WP8_ D8.1

Estimates of intervention effects using compartment model

Helmholtz Zentrum München - Deutsches Forschungzentrum Gesundheit und Umwelt GmbH (HMGU)

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Executive summary

Different nations, states and cities implemented different interventions, ranging from voluntary physical distancing to a mandatory shutdown, to slow down the spread of SARS-CoV-2 and to avoid an overload of the healthcare systems. However, the effectiveness of these interventions is still unclear and there are contradicting findings. The objective of this report is to summarize the available knowledge about the effects of non-pharmaceutical intervention (NPI) and to illustrate the prototype of the model-based data analysis pipeline developed in ORCHESTRA.

This deliverable provides a meta-analysis of dozens of scientific publications reporting the effect of different NPIs. To understand the impact of individual NPIs on different outcome variables (e.g., mobility and effective reproduction number), various categories are considered, ranging from general lockdown over school closure to the availability of paid sick leave. Furthermore, the deliverable provides a description of the established modeling pipeline and the results of its application to data of a representative population cohort which is part of ORCHESTRA.

Core content

Non-pharmacological interventions are used worldwide to slow down the spread of SARS-CoV-2. However, in many cases the intended goals were not achieved, and infection numbers stayed much higher than expected. A potential reason is that the effectiveness of NPIs is still partially unknown.

To address this issue, ORCHESTRA will provide a continuous assessment of the effects of NPIs on different OUTCOME measures. This will be based on the assessment of scientific publications, as well as a detailed analysis of representative population cohorts. Here, we report the results of the first four months, our conclusions and the next steps.

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1. Meta-analysis of published reports on the impact of non-pharmaceutical interventions

To obtain a comprehensive overview about the available information on the effects of NPIs for SARS-CoV-2, a team of PostDocs, PhD students, and student assistants screened the scientific literature and curated selected publications. The process is visually outlined in Figure 1.

To ensure the reliability of our meta-analysis, we implemented selection criteria for the inclusion of scientific reports. Most importantly, we focused on peer-reviewed publications written in English. Yet, to ensure that also important recent results are included, which is essential as the effect of interventions might be time-dependent, we also considered high-quality preprints (as judged by the curators). For the search we used PubMed, MedRxiv, BioRxiv and Google. Furthermore, members of ORCHESTRA were asked to share manuscripts which they consider relevant.

The analysis focused on studies in the EU (41%), but also manuscripts reporting findings for the US, China, the UK and others (59%) are included. The full text articles were read by at least two individuals to ensure a reliable information extraction. Key manuscripts considered in the meta-analysis are included in the list of references.

The information of NPIs reported in each publication was included in a central database which will be included in the ORCHESTRA portal. This included the reported effect of a NPI (with confidence intervals) on different outcome variables. As it was initially not clear on which NPIs and outcome variables we would find information, the structure of this database was dynamically refined. This allowed us to include less common outcome variables such as the need for ICU beds. For the generation of this report some categories were collapsed to improve interpretability.

The results of the initial meta-analysis, which includes 34 manuscripts, is provided in Figure 2. As expected, there is a substantial variability between studies. There are various potential reasons, including the use of different statistical tools and computational models for data analysis. Yet, in particular for commonly implemented measures such as general lockdown and school closure, there is a surprisingly good agreement and a clear indication of a strong effect.

The meta-analysis will be continuously extended during the course of the ORCHESTRA project.

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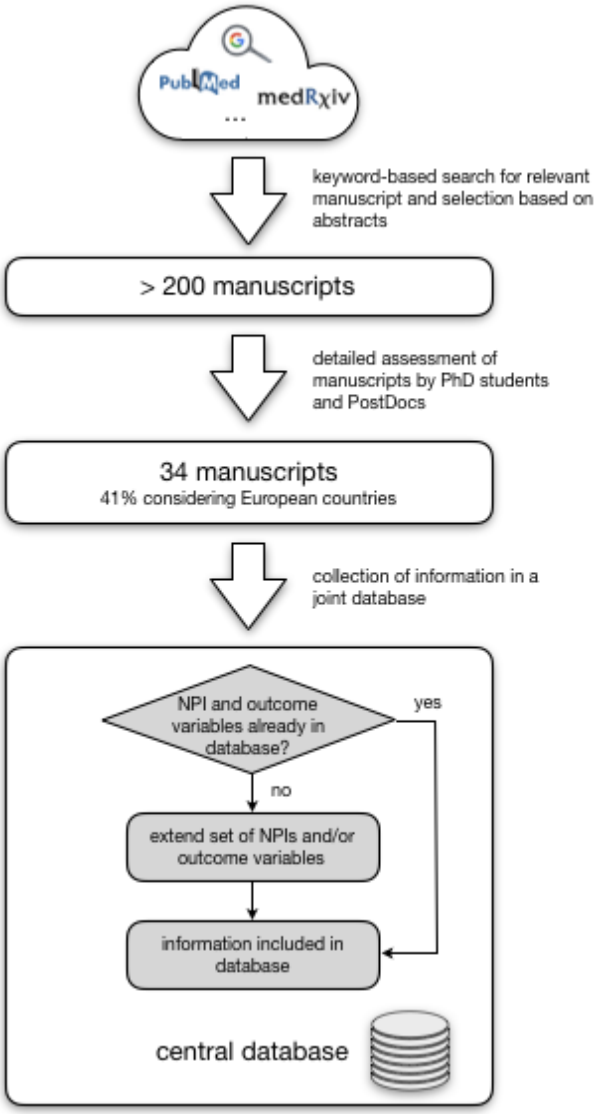

Figure 1. Visual outline of the workflow used to generate the database.

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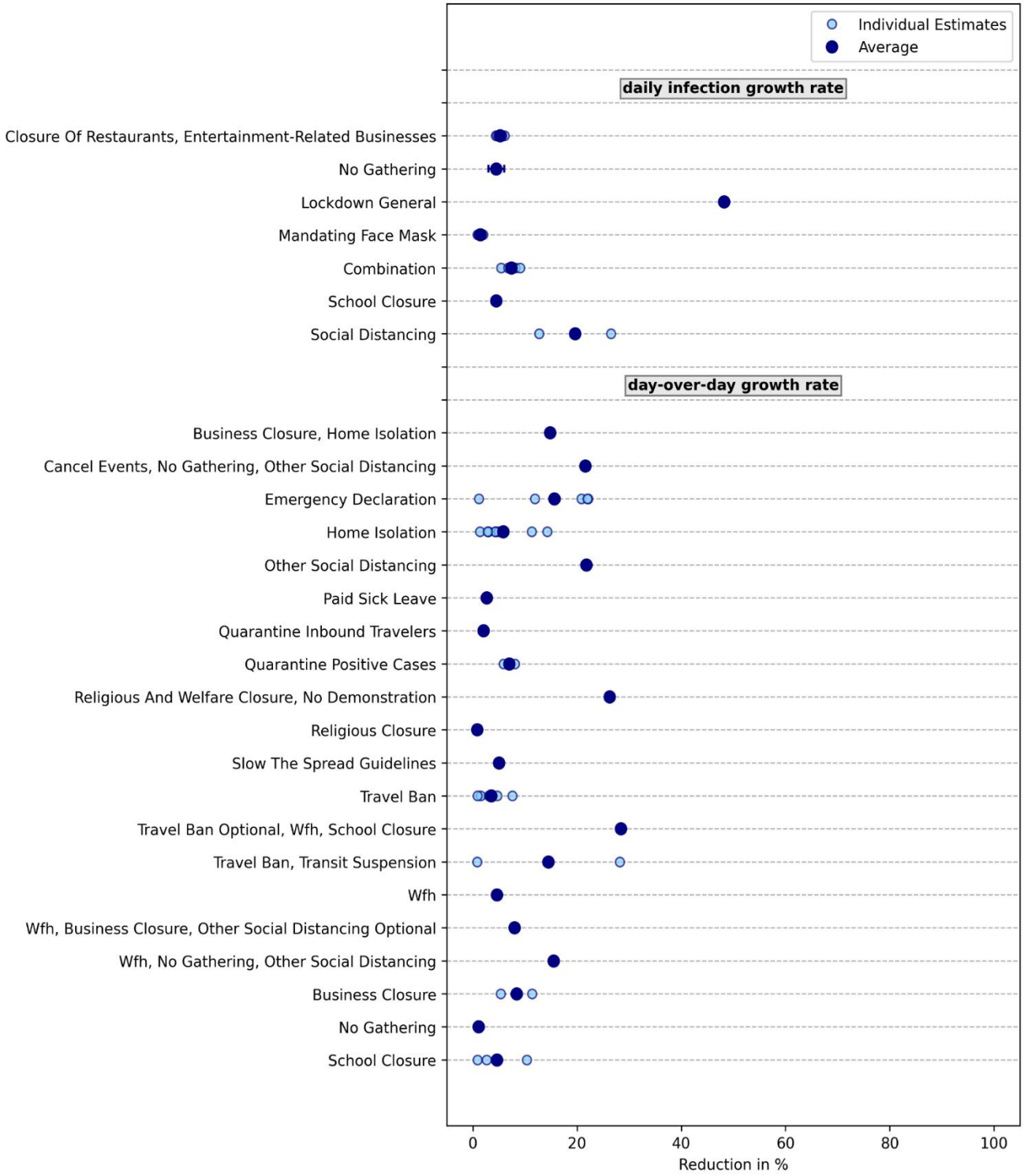

Figure 2a. Part a of the results of the meta-analysis. Dark blue points indicate the average reported effects, while light blue points indicate the effects reported in individual studies. The manuscripts included in the meta-analysis are provided in a separate reference list.

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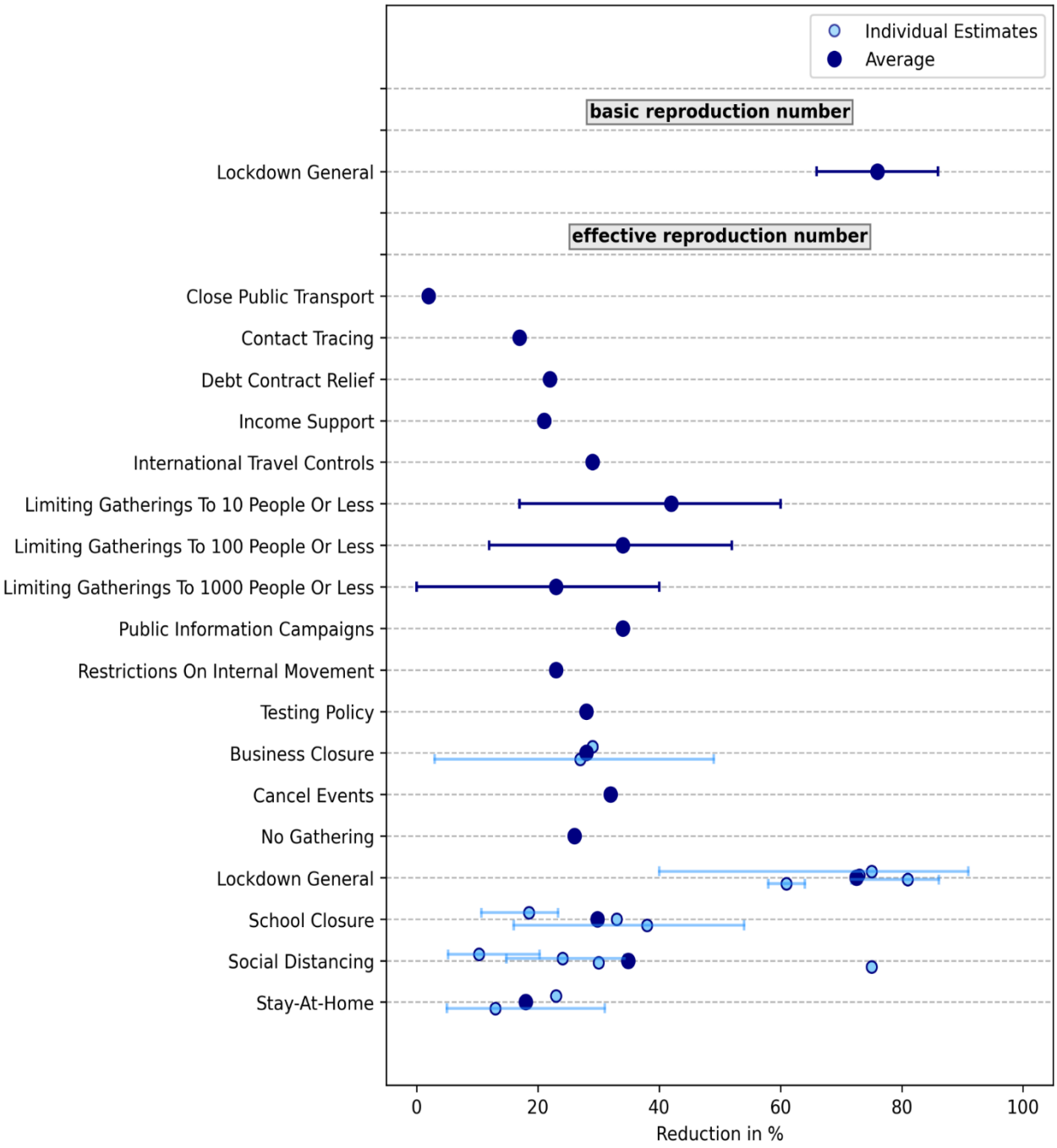

Figure 2b. Part b of the results of the meta-analysis. Dark blue points indicate the average reported effects, while light blue points indicate the effects reported in individual studies

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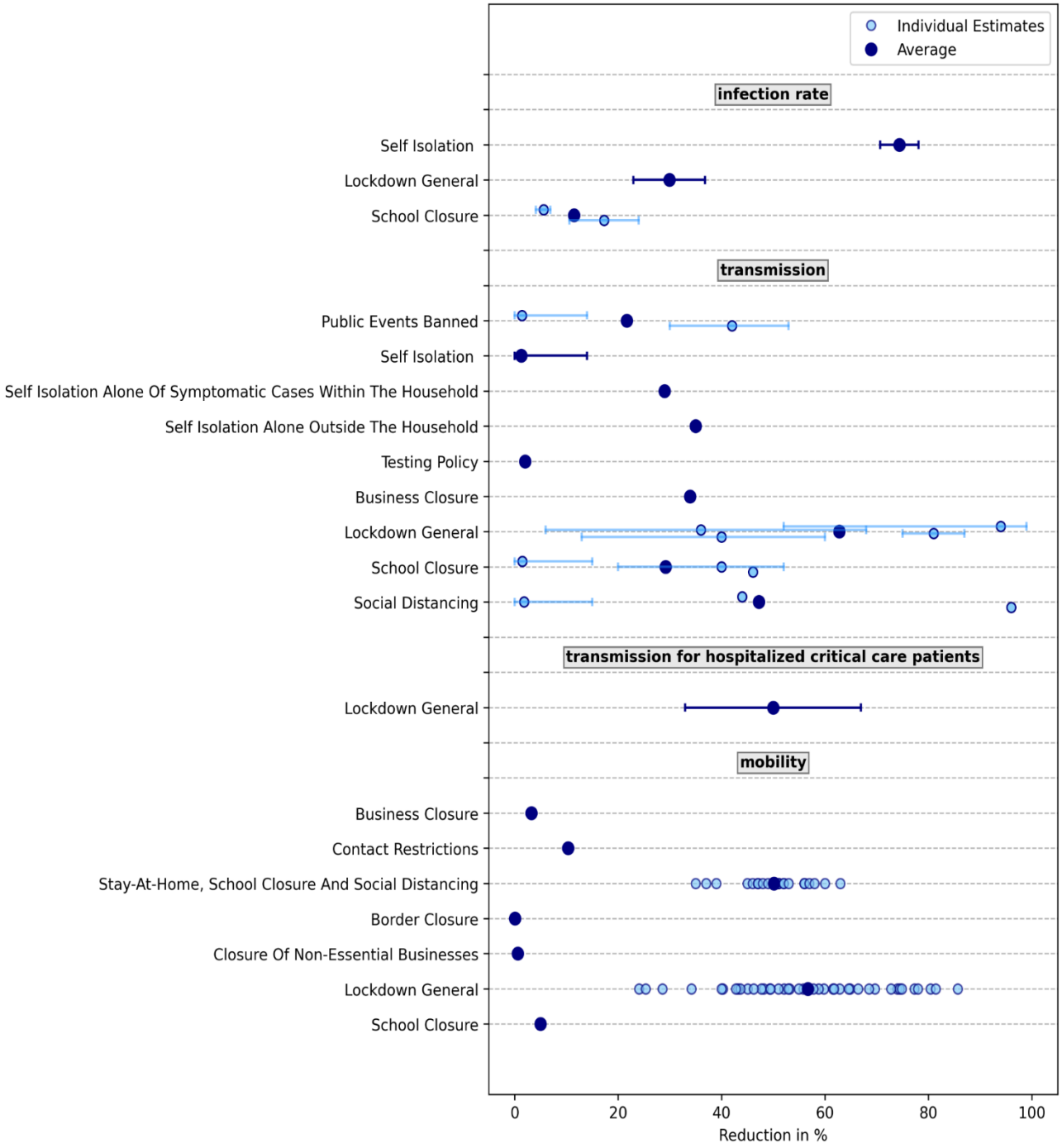

Figure 2c. Part c of the results of the meta-analysis. Dark blue points indicate the average reported effects, while light blue points indicate the effects reported in individual studies.

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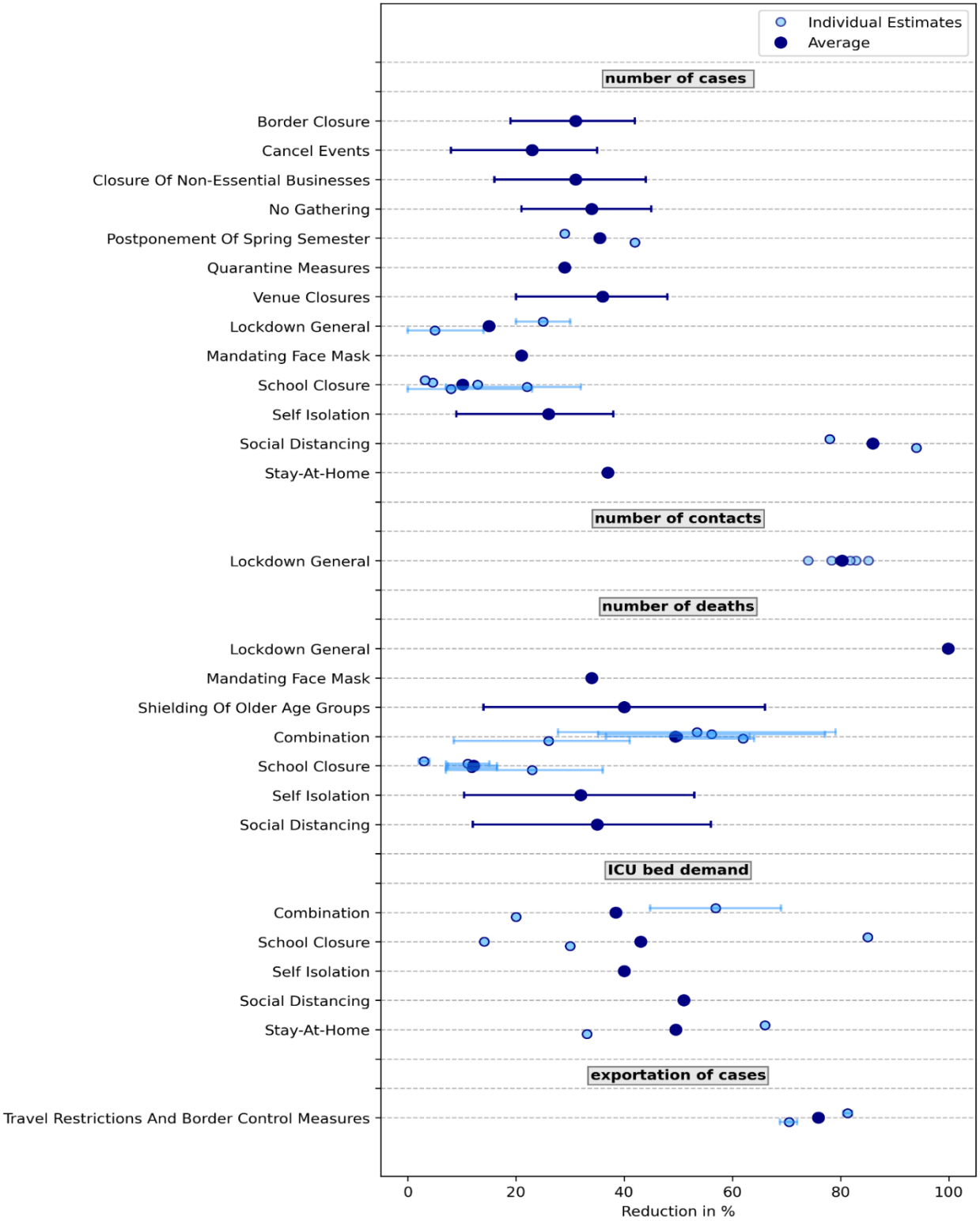

Figure 2d. Part d of the results of the meta-analysis. Dark blue points indicate the average reported effects, while light blue points indicate the effects reported in individual studies.

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2. Description of established model-based analysis pipeline for population cohorts

To assess the impact of NPI in the representative population cohorts included in ORCHESTRA, we will use (1) established compartment models and (2) novel individual-based models. The models will specifically formalize the transmission process accounting for the impact of various factors, including intervention measures, level of (dis)information about the pandemic and economic activity. In contrast to most studies, we not only integrate publicly available numbers on new cases, but also the results of antibody testing and hospitalization data.

In the first three months, we focused on the compartment models already developed by HMGU and established a reusable parameter estimation pipeline. The pipeline estimates the effects of NPIs from different available datasets and accounts for prior knowledge (collected, e.g., in the course of the meta-analysis). In Section 2.1 and 2.2 the different components of the pipeline are described, while in Section 2.3 we report the results of its application to the data from the representative population cohort KoCo19 organized by the Ludwig-Maximilian-Universität (LMU) which is part of ORCHESTRA.

2.1. Formulation of mathematical model

We developed a compartment model which consists of a system of ordinary differential equations (ODEs). To provide a detailed view of the epidemic evolution and integrate not only information from the representative cohort studies but also information about positive PCR tests and hospital count data, a large number of compartments is considered. The rough

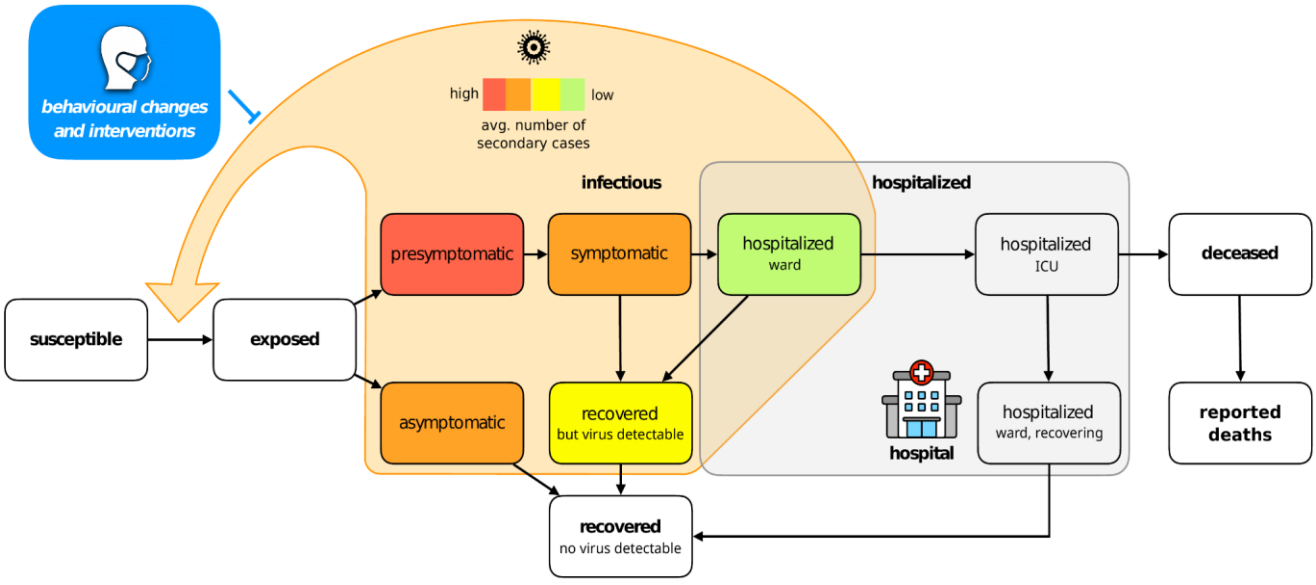

Figure 3. Illness phases captured in the compartment model.

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structure of the model is illustrated in Figure 3, including information about the assumed infectiousness of different groups of individuals.

To model the testing process, each state is duplicated into a tested-positive and non-tested-positive variant resulting in two parallel tracks the illness can progress onto (Figure 4). The rates at which individuals transit from the untested to the tested branch encode the efficacy of the testing system set up by the healthcare authorities, while transitions from the tested to the untested branch are not allowed. The test rates depend on the illness phase: in particular, the test rate for asymptomatic and presymptomatic individuals is a measure of contract tracing effectiveness. Figure 4 also shows that each illness phase can be split into several sub-states so that the transition times between different phases are Erlang-distributed. This is due to the fact that some important times related to the COVID-19 disease (such as the incubation time) have been shown to be approximately log-normal- or Weibull-distributed and thus cannot be reasonably modeled by an exponential distribution (which is disregarded by almost all studies).

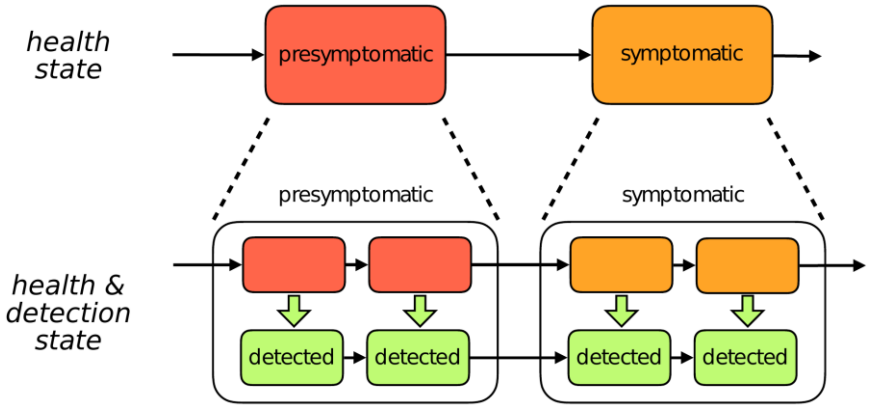

Figure 4. Modeling of the testing process.

Since the policies set by the government and the healthcare authorities vary in response to the evolution of the epidemic, the model parameters must depend on time. Here, we choose three parameters to be time-dependent: the test rates for symptomatic and asymptomatic individuals respectively and the fractional reduction in the number of infectious contacts due to government restrictions such as the lockdown. Such time dependency is modeled by splines with an inter-node distance fixed at 2 weeks (in order to reduce the required computational resources needed). Moreover, the evolution of the test rates has also a week-periodic component in order to account for the lower-case counts around the weekends that has been observed in Germany and elsewhere in the world.

2.2. Computational modeling pipeline

We established a reusable computation pipeline to automate the fitting process. This will facilitate the continuous update of results throughout the runtime of ORCHESTRA.

The compartment model is encoded in the Systems Biology Markup language (SBML) (Hucka

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et al., 2003), a widely used standard in the systems biology community. This standard facilitates the reproduction of the results in various different tools and adds to the reusability.

To construct the dataset used for fitting, we implemented scripts for the extraction of the information from the representative cohort studies. These scripts are already working for the representative cohort by the LMU and the general situation in Germany (as reported by the Robert Koch-Institute[1]). As data becomes available via the ORCHESTRA platform, these scripts will be updated. Furthermore, we extracted priors on different process parameters (e.g., transition rate between compartments) from the literature. The processed information is stored in the Parameter Estimation Table format (PEtab) (Schmiester et al., 2021), a standard format for the formulation of estimation problems.

Using the SBML models and the data in PEtab format, we perform parameter estimation in the Python Parameter Estimation Toolbox (pyPESTO). This tool offers a broad spectrum of functionalities, including advanced nonlinear optimization, profile calculation, sampling, and ensemble uncertainty analysis. In the current phase, we are using the optimization and the sampling capabilities to infer the unknown process parameters, including the effects of different interventions. The observation model for the case counts is negative binomial since we have observed such data to be overdispersed; a normal noise model is used for the remaining data.

As the parameter estimation is computationally demanding, we wrote scripts to easily deploy it on the local compute cluster accessible to members of HMGU. This allows parallelization on a large number of cores. Yet, as sampling is a sequential process, individual runs can still take weeks, and we are currently exploring ways to accelerate this. The planned use of the HPC infrastructures at CIENCA and HLRS will be very useful.

2.3. Results for the computational modeling pipeline

For a first application of the pipeline, we consider the data from the prospective COVID-19 Cohort Munich (KoCo19) for the first wave. KoCo19 is organized by the LMU and is currently monitoring nearly 3000 households in the Munich city area [Radon et al., 2020]. At regular intervals blood samples for each household member are gathered and tested for several indicators of the presence of antibodies to SARS-CoV-2 [Olbrich et al., 2021]. This data is used to impute the lifetime prevalence of COVID-19 in the general population, which due to the potentially large number of asymptomatic cases is impossible to recover from the case counts released by the national health authorities. In addition to the blood tests, study participants are also asked to fill in questionnaires about lifestyle and clinical history, which are then used to investigate potential risk factors for COVID-19 [Pritsch et al., 2021].

We have selected KoCo19 for the initial assessment as we already have access to these data.

The proposed model has been fitted against several data sources describing the evolution of

[1]COVID-19 dashboard of the Robert Koch-Institute:
https://experience.arcgis.com/experience/478220a4c454480e823b17327b2bf1d4

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the epidemic in Munich: the new case and death counts reported by the RKI; the number of symptom onsets reported to the RKI (these are often overlooked but are easily integrated in our model due to the explicit modeling of the testing process); the number of hospital beds occupied by COVID-19 patients, distinguishing ward and ICU; the prevalence estimates produced by the KoCo19 project.

Graphic representations are used to illustrate our preliminary results. As can be seen in Figure 5, our model is able to fit the data, up to the weekend-related oscillations. However, as shown in Figure 6, the uncertainty in the underlying model dynamics remains large. Figure 7 shows the inverses of the time-dependent test rates and indicates a clear improvement (up to the relaxation of government restrictions) which is associated with the increased testing capabilities and contract tracing. Another way to visualize this quantity is by plotting the fraction of infected individuals that actually gets reported to the healthcare authorities, as shown in Figure 8.

For the assessment of the effect of NPIs, we will in the future study the fractional reduction in the disease transmission compared to the start of the epidemic. Preliminary results for this for KoCo19 are depicted in Figure 9. The model is not only able to clearly capture the drop in infectiousness due to restrictions enforced from the beginning of March, but also an uptick in disease transmission after the restrictions have been lifted.

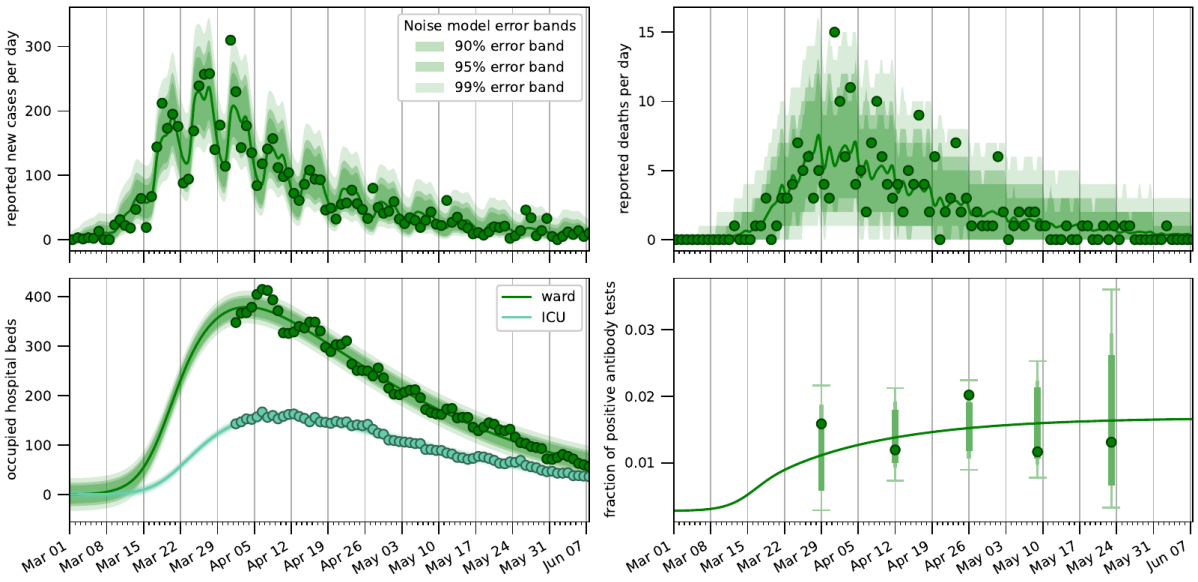

Figure 5. Fit of the epidemic data by the compartment model. The solid line corresponds to the most probable trajectory encountered during MCMC sampling, while the bands show the measurement noise for such a trajectory.

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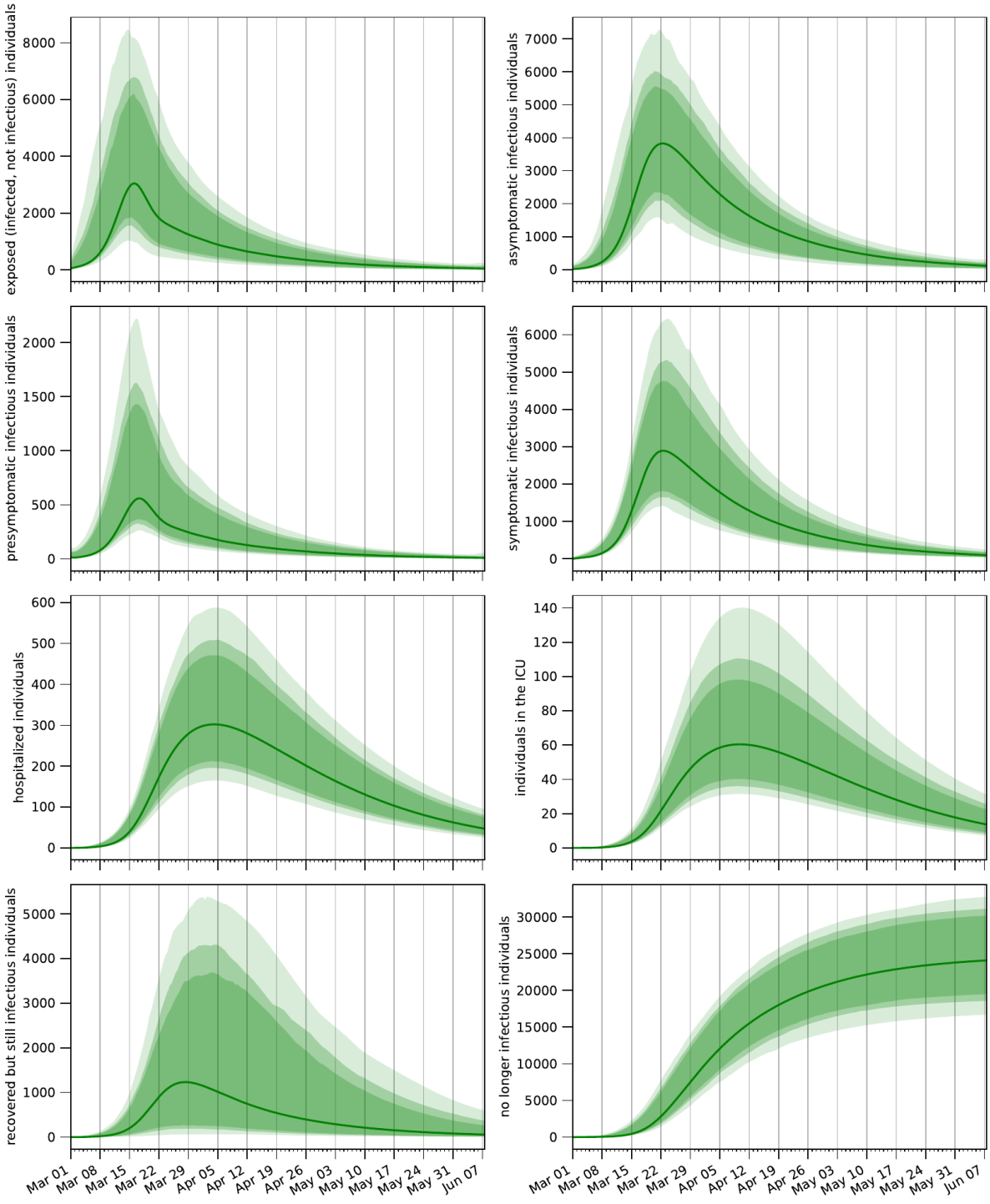

Figure 6. Time evolution of the underlying illness state. Solid line is the median of the posterior distribution, while the bands correspond to the 85/90/95% Bayesian CIs.

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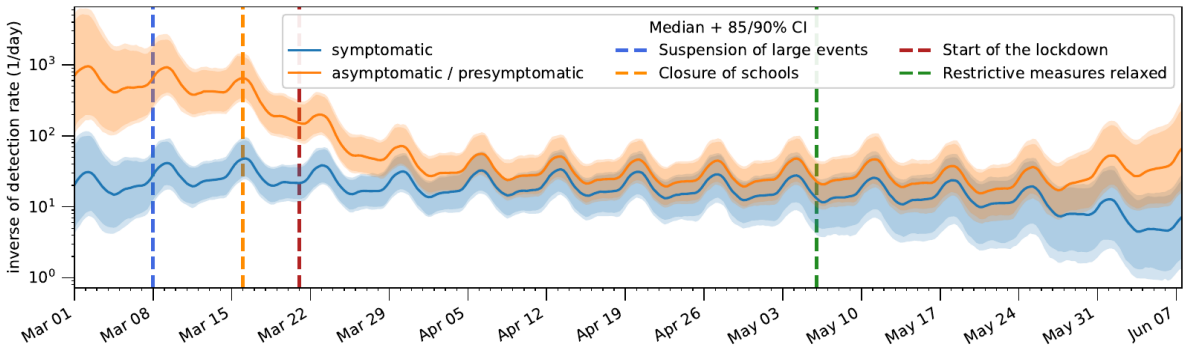

Figure 7. Time evolution of the test rate. Solid line is the median of the posterior distribution, while the bands correspond to the 85/90% Bayesian CIs.

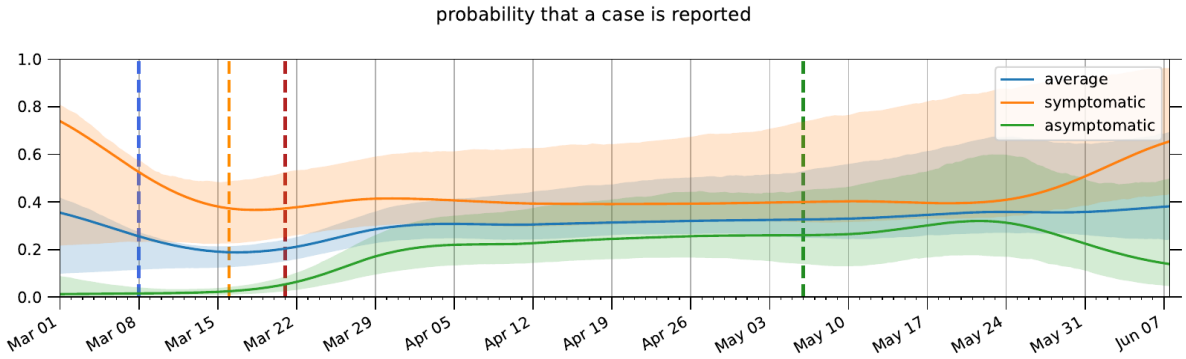

Figure 8. Probability that an infected individual is eventually reported to the RKI. Solid line is the median of the posterior distribution, while the bands correspond to the 90% Bayesian CIs.

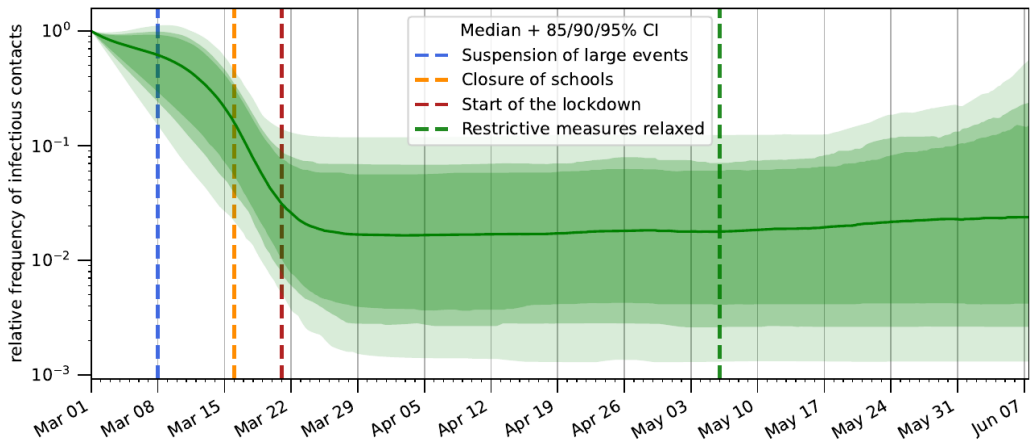

Figure 9. Fractional reduction of disease transmission due to government restrictions. The plot shows the relative reduction compared to the number of contacts at baseline. Solid line is the median of the posterior distribution, while the bands correspond to the 85/90/95% Bayesian CIs.

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3. Conclusions and next steps

The preliminary results of the meta-analysis and computational modelling provide already several interesting results. In particular, we found that the effect sizes of non-pharmaceutical interventions reported in different studies widely differ. While a certain level of difference is expected, due to slight differences in the implementations of rules in different countries and different baseline situations, the magnitude was still surprising. In a next step, we will plan to explore how this depends on the methods used to assess the effect – and more importantly – on the time point of the intervention and socio-economic indicators in the region.

For the computational modelling, a key result is the demonstration of the feasibility of a joint reconstruction of testing and infection rates from a combined set of case reports, clinic usage and seroprevalence data. Our model estimates that the effective rate with which infectious individuals are detected by PCR testing in Munich, Germany was improved substantially between beginning and end of March 2020 and levelled off afterwards. The resulting fraction of infectious individuals which were reported changed substantially over this time interval. The model estimates that at the beginning of March only 10-40% (90% CI) of infected individuals were reported, while in April and May the fraction was 25-50% (90% CI). The largest contribution is the increase in the detection probability for asymptomatic cases, which jumps from 0-10% (90% CI) to 15-40% (90% CI). For the time-dependent infection rate, the model estimates a substantial drop from the beginning of March. Interestingly, we found that the correlation of the parameters for the different splines is rather low, hence, testing and infection rates can be deconvoluted if the case reports and representative data are available. In a next step, we hope to apply the proposed approach to representative data collected by cohorts in other countries.

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