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SARS-CoV-2 variants and vaccination in Belgium

Modelling results by the SIMID consortium

This document contains model estimates of COVID-19 related burden of disease in Belgium based on a stochastic dynamic transmission model using observational data up to April 11th, 2022. This analysis focuses on developments according to the spread of the Omicron VOC in Belgium. All previous reports are available via simid.be and the covid-en-wetenschap blog.

UPDATE: We added additional hospital data up to April 21st, 2022, to Figures 1 and 2. The text and conclusions are not adjusted to the new information.

Preliminary conclusions

- We explored the impact of the Omicron Variant of Concern (VOC) for Belgium with a country-level stochastic transmission model that incorporates infection- and vaccine-induced immunity levels in the population. Under a baseline scenario without any future change in currently estimated transmission dynamics or circulating VOCs, the model projects decreasing numbers of infections and hospital admissions and load in the coming weeks. This trend is caused by a persisting decrease in overall susceptibility in the population, even when we account for waning of vaccine-induced and natural immunity over time. Due to uncertainty with regard to the dynamics for March-April 2022, we explored different assumptions on drivers for these dynamics on the projected outcomes in terms of hospital admissions and load for May-June 2022.
- The three recent COVID-19 waves (between November 2021 and April 2022) are characterised by large differences in ICU load, while the peaks in hospital load were quite similar. The model partly captures this through the inclusion of VOC-specific hospital admission and ICU hazard rates, but the model is not able to capture the latest trends in ICU load at this moment in time. More information is therefore required to explain the changing ICU to hospitalisation ratio observed across these three waves, which could then inform the ICU projections in a better way.
- We explored the impact of additional booster doses by increasing the age-specific booster uptake in the population to the uptake level of at least two doses of a COVID-19 vaccine by May 15th, 2022. With increased transmission dynamics for March-April 2022, the model output shows only small differences between the scenarios on booster dose uptake. The incremental effect of the additional booster doses decreases when the circulation of the virus decreases. Note that the model does not account for local differences in immunity and clustered social contact networks. General trends are captured well, though local outbreaks are underestimated and herd immunity effects are overestimated in sub-populations with immunity levels below the national level.
- We explored a counterfactual historical scenario with an overall 50% reduction in booster dose uptake in the past, while all other factors (i.e., social contact behaviour, VOC, etc.) are assumed to remain constant based on the most up to date available information from the literature, empirical observations and model calibration. As expected, the model shows that the peak in hospital admissions and load in January 2022 could have been much higher (as a direct result of lower vaccine-induced immunity levels) while the peak of the second Omicron wave in March could have been lower. The model accounts for substantial waning of immunity against infection with the Omicron VOC after two doses of any vaccine type, though protection against severe disease is considered to remain substantial (see Table 1). The booster dose re-establishes protection against infection and severe disease, which explains the lower hospital load in the scenario based on the reported uptake. A higher number of infections in the first year 2022 (mainly Omicron) wave, hence

increased natural immunity levels upon recovery, explains the reduced peak of the second wave in 2022. These conclusions hold in the absence of re-infections with the same VOC.

- We are making the implicit assumption that the current Omicron VOC will remain dominant throughout the entire simulation period. Nonetheless, other (new emerging) VOCs may have different transmission probabilities and probabilities to cause disease, hospitalization, death, and different vaccine effectiveness characteristics against each of these manifestations.

- New information on the relative hospital hazard ratio of Omicron vs. Delta VOC was essential to capture current dynamics. Longitudinal serological data would be especially informative to model the underlying transmission dynamics better, and this would inevitably improve the more recent estimates of these dynamics from model calibration to hospital admissions.

- Individuals who have been both fully vaccinated (with or without a booster) and infected, irrespective of the sequence of these events, are currently assumed in the model to remain immune from further reinfections. That is, waning of combined immunity from infection and vaccination does not apply to them, which can be deemed reasonable when focusing hospital admissions with relatively short-term forecasts. Clearly, this should be revisited when observational studies are able to quantify waning immunity for this subgroup of vaccinated persons, or if new VOCs emerge.

Dynamic Transmission Model

Summary: The stochastic model as described by Abrams et al. (2021) has been adapted to include vaccination and the emergence of one VOC from December 2020 (i.e., B.1.1.7 or "Alpha"), another VOC from May 2021 (i.e., B.1.617.2 or "Delta") and a third VOC from November 2021 (i.e., B.1.529 or "Omicron"). The model is calibrated on early sero-prevalence data, genomic surveillance data, hospital admission data, mortality data and social contact data from the Belgian CoMiX survey.

Model input and assumptions

1. **Gradually accumulating naturally-acquired immunity** in the population is accounted for, as well as immunity induced by vaccination. Immunity after infection is assumed to last till the end of the simulations, except for the Omicron VOC. Recovered individuals without any vaccine-induced protection experience an Omicron infection risk of 3% of the Omicron force of infection as compared to fully susceptible individuals, thereby allowing for reinfections. This is based on the reported risk ratio of reinfection for Omicron of 3.3 (95% CI: 2.8 to 3.8) by the UK Health Security Agency (Technical briefing 32).

2. The **introduction of VOCs in the Belgian population** is accounted for using data from the baseline genomic surveillance of SARS-CoV-2 in Belgium by the National Reference Laboratory.

3. **Alpha VOC:** We aggregated the proportion of Alpha, Beta and Gamma VOC in the population to account for the replacement of the wild-type variant by more infectious VOCs The additional transmissibility of the aggregated VOC, which we will denote in this report by the dominant VOC Alpha, is estimated by the model at 35% (95% credible interval (CrI): 29%-40%) relative to the wild-type variant. The model assumes no differential hospital admission probability with respect to the Alpha VOC. Upon infection, the model allows for a VOC-specific differential hospital length-of-stay and risk of ICU admission.

4. **Delta VOC:** The impact of the Delta VOC is modelled by the introduction of a second VOC from May 2021 onward with an average increase in transmissibility of 80% (95% CrI: 65%-99%) relative to the Alpha variant. This increase is estimated based on the baseline genomic surveillance data. We assume a hazard ratio for hospitalization of 2 for the Delta VOC relative to the Alpha VOC. Mean values of 1.8-2.6 have been reported in the UK (with upper limit of a 95% confidence interval for the mean ranging up to 4.36, see PHE, Sheikh et al., 2021).

5. **Omicron VOC:** The impact of the Omicron VOC is modelled by the introduction of a third VOC from the end of November 2021 onward. To account for an adjusted serial interval for Omicron, as reported by Kim et al. (2021), the duration of the latent period for Omicron is estimated in the calibration process based on the baseline genomic surveillance of SARS-CoV-2 data for Belgium. This resulted in an increase

of 30% in transmissibility relative to the Delta variant in combination with an almost instant transition from the exposed to the pre-symptomatic infectious stage after infection with Omicron. In addition, a differential hazard ratio for hospitalization for Omicron relative to Delta has been pivotal. According to recent literature (Nyberg et al., 2022), we restricted our analysis to the scenario based on a ratio of 60%. Age-specific adjusted hazard ratios should be evaluated in future work. **The calibration period covers both the emergence of Omicron sub-lineages BA.1 and BA.2, the latter became dominant in Belgium on February 28th, 2022. Differences in transmission for BA.2 are absorbed in the wave-specific q-parameters for February-March 2022, hence these differences are implicitly considered when extrapolating the "current dynamics" into the future and part of the scenario analysis.**

6. Our model results contain stochastic variation in the transmission process and parameter uncertainty based on 40 model parameter configurations. The calibration procedure relies on likelihood-based MCMC sampling resulting in 40 posterior samples of the joint distribution, each of which is used to generate a single stochastic realization within each social mixing and/or vaccine uptake scenario. The MCMC procedure is, in general, based on the adaptive Metropolis-within-Gibbs algorithm, and parameter configurations are updated starting from previous calibration results based on an additional number of iterations (100 iterations) with 10 realizations per iteration, periodicity of 10 iterations and leading to 40 different chains based on 40 initial starting configurations.

7. This model is **fully age-structured** but does not simulate the physical interactions of subgroups like nursing home residents and nursing home personnel or healthcare workers in general. Vaccine uptake for health care workers is therefore implemented at the level of the ages of the target group.

8. Hospital admission data is still the main source of information to inform and calibrate the model given the frequent changes in the Belgian SARS-CoV-2 testing policy (and its impact on the daily number of confirmed COVID-19 cases). The reported hospital admissions are complemented with the number of new positive cases in the Belgian hospitals in the last 24h that have been admitted for another pathology. Given that these positive cases contribute to the COVID-19 related hospital load, we include these new patients in our parameter fitting procedure.

9. The model is calibrated using social contact data of the Belgian CoMiX survey. For each survey wave (with the latest included wave, the 43rd conducted between March 1-8, 2022), we estimate age-specific q-parameters (i.e., proportionality factors) to translate social contact data into transmission rates, with estimated social contact rates used as a proxy for effective contacts enabling disease transmission and proportionality factors adjusting for other factors that influence this relation. This captures, among other things, age-specific susceptibility and risk behavior during social contacts.

10. We evaluate different **scenarios** to explore the combination of vaccine effectiveness and social contact patterns. None of the scenarios include the introduction of infected cases as a result of international travel. We start with the latest model calibration and the reported vaccine uptake scheme as presented in Figures S1 and combine the following options:

    - **Increased transmission**: We explore the effect of an increased risk in contracting SARS-COV-2 as a result of increased social contact or risk behaviour, a more virulent sub-strain of Omicron, or a combination of the two. In particular, we investigate an increase of +10% from March 14th, +20% or 40% from March 28th, and +0% or +70% from April 11th onward. These time points are chosen in view of the absence of bi-weekly CoMix data that we previously included for our modeling, given that the frequency of our social contact survey waves was reduced for budgetary reasons. A direct translation of these scenarios in terms of increases in contact frequency or risk behaviour relative to pre-pandemic (contact) behaviour is not possible.
    - **Increased booster dose uptake**: We increased uptake of booster doses from April 12th, 2022, to equal the age-specific 2-dose uptake levels by May 15th, 2022 (ie, in this scenario, we assume that everyone who is eligible for a booster dose, received a booster dose by May 15th).
    - **Reduced booster dose uptake**: We explore the effect of reducing the historical booster dose uptake by 50% over time: at each time point only 50% of the actual, observed number of administered booster doses are assumed to have been administered in the model.

11. **Vaccine protection**

- **Infection:** we use a "leaky" vaccination approach. For example, vaccination with 50% effectiveness, implies that for a vaccinated individual the likelihood to acquire infection is 50% less compared to a non-vaccinated individual of the same age. The levels of protection against infection for different VOCs are presented in Table 1.
- **Hospital admissions:** vaccinated individuals who acquire infection are at lower risk of hospital admission with COVID-19. The level of protection against severe disease, which we assume to be in line with hospital admissions, is presented in Table 1.
- **Transmission:** Fully vaccinated individuals (with or without a booster in the model) who acquire infection have a 45% lower risk of transmitting the disease. This assumption is based on a study in the UK on the effect of vaccination on household transmission of SARS-CoV-2 (Harris et al., 2021).
- **Severe non-hospitalized cases** are currently not separately modelled, hence the impact of vaccination on non-hospitalized severe cases, seen in primary care, is not separately shown.
- **Vaccine-induced immunity** against infection is implemented as a step function with a switch from, e.g., 0% to 50% protection against infection 21 days after the first vaccine dose. Vaccine-induced protection against hospital admission is implemented incrementally on top of the protection against infection. Protection induced by the second and booster vaccine doses is assumed to be achieved fully (i.e., depending on the maximal vaccine effectiveness as reported in Table 1) 7 days after administration. We consider differences between mRNA and adenovirus-based vaccines in how they induce immunity and in terms of protection (see Table 1).
- The reported Johnson & Johnson (JnJ; Ad26.COV2.S) and Curevac (CV07050101) vaccines are accounted for in the model as (being similar to) the AstraZeneca vaccine (ChAdOx1). The numbers of administered vaccine doses is too low to outweigh the increase in computational burden and complexity of the model when adding an additional subdivision in the model.
- **Waning of vaccine-induced immunity is included in the transmission model as a separate set of health-related compartments.** We assume a transition rate of 1/180 days towards the waning immunity compartments with reduced vaccine efficacy levels based on the literature (see Table 1). This implies that after 180 days vaccine-induced immunity has fully waned in vaccinated people, unless they received a booster dose in the mean time (see next bullet) or they were also exposed to infection before or after having been vaccinated with their primary schedule (see bullet point further down).
- **Third doses (boosters) are included in the transmission model as a separate set of health-related compartments.** We assume that all booster doses are mRNA-based vaccines and waning of vaccine-induced immunity 10 weeks after the booster dose is VOC-specific and based on recent literature (see Table 1).
- **Individuals who have been both fully vaccinated (with or without a booster) and infected, irrespective of the sequence of these events, are currently assumed in the model to remain immune from further reinfections.** That is, waning of combined immunity from infection and vaccination does not apply to them, which can be deemed reasonable when focusing hospital admissions with relatively short-term forecasts. Clearly, this should be revisited when observational studies are able to quantify waning immunity for this subgroup of vaccinated persons, or if new VOCs emerge.

12. **Vaccine uptake**

- The vaccine-type and age-specific uptake in the model of first, second and booster doses over time at the national level is based on the reported data by Sciensano, derived from Epistat up to April 5th, 2022. The uptake by age is presented in Figure S1. For the model projections, we assume no increase in vaccine uptake.
- We do not account explicitly for risk-group vaccination, since the model structure does not allow to model a sub-population with a differential risk and potentially a more severe COVID-19 disease episode once infected (i.e., a higher probability of hospitalization and/or a higher probability of death, if hospitalized).

Table 1: Vaccine efficacy against infection and hospital admissions after infection by VOC for adeno-based and mRNA-based vaccines by dose. The references and assumptions are provided at the bottom of the table.

Vaccine type	Alpha		Delta		Omicron	
	Infection[1]	**Hospital**[2]	**Infection**[3]	**Hospital**[4]	**Infection**[3]	**Hospital**[5]
Adeno: 1st dose	49%	76%	43%	76%[6]	18%	65%[7]
Adeno: 2nd dose	74%	86%	83%	95%	49%	81%[7]
mRNA: 1st dose	48%	83%	72%	79%[6]	32%	65%[6]
mRNA: 2nd dose	94%	95%	91%	99%	66%	81%
Waning after 2nd dose	-	-	63%	92%	9%	57%
Booster (mRNA)	-	-	95%	99%[8]	67%	90%
Waning after booster	-	-	90%	92%[8]	48%	81%[9]

[1](Bernal,2021); [2](Stowe,2021); [3](Andrews,2022a); [4](Andrews,2022b); [5](CDC report,2022); [6](Assumed equal to 80% of 2 doses); [7](Assumed equal to mRNA); [8](Assumed equal after 2 mRNA doses); [9](Assumed 90% of booster mRNA dose)

Major limitations

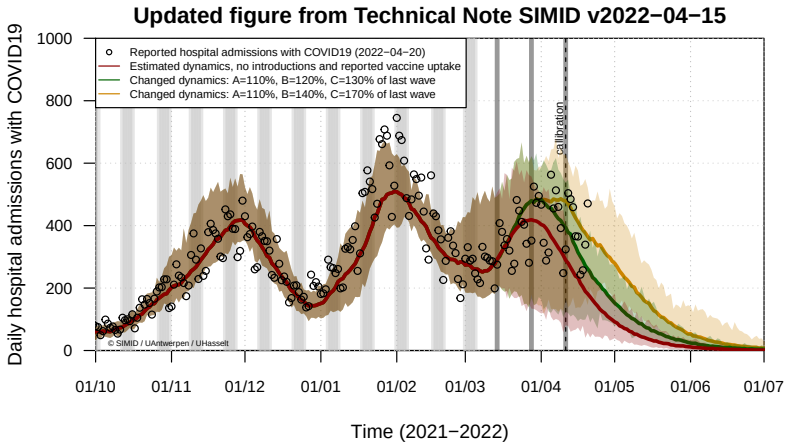
- **This transmission model is suited for scenario analyses to investigate possible future or counterfactual (retrospective) paths, it is not a prediction model.**
- The model is calibrated on hospitalizations and informed by social contact data from the Belgian CoMiX survey. These empirical social contact data inform mainly the frequency and age structure of person-to-person social interactions, but are less informative with regard to the adherence to restrictions. The fact that the model is primarily calibrated on hospitalization data, and given the time lag between incurring infection and being admitted to hospital, makes this model less sensitive to rapidly changing dynamics. Another issue is that empirical data on social contact patterns is also lagging behind.
- The daily age distribution of hospitalized patients is derived from the individual hospital survey **up to March 31st, 2021**, in which patients are only included at hospital discharge. This implies a considerable delay in the availability of up to date information concerning the age distribution of hospitalizations. In a transition phase in which the age distribution changes drastically, e.g., due to the depletion of susceptible persons in older age groups as a result of vaccination, this delay could have a considerable impact on future trajectories.
- We are making the implicit assumption that the BA.2 Omicron VOC will remain the dominant strain throughout the entire simulation period. Nonetheless, other (new emerging) VOCs may have different transmission probabilities and probabilities to cause disease, hospitalization, death, and different vaccine effectiveness characteristics against each of these manifestations.
- The transmission model does not evaluate (severe) outpatient cases, which affect pressure exerted on primary care. Also, the model does not include parameter uncertainty with respect to vaccine effectiveness yet.
- The incremental transmissibility induced by the emergence of different VOCs, which we include in the model, is considered to be age-invariant.
- We attribute the growth advantage of the Alpha and Delta VOCs completely to transmissibility, and as such, ignore the potential effect of immune escape on the speed of penetration. For Omicron, we do include immune escape by allowing for reinfections in addition to reduced vaccine-related protection.
- The reduced serial interval for Omicron is fully attributed to a reduction in the latent, or exposed, period. As such, a potential reduction in the infectious period is not captured by the model at this stage.
- Vaccine-induced immunity is implemented by a step function. As such, it is assumed that build-up of immunity in vaccinated persons is not a gradual, but a stepwise process.
- This model does not explicitly account for importation of cases by returning travelers which could have impact on the evolution of the epidemic. Importantly, an implicit attribution of such cases to local transmission is used instead.

- We present our modelling results by the mean and pointwise 95% credible interval based on 40 model realizations, which capture stochastic effects and parametric uncertainty. The interplay between these two sources of uncertainty is subject of future research.
- Social mixing behaviour is assumed to be constant in the forward projections, unless explicitly stated in the scenario definitions. Without increased risk behaviour, the incidence of new infections decreases due to decreasing number of susceptible individuals. Behavioural changes might counter this decreasing force of infection, though this is not studied here thoroughly.
- The model projections are based on the hospital admissions with COVID-19, hence one can interpret them to represent the upper limit for hospital admissions due to COVID-19.
- The national model does not account for local differences in immunity and assumes random mixing in the population. As such, local outbreaks and herd immunity effects in sub-populations with immunity levels below or above the national level, respectively, are underestimated.

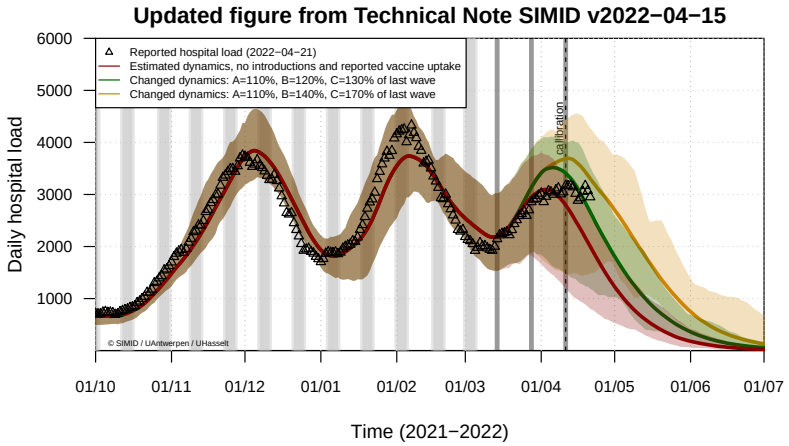
Model results

The following figures depict the results of the different scenario analyses specified by changing social mixing and vaccine uptake assumptions. All projections show a large 95% credible interval and should therefore be interpreted with great caution. The main conclusions are listed at the start of this document.

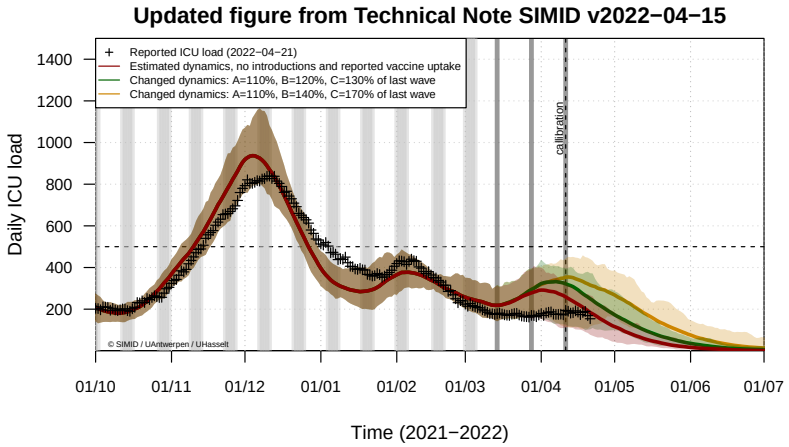
Disease burden with constant (as estimated from the last model calibration) and increased transmission dynamics in March-April 2022.



(a) Daily hospital admissions with COVID-19



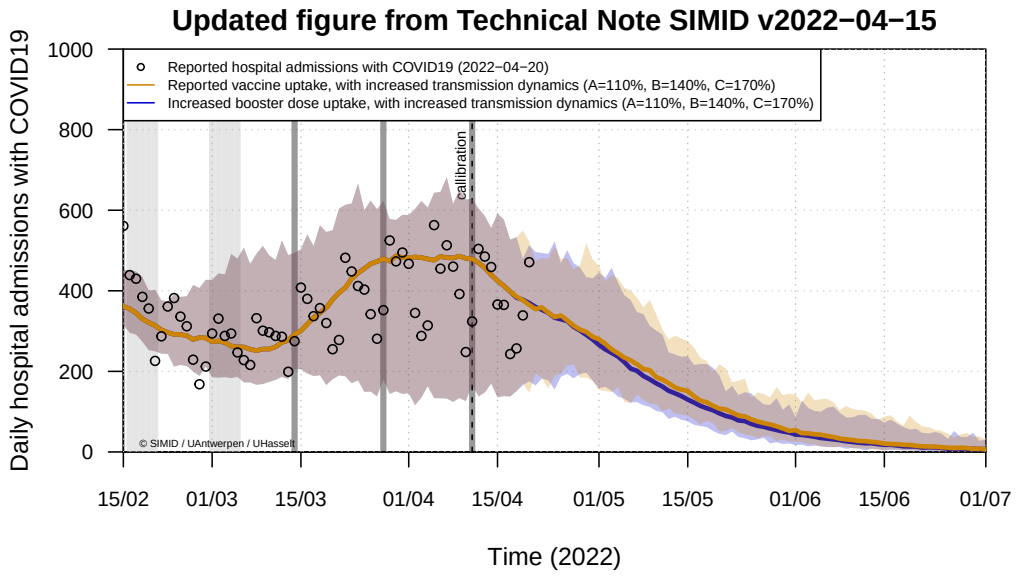
(b) Daily hospital load



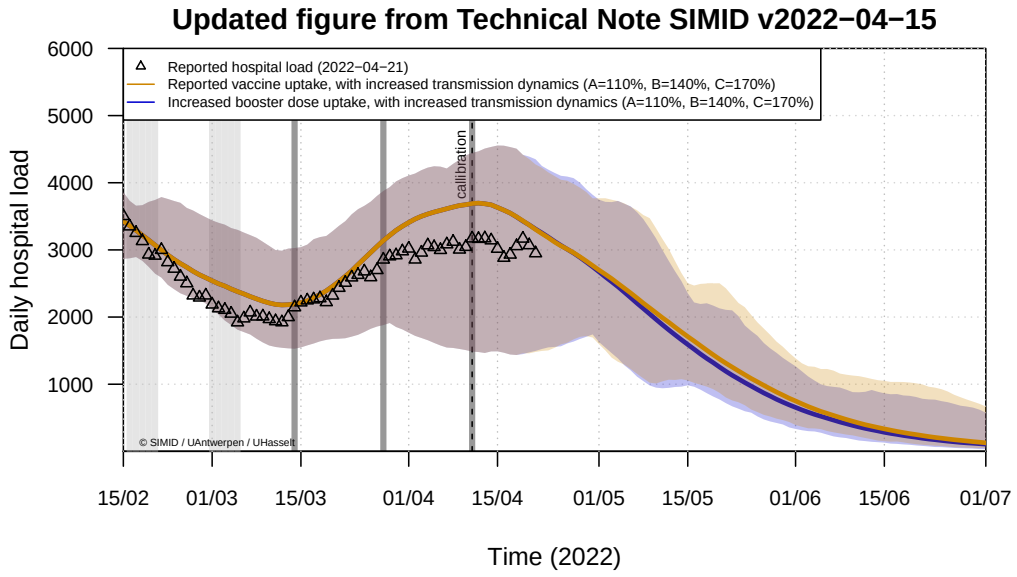
(c) Daily ICU load

Figure 1: Model projections for Belgium for different clinical outcomes, assuming different transmission dynamics in March-April 2022. The results are summarized by the mean (line) and 95% point-wise credible intervals (shaded area) of 40 model runs.

Disease burden with increased transmission dynamics in March-April 2022 and different booster dose schemes.



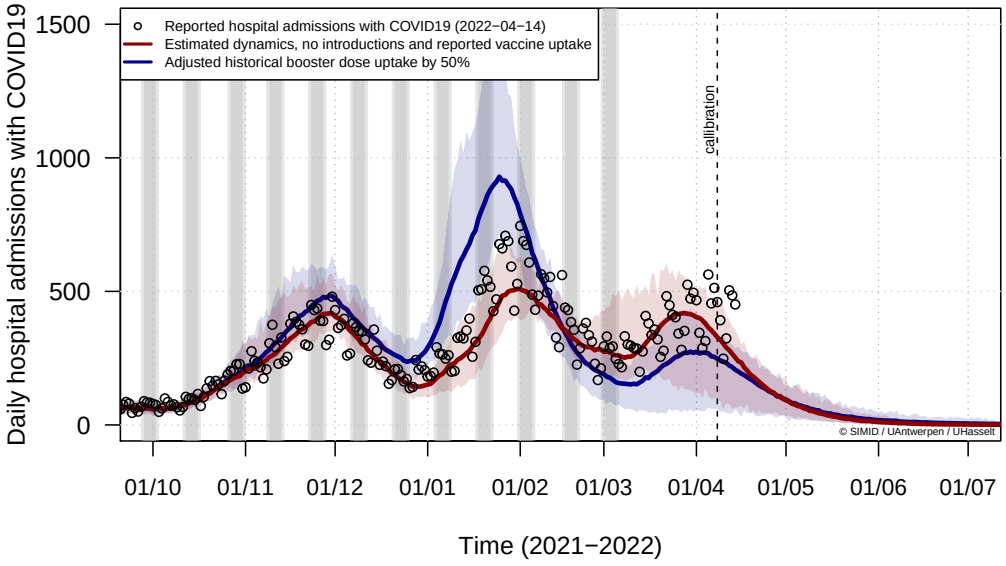
(a) Daily hospital admissions with COVID-19



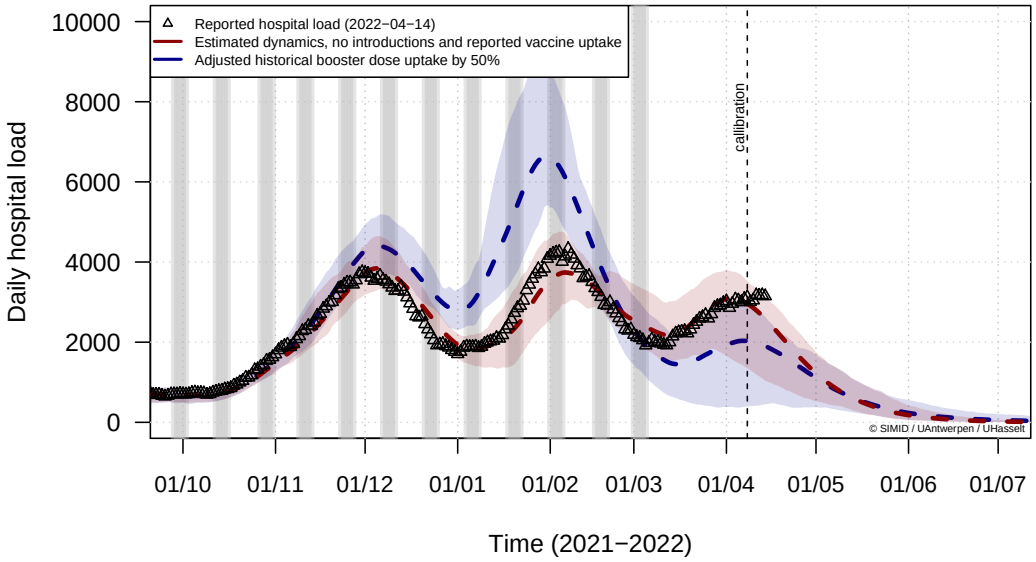
(b) Daily hospital load

Figure 2: Model projections for Belgium for different clinical outcomes, assuming increased transmission dynamics in March-April 2022 (A: 110%, B:140%, C:170%) with current and increased uptake of the booster dose in April 2022. The scenario with increased booster dose uptake (blue) is mostly overlapping with the current uptake scenario, except for May 2022. The results are summarized by the mean (line) and 95% point-wise credible intervals (shaded area) of 40 model runs.

Disease burden with the estimated transmission dynamics and different uptake schemes of the booster dose.



(a) Daily hospital admissions with COVID-19



(b) Daily hospital load

Figure 3: Model projections for Belgium for different clinical outcomes, assuming estimated transmission dynamics for March 2022 with reduced booster dose uptake in the past (i.e., counterfactual). The results are summarized by the mean (line) and 95% point-wise credible intervals (shaded area) of 40 model runs.

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SUPPLEMENT

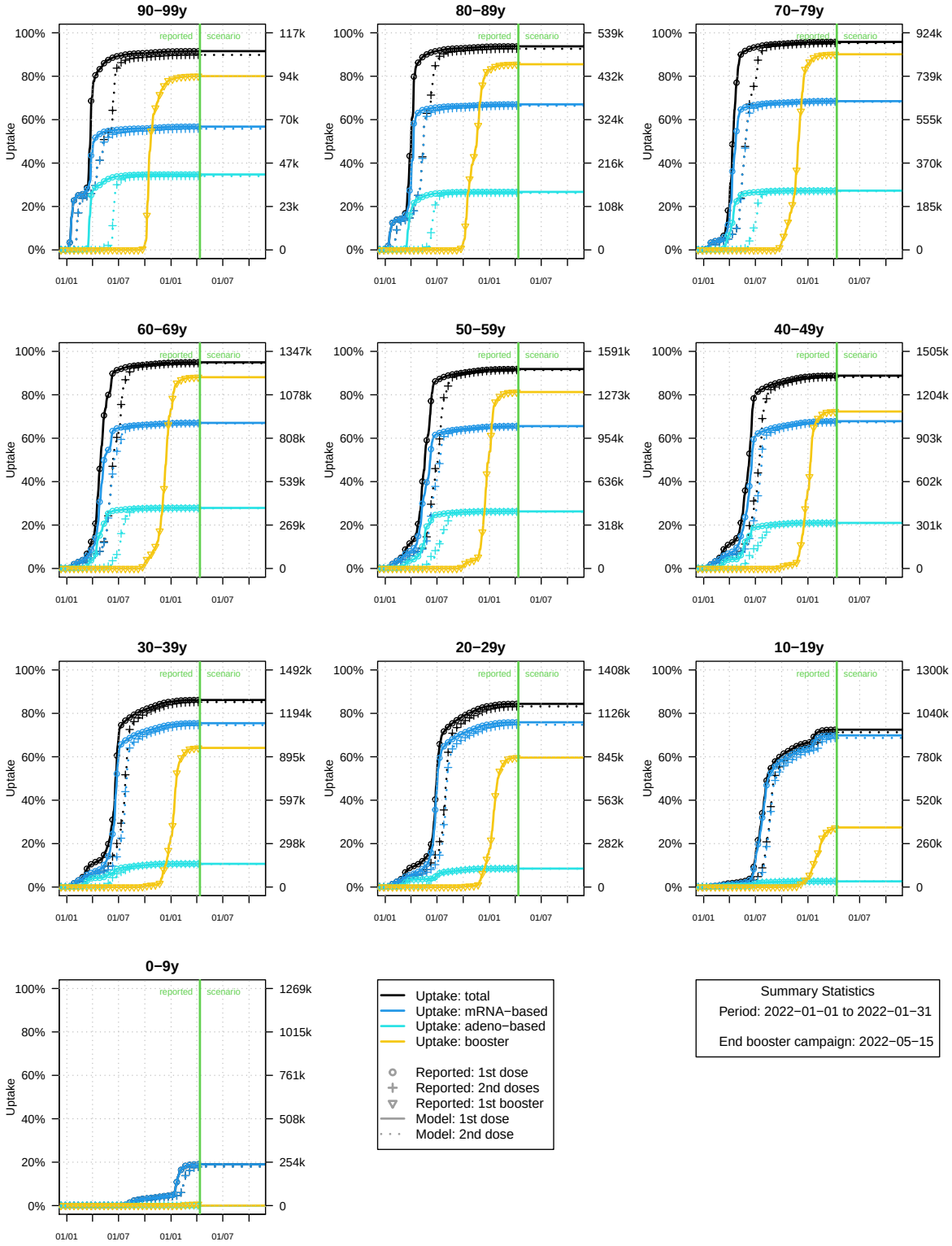

Figure S1: Vaccine uptake by age, vaccine-type and dose based on the reported uptake for Belgium on April 12th, 2022.

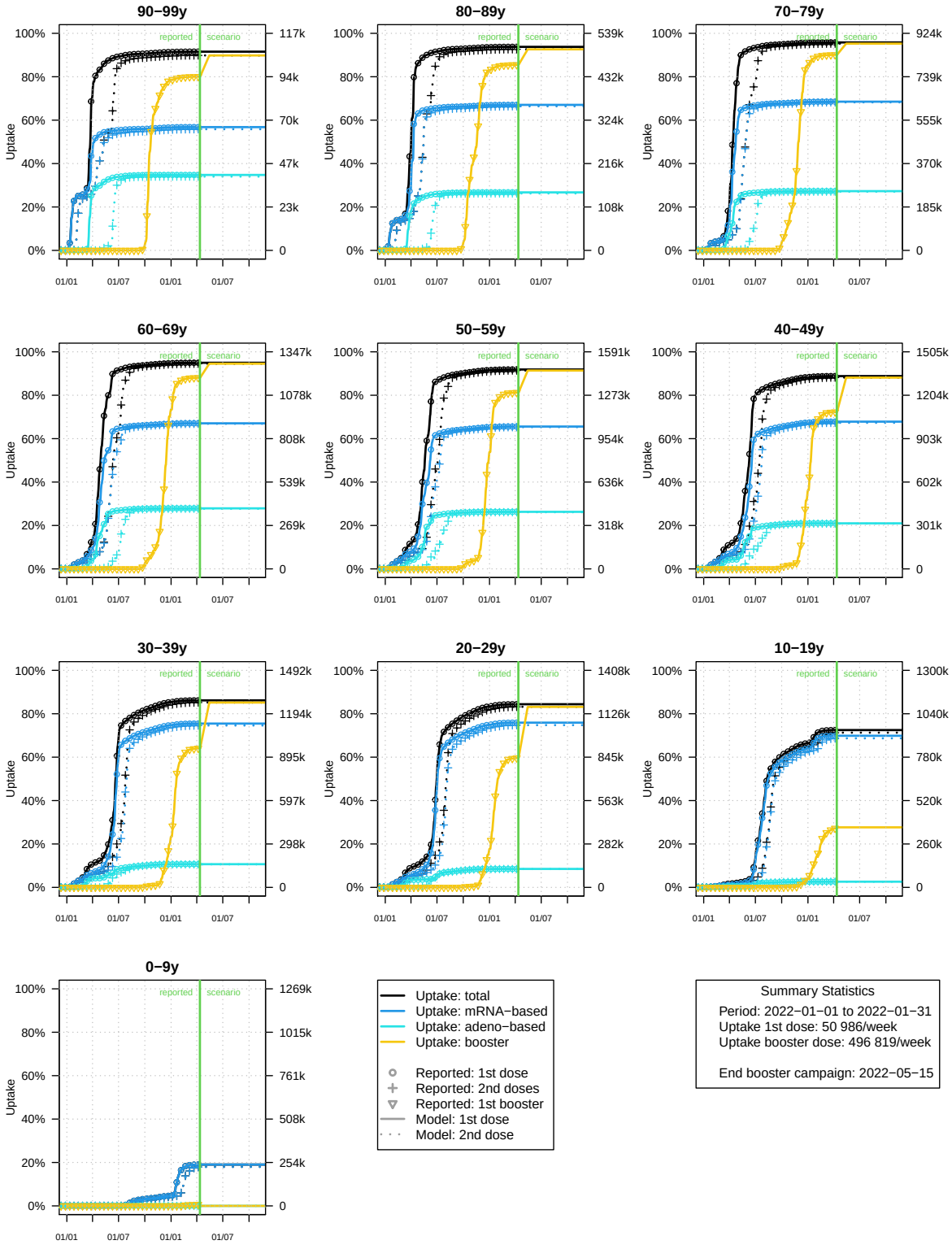

Figure S2: Vaccine uptake by age, vaccine-type and dose based on the reported uptake for Belgium with an increase of the booster dose uptake up to the 2-dose level by May 15th, 2022.

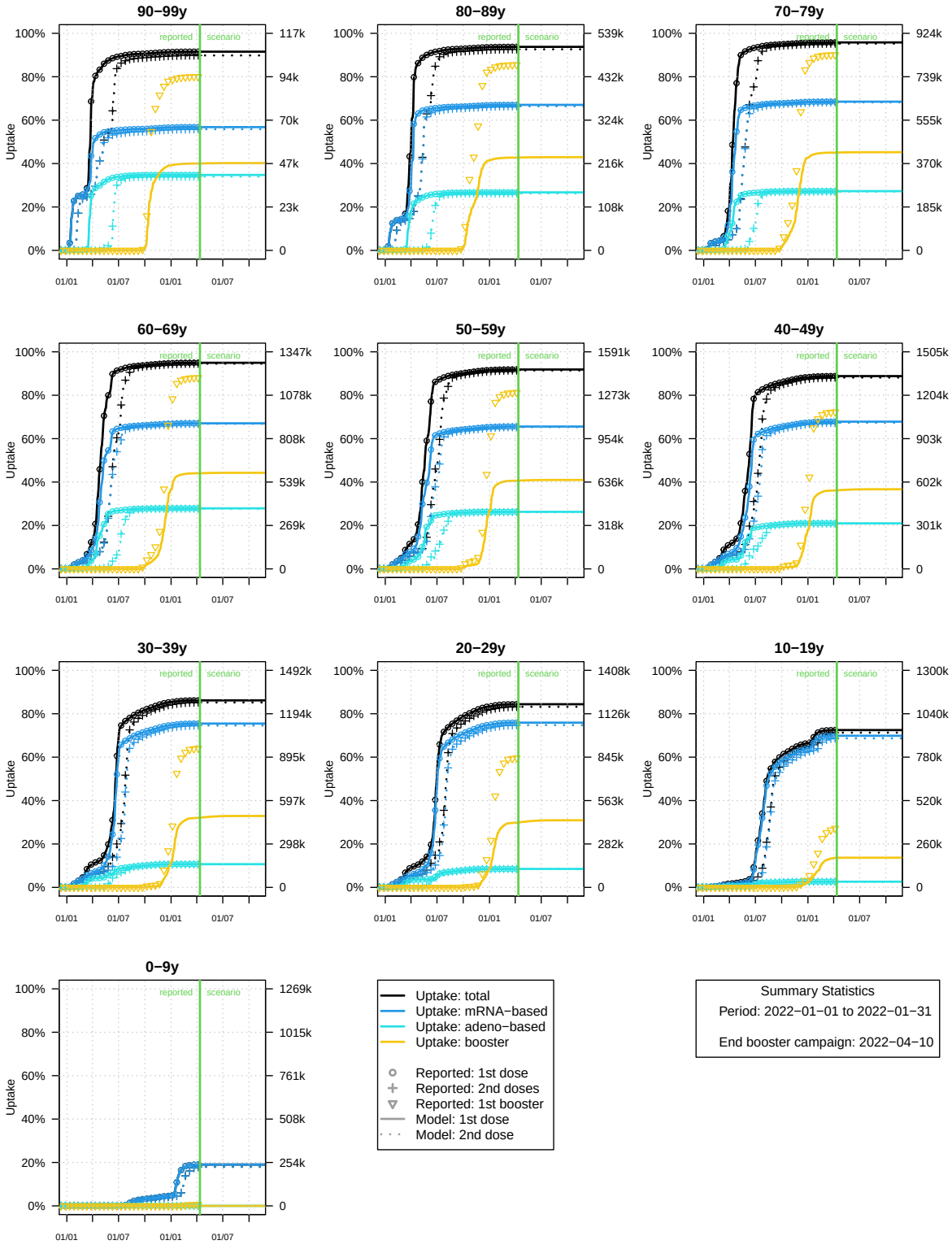

Figure S3: Vaccine uptake by age, vaccine-type and dose for Belgium with 50% reduction of the reported the booster dose uptake until April 10th, 2022.