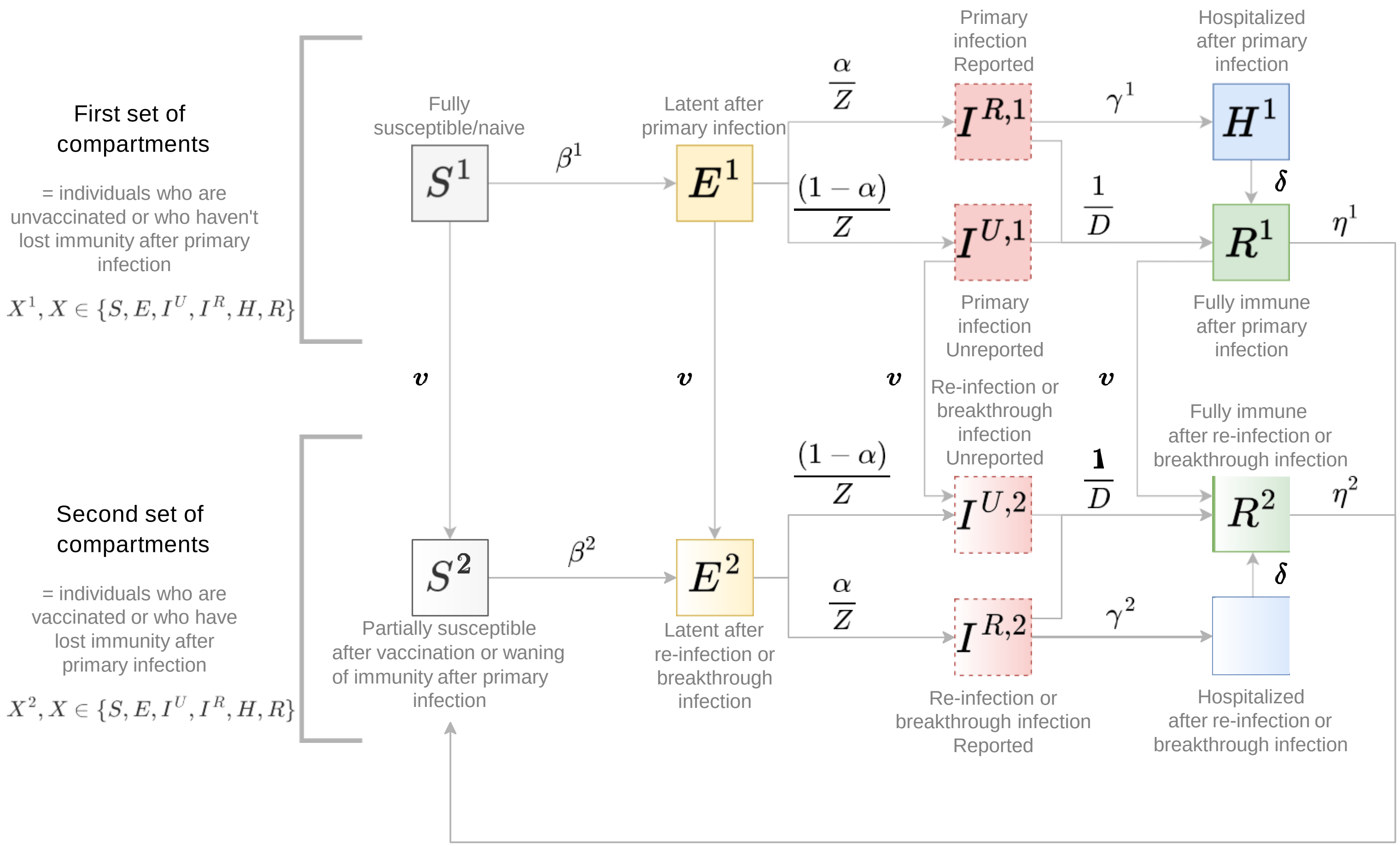
- Provided estimates of reported and unreported infection and hospitalization burden by age, region of the country, VoC period and immune status (primary infections vs reinfections and breakthrough infections)

My methods

- Mathematical model stratified by
  - Age: children (0-9 y.o.), adolescents (10-19 y.o.), adults (20+ y.o.)
  - Region: 12 provinces
  - Disease status: *next slide*
- Seasonally-forced
- Compartmental
- Metapopulation
- Stochastic
- Fitted to the data using an Ensemble Adjustment Kalman filter

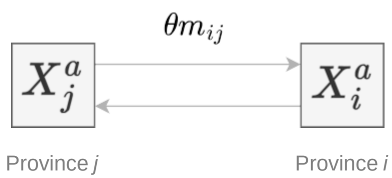
Metapopulation transmission model

A Disease dynamics



Metapopulation transmission model

B Mobility dynamics



$$X \in \{S, E, I^U, R\},\ a \in \{1, 2\},\ j \neq i$$

C Overview of the parameters

Age-specific parameters

β^1	- force of infection for fully susceptible
β^2	- force of infection for partially susceptible
α	- case detection rate
γ^1	- hospitalization rate after primary infection
γ^2	- hospitalization rate after re-infection or breakthrough infection
v	- vaccination rate
$1/\delta$	- hospitalization period
θ	- mobility reporting error
m_{ij}	- mobility between province *j* and province *i*

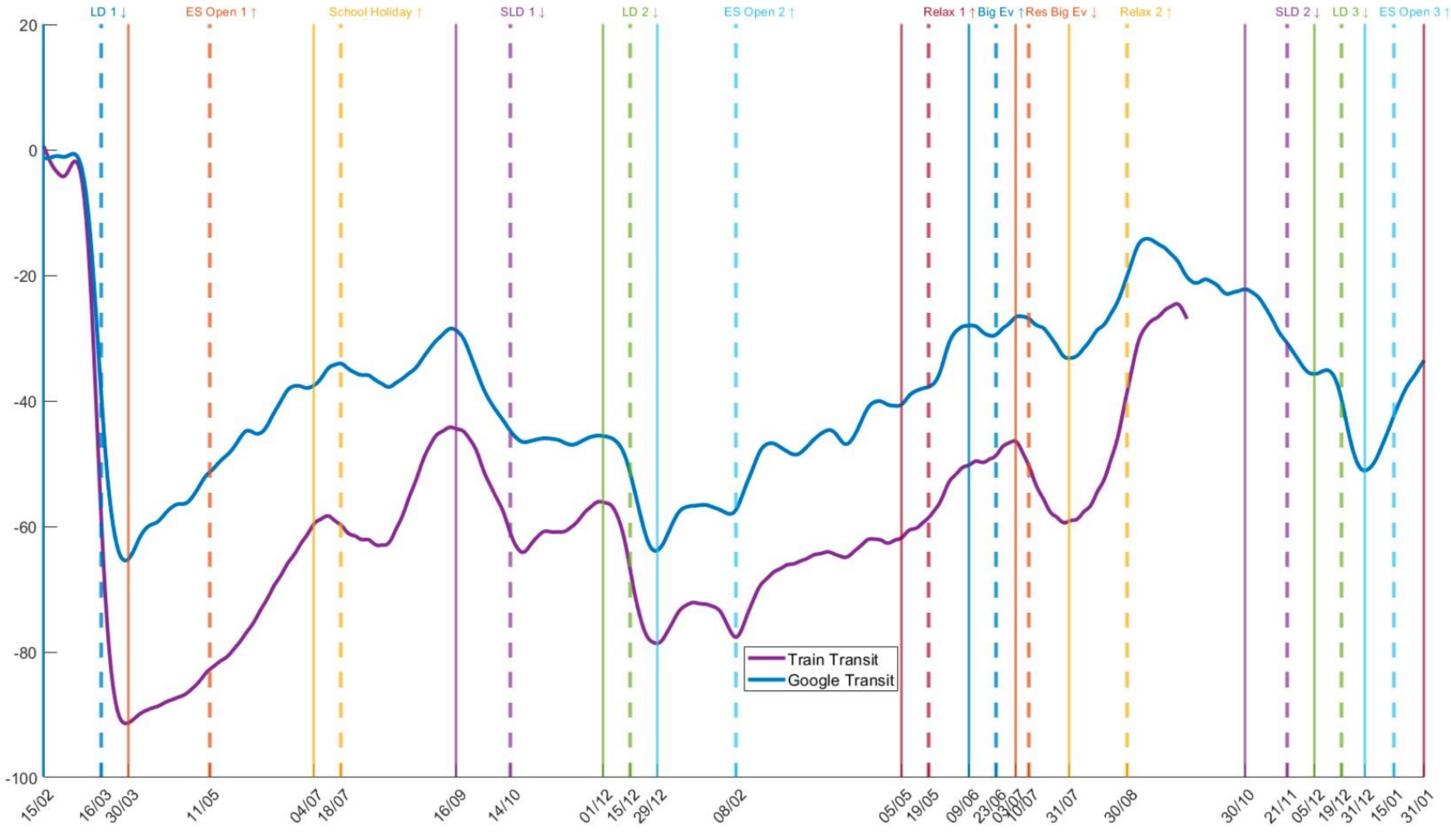
Constant parameters

Z	- latent period
D	- infectious period
$1/\eta^1$	- duration of immunity after primary infection
$1/\eta^2$	- duration of immunity after re-infection or breakthrough infection

Metapopulation

- Regional stratification is augmented with **real-world mobility** across provinces
- Susceptible, exposed, unreported infected and recovered travel across provinces
- **Assumption:** unreported infected travel and infect others, susceptible travel and get exposed by others, while reported infected do not travel
  - Because of heterogeneity in population size and mobility across regions, this assumption equips the model with additional dynamics for unreported infected compared to reported infected
- We introduce **age-specific mobility reporting error** that is estimated to account for biases in the mobility data construction
- Unreported cases have **lower infectivity** than reported cases

Mobility



LD 1 ↓
ES Open 1 ↑
School Holiday ↑
SLD 1 ↓
LD 2 ↓
ES Open 2 ↑
Relax 1 ↑
Big Ev ↑
Res Big Ev ↓
Relax 2 ↑
SLD 2 ↓
LD 3 ↓
ES Open 3 ↑
20
0
-20
-40
-60
-80
-100
15/02
16/03
30/03
11/05
04/07
18/07
16/09
14/10
01/12
15/12
29/12
08/02
05/05
19/05
09/06
23/06
03/07
10/07
31/07
30/08
30/10
21/11
05/12
19/12
31/12
15/01
31/01
Train Transit
Google Transit

Force of infection

$$\beta^a_{ik}(t) = \epsilon \times f_{\epsilon,k} \times voc(t) \times season(t) \times \lambda^a_{ik}(t)$$

- Differs for **fully** and **partially susceptible**, province and age
- **Probability of transmission per contact** for the wild-type variant
- **Susceptibility** of adolescents and children relative to adults
- Increase in the probability of transmission per contact due to **VoC** (calibrated, sensitivity analyses)
- Change in the probability of transmission per contact due to **seasonality** (calibrated, sensitivity analyses)
- **Time-dependent number of contacts** one individual in given province and age makes per day with all individuals in other age groups X proportion of infectious individuals in those age groups

$$\lambda_{ik}^1(t) = \sum_{k^*=1}^{3} c_{i,kk^*}(t) \sum_j \left[\frac{I_{ijk^*}^{R,1}(t) + [1 - p_{TR,k^*}(t)] I_{ijk^*}^{R,2}(t)}{N_{ik^*}} + \mu \frac{I_{ijk^*}^{U,1}(t) + [1 - p_{TU,k^*}(t)] I_{ijk^*}^{U,2}(t)}{N_{ik^*}} \right]$$

$$\lambda_{ik}^2(t) = [1 - p_{I,k}(t)]\, \lambda_{ik}^1(t),$$

- $0 \leq p_{I,k}(t), p_{TR,k}(t), p_{TU,k}(t) < 1$, protection levels against infection and transmission due to vaccination or previous infection.
- $0 \leq \mu < 1$ relative infectivity of unreported infected compared to reported infected .
- $c_{\mathrm{i},kk^*}(t)$ time−varying contact matrices.

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Contacts Structure

Contacts = School contacts + NON-School contacts

School contacts = Elementary school + Secondary school

$$c_{\mathrm{i},kk^*}(t) = c_{\mathrm{i},kk^*,S}\,(t) + c_{kk^*,NS}\,(t)$$

$$c_{\mathrm{i},kk^*,S}(t) = c_{\mathrm{i},kk^*,ES}\,(t) + c_{\mathrm{i},kk^*,SS}\,(t) \qquad k, k^* = 1, 2, 3$$

the average number of contacts per day of one person in age group k with all people in age group k^* in region i at day t.

$c_{kk^*}^{(r)} \longrightarrow$ All-settings survey-based contact matrices, defined as the average number of daily close contacts in all settings for one individual in age category k with all individuals in age category k* in survey r = 1, 2, 3.

- r =1, before the pandemic
- r =2, during the first lockdown
- r =3, summer 2020

$$c_{kk^*}^{(r)} = \sum_{\ell \in G_k} \frac{N_{\ell k}}{\sum_{\ell^* \in G_k} N_{\ell^* k}} \left[\sum_{j \in G_{k^*}} cont_{k\ell\ell^*}^{(r)} \right], \text{where } r = 1, 2, 3.$$

School Contacts

We first calculate the school contact matrices before the pandemic and the all-setting contact matrices, obtaining the fraction of school contacts when schools are fully open:

$$f^{(1)}_{kk^*,S} \rightarrow f^{(1)}_{kk^*,ES}$$

$$f^{(1)}_{kk^*,S} \rightarrow f^{(1)}_{kk^*,SS}$$

- $c^{(\&)}_{kk^*,ES} = f^{(\&)}_{kk^*,ES} \times c^{(\&)}_{kk^*,S}$ $\quad$ $c^{(\&)}_{kk^*,SS} = (1 - f^{(\&)}_{kk^*,ES}) \times c^{(\&)}_{kk^*,S}$

- $c^{(()}_{kk^*,S} = 0$

Daily elementary and secondary school opening index: $es_{(t}$, $ss_{(t}$.

Time-varying school contacts over each province: $c^{(1)}_{(kk^*,ES}(t) = es_{(t}\, c^{(1)}_{kk^*,ES}$, $c^{(1)}_{(kk^*,SS}(t) = ss_{(t}\, c^{(1)}_{kk^*,SS}$.

Survey-based contact matrices, $c_{kk^*}^{(r)}$ for ages $k, k^* = 1,2,3$ in survey $r = 1,2,3$

	Survey 1			Survey 2			Survey 3		
Category	adults	adolescents	children	adults	adolescents	children	adults	adolescents	children
adults	11.18	1.50	1.05	4.15	0.50	0.45	6.85	0.98	0.92
adolescents	9.99	11.19	2.17	3.40	1.52	0.65	6.61	7.96	1.92
children	7.85	2.43	10.37	3.41	0.73	1.72	6.98	2.16	15.42

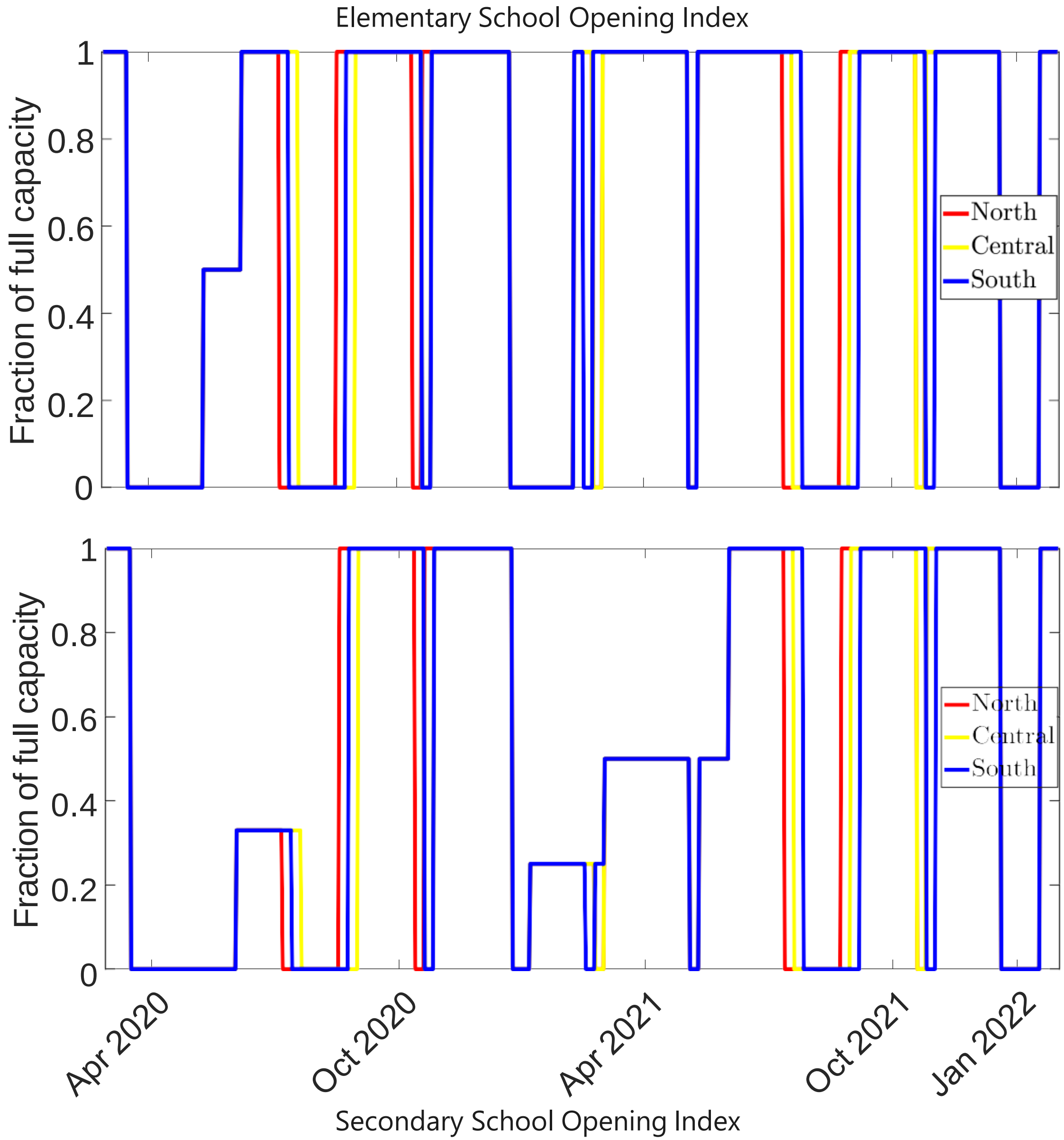
Constructed non-school contact matrices, $c_{kk^*,NS}^{(r)}$ for $k, k^* = 1,2,3$

	Survey 1			Survey 2			Survey 3		
Category	adults	adolescents	children	adults	adolescents	children	adults	adolescents	children
adults	10.20	0.97	0.94	4.15	0.50	0.45	6.37	0.84	0.82
adolescents	6.51	1.75	0.60	3.40	1.52	0.65	5.69	4.93	0.53
children	7.02	0.68	2.20	3.41	0.73	1.72	6.25	0.60	3.27

School contact matrices before pandemic, $c_{kk^*,NS}^{())}$ for $k, k^* = 1,2,3$

	Elementary Schools			Secondary Schools		
Age category	adults	adolescents	children	adults	adolescents	children
adults	0.68	0.05	0.11	0.31	0.47	0
adolescents	0.35	1.71	1.57	3.13	7.74	0
children	0.83	1.75	8.17	0	0	0

Elementary and secondary school contacts



School contacts = elementary + secondary school contacts

Conterfactual Analysis

Aim: To evaluate retrospectively the impact of different pharmaceutical and non pharmaceutical measures during the pandemic in the Netherlands.

Period of interest: 27 February 2020 – 10 May 2020, 74 days

Variant: wild-type

- Some parameters are not well identified
- Kicked out hospitalizations
- Fixed some parameters

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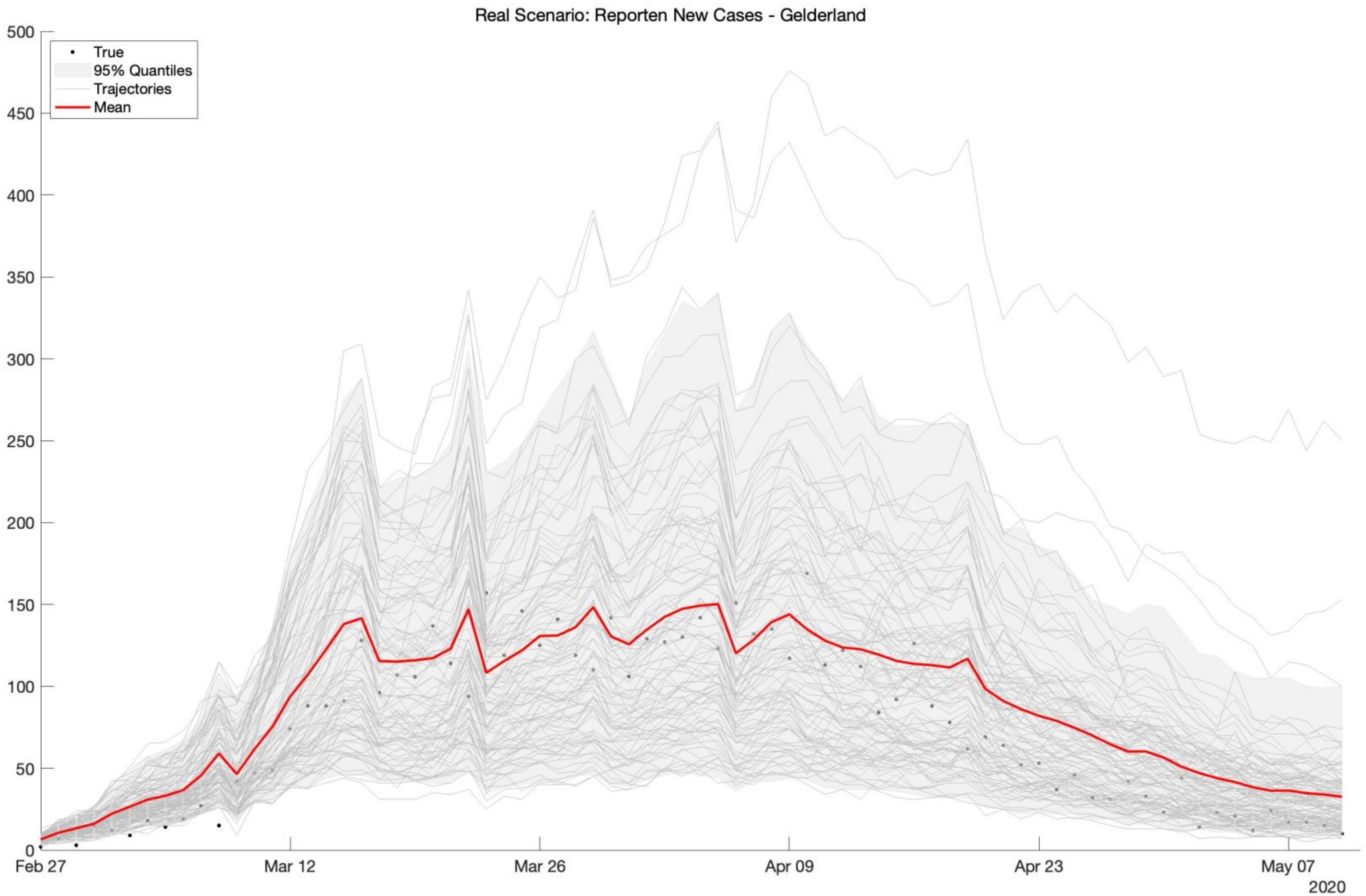
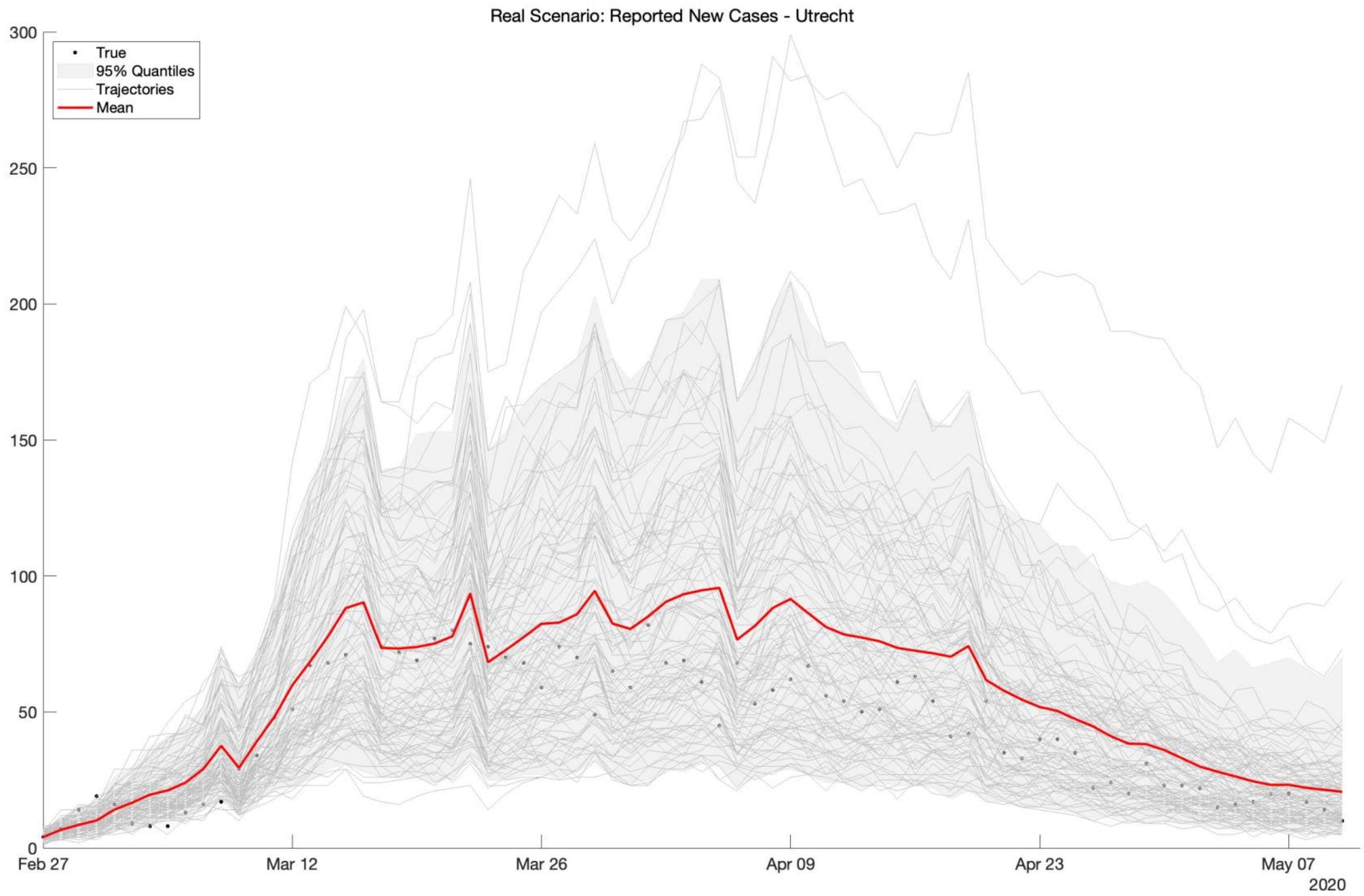
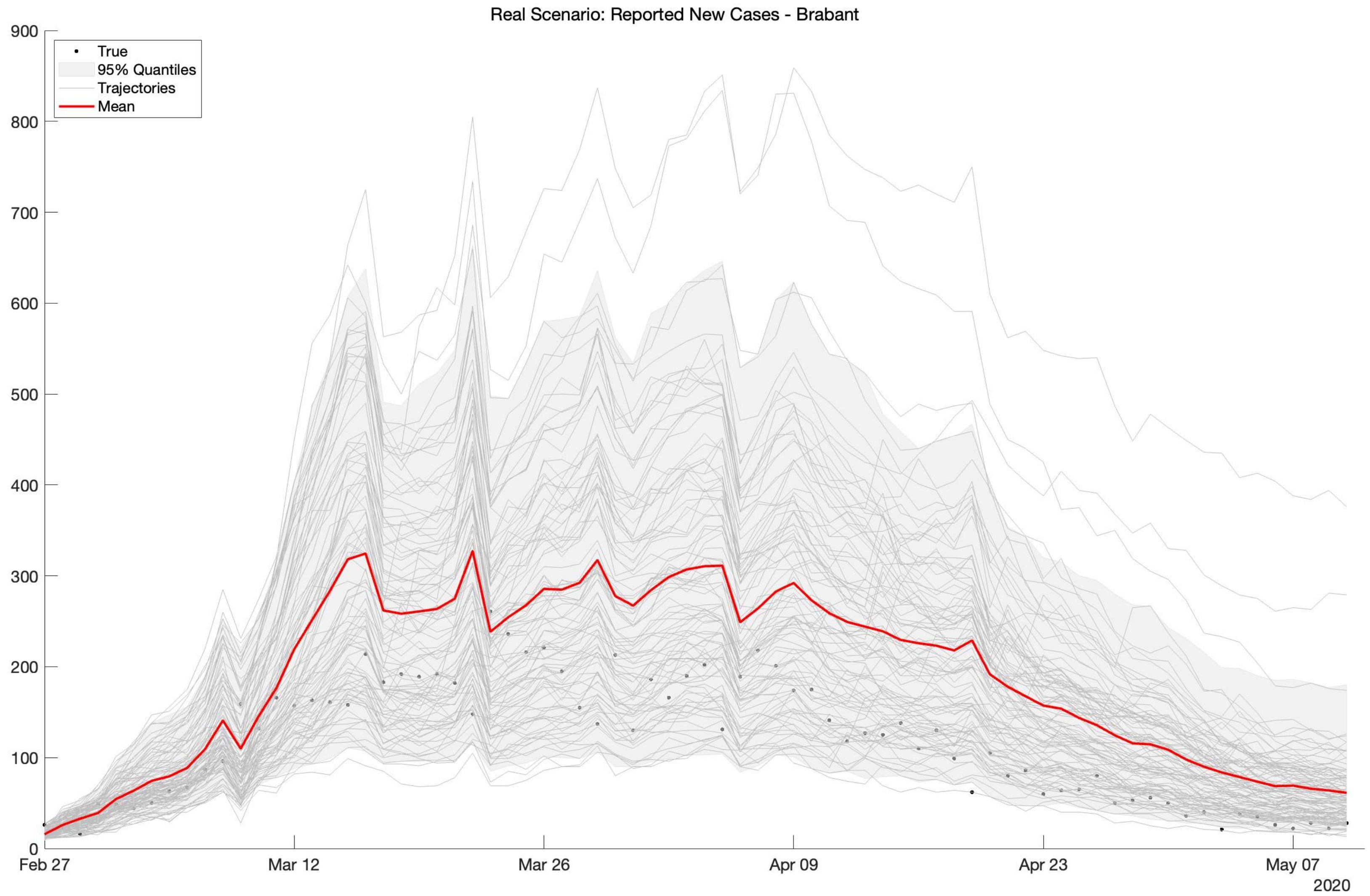
Reported New Cases for all ages in the Gelderland province



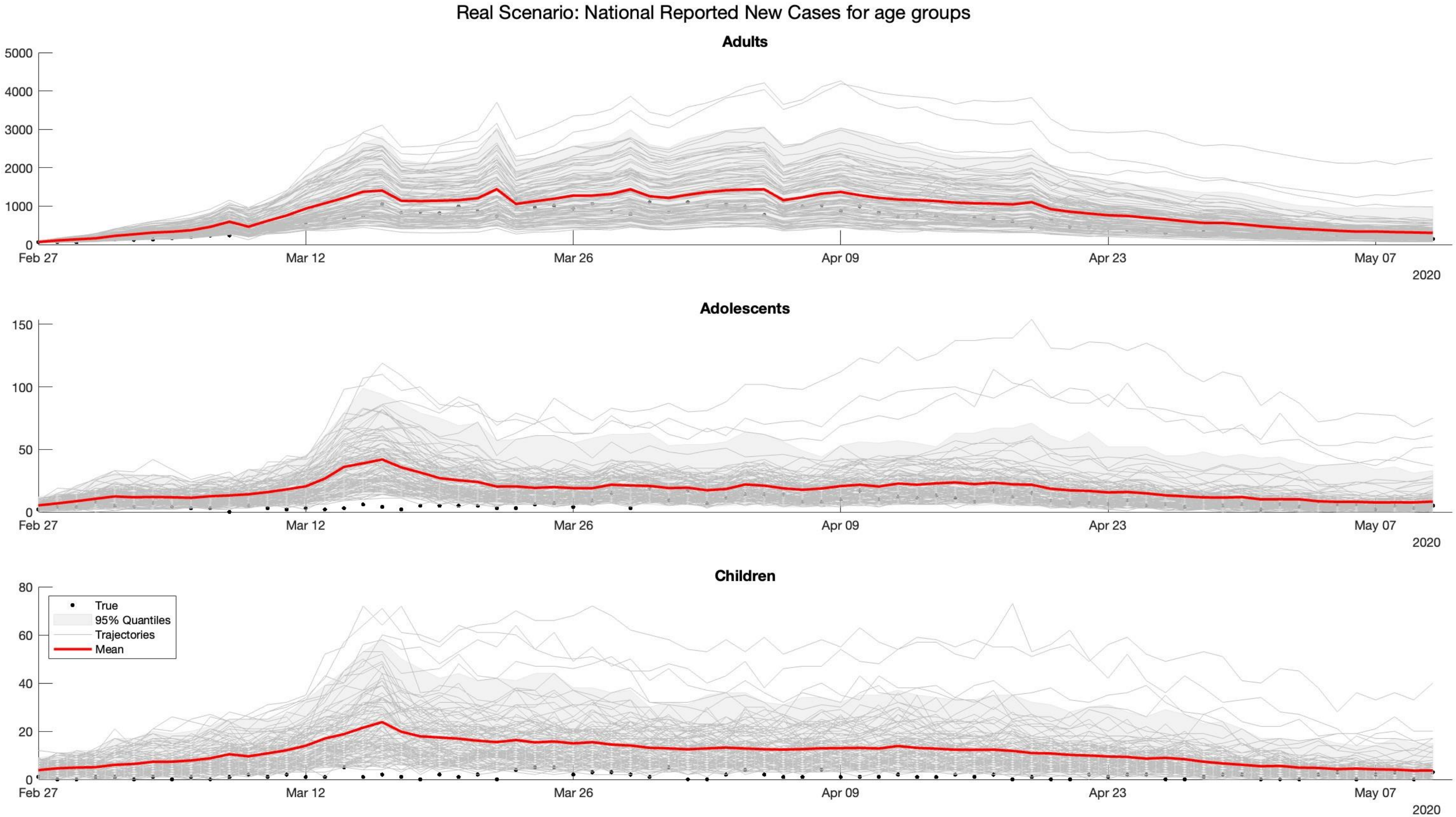
Reported New Cases for all ages in the Utrecht province



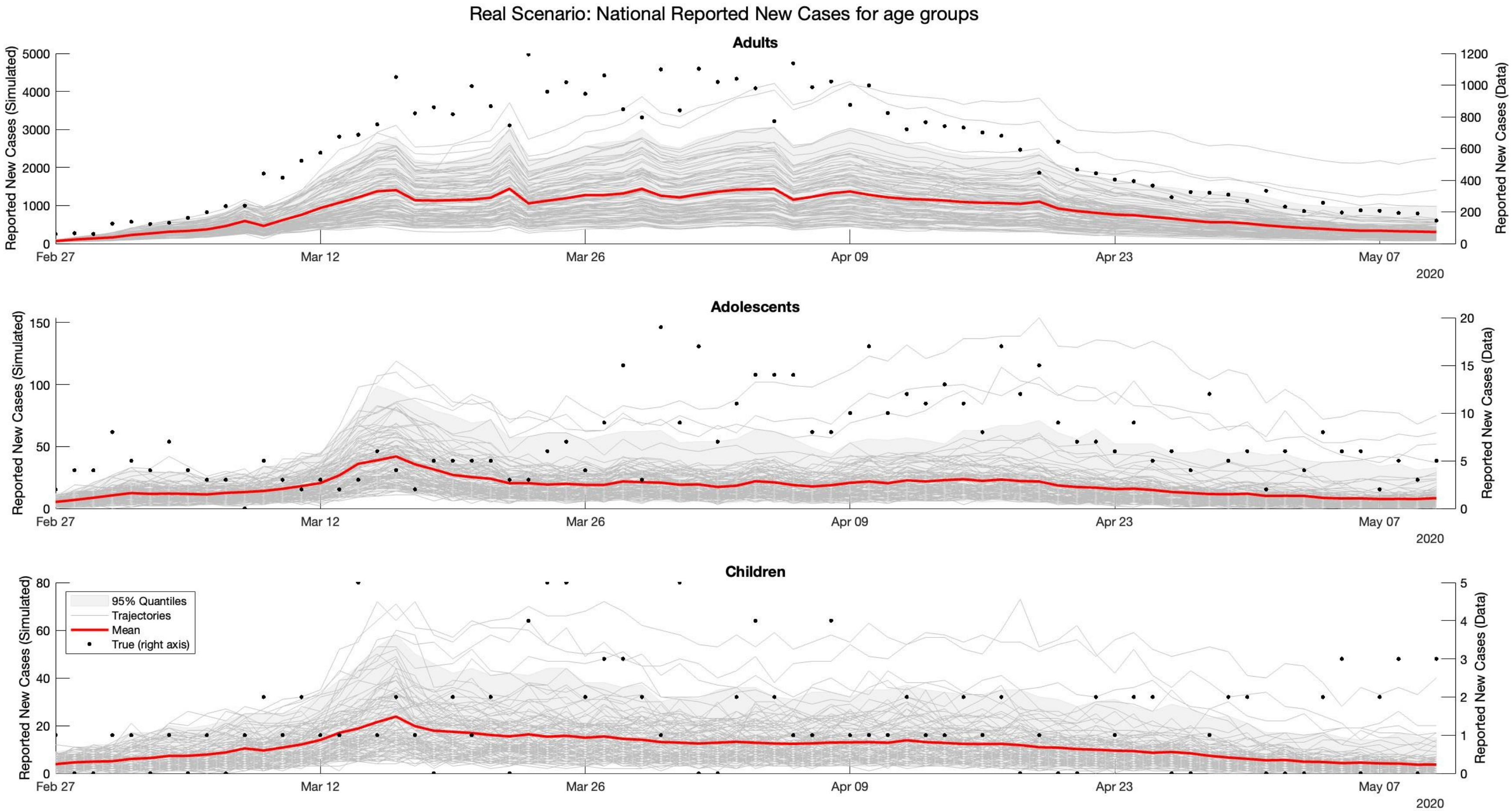
Reported New Cases for all ages in the Brabant province



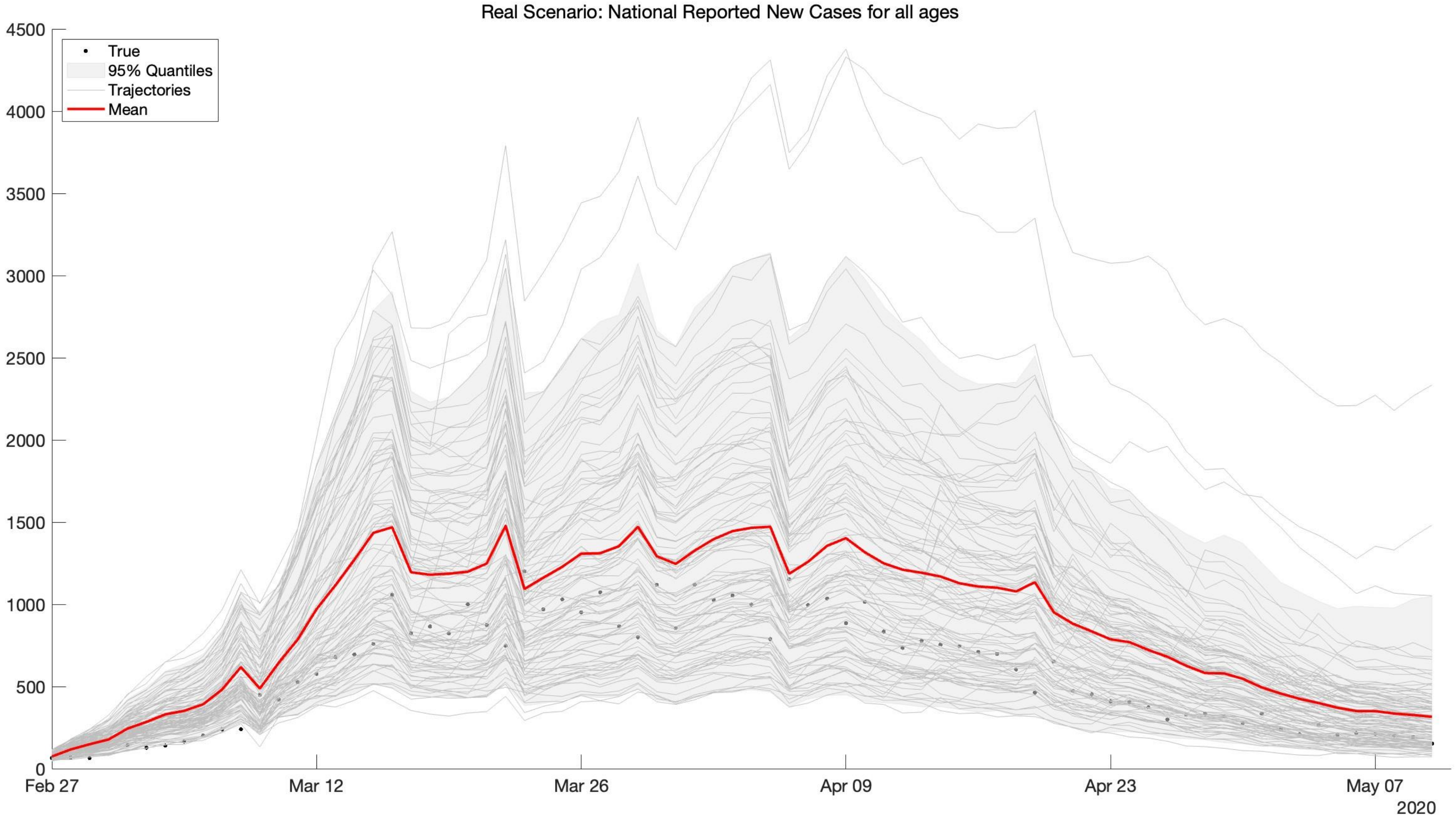
National Reported New Cases Divided by age categories



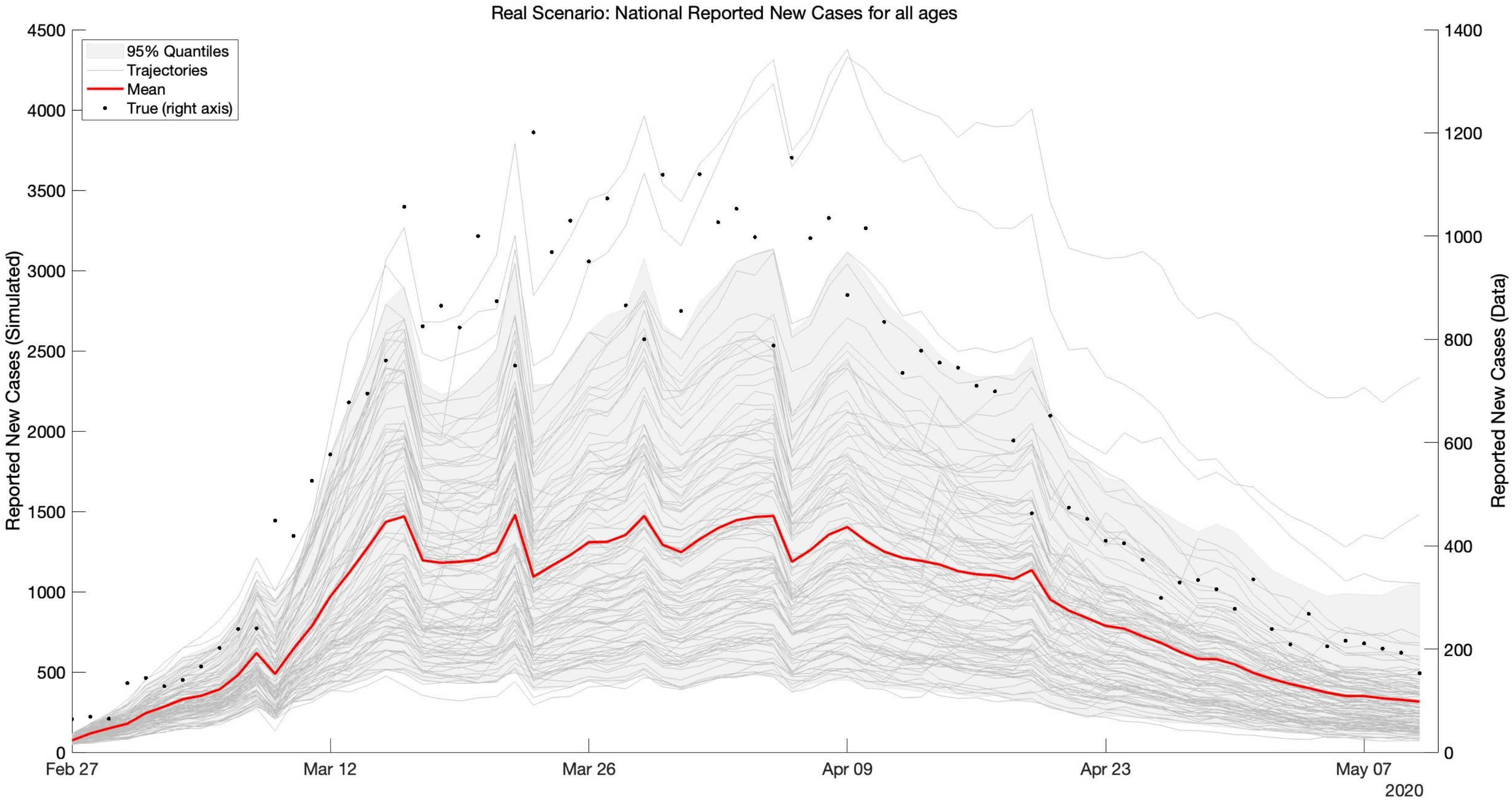
National Reported New Cases
Divided by age categories



National Reported New Cases for all ages



National Reported New Cases for all ages



Different scenarios

SCENARIO 1: Open Schools
Lockdown conditions but open schools

SCENARIO 2: ES opened, SS closed
Lockdown conditions but ES opened

SCENARIO 3: ES closed, SS opened
Lockdown conditions but SS opened

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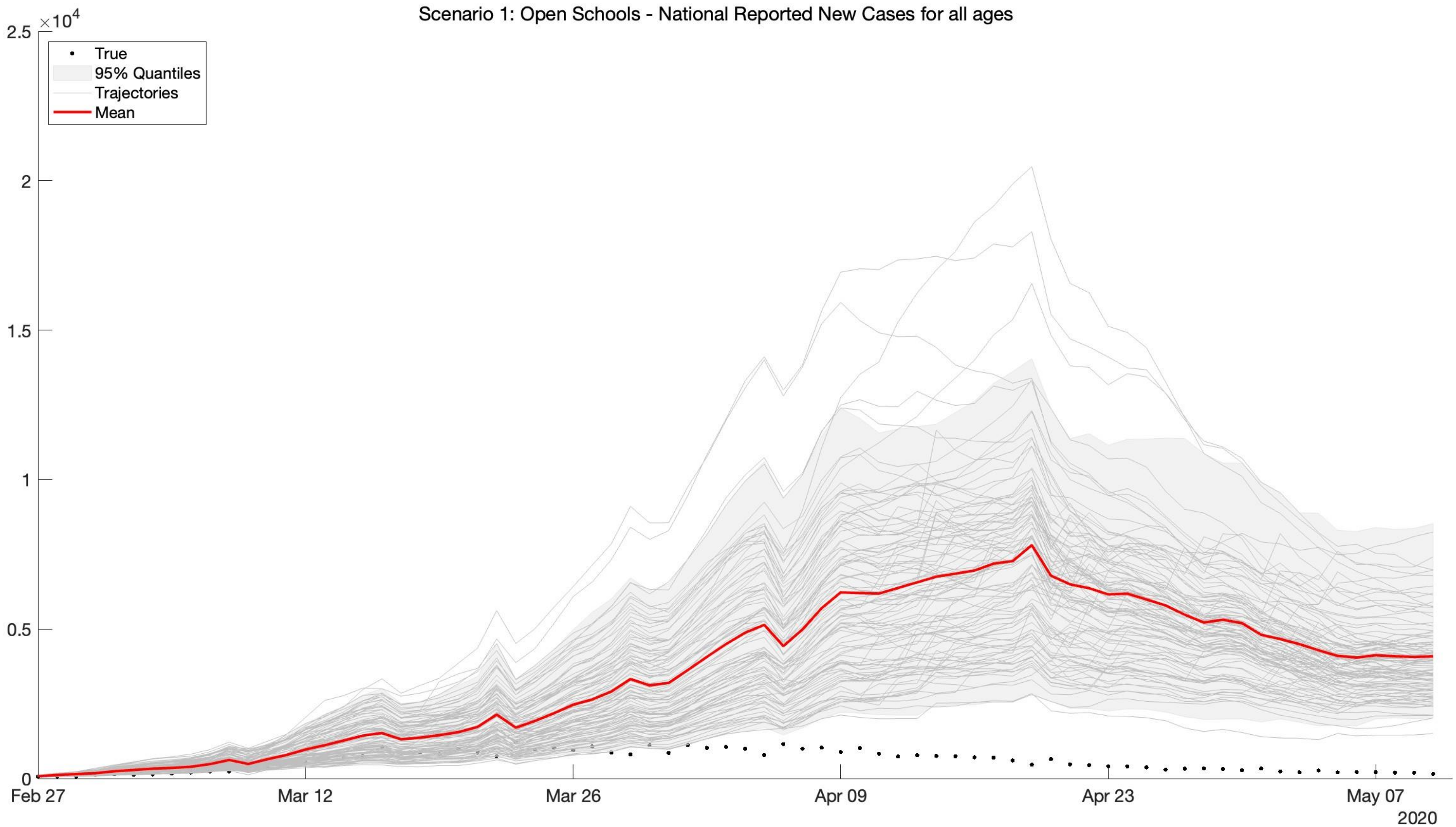
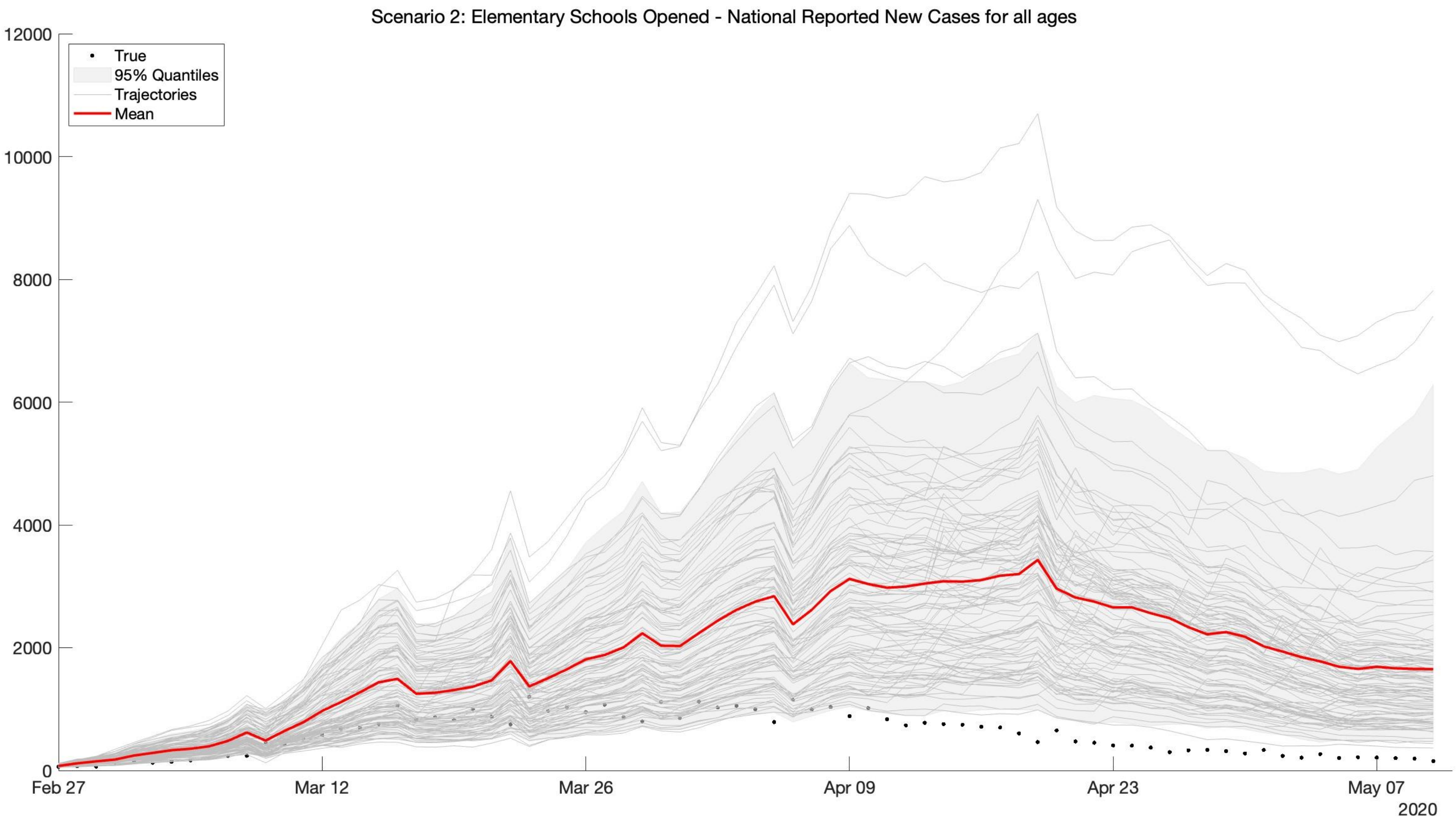
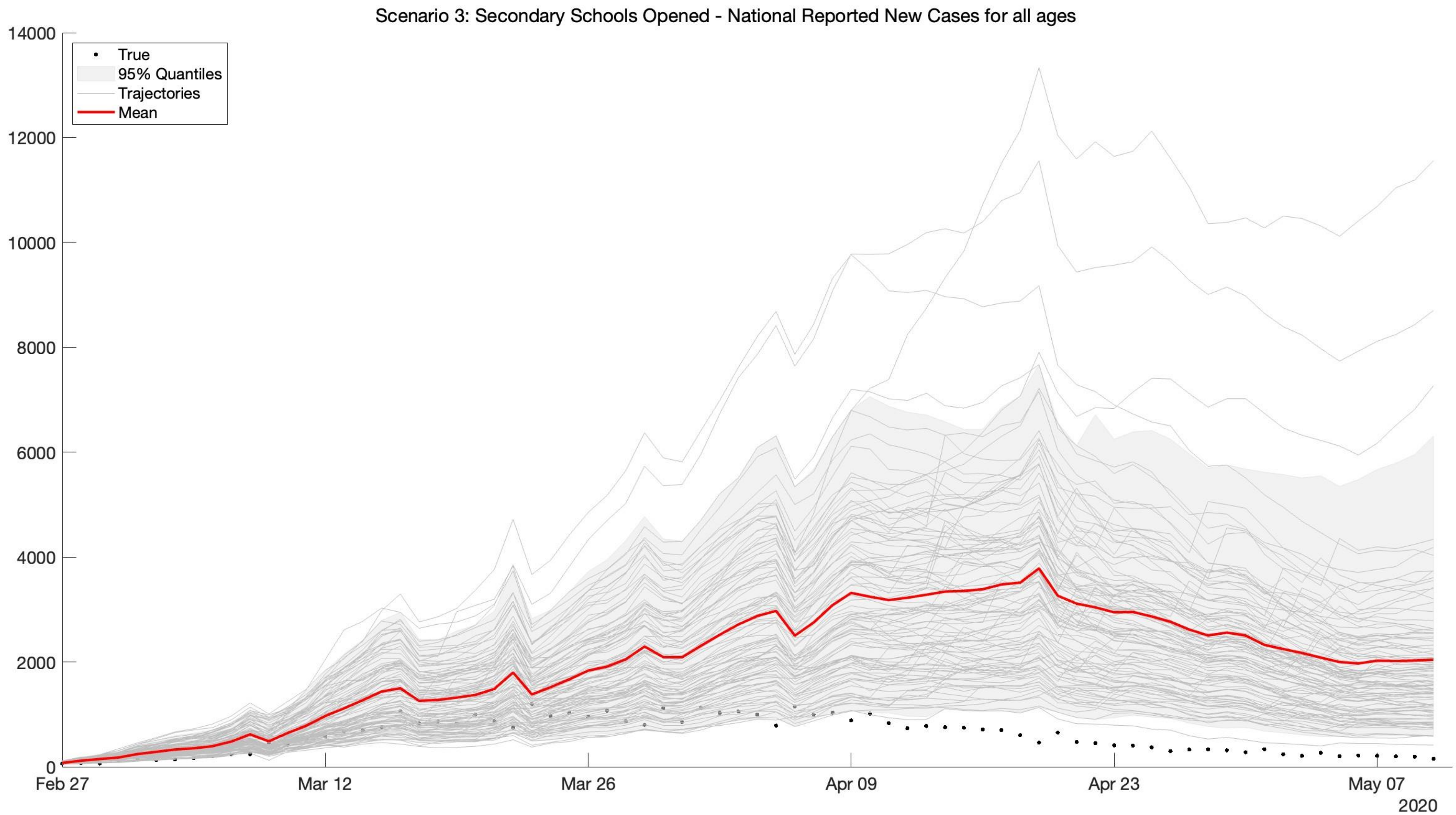
SCENARIO 1: Lockdown conditions but open schools



SCENARIO 2: Lockdown conditions but ES opened



SCENARIO 3: Lockdown conditions but ES opened



My ongoing work summary

Learning to use the model code and implementing several model improvements:

- Added estimation of the initial conditions that used to be sampled randomly in the prior model implementation
- Changed ensemble Kalman filter to iterated Kalman filter (iterative estimation of parameters in time windows)
- Exploring the impact of the window length (1, 2, 3 weeks) where parameters are estimated
- Exploring the impact of the number of iterations on the model fit for infections and hospitalizations

Filtering

In the theory of stochastic processes, filtering describes the problem of determining the state of a system from an incomplete and potentially noisy set of observations.

The filtering problem is the following:

given observations Z_s for $0 \leq s \leq t$, what is the best estimate $\hat{Y}_t$ of the true state Y_t of the system based on those observations?

It attempts to obtain sequentially the posterior distribution of the state at the current time point based on all observations collected so far.

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Kalman Filter

Kalman filtering is an algorithm that uses a series of measurements observed over time, including statistical noise and other inaccuracies, and produces estimates of unknown variables, by estimating a joint probability distribution over the variables for each timeframe.

The algorithm works by a two-phase process:

1. prediction phase: the Kalman filter produces estimates of the current state variables, along with their uncertainties;
2. update phase: once the outcome of the next measurement (necessarily corrupted with some error, including random noise) is observed, these estimates are updated using a weighted average.

With linear models with additive Gaussian noises, the Kalman filter provides optimal estimates.

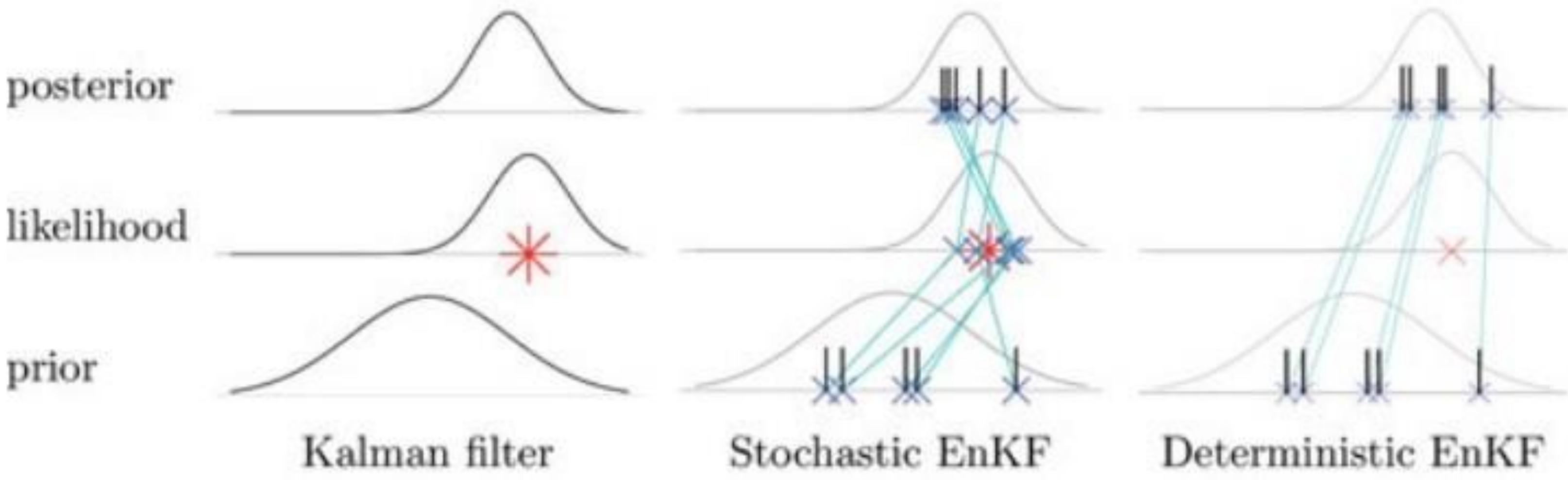
Ensemble Kalman Filter – deterministic update

The Ensemble Kalman Filter can be viewed as an approximate version of the Kalman filter for large problems. EnKFs represent the distribution of the system state using a collection of state vectors, called an ensemble, which is is then propagated forward through time and updated when new data become available.

EnKF uses a linear updating rule that converts the prior ensemble to a posterior ensemble after each observation.

Deterministic EnKFs obtain an approximate ensemble from the posterior by deterministically
shifting the prior ensemble, without relying on simulated or perturbed observations.

Thus, the deterministic update involves shifting and scaling each prior draw so that the resulting posterior draws are shifted toward the data and have a smaller variance than the prior.



posterior
likelihood
prior
Kalman filter
Stochastic EnKF
Deterministic EnKF

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Iterated Filtering

The IF framework can be used to infer the maximum likelihood estimates of parameters in epidemic models and has been successfully applied to infectious diseases such as cholera and measles .

The IF framework is designed as follows: an ensemble of system states, which represent the distribution of parameters and variables, are repeatedly adjusted using filtering techniques in a series of iterations, during which the variance is gradually tuned down. In the process, the distribution of parameters is iteratively optimized per observations and converges to values that achieve maximum likelihood.

In each iteration of the IF, the standard deviation of each parameter is shrunk by a factor $a \in (0,1)$.

The number of iterations required for this convergence was determined by inspecting the evolution of posterior parameter distributions.

Windows

Period of interest: 27th February 2020 – 10th May 2020, 74 days

Length of the window: 14 days

Window 1: 27th February – 11th March
Window 2: 12th March – 25th March
Window 3: 26th March – 8th April
Window 4: 9th April – 22nd April
Window 5: 23rd April – 6th May
Window 6: 7th May – 10th May

Number of iterations: 3, 8 and 15

Future work and outlook

- To check, systematically, how the fit depends on the length of the window (ongoing work)
- Be sure that the initial conditions are estimated only in the first window (ongoing work)
- Be sure of the stability of the parameters and investigate how we can implement it (ongoing work)
- (To do) running counterfactual analyses
- Implementing the different scenarios in order to understand the role of the schools in the transmission dynamics
- Comparing the impact, on the dynamics, of elementary and secondary schools closures

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Thank you!